2025 SID ANNUAL MEETING

Abstract Book

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Abstract Booklet

Society for Investigative Dermatology **May 7-10, 2025**

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0001

Structural and functional characteristics of binding of pemphigus vulgaris antibody to keratinocyte M3 muscarinic acetylcholine receptor

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Patients with pemphigus vulgaris (PV) develop IgG autoantibodies (AuAbs) binding to keratinocyte desmogleins (Dsg), acetylcholine (ACh) receptors, mitochondrial proteins, and some other autoantigens. In this study, we used epitomic approach to immunoselect random sequences from a phage display library and determine the sequence patterns that are common to PV AuAbs. We wanted to identify linear and discontinuous peptide epitope segments of Dsg1, Dsg3 and M3 muscarinic ACh receptor (M3AR) targeted by different AuAbs on the same protein target. PV sera specifically targeted 278 Dsg1, 242 Dsg3, and 122 M3AR tetramers. Since the M3AR protein shares only 2 tetramers with Dsg1 and 4 with Dsg3, targeting of M3AR by cross-reacting anti-Dsg1/3 PV was ruled out. The targeted M3AR pentamers encompass the 10 amino acids-long epitope LSEPTITFGT (amino acids 226-235) located on the border of the second extracellular loop and the fifth transmembrane helix, including the tetramer TFGT containing Thr235 which is a part of the ACh-binding pocket. Previously, it has been demonstrated that the anti-M3AR AuAb produces an agonist-like effect on downstream signaling, but its long-term effect is receptor desensitization, because of which ACh regulation of keratinocytes via M3AR is lost. In this study, we compared the functional consequences of binding anti-M3AR AuAbs that targeted the ACh-binding pocket with that of AuAbs that targeted M3AR outside of its ACh-binding pocket. While the former AuAbs induced a very high elevation of phospholipase C, which is consistent with an agonist-like effect, the latter AuAbs produced a much weaker response. These results indicate that PV patients develop two types of anti-M3AR AuAbs. One type attaches to orthosteric, ie, ACh-binding, site and elicits a very strong signaling response comparable to a full pharmacologic agonist, whereas another type binds to an allosteric site and elicits submaximal signaling response comparable to a partial (allosteric) pharmacologic agonist.

0002

Tumor-rejecting neoantigens in cutaneous squamous cell carcinoma

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Challenges in identifying neoantigens that mediate tumor rejection limit the efficacy of neoantigen vaccines to treat cancers, especially for high mutational burden tumors like cutaneous squamous cell carcinoma (cSCC). We found that a minority of human cSCC tumors shared neoantigens, supporting the need for personalized cancer vaccines. To identify characteristics that define tumor-rejecting neoantigens, we first generated transplantable murine cSCC cell lines, from solar UV-induced tumors, which recapitulated the mutational signature and driver mutations found in human disease. Antibody depletion revealed that CD8 T cells constrained cSCC. Vaccination with irradiated cSCC cells completely protected mice from tumor challenge, and this response was dependent on CD8 T cells. Neoantigens were prioritized based on predicted MHC binding affinity, MHC presentation, and expression. IFN-γ-secreting CD8 T cells recognizing two neoantigens were identified in tumors and tumor-draining lymph nodes. Prophylactic vaccination with these neoantigens constrained cSCC growth. Activated, cytolytic CD8 T cells recognizing these neoantigens were detected in tumors with tetramer staining. Evaluation of tumor-rejecting neoantigens in our model and other cancer models revealed two distinct sets of characteristics that define tumor-rejecting neoantigens: improved MHC binding or increased solvent accessibility of the mutated residue compared to the wild-type residue that is anticipated to facilitate T cell receptor recognition. This work reveals characteristics of tumor-rejecting neoantigens that may be of considerable importance in identifying optimal vaccine candidates in cSCC and other cancers.

0003

PN-881: First-in-class oral peptide targeting the IL–17 pathway

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IL-17 is a key mediator of psoriasis, psoriatic arthritis, hidradenitis suppurativa, and spondyloarthritis. There are currently multiple approved injectable IL-17 antagonists but no orally delivered antagonists. Clinical trials of these agents have shown that inhibition of IL-17A and F and their 3 dimeric forms (AA, AF, and FF) yield greater efficacy in psoriasis than inhibition of IL-17A alone. Here we report for the first time the preclinical characterization of PN-881, an orally delivered macrocyclic peptide that potently and selectively binds IL-17A and F, thus blocking all 3 dimeric forms. PN-881 inhibits IL-17-induced IL-6 production in human HT-1080 fibrosarcoma cells and in primary human dermal fibroblasts (nHDF) with concentration-dependent potency (IC_{50}) values comparable to bimekizumab. The HT-1080 IC_{50} values for PN-881 are 0.13 nM (AA), 27 nM (AF), and 14 nM (FF) and for bimekizumab are 0.17 nM (AA), 19 nM (AF), and 13 nM (FF). PN-881 is resistant to the proteolytic and reducing environment of the gastrointestinal tract and stable in serum after absorption, making it a suitable candidate for oral delivery. Pharmacokinetic (PK) evaluations in a variety of preclinical species indicate PN-881 achieves systemic exposures and skin distribution multiple folds above the IC_{50} after oral administration. Orally dosed PN-881 blocked IL-17-induced chemokine ligand 1 (CXCL1) production in mice in a dose-dependent manner. PN-881 also dose-dependently inhibited IL-23-induced rat skin inflammation and thickening with significant effects at oral doses as low as 2 mg/kg/day. These preclinical potency, PK, PD, and efficacy results support the potential for a first-in-class oral peptide targeting IL-17-mediated diseases.

0004

Circulating B cell responses associate with merkel cell carcinoma outcomes

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Merkel cell carcinoma (MCC), a rare skin cancer, is mostly driven by integration of the Merkel cell polyomavirus which encodes T-antigen (T-Ag) oncoproteins. Previous research has shown that T & B lymphocytes target T-Ag. Indeed, patients with virus-driven MCC produce T-Ag-specific antibodies that are clinically useful to track disease recurrence. These antibodies do not play a direct role in MCC immunity as T-Ag oncoproteins are intracellular. Our group has recently found that in tumors, T-Ag-specific B cells with germinal center or antibody-secreting phenotypes strongly predict improved MCC outcomes. These intratumoral B cell phenotypes reflect a robust cancer-specific T cell response. In contrast, T-Ag-specific B cells circulating in the blood of MCC patients are predicted to predominantly have a memory or naive phenotype, and it is unknown if they may contribute to anti-tumor immunity. We used fluorescently labeled T-Ag-oncoproteins and flow cytometry to assess B cell responses in blood at the time of MCC diagnosis. In total, we analyzed samples from 23 patients whose MCC recurred within 3 years of diagnosis and 24 samples from stage- and age-matched MCC patients whose disease did not recur. We found no difference in the frequency of all circulating B cells (regardless of T-Ag-specificity) between patients who did and did not develop MCC recurrence. In contrast, higher frequencies of total memory B cells (CD27+IgD-IgM-) were associated with an increased risk of disease recurrence (HR 3.67 [1.58- 8.55], p=0.003). Intriguingly, T-Ag-specific memory B cells were also more abundant in the blood of patients who ultimately developed MCC recurrence (HR 2.82 [1.22- 6.53], p=0.012). Together, our results demonstrate that higher frequencies of circulating memory B cells associate with worse MCC outcomes. These findings suggest that the functional state of total and T-Ag-specific circulating B cells reflect their immune response within MCC tumors.

0005

Calcitonin gene-related peptide (CGRP) induces interleukin-6 (IL-6) production by microvascular endothelial cells (ECs)

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Exposure of murine dermal microvascular ECs to CGRP endows them with the ability, acting as bystanders, to bias the outcome of antigen presentation by Langerhans cells (LCs), or bone marrow-derived dendritic cells, to responsive T cells away from Th1-type immunity and toward Th17-type immunity. We have previously demonstrated that treatment of ECs with small siRNA to IL-6 partially inhibits this CGRP effect. Furthermore, when IL-6 knockout ECs are used in the system, the CGRP effect is lost. We have now directly examined the ability of CGRP to induce IL-6 production by microvascular ECs. $CD31^+$, $CD45^-$ ECs were obtained from the dermis of wild-type C57BL/6 mice and IL-6 knockout mice (C57BL/6 background) by magnetic antibody techniques. Twenty-five thousand ECs per ml were cultured in 12-well plates in complete endothelial cell growth medium for 24 hours. Then, complete medium was replaced with basal medium plus only 2% FBS and 100 U/ml penicillin/100 µg/ml. CGRP 0, 10 or 100 nM CGRP was added to wells. After 24 hours of culture, supernatants were harvested and IL-6 content assessed by ELISA: 0 nM CGRP – 9.7+/- 3.8 (SEM) pg/ml, 10 nM CGRP – 312.7+/- 47.0 (SEM) pg/ml, 100 nM CGRP 480.0+/- 41.5 (SEM) pg/ml [N=3; $p<0.001$ for 0 nM vs. 10 nM, $p<0.001$ for 0 nM vs. 100 nM]. These results are in accord with earlier experiments and definitively confirm that CGRP induces IL-6 production by microvascular ECs.

0006

Regulation of IL-6 and calcitonin gene-related peptide (CGRP) expression by vitamin (VD) in transformed dorsal root ganglion (DRG) cells

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IL-6 and the neuropeptide CGRP promote generation of Th17 helper T cells and Th17-type immunity is involved in several autoimmune disorders including psoriasis. Some evidence implicates CGRP in the pathogenesis of psoriasis. Also, there is evidence that sensory nerves play a role in Th17-type immunity and inflammation, including in psoriasis. Our preliminary experiments have shown that 25-hydroxyvitamin D_3 [$25(OH)D_3$] inhibits production of IL-6 by murine transformed DRG neurons (MED17.11 cells) as a surrogate for primary DRG neurons. MED 17.11 cells were derived from DRG cells from an Immortomouse and express the temperature-sensitive SV40 large T antigen. They express markers of committed sensory neuron progenitors and, when cultured in differentiation medium (containing interferon gamma, fibroblast growth factor 2, dibutyryl cAMP, forskolin, nerve growth factor, Y-27632 and glial cell derived neurotrophic factor), they express markers of mature DRG neurons. Lymph nodes are innervated, so IL-6 and CGRP released from nerves is anatomically situated to influence Th17 cell generation. We have now asked if the active form of VD, 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$], similarly regulates IL-6 expression and whether VD also regulates CGRP expression. MED 17.11 cells were cultured (10^5/ml) in differentiation medium for 48 hrs to induce differentiation. Then, medium in each well was replaced with differentiation medium containing a range of concentrations of $25(OH)D_3$ or $1,25(OH)_2D_3$. Twenty-four and 48 hrs later supernatants and cells were harvested and cells lysed. IL-6 and CGRP content of supernatants and lysates was assessed by ELISA. Both $25(OH)D_3$ and $1,25(OH)_2D_3$ significantly inhibited IL-6 content of supernatants and CGRP content of lysates in a dose-dependent manner with $1,25(OH)_2D_3$ more potent. Interestingly, very little IL-6 could be detected in lysates and CGRP could not be reliably detected in supernatants. VD may beneficially affect disorders involving Th17-type immunity (such as psoriasis) by decreasing expression of IL-6 and CGRP by DRG nerves.

0007

Anifrolumab for adult patients with refractory juvenile dermatomyositis

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Juvenile dermatomyositis (JDM) is an autoimmune connective tissue disorder with a chronic, relapsing course that can persist into adulthood. Current therapies exhibit widely variable efficacy. While JDM pathogenesis remains incompletely understood, continuous activation of type-I interferon (IFN) signaling is thought to play a key role, leading to changes including activation and infiltration of CD4+ and CD8+ T-cells, mitochondrial dysfunction, microvascular remodeling, and reduced muscle stem-cell repair and proliferation. IFN activity has been shown to correlate with histological and clinical measures of disease activity. Anifrolumab, a monoclonal antibody that blocks the type I IFN receptor IFNAR1, has been approved for treatment of SLE and is currently undergoing a phase III trial in adult DM, with some case reports and series showing encouraging prospects. We report three female patients, ages 22, 24, and 48, who had failed to obtain durable control of cutaneous JDM through combinations of methotrexate, mycophenolate, hydroxychloroquine, intravenous/subcutaneous immune globulin, or prednisone. Two had also failed systemic janus kinase inhibitors (JAKi), two had failed rituximab, one had failed quinacrine, one had failed azathioprine, one had failed cyclophosphamide, and one had failed cyclosporine. After initiation of anifrolumab at 300 mg per month alongside existing therapies, each patient saw remarkable improvement in cutaneous disease. Each patient was able to reduce systemic glucocorticoids and taper other therapies, including cessation of prior intravenous or subcutaneous immune globulin in two cases and JAKi in one case. These encouraging results illustrate the relationship between type-I IFN modulation and JDM as well as the promise of anifrolumab as a rescue medication for refractory cases. As there are no current FDA-approved therapies for refractory cutaneous JDM, these cases also highlight the need for further systematic investigation into type-I IFN modulation in JDM therapy.

0008

A novel humanized mouse model closely mimics human vitiligo

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Vitiligo is a complex depigmentation disorder resulting from epidermal melanocyte apoptosis and premature senescence of the epidermal pigmentary unit, mainly driven by oxidative damage and CD8+ T cell-produced IFN-γ. Current vitiligo mouse replicate this complexity insufficiently. The aim of the study is to develop the first "humanized" mouse model that optimally replicates human vitiligo. Healthy human dark skin xenotransplants on SCID/beige mice were oxidatively stressed (topical catalase inhibitor plus H2O2-NaN3). Autologous PBMCs were pre-stimulated to induce a vitiligo-typical Th1 phenotype, while autologous melanocytes were cultured with menadione, MART1, gp100, and tyrosinase. Th1-skewed PBMCs and pre-treated melanocytes were co-cultured and injected intradermally into xenotransplants. Moreover, mice were intravenously treated with IgG4 from vitiligo patients and HSP70. Key vitiligo characteristics and the model's response to established vitiligo therapeutics were assessed. Vitiligo-like depigmented lesions developed in 80% of xenotransplants. Quantitative immunohistomorphometry demonstrated depletion of epidermal melanocyte numbers and markers (Melan-A, gp100, c-KIT) and decreased melanin content, elevation of keratinocyte-derived key cytokines (IFN-γ/Krt10, IFN-α/Krt10, IL-15/Krt10, IL-18/Krt10), enhanced GP100/NKG2D/MICA and CD8/NKG2D/gp100 interactions, along with elevated CD11c+ and pDC cell numbers. The number of epidermal TRM was also increased. Lesional keratinocytes and melanocytes showed elevated senescence markers (increased P16INK4A, SIRT1, p-S6), alongside reduced antioxidant and mitochondrial markers (e.g., ,NRF2, MTCO1, Porin/VDAC, PGC1α,) preceding depigmentation. Tacrolimus and Opzelura effectively promoted repigmentation in experimentally induced vitiligo lesions, achieving 30% and 70% repigmentation, respectively. In this preclinical model, vitiligo pathogenesis can be interrogated and candidate vitiligo therapeutics tested under clinically relevant conditions *in vivo*.

0009

Regulatory γδ T cells protect human scalp hair follicles from alopecia areata *in vivo* and represent potential therapeutic target

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Recently, we showed that IFN-γ-secreting, NKG2D+/Vδ1+ γδT cells can induce alopecia areata (AA). However, the role of immunosuppressive Foxp3+ γδTregs in AA remains unexplored. The aim of the study is to clarify whether Foxp3+ γδTregs can prevent or treat human AA. Autologous Foxp3+γδTregs were generated by pre-stimulating PBMCs with IL-2, TGF-β1, IL-15, and zoledronate. Recognized γδTreg markers and secretory activities were confirmed by FACSAria analysis and ELISA (see below). These γδTregs were either co-cultured with stressed human scalp hair follicles (HFs) *ex vivo* or were injected intradermally into experimentally induced AA lesions in human skin xenotransplants on SCID/beige mice *in vivo*. The number of Foxp3+ γδTregs was increased around lesional AA HFs. When these γδTregs (CD3+, TCRVδ2+, FOXP3+, ICOS+, CTLA4+; TGFb1- and IL-10-secreting) were co-cultured with stressed, MICA/B-overexpressing human scalp HFs *ex vivo* in the presence of AA-pathogenic NKG2D+/CD8+ T cells, γδTregs mitigated CD8+T cell-induced HF immune privilege collapse and hair growth inhibition *ex vivo* by secreting IL-10 and TGF-β1. *In vivo*, intradermal injection of peripheral blood-derived human autologous γδTregs significantly reduced the development of experimentally induced AA lesions in human scalp skin xenotransplants on SCID/beige mice, reduced lymphocytic HF infiltration, and restored HF immune privilege. We provide the first evidence that γδTregs are both preventive and therapeutic in human AA and thus as a potent autoimmunity-protective immune cells. This invites the use of autologous γδTregs as novel cell-based therapeutics in future AA management.

0010

Neurogenic inflammation as a key causative factor in stress-induced psoriasis reversed by aprepitant treatment

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Psychoemotional stress is suspected to trigger or exacerbate psoriasis, but robust preclinical models to study this *in vivo* are lacking. This study evaluated whether perceived sonic stress promotes psoriasis development in a "humanized" mouse model and assess aprepitant, an NK-1R blocker of substance P signaling, as an anti-stress therapy. SCID/beige mice grafted with human skin underwent four experiments to study psoriatic lesion development and stress impact. Experiment 1 tested lesion reappearance and topical aprepitant under sonic stress after remission with dexamethasone. Experiment 2 examined stress-induced psoriasis onset with sonic stress post-PBMC injection, with controls and a betamethasone-treated group. Experiment 3 investigated neuroimmune pathways using CRHR1 blockers, ketotifen, NGF-neutralizing antibodies, or vehicles under stress. Skin grafts were analyzed nine days post-injection via IHC and FACS for inflammatory markers. Exposing mice to sound stress accelerated psoriasis lesion development, exacerbating features like Munro microabscess, absence of granular layer, epidermal hyperplasia, parakeratosis, and angiogenesis (VEGF, MMP1), alongside upregulation of psoriasis-specific markers (ADAMTSL5, K16, IL-17A/F, IL-22, IL-36γ). Immune infiltration (CD3+, CD8+ T cells, plasmacytoid DCs, ILC3, γδT cells) and neurogenic inflammation (mast cell degranulation, NGF, NK-1R Substance P, CGRP, TRPV-1) were also elevated. DXA achieved complete remission, but lesions reappeared post-treatment unless aprepitant was applied. Additionally, perceived stress triggered disease onset, which betamethasone failed to prevent. NGF neutralization, CRHR1 blockade, and ketotifen mitigated stress-induced psoriasis, reducing inflammatory and neurogenic markers. Our study conclusively documents that perceived stress can both exacerbate and re-trigger psoriasis lesions in human skin *in vivo* by inducing neurogenic skin inflammation. This can effectively be antagonized pharmacologically.

0011

JAK2 is a key target for itch induced by AD-associated cytokines and pruritogens in human sensory neurons

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Atopic dermatitis (AD) is a common inflammatory skin disease associated with a type 2 immune response and intense itching. Despite the development of new therapeutic options for AD, itch in patients with AD has not yet been sufficiently alleviated. Previous studies have identified several molecular targets and genes in the itchy-sensory neurons. However, these studies have used mouse or rat nerves or their cell lines, and no research has been conducted using human nerves.In this study, we aimed to identify key molecules for itch in human sensory neurons in response to multiple pruritogens associated with AD. Cultured human iPS cell-derived sensory neurons were treated with type 2 cytokines, such as IL-4, IL-13, IL-31, and pruritogens like histamine, chloroquine, and SLIGRL-NH2. As controls for type 2 cytokines and pruritogens, the neurons were treated with IFN-γ, bradykinin, and serotonin. RNA was isolated from cells for RNA sequencing analysis. As a result, we found that JAK2 was the only elevated gene that was common to neurons treated with type 2 cytokines and pruritogens, but not to those treated with IFN-γ, bradykinin, and serotonin. This result suggests that itch mediators and AD-related cytokines activate human sensory neurons via JAK-mediated signaling pathways, especially through JAK2. Our data provide valuable insights into the molecular mechanisms of itch in AD and may help the development of treatments for itchiness.

0012

Increased serum levels of C-C motif chemokine ligand 2 and M2 macrophages in the skin lesions are associated with the keratinocyte death of Stevens-Johnson syndrome and toxic epidermal necrolysis

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Background: Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) are life-threatening disorders characterized by widespread epidermal necrosis of the skin. We have previously reported that increased level of C-C motif chemokine ligand 2 (CCL2) in SJS/TEN. However, the clinical significance of CCL2 and its contribution to keratinocyte necroptosis in the pathogenesis of SJS/TEN are unknown. In this study, we focused on CCL2 and macrophages in association with keratinocyte death. Methods: CCL2 levels in pre-treatment serums were measured using ELISA. Skin infiltrating macrophages were identified by immunohistochemistry (IHC). *In vitro* experiments, normal human epidermal keratinocytes (HEKs) were used for necroptosis and CCL2 stimulation. Results: Serum levels of CCL2 were significantly higher in SJS/TEN than those in healthy controls and patients with another type of drug eruption. A positive correlation was found between the CCL2 and prognostic score. IHC analysis revealed a significant infiltration of CD68 positive macrophages in SJS/TEN skin lesions, with a predominance of M2 macrophages (CD163 positive) over M1 macrophages (CD80 positive). *In vitro*, CCL2 stimulation did not directly induce an inflammatory response in HEKs while necroptosis in HEKs increased CCL2 expression. CCL2 expression in HEKs was upregulated by co-culture with macrophages. Furthermore, stimulation with conditioned media from M2 macrophages significantly enhanced necroptosis in HEKs. Conclusion: These findings suggest elevated CCL2 levels in SJS/TEN contribute to increased macrophage infiltration, particularly M2 macrophages. These macrophages, in turn, likely promote keratinocyte necroptosis through the release of soluble factors, highlighting a crucial role for the CCL2-macrophage axis in the pathogenesis of SJS/TEN.

0013

Granzyme B as a regulator of IFNα production in cutaneous lupus erythematosus

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Recent studies have shown that monocytes, macrophages, and conventional DCs, but not plasmacytoid dendritic cells (pDC), are major source of IFNα in cutaneous lupus erythematosus(CLE). However, novel medications targeting pDCs reduce IFNα levels and improve CLE. Granzyme B is a proteolytic enzyme that induces apoptosis, and large concentrations are produced by pDCs in CLE, yet its role in modulating signaling pathways, including IFNα release, has not been elucidated. Peripheral blood mononuclear cells (PBMCs) were obtained from 18 CLE patients. PBMCs were co-incubated for 24 hours with 500U recombinant human granzyme B alone or with either 10ug/mL TL8-506 (TLR8 stimulator), 1.5uM CpG (TLR9 stimulator) or 60ug/mL cGAMP (STING stimulator). Positive controls were PBMCs stimulated separately with only TL8-506, CpG or cGAMP. Supernatants were then analyzed for IFNα via ELISA. PBMCs incubated with granzyme B alone did not produce any IFNα (n=5). PBMCs co-incubated with granzyme B and CpG (n=5) significantly reduced IFNα production compared to PBMCs incubated with CpG alone (mean IFNα 20.6±9.1 vs. 95.2±21.5 pg/mL respectively, $p<0.01$). However, PBMCs co-incubated with granzyme B with either TL8-506 (n=3) or cGAMP (n=5) produced significantly increased IFNα compared to PBMCs incubated with either TL8-506 or cGAMP alone (for TL8-506, mean IFNα 21.0±3.4 vs. 3.0±1.0 pg/mL respectively, $p<0.05$; for cGAMP, mean IFNα 14.1±2.2 vs 6.1±2.0 pg/mL respectively, $p<0.01$). CpG stimulates the TLR9 pathway primarily on pDCs and granzyme B may have a negative feedback effect in suppressing TLR9-induced IFNα release from pDCs, as suggested by recent studies. However, monocytes and macrophages primarily use the TLR8 and STING pathways for IFNα production. Granzyme B which is produced in large numbers by pDCs may potentiate IFNα release by enhancing the TLR8 or STING pathways on macrophages and monocytes in CLE. Outside of its role in inducing apoptosis, granzyme B may be a bridge between pDCs and other immune cells by modulating signaling pathways, in particular that of type-1 IFN in CLE.

0014

Understanding the phenotypic switch between atopic dermatitis and psoriasis

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Atopic dermatitis (AD) and psoriasis (PsO) are common immune-mediated skin conditions with overlapping pathophysiological features, which is exemplified by a phenotypic switch from one to the other after the initiation of immunomodulatory therapy. This study uses a pharmacovigilance-based disproportionality analysis on the FDA Adverse Events Reporting System to investigate this phenomenon. When looking at dupilumab for the treatment of AD, eczema, or dermatitis, a signal emerges for psoriasiform dermatitis (Reporting Odds Ratio [95% Confidence Interval]=3.23 [4.39, 2.37]) as an adverse event (AE), but not psoriasis (0.56 [0.61,0.52]). For biologics used in the treatment of PsO, psoriasiform dermatitis emerged as a signal for TNF-α inhibitors=1.51 [1.69,1.35], IL-17 inhibitors=3.89 [4.58,3.30], and IL-12/23 inhibitor=1.79 [2.41,1.33]. Limiting the indication to PsO strengthened signals for psoriasiform dermatitis (TNF-α =3.01 [4.26,2.13] and IL-17 inhibitors=11.46 [14.34,9.16]), and allowed new ones to emerge for psoriasiform dermatitis (IL-23 inhibitors=2.49 [4.80,1.29] and apremilast=2.04 [3.71,1.13]), eczema (IL-17 inhibitors=1.84 [2.06,1.64]), and dermatitis (IL-17 inhibitors=1.95 [2.29,1.66]), but not AD. This suggests that paradoxical reactions create an intermediary physiologic and immunologic presentation between psoriasis and AD. For the interleukin biologics, the signal strength of IL-17 inhibitors is significantly stronger than IL-23 and IL-12/23 inhibitors, suggesting that Th17 and Th22 cells are involved in the switch. AE signals for Th2-mediated allergic conditions emerged for all biologic classes as well, providing evidence that the paradoxical reaction could potentially involve increased Th2 activity. Taken together, our study proposes a comprehensive model for the phenotypic switch between atopic dermatitis and psoriasis.

0015

Programmed death-1 (PD-1) inhibitors aggravate the effector phase in a model of pemphigoid diseases by disinhibition of dermal γδ T cells

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Checkpoint inhibitors (CIs), particularly inhibitors of programmed death-1 (PD-1) and its ligand PD-L1, have become a mainstay of cancer therapy. The use of checkpoint inhibitors is supposedly associated with an increased risk for the development of bullous pemphigoid (BP). The mechanisms behind this putative side-effect are, however, still elusive. Thus, it is unknown, e.g., whether CIs may promote the break of tolerance or rather the precipitation of the effector phase. We therefore investigated the effect of ablating PD-1 signaling on skin inflammation in a mouse model of the effector phase of pemphigoid diseases, specifically the antibody transfer model of BP-like epidermolysis bullosa acquisita. Both inhibition of PD-1 by CIs and genetic deficiency of its gene Cd274 aggravated skin inflammation significantly. PD-1 inhibition increased the number of neutrophils in lesional skin, which is consistent with central role of this effector cell population in pemphigoid diseases. We profiled the cellular expression of PD-1 and PD-L1 in lesional skin by single-cell (sc)RNA sequencing and flow cytometric analysis and found PD-1 predominantly expressed on γδ T cells and NKT cells. PD-L1, in contrast, was widely expressed, including on neutrophils. Depleting of γδ T cells but not that of NKT cells nullified the aggravation of disease by PD-1 inhibition highlighting γδ T cells as crucial PD-1$^+$ cell population. By gene expression analysis we found IL-17A expression significantly upregulated in γδ T cells upon PD-1 inhibition. IL-17A is known, among other, to amplify the recruitment of neutrophils into the skin and to extend the lifespan of neutrophils in inflamed tissues. Collectively, our results suggest that CIs may promote the effector of pemphigoid diseases by upregulating the expression of IL-17A in dermal γδ T cells.

0016

Oxidative stress-induced activation of transient receptor potential vanilloid 4 (trpv4) may regulate type 2 immunity and pruritus in mc903-induced atopic dermatitis mouse model.

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Transient receptor potential vanilloid 4 (TRPV4), a member of the TRP channel family, is highly expressed in the skin and plays diverse roles, including chemical sensing, cell proliferation, and immune responses in multiple organs. Recently, we found increased TRPV4 expression in the lesional skin of patients with atopic dermatitis (AD). However, its precise role in AD pathogenesis remains unclear. This study aimed to elucidate the role of TRPV4 in AD using an MC903-induced AD model in wild type (WT) and TRPV4 knockout (KO) mice. Our results demonstrated that dermatitis score ($p = 0.02$), TEWL ($p = 0.02$), and scratching behavior ($p = 0.03$) were significantly reduced in TRPV4 KO mice compared to WT mice. Histopathological analysis revealed significantly fewer infiltrating CD4$^+$ T cells and mast cells in TRPV4 KO mice. FACS analysis of skin tissue confirmed a reduced number of CD45$^+$CD4$^+$IL-4$^+$ cells in TRPV4 KO mice compared with WT mice. The qPCR analysis showed decreased mRNA levels of Th2 cytokines, including TSLP, IL-4, IL-13, and IL-31, in TRPV4 KO mice compared with WT mice. Treatment with TRPV4 antagonist also significantly improved dermatitis score, TEWL, scratching behavior, and suppressed TSLP and IL-4 mRNA expression in MC903-treated mice. *In vitro* experiment revealed that oxidative stress induced by hypoxia or hydrogen peroxide stimulation increased TRPV4 expression in HaCaT cells. Moreover, siRNA-mediated TRPV4 knockdown suppressed TSLP production. In conclusion, our findings suggest that TRPV4, possibly activated by oxidative stress, regulate type 2 inflammation and pruritus through TSLP production and inflammatory cell infiltration in MC903-induced AD-like dermatitis. TRPV4 may serve as a potential therapeutic target for pruritic dermatitis, such as AD and prurigo.

0017

Incidence of malignancy in idiopathic inflammatory myopathies

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Idiopathic inflammatory myopathies comprise a group of autoimmune conditions which can be paraneoplastic and which include both dermatomyositis (DM) and polymyositis (PM). DM is twice as common in women compared to men and is most closely associated with malignancy; as such, DM patients may undergo enhanced cancer screening as per recently published guidelines. However, PM may also be associated with increased risk of certain cancers, e.g. breast and colon cancer. In this study, we re-examine the associations of female DM and PM patients with cancer in a large US database (All of Us) which may reduce variations seen in smaller regional studies. We performed a matched, case-control study; female patients with a diagnosis of DM or PM up to 10 years before their enrollment in the All of Us study were included. We identified morphea controls with the nearest neighbor propensity score matching by age at condition diagnosis and race/ethnicity; morphea controls with comorbid systemic sclerosis or rheumatoid arthritis were excluded. To compare incidence of malignancy between groups, Kaplan-Meier curves were generated, and log-rank tests were performed. Malignancy was defined as hematologic and solid tumor malignancy for patients whose earliest diagnosis began after diagnosis of DM or PM. Within the All of Us dataset, we identified 168 patients with DM and 336 controls, and 140 patients with PM and 420 controls. Compared to controls, DM was associated with incidence of a malignant neoplastic disease within 1 year (5.49% vs 2.15%) and 5 years (17.5% vs 10.1%, p = 0.00923). PM was associated with incidence of a malignant neoplastic disease within 1 year (3.71% vs 2.19%) and 5 years (17.5% vs 9.31%, p = 0.0349). This study presents an association between incidence of malignancy and diagnosis of both DM and PM in US patients. Next steps include further elucidation of specific cancer types and timing of cancer onset with respect to onset of the DM/PM in this population, with the goal of further informing cancer screening approaches.

0018

An analysis of common allergens associated with contact dermatitis in microneedle acne patch product ingredients

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While hydrocolloid acne patch products have been sold in South Korea and grown in popularity internationally since the early 2010s, microneedle acne patches are a newer product intended for the treatment of acne. Microneedle acne patches are designed with hollow microneedles which are intended to penetrate the stratum corneum in order to deliver active ingredients. These ingredients are often not regulated because they are sold as cosmetic products. This project aims to analyze the ingredients of popular microneedle acne patch products for the inclusion of common allergens associated with contact dermatitis. “Microneedle Acne Patch” was searched at seven large retail websites, including Target, Amazon, Sephora, Ulta Beauty, CVS, Walgreens, and Walmart on February 13th, 2024. The first five listed products matching the inclusion/exclusion criteria were included in the analysis. Ingredients were then cross referenced with the North American Contact Dermatitis Group (NACDG) to identify common allergens. Overall, the search term “Microneedle Acne Patch” yielded 17 unique products and 74 unique ingredients across five different retail websites, which included Target, Amazon, Sephora, CVS, and Walmart. Melaleuca alternifolia (tea tree) extract, ethylhexylglycerin, and propolis extract were identified as common allergens based on the North American Contact Dermatitis Group. Of the 17 products, eight contained a common allergen screened for by NACDG. Melaleuca alternifolia (tea tree) extract was the most common allergen found in microneedle acne patches, identified in six different products. Propolis extract and ethylhexylglycerin were each found as a common allergen in one product, respectively. Future studies should continue to analyze the prevalence of common allergens as screened for by NACDG and the potential for contact dermatitis following the use of microneedle acne patch products.

0019

Comparative gene expression analysis in Asian atopic dermatitis and psoriasis: Identifying key molecular targets for precision therapy

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Atopic dermatitis (AD) and psoriasis are chronic inflammatory skin diseases characterized by distinct immune and molecular signatures. However, in clinical practice, differentiating between AD and psoriasis can be particularly challenging in Asian patients due to overlapping or atypical clinical features. This study aimed to delineate differentially expressed genes (DEGs) and associated pathways in lesional skin samples from Asian patients with AD and psoriasis to identify potential diagnostic/therapeutic targets. Transcriptomic analysis was performed on skin samples from six AD patients, seven psoriasis patients, and twelve healthy controls. A total of 6,445 DEGs were identified. Functional enrichment analysis revealed distinct immune signatures, with Th2 cell differentiation predominating in AD and Th17 cell differentiation in psoriasis. Additionally, pathways related to keratinization and epidermal differentiation were elevated in both AD and psoriasis, suggesting a shared inflammatory mechanism. Among these, 52 genes demonstrating the most significant differential expression were selected for further analysis. Among these, filaggrin (FLG) expression was significantly reduced in both AD (P=0.0116) and psoriasis (P=0.0002) compared to controls. Serine protease inhibitor Kazal-type 5 (SPINK5) expression was elevated in psoriasis (P<0.001) but showed a downward trend in AD. Loricrin (LOR) expression was significantly decreased in AD (P=0.0031) and psoriasis (P=0.0021), while Serine family B member 4 (SERPINB4) expression was substantially upregulated in both AD (P<0.0001) and psoriasis (P<0.0001), which were validated by immunofluorescence staining. Key genes such as FLG, SPINK5, LOR, and SERPINB4 reflect the unique molecular mechanisms of AD and psoriasis in Asian patients. These findings provide critical insights into the disease pathogenesis and a foundation for novel diagnostic/therapeutic strategies.

0020

The novel role of Th2 dysregulation in pyoderma gangrenosum pathogenesis

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Pyoderma gangrenosum (PG) shares characteristic Th1/Th17 dysregulation, neutrophilic infiltration, and high NETosis activity with other neutrophilic dermatoses (ND); however, PG is the only ND that ulcerates, indicating there must be additional immune dysregulation driving PG pathogenesis. Th2 cytokines are known to mediate the transition from tissue inflammation to repair in wound healing, however, no studies to date have investigated the role of Th2 dysregulation in PG pathogenesis and its interplay with NETosis and Th17 activation within PG. This study utilized RNA sequencing of perilesional PG dermis, ELISA quantification of Th2 cytokine IL-4 in PG wound fluid, and quantification of complement C5a-mediated NETosis activity in healthy neutrophils pre-treated with Th2 cytokine IL-4 to investigate dysregulation of the Th2 pathway in PG. RNAseq analysis of PG perilesional dermis (n=8) revealed a 3-fold decrease in Th2 transcription factor GATA3 mRNA compared to healthy control (n=8) tissue (p<0.0001). ELISA quantification of wound fluid cytokine levels revealed a marked decrease (p=0.0097) of Th2 cytokine IL-4 in PG wound fluid (n=13) compared to acute traumatic wound fluid (n= 26). Our previous studies showed that C5a-induced NETosis is increased in PG wound fluid and that C5a is the most potent trigger of NETosis in PG. An analysis of the role of Th2 cytokines in C5a-mediated NETosis revealed that neutrophils pre-treated with IL-4 showed a 2.3-fold decrease in NETosis activity (p=0.0050) compared to neutrophils without IL-4 pre-treatment. Taken together, these novel findings support a potential role of Th2 dysregulation in enhancing C5a-mediated NETosis which contributes to our understanding of PG pathogenesis and suggests novel therapeutic interventions.

0021

Epidermal keratinocytes in hidradenitis supprativa fistulas and pyoderma gangrenosum lesions are similarly innate-immunologically activated

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Hidradenitis suppurativa (HS) is a neutrophilic dermatosis that typically arises after puberty, presenting with characteristic skin lesions such as inflammatory nodules and painful abscesses primarily in the axillae and groin. These lesions originate from the hair follicles and are driven by follicular obstruction, cyst formation, and rupture, triggering acute inflammation. Pyoderma gangrenosum (PG) is also a neutrophilic dermatosis that begins after minor trauma with painful erythema, folliculitis-like nodules, blisters, and pustules, which quickly ulcerate and expand. Neutrophils play an important role in the pathology of these diseases, and epidermal keratinocytes are also thought to be involved in the pathology, but there have been no detailed analyses of this point. Here, we focused on the keratinocytes in these lesions and performed spatial transcriptome analysis using GeoMx. Regions of interest (ROIs) were selected from the keratinocytes in the fistula areas of HS, the lesional epidermis of PG, and normal epidermis. Transcriptomic comparisons revealed that neutrophil-associated and immune-related pathways were activated in both HS fistula and PG lesional epidermis. Specific genes, including CXCL1, S100A8, S100A9, and DEFB4B, showed elevated expression in both conditions, highlighting shared molecular mechanisms. Additionally, in HS fistula epidermis, increased expression of B cell-related genes was observed, suggesting a potential role for B cells in local immune responses and inflammation regulation. These findings demonstrate that HS and PG share a molecular basis as neutrophilic dermatoses and provide insights into the pathogenesis of these conditions. This study contributes to the understanding of HS and PG and may guide the development of novel therapeutic strategies.

0022

T-antigen-specific B cell responses in Merkel cell carcinoma tumors predict disease outcomes

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Merkel cell carcinoma (MCC) often results from integration of a truncated version of the Merkel cell polyomavirus T-antigen (T-Ag) gene into a host cell chromosome. This gene encodes T-Ag proteins that promote MCC tumorigenesis and are recognized by T & B lymphocytes. While extensive studies have established the importance of T-Ag-specific T cells in anti-MCC immunity, the roles that B cells play in MCC control have not been explored. Using single cell technologies, we analyzed the phenotype and antibodies of T-Ag binding B cells found in 14 MCC-infiltrated lymph nodes. Strikingly, 9/9 patients with tumors that had T-Ag-specific B cells with germinal center (GC) or antibody-secreting (ASC) phenotypes experienced extended progression-free survival, with no MCC progression by 4 years after tumor excision. In contrast, 5/5 patients with MCC-infiltrated lymph nodes that lacked these B cells experienced rapid disease progression by a median of 0.35 years ($p<0.0001$). Additionally, tumors with T-Ag-specific B cells with GC or ASC phenotypes had higher frequencies of follicular helper CD4+ T compared to tumors without these B cells (median 11% vs 4% out of total CD4+ T cells, $p=0.002$). These results suggest strong B and T cell synergy in patients with better MCC control. Of note, adverse clinical risk factors present at the time of tumor removal were not significantly different between MCC patients whose tumors had T-Ag-specific GC or ASC B cells and patients with tumors lacking these cells (Fisher's exact test, $p= 0.99$). Together, our findings suggest that cancer-specific B cells may promote anti-tumor immunity via increased T cell responses and that approaches to augment cancer-specific B cell function could benefit MCC patients.

0023

Neuro-immune interplay in candida albicans-induced itch mouse model

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"Itch-scratch cycle" is a debilitating feature that underlies a range of inflammatory dermatoses. Recently, skin has been recognized as a complex barrier organ capable of synchronizing neuronal and immune cells' activation in response to microbiota. Candida albicans is a commensal fungus asymptomatically colonizing human barrier tissues including skin. It has been known that any skin barrier dysfunction leads to increased fungal load and subsequent activation of Th17 cells. However, the precise mechanisms of pruritis in C. albicans skin infection are yet to be discovered. Therefore, in this study we aimed to establish a murine model of C. albicans skin infection and assess itch behavioral phenotype. To evaluate the role of type 2 immune response in eliciting itch in C. albicans skin infection model, we examined C. albicans-specific IgE serum levels and confirmed its increase under daily epicutaneous treatment of mice with C. albicans. To further explore the precise mechanisms of pruritis and involvement of type 2 immune response in C. albicans-induced itch mouse model, we performed single cell RNA sequence analysis of mouse skin and dorsal root ganglion (DRG) cell-cell interaction. Thus, this research aims to be one of the initial studies contributing to exploration of mechanisms underlying Candida albicans-induced itch sensation via single cell transcriptomic approach. Key words: Candida albicans, pruritis, neuro-immune interaction, dorsal root ganglion, type 2 immunity

0024

Analysis of T cell receptor repertoire and TCR-HLA interactions in pemphigus vulgaris

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Pemphigus vulgaris (PV) is a prototypical organ specific human autoimmune disease that presents clinically with flaccid blister formation on the skin and mucous membranes. The disease genetic risk factors are polygenic with both Human Leukocyte Antigen (HLA) and non-HLA susceptibility genes playing important roles in disease progression. Previous studies in ethnically diverse populations show that DRB1*0402, and DQB1*0503 HLA alleles are significantly overrepresented in PV patients. In autoimmune diseases, the T cell receptors (TCRs) recognize self-antigenic proteins presented by HLA. Analyzing the TCR repertoire and TCR-HLA interactions can provide major insights into disease mechanisms driving the initiation and progression of the autoimmune response in PV. This study leverages computational models to analyze TCR repertoire and TCR-HLA interactions and identify common somatic mutations in TCRs associated with recognition of self-antigens in PV. We evaluated 15 subjects, including 4 active PV patients (PV-A), 3 patients in late remission (PV-LTR), 2 patients in partial remission (PV-PR), 3 HLA-matched controls, and 3 HLA-unmatched controls. PCMBs were collected from patients and RNA was isolated for Single Cell RNA Sequencing. The data was analyzed using 10X Genomics tools and R. Out of 85,736 sequenced cells, 50,335 cells (58.71%) produced V-J spanning pairs, yielding 79,219 distinct TCR clonotypes. Overall, we found TCR clonotypes to be very diverse across the different patient and control groups. TCR V(D)J gene usage was analyzed and differentially expressed genes were identified. Analysis of TCR clonotypes of individual patients revealed the presence of somatic mutations in the V(D)J sequences, which are hypothesized to be associated with PV. These mutations were found in both HLA binding regions and other sites. To assess the significance of these mutations, binding scores of these TCRs and the HLA alleles were predicted. The study aims to identify shared mutations that may contribute to the development of PV.

0025

TSST-1-specific changes in peripheral T cell function are not observed in BP patients colonized with TSST-1+ staphylococcus aureus.

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Bullous pemphigoid (BP) is an autoimmune skin blistering disease that primarily affects the elderly over the age of 65. Studies have found that cutaneous microbiota profiles in patients in autoimmune bullous diseases differ from that of healthy individuals. Most (~90%) BP patients are colonized with Staphylococcus aureus (S. aureus) that produces toxic shock syndrome toxin-1 (TSST-1), a known T cell superantigen that binds T cell receptor (TCR) Vβ2 chain. However, it is not known if S. aureus colonization contributes to immune dysfunction in BP. We evaluated peripheral homeostasis through examination of TCR Vβ repertoire utilization of BP patients and controls. Surprisingly, there was no expansion of Vβ2 in BP patients when both expression of 24 TCR Vβ genes was evaluated in purified CD4+ T cells by RT-qPCR and cell surface expression measured by flow cytometry. However, significant decreases in Vβ7, 13c, and 17 in BP patients were observed by RT-qPCR ($p<0.05$), and increases in Vβ5.2 and 5.3 expression were observed by flow cytometry ($p<0.05$). To assess T cell function, the proliferative response of CD4+T cells to staphylococcal toxins (TSST-1, staphylococcal enterotoxin G, staphylococcal enterotoxin-like I) was examined *in vitro*. As above, no significant differences were seen between BP patients and controls. These findings suggest that peripheral T cells in BP patients may not be influenced by immunoregulatory events that are TSST-1+ specific, and that peripheral immune status may not reflect what is happening in the skin.

0026

Epidermal IFN-κ drives cutaneous lupus-like lesions, photosensitivity and systemic autoimmunity in mice

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Keratinocyte-derived interferon kappa (IFN-κ) is an important mediator of photosensitive responses in cutaneous lupus erythematosus (CLE) and is chronically overexpressed in systemic lupus erythematosus (SLE) skin. Recent evidence suggests that the epidermis itself instructs the innate and adaptive immune system in SLE to contribute to disease onset and flares, but whether epidermal IFN-κ alone is sufficient to drive CLE or SLE has not been investigated. We compared three month (young) and twelve month (aged) old Balb/c mice that overexpress Ifnk in the epidermis under the keratin 14 promoter (transgenic, TG) with Balb/c wild type mice (WT) and assessed local and systemic immune responses at baseline and after UV exposure. Skin lesions were assessed by histopathology and bulk RNA sequencing and subsequently compared to human CLE. Flow cytometry on lymph nodes and splenocytes at baseline and after UV exposure was performed to phenotype immune cell compositions. Importantly, 75% of aged TG mice exhibited CLE-like lesions with strong lymphocytic infiltration and a transcriptional signature reflective of cytokine/chemokine secretion, IFN-signaling and T-cell activation, as seen in human CLE. Strikingly, UV exposure in young TG mice resulted in a significant shift of splenic naïve $CD8^+$ T cells ($CD62L^+CD44^-$) towards effector memory $CD8^+$ T cells ($CD62L^-CD44^+$) in TG compared to WT mice. Furthermore, aged TG mice developed spontaneous signs of systemic autoimmunity reflected by autoantibodies against dsDNA, high total IgG and lymphopenia, but they did not exhibit detrimental organ failure. Our results indicate an axis from an IFN-rich epidermis towards systemic inflammation and provide a new murine CLE model with strong parallels to human CLE.

0027

Epicutaneous Staphylococcus aureus infection activates the pentose phosphate pathway and fatty acid oxidation in IL-17/TNF-producing murine MAIT cells.

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Staphylococcus aureus colonization significantly contributes to the pathogenesis of inflammatory skin conditions, such as atopic dermatitis (AD). While the role of conventional T-cells in response to S. aureus infection in the skin has been well-characterized, the involvement of mucosal-associated invariant T cells (MAIT cells) remains unclear. MAIT cells are unconventional, MR1-restricted T cells enriched in mucosal tissues, including the skin. Based on their metabolic profiles, these cells can be classified into functional subsets in mice. Therefore, this study aimed to characterize the functional and metabolic responses of MAIT cells during S. aureus epicutaneous infection. Epicutaneous S. aureus infection increased the number of IL-17- and TNF-producing MAIT cells in the skin but did not affect IFN-γ production. Functional metabolic flow cytometry demonstrated that these MAIT cells engage the pentose phosphate pathway and fatty acid oxidation, corresponding with increased expression of G6PD and CPT. *In vivo* blockade of the pentose phosphate pathway using the G6PD inhibitor polydatin reversed this metabolic state, shifting towards glycolysis, oxidative phosphorylation, and fatty acid synthesis. This change resulted in a functional shift characterized by decreased IL-17 and increased IFN-γ production. To validate the functional immunometabolic profile of MAIT cells in S. aureus infection, we conducted a modified flow cytometry-based SCENITH assay, employing metabolic inhibition to measure MAIT cell energy dependence on the pentose phosphate pathway. Additionally, human *ex vivo* skin samples infected with S. aureus were used to explore the immune metabolic role of MAIT cells in a human model of AD. This study defines the metabolic and functional profiles of MAIT cells in murine and human models, offering new targets for therapeutic interventions against S. aureus infections in AD pathology.

0028

Sweat suppression promotes a Th2-biased sensitization to food allergens and anaphylaxis in an IL-6-dependent manner

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Background: Although sweat suppression is not generally considered to contribute to skin barrier dysfunction, sweating disturbance is frequently observed in atopic dermatitis (AD) patients with food allergy (FA) as well as in AD mouse models such as flaky tail mice. Our previous studies demonstrated that epicutaneous exposure of the BALB/c mouse footpad to the food allergen ovalbumin (OVA) results in sensitization to OVA and an anaphylaxis when the footpad skin is sweat-suppressed. Objectve: In the present study, we investigated the relevance of sweat suppression in a mouse model of FA. We examined whether sweat suppression exhibits adjuvant-like effects by inducing innate cytokine responses. Results: Surprisingly, sweat suppression alone led to a robust induction of IL-6 from epidermis without tissue damage and this induction was abolished by exposure to high humidity (>80% relative humidity). This result indicates that sweat suppression has a strong impact on the ability to induce innate cytokine responses leading to FA. The ear swelling after OVA elicitation in OVA-sensitized mouse model facilitated by sweat suppression was completely abolished by exposure to high humidity during the sensitization process. Blockade of IL-6 signaling prior to OVA sensitization also led to markedly reduced OVA-IgE levels, indicating that sweat suppression may act as an adjuvant-like factor to promote OVA-IgE production through IL-6. Conclusion: Our data support the hypothesis that primary sensitization to food allergens in AD may occur through the sweat-disturbed, albeit normal-appearing, finger skin of infants who have not sufficiently developed their sweating function, considering that sweating responses in murine footpads are homologous to those in human fingers. Sweating disturbance may serve as an early biomarker predictive of AD and FA.

0029

Single-cell and spatial profiling reveals a pathogenic cDC2A-CXCL13$^+$ CD8$^+$ T-epithelial cell communication network in lichen planus

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Lichen planus (LP) is a chronic inflammatory disease that primarily impacts the skin and mucous membranes. While cutaneous LP is histologically characterized by T cell infiltration and keratinocyte apoptosis, the immune microenvironment and molecular dysregulation underlying LP and its clinical subtypes remain poorly defined. In this study, we integrated single-cell RNA sequencing and spatial transcriptomics to analyze samples from 45 patients, including 15 cutaneous lichen planus (CLP) with 9 matching healthy control skin samples, 6 lichen planopilaris (LPP) with 5 matching healthy scalp controls, and 6 mucosal lichen planus (MLP) with 4 healthy control mucosa samples. We identified increased cytotoxic and interferon (IFN)-response signatures localizing to CXCL13$^+$ CD8$^+$ T cells in LP and MLP, while these signatures were absent in LPP. The CXCL13$^+$ CD8$^+$ T cell communication network involved production of TNF and IFNy, spatially connected by ligand receptor interactions to epithelial cells, accounting for the robust epithelial damage in both CLP and MLP. CLP and MLP, but not LPP, were characterized by predominant transcriptional dysregulation of type I & II IFN downstream genes, including CXCL9, CXCL10, CXCL11 and IFI44L. Notably, we also identified a central role for cDC2A cells, which were abundant in CLP and MLP and spatially proximate to CXCL13+ CD8+ T cells, in fueling their cytotoxic activity. In summary, our data provide novel and comprehensive insights into the pathogenesis of LP across its major clinical subtypes and highlight the central role of cDC2A-CXCL13$^+$ CD8$^+$ T-epithelial cell crosstalk in CLP and MLP.

0030

Apremilast prevents psoriasis-related osteoporosis through RANKL suppression in IMQ-induced psoriasi mouse models

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Background: Psoriasis is associated with increased risk of osteoporosis and fractures, but the underlying mechanisms and potential preventive treatments remain unclear. This study investigated the pathogenic relationship between psoriatic inflammation and bone density, focusing on the therapeutic potential of apremilast in preventing psoriasis-related bone loss. Methods: We used an imiquimod-induced psoriasis mouse model to evaluate bone density changes. Mice received topical imiquimod (5%) or vehicle control for 4 weeks, with or without oral apremilast (3mg/kg/day). Bone microstructure was analyzed using micro-computed tomography (μCT). RANKL expression was assessed in human psoriatic skin samples and THP-1 macrophages under TLR7 stimulation. The effect of apremilast on RANKL expression was evaluated in both *in vivo* and *in vitro* systems. Results: Imiquimod-treated mice showed significant reduction in bone mineral density, while RANKL inhibitor treatment prevented this bone loss, demonstrated by higher bone volume/tissue volume (BV/TV) ratios compared to controls. RNA-sequencing analysis revealed elevated RANKL expression in psoriatic skin lesions compared to healthy skin or non-lesional psoriatic skin. Immunohistochemistry confirmed increased RANKL expression in both epidermal keratinocytes and dermal cells of imiquimod-treated skin. *In vitro* studies showed that TLR7 agonist gardiquimod induced RANKL expression in THP-1 cells, which was significantly suppressed by apremilast treatment. Conclusions: Our findings demonstrate that psoriatic inflammation promotes osteoporosis through enhanced RANKL expression, and apremilast can prevent this bone loss by suppressing RANKL production. These results suggest apremilast as a potential therapeutic option for preventing osteoporosis in psoriasis patients.

0031

Spatial transcriptomics uncovers progressive osteopontin expression, mitochondrial dysfunction, and IL-6 inflammatory signature in dermatomyositis-associated calcinosis cutis

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To understand the pathophysiology of calcinosis cutis in dermatomyositis, we conducted spatial transcriptomics on 4 active calcinosis samples from adult DM patients meeting 2017 ACR/EULAR criteria and 3 control samples from healthy adults. Analysis revealed a distinct inflammatory signature characterized by elevated IL-6 expression, upregulation of macrophage markers CD68 and MSR1, and increased expression of IgG/A heavy, light, and J chains ($p<0.01$). ECM composition showed global dysregulation, with elevated MMPs 1/9/13, cartilage-specific collagens X and XI, and markedly increased osteopontin, a glycoprotein implicated in pathological calcification ($p<0.01$). UMAP analysis identified distinct clusters of spatial transcriptomic spots arranged such that linear movement through UMAP space traversing these clusters corresponded to increasing calcification burden. Differential expression analysis along this trajectory revealed three distinct phases. The early, pre-calcific phase showed barrier dysfunction, immunoglobulin transcription, elevated IL-6 target gene FOS expression, and loss of stemness maintenance genes ($p<0.01$). The middle, propagative remodeling phase was characterized by enhanced MMP9 expression, increased transcription of lysosomal enzymes, and distinctly dysregulated extracellular matrix deposition ($p<0.01$). The late-stage calcification phase exhibited increased expression of 11 mitochondrial genes, and ferritin heavy and light chains ($p<0.01$), suggesting an oxidative stress response. Osteopontin expression increased consistently until final transition to acellular calcification ($p<0.01$). These findings reveal a complex pathogenic cascade involving early antibody synthesis and macrophage recruitment, IL-6/FOS signaling, extracellular matrix dysregulation, and mitochondrial dysfunction leading to eventual tissue replacement with calcinosis. This spatial analysis provides the first detailed molecular map of calcinosis progression in dermatomyositis.

0032

Antigen hotspots reveal novel autoantibodies against XIST ribonucleoproteins in sex-biased autoimmune disease

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Four out of five patients with autoimmune diseases are women. The XIST ribonucleoprotein complex, comprising the female-specific XIST long noncoding RNA and more than 100 XIST-associated proteins, plays a crucial role in several autoimmune diseases that disproportionately affect women, who have elevated levels of anti-XIST RNP antibodies (AXA). However, the structural and clinical significance of AXA subtypes, as well as potential impact on disease phenotype, have remained unexplored. Here, by analyzing a publicly available database of human autoantigens, we find that AXA targets are enriched among autoantigens associated with female-biased autoimmune conditions. In addition, by mapping AXA targets to known protein binding sites within the XIST sequence, we find that AXA targets are concentrated at discrete “hotspots” along the length of XIST, notably the A-repeat. Cell-specific protein expression data nominated neutrophils as a predominant source of XIST “hotspot”-associated proteins, and we confirmed the presence of both XIST and “hotspot”-associated proteins in neutrophil extracellular traps during NETosis, an immunogenic programmed cell death pathway triggered by neutrophil activation upon which neutrophils extrude their nuclear content. Furthermore, we found that levels of autoantibodies against SPEN, a key XIST-associated protein that binds to the A-repeat, correlate with severe digital ischemia in systemic sclerosis in two independent cohorts at two centers. Together, these data show a plausible mechanism for the origin of AXA, guided by RNA structure and RNA-protein interactions, and show that AXA holds promise for disease endotyping and prognostication in female-biased autoimmune conditions.

0033

Loss of CXCR6 in antigen-specific CD4+ Th2 cells reduces exhaustion and increases cytotoxicity in mouse models of autoimmunity and cancer

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CXCR6 is a key component of the tissue-residency gene program, contributing to CD8+ T cell resident memory (Trm) maintenance in tissues such as the lungs and skin in the context of melanoma. Its ligand, CXCL16, is expressed by epithelial cells under homeostatic conditions in both membrane-bound and cleaved forms. Our lab previously demonstrated that CXCR6 is highly expressed on antigen-specific CD4+ Th2-skewed cells (OT2) in a mouse model of cutaneous lupus erythematosus (CLE) and that the cognate ligand CXCL16 is expressed in lesional skin. Based on the importance of CXCR6 expression on CD8+ T cells, we hypothesized that CXCR6 expression is also important in CD4+ memory T cell generation in the skin. To test this, we injected CXCR6 KO versus WT Th2 skewed OT2 cells into CLE recipient mice. CXCR6 KO OT2 induced more severe skin lesions and greater weight loss compared to mice receiving wild-type (WT) T cells. Examination of activation markers on preinjection T cells revealed that CXCR6 KO OT2 expresses more CD127 and NKG2A/C/E. Since these CD4+ T cells seemed to be more activated and less exhausted, we hypothesized that they would be beneficial in a cancer model. To test this, we transferred activated CXCR6 KO or WT OT2 T cells into Rag1 KO mice engrafted with B16-OVA melanoma cells 10 days prior. Mice that received CXCR6KO OT2 exhibited increased survival and reduced PD-1 expression on antigen-specific CD4+ T cells compared to those receiving WT OT2 T cells. Together, these findings suggest that CXCR6 plays a critical role in CD4+ T helper cell effector function and exhaustion, and may have implications for CAR-T cell therapy. Further studies are warranted to determine how CXCR6 signaling may differ in CD4 T cells versus CD8 T cells, and the importance of the Th2 skewing protocol on this signaling pathway during CD4 T cell activation.

0034

Cross-species insights into hair follicle-T cell interactions in discoid lupus erythematosus: A comparison of human, canine and mouse models using spatial transcriptomics

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Discoid lupus erythematosus (DLE) is a type of primary cicatricial alopecia (PCA), causes scarring hair loss via lymphocytic inflammation. To explore the mechanism of disease, we performed spatial transcriptomics across humans,dogs with spontaneous DLE and a novel murine PCA model. This cross-species study sought to identify shared molecular pathways and potential therapeutic targets. In human DLE, perifollicular T cells were significantly enriched and showed increase gene expression of CXCR3 ligands (e.g., CXCL9, CXCL11) , interferon-response genes (e.g. IRF7, ISG15), and fibrotic markers. These findings suggest robust immune activation and extracellular matrix remodeling in the hair follicle, contributing to follicular damage and scarring. Similarly, canine DLE samples demonstrated immune cell infiltration around hair follicles with elevated gene levels of S100A8/9 and loss of protective elements such as PPARG, supporting the relevance of canine DLE as a translational model for human disease. In PCA mouse model, CD8+ T cells were observed to arrest near hair follicles, leading to the depletion of CD34+ bulge stem cells and subsequent fibrosis. Comparing gene expression in the hair follicle from PCA vs healthy mice revealed many differentially expressed genes, including ATF4, an upregulated transcription factor involved in the integrated stress response .Comparative transcriptomic analysis across species highlighted overlapping pathways, including interferon signaling and complement activation. Notably, therapeutic targets such as CFD and S100A8/9 were identified across human, canine and murine samples. These genes, implicated in keratinocyte activation and immune regulation, represent promising candidates for developing new treatments. Conservation of these pathways highlights the potential for cross-species therapeutic trials to benefit both veterinary and human medicine.

0035

Comparing chemokine receptor CXCR4 signaling pathways in T cells and B cells

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Chemokine receptors are expressed broadly throughout different cells in the immune system. However, it is unclear if the signaling pathways used by the same receptor are similar or different between cell types. The purpose of this study was to test the hypothesis that the chemokine receptor CXCR4 utilizes different signaling partners in T cells compared to B cells. CXCR4 was chosen as the receptor of interest as it is highly expressed on both B and T cells and plays a critical role in appropriate bone marrow extravasation and coordinating immune responses. CXCR4 is also a HIV co-receptor and is thought to be involved in cancer metastasis. Utilizing CRISPR-Cas9 gene editing, a peroxidase tag, APEX2, was appended to the endogenous loci of CXCR4 at the C-terminus in B cells (Raji) and T cells (Jurkat). APEX2 labels proteins with biotin in a radius of approximately 200 angstroms following a pulse of hydrogen peroxide. Biotin-labeled proteins allow for enrichment by streptavidin beads and subsequent analysis by mass spectrometry. We validated efficient biotin labeling by anti-biotin western blotting. We confirmed that the APEX2 tag does not interfere with G protein activation by CXCL12 or prohibitively impair surface expression. We further probed downstream signaling events using RNA-seq following treatment of wild-type B cells or T cells with CXCL12 compared to CXCR4 knockout B cells or T cells. Our integrated multi-omics workflow allows for rigorous evaluation of key signaling mediators of a common chemokine receptor in different immune cells, illuminating fundamental principles of signal transduction.

0036

IL-27 generates immunosuppressive CD4 T cells and and prevents the development of alopecia areata

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Alopecia areata (AA) is a T cell-mediated autoimmune disease of the hair follicle (HF) that presents as non-scarring hair loss and has a 2% lifetime incidence. AA is thought to occur from the breakdown of immune privilege of the HF resulting in infiltration of NKG2D-expressing CD8 T cells and attack of the HF. Recently, JAK inhibitors have been approved by the FDA for the treatment of AA, however, they have shown incomplete efficacy in clinical trials and have been associated with increased risk of catastrophic adverse events, thus supporting the need to find additional therapeutic options. IL-27 is a pleiotropic cytokine with context-dependent pro- and anti-inflammatory properties that has been investigated as a therapeutic option in models of autoimmunity and cancer. The aim of our study was to determine if IL-27 affected AA pathogenesis. We used an adeno-associated virus that drives expression of IL-27 (AAV-IL27) in the skin-graft induction model of AA and found that AAV-IL27 treatment protected mice from developing AA. In mice that were protected from AA, we saw an increase in IL-10 producing $FoxP3^{-}CD4^{+}$ T cells in the skin draining lymph nodes (SDLNs). Additionally, in mice that were treated with AAV-IL27, we observed a 1.3-fold decrease in CD127 expression in SDLN CD8 T cells, and a marked decrease in expression in skin CD8 T cells. Together these data suggest that IL-27 can lead to an increase in immunosuppressive CD4 T cells and diminished CD8 T cell responsiveness to IL-7, a cytokine pathway previously implicated in AA pathogenesis. Further studies are needed to examine the mechanisms by which IL-27 contributes to the prevention of disease and its utility as a therapy for AA.

0037

Inflammatory implications in female pattern hair loss: unraveling B cell-related immune activation through comparative transcriptome profiling

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Female pattern hair loss (FPHL) is a common, progressive condition rarely linked to immune dysregulation, with its transcriptomic profile remaining poorly understood. 10 paired punch biopsies from the vertex and occipital scalp were collected from patients with Sinclair grade 3 or above FPHL. Each biopsy was bisected for pathological examination and transcriptomic analysis. Differential gene expression analysis was followed by over-representation analysis and gene set enrichment analysis (GSEA). Cellular composition was evaluated with CIBERSORT, and immune repertoire diversity was assessed using TRUST4 and Immunarch. 71 upregulated and 33 downregulated genes were identified in the affected vertex scalp compared to the unaffected. Upregulated genes were enriched in Gene Ontology (GO) terms including “immunoglobulin production” and “antigen receptor-mediated signaling pathway”. We extended our analysis using MSigDB and GSEA method to mitigate potential biases caused by thresholding criteria. GSEA also highlighted similar immune-related terms, including “B cell-mediated immunity” and “immunoglobulin-mediated response”. C5 gene sets included “immunoglobulin complex” and “antigen binding”, while Hallmark gene sets showed enrichment in “IFN-α/γ response” and “TNF-α signaling”. CIBERSORT analysis indicated a higher abundance of B cells in the vertex scalp (P = 0.0273). Notably, CD8+ T cell infiltration was also elevated in the vertex scalp, while Tregs were reduced (P = 0.0346 and 0.0472 respectively). After TRUST4 reconstruction, Immune repertoire analysis showed significantly higher diversity (Chao1, true diversity, and D50 diversity index) in the vertex. Taken togenther, this study revealed immune-related transcriptomic changes in FPHL, with increased B cell/CD8+ T cell infiltration and associated immune-related pathways activation in the vertex scalp as key characteristics. Findings suggest a potential role of immune modulation in FPHL pathogenesis, offering insights that may inform future therapeutic strategies.

0038

Therapeutic insights from spatial mapping of hidradenitis suppurativa skin lesions at single cell resolution

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Hidradenitis Suppurativa (HS) is a debilitating inflammatory skin disease characterized by abscesses and purulent draining sinus tracts. Effective treatments remain elusive, underscoring the need for deeper mechanistic understanding. Using 45-antibody CODEX immunofluorescence imaging, flow cytometry, and Xenium spatial transcriptomics, we generated a spatial atlas of cell types in HS lesions at single-cell resolution. Our CODEX analysis demonstrated increased densities of B cells, plasma cells (PCs), neutrophils, CD4 T, and CD8 T cells in HS lesions compared with control skin ($p < 0.001$). These immune infiltrates often formed tertiary lymphoid structures (TLS) and bona fide germinal center reactions. PCs were a dominant immune population in lesional skin; we estimated PC numbers in lesions of a severe HS patient were similar to the PC numbers found in all lymphoid organs of a healthy adult. TLS were increased in more severe disease, and PC densities correlated strongly with TLS densities ($r=0.69$; $p=2.6e-10$), suggesting TLS may generate PCs in situ. PCs were not reduced in HS lesions from TNF inhibitor-treated versus biologic-naïve patients. This may explain the limited efficacy of TNF inhibitors, and highlights PCs as potential therapeutic targets. CODEX analyses further revealed heterogeneity in sinus tracts in HS lesions; only 40% of tracts were surrounded by dense immune infiltrates. Spatial transcriptional profiling of HS lesions identified IL-36γ as specifically expressed in keratinocytes of inflammatory tracts compared with non-inflammatory tracts ($p<0.01$), with undetectable expression elsewhere in the dermis. This finding explains why Phase 2 clinical trials targeting IL36R with spesolimab reduced draining sinus tracts but not abscesses or nodules. Together, our findings advance our understanding of HS pathogenesis and highlight PCs and the IL-36 pathway as therapeutic targets in HS.

0039

Fate induction through asymmetric T cell division is modulated by chimeric antigen receptor co-stimulatory domains

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Chimeric antigen receptor T (CART) cell therapy has revolutionized the treatment of certain blood cancers and shows emerging promise in autoimmune diseases. These receptors frequently include 4-1BB or CD28 costimulatory domains. However, how these signals govern early T cell fate remains incompletely understood. Using single-cell multi-omic analyses of CD8 CART expressing 4-1BB (BBζ) or CD28 (28ζ) costimulatory domains, we show these domains distinctly inform asymmetric T cell division (ATCD) into proximal (PD) and distal daughters (DD) with divergent effector and memory phenotypes, respectively. BBζ induces more pronounced transcriptional and epigenetic remodeling following ATCD, with 1,100 differentially expressed genes (fold change >1.2, FDR < 0.05) versus 270 for 28ζ, and 2,276 differentially accessible chromatin regions versus 163 in 28ζ daughters (fold change > 1.5, FDR < 0.05). In a humanized leukemia model, BBζ daughters persisted at higher levels and provided sustained tumor control, while 28ζ daughters failed to prevent leukemic outgrowth (n=4-9/group, $p<0.01$). Mechanistically, BBζ daughters displayed heightened oxidative metabolism, coupled with elevated anti-apoptotic gene expression. Single-cell gene regulatory network analysis revealed both BBζ and 28ζ utilize similar transcription factors (e.g. PRDM1, TBX21 in PD; BCL11B, STAT1 in DD), but BBζ drives greater asymmetry, with DD acquiring an epigenetic phenotype like stem cell memory T cells marked by reduced activity of chromatin architecture factors (CTCF, RAD21, SMC3). In contrast, 28ζ daughters exhibit less molecular and functional polarization and diminished persistence. By integrating transcriptomics and chromatin accessibility, these findings highlight how costimulatory domains fine-tune fate-determining factors during ATCD to shape early CART outcomes and inform the design of improved cellular immunotherapies for cancer and autoimmune diseases.

0040

Machine learning algorithms as tools for identifying predictive autoantibody biomarkers in pemphigus vulgaris

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While the role of autoantibodies (autoAbs) against desmoglein (Dsg)3 and -1 in Pemphigus vulgaris (PV) is well established, non-Dsg autoAbs are also being increasingly implicated but not yet extensively studied. Using multiplexed protein microarray technology, we examined reactivity to 52 putative PV relevant autoantigens in 633 serum samples (421 patients, 212 controls) stratified by HLA haplotype. Limma analysis revealed increased reactivity to 37 autoantigens, including IgE Fc, HLA-DRA, Human M1, -2, -3, -4, Thyroglobulin, and Dsg3/-1 in active PV (PVA, n=209) vs. controls (CR, n=212). HLA-negative patients (lacking the PV associated DRB1*0402/DQB1*0503 alleles, n=34) showed increased reactivity to 28 antigens compared to HLA-positive (n=169) patients, including annexin A9, Human M2, Thyroglobulin, and Dsg-1. Among HLA-positive patients, DQB1*0503 carriers exhibited heightened reactivity to 28 autoantigens compared to DRB1*0402 carriers, including TPO, Dsg3/-1/-4, Integrin alpha X, and C5a receptor 1. K-Nearest Neighbor (KNN) accurately distinguished PVA from controls (8/10), *0402-positive from *0503-positive (9/10), and PVA from remission patients (10/10). In a longitudinal analysis of 22 patients, autoAb reactivity varied over time across phases of disease activity, yet each patient retained a unique autoantigen profile signature. A core set of antigens with significant reactivity changes included Dsg2, HSP60, Human M2, HLA-DRA, FH, and IgE Fc. These data provide strong support for the presence and potential active role of both Dsg and non Dsg specific autoAbs in PV pathogenesis, and highlight the importance of HLA genetics in shaping autoimmune specificity. This information provides new insights into disease mechanisms and suggests predictive biomarkers for disease classification, clinical course and future individualized therapies.

0041

Comparative multi-omics highlights inflammatory monocyte-derived dendritic cells as key mediators of UVB-induced photosensitivity

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Ultraviolet (UV) radiation presents a paradox in inflammatory skin biology: while widely used to treat conditions like psoriasis, it exacerbates diseases such as cutaneous lupus erythematosus (CLE) and dermatomyositis (DM). The mechanisms behind these divergent responses remain unclear. To address this, we conducted a systematic, multi-omics analysis—integrating proteomics, single-cell RNA sequencing, and spatial transcriptomics—comparing two photosensitive disorders (CLE and DM) to two photoresponsive conditions (psoriasis and vitiligo). Our findings identify monocyte-derived dendritic cells (moDCs) as central mediators of photosensitivity. In CLE and DM, moDCs are enriched in lesional skin, colocalizing with cytotoxic CD4+ T cells in the superficial dermis and expressing high levels of MMP9, a matrix metalloproteinase that degrades collagen IV at the dermo-epidermal junction. This degradation facilitates immune cell infiltration and amplifies interface dermatitis. *In vitro*, keratinocytes preconditioned with IFN-β displayed heightened susceptibility to UVB-induced cell death, releasing supernatants that activated moDCs and triggered chemokine production (e.g., CCL2, CCL7, CCL8). This established a positive feedback loop of moDC recruitment, IFN-β amplification, and cytotoxic T cell-driven tissue damage. Our findings highlight the pivotal role of moDCs and MMP9 in driving photosensitivity through a positive feedback loop that involves extracellular matrix remodeling, lymphocyte and immune cell recruitment and activation of recruited cells. Targeting MMP9 or disrupting moDC recruitment pathways offers a promising therapeutic approach to mitigate UV-induced inflammation in photosensitive dermatoses.

0042

Regulation and dysregulation of disease specific immune responses by human dendritic cell subset

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Dendritic cells (DCs) are crucial for controlling immune responses. Different DC subsets exist, each with unique functions. Our research focuses on a subset found in the skin called CD5+ DCs. These cells are highly effective at activating immune responses, particularly those that kill infected cells and promote inflammation. Interestingly, CD5+ DCs are abundant in inflamed skin conditions like psoriasis but reduced in tumors. This suggests they play a complex role in different diseases. We found that CD5 on DCs promotes inflammation and enhances anti-tumor immunity, including responses to immunotherapy. Deleting CD5 from DCs hinders tumor rejection and reduces the effectiveness of immune checkpoint blockade (ICB) immunotherapy, a cancer treatment. Successful ICB therapy is associated with increased CD5+ DCs, which are essential for interacting with specific immune cells. Our findings highlight the importance of CD5+ DCs in regulating immune responses and provide valuable insights into how ICB immunotherapy works. harnessing CD5 on DCs could be a promising strategy to improve treatment outcomes for cancer patients and inhibiting CD5 could therefore attenuate autoimmuity..

0043

CD301b$^+$ cDC2 facilitate cytotoxic T lymphocytes activation within inducible skin-associated lymphoid tissue in contact dermatiti

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Dermal dendritic cells (dDCs) have been found to activate cytotoxic T lymphocytes (CTLs) in inducible skin-associated lymphoid tissue (iSALT) during the elicitation phase of contact hypersensitivity (CHS). To elucidate the molecular mechanism of CTL activation within iSALT, photoconvertible protein (KikGR)-expressing mice induced CHS with 2,4-dinitrofluorobenzene (DNFB) were used to selectively photoconvert cells within iSALT by laser irradiation. Analysis by scRNA-seq revealed that among multiple dDC subsets, CD301b$^+$ cDC2, a subpopulation of cDC2 residing in non-lymphatic barrier tissues including skin, accumulated inside iSALT, while other DC subsets were comparable inside and outside iSALT. To investigate the role of CD301b$^+$ cDC2, CD301b-diphtheria toxin (DT) receptor mice were used to selectively deplete CD301b$^+$ cDC2. DT injection significantly suppressed ear swelling, iSALT formation, and IFN-γ$^+$ CTLs. Traditionally, cDC1 has been considered the primary inducer of CTL activation due to its high cross-presentation ability, whereas the mechanism by which cDC2 activates CTLs has remained elusive. Co-culture of CTLs from DNFB-sensitized mice with CD301b$^+$ cDC2 rapidly induced IFN-γ production after 72 hours of dinitrobenzene sulfonic acid stimulation, which was not suppressed by cross-presentation inhibitors, suggesting that CD301b$^+$ cDC2 presents antigen directly to CTLs without processing. In addition, scRNA-seq analysis identified IL-15 and CCL5 as CTL activation factors derived from CD301b$^+$ cDC2, with IL-15 neutralization suppressing ear swelling and IFN-γ$^+$ CTLs during CHS and CCL5 neutralization attenuating iSALT formation. Finally, immunohistochemical analysis of human allergic contact dermatitis skin showed that CD301b$^+$ cDC2 expressed IL-15 and adhered to CTLs. These results suggest that CD301b$^+$ cDC2 recruits CTLs into iSALT via CCL5 and promotes their activation by IL-15. The novel concept of cross-talk between CD301b$^+$ cDC2 and CTLs will advance the understanding of CTL-mediated skin diseases.

0044

Using the hair follicle *ex vivo* model to explore initial events in hidradenitis suppurativa pathogenesis

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In Hidradenitis Suppurativa (HS), hair follicle (HF) keratinocytes hyperproliferate and release pro-inflammatory chemokines that attract immune cells. The molecular mechanisms beyond these initial events of HS remain elusive. Here, we evaluated the potential of the human HF organ culture model to explore early events in HS pathogenesis and as a screening tool to pre-clinically test HS therapeutics. Full-length anagen HFs from 2 male healthy donors were stimulated with, 1) a triple cytokine cocktail of TNF-α, IL-17A, and IL-1β - linked to HS pathogenesis and targeted in the clinic, 2) the triple cocktail + IFN-γ – to include Th1 responses, 3) the triple cocktail + TGF-β – to model fibrosis phenotype, or 4) vehicle control. Gene expression analysis showed that the triple cocktail had a minor effect on IL1A, LCN2, and CAMP but significantly upregulated DEFB4, CCL20, and CXCL8 expression, suggesting a pro-inflammatory phenotype promoting immune cell recruitment and bacterial dysbiosis. In line, increased CXCL8 secretion was confirmed by ELISA. Surprisingly, the triple cocktail also inhibited keratinocyte proliferation and differentiation, demonstrated by downregulation of KRT1, FLG, and MKI67. Further administration of IFN-γ or TGF-β caused only minimal additional effects. To evaluate immune cell activation and attraction, elicited by HF keratinocyte CXCL8 production, we pre-stimulated with the triple cocktail full-length HFs from 2 healthy female donors, and co-cultured them with donor-matched PBMCs. Qualitative analysis confirmed immune cell infiltration in the HFs and enhanced CXCL8 released was detected in the medium of pre-stimulated and co-cultured HFs, indicating PBMC-HF cross-talk. These pilot data highlight TNF-α, IL-17A, and IL-1β as key drivers of HS pathogenesis, particularly in inducing a pro-inflammatory phenotype in HF keratinocytes. Additionally, this study supports the use of the HF organ culture as a model to investigate HS-related mechanisms and for pre-clinical testing of potential HS treatments.

0045

Label-free proteomics-based analysis: Comparison of two atopic dermatitis-like cell models

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Atopic dermatitis (AD) is the non-fatal skin disease with the highest global disease burden. In recent years, although targeted drugs have been developed with favorable therapeutic effects. However, the high cost of treatment has limited their accessibility. To increase treatment options for patients, it is critical to develop drugs that work faster, effectively relieve itching, and have fewer side effects. Therefore, the establishment of viable *in vitro* models is crucial for the screening of new drugs. The complicated interactions of keratinocytes (KCs) with environmental factors, skin microbiota, inflammatory cells, and nerves are vital in the pathogenesis and development of AD. The multi-functionality of KCs allows them to be used as models for studying a variety of pathological processes, including AD.The HaCaT cell line is the most widely used cell line for constructing *in vitro* models of AD. The results showed that IL-4 combined with IL-13 administration was mainly involved in the acute phase inflammatory response, and TNF-α combined with IFN-γ administration was mainly involved in the innate immune response. In addition, qPCR results showed that both modeling methods induced HaCaT cells to overexpress AD-related cytokines and inflammatory factors (IL-1β, IL-8, TSLP, and CXCL1/2/9/10). These suggest that both methods can be used as *in vitro* models to mimic AD disease for drug screening.

0046

CD1a-targeted PD-1 agonists for localized immunosuppression in atopic dermatitis

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T cells play a central role in the pathogenesis of atopic dermatitis (AD). They respond to environmental allergens in the context of barrier defects and orchestrate the inflammatory response. The PD-1 receptor is a key immune checkpoint that restrains T cell responses. PD-1 inhibitory signals regulate the threshold for T cell activation to limit effector T cell responses, facilitate resolution of inflammation and establish T cell tolerance. We developed a skin-targeted PD-1 agonist as a novel strategy to treat inflammatory skin diseases. These cell-bridging bispecifics comprise a high affinity targeting domain, which binds CD1a, an HLA-related molecule that is highly expressed on skin antigen presenting cells (APCs) and a PD-1 agonist to modulate T cell activity at the immune synapse. In co-culture assays, using $CD1a^+$ or $CD1a^-$ APCs and non-targeted PD-1 agonist-control bispecifics, we show that CD1a-directed PD-1 agonists only suppress T cell activation when bound to APCs. The CD1a-targeted PD-1 bispecific does not compete with PD-L1 or PD-L2 binding to PD-1 and co-culture studies, using monocyte-derived Langerhans (MoLCs) cells that express both PD-1 ligands, confirmed the ability of the bispecific to act additively to enhance T cell suppression. Specifically, the bispecific potently inhibits MoLC-stimulated Jurkat NFAT reporter activity and HDM-stimulated IL-13 release in autologous MoLC - T cell assays. Finally, target engagement studies in *ex vivo* human skin explants demonstrate specific binding of fluorescently labelled molecules to $CD1a^+$ APCs in healthy and AD skin. Furthermore, quantitative immunohistomorphometry and cytokine array analyses show that the bispecifics suppress T cell proliferation and activation in AD lesional and perilesional skin. These studies demonstrate the potential for CD1a-targeted PD-1 agonists to provide localized inhibition of inflammatory T cells in the skin, whilst avoiding systemic immunosuppression.

0047

Abrocitinib reduces circulating, skin homing, and resident memory T-cells in atopic dermatitis samples *in vitro* and *ex vivo*, and disease flare severity in a humanized mouse model

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In patients suffering from moderate to severe atopic dermatitis (AD), Abrocitinib treatment efficiently reduced clinical signs and itch, and impacted breakthrough disease flare frequency. Memory T-cells are postulated to mediate disease reappearance, and therefore we experimentally assessed the effect of Abrocitinib on circulating ($_{CI}$) and resident ($_R$) memory ($_M$) T-cells in AD. Treatment of PBMCs isolated from AD patients with Abrocitinib did not alter the number of $T_{CI\text{-}M}$ but prevented anti-CD3/CD28 induced expansion of central and/or effector $T_{CI\text{-}M}$, including CLA+ (skin homing) and CCR4+ (skin tropic) CD4+ and CD8+ subpopulations. Similar to clinical outcomes, RNAseq and cytokine array analyses demonstrated diseased phenotype amelioration in treated AD peri-lesional and lesional samples *ex vivo*. Additionally, abrocitinib reduced the number of CD3+CD45RO+CD69+ cells, and CD3+CD45RO+CLA+ T_{RM} in peri-lesional and/or lesional AD samples predominantly in the epidermis, and tended to restore filaggrin expression, as shown by quantitative (immuno-)histomorphometry. Furthermore, application of the abrocitinib surrogate molecule (ASM) resolved disease manifestation, and alleviated the phenotype of flares induced by sonic stress in a humanized mouse model of AD. This was revealed by transcriptomic and histological analysis, as well as the detection of higher filaggrin and claudin-1 expression, and lower $CD3^+$ cells in treated versus control xenotransplants. Taking together, our data indicate that Abrocitinib impacts breakthrough AD flare severity potential and possess interesting disease modifying properties linked, at least in part, also to its ability to interfere with the expansion/survival of T_M.

0048

Innate cell infiltration into the skin is suppressed in dirty mice following alarming stimulation.

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Tissue resident memory T (Trm) cells sequestered at barrier tissues are a swift first line defense against peripheral reinfections. Moreover, when aberrantly activated, Trm cells can mediate autoimmune diseases, such as psoriasis. As an effector mechanism Trm cells can stimulate the influx and activation of memory T cells and innate immune cells. However, there is significant heterogeneity in the inflammatory responses that Trm cell populations can induce, specifically in the activation of the innate profile. Most studies to date have utilized a reductionist approach to examine single Trm populations, specific pathogens, and defined tissues. To complement these studies in the skin, we have adopted a holistic approach utilizing barrier-free 'dirty' mice to profile activated innate cells attracted into the skin in the presence of quiescent cutaneous Trm cells. Notably, dirty mice are a more human predictive model due to having a diverse microbial experience that leads to the development of a complete complement of Trm cells in the skin. We demonstrate that in the dirty mouse model mice have a significant reduction in cutaneous neutrophils and monocytes compared to specific pathogen free mice following local treatment with two separate innate stimuli. These findings reveal that cutaneous Trm cells have the capacity to temper the innate immune response and further substantiate the implication that Trm cells are heterogenous in their functions depending in large part on their tissue residency. However, in a psoriasiform microenvironment Trm cells are capable of recruiting innate cells to the site of an alarmin exposure. Likely due to the imbalance of IL-17 and IFN-γ.

0049

Vitamin D receptor signaling antagonizes rorgt signaling to reprogram Th17 cells

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Vitamin D3 deficiency has been associated with susceptibility to autoimmune diseases commonly linked to dysregulation of the T helper 17 (Th17) program. Th17 cells rely on the nuclear receptor (NR) RORγt as the master transcription factor for differentiation and function, establishing a metastate that can drive pro-inflammatory or alternative pathways depending on external cues. The active hormone of vitamin D3, 1a,25(OH)2D3, signals through another NR, the vitamin D receptor (VDR), to inhibit IL-17A in favor of the immunosuppressive cytokine IL-10; however, the mechanism remains unclear. We developed a novel dual Vdr reporter and conditional knockout mouse model and, for the first time, have identified heterogeneous Vdr expression in Th17 cells, defining a subset of vitamin D3-responsive Th17 cells. Expression of Vdr was restricted to the most highly activated Th17 cells and was dependent on RORγt signaling, establishing a feedforward-feedback mechanism wherein activation of Vdr by the extrinsic ligand 1a,25(OH)2D3 antagonized the intrinsic RORγt-driven program, leading to a marked reduction in RORγt binding at key RORE sites within Th17 loci. Although 1a,25(OH)2D3 enhanced Vdr binding to VDRE sites, this did not directly compete with RORγt but instead facilitated the locus accessibility and transactivation of a unique Vdr-Th17 gene program that resulted in the transdifferentiation of Th17 cells into pro-tolerogenic ex-Th17 cells. The antagonistic role of vitamin D3 in limiting reactive Th17 cells offers insight into the strong association between vitamin D and autoimmune disease.

0050

Unveiling the IL-36/IFNK axis in sex-biased generalized pustular psoriasis

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Generalized pustular psoriasis is a severe subtype of psoriasis characterized by significant morbidity, mortality, and a pronounced female sex bias. This condition is associated with elevated expression of IL-36 cytokines, including IL-36A, IL-36B, and IL-36G, as well as the IL-36 receptor antagonist (IL-36RA/IL36RN). Single-cell and spatial transcriptomic analyses revealed that IL-36 activity is primarily localized to the supraspinous layer of the epidermis and acts downstream of IL-17A and TNF pathways. Using CRISPR/Cas9-mediated knockout, we demonstrated that deleting IL36G and its receptor IL36R in keratinocytes significantly suppressed IL-17A and TNF responses ($p<0.001$), suggesting a prominent role for IL-36G in epidermal inflammation. Further, RNA sequencing of primary keratinocytes (n=47) revealed a marked sex-specific response, with female keratinocytes exhibiting a more robust pro-inflammatory reaction compared to male keratinocytes ($p<0.001$). Female keratinocytes also showed elevated expression of type I interferon, IFNK ($p<0.001$; FC-3.84), and its signature genes, such as MX1 ($p<0.001$; FC-4.78), indicating a potential interaction between IFN-κ and the IL-36 axis. Moreover, RNA sequencing data from 3D skin rafts showed decreased expression of both TNFRSF25 (TNFSF15 receptor) and IFNK during epidermal differentiation, suggesting coordinated regulation. Spatial sequencing analysis identified the close proximity of TNFSF15+ neutrophils to IL36G+ TNFRSF25+ keratinocytes in the epidermis of pustular psoriasis lesions. These findings provide novel insights into IL-36 biology, highlighting its role in IL-17 and TNF responses within the epidermis. The sex-specific IL-36 response and its interaction with the TNFSF15 and IFNK axes may contribute to the predominance of pustular psoriasis in women, offering potential therapeutic targets for managing this condition, particularly in female patients.

0051

A Cutaneous immunotherapy for peanut allergy

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Treatment of peanut allergy (PA) remains recalcitrant to improvement owing to the fundamental safety and efficacy limitations of existing therapeutic approaches. Here, we report on the progress of our novel microneedle patch (MNP)-based immunotherapy strategy to treat PA. Our approach leverages the power of the skin immune system via co-delivery of peanut extract (PE) and rationally selected immune modifiers with MNPs to induce PE-specific neutralizing IgG and Treg responses in a well-tolerated fashion to reverse the symptoms of PA. First, we established a new murine model of PA through cutaneous sensitization via co-delivery of PE and a Th2-skewing adjuvant. This model recapitulated the key features of atopic skin, such as impaired barrier function and heightened local inflammation with Th2-predominant pro-inflammatory cytokines. This model also exhibited the systemic hallmarks of clinical PA, such as Th2 responses and elevated peanut-specific serum IgE levels. Mimicking these key local and global features of skin-sensitized PA patients in an experimental model facilitated the robust induction of anaphylaxis in upon systemic challenge with PE, indicated by increased clinical symptoms. Anaphylaxis was further confirmed by evident hypothermia and higher serum levels of systemic anaphylaxis mediators, such as mast cell protease-1 (MCPT-1) in sensitized mice with respect to control (unsensitized) mice upon a systemic challenge with PE. Next, we used this model to test the efficacy of our MNP-based PA immunotherapy. Murine studies showed that MNP-directed PA immunotherapy elicited increased PE-specific IgG and Treg responses, as well as improved Th1-skewing compared with MNPs loaded with PE alone. Notably, MNP-based PA immunotherapy prevented anaphylaxis, determined by significantly reduced hypothermia, clinical scores, and systemic levels of MCPT-1 in treated mice compared with control (sensitized and untreated) mice upon systemic challenge with PE. These findings support the further development of MNP-based cutaneous immunotherapies for PA.

0052

Efficacy and safety of combination therapy of ponatinib and blinatumomab in Philadelphia chromosome positive acute lymphoblastic leukemia (ALL): A meta-analysis

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Philadelphia chromosome-positive acute lymphoblastic leukemia(Ph+ALL) comprises 20-30% of adult ALL cases worldwide, characterized by aggressive progression and high mortality.Common symptoms include fatigue, fever, bruising, and recurrent infections. While combining tyrosine kinase inhibitors (TKIs)with chemotherapy has improved outcomes, it also presents significant toxicity. Recently, ponatinib, a third-generation TKI, and blinatumomab, a bispecific T-cell engager, have shown potential to improve survival and reduce toxicity. This study evaluates their efficacy and safety in Ph+ ALL treatment. A systematic review and meta-analysis was conducted using PubMed,Embase,Scopus, and Cochrane databases,including literature up to December 2024.Seven studies with 338 patients (294 newly diagnosed and 44 refractory cases, mean age 52.43 years,SD 15.21) met predefined criteria.Data were analyzed using OpenMeta software,with prevalence rates pooled under a random effects model. Heterogeneity was assessed using I^2andχ^2,with $I^2 > 50\%$ indicating significant heterogeneity.Results showed an event-free survival rate of 0.62 (95% CI 0.35-0.89, I^2=94.15%, P<0.01), hematologic response of 0.51(95%CI 0.26-0.75,I^2=96.99%,P<0.01), and measurable residual disease negativity of 0.78 (95% CI 0.67-0.89, I^2=75.91%,P=0.006).Overall survival reached 0.84(95%CI 0.75-0.93,I^2=79.7%,P<0.01), relapse rates were 0.11 (95% CI 0.03-0.19,I^2=82%,P<0.01), and complete molecular response was 0.87(95% CI 0.79-0.96,I^2=76.06%, P<0.01). Adverse events across grades 1-4 were 0.16(95% CI 0.05-0.28, I^2=77.51%, P=0.004).This analysis suggests ponatinib and blinatumomab can achieve improved survival, molecular responses, and low relapse rates within 24 months with manageable toxicity. Further large-scale studies are needed to confirm these findings and establish this combination as a standard therapy for Ph+ALL.

0053

A new player in alopecia areata management: Butyrophilin-like 2 (BTNL2) to the rescue?

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In alopecia areata (AA), excessive secretion of IFN-g by T and NK cells promotes the collapse of the hair follicle's (HF) immune privilege (IP), characterized, e.g., by overexpression of MHC class Ia and the NKG2D-stimulating "danger" signal, MICA. Pathogenic interactions between NKG2D expressed on T cells and MICA overexpressed by HF keratinocytes can trigger HF IP collapse and thus promote AA via an auto-antigen-independent, non-autoimmune pathway. Since JAK inhibitors fail to target this mechanism, we have explored if Butyrophilin-like 2 (BTNL2), a transmembrane protein known to down-modulate T-cell activation and maintain immune tolerance, can protect HF IP. IF microscopy showed that BTNL2 is predominantly expressed by outer root sheath keratinocytes of healthy human scalp HFs. *Ex vivo*, BTNL2 expression was significantly lower in stressed MICA-overexpressing HFs with weakened IP than in non-stressed HFs with intact IP. When isolated, autologous human scalp Vd1- g/dT and CD8 T cells were co-cultured with HFs NKG2D, and IFNg expression by Vd1-T cells was increased. In stressed HFs, NKG2D-driven cytotoxicity by Vd1-T and $CD8^+$ T cells was heightened, leading to melanin clumping and premature catagen induction, i.e., hallmarks of AA-like HF damage. Conversely, non-stressed HFs with high levels of BTNL2 Vd1-T and $CD8^+$ T cells failed to induce signs of IP collapse/HF damage. These pilot data support the novel working hypothesis that BTNL2 is an important player in human HF IP, whose reduced epithelial expression in stressed HFs promotes increased T-cell cytotoxicity and HF IP collapse and thus facilitates AA development. Instead, the therapeutic upregulation of BTNL2 may help to maintain HF IP and reduce NKG2D-mediated IFNg secretion by AA-pathogenic immune cells.

0054

Treg-targeted therapies restrain disease in a murine model of alopecia areata

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Alopecia Areata (AA) is a common autoimmune disease that presents as nonscarring hair loss. Current FDA-approved treatments for AA are limited to JAK inhibitors; however, potential adverse effects and refractory patients invites the development of alternative therapeutic strategies. Our lab has shown that selective depletion of regulatory T cells (Tregs) in the C3H/HeJ murine model of AA enhances disease development, suggesting that Tregs may play a role in defending the hair follicle from attack. We have also observed that emergence of disease is marked by a robust expansion of CD8 effector T cells (Teffs) that results in this population outnumbering Tregs 20-fold. We hypothesized that pharmacologic enhancement of the Treg pool may be an effective strategy for modulating disease. While low dose recombinant human IL-2 (hIL-2) for the purpose of Treg expansion has not shown great promise for AA patients, IL-2 fusion proteins have shown benefits in other disease models and offer advantages over hIL-2. HCW9302 is a recombinant fusion protein containing two human IL-2 domains fused to a soluble human tissue factor domain. It has a longer half-life than hIL-2 and can selectively expand and activate either human or murine Tregs. Using a murine skin-graft induction model of AA, we observed HCW9302 treatment protected mice from developing AA. We also noted a significant reduction in the number of Teff found infiltrating the skin and a recovery of skin Tregs to outnumber Teff 4:1. Overall, our findings suggest that Tregs play a protective role towards the hair follicle, and their enhancement is effective at restraining disease. Our data provides translational support for the use of IL-2 fusion proteins as a therapeutic strategy for patients with AA.

0055

Molecular basis for rapid activation of resident memory T cells (T_{RM}) after antigen encounter in skin

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We have previously reported on a single cell RNA sequencing (scRNAseq) analysis of a temporal of T_{RM} development after a cutaneous vaccinia virus infection. A unique feature of this time course analysis was a steadily increasing expression of AP-1 factor mRNA as T_{RM} matured; this was not seen in T_{CM} generated from the same infection. Analysis of >day 30 T_{RM} by Assay for Transposase Accessible Chromatin sequencing (ATACseq) motif analysis revealed abundant AP-1 binding sites. While this accumulation of AP-1 mRNA was seen in T_{RM} from multiple tissues, we asked whether AP-1 proteins could be detected in the mature T_{RM} nucleus. Using skin >100 days after VACV infection and imaging by Cyclic Immunofluorescence microscopy (CyCIF), we could detect T_{RM} that co-expressed cFos and JunB protein in a nuclear location, suggesting DNA binding of AP-1 complexes in resting skin T_{RM}. Importantly, T_{RM} in FFPE skin samples were not subjected to tissue digestion. This co-expression of cFos and/or JunB was seen in 39% of $CD8^+$ $CD103^+$ T_{RM}. To further determine the location of these occupied AP-1 binding sites in the genome, we performed "cleavage under targets and release using nuclease" (CUT&RUN) analysis using a JunB-specific antibody. Among the top ten contiguous TF binding sites were interferon regulatory factors (IRF3/IRF8) sites and nuclear factor of activated T cells (NFAT, NFATC2) sites. Both NFAT/AP-1 and IRF8/AP-1 proteins bound to contiguous DNA sites form complexes which serve as potent transcriptional amplifiers for T cell activation. We suggest that the constitutive presence of DNA-bound cFos/JunB allows T cell receptor ligation (signal 1) and subsequent cytoplasmic NFAT nuclear translocation to rapidly initiate T_{RM} activation. This obviates the temporal delay required for gene transcription and translation of AP-1 factors after signal 2 activation of conventional T cells, providing an explanation for the uniquely rapid kinetics of T_{RM} activation in situ.

0056

CD8 T cell-mediated pathogenicity in AA is linked to IFNg production and not cytolytic capacity

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Alopecia Areata (AA) is a prevalent autoimmune disease that presents as nonscarring hair loss. In AA, CD8 T cells accumulate around and within the hair follicle and have been identified as pathogenic effectors of disease. Our transcriptional analysis has revealed that CD8 T cells that infiltrate AA skin exhibit increased gene expression of cytolytic mediators, such as perforin and granzymes, and increased gene expression of the pro-inflammatory cytokine interferon gamma (IFNg). Given the close spatial relationship between CD8 T cells and the hair follicle end-organ target, our objective was to assess the relative contributions of CD8 T cell-derived molecules in the onset of disease. To address this, we used C3H/HeJ mice globally deficient in Prf1 (PKO), IFNg (IFNgKO) and IFNg-receptor (IFNgrKO). Although these global knockouts exhibited markedly different rates of AA development, we were able to leverage gene-deficient mice that developed AA from all groups to perform mechanistic studies. We assessed the relevance of CD8 T cell-derived perforin and IFNg in a C3H/HeJ murine model of AA, wherein pathogenic $NKG2D^+$ CD8 T cells are flow-cytometrically sorted from the skin draining lymph nodes of AA mice, expanded *in vitro*, and then intradermally injected into naïve recipients. We observed that CD8 T cells from PKO AA mice were able to induce AA in a comparable manner to those from WT AA mice. Conversely, CD8 T cells from IFNgKO AA mice were unable to induce AA, suggesting that CD8 T cell-derived IFNg is critical for the initiation of disease. To further support this, we found that adoptive transfer of wild-type CD8 T cells into IFNgrKO global KO mice failed to induce AA. Overall, our findings suggest that perforin-mediated cytolysis is not required for the attack of the hair follicle, and that IFNg production is a crucial pathogenic effector mechanism employed by CD8 T cells in AA.

0057

CD1 and lipid dependence of the human CD4-/CD8- double-negative T cell repertoire

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Double-negative T cells (DN T cells), which lack both CD4 and CD8 co-receptor expression, represent a small fraction of T cells in peripheral blood but are more prevalent in tissues. These T cells are often expanded in autoimmune disease, in particular in SLE. In preclinical models, DN T cells have been harnessed for anti-tumor immunity, transplant tolerance, and the prevention of graft-versus-host disease (GvHD). The apparent contradiction between their pro-inflammatory and immunoregulatory roles is likely due to the heterogeneity within the DN T cell population. Indeed, our preliminary analysis of αβ double-negative (DN) T cells from 19 healthy donors using single-cell RNA sequencing and TCR sequencing revealed several clusters with distinct gene expression profiles, reflecting both pro-inflammatory and anti-inflammatory functions. Given the absence of CD4 and CD8 co-receptors, DN T cells likely interact with antigen-presenting molecules other than MHC. In line with this, we have recent data showing that the human DN αβ T cell repertoire is highly enriched for T cell populations restricted by CD1 proteins. These non-polymorphic antigen-presenting molecules present lipid antigens to T cells. Using fluorescently labeled CD1 tetramers, we identified distinct populations of DN T cells restricted by CD1a, CD1b, CD1c, and CD1d, all of which exhibited CD1-autoreactivity, meaning they bind to CD1 molecules presenting endogenous self-lipid antigens. Using Clonotype Neighbor Graph Analysis (CoNGA), we are determining correlations between gene expression profiles and TCR sequences, and are further linking TCR sequences to CD1-specificities to identify novel conserved CD1-autoreactive T cell populations. These studies will provide a detailed and comprehensive view of the human DN T cell repertoire, and provide a resource for further investigating these populations in disease.

0058

Oral desensitization therapy for poison ivy urushiol contact allergy: A systematic review

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This study evaluates the potential of oral desensitization to mitigate hypersensitivity to poison ivy, a common cause of allergic contact dermatitis. We systematically reviewed prior research on the efficacy of oral exposure to urushiol, poison ivy's allergenic oil, to reduce dermatologic complications. A PRISMA-guided review identified studies from 1959 to 2003, including six human trials with 563 participants and two animal studies. Studies assessed oral administration of urushiol derivatives in liquid or tablet form against placebo or untreated controls. The results showed that oral desensitization reduced hypersensitivity in 44%-94% of participants. Complications were mild, with the most common side effects being vesicular rash, flushing, and pruritus ani, none exceeding typical poison ivy reactions. Quality assessments using the NHLBI tool classified four studies as "good" and four as "fair." While limited by small sample sizes and dated methodologies, these studies highlighted a promising trend of decreased reactivity to poison ivy exposure following oral desensitization. This research highlights the importance of exploring allergen-specific immune modulation, particularly for high-risk populations such as outdoor workers. Although foundational, these findings call for modern clinical trials to validate and expand upon this therapeutic approach, addressing critical gaps in prophylactic measures against poison ivy hypersensitivity.

0059

Oleanane saponin from green tea root extract modulates immune cell function and regulates immunometabolic responses to particulate matter (PM) exposure in PBMCs

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Exposomal aging is a process influenced by environmental exposures, including but not limited to air pollution. Particulate matter (PM) is an air pollutant associated with increased susceptibility to infectious diseases and is recognized by immune system cells. While the effects of Oleanane saponin-green tea root extract (Senomune) on structural skin cells have been studied, its role in modulating immune cells remains unexplored. In this study, we examined the impact of Senomune (100 μg/mL) by pretreating peripheral blood mononuclear cells (PBMCs) before PM exposure to assess their ability to modulate the immune response. Using a functional Met-Flow assay, we profiled the immune cell landscape, metabolic modifications, and cytokine profile in immune cells pre-treated with Senomune, with or without PM (50 μg/mL) exposure. PBMCs treated with PM alone exhibited a reduction in the number of peripheral T-regulatory (CD4+CD25+) cells (pTregs) and B-cells (CD19+). However, pretreatment with Senomune increased the numbers of pTregs ($p<0.0001$) and B-cells ($p<0.001$) in PM-exposed PBMCs. Similarly, PBMCs treated with PM alone showed increased levels of M2 Macrophages (CD11b+CD163+) ($p<0.01$), which were reduced by treatment with Senomune ($p<0.001$). Notably, Senomune pretreatment decreased glycolysis ($p<0.001$), increased OXPHOS ($p<0.001$), and boosted fatty acid synthesis ($p<0.01$) in live CD45+ cell populations compared to untreated PBMCs. Furthermore, pretreatment with Senomune also lowered the expression of pro-inflammatory cytokines such as TNF ($p<0.001$) and IFN-γ ($p<0.01$) in PM-exposed PBMCs. In summary, pretreatment with Senomune can modulate immune cells and their functions in response to PM exposure and regulate the immunometabolic profile of these immune cells, showing the potential to impact immunosenescence/inflamm-aging.

0060

CGRP-ramp1 signaling tunes memory CD8 T cell responses through langerhans cells

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Vaccinia virus (VACV) immunization using a bifurcated needle provides complete protection against Variola major, the causative agent of smallpox, and a vaccination campaign based on this strategy led to the worldwide eradication of smallpox as a disease. CD8+ T cells have a critical role in antiviral immunity in target epithelial tissues. Using a cutaneous VACV infection model, we demonstrate that VACV immunization by skin scarification (s.s.) protects mice more effectively against lethal respiratory challenge than other routes of delivery including intramuscular (i.m.). The skin is innervated by an extensive network of low- and high-threshold sensory nerves, including nociceptive sensory neurons which specialize in detecting noxious stimuli and eliciting pain perception. We found that immunization s.s. with VACV activates Trpv1+ pain fibers and induces pain in mice. However, the role of this phenomenon in shaping CD8 T cell immune responses remains unknown. Here, we show that VACV immunization through s.s. promotes release of the neuropeptide calcitonin gene-related peptide (CGRP) in the skin. Moreover, in the absence of Trpv1+ neurons which are involved in pain perception and the main producer of CGRP, the CD8 T cell response is significantly blunted during both the primary effector and memory phases. By using Kaede X Trpv1-DTA mice, we further show that Langerhans cells (LCs) are critical cellular mediators that respond to CGRP-Ramp1 signaling during VACV immunization. This signaling facilitates their migration from epidermis to draining lymph nodes (dLNs) after s.s. immunization, where they prime antigen specific naïve CD8 T cells. Our findings thus reveals an unanticipated crosstalk between sensory neurons, LCs, and memory CD8 T cells during VACV s.s. immunization, suggesting the potential for enhancing CGRP-Ramp1 signaling to improve vaccine efficacy.

0061

Interstitial granulomatous dermatitis: A case highlighting possible associations with myeloma and TNF-α inhibitor therapy

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Interstitial granulomatous dermatitis (IGD) is an uncommon inflammatory skin condition often associated with systemic diseases and drug reactions, including TNF-α inhibitors. We present the case of a 64-year-old female with multiple myeloma undergoing pomalidomide and daratumumab therapy, who developed pruritic erythematous papules on her extremities and trunk. Histopathological examination of punch biopsies revealed interstitial histiocytic inflammation with necrobiosis, confirming the diagnosis of IGD. More recently, IGD is grouped under the umbrella term reactive granulomatous dermatitis with palisaded neutrophilic and granulomatous dermatitis and interstitial granulomatous drug eruption. Laboratory tests were conducted to rule out infectious causes and other systemic conditions, supporting the IGD diagnosis. Given the patient's underlying hematologic malignancy and immunosuppressive therapy, a thorough diagnostic workup was essential. Treatment involved the discontinuation of pomalidomide and daratumumab, after which the patient reported no new lesions, suggesting a possible drug-induced etiology. This case highlights the importance of considering both drug-related and systemic causes in patients presenting with granulomatous dermatitis, particularly those with hematologic malignancies. Comprehensive histopathological evaluation, laboratory data analysis, and clinical correlation are crucial in managing such cases. Further research is needed to elucidate the pathophysiologic mechanisms and optimize management strategies for IGD in this patient population.

0062

Severe pemphigus foliaceus consequence secondary to medication-non-adherence

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Background: Pemphigus foliaceus (PF) presents clinically with widespread superficial crusted erosions, notably lacking mucosal involvement. Serology reveals positive desmoglein-1 antibodies and histology demonstrates subcorneal acantholysis with intercellular deposition of IgG/C3 on direct immunofluorescence (DIF). PF usually exhibits a relatively benign, favorable course with remission typically achieved within the first year of consistent treatment. Case: 40-year-old male with biopsy-proven PF who returned to clinic following three years without therapy. Previous work-up included characteristic histology, DIF, indirect immunofluorescence, and positive antibody against desmoglein-1 with negative desmoglein-3. PF was previously controlled with prednisone, doxycycline, mycophenolate mofetil and topical steroids. Due to social and financial constraints he was unable to continue his medications. Over the subsequent years, his disease significantly progressed with nearly 100% BSA involvement. Physical exam was notable for diffuse, thick hyperkeratotic malodorous crusting and scaling of scalp, face, trunk, upper and lower extremities. Treatment included prednisone, doxycycline, chlorhexidine 4% liquid and weekly wound care visits for debridement of thick adherent scalp crust. Crust removal revealed a filiform mass on the occipital scalp; biopsy demonstrated angiolymphoid hyperplasia with eosinophilia despite disease control with prednisone 15mg/day. Conclusion: A case of previously controlled PF with severe progression in the setting of therapy non-adherence. Poorly controlled PF is associated with significant negative impact on quality of life and secondary complications including superinfection and sequelae of chronic inflammation.

0063

Pityriasis rubra pilaris with symmetric polyarthralgia and lymphadenopathy

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Pityriasis rubra pilaris(PRP) is a rare, inflammatory cutaneous disorder of unknown etiology and its association with inflammatory joint disease has not been well established. Here, we present a case of biopsy-confirmed PRP presenting with symmetric polyarthralgia and lymphadenopathy treated with ixekizumab, an IL-17 inhibitor. The disease typically presents with follicular papules and palmoplantar keratoderma. Paraneoplastic PRP has been proposed in several case studies and presents the possibility that immunologic dysregulation or elevated growth factors due to a primary neoplasm contribute to PRP pathogenesis. The lack of definitive evidence or clear guidelines makes PRP treatment difficult. Proposed treatments include immunomodulators, acitretin, methotrexate and isotretinoin. In the case of paraneoplastic PRP, surgical excision of neoplasms can serve as treatment. Our patient presented with multiple non-melanoma skin cancers and a nonspecific erythematous, pruritic eruption on the upper back and chest. His course was complicated by arthralgias of the bilateral hands and reactive lymphadenopathy of the axillary lymph nodes. He saw slow improvement in his rash after treatment with ixekizumab. He also had an impressive response to sonidegib, with shrinking of the large BCC tumors on his back, which were subsequently excised via Mohs. One large BCC on the left neck was removed via wide local excision. Regarding treatment of the patient's joint pain, the patient was continued on ixekizumab and started on celecoxib as needed for pain. PRP-associated arthritis is a rare component of the primarily dermatologic disorder, and it is important for clinicians to be aware of this association to adequately address joint manifestations. When applicable, paraneoplastic PRP should be explored, and underlying neoplasms should be treated.

0064

Uncovering molecular mechanisms involved in the IL-37-mediated tolerogenic dendritic cells

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Mounting evidence suggests that therapies based on monocyte-derived tolerogenic dendritic cells (tolDCs) offer significant potential for treating autoimmune and chronic inflammatory diseases and preventing transplant rejection. In our previous work, adoptive transfer of hapten-sensitized DCs from mice expressing the human IL-37b isoform (IL-37tg) significantly reduced contact hypersensitivity in wild-type recipients, illustrating that IL-37 suppresses antigen-specific adaptive immune responses through the induction of tolDCs. In this study, we investigated the molecular mechanisms underlying IL-37-mediated tolDC induction. We observed that IL37 expression was markedly upregulated in human tolDCs generated by various pharmacological agents (e.g., vitamin D3, dexamethasone). Promotor-binding transcription profiling and siRNA-mediated knockdown identified VDR, CEBPB, AP1, and SOX9 as key transcription factors driving IL-37 induction in tolDCs. Gene expression analysis further revealed IL-37-mediated changes in immune genes (CXCL1, IL10), pathways (NFkB, IL10, CD40, HMGB1), and immunosuppressive miRNAs. Consistent with these findings, the knockdown of IL37 in vitamin D3 (VitD3)-treated tolDCs reversed their tolerogenic phenotype and enhanced their ability to stimulate allogeneic T cells, underscoring the role of IL-37 in VitD3-induced tolDC function. To explore their *in vivo* efficacy, we compared IL-37-expressing tolDCs with VitD3-treated tolDCs in suppressing GVHD. While IL-37-expressing human tolDCs provided sustained GVHD suppression for over a month, VitD3-treated human tolDCs had a limited response. Furthermore, exposing VitD3-treated tolDCs to proinflammatory cytokines (IL-6 and TNFα) lowered IL-37 levels and increased IL-12 expression, suggesting diminished *in vivo* efficacy under inflammatory conditions. Collectively, our findings identify IL-37 as a critical mediator of dendritic cell tolerance, providing new insights into the molecular pathways that govern tolDC induction and maintenance.

0065

DNA methyltransferase inhibition as a strategy to potentiate anti-tumor CD8+ T cell function in melanoma.

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This work aims to elucidate the impact of inhibition of DNA methylation on the anti-tumor immune response in melanoma. Dysregulated DNA methylation is a key feature of melanoma. Abnormal DNA methylation in melanoma is associated with genomic instability, repression of tumor suppressor genes, and dysregulation of oncogene expression. With the success of immune checkpoint blockade for melanoma, new roles for DNA methylation are emerging at the tumor-immune cell interface, particularly in the CD8+ cytotoxic T lymphocyte (CTL) compartment. The development and phenotypic trajectory of CTLs is shaped by characteristic patterns of DNA methylation. Modulating the anti-tumor immune response with DNA methylation inhibitors may work in tandem to both directly impact tumor growth and the responsiveness of immune cells in the tumor microenvironment, particularly when combined with immunotherapy. Recent studies have shown that certain populations of CTLs that retain stem-like features are the key responders to immunotherapy, while exhausted CTLs lacking certain stemness markers are more refractory to immunotherapy. In a mouse model of melanoma, we have demonstrated that treatment of these hypofunctional CTLs from the tumor-draining lymph node and tumor microenvironment with the DNMT inhibitor RG108 can rescue anti-tumor function and induce the expression of key stemness and activation markers. Together these data suggest that DNA methylation plays an important role in shaping the phenotype and function of anti-tumor CTLs and posits DNMT inhibition as a potential strategy for productively recruiting CTLs into the anti-tumor immune response thereby broadening the scope of immunotherapy in melanoma.

0066

Spatial single cell RNA sequencing of cutaneous lupus reveals distinct tissue level changes with anifrolumab treatment

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Cutaneous lupus erythematosus (CLE) is a disfiguring autoimmune skin disease with no FDA-approved therapies. Anifrolumab, a monoclonal antibody targeting the type I interferon receptor, has shown promise in treating systemic lupus erythematosus, and emerging data suggest it may be highly effective in CLE. However, the molecular and cellular mechanisms underlying its effects on CLE remain incompletely understood. This study utilizes spatial transcriptomics and single-cell RNA sequencing to explore the impact of anifrolumab on gene expression and cellular composition in CLE-affected skin. Skin biopsies from uninvolved skin (n=2), discoid lupus erythematosus (DLE, n=4), and pre- and post-anifrolumab therapy samples (n=6) were analyzed. Spatial transcriptomics revealed distinct gene expression profiles across different skin compartments, with principal component analysis demonstrating that post-therapy samples shifted towards gene expression profiles characteristic of uninvolved skin. Differential gene expression analysis highlighted compartment-specific changes following anifrolumab treatment, including downregulation of inflammatory keratins (KRT6C, KRT16, KRT17) in the epidermis and upregulation of extracellular matrix genes (COL1A1, COL3A1) in the dermis. Vascular regions showed decreased expression of chemokines CXCL10 and CXCL11. Interferon-stimulated genes were downregulated across all compartments, confirming the on-target effects of anifrolumab. Notably, IFNAR1 expression increased post-treatment, particularly in the epidermis and vasculature, suggesting a potential loss of negative feedback regulation. Integration of single-cell RNA sequencing data revealed a reduction in T and B cell frequencies in lesional skin post-therapy. These findings offer novel insights into the molecular and cellular effects of anifrolumab in CLE, demonstrating its potential to restore skin homeostasis by modulating gene expression and immune cell composition.

0067

The disease-residual transcriptomic profile of B cells drives distinct Dsg-specific antibody regeneration in pemphigus

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B cells are critical effectors in the onset and relapse of pemphigus. To unravel the characteristics of pathogenic B cells responsible for disease relapse, we constructed a comprehensive B cell blueprint using single-cell transcriptomics and B cell receptor (BCR) repertoire analysis in patients with pemphigus vulgaris (PV). The study included pemphigus vulgaris (PV) patients during remission with anti-Dsg1 or anti-Dsg3 antibodies (Dsg+ PV), patients who had undergone seroconversion to negativity (Dsg- PV), PV patients during active disease (Act PV), and healthy controls.

Through integrated analyses, we characterized the cellular composition, transcriptomic landscape, and BCR features of B cell subtypes across different disease groups. Notably, we identified immunoglobulin class switching differences among Act PV, Dsg+ PV and Dsg- PV. By combining single-cell sequencing with flow cytometry, we observed an enrichment of age-associated B cells (ABCs) in Dsg+ PV, along with dysregulated regulatory B cells (Bregs). BCR lineage tracing and pseudotime trajectory analysis revealed that plasma cells in PV patients exhibit distinct developmental origins based on specific autoantibody profiles. ABCs are located at the terminal end of the B cell developmental trajectory in Dsg+ PV and share some BCR clones with plasma cells. Furthermore, we identified a unique disease-residual transcriptomic profile (DRTP) that underpins ABCs perturbations in patients with high Dsg-specific antibody during remission.

Our findings suggest that PV patients with high Dsg-specific antibody titers during remission retain a DRTP, which drives ABCs developmental programs and potentially contributes to disease relapse.

0068

Skin eruption shape-based pathological state inference for personalized treatment in chronic spontaneous urticaria

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Urticaria is a common skin disorder characterized by wheals that appear in various shapes. Chronic spontaneous urticaria (CSU), a major subtype which can persist for years or even decades, significantly impacts patients' QOL. Although it is well accepted that urticaria symptoms are induced by various mediators released from skin mast cells, including histamine, the mechanism of CSU remains elusive, largely due to the lack of animal models and specific clinical biomarkers. To address this, we have developed a novel systematic framework capable of inferring pathophysiological states from the shape of skin eruptions and linking them to patient-specific treatments. We first developed a mathematical model to capture the wheal dynamics in CSU, based on pathomechanisms inferred from *in vitro* experimental results. This mathematical model successfully reproduced the spatiotemporal dynamics of actual wheal patterns in CSU patients, and we validated it through a clinical study that compared live images of wheal dynamics with in silico data. To infer a patient's pathological state from imaging data of wheal, we constructed a novel mathematical tool that quantitatively captures the geometrical features of wheals by integrating topological data analysis with the mathematical model. Using this tool, we successfully extracted not only the geometrical features of patient's wheals but also patient-specific parameter sets that reflect their *in vivo* pathological state. With the mathematical model incorporating these patient-specific parameters, we predicted the efficacy of H1-antihistamines. This approach provides a novel framework for dermatology, enhancing diagnostic accuracy and predicting treatment efficacy by leveraging features of skin eruption shape, integrating mathematical modeling, data analysis, and accessible clinical data.

0069

Establishment of dermatopathology image encyclopedia DermpathNet using artificial intelligence empowered workflow

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Accessing high-quality open-access dermatopathology image databases for learning and cross-referencing poses a common challenge for clinicians and dermatopathology trainees. While existing platforms like VisualDx offer collections, they often require subscriptions which limit accessibility. Here, we employed an artificial intelligence (AI)-enabled workflow to curate and categorize images from the PubMed Central (PMC) database, covering 166 benign and malignant cutaneous neoplasms. We aimed to establish a comprehensive dermatopathology database for educational, cross-referencing, and machine-learning purposes. Our workflow involved retrieving full-length articles from PMC using specific keywords, extracting relevant images, and classifying them using a novel hybrid method. This approach combined deep learning-based image modality classification with figure caption analyses. Validation on 651 manually annotated images demonstrated the robustness of our workflow, with precision rates of 87.02% for the deep learning approach, 84.44% for the keyword-based retrieval method, and 92.64% for the hybrid approach. To enhance accessibility, we developed a new website DermpathNet featuring a fully annotated image database of over 7,000 images. The website organizes images based on their ontological relations and offers a user-friendly search bar for rapid retrieval of specific diagnoses. Finally, we conducted an open-ended challenge study to assess the performance of AI algorithms, including GPT-4v, on the retrieved image dataset. Our analysis revealed limitations in current AI image analysis algorithms, with a zero F1-score in the open-ended setting. Additionally, existing AI algorithms may rely on non-image features to arrive at inaccurate diagnoses. These findings underscore the current challenges in AI-assisted image analysis and need for future development.

0070

Single-cell RNA sequencing informs enhanced antitumor immunity after brentuximab vedotin and combination strategy in mycosis fungoide

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Mycosis fungoides with large-cell transformation (MF-LCT) has a poor prognosis and lacks effective therapies. Brentuximab vedotin (BV), an antigen-drug conjugate targeting $CD30^+$ cells, is approved for $CD30^+$ MF after prior systemic therapy. However, many patients suffer progression and resistance. We applied single-cell RNA and TCR sequencing on 13 paired samples from BV-treated MF-LCT patients to uncover the underlying mechanism. Post BV, tumor improved remarkably while the $CD30^+$ cell fractions remained invariable, confirming its bystander effect on $CD30^-$ cells. Notably, BV might have similar yet different impacts on $CD30^+$ and $CD30^-$ cells. Genes related to mTOR signaling and inflammatory response were enriched in $CD30^+$ tumor cells after BV, mainly driven by autocrine IL4 and IL13. The alterations in $CD30^-$ tumor cells were chiefly ascribed to IFNγ and IFNα ligands. Beyond its toxicity, BV exerted a multifaceted boost on the antitumor immunity. The antigen-presenting mediated by MHC-II molecules in tumor cells and by dendritic cells (DCs), especially mregDC derived from classic DCs, was enhanced. This led to a stronger recruitment of NK and $CD8^+$ T cells, which were less exhausted. Moreover, the inhibitory signals from Tregs (e.g. CTLA4) to effector cells were reversed, and the dominant phenotype of macrophages shifted towards M1 type. Additionally, three non-responsive lesions were included. They showed higher malignant signature of tumor cells, sparse immune cell infiltration, and impaired response to comparable IFNγ level. Their resistance to BV might stem from defective clathrin-mediated endocytosis caused by decreased AP2 subunits, increased drug efflux mediated by MDR1, and anti-apoptosis effect due to increased BCL2. Combining BV with BCL2 inhibitor, venetoclax, showed promising synergistic effect in $CD30^+$ cutaneous T cell lymphoma cell lines. These findings highlight the comprehensively enhanced antitumor immunity after BV beyond its cytotoxicity and inspires potential combination with venetoclax to overcome the drug resistance.

0071

A 3D-optimized AI imaging model for the skin tumor burden assessment of cutaneous T-cell lymphoma

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Cutaneous T-cell lymphoma (CTCL) is characterized by widespread skin patches that may progress to plaques and tumors, necessitating precise tumor burden assessment for staging, prognosis, and treatment guidance. However, existing methods, including the widely accepted modified Severity Weighted Assessment Tool (mSWAT), present significant challenges in routine practice due to their time-consuming nature and inter-observer variability. This study developed an AI model, mSWAT-Net, to estimate mSWAT scores using clinical images of CTCL patients. The model integrates three segmentation sub-modules for lesion type, body region, and overlap area segmentation, each trained on annotated images using UNet or DeeplabV3+ backbones. Notably, the overlap area segmentation sub-module addressed errors related to double-counting overlap areas in photos captured from different angles, utilizing 3,904 annotated images generated from 61 3D human images. Subsequently, mSWAT-Net was trained and validated on clinical photos with performance evaluated against junior dermatologists, experienced specialists, and objective ground truth derived from 3D imaging of CTCL patients. The three sub-modules achieved Jaccard Indices of 0.669, 0.767, and 0.738 for lesion type, body region, and overlap area segmentation, respectively. Across 2,410 images from 131 imaging series, mSWAT-Net achieved intraclass correlation coefficients (ICCs) of 0.917 and 0.858 in internal and temporal validation, demonstrating comparable performance to experienced CTCL specialists and surpassing junior dermatologists (ICC: 0.917 vs. 0.777). When compared to a more convincing ground truth derived from 3D patient imaging, the model achieved an ICC of 0.812. Follow-up datasets further confirmed mSWAT-Net's ability to closely align with bedside mSWAT scores, reliably tracking skin tumor burden and measuring treatment response. These findings highlight mSWAT-Net's potential as an accurate, automated tool for CTCL tumor burden assessment, patient follow-up, and remote consultations.

0072

Single-cell transcriptome reveals keratinocyte subclusters that contribute to altered differentiation and inflammatory responses in atopic dermatitis

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Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases, posing significant burden on healthcare systems and patient quality of life. However, AD pathogenic mechanisms remain unclear. Here, we performed single-cell RNA-seq on 116 biopsies from lesional (LAD) and non-lesional AD (NAD) skin of 42 patients and normal skin of 23 healthy controls (HC). Focused on keratinocytes (KCs), we identified basal, differentiated (DK1-7), and keratinized KC (KK1-2) clusters, uncovering several novel findings: First, KC trajectory analyses revealed altered terminal differentiation of KKs, with HC KCs differentiating from KK1 to KK2, whereas LAD showed the reverse. Second, APOD and LYZ were identified as potential pathogenic players in LAD: their expression was strongly associated with altered terminal differentiation, and their knockdown in N/TERT KCs ameliorated ER dysregulation and oxidative stress induced by IL-13 and IL-22. Third, mitochondrial and ER dysfunction were significantly enhanced in LAD DK6 but absent in other KC subclusters, suggesting DK6 as a potential pathogenic compartment in AD epidermis linked to IL-13/IL-22 activation. Fourth, cell interaction analysis highlighted TWEAK secreted by IL13+ Th2 and cycling T cells as a key signal influencing basal and differentiated KCs via upregulated FN14 receptor in LAD. Xenium spatial transcriptomics and IHC corroborated this LAD-specific interaction, solidifying TWEAK/FN14 signaling as a contributor to AD epidermal responses. Altogether, these findings connect disrupted epidermal differentiation to specific inflammatory responses in AD skin and delineate distinct epidermal compartments and inflammatory responses underlying AD pathogenesis.

0073

Spatial anatomic and microanatomic diversity across human skin at single-cell resolution

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The spatial organization of human skin underlies its many critical functions, including barrier establishment and immune surveillance. While skin physiological differences across anatomic sites are well documented, the molecular programs and cell communication networks that govern this patterning are not well understood. Given the anatomic predilection of skin disease and that disruption of proper cell communication is a hallmark of disease, there is an unmet need to better understand the molecular mechanisms of anatomic site-specific skin function. To address this, we applied single-cell resolution spatial transcriptomics profiling via multiplexed error robust fluorescence in situ hybridization (MERFISH) to characterize the anatomic heterogeneity of the skin microenvironment across 114 samples representing 15 anatomic sites from 22 donors (n_{cells}=889,421). We quantified cellular diversity across donor-matched anatomic sites and identified the spatially dynamic and stable cell types within them. Dynamic cell types such as sole-specific keratinocytes correlating with epidermal thickness and immune populations less abundant in the scalp reflected site-specific specialization. In contrast, the cellular composition of anatomic sites like the inguinal fold and buttocks was less diverse. We next defined 6 spatially resolved multicellular neighborhoods defined by cell-cell proximity, which varied in abundance across anatomic sites and provided a spatial framework for cell-cell interaction inference. Finally, we quantified spatially informed ligand-receptor interactions in each neighborhood and intersected them with interactions found in publicly available scRNA-seq data to describe cell-cell signaling networks, uncovering distinct epithelial-stromal and stromal-immune interactions across neighborhoods. In summary, these data provide a novel framework exploring the human skin microenvironment and serve as a comprehensive resource for understanding cellular neighborhoods in homeostasis that may be disrupted in skin diseases.

0074

Transcriptomic analysis reveals immune signatures associated with specific cutaneous manifestations of lupus in systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) presents with heterogenous cutaneous manifestations. However, the molecular and immunologic pathways driving these manifestations of SLE are poorly understood. Here, we leverage transcriptomics from a well-phenotyped longitudinal cohort of SLE patients to map molecular pathways linked to ten distinct SLE-related rashes. Through whole blood (N = 449) and immune cell-sorted bulk RNA sequencing on CD4+ T cells, CD14+ monocytes, CD19+ B cells, and NK cells (N = 120), we identified blood immune signatures and molecular fingerprints specific to cutaneous subtypes of SLE via differential expression (DESeq2) and pathway enrichment (GSEA) analysis. We conducted these analyses on SLE patients within the cohort with and without each of the ten cutaneous phenotypes. Subacute cutaneous lupus erythematosus (SCLE) (N = 30) exhibited broad upregulation of type I interferon, TNF-α, and IL6-JAK-STAT3 pathways, suggesting JAK and type I inhibition as potential therapies. While type I interferon signaling is prominent in some SLE rash subtypes such as acute cutaneous lupus (N = 228), discoid lupus (N = 63), and livedo reticularis (N = 56), it is unexpectedly absent in other cutaneous manifestations such as mucosal ulcers (N = 195). Pathway and cell-type enrichment analysis revealed unexpected roles for CD14+ monocytes in photosensitivity of SLE and NK cells in alopecia (N = 183), mucosal ulcers (N = 195), and livedo reticularis (N = 56). These findings illuminate the immune heterogeneity of rashes in SLE, highlighting subtype-specific mechanistic targets, and presenting opportunities to identify precision therapies for SLE-associated skin phenotypes.

0075

Advancing noninvasive diagnostics with 3D high-frequency ultrasound for early detection of inflammatory changes in cicatricial alopecia

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Three-dimensional high-frequency ultrasound (3D-HFUS) is an emerging technology that enables microstructural skin visualization, including hair follicles (HFs). We developed a novel 3D-HFUS device equipped with an automated transducer and attempted to assess its utility in diagnosing cicatricial alopecia (CA). Thirteen CA patients, including 4 lichen planopilaris (LPP), 3 fibrosing alopecia in a pattern distribution (FAPD), 2 folliculitis decalvans (FD), 2 frontal fibrosing alopecia (FFA) and 2 chronic cutaneous lupus erythematosus (CCLE) were involved along with one healthy control. Ultrasonographic data were analyzed in comparison with trichoscopic and/or histopathological findings. Contrary to healthy control, 50% of CA patients (3 LPP, 2 FD, 1 FFA) demonstrated a smaller number of follicular openings than that of follicular units (FUs), reflecting the distal disappearance of HFs. Notably, some FUs manifested a linear hypoechoic tract, namely a "tadpole" sign, at the isthmus level of transverse images. This sign was observed in 3 LPP, 2 FAPD, 1 FFA and 2 CCLE patients. Patients with perifollicular scales or erythema tend to present more tadpole signs, while the sign was absent in those with tufted hairs. Tadpole signs tended to be associated with perifollicular inflammation. Interestingly, the percentage of hair follicles with the sign showed a negative correlation with that of hair follicles accompanying perifollicular fibrosis (r = -0.483), suggesting that the sign may reflect early inflammatory changes preceding full-blown fibrosis and hair tufting. Additional analyses are indispensable to draw a definitive conclusion; the outcome suggested the usefulness of 3D-HFUS in CA diagnosis and highlighted the possibility of noninvasively detecting incipient and clinically indistinguishable pathological changes, which potentially facilitates therapeutic intervention before HFs are irreversibly damaged.

0076

Validation of the guideline to identify adherent and rolling leukocytes in skin microvasculature by reflectance confocal videomicroscopy

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We aimed to validate our previously developed guideline to identify adherent and rolling leukocytes in videos of skin microvasculature by reflectance confocal videomicroscopy. Eight raters with no prior experience in reflectance confocal videomicroscopy reviewed the published guideline for identifying adherent and rolling leukocytes in videos of human skin microvasculature. Subsequently, each rater independently counted adherent and rolling leukocytes in 113 videos in a predetermined random order. The raters were unaware that 13 videos were repeated for intra-observer variability assessment. The average error across eight raters for counting adherent and rolling leukocytes was 0.32 (95% confidence interval: 0.22 – 0.41, n = 113 videos, N = 8 raters) and 0.93 (0.52 – 1.34, n = 113, N = 8), respectively. Inter-observer reproducibility for counting adherent and rolling leukocytes was 0.41 (0.39 – 0.46, n = 100, N = 8) and 1.04 (0.95 – 1.13, n = 100, N = 8), respectively. Intra-observer reproducibility for counting adherent and rolling leukocytes was 0.10 (0.01 – 0.18, n = 13, N = 8) and 0.55 (0.27 – 0.82, n = 13, N = 8), respectively. The average error increased with an increased number of adherent or rolling leukocytes in a video. By analyzing the 113 training videos, the raters' ability to accurately identify adherent or rolling leukocytes did not change as they gained experience by reviewing more videos. Reviewing the published guideline was sufficient to train all eight raters to identify adherent and rolling leukocytes within an error of less than one leukocyte. The guideline can effectively train raters with no prior experience in analyzing reflectance confocal videomicroscopy data of skin microvasculature.

0077

Wearable computational optical sensing for inflammatory skin diseases

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Inflammatory dermatoses, such as atopic dermatitis, psoriasis, and allergic contact dermatitis (ACD), are prevalent and often chronic disorders that can severely impact patients' quality of life. ACD, affecting approximately 1 in 5 individuals, serves as an ideal model for our study of inflammatory skin diseases. The purpose of this study is to develop a wearable optical sensor for real-time, non-invasive monitoring of skin inflammation, using ACD as a model. Despite the prevalence of ACD, the diagnostic gold standard, patch testing, has been fundamentally unchanged since its introduction in 1895, remaining a time-consuming and clinic-dependent method. This study aims to address these limitations by designing and fabricating a low-cost optical sensor capable of detecting changes in skin optical properties, such as scattering and absorption, which are indicative of early inflammatory responses. To support the sensor's development, custom skin phantoms were created to replicate the optical characteristics of human tissue across the full spectrum of Fitzpatrick skin tones. These phantoms provide a controlled testing environment for calibration and validation of the device, ensuring inclusivity and accuracy across diverse skin types. A prototype sensor was engineered to perform time-lapse optical measurements and was validated on these phantoms under simulated inflammatory conditions. This study represents a critical step toward the development of non-invasive diagnostic tools for ACD. By combining custom skin phantoms with advanced sensor technology, this project lays the groundwork for future clinical studies and broader applications to other inflammatory skin diseases, ultimately improving diagnostic accessibility and addressing healthcare disparities.

0078

In vivo clinical raman spectroscopy for non-invasive quantification of calcinosis cutis in rheumatic disease

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Calcinosis cutis (CC) is a challenging sequela of rheumatic skin diseases. The nature of CC is poorly understood and there are no validated outcomes, creating a barrier to therapeutic development. Raman spectroscopy (RS) is a non-invasive method that can quantify compounds based on the scattering of incident light, allowing rapid chemical characterization. This makes RS a promising tool to better characterize the composition of CC lesions and assist with diagnosis. Thus, we performed a pilot study using RS to compare the relative composition of hydroxyapatite, collagen, and lipid in a single center, convenience sample of 15 calcinosis compared to 15 control sites in nine participants with systemic sclerosis (N=4), dermatomyositis (N=3), and morphea (N=2). The *in vivo* spectra were fitted with a non-negative least squares algorithm to determine the relative concentration of these pure compounds. For univariate analysis, Wilcoxon signed-rank test was utilized for paired data. We found, consistent across all sites, that lesional CC sites contained a higher relative concentration of hydroxyapatite (median: 0.28 (interquartile range, IQR: 0.17-0.46) vs. median: 0.04 (IQR: 0.003-0.12); p<0.001) and lower relative concentration of collagen compared to their control sites (median: 0.68 (IQR: 0.53-0.78) vs. median: 0.91 (IQR: 0.81-0.96); p=0.002). We did not find any significant difference in relative lipid concentration (median: 0 vs. median: 0; p=0.38). This non-invasive feasibility study was limited by the lack of histological confirmation, as biopsy was not indicated. As additional studies are being conducted to confirm findings, these results suggest that Raman spectroscopy is a novel method for the *in vivo* differentiation of CC from unaffected skin in patients with rheumatic skin diseases.

0079

Body mass index estimation using photogrammetry and whole-body videography

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Current proof-of-concept methods for using total body photography to assess body mass index (BMI) utilize expensive commercial whole-body scanners that are inaccessible to patients. This study aims to validate a novel approach using smartphone videos and publicly available software libraries for photogrammetry. Our approach leverages Apple's RealityKit (RK) software package and publicly available python libraries to parse a video recorded from an iPhone 16 Pro (with 4K resolution at 60 frames per second). Videos were taken of two participants in a spiral fashion beginning at the head and ending at the feet. Their heights and weights were recorded at that time. The videos averaged 600.4 megabytes in size and 89 seconds in length (with an average of 5340 frames). 1000 frames were extracted at equal intervals, per video, from which three-dimensional (3D) models were reconstructed using RK on a MacBook Pro (Model: A2485). Model volumes were calculated using Riemann summation of two-dimension axial slices. The average percent error of the slice-based BMI was 2.37% (SD=0.57%) with a mean difference of -0.6 units with 95% limit of agreement (LoA) of ±0.12 using Bland-Altman analysis, compared to commercial systems which had a mean difference of −0.1 units with 95% LoA of ±2.1 units. Literature shows that increases in BMI and height are associated with increased Breslow thickness and melanoma risk, respectively. Our approach provides a low-cost alternative to commercial whole-body scans, increasing accessibility to novel technology without compromising precision. The minimum achievable cost of our proposed system is 0.01% of the cost of previously studied commercial systems ($429 vs $435,000), and our entire process can be completed on any iPhone that supports iOS 17.0 onwards. Our approach can also be applied to determine body surface area involvement of inflammatory skin diseases, helping to more objectively monitor disease progression or improvements on therapy, in clinical and research settings. The same calculations will need to be performed on a larger, representative populations.

0080

Using large language models to identify cutaneous immune-related adverse events in response to immunotherapy.

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Cutaneous immune-related adverse events (cirAEs) are the most frequent adverse reactions among patients receiving immune checkpoint inhibitors (ICIs) and have emerged as predictors of therapeutic response. However, identifying these events is challenging due to their varied presentation and absence of specific diagnostic codes to capture their occurrence, requiring time-consuming manual chart review by trained personnel. This study explores using Large Language Models (LLMs) to identify cirAEs from unstructured outpatient and inpatient clinical notes. Unlike previous work focused on structured inpatient notes, we address the novel challenge of analyzing the far more heterogeneous outpatient documentation where most cirAEs are documented. We developed and validated our approach using a multi-institutional cohort of ICI patients from the Mass General Brigham Healthcare System and Dana-Farber Cancer Institute. We evaluated three state-of-the-art open-source language models (LLaMa-3.1, Gemma-2, and Qiwen-2.5) and GPT4o, implementing a Retrieval Augmented Generation (RAG) system utilizing a vector database and hybrid search re-ranking. We further performed example-based finetuning to increase our models' performance. On a random sample of 100 patients' notes, ChatGPT achieved the highest performance with a sensitivity of 0.82 and specificity of 0.88, while LLaMa-3.1, Gemma-2 and Qiwen-2.5 achieved sensitivities of 0.55, 0.68 and 0.23, and specificities of 0.63, 0.64 and 0.94 respectively. The LLMs vectorized and analyzed 100 patient notes in just 45 minutes (27 seconds per patient), a significant improvement over the 15 minutes typically required per patient for manual review. With more optimization, LLMs may replace manual annotation entirely, requiring a human in-the-loop only for final verification. This approach provides tremendous time savings that could unlock valuable data from unstructured clinical notes, enabling further study that could advance understanding of cirAEs, their clinical implications, and biological mechanisms.

0081

ResNet-based deep learning for atopic dermatitis diagnosis using the SCIN dataset

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The diagnosis of atopic dermatitis (AD), a chronic inflammatory skin condition, is primarily reliant on clinical expertise, which can introduce variability and limit accessibility in resource-constrained settings. This study aimed to evaluate the potential of ResNet-based deep learning models to enhance diagnostic accuracy and efficiency for AD using the Skin Condition Image Network (SCIN), a publicly available dermatological image dataset. Data preprocessing involved resizing, normalization, and augmentation to optimize image quality and mitigate class imbalances. Three pre-trained architectures, including ResNet18, ResNet50, and ResNet152, were fine-tuned via transfer learning, with performance assessed using the area under the receiver operating characteristic curve (AUROC). Among the tested architectures, ResNet18 demonstrated the best generalization with a test AUROC of 0.58, outperforming deeper models that showed overfitting tendencies. ResNet50 and ResNet152 achieved superior training metrics but underperformed on the test set, reflecting the trade-offs between model complexity and dataset limitations. Notably, the SCIN dataset's underrepresentation of eczema-positive cases constrained the models' performance and underscored the need for larger, class-balanced datasets. Our findings emphasize the promise of deep learning in automating AD diagnosis while identifying critical areas for improvement, including dataset curation, interpretability, and scalability. Future work will explore lightweight architectures for mobile deployment, aiming to democratize access to diagnostic tools and improve outcomes in underserved populations. This research represents a step towards integrating artificial intelligence into clinical dermatology, paving the way for equitable and precise care.

0082

Using random forest models to predict drug reaction with eosinophilia and systemic symptoms development from CBC parameters

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Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe adverse drug reaction that is often clinically indistinguishable from simple morbilliform drug eruptions at rash onset. We implemented Random Forest models to classify patients as DRESS-positive or DRESS-negative using CBC + differential metrics, monocyte-to-lymphocyte ratio (MLR), neutrophil-to-monocyte ratio (NMR), neutrophil-to-lymphocyte ratio (NLR), and pan-immune inflammation value (PIV: [neutrophil * platelet * monocyte]/ lymphocyte), collected within 10 days of rash onset. Models with varying tree depths (no maximum depth, 3, 5, and 7) were trained on a dataset of 261 patients, with a 75:25 train-test split. The performance of each model was compared to identify the optimal depth for accurate DRESS prediction. The no-depth model achieved the highest accuracy (90.5%) but showed signs of overfitting, with precision and recall scores of 92% for the DRESS-positive group. The 3-depth model underfit, achieving an accuracy of 71.4% and F1 scores of 0.75 and 0.67 for DRESS-positive and -negative groups, respectively. The 5-depth model had better balanced performance, achieving 81% accuracy and F1 scores of 0.82 and 0.80. The 7-depth model demonstrated the highest balance of metrics, with an accuracy of 85.7%, precision of 91%, recall of 83% for DRESS-positive predictions, and F1 scores of 0.87 and 0.84. These results demonstrate the potential of random forest models for early DRESS diagnosis. The 7-depth model, in particular, showed strong diagnostic capabilities, suggesting that routine CBC parameters could support accurate DRESS prediction at rash onset, prior to the development of additional clinical indicators.

0083

Intratumoral genetic reprogramming of murine melanoma engineers an inflamed tumor microenvironment, generates tertiary lymphoid structures, and forms CD4-CD8-APC triads

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This study examines local administration of reprogramming nanoparticles (NPs) on the melanoma tumor microenvironment (TME) in mice via application of a multiplex immunofluorescence (mIF) PhenoCycler panel that we previously developed for profiling murine TMEs. We administered biodegradable NPs that co-delivered 4-1BBL/IL-12 or GFP (control) plasmids intratumorally to B16F10 murine melanoma flank tumors with systemic anti-PD1 in a flank and lung metastasis model. We generated a tissue microarray from flank tumors, stained/imaged tissues, and analyzed proteomics data using QuPath and the FlowSOM R package. Initial analysis of flank tumors found that 4-1BBL/IL-12 NPs with anti-PD1 decreased melanoma cell density 2.3-fold ($p=0.0001$) and increased intratumoral immune cell infiltration 2.3-fold ($p=0.0002$), with increases in CD4 T-cell density ($p=0.0001$), CD8 T-cell density ($p=0.0001$), CD8/Treg ratio ($p=0.0007$), M1/M2 macrophage ratio ($p=0.0001$), dendritic cell (DC) density ($p=0.0004$), and natural killer cell density ($p=0.0031$). mIF images identified 7 total stromal tertiary lymphoid structures (TLSs) across all flank tumor sections treated with 4-1BBL/IL-12 NPs and anti-PD1 compared to 0 TLSs in control sections. We also found significantly increased antigen presentation markers (LMP2 and beta-2 microglobulin) on tumor cells, M1 macrophages, and dendritic cells following 4-1BBL/IL-12 NPs and anti-PD1. Additionally, 4-1BBL/IL-12 NPs and anti-PD1 induced 7.04 intratumoral CD4/CD8/proinflammatory antigen-presenting cell (M1 macrophages and DCs) triads/mm^2 in flank tumors compared to 0.02 triads/mm^2 in control sections ($p=0.0005$). These data suggest that 4-1BBL/IL-12 NPs and anti-PD1 potentiate a pro-inflammatory TME and coordinate an adaptive anti-tumor immune response through TLS generation, antigen presentation, and colocalized efforts of helper/effector T cells.

0084

Genome-inferred metabolic interactions and microbial coexistence in aging skin microbiomes under nutrient stress

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Microbial communities adapt to their environment through complex metabolic interactions that drive species coexistence. We present a workflow to infer species interactions from microbial abundance dynamics, integrating metabolic niche overlap, abundance rank, functional overlap differences, and environmental associations. Applied to nutrient-stressed skin, this framework reveals that competition, kin selection, and antagonism predominantly shape coexistence mechanisms in skin aging. Stronger species correlations align with higher metabolic functional overlap, while positive abundance correlations inversely relate to phylogenetic distance. Aging reduces key species like Cutibacterium acnes and Staphylococcus epidermidis while increasing stress-resistant genera such as Moraxella and Chryseobacterium. Aging also shifts metabolic functions, enhancing drug resistance and xenobiotic biodegradation while reducing carbohydrate metabolism and glycan biosynthesis. Cutibacterium acnes competes via energy metabolism, while Moraxella thrives through niche differentiation, particularly in nucleotide metabolism. Antagonistic resistance, such as polyketide metabolism, aids species like Streptococcus and Cutibacterium in countering competition. This workflow provides insights into microbial coexistence and its implications for host health.

0085

Spatial transcriptomics of hidradenitis suppurativa lesions informs key cell-cell communication networks between histological features

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Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by abscesses, draining tunnels, and fibrotic scars, most often occurring in intertriginous areas. HS pathogenesis involves follicular occlusion and rupture, followed by complex interactions between keratinocytes, immune cells, and fibroblasts that drive lesion development. To investigate these cellular interactions within HS lesions, we used spatial transcriptomics (10x Genomics Visium platform) to map gene expression to histologic features in lesional tissue from four patients with severe axillary HS (Hurley stage III). Fresh-frozen samples of HS tissue were selected for spatial transcriptomics due to superior RNA quality compared to FFPE blocks. Samples showed histopathological features characteristic of severe HS including epidermal hyperplasia, plasmocytic infiltrate, cystic structures, and epithelialized tunnels. Compared to keratinocytes in the epidermis, tunnel and cyst keratinocytes showed enrichment of gene ontology terms involved in adaptive immunity. These dermal epithelial features were also marked by increased expression of B cell marker genes (e.g., MZB1, JCHAIN, IGHG3) in the surrounding tissue. Cell-cell communication analysis of the interplay between keratinocyte features, fibroblasts, and immune cells showed significant activation of chemokine signaling. Across multiple samples, CXCR4/CXCL12 signaling between the stroma and immune cells was the most significantly activated pathway. This pathway is a known mediator of inflammation as CXCL12 leads to chemotaxis of CXCR4 positive immune cells. Most of the immune infiltrate surrounding tunnels and follicular structures expressed CXCR4, while the region of the stroma immediately adjacent to these epithelial structures additionally expressed CXCL12. Our results indicate that the CXCL12/CXCR4 axis likely plays a role in the recruitment of B cell populations to dermal epithelial structures in HS.

0086

Immunological differences in atopic dermatitis across age groups: Insights from single-cell multi-omics

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Atopic dermatitis (AD) is the most common chronic inflammatory skin disease, characterized by dry skin, eczematous lesions, and severe itching. AD affects a significant portion of the population, with a prevalence of 2.7% to 20.1% in children and 2.1% to 4.9% in adults, posing substantial socio-economic burdens. The disease exhibits high heterogeneity in its clinical presentation and progression, varying by age, severity, and ethnicity. This study investigates immunological differences in AD across age groups using single-cell transcriptomic and cell surface proteomic analysis of peripheral blood mononuclear cells (PBMCs) from 31 AD patients—12 pediatric, 14 adult, and 5 geriatric—and age-, gender-, and race-matched healthy controls (HC). After quality control, approximately 217,000 cells were analyzed comprising 28 distinct immune cell types. Initial findings revealed that effector populations including CD14 monocytes, CD4 TEM, CD4 CTL, and CD8 TCM increased in cell proportion with age, whereas naïve populations, including CD4 naïve, CD8 naïve, and B naïve cells, decreased with age. Differential gene expression and pathway analyses, focused on CD14+ monocytes across pediatric, adult, and geriatric groups, revealed distinct age-dependent trends in inflammation and immune responses. Pro-inflammatory cytokines and chemokines such as IL1B, TNF, and CCL3 showed increased upregulation with older age, while interferon-stimulated genes were predominantly upregulated in pediatric patients, highlighting a stronger antiviral response in younger individuals. These findings provide early insights into the age-dependent molecular mechanisms of AD, linking immune system development to disease heterogeneity. By evaluating single-cell immune data, this study lays the foundation for identifying age-specific biomarkers and developing machine learning models of age-dependent AD, enabling more personalized treatment strategies for AD across the lifespan.

0087

Artificial intelligence-powered teledermatology solution for skin cancer screening using 3D total body photography images

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Skin cancer, including Basal Cell Carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma, poses a significant health challenge, with early detection being critical for better outcomes. This study utilizes Artificial Intelligence (AI) to differentiate between benign and malignant lesions using 3D total-body photography (3D-TBP) images, whose quality closely resembles that of smartphone images commonly used in telemedicine. By enabling effective skin cancer screening in non-specialist settings, this approach aims to expand teledermatology initiatives, particularly in underserved regions. The SLICE-3D dataset, by the International Skin Imaging Collaboration, was used for model development. This dataset comprises 629,941 images, which includes 302,771 benign and 327,170 malignant acquired via 3D-TBP systems and includes comprehensive lesion phenotypes from diverse populations across six continents. The data were split into an 80:20 training-to-testing ratio, and AI models—including Random Forest, Logistic Regression, ResNet, Support Vector Machines, and Convolutional Neural Networks (CNN)—were evaluated. CNNs achieved the best performance with 99.3% accuracy, 80% sensitivity, 99.4% specificity, and F1 score of 0.99. By utilizing the "ugly duckling sign," which identifies outlier lesions against a patient's baseline phenotype, the AI models address lesion-selection bias inherent in traditional dermoscopic datasets. This approach ensures accurate differentiation of malignant lesions, even with lower-resolution images. Moreover, its adaptability to smartphone-quality photos enhances its potential for broader telemedicine applications. This study demonstrates the transformative role of AI-powered teledermatology in expanding early skin cancer detection in underserved regions. By enabling timely triage and intervention, this approach could significantly reduce the global burden of skin cancer.

0088

Single cell resolution expression profiling of prurigo nodularis highlights enhanced cell-cell interactions and IL-31 signaling modulations in keratinocytes

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Spatial expression profiling at single-cell resolution provides complementing information for the widely used scRNA-seq. This approach enhances our understanding of tissue architecture and cellular interactions in both healthy and diseased states. Here, we spatially profile three prurigo nodularis (PN) and two control samples using the 10X Genomics Xenium platform, and generated high-resolution cell type projection using fully annotated scRNA-seq. We conducted differential ligand-receptor (LR) signaling analysis, highlighting increased LR signals in PN skin. Notably, keratinocytes harbor the most differential LR interactions, including profibrotic signals involving TGFβ2-TGFβR1 (FC = 9.0, p = 1.2×10^{-4}), and TGFβ3-TGFβR1 (FC = 4.1, p = 9.6×10^{-10}), with primary source of ligands from fibroblasts and T cells. In addition, vascular growth factor interactions were prominent in PN skin including VEGFB-FLT1 (FC = 12.2, p = 7.1×10^{-73}) and VEGFA-EPHB2 (FC = 30.0, p = 7.3×10^{-19}), with fibroblasts and endothelial cells serving as main target cell population. We also captured interactions involving nerve cells in PN skin, relating to angiogenesis and neurogenic inflammation, involving VEGFB-FLT1 (FC = 5.0, p = 3.8×10^{-2}), TGFβ3-TGFβR1 (FC = 4.1, p = 7.3×10^{-7}), and PDGFB-PGFRB (FC = 5.5, p = 2.9×10^{-2}). By computing a module score incorporating IL-31 induced genes available in the xenium panel, we then assessed the spatial distribution of IL-31 responses in keratinocytes. This revealed prominent and highly enriched module score for keratinocyte - T-cell interactions, with the highest module score for keratinocytes neighboring Th2 cells (p = 6.4×10^{-16}). Our study underscores the pivotal role of spatial transcriptomics in uncovering candidate LR signaling pathways specific to PN and elucidating the critical interactions among keratinocytes, nerve, and T cells, offering novel insights into the pathophysiology of PN and potential therapeutic targets.

0089

Coloring the invisible – leveraging short wave infrared wavelengths to equitably visualize skin inflammation in real-time across the full spectrum of human pigmentation

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Visual and photographic assessment of disease in skin of color (SoC) is prone to misdiagnosis and underestimation of severity, as melanin's strong absorption at visible (VIS) wavelengths (λs) masks cues like erythema. Shifting from conventional VIS and near-infrared (NIR) imaging λs to short-wave infrared (SWIR, λ=1–1.7 μm) may be more equitable for those with SoC, because melanin absorbs weakly in SWIR. Unlike VIS and NIR, SWIR penetrates deeper into skin and detects chromophores like lipid and water, which are relevant to inflammatory skin disease. However, while SWIR-sensitive cameras are available, they capture grayscale images that are no more useful than black-and-white VIS photos. To fully harness SWIR imaging's potential, we need VIS-like color photography, where chromophore-specific absorption creates pathognomonic color differences. We developed multispectral imaging systems (MSI-SWIR) that map reflected light intensities at SWIR λs to RGB color channels, leveraging λ-related differences in chromophore absorption to make SWIR λs visible to the eye. Our first system used bulky halogen lamps and a motorized filter wheel to separate reflected light into specific SWIR λs, requiring subjects to stay still for several seconds to generate pseudocolor images. To overcome this limitation, our 2nd-gen system uses compact high-power SWIR LEDs with rapid electronic switching synchronized to camera frames, enabling real-time pseudocolor SWIR imaging. In lightly pigmented and SoC subjects, imperceptible wheals (23 subjects) formed by intradermal saline injection and subtle inflammatory acne lesions (9 subjects) were easily visualized by MSI-SWIR (with high contrast in SWIR pseudocolor regardless of pigmentation and poor contrast in VIS for SoC subjects). SWIR is a novel window into skin physiology that is insensitive to melanin, and thus SWIR-MSI may transform practice by providing an equitable tool for assessing skin inflammation.

0090

Data engineering improves recurrence prediction in merkel cell carcinoma

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Background: Merkel cell carcinoma (MCC) is an aggressive skin cancer with high recurrence rates. Predicting recurrence has been challenging due to limited sample sizes and heterogenous data. Here, we demonstrate that data engineering techniques applied to a small dataset can significantly improve machine learning (ML) model performance in predicting MCC recurrence. Methods: We used a dataset of 105 deidentified MCC cases from University Hospitals Cleveland Medical Center, including variables like age, sex, immunosuppression, UV exposure, tumor visibility, radiation therapy, tumor stage, and outcomes. After removing confounding columns and rows with missing data, 80 samples (22 with recurrence) remained. Correlation analysis was used to reduce feature size, which was confirmed by Least Absolute Shrinkage (Lasso) regression model. Using stratified splitting, we allocated 48 patients for training and 32 for testing. Minority upsampling was applied to the training set. We trained an extreme gradient boost (XGBoost) model using cross-validation and grid search. Results: The upsampled XGBoost model achieved an accuracy of 0.72 and an area under receiver operating characteristic curve of 0.75 on the test set. Radiation therapy was the most significant predictor of recurrence, followed by tumor stage (AJCC 8th Edition). Sex and tumor visibility were not predictive. The model's low false negative rate highlights its potential for identifying high-risk patients. Conclusions: Recurrence prediction in MCC using ML models trained on clinical data is feasible but limited by sample size and single-institution data. Future work should focus on larger sample size to improve prediction accuracy and generalizability.

0091

Artificial intelligence in dermatology: A guide for clinicians to evaluate and compare models

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This study aims to address the growing need for clinicians in dermatology to effectively evaluate artificial intelligence (AI) and machine learning (ML) tools by providing a structured framework. Dermatology, with its basis in visual data and histopathological analysis, is well-positioned to benefit from AI and ML advancements. However, claims promising enhanced diagnostic and predictive capabilities must be approached critically. We developed a checklist encompassing five domains: model development, model selection, validation, performance evaluation, and real-world impact. The checklist was refined using 25 key publications and tailored for relevance in dermatological contexts such as lesion classification, outcome prediction, and diagnostic assistance. Three case-based examples demonstrate the checklist's application in dermatology, emphasizing clinical utility. Key findings include gaps in external validation and limited use of explainability tools for dermatological AI models. Existing tools often lack fairness metrics and generalizability testing across diverse skin types and populations. For example, the checklist applied to a risk-prediction model showed the need for stratified validation to address skin phototype variability and evaluation when integrated with clinical workflows. Furthermore, randomized controlled trials are needed to quantify the impact of AI/ML tools on patient care. Our results highlight the importance of active participation in evaluating AI/ML models to ensure clinical relevance, transparency, and equity. This checklist provides a practical resource for dermatologists and clinicians, enabling informed decision-making and supporting the evidence-based integration of AI/ML into dermatological care.

0092

Digital dermatopathology analysis with artificial intelligence integration on donor-matched skin across 12 anatomical sites

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Cutaneous architecture is divided into the layers of the epidermis, dermis, and subcutis with unique histological features found in each layer. Here, we used QuPath to perform digital dermatopathology analysis on skin samples from 7 donors across 12 anatomical sites by quantifying layer thickness and cellular density across 84 samples in addition to training an artificial intelligence algorithm for detailed cellular analysis. We measured the epidermis thickness, stratum corneum thickness, and hair follicle diameters. Using the StarDist cell segmentation algorithm, we quantified cell density across the epidermal, dermal, and subcutis layers. Tissue-level analysis revealed that the sole contains mechanoprotective features, including an epidermis 6 times thicker than all other sites ($p<0.001$), despite being the least cell dense per um^2 ($p<0.05$). The dermis of the scalp and post-auricular skin were the most cell dense ($p<0.05$). Scalp hair was thicker than all sites other than elbow, popliteal fossa, and inguinal fold ($p<0.01$). The epidermis had the greatest average cell density per unit area across all sites, with a 6 times greater density than the dermis ($p<0.001$), and a 10 times greater density than the subcutis ($p<0.001$). We aim to train an artificial intelligence algorithm for the detection of cell types like keratinocytes, fibroblasts, and lymphocytes, while excluding non-cell detections and other cutaneous cells like non-nucleated erythrocytes. Once validated, the cell classifier algorithm will be tested on additional normal skin samples and can be applied to additional histological sections of human and murine skin with subsequent benchmarking for sensitivity and specificity. We propose that with additional training, the algorithm can be applied for detailed cellular detection with potential diagnostic and research applications.

0093

Comparative analysis of single-cell and spatial data from multiple fibrotic skin conditions

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Cutaneous fibrotic conditions are characterized by over-production of extracellular matrix (ECM) components, inflammation, and vascular dysregulation. However, whether these share unique or overlapping mechanisms is unknown. We performed single-cell RNA sequencing of skin biopsies from 4 healthy controls, 8 hypertrophic scars (HS), 8 keloid scars (KS), 5 morphea, 4 post-radiation morphea, 2 lichen sclerosus (LS), and 4 early systemic sclerosis (SSc) patients, along with single-cell resolution spatial profiling (Xenium). A total of 206,882 cells were annotated into 12 major cell types. This included 67,347 fibroblasts (FB) in eight clusters, with four clusters showing a profibrotic signature. These included two distinct myofibroblast (MF) subsets – COL8A1+ and TNC+ MF – that segregated along separate pseudotime trajectories. KS, HS, and morphea showed expansion in both MF subsets, but SSc showed an increase only for COL8A1+ MF. Variable immune infiltrate was seen across fibrotic diseases, with notable T cell expansion in SSc, morphea, and LS but not KS or HS. Nine upregulated genes in FBs were common to all fibrotic conditions: JUNB, FOS, RUNX1, EGR1, CCN1, CCN2 (CTGF), TNC, PRSS23, and MCL1, also validated on spatial profiling. Distinct mechanisms included enrichment of Wnt signaling terms in KS and HS but TGFb signaling terms in SSc, morphea, and LS. Of the five endothelial cell subtypes, only the pre-venular capillary (PVC) subtype also overexpressed mesenchymal cell markers. Highest ECM production by COL8A1+ MFs and the PVC endothelial cell subtype was observed in SSc, with cellular crosstalk between COL8A1+ FBs and PVCs being strong only in SSc. Our data identify a defined number of shared pathways as well as distinct disease mechanisms involving FBs and endothelial cells in different fibrotic skin conditions, with immune contribution being highly variable among different fibrotic states.

0094

A comparison between reflectance confocal microscopy and multiphoton microscopy for the in vivo study of the aging skin

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The purpose of our review article is to compare reflectance confocal microscopy (RCM) and multiphoton microscopy (MPM) for the *in vivo* study of the aging skin. Multiple databases including Google Scholar, PubMed and Clinical Key were searched and all pertinent articles since inception were included. Our study revealed that both RCM and MPM are revolutionary non-invasive imaging modalities for the *in vivo* study of the aging skin, each with its own unique set of strengths and weaknesses. RCM provides reasonably accurate information about skin aging while being relatively cost-effective (~100k). Its major limitations include low penetration depth (up to level of superficial dermis), inability to differentiate between collagen and elastin fibers and relative difficulty in interpretation of images due to absence of color staining. MPM is an excellent skin imaging modality that provides great detail about the skin at a considerable depth (up to level of deep dermis). Unlike RCM, not only does it provide colored images of the skin, it is also able to differentiate between elastin and collagen. This translates into increased ease of image interpretation and more accurate assessment of skin aging, respectively. Its major limitations are its cost (~500k) and small field of view which makes the image acquisition process time consuming. Future efforts should focus on improving the MPM commercial setups in the form of increasing efficiency (decreasing the image acquisition time) and reducing cost.

0095

3D imaging of central centrifugal cicatricial alopecia treated with 6% topical gabapentin demonstrates re-innervation of the epidermis

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To evaluate the effect of 12 weeks of twice daily 6% topical gabapentin solution, we used hybrid open-top light sheet (OTLS) microscopy to analyze 3D spatial organization and cutaneous innervation in a patient with central centrifugal cicatricial alopecia (CCCA). In this qualitative study, pre- and post-treatment biopsy specimens from affected and unaffected scalp of a patient with CCCA were stained with TO-PRO-3, PGP9.5, and CD45, optically cleared with a modified iDISCO protocol, and imaged with a hybrid OTLS microscope at varying resolutions. OTLS microscope imaging of scalp tissue produced a detailed 3D assessment of intact hair follicle structures and cutaneous innervation. This technology rapidly imaged overall tissue architecture at lower resolution (2 µm/pixel), with deeper analysis of pathologic features at higher resolution (0.17 µm/pixel). A clear increase in epidermal nerve fiber density in the affected scalp after topical gabapentin treatment was observed. Results demonstrated that 6% topical gabapentin solution was potentially linked with improved peripheral cutaneous innervation of CCCA-affected scalp tissue. 3D spatial imaging with OTLS microscopy enabled visualization and quantification of structures that are typically poorly visualized with 2D histopathologic evaluation, such as nerve fibers innervating the hair follicle and epidermis. Application of OTLS technology to samples with CCCA provided new insights into pathologic changes in CCCA and neuronal remodeling with 6% topical gabapentin. This technology addresses sampling bias inherent in traditional 2D slide-based methods by capturing the entire sample volume and by providing a comprehensive view of spatial structures. OTLS microscopy holds potential to enhance scalp biopsy analysis, offering new opportunities for histopathologic evaluation of cicatricial alopecias and correlation with trichoscopic findings.

0096

Spatial transcriptomics reveals heterogeneous schwann cell activity and poor immune infiltration in cutaneous neurofibromas

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Cutaneous neurofibromas (CNs) are benign skin neoplasms that characterize neurofibromatosis type 1 (NF1) and can cause psychological distress as well as physical pain and discomfort. The spatial organization and function of cell types within CN pathogenesis remains unclear. Better understanding of spatially divergent molecular pathogenesis is needed to inform treatment. Here, we perform spatial transcriptomic analysis on 5 CNs from NF1 patients–capturing transcripts from 970,224 8µm-wide wells–representing, to our knowledge, the largest spatial transcriptomics study of CNs to date. Unsupervised clustering of transcriptional data yielded 13 clusters corresponding to fibroblasts, Schwann-lineage cells, antigen-presenting cells (APCs), lymphocytes, endothelial cells, keratinocytes, and sebaceous glands. Expression of both MTOR (MTOR, AKT1, PIK3CA) and RAS/MAPK (HRAS, KRAS, RAF1) pathways, known to be upregulated in NF1, was found in all CNs. Gene set enrichment of clusters identified upregulation of vascular development (p=1.08e-05) by fibroblasts and APCs throughout superficial areas of the tumors, suggesting attempted vasculature redirection to CNs. Spatially-aware clusters identified a deep apoptotic core of Schwann cells (enriched for apoptosis, p=1.05e-19) surrounded by superficial tumor regions with Schwann cells and proliferative infiltrating cells such as fibroblasts and endothelial cells (upregulated cell motility, p=8.82e-06), along with a peripheral grenz zone and epidermis. Immune cells largely clustered around superficial CN layers and the periphery, demonstrating little infiltration. This suggests that deep and poorly perfused regions of CNs lead to Schwann cell apoptosis, and lack of vasculature may inhibit deep infiltration of tumor-targeting immune mechanisms. Therapies aimed at improving immune infiltration of CNs may facilitate tumor regression.

0097

Testing the performance of a deep learning-based mobile application with non dermatologist-phyiscians in the diagnosis of common skin diseases.

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Background: Artificial intelligence-driven mobile phone applications had been used recently in the diagnosis of skin cancers to screen for diabetic retinopathy. This study shows that the use of mobile phone applications can effectively diagnose common skin diseases by primary care physicians. This is the first study done on an AI-driven app for the diagnosis of common skin disease, previously it was used for the diagnosis of skin cancers. Objective: To test the sensitivity, specificity, and positive and negative predictive values of AI-based mobile app as compared to dermatologist diagnoses. Methods: Convolutional neural network-based algorithm was trained with clinical images of 40 skin diseases. The result of this app was compared against the dermatologist's diagnosis. Results: 1,004 patients (675 males and 329 females, age range: 18–74 years), 670 belonged to the group of 40 diseases which was included in the app, and 334 belonged to 41 other diseases not represented in the app training. Only the disease classes with more than 10 patients were included in the analysis. The overall top-1 accuracy of the app at 72.04% was significantly higher than the top1 accuracy of two non-dermatologists at 45% and 34.85%, respectively. The area-under-the-curve (AUC) values for the algorithm for most of the diseases were in the range of 0.8–0.9 except for herpes zoster and urticaria with an AUC of around 0.75. The NDPs were able to diagnose common diseases with distinctive and easily recognizable morphology like acne, alopecia, eczema, and keloid with accuracies comparable to the app. Conclusions: The artificial intelligence-driven app has high diagnostic accuracy compared to NDPs and is, therefore, a useful, point-of-care, clinical decision support tool for physicians to detect a range of common skin conditions.

0098

Identification of novel druggable targets for rosacea: Triangulating evidence from multi-omics mendelian randomization, transcriptomic, and animal experiments

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To identify potential druggable targets for rosacea, we conducted a comprehensive study that integrated evidence from multi-omics Mendelian randomization (MR), human skin transcriptomics, and animal experiments. The MR study included 1,529 genetically proxied druggable proteins derived from three large European ancestry studies, and a meta-analysis was performed to obtain more accurate causal estimates. After accounting for multiple comparisons, pleiotropy and heterogeneity, we identified 28 proteins linked to rosacea risk, 23 of which were validated in at least two independent datasets. Further sensitivity analyses confirmed the robustness of these results across different algorithms, instrument selection criteria, and rosacea subtypes. Following validation through colocalization, differential gene expression analyses and summary-data-based MR (SMR) using tissue-specific transcriptome-wide data, the targets were categorized into four tiers, with 18 targets in Tiers 1–3 considered reliable. Then, we queried candidate drugs that may target these 18 proteins, and selected three (lipoic acid, ARN19702 and lithium citrate) for experimental validation. The ARN19702 (Tier 2) and lithium citrate (Tier 3) were found to alleviate skin thickness, angiogenesis, and inflammatory cell infiltration in rosacea-like mice model, whereas lipoic acid (Tier 1) did not. Molecular docking elucidated that ARN19702, and lithium citrate strongly bound to NAAA and IMPA1, respectively, whereas lipoic acid failed to bind to POR. Furthermore, the Phewas analysis found no significant side effects for these 18 targets. This study provides robust, triangulated evidence identifying 18 novel druggable proteins genetically linked to rosacea risk. Candidate drugs targeting these proteins may be repurposed for the treatment of rosacea.

0099

High-resolution transcriptomic atlas of inflammatory skin diseases

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Atopic dermatitis (AD), psoriasis (PSO), hidradenitis suppurativa (HS) and vitiligo (VIT) are inflammatory skin diseases with distinct immunophenotypes. As we hypothesized that these diseases may share immunopathomechanisms for targeted therapeutics, we aimed to profile and identify the shared pathogenic loop as well as the unique molecular mechanisms of each disease. An atlas of over one million cells was generated by conducting single-cell RNA sequencing (scRNAseq) on lesional tissue biopsies and peripheral blood mononuclear cells (PBMCs) from approximately 80 patients. We report the immune signatures of each disease in both the active lesion and circulation. For keratinocytes (KC), the frequency of proliferating KC increased in both types of PSO, plaque and pustular, while that of basal KC was decreased in AD and PSO compared to control or VIT lesions. In AD lesions, T helper type (Th) 2 and Th22 responses were elevated, while in PSO lesions, Th1 and Th17 responses were upregulated. In the circulation of HS patients, Th1, Th2, Th17 and Th22 responses were elevated suggesting its complex immune response. Other disease-specific signatures in immune cell subsets were explored, including regulatory T cells, which were elevated in the circulation of AD patients, and macrophages, which were elevated in PSO lesions. We validated our findings at the protein level using multiplex immunofluorescent imaging (MACSima) and plan to validate using mass cytometry. In addition, a comprehensive spatial atlas is simultaneously being constructed using spatial transcriptomics profiling with a customized skin panel (Xenium). These integrated approaches aim to identify unique molecular mechanisms of inflammatory skin diseases, offering insights for the development of personalized treatment strategies and prediction of treatment response.

0100

Redefining the origins and pathogenesis of epidermal cysts using spatial transcriptomics

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Hematoxylin-eosin (H&E) staining has been a cornerstone of histopathology for over a century, enabling morphological studies of tissues. However, functional insights into tissue dynamics remain limited. The advent of spatial transcriptomics, allowing molecular and spatial analyses, opens new avenues for understanding complex pathologies. Epidermal cysts, benign tumors common in dermatology, were long believed to originate from hair follicle infundibula. However, their presence in hairless areas such as palms and soles challenges this view. To investigate epidermal cyst origins, we analyzed a specimen using 10x Genomics' Visium Spatial Gene Expression platform. The cyst epithelium exhibited a unique expression profile distinct from both epidermis and hair follicle infundibula. While keratinization resembled the epidermis, lipid metabolism and immune response pathways were absent. Instead, the epithelium showed active inflammation and tissue remodeling. This discovery contradicts the theory of cyst formation due to clogged pores, providing a new explanation for their occurrence in hairless regions and resolving a long-standing dermatological question. Spatial analysis revealed ripple-like gene expression patterns surrounding the cyst, with an inflammatory core transitioning into tissue remodeling. Functional enrichment analyses highlighted tissue changes undetectable with conventional techniques. These findings underscore spatial transcriptomics' ability to provide spatiotemporal insights into tissue pathology. Our results challenge traditional paradigms of epidermal cyst origins and highlight the necessity of integrating spatial transcriptomics into dermatopathology. This approach enables unprecedented insights into pathogenesis, advancing precision diagnostics and therapeutic strategies.

0101

Skin cancer diagnosis with electrical impedance dermography

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Machine learning (ML) can provide objective and rapid non-invasive assessment of potential skin cancers to guide biopsy and management decisions. While ML has been applied to large datasets of dermatoscopic images, when combined with electrical impedance dermography (EID), ML can detect electrical differences not apparent in images and improve diagnostic accuracy. We report the validation results from our URSKIN device and ML analytics in a blinded study. Thirty-five lesions scheduled for biopsy were measured, including 10 basal cell carcinoma (BCC), 11 squamous cell carcinoma (SCC)- in-situ, 8 invasive SCC, and 6 seborrheic keratosis (SK). We trained 10 ML classifiers to make the following diagnostic predictions: Healthy (adjacent skin) vs. SK, Healthy vs. SCC, Healthy vs. SCC-in-situ, Healthy vs. BCC, SK vs. SCC-in-situ, SK vs. SCC, SK vs. BCC, SCC vs. SCC-in-situ, SCC vs. BCC, and SCC-in-situ vs. BCC. The models were tested on each of the 10 comparisons for 100 models trained and tested per dataset type. The percent correct diagnoses was determined by the number of accurate predictions from the total applicable diagnoses in a comparison. The Adaboosting random forest model yielded 100% correct diagnoses (AUC 0.747), specificity of 94%, and sensitivity of 56% for the healthy tissue vs BCC comparison. The models performed less well for the other comparisons. Despite the use of a small training-test set from our previous pilot BCC and SCC studies, this blinded study achieved promising accurate predictive capability for BCC, SCC, and SK. These results warrant further work to obtain larger training sets to improve accuracy of EID.

0102

Single cell sequencing reveals the presence of cancer-associated fibroblasts in cutaneous neurofibromas

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Cutaneous neurofibromas (CNs) are a manifestation of neurofibromatosis type 1 (NF1) that cause significant psychosocial burden to patients. Little is known about the cellular interactions within CNs. We assessed the cellular makeup of 7 CNs from 6 different NF1 patients using single-cell RNA sequencing analysis (scRNA-seq). We determined the genetic markers for each cell type cluster and ascertained the cell identity for each cluster based on canonical gene markers. ScRNA-seq generated 40,490 cells after filtering out low quality cells. We identified clusters of the following cell types (in descending order, based on proportionality): fibroblasts, which represented the largest portion of the cell population, followed by antigen-presenting cells, T cells, neuronal/glial cells including Schwann cells, vascular endothelial cells, lymphatic endothelial cells, keratinocytes, smooth muscle cells/pericytes, and melanocytes. Using the CellChat function, the most numerous cell-cell interactions occurred between fibroblasts and neuronal/glial cells, followed by fibroblasts and lymphatic endothelial cells. We identified 12 clusters of fibroblasts, and using markers of "cancer-associated fibroblasts" (CAFs) from prior literature of porcine plexiform neurofibromas containing the markers CXCL2, IL6, CCL2, and markers of other types of cancers, determined that four fibroblast clusters may contain CN-associated-CAFs, representing 32.2% of fibroblasts. We identified a subtype of CAF which showed highly enriched vascular endothelial growth factor (VEGF) related pathways, suggesting a potential pathway for targeting future therapies for CNs.

0103

Single-cell spatiotemporal profiling of type 2 skin inflammation reveals coordinated multicellular neighborhood and cell-cell communication network remodeling

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This study aims to elucidate critical cell-cell signaling interactions occurring in type 2 skin inflammation through the use of spatiotemporal transcriptomic profiling of MC903 and oxazolone murine atopic dermatitis (AD) models. To date, it remains poorly understood how celltype communication in AD and other type 2 skin diseases is dysregulated to initiate and exacerbate inflammation. We used unbiased approaches of single-cell spatial transcriptomics (MERFISH) and matched scRNA-seq to profile 39 different cell types captured across 16 tissues at various timepoints during MC903- and oxazolone-treated murine type 2 skin inflammation. Through mapping multi-cellular neighborhoods using CellCharter, we established a framework to observe cellular composition and signaling pathway remodeling occurring in the epidermal and dermal regions across time, including one epidermal, one dermo-epidermal junction (DEJ), and two dermal inflammation-associated neighborhoods (IANs). Epidermal remodeling was marked by the activation of stressed keratinocytes (KCS) exhibiting Tslp and Il33 alarmin expression, and at the DEJ, where these KCS were predicted to signal to papillary fibroblasts and immune cells such as basophils. Dermal neighborhood remodeling was marked by chemokine-producing pro-inflammatory fibroblasts (PIFBs) that transcriptionally resemble human AD fibroblasts recently identified in at least four independent human AD scRNA-seq studies. These PIFB emerge spatially in the papillary dermis, increasing depth into the reticular dermis with more severe inflammation. PIFBs were prominent in dermal IANs containing elevated immune infiltrate, with high predicted chemokine signaling with basophils, CD4 T cells, macrophages, and dendritic cells by Cellchat analysis. In summary, we define the progression of inflammation through the spatiotemporal coordination of multicellular neighborhoods and provide a comprehensive spatial transcriptomic resource of type 2 skin inflammation for further exploration.

0104

Clonotype neighbor graph analysis (CoNGA) reveals tumor-infiltrating population of EBV antigen-specific T-cells in cutaneous T-cell lymphoma

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Despite the morbidity associated with cutaneous T-cell lymphoma (CTCL), its pathophysiology remains incompletely understood, and a definitive antigen driver has yet to be determined. We aimed to identify reactive tumor-infiltrating lymphocytes (TILs) in CTCL tumor skin biopsies and characterize their antigen specificities. To this end, we utilized Clonotype Neighbor Graph Analysis (CoNGA), a novel computational tool for uncovering functionally related groups of T-cells, to analyze publicly-available single-cell TCR and gene expression sequencing data. From a cohort of 10 patients with Mycosis Fungoides, three were found to harbor TILs with TCRs specific for Epstein-Barr Virus (EBV) epitopes. In two of these patients, an EBV-specific clone was found to be among the 15 most expanded clones within the skin tumor sample. Gene expression analysis revealed upregulation of genes such as GZMA, GZMK, and CCL5, suggesting a cytotoxic effector function of these clones. These findings highlight a potential role for EBV antigens in previously-infected patients with CTCL, possibly contributing to enhanced lymphocyte stimulation by these epitopes within the tumor microenvironment. A broader analysis of EBV-reactive T cells in a larger cohort of CTCL patients could provide deeper insights into their role in anti-tumor immunity. Additionally, this study demonstrates the utility of CoNGA in uncovering antigen-specific T-cells within heterogeneous tumor samples. The algorithm allows for the discovery of T-cell populations beyond the malignant clone that share antigen specificity and function, providing a powerful means of understanding anti-tumor immune dynamics and identifying novel therapeutic targets.

0105

Addressing generalizability and clinical utility of AI-enabled virtual-IHC for melanocytic cells

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The use of histologically stained slides has long had an important role for diagnoses, with immunohistochemical (IHC) stains used to confirm important cell types and regions of interest needed for diagnosis. However, the material and monetary cost to regularly produce these stains, when necessary, can be costly or difficult for cases with limited sample availability. We developed a virtual IHC method using a deep learning model to perform segmentation of melanocytes from paired adjacent Melan-A IHC and H&E whole slide images (WSI) for the diagnosis of melanoma, as proof of principle. We developed a pipeline in which image processing was used to generate melanocytic masks from the paired slides without human annotation and then trained and evaluated on 23 WSI from a range of diagnostic classes (benign\dysplastic nevi, melanoma-in situ and malignant melanoma), achieving a mean intersection-over-union (mIoU) of 0.65. The robustness of the model was then tested against domain shifts from a different scanner (23 WSI), batch (49 WSI) and negative control vitiligo cases (23 WSI). We found that although these datasets showed initial decreased performance, we could recover both mIoU and visual performance with minimal fine-tuning of the model or the addition of out of domain data for the case of vitiligo. In a test of clinical utility, we also found no significant difference in diagnostic accuracies when a panel of 3 dermatopathologists were asked to make diagnoses with the actual IHC WSI compared with virtual IHC WSI. Together we find that the use of virtual IHC can closely match that of a real IHC and that with fine-tuning the model can be robust to different domain shifts.

0106

Single-cell and spatial transcriptomic analysis reveals regulatory Th17 cells and keratinocyte interactions driving inflammation in palmoplantar pustulosis

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Palmoplantar pustulosis (PPP) is a chronic inflammatory skin disorder characterized by pustules and scaling on the palms and soles, with a significant impact on patients' quality of life. Despite the involvement of IL-17 pathways in PPP, treatment with IL-17 inhibitors has yielded mixed results, suggesting a need for a more detailed understanding of its immune mechanisms. In this study, we employed single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics to analyze skin biopsies from PPP patients and healthy controls, uncovering complex immune dynamics in PPP pathogenesis. Our analysis identified distinct immune and keratinocyte populations in PPP lesions, revealing a unique regulatory Th17 cell subpopulation that produces IL-17A, IL-17F, and IL-26. These regulatory Th17 cells, which exhibit features of both Th17 and regulatory T cells, engage with IL36G+ supraspinous keratinocytes, amplifying the inflammatory response. Additionally, we observed significant expression of TNFRSF18 and TNFRSF4, which are implicated in regulating immune interactions within PPP lesions. These findings suggest that PPP is driven by a complex interplay between regulatory Th17 cells and keratinocytes, mediated by immune signaling pathways such as OX40/OX40L and GITR/GITRL. By identifying these key cellular interactions and signaling networks, we highlight potential therapeutic targets for PPP, including IL-26, OX40, and GITR, which could pave the way for more effective, targeted treatments. This work provides valuable insights into the immune landscape of PPP and underscores the importance of personalized therapeutic strategies.

0107

Spatial transcriptomics reveals molecular determinants of mortality in thin melanoma

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Despite their excellent prognosis, thin cutaneous melanomas (<1 mm) account for one-quarter of total melanoma deaths. Current prognostic factors demonstrate limited accuracy in thin melanoma, precluding identification of high-risk individuals who could benefit from adjuvant therapeutic strategies. Here, we apply spatial transcriptomics to profile a nested case-case series comprising 15 fatal and 15 non-fatal thin melanomas, individually matched by age, sex, tumour thickness, and follow-up duration. Relative to non-fatal cases, fatal cases demonstrated differential upregulation of multi-gene signatures associated with two independent tumour phenotypes: an invasive-state cluster driven by epithelial-mesenchymal transition, and an immune-cold cluster characterized by immunosuppressive ligand-receptor interaction and reduced lymphocyte proportions. On prognostic analysis, we identified a five-feature combination that demonstrated a sensitivity of 75% and specificity of 91% for predicting mortality in a validation cohort of 23 additional patients. Broadly, we present a spatial transcriptomics framework for the discovery of prognostic features in thin melanoma, which could enhance stratification and inform clinical management of early-stage disease.

0108

Exploring large language models for dermatology inbox management: A solution for provider burnout

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Background: Studies have shown that dermatologists spend a significant portion of their workday responding to patient messages, with recent data identifying inbox management as a leading contributor to provider burnout and decreased job satisfaction. Large Language Models (LLMs) have demonstrated capabilities in natural language processing and content generation across various industries, suggesting potential applications in clinical communication management. Methods: This paper explores the theoretical framework and practical considerations for implementing LLM assistance in dermatology inbox management. We review current challenges in message handling, examine available LLM technologies, and analyze potential integration strategies within existing electronic health record systems. Key considerations include message categorization, response automation capabilities, provider oversight requirements, and patient privacy protection. Results: Our analysis suggests that LLM implementation could streamline common inbox tasks such as medication inquiries, appointment scheduling clarifications, and basic skincare questions. Critical factors for successful integration include maintaining appropriate provider oversight, ensuring HIPAA compliance, and developing dermatology-specific training datasets. Potential benefits include reduced provider time burden, standardized response quality, and improved work satisfaction while maintaining patient care quality. Conclusion: LLM technology presents a promising solution for dermatology inbox management challenges. Future research should focus on developing specialized dermatology language models, establishing safety protocols, and conducting controlled trials to measure the impact on provider workload and patient satisfaction.

0109

Large-scale proteomic analysis across the inflammatory skin disease spectrum reveals widespread immune dysregulation with distinct biomarker signatures

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Background: Although the molecular characteristics of inflammatory skin diseases are under investigation, a large-scale proteomic expression study of the most common skin conditions is lacking. Objective: To evaluate the tissue proteomic signature of alopecia areata/AA, atopic dermatitis/AD, psoriasis, hidradenitis suppurativa/ HS, and vitiligo and determine biomarkers associated with increased disease severity. Methods: In a cross-sectional study, we assessed 1472 inflammatory, cardiovascular, and exploratory proteins using the OLINK high-throughput Explore panel in moderate-to-severe AA (n=40), AD (n=44), psoriasis (n=32), HS (n=12), and vitiligo patients (n=25) compared to healthy-matched controls (n=52). Results: Our results reveal distinct and shared patterns of immune dysregulation across inflammatory skin diseases. HS contained the greatest dysregulation compared to controls, followed by psoriasis, AA, AD, and vitiligo. Differentially expressed proteins amongst HS and psoriasis patients include markers related to T cell activation (IL2RA/CCL19/CD40LG), innate immunity (IL6R/IL18), Th1 (IFNGR1/CXCL9/CXCL10/CXCL11/IL12B), and Th17 (IL17A/IL17F/PI3/IL19/CCL20). AA and AD contain dysregulated markers related to dendritic cells (ITGAM/CD83), Th1 (IFNGR1/ CXCL9/CXCL10/ CXCL11), and Th2 (IL4R/OX40/IL7R/eotaxin-1/CCL13/CCL26; all FDR<.05). Pathway analysis revealed dysregulation across several immune/cardiovascular axes, including JAK/STAT/atherosclerotic proteins. Multiple positive correlations existed between key immune markers (OX40/IL7R/IL17F/TNF/IL6) and clinical severity scores (P<.05). Conclusion: This study revealed shared and distinct molecular protein expression levels across the spectrum of inflammatory skin diseases, suggesting that shared and targeted therapeutic approaches may optimize patient outcomes.

0110

Comparative single-cell transcriptome analysis reveals ethnicity-specific immune activation in psoriasis.

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Psoriasis (PSO) is a chronic inflammatory disease with varying clinical presentations and severity among populations. While large plaque psoriasis is more common in Caucasians, Asians typically present with small plaques despite increased levels of IL-17-related inflammatory cytokines. We performed single-cell transcriptomics analysis on skin biopsy samples from Korean PSO patients to comparative analyze the Caucasian PSO and healthy controls (HC). We analyzed a total of 281,731 cells and identified TNC+IL1R1+ fibroblasts and CCR7+LAMP3- Myeloid cells, both of which were significantly increased in PSO lesion compared to HC. TNC+IL1R1+ fibroblasts which exhibit activation of the TNF pathway and contribute to type 3 inflammation. By expression of CCL2 and CCL19, TNC+IL1R1+ Fibroblasts also promote the migration of myeloid cells, which contribute to keratinocyte proliferation and activation adaptive immune response. Among these myeloid cells, CCR7+LAMP3- myeloid cells were significantly enriched in Caucasian lesions compared to HC and Asian lesions. These cells expressed IL23A and CCL20 contributing to the radial expansion of psoriasis. We suggest that the progression of psoriasis is driven by specific fibroblasts and myeloid cells, which together amplify inflammation and tissue remodeling. These findings highlight the need for ethnicity-specific therapeutic strategies in psoriasis management.

0111

Predicting the interaction between RGR and TRPV1 using chai-1

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RPE-retinal G protein-coupled receptor (RGR), as an important photoreceptor protein, is involved in various physiological functions in the human body, such as the perception of light signals and the regulation of the retinaldehyde cycle. Our previous research found that RGR is also expressed in the skin and influences the proliferation and migration of keratinocytes. In recent experiments, we found that the expression of RGR in the skin also be regulated by temperature (data not show). TRPV1 (Transient Receptor Potential Vanilloid 1) is a non-selective cation channel protein and a typical heat-sensitive ion channel. In previous studies, it was found that RGR and TRPV1 appear to share common downstream factors, such as Ca^{2+}. All these observations may indicate that the RGR and TRPV1 have certain interaction or even form complex. To investigate whether the RGR and TRPV1 interact during physiological processes, we used the Chai-1, an open-source tool, to predict the protein complex of RGR and TRPV1. By using the Chai-1 default parameters, several protein complex structures were successfully generated. Using the TRPV1 (PDB Code: 8x94) protein structure chain A aligned with the protein complex TRPV1 part, a RMSD value, 2.01, was got, which indicated that the predicted protein complex accuracy is acceptable. Further analysis was conducted for the predicted protein complex, a special loop (DTCPDPLDGDPNSRPPP) from TRPV1 was identified which shows strong interaction with RGR protein, lots of hydrogen-bonding were found between this loop and RGR protein. This exploration work suggest that the two proteins may interact. In future studies, we will continue to study the potential interaction through molecular dynamic simulation and experimentally validate their potential interaction and determine whether they jointly regulate skin physiological functions.

0112

Accurate visual diagnosis of pathology-proved subungual melanoma among longitudinal melanonychia by deep learning surpasses that by board certified dermatologists

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Subungual melanoma remains a significant issue and poses an important diagnostic dilemma to making biopsy or observation. Deep learning has revolutionized to assist in visual diagnosis for several skin diseases, including melanoma. However, less is known whether deep learning could assist in the clinical diagnosis for the longitudinal melanonychia for subungual melanoma. This study aims to develop an effective method to achieve high quality of image recognition, assisting the diagnosis for subungual melanoma. A dataset including 260 nail images of melanonychia with pathology-proved diagnoses was adopted. The data was trained by validated by ensemble deep learning (EDL) with fusing a set of convolutional neural networks (CNNs), coupling with data augmentation and transfer learning to enhance the recognition. A combination of EDL with CNNs were compared for the accuracy. The results show that among the CNNs, the accuracy for a single CNN model, ResNet50, reached an accuracy of 87.31%. Moreover, the accuracy for EDL reached 91.15%, which is superior to that of the existing model by 7.3%, and that of board-certified dermatologists by 21.06 %. Although limitation applies to the single source from a referral hospital, this study developed a good model by EDL in increase the accuracy for detecting subungual melanoma. The accuracy of this model, which is superior to the currently existing model and the dermatologists, could be used to assist to help the clinical dilemma in dealing with longitudinal melanonychia.

0113

A high resolution spatial transcriptomic atlas of korean atopic dermatitis

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Atopic dermatitis (AD) is a chronic skin disorder linked to a Th2-dominant immune response. Recent studies have identified Asian-specific AD phenotypes, but their findings are limited by small sample sizes and bulk RNA or single-cell sequencing. This underscores the need for atlas-scale immune phenotyping combining single-cell RNA sequencing and spatial transcriptomics. This study explores immune pathways in AD at single-cell resolution, focusing on fibroblasts in lesional and non-lesional skin, and analyzing blood samples to capture local and systemic immune changes. Standardized protocols were followed for skin biopsy and blood sample collection from pediatric, adult, and elderly patients, and healthy controls. A total of 41 skin and 46 blood samples, containing 210,000 and 380,000 cells, respectively, were analyzed. Single-cell RNA sequencing identified immune signatures linked to Asian AD endotypes, disease severity, and age-related differences. The baseline immune profile of the Asian AD phenotype shows a decrease in the Th1 axis and upregulation of the Th17 axis, with Th17 abundance increasing with age. This atlas will expand our understanding by unraveling new immunophenotypes of AD, contribute to precision medicine, and enable cross-disease comparisons. The atlas, incorporating datasets from Singapore and Japan, will be released in late 2025.

0114

Integrating clinical controls in convolutional neural networks for prick test classification

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Prick testing is a diagnostic tool used to identify allergens involved in immediate-type (Type 1) hypersensitivity reactions. However interpreting prick test results can be challenging due to the variability of skin reaction intensity and dermatographism, which can lead to false-positive and false-negative results. In practice, clinicians may use a positive control (histamine) and a negative control (saline) to distinguish true allergen reactions from artifacts. These challenges extend to convolutional neural network (CNN) image classification models, which may limit accuracy and reproducibility of results. This study aimed to evaluate whether incorporating positive and negative controls into CNNs improves their classification performance for interpreting prick test results. We performed a retrospective analysis of prick test images collected from 2023-2024. For training and validation, a total of 650 images from 33 subjects were collected, while a separate testing dataset comprised of 204 images from 10 subjects. The majority of subjects in both cohorts were skin types I-II (70% in training, 77.4% in testing). Two neural network models were trained: one that used only the allergen test image as the input, and another that integrated allergen test images with their corresponding positive and negative controls as the input. Each model was a CNN with two convolutional layers and a final dense layer with a sigmoid activation for binary classification. Performance of both models were based on metrics such as area under the receiver operating characteristic curve (AUC) and area under the precision-recall curve (AUPRC). The model incorporating controls achieved higher AUC (0.91 vs. 0.74) and AUPRC (0.54 vs. 0.30), suggesting that including controls improved overall classification performance between positive and negative prick tests. This research highlights the potential utility of integrating positive and negative controls into CNN models to enhance their diagnostic accuracy for allergy testing.

0115

Single cell analysis of senile atopic dermatitis in Korean population

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Atopic Dermatitis (AD) is a chronic inflammatory skin disease accompanied by pruritus. It is classified into infancy, childhood, adolescence (including adulthood), and old age, each presenting distinct pathological characteristics. While most studies to date have focused on populations up to adulthood, the growing elderly population underscores the need for research on senile AD. AD is generally considered a Th2-skewed disease. However, in Asian populations, a pronounced shift toward the Th17 axis has been observed compared to Caucasians, and there are reports of strong Th17 signatures at the serum level in senile AD patients. Building on these previous findings, we performed single-cell RNA sequencing (scRNA-seq) on blood and pathological tissue samples from a Korean cohort of senile AD patients. Specifically, we collected skin punch biopsy samples from nine AD patients (including lesional and non-lesional sites) and six healthy controls, and additionally obtained a total of 15 blood samples from both patients and controls to characterize the unique immunological profile of senile AD. Through single-cell analysis of these samples, we identified 15,064 skin-derived cells, and plan to comprehensively evaluate the immune environment of senile AD by comparing these data with our in-house inflammatory skin disease atlas. Through this approach, we aim to determine whether a distinct immune axis exists in senile AD that diverges from the conventional Th2-dominated axis of AD. Furthermore, we seek to elucidate the unique changes observed in keratinocytes and fibroblasts, as well as their immunological interactions in senile AD. Ultimately, this study will provide deeper insights into the age-related immunological dynamics of AD and contribute to the development of tailored diagnostic and therapeutic strategies for senile AD.

0116

ESK-001, an allosteric TYK2 inhibitor, inhibits TYK2-and psoriasis-relevant biomarkers in skin using spatial transcriptomics

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The pathogenesis of plaque psoriasis is driven by dysregulated signaling of the IL23/IL17 axis. ESK-001 is an oral, highly selective small molecule allosteric inhibitor of TYK2. In the ESK-001 STRIDE trial, a phase two placebo-controlled 12-week trial in 228 moderate-to-severe plaque psoriasis patients, the primary and secondary endpoints were met at the highest doses with clear dose dependent improvement in efficacy. STRIDE undertook bulk and spatial transcriptomic analysis in patients to characterize TYK2- and psoriasis-relevant biomarker inhibition in response to ESK-001. Skin punch biopsies from 40mg BID, 40mg QD, and placebo dose arms were collected at baseline and week 12 and split for bulk and spatial transcriptomics. Spatial transcriptomics was performed using the 10X Genomics Visium HD platform and analysis with Space Ranger. For bulk RNAseq, reads were aligned to the genome and transcriptome using STAR, and transcripts were quantified with Salmon. Spatial transcriptomics show high expression of TYK2- and psoriasis-relevant biomarkers in the epidermis of baseline lesional samples. Expression of biomarkers KRT16 and TYK2-relevant cytokines are decreased in baseline non-lesional samples compared to lesional. After 12 weeks of ESK-001 administration, lesional samples show significant decrease in expression of KRT16 and other psoriasis-relevant biomarkers in the epidermis in 40mg BID and 40mg QD dose groups compared to placebo. These results align with bulk RNAseq analysis of paired punch biopsies where the same biomarkers returned to baseline non-lesional expression post ESK-001 administration. Disease-relevant bulk and spatial transcriptomic analysis in skin tissue shows decreased expression of key psoriasis biomarkers in non-lesional skin compared to lesional. Analysis after ESK-001 administration further indicates a return of key psoriasis biomarkers to non-lesional baseline levels.

0117

WITHDRAWN

0118

Discovery of a potent anti-wrinkle peptide from natural origin through rational design

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Reducing the signs of skin aging can be achieved by targeting several biological pathways. One effective strategy is to conceal wrinkles by relaxing the underlying muscles in the dermis. At the neuromuscular endplate, the muscular nicotinic acetylcholine receptor mediates muscle contractions by facilitating the flow of sodium and potassium ions leading to depolarization of the muscle cell membrane and subsequent initiation of an action potential. While current cosmetic ingredients target the acetylcholine binding site, we discovered a series of modified peptides targeting the ion channel pore of the receptor. The molecular designs were inspired from natural toxin produced by an Egyptian insect with an aliphatic chain attached to the peptide core. We generated a combinatorial library of more than 1000 peptide designs in silico that were triaged using a three-dimensional atomistic model of the human receptor through molecular docking computations, as well as machine learning models trained with bioactivity data. The synthesizability and natural carbon origin was considered before the most promising candidates were synthesized with solid-phase peptide synthesis and evaluated in two biological assays as well as a formulation study. In total, we synthesized and biologically evaluated 134 compounds to identify our lead candidate, which shows nanomolar inhibitory activity in a patch-clamp receptor assay. In subsequent biological tests with isolated human muscle cells, we observed a highly significant reduction calcium flux in human skeletal myotubes. A formulation study with the lead candidate showed excellent stability in terms of pH, visual aspect, and odor for four months at 4°C and 40°C. In conclusion, we report the computationally supported discovery of a novel anti-wrinkle peptide of natural origin, exhibiting best-in-class biological potency through a new mode of action that can be readily formulated into cosmetic products.

0119

Explainable AI for skin cancer detection using convolutional neural networks(CNNs) with SE and grad-CAM

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Early detection of melanoma,a life-threatening skin cancer,is crucial as it spreads rapidly if untreated.Dermoscopic patterns help dermatologists distinguish benign from malignant lesions.CNN has shown promise in automating and enhancing diagnostic accuracy for skin cancer classification.This study reviews AI-driven approaches for skincancer classification,focusing on models with attention mechanisms to improve diagnostic performance.Our goal is to bridge gaps in computational efficiency and model explainability using the Squeeze and Excitation(SE) mechanism and the Grad-CAM EAI technique.The SE mechanism enhances the model's focus on critical image features,while Grad-CAM provides heatmap visualizations,allowing clinicians to understand the model's predictions.A systematic review of 650 articles from 2012–2024 from PubMed,PMC and Scopus was conducted.Studies on image-based skin cancer classification were analyzed,emphasizing segmentation and classification of dermoscopic patterns.The dataset included dermoscopic images from ISIC,HAM10000,and PH2 repositories,ensuring diversity in global skin types and conditions.The proposed CNN-SE model demonstrated superior performance metrics compared to traditional CNN approaches.Across a dataset of dermoscopic images,the model achieved 92%accuracy,94% sensitivity,and 90%specificity.Grad-CAM visualizations highlighted lesion regions critical to diagnosis, aligning with dermatological expertise and reinforcing the model's reliability.Compared to existing models such as ResNet,the CNN-SE model achieved 10%improvement in diagnostic accuracy and reduced computational time by 15%.Integrating this model into teledermatology and resource-limited settings can improve early diagnosis and reduce global melanoma detection disparities.By utilizing diverse datasets,it has the potential to enhance outcomes and lower melanoma-related mortality.Future work will focus on validating the model with larger,multi-ethnic datasets and real-time clinical integration.

0120

Meta-analysis of single-cell RNA sequencing data of human psoriasis implicates IL-32-expressing fibroblasts in disease pathogenesis

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Psoriasis is a chronic inflammatory autoimmune skin condition primarily mediated by immune cells and keratinocytes, however, the contribution of fibroblasts to psoriasis pathogenesis remains underexplored. Emerging evidence suggests that fibroblasts express pro-inflammatory mediators IL36 and CXCL2/12, which recruit Tc17 cells and neutrophils. To investigate the role of fibroblasts in psoriasis, we performed a meta-analysis of four single-cell RNA sequencing (scRNA-sequencing) datasets from keyword-based search of literature on the Gene Expression Omnibus database. The aggregate scRNA-sequecing data comprised 15 control skin samples, 26 untreated psoriatic lesions, and 3 treated psoriatic lesions from 35 unique patients. Integrated analysis of 121,000 cells revealed diverse cell types, including fibroblasts, keratinocytes, endothelial cells, and immune cells. Among fibroblast subpopulations, one expressing IL32 was significantly enriched in psoriatic lesions compared to controls (33% vs. <1%, $p<0.01$). Treated psoriatic lesions exhibited a relative reduction in this subpopulation (24% treated vs. 33% untreated, $p=0.62$). As a proinflammatory cytokine, IL32 amplifies local inflammation through initiating downstream cytokine release. These findings reveal an active role of IL32-expressing fibroblasts in psoriasis pathogenesis, extending their function beyond canonical stromal support. Targeting fibroblast-mediated pathways represents a promising therapeutic strategy for addressing psoriatic inflammation.

0121

Spatial transcriptomics unveils myeloid cell dynamics in autoimmune skin diseases

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Spatial Transcriptomics Unveils Myeloid Cell Dynamics in Autoimmune Skin Diseases Single-cell RNA sequencing (scRNA-seq) captures cellular heterogeneity but lacks spatial context. Sequential fluorescence in situ hybridization (seqFISH) outperformed current spatial methods with its subcellular resolution, high sensitivity and specificity in skin samples, but is limited to pre-selected genes. We addressed this limitation by integrating scRNA-seq with seqFISH in the study of dermatomyositis (DM), cutaneous lupus erythematosus (CLE), psoriasis, and vitiligo. Using scRNA-seq data from 44 patients, we designed a 511-gene panel targeting cell type markers and disease-related genes. SeqFISH analysis of 13 sections from 7 skin biopsies profiled ~138,000 cells, detecting 594 transcripts per cell. To examine cell interactions, we developed an asymmetric colocalization heatmap, uncovering typical skin features and disease-specific patterns. Gene expression showed interaction-dependent changes. We also traced skin surface to measure cell depth. This approach provided new insights into myeloid cell biology. Plasmacytoid dendritic cells (pDCs), a source of IFNα, were present in all diseases, but localized deeper in CLE lesions. CD163+ myeloid cells (MCs) transitioned from LYVE1+ among mesenchymal fibroblasts (FBs) to MMP9+ in immune infiltrates near proinflammatory FBs and the superficial dermis, indicating resident MCs gained inflammatory phenotypes in certain regions of the skin. This aligns with the need for stimulated-fibroblast co-culture to induce MMP9 in DCs. IL6, an inducer of MMP9, is highly expressed by proInf FB in top dermis. scRNA-seq showed a substantial expansion of moDC, the source of IFNβ, in DM and lupus. This moDC mapped to MMP9+ MCs based on markers. Our study highlights seqFISH's value for spatially resolving immune cell functions in autoimmune skin diseases.

0122

Transfer learning to integrate multiomic data to enhance nemolizumab response assessment in atopic dermatitis and prurigo nodularis

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The effectiveness of nemolizumab, an antagonist of IL-31 receptor, has recently been demonstrated in atopic dermatitis (AD) and prurigo nodularis (PN). However, both AD and PN are highly heterogeneous clinically and pathologically, and therefore identifying biomarkers of response to IL-31 targeting is important. To address this, we set up a large-scale prospective cohort. Over 1,200 omics experiments were conducted to profile gene expression and protein in blood, skin, and tape strips from 126 patients with AD and 113 patients with PN receiving nemolizumab treatment. Different clinical outcome variables, including investigator global assessment and weekly average peak pruritus numerical rating scale measured at baseline and week 16 post treatment were assessed. To overcome limitations of machine learning approaches secondary to the multi-layer partially overlapping data, we devised a hybrid transfer learning model, combining LASSO with additional penalty for the discrepancy with prior tissue information and the factor decomposition approach. Benchmarking results showed that the hybrid model significantly outperformed traditional LASSO. Furthermore, we illustrate that combining prior non-lesional tissue information enhances the model performance in contrast to using only lesional tissue. Notably, the drug response prediction for AD was more stable compared with PN, where we achieved AUROC of 0.819 for AD, compared to 0.581 with the baseline LASSO model; while for PN the AUROC ranged between 0.652 and 0.749. This suggests that the biological mechanisms underlying IL-31-targeting therapy in AD are more consistent compared to PN. Significantly, our analysis identified the interferon signature genes ISG15 and IFI6 as critical predictive genes for AD, highlighting their presence in up to 90% of the random cross-validation sets. Our study highlights the value of integrating inter-tissue information for enhancing prediction accuracy in clinical outcomes.

0123

Predicting malignancy in longitudinally monitored skin lesions with ai

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Background: Evolution is a trait of the deadliest type of skin cancer, melanoma, highlighting the need for expert dermatologic monitoring. AI is a non-invasive tool that can aid clinicians in cancer detection. While many algorithms detect skin cancer in single images, the benefit of monitoring calls for investigation into enhancing diagnostic accuracy with prior data. Objective: To develop an algorithm that estimates malignancy probability using current and prior images and compare performance to a single-image classifier. Methods: Dermoscopic images of 20,000 lesions collected over multiple visits were acquired from the ISIC Archive. Lesions were split into five folds with a 3:1:1 ratio of training/validation/test. A Swin Transformer pre-trained on ImageNet extracted features from each image.These features were used to train a cross-attention layer between lesion pairs from separate visits, followed by a classification head to estimate malignancy probability of each pair. Test predictions of each lesion were generated and pooled into a common dataset. AUCs were computed for the two-image model and a single-image classifier (Swin features + classification head). Results: The two-image model had a test AUC of 0.8501. The single-image model had a test AUC of 0.8494. While not statistically significant ($p=0.9696$ using DeLong's test), the two-image model shows higher sensitivity (0.85-0.95) at lower false positive rates. Limitations: The data has few positive samples, the Swin Transformer was not fine-tuned, and sampling bias is inherent in retrospective data. Conclusions: Utilizing longitudinal data through a cross-attention mechanism improves performance in AI-based diagnostic classification at certain sensitivity/specificity thresholds.

0124

The role of isotretinoin on nasal contouring using facial landmark detection technology

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We present a case of a female with severe acne treated with isotretinoin who experienced a clinically significant reduction in nasal size and appearance with therapy. A 2024 study demonstrated that isotretinoin has shown promise in enhancing rhinoplasty outcomes in patients with thick nasal skin. A healthy 17-year-old female with Fitzpatrick type IV skin and no prior medical history presented to the dermatology clinic with a 6-month history of severe acne on her face. Examination revealed numerous inflammatory papules and pustules over bilateral cheeks and forehead with occasional cystic nodules, moderate scarring, and post-inflammatory hyperpigmentation with centrofacial erythema, flaking, and seborrhea. She was prescribed oral isotretinoin 20 mg (0.34 mg/kg) daily for one month, with an increase to 30 mg (0.52 mg/kg) daily thereafter. The patient completed 11 months of isotretinoin treatment with intermittent breaks in therapy and reached a cumulative dose of approximately 11,000 mg. After completion of treatment, acne lesion count and severity had decreased. Serial photographs taken before and after treatment revealed a visible reduction in nasal size. A visual comparison of these images revealed decreased nasal skin thickness, a more defined nasal dorsum, and a narrower alar base, with enhanced contouring of the nasal tip. The Google AI Edge facial landmark detection algorithm was used to assess quantitative changes in nasal size. This pre-trained algorithm identifies 478 invariant facial features, which we used to calculate alar width in each image. The intrapupillary distance in each image served as a scaling factor to allow for the comparison of alar widths between images. Our analysis calculated a 10% reduction in alar width from baseline at the start of treatment to 3 months after the end of treatment. This case demonstrates that isotretinoin shows promise as a non-surgical treatment for decreasing nasal skin thickness and enhancing nasal definition.

0125

Quantification of standing cones in elliptical closures using digital image correlation

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Optimal results of linear closures using a surgical ellipse can be hindered by standing cone deformities, which are characteristic bunching of excess tissue formed during closure. Current surgical dogma suggests standing cones are inevitable when a surgical ellipse's length-width ratio is less than 3-4:1. To date, there have been no attempts to experimentally quantify standing cones in cutaneous surgery. Prior modeling attempts fail to capture the true mechanical behavior of skin as it is difficult to model its anisotropic, non-linear, and inhomogeneous properties. This study adopted three-dimensional (3D) digital image correlation (DIC) to examine porcine skin tissue deformation. DIC is an optical measuring technique that accurately quantifies changes in displacement of speckles into local mechanical strain forces. 3D DIC successfully captured the expected tissue deformation following linear closure of a surgical ellipse, demonstrating vertical end compression along the ellipse's long axis, consistent with standing cone formation. Normal strain was estimated from summation of major and minor principal strains. Standing cone severity was quantified using the standard deviation along the ellipse's long axis of sampled average normal strains in the short axis in a rectangular bounding box dependent on ellipse length. Using triplicates, average standing cone severity was 0.066 for the 2:1 ellipses, 0.052 for 3:1, and 0.035 for 5:1. Our work successfully maps the expected decreasing standing cone formation with increasing length-width ellipse ratios. We demonstrate a quantitative model for capturing standing cone deformities, enabling future research for analyzing the impact of various surgical techniques on standing cone formation.

0126

Spatial and single cell proteomic analysis reveal alterations in type2 inflammation in prurigo nodularis and atopic dermatitis

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Type 2 inflammation is a shared feature of prurigo nodularis (PN) and atopic dermatitis (AD), driven by Th2 cell activation and cytokines such as IL-4, IL-13, and IL-31. Despite recent advances, the spatial and single-cell resolution of immune cell localization in skin lesions remains limited. Imaging Mass Cytometry (IMC) integrates high-dimensional antibody-based detection with spatial tissue architecture, offering a novel approach to studying immune dysregulation in PN and AD. We prospectively analyzed lesional and non-lesional skin biopsies from 24 PN patients, 10 AD patients, and 10 healthy controls. Spectral analysis identified significant enrichment of Th2 cells and elevated expression of IL-4, IL-13, TSLP, and IL-31 in lesional PN skin and lesional AD skin compared to non-lesional ($p < 0.05$) and healthy control tissues ($p < 0.01$ for all). Co-localization of type 2 cytokines with dermal fibroblasts and keratinocytes suggested an immune-stromal interplay in chronic inflammation. Additionally, we observed enrichment of IFN-γ in subsets of keratinocytes and fibroblasts neighboring M2 macrophages in lesional PN ($p < 0.05$), indicating a complex inflammatory milieu involving both Th2 and Th17 pathways. IMC also revealed distinct more numerically dense clusters of macrophages and dendritic cells within the dermis neighboring VIM+ and SMA+ fibroblast clusters ($p < 0.05$) that may contribute to skin fibrosis in PN. This study demonstrates the power of IMC to map the spatial and cellular landscape of type 2 inflammation in PN and AD, laying the groundwork for targeted therapies that address key pathogenic interactions.

0127

Developing a custom calibration target for objective skin color measurement with color corrected dermoscopy

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Reliance on subjective skin color assessment can perpetuate inequities for patients with skin of color(SoC). Erythema appears more subtly in SoC, making it difficult to assess/monitor. Subjective assessment also limits diversity in clinical trials and AI image training sets. Colorimeters are used to objectively assess skin color in the L*a*b* color space or individual typology angle(ITA=atan[(L*-50)/b*]) to estimate melanin but can be costly or bulky for curved/small anatomic sites. Photography can be an accessible colorimetry tool but is limited in color consistency due to non-uniform illumination and camera calibration. We hypothesized a dermatoscope can be repurposed as a colorimeter when combined with a color calibration target. A pilot study with 23 subjects with dark to light pigmentation(ITA-52 to 65) tested the ability of color-calibrated dermoscopy to estimate ITA using a 9.5x5.6mm standard calibration target with 30 colors. Spectrophotometry was performed at each site to measure gold-standard L*a*b* values and calculate ITA_{GS}. For each image, a correction matrix was applied to minimize the color difference between known and measured L*a*b* values in the target. L*a*b* values were extracted from the uncorrected and corrected images to calculate ITA(ITA_{cor}, ITA_{uncor}). ITA_{cor} had lower mean error(ME=18°±9.8) and stronger correlation(r=0.96) than ITA_{uncor}(ME=29°±24,r=0.77) when compared to ITA_{GS}. However, standard targets occupy most of the dermatoscope's field of view(FOV), and their colors do not represent skin tones. To improve calibration for skin color while integrating colorimetry into dermatoscopes, a 21mm diameter custom target with 24 patches(each 1.6x1.6mm), was designed and 3D printed to fit peripherally in the dermatoscope's FOV. The target is made from the Pantone SkinTone Guide with known L*a*b* values from diverse skin reflectance spectra. Preliminary results show a more accurate estimate of L*a*b* values. The development of this target suggests that color-corrected dermoscopy can provide easily accessible and objective skin color assessment.

0128

Advanced-stage cutaneous T-cell lymphomas show distinct immune profiles in erythroderma vs. tumor lesions

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Advanced-stage cutaneous T-cell lymphoma (CTCL) is defined by either skin tumor formation or erythroderma. Erythroderma is clinically defined by diffuse erythema covering >80% of the body surface area, whereas tumors are defined by vertical growth. Previous studies attribute erythroderma with the acquisition of a central memory phenotype by malignant T cells, but underlying mechanisms remain unclear. We used single-cell RNA sequencing of skin biopsies from 8 erythrodermic CTCL (eCTCL) vs. 7 tumor-stage MF (tMF) samples. Both eCTCL and tMF lesions displayed massive expansion of a single CD4+ T-cell clone expressing shared disease markers, including TOX, IL2RG, and CD27. All malignant clones expressed tissue-residency markers such as CD69, CXCR4, RGS1, and NR4A1, but at reduced levels in eCTCL, corresponding with their increased migratory potential. Thus, eCTCL clones exhibit features of central memory T cells while retaining tissue residency markers, underscoring their overall functional versatility. While advanced-stage CTCL is generally considered a type 2-skewed disease, tMF lesions demonstrated a significantly stronger Th2/Tc2 bias in our dataset, as evidenced by the overexpression of CCL17 and CCL13 in myeloid cells. In contrast, eCTCL lesions displayed a more type 1-associated immune profile with upregulation of CXCL9. Interestingly, malignant T-cell clones in tMF lesions exhibited a higher degree of inter-patient transcriptomic heterogeneity compared to the more homogeneous profiles in eCTCL. Trajectory analyses revealed distinct transcriptomic states across both eCTCL and tMF, though tMF clones uniquely occupied a CCR6+CD69+RGS1+ branch that was absent in eCTCL. Taken together, these findings reveal key molecular differences between eCTCL and tMF lesions, providing a foundation for future targeted treatment approaches.

0129

An overview of data analytic-based strategies for assisting with post-surgical adjuvant treatment in melanoma

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Data-driven and deep-learning strategies can be critical in improving post-surgical adjuvant melanoma treatment by providing personalized recommendations to reduce recurrence. This paper explores multiple studies where data analytics was applied and suggests how machine learning (ML) can enhance outcomes. A study by Sha utilized ML models to predict recurrence risk based on patient demographics and tumor characteristics. This resulted in greater optimized selection of candidates for adjuvant immunotherapy[1]. A study by Liu combined genomics data with predictive algorithms to target adjuvant therapies for patients with specific genetic mutations, resulting in improved survival rates[2]. A study by Wang incorporated real-time data analytics using electronic health records to monitor treatment responses and adverse effects in melanoma patients receiving PD-1 inhibitors. This adaptive approach allowed rapid treatment adjustment, which reduced toxicity and maintained efficacy[3]. Liu's genomics-based predictive modeling proved most effective, as it achieved higher survival rates and fewer adverse effects. Integrating deep learning models could further improve the predictive capabilities. Recurrent neural networks (RNNs) can process sequential medical data. By banking on their ability to model time-dependent relationships, RNNs can enhance personalized treatment planning and improve predictive outcomes. RNNs with Gated Recurrent Units (GRUs) have outperformed traditional methods in predicting treatment outcomes[4]. RNN also has potential in epidemiological surveillance frameworks, which can further help in monitoring disease progression as well as tracking treatment effectiveness in poopulations[5]. Incorporating such advanced strategies can provide a more personalized approach to post-surgical adjuvant melanoma care[6,7].

0130

Utilizing self-supervised machine learning to improve risk stratification in cutaneous squamous cell carcinoma

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Staging systems for cutaneous squamous cell carcinoma (cSCC) often fail to reliably predict poor outcomes. Up to 40% of poor-outcome cases are classified within low-risk groups (BWH), while high-risk cSCC cases show a 46% upstaging rate[1,2]. We developed the rank-aware contextual reasoning (RACR) multiple instance learning (MIL) approach to predict metastasis risk and identify novel histological phenotypes[3]. Our approach combines self-supervised histological features with hierarchical graph networks to capture the tumor microenvironment and structural context. The model was trained on 307 patients and validated on 77 patients from Mayo Clinic, Arizona, and Complejo Asistencial Universitario de Salamanca, Spain. Metastatic risk was binary, defined as metastasis within 5 years of biopsy. The model achieved a mean AUC of 0.774 (±0.038) across 5-fold cross-validation, outperforming existing MIL methods by 3-5%. High-risk tissue regions identified by the model were clustered and validated by a board-certified pathologist, revealing histopathological clusters with key patterns and features: 1) Poor differentiation with sheet-like growth pattern and large tumor cells with prominent nucleoli 2) Tumor infiltration with desmoplastic stroma and fibrosis and tumor strands at tumor-stromal interface 3) Acellular benign structures, suggesting proximity to deeper structures and 4) Lymphocytic inflammation with variable differentiation. These findings demonstrate the potential of our model to enhance risk stratification in cSCC by identifying histopathologic features associated to metastasis.

0131

Digital twins in dermatology education: A systematic review and pilot study framework

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Background: Digital twins—virtual replicas of patients—have emerged as a transformative tool in medical education, offering dynamic, interactive simulations. However, their application in dermatology education remains unexplored. Objective: To evaluate the current use of digital twins in dermatology education and propose a framework for a pilot study to address this gap. Methods: A systematic review was conducted across PubMed, Scopus, Embase, Cochrane and Web of Science to identify studies on digital twins in dermatology education. Despite an exhaustive search, no relevant studies were found. Instead, we reviewed their use in other fields, such as surgery and radiology, to develop a tailored framework for dermatology education. Results: Digital twins have been successfully used in other specialties to simulate rare cases, enhance procedural skills, and provide personalized feedback. Drawing from these insights, we propose a pilot study framework that incorporates AI-powered models representing a diverse range of skin tones, ages, and disease severities; interactive training modules for diagnostics and procedures such as biopsies and cryotherapy, with real-time feedback; and an integrated approach linking virtual microscopy to clinical presentations to deepen understanding of dermatopathology. Conclusion: Although no studies currently explore digital twins in dermatology education, adapting their proven benefits from other fields offers a justified and innovative approach. Our pilot framework aims to evaluate feasibility and educational outcomes, paving the way for integrating digital twins into dermatology training. Impact: This study addresses a critical gap, offering a forward-thinking solution to enhance dermatology education through technology-driven learning.

0132

Predicting cSCC grade using RACR-MIL: A comparative study with dermatopathologists

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Cutaneous squamous cell carcinoma(cSCC) is common, yet current staging systems often fail to predict poor outcomes; prior studies have shown up to 46% rate of under-staging of high risk cases. Tumor differentiation is crucial for staging and pathologists use variable approaches to assess it. More consistent and accurate identification of tumor grade is needed to recognize tumors at risk for poor outcomes. Eighteen histopathologically challenging cases were annotated and interpreted by 5 dermatopathologists and grouped by consensus diagnosis. We used a rank-aware contextual reasoning-based machine learning model(RACR-MIL) to predict cSCC grade using whole-slide images and examined its impact upon inter-rater reliability and consensus diagnosis. Majority consensus (agreement among ≥3 pathologists) occurred in 12 cases (66.7%). Minority consensus (agreement among a significant minority or combined adjacent groupings) occurred in 6 cases (33.3%). The model's prediction achieved an overall agreement of 77.8% with consensus, aligning with the majority consensus in 10/12 cases (83.3%) and the minority consensus in 4/6 (66.7%) cases. RACR-MIL shows promising results with up to 50% higher alignment with pathologist's annotations compared to baselines, capturing subtle features such as nuclear atypia in inflammatory cells and infiltrative patterns at the tumor edge.These results highlight the variation inherent in cases and the challenge of assigning a grade at the whole-slide level. Future directions for reporting grading as continuous variables to reflect tumor heterogeneity are warranted.

0133

Interaction between hyaluronan and hyaluronan-mediated motility receptor affects telomere maintenance in skin fibroblasts with Hutchinson-Gilford progeria syndrome

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Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare genetic and premature aging disorder characterized by shortened telomeres, leading to significant skin changes, including loss of elasticity, wrinkling, depigmentation, and extracellular matrix (ECM) disruption. Currently, treatment options for HGPS are limited. Hence, we aimed to explore a novel approach to manage HGPS by regulating telomere shortening through manipulating cell-matrix interactions. Hyaluronan is a vital viscoelastic polysaccharide in the skin's ECM that maintains skin elasticity, integrity, and moisture. Its metabolism is significantly altered during aging and is implicated in HGPS. We demonstrated that growth factors and transcription factors differentially regulate hyaluronan synthases in skin cells, contributing to aging. Furthermore, we found that the matrix hyaluronan modulates telomerase reverse transcriptase transcription in cancer cells, depending on its molecular weight. The hyaluronan-mediated motility receptor (HMMR), an oncogene, is unconventionally exported to the cell surface and binds to hyaluronan under stress. We observed that HMMR enhances telomerase-mediated telomere elongation in mice, prompting us to explore HMMR's role in regulating telomere length in HGPS. Upon eliminating HMMR and its natural antisense long noncoding RNA HMMR-AS1 in primary HGPS skin fibroblasts, we observed a suppression of p21 and p16INK4a mRNA expression ($p<0.05$), indicating HMMR's role in regulating senescence and telomere shortening in HGPS. Culturing HGPS skin fibroblasts in two ECM-mimetic hydrogels revealed that the hybrid hydrogel (low + high molecular weight hyaluronan) increased HMMR expression. In contrast, the low molecular weight hydrogel suppressed it ($p<0.05$). These results highlight the significance of hyaluronan-HMMR interaction in telomere maintenance in HGPS, positioning HMMR as a potential biomarker for aging and a likely target for HGPS therapy.

0134

Pleiotrophin-mediated improvement of collagen fibrous structure leads to dermal regeneration.

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Pleiotrophin is a secreted growth factor expressed in various tissues, including the nervous system, and has been reported to be involved in development and regeneration. It is also expressed in the skin and is expected to influence regeneration, although the findings remain limited. In this study, the effects of pleiotrophin on dermal component cells were examined from the perspective of tissue regeneration. The effects of pleiotrophin added to three cell types considered to contribute to dermal regeneration were evaluated, and the results were as follows: (1) Fibroblasts: Pleiotrophin enhanced the expression of genes involved in the organization and degradation of the extracellular matrix, as well as secreted factors such as growth factors. It is possible that pleiotrophin not only promotes the remodeling of fibrous structure, but also affects the surrounding cells via secreted factors. (2) Vascular endothelial cells: Pleiotrophin enhanced angiogenesis, which may promote the exchange of nutrients and other substances necessary for dermal regeneration. (3) Macrophages: Phagocytosis was enhanced by pleiotrophin. By removing unnecessary cells and substances from the tissues, it may contribute to preparing the tissue environment for dermal regeneration. Next, the effects of pleiotrophin on dermal collagen fibrous structure were evaluated using fresh skin fragments that were just excised from the living body and in which the responsiveness of cells was maintained. When the skin fragments were cultured in the presence of pleiotrophin for 7 days, not only was there an improvement in fiber density, but also a decrease in contracted fiber structure and the neogenesis of fine fibers, indicating an improvement in dermal structure. In summary, our findings suggest that pleiotrophin may play a key role in improving the structural deterioration of dermal collagen associated with aging, by affecting dermal component cells and promoting dermal regeneration.

0135

Role of hyaluronan tetrasaccharide in macrophage-mediated skin inflammation and collagen remodeling of fibroblasts

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Hyaluronan (HA) has moisturizing properties and bioactive functions. While the biological effects of HA are primarily influenced by its molecular weight, hyaluronan tetrasaccharide (HA4) remains relatively unexplored. This study investigates HA4's potential to regulate macrophage-induced inflammation and fibroblast-mediated collagen remodeling, focusing on proinflammatory M1 macrophages (M1-Mφ) associated with photoaging. Adding HA4 during macrophage (M0) differentiation into M1-Mφ partially inhibited this process and significantly reduced the production of proinflammatory cytokines IL-6. Although IL-1ra, an M2 marker, was upregulated, no clear polarization toward antiinflammatory M2 macrophages was detected. The effects of M1-Mφ-conditioned medium (M1-CM) and HA4-supplemented M1-CM (M1+HA4-CM) on human fibroblasts were also examined. Fibroblasts treated with M1+HA4-CM showed a significant reduction in IL-6, IL-8, and the collagen-degrading enzyme MMP1 expression compared to those treated with M1-CM alone. Fibroblast collagen synthesis assays revealed that M1+HA4-CM enhanced collagen fiber formation. These results were supported by RNA-seq, which showed increased collagen synthesis-related genes and decreased collagen degradation-related genes in fibroblasts treated with M1+HA4-CM. Further, TLR4 neutralization assays indicated that the IL-6 suppression found in fibroblasts treated with M1+HA4-CM is independent of the TLR4 signaling pathway. Thus, HA4 mitigates M1-Mφ-induced inflammatory responses and collagen degradation while promoting collagen fiber formation. These findings highlight HA4's potential for managing inflammatory skin conditions, including photoaging.

0136

Par1 signaling between T cells and keratinocytes mediates Klk6-elicited skin inflammation in a Rock2-independent

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Kallikrein 6 (KLK6) is increased in lesional epidermis of human psoriasis skin, and keratinocyte-specific overexpression of Klk6 (Klk6+) in mice results in the development of psoriasis-like skin lesions that are eliminated in the global absence of the protease-activated receptor 1 (Par1). Par1 is a G-protein coupled receptor expressed in keratinocytes (KCs) and T cells and signals via phosphorylating Rock2. Klk6+ mice have increases in cutaneous Rock2 activity compared to littermate controls that decreases in the absence of Par1 suggesting a plausible pathogenic pathway involving T cells, KCs, Par1 and Rock2. To define the cellular mechanisms responsible for Klk6-induced skin inflammation we first mated Klk6+ mice with KC (K14cre) or T cell (Lckcre)-specific Par1 knockout mice to identify the cell type responsible for the Klk6-Par1-elicited skin phenotype. Klk6+-Par1 ^{KC} and Klk6+Par1 ^{Tcell} mice develop less severe skin inflammation than Klk6+ mice, demonstrated by improvement in appearance and decreases in acanthosis, cutaneous T cell numbers and IL-17A. Moreover, Klk6-Par1 signaling in primary mouse T cells and KCs led to increases in Il17a/f, Il22 and Ifng, and Il17c, Ccl20, Il19, Il36, Cxcl1 and Klk13, respectively, which are abrogated in the absence of Par1. Next, to identify Rock2 signaling as a pathogenic downstream molecule of Par1, Klk6+ mice were treated systemically with the Rock2 inhibitor (KD025) for 4-wks. KD025 treated Klk6+ mice showed no improvement in skin inflammation, despite Rock2 activity decreasing to control mouse levels. Increases in phospho-c-Jun and decreases in phospho-Sapk3 were found in Klk6+ skin that reverse in the absence of Par1 suggesting alternative Par1-dependent pathways may be responsible for skin inflammation. Together, these findings demonstrate that Klk6-Par1 signaling between T cells and KCs are critical for skin inflammation and occur in a Rock2 independent manner.

0137

Comparison of passive diffusion with enzymatic digestion in extracellular vesicle isolation from the skin

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Extracellular vesicles (EVs) are lipid bilayer nanoparticles that mediate cell-cell communication. EVs play a pivotal role in several autoimmune skin diseases. Isolating EVs from the skin remains challenging, with most protocols using enzymatic digestion of biopsies for their release. We compared the efficiency and purity of tissue EV isolation using the current standard enzymatic digestion vs passive diffusion. EVs were isolated from the finely cut skin of three C57BL/6J mice using collagenase-dispase digestion or passive diffusion in saline, followed by differential ultracentrifugation. Enzyme-isolated EVs demonstrated higher protein concentration (1.00 ± 0.40 mg/mL vs. 0.44 ± 0.13 mg/mL, p = 0.04) particle count ($1.57 \pm 0.23 \times 10^{12}$ vs. $1.77 \pm 1.07 \times 10^{11}$ particles/mL, p = 0.0007) and particle size (130.0 ± 4.5 nm vs. 119.0 ± 2.3 nm, p = 0.01) than diffusion-isolated EVs. Diffusion-isolated EVs, however, exhibited 9.5-fold greater content of the tetraspanin surface EV marker CD81 (p = 0.0008) and 2.2-fold greater content of the internal EV marker TSG101 (p = 0.0006) than enzyme-isolated EVs by immunoblot. Notably, enzyme treatment resulted in cleaved protein bands, lowering the expected molecular weight of calnexin and other proteins. Antibody chip-based Exoview further confirmed higher content of the tetraspanins CD81, CD9, and CD63 in diffusion-isolated EVs. In summary, enzymatic digestion releases far more particles but with far lower EV marker detection, with evidence of protein degradation and possibly dilution from the production of non-specific particles. Conversely, passive diffusion releases fewer particles but higher EV marker detection, without degradation. Our results suggest that passive diffusion into saline is the superior alternative for skin EV isolation, providing cleaner isolates suitable for downstream analyses such as immunodetection of skin EV markers and biological effects in cell-cell communication.

0138

Fighting collagen loss with potent technologies treatment optimized with Nrf-2 activation

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Skin aging is a result of intrinsic and extrinsic factors with the appearance of wrinkles and sagging. Critical proteins part of our body and highly impacted by the aging process are collagen proteins. While there are at least sixteen different types of collagen, types I, II and III-collagens comprise between 80-90% of all collagen in the human body. More specifically in skin, collagen types I, III, and V are fibrillar collagens and all connected. They are particularly sensitive to environmental factors, such as sun, that activate collagenase. Here, we show that skin cells, both young and mature, also losetheir ability to produce collagen when exposed to UV day after day. A few years ago, we showed that collagen production peaks at night. Therefore, it is essential to develop the right treatment to rebuild these collagen networks and also to treat at the optimal time, which is during the night. Our findings here show that the combination of 4 actives including an exclusive flower extract, peptide, algae extract and whey protein, is extremely efficient at boosting collagen. We also show that the addition of our exclusive Nrf-2 activator, boosts collagen-I even further, increasing collagen-I production 10 times vs control. This powerful combination not only boosted collagen-I but also collagen-III and collagen-V increasing 1.9 and 18.8 times, respectively. This exclusive and potent complex helps to rebuild the essential collagen fibrils to strengthen and firm the skin and fight signs of aging, re-establishing skin integrity with youthful mechanical properties.

0139

Age-associated fibroblasts identified by single cell RNA-seq of human dermis disrupt fibroblastic identity as a hallmark of aging skin

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Skin aging is characterized by marked atrophy and loss of elasticity within the dermal connective tissue. Fibroblasts (FBs), which primarily regulate dermal components, exhibit cellular diversity. However, the alterations in FBs diversity and communication signals during aging remain poorly understood. Here we show that single-cell RNA sequencing (scRNAseq) on human dermis from healthy individuals of varying ages, clarified seven distinct FB clusters, including age-associated fibroblasts (AAF) with canonical senescent features. Immunostaining revealed the localization of seven FB subpopulations and a dramatic increase in the number of AAF with age. The putative trajectory of seven FB clusters revealed a lineage progression from stem cells to terminal differentiation states characterized by AAF. Immunostaining for AAF markers showed a significant overlap with oxidative DNA damage. Furthermore, ligand-receptor analyses indicated that AAF interact with other FB clusters through TGFβ superfamily to affect the fate of dermal mesenchymal cells. Indeed, genes enriched in papillary FB cluster from old donors showed adipogenic and chondrogenic traits compared to young. The combination of TGFβs and BMPs enhanced the commitment to adipocyte lineages and upregulated chondrocytes-related genes in isolated papillary FBs. Finally, aged human dermis showed ectopic adipogenesis and the accumulation of cartilage-related matrix protein. In summary, we identified AAF within the diverse population of dermal FBs and their function. AAF not only causes inflammation due to the cellular senescence, but also disrupts the nature of FBs and even shakes the fate of FBs to adipogenic and chondrogenic lineages in skin aging. A "loss of fibroblastic identity" can be introduced as a novel concept in the understanding of dermal skin aging.

0140

Delineating key molecular programs that induce hair-follicle-inductive dermal fibroblasts using a novel single-cell genomic approach

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Hair follicles (HFs) form by signals communicated between epithelial cells and specialized dermal cells,dermal condensate (DC) cells. Although it has been long recognized that DC cells can induce new HF growth, how they initially form has remained elusive. We recently showed that Wnt and SHH corporate to induce DCs through a rapid sequence of cell cycle exit followed by molecular DC differentiation. This sequence spatially corresponds to different levels of Wnt and SHH activity in the dermis. If and how different levels of Wnt and SHH are responsible for the distinct steps of DC genesis is unknown, largely because they occur spatiotemporally tightly coupled. Here, we genetically repatterned levels of Wnt and SHH and found that this disrupts the sequence of cell cycle exit and molecular DC differentiation such that they occur independently of each other. This resulted in disorganized DCs and revealed that the two typically coupled processes can be separately triggered by changing Wnt and SHH levels. We applied a novel computational method, GeneTrajectory, to dissect out these two distinct processes and their regulation. Unexpectedly, we show that SHH activity augments Wnt signaling and that high Wnt signaling is sufficient to elicit cell cycle exit irrespective of DC gene expression. Further, we found that this Wnt level utilizes GLI3, a SHH transcription factor, to coordinate cell cycle exit with SHH activity. Next, by recreating covarying Wnt and SHH levels over the entire dermis, we show that the mere coupling of Wnt and SHH gradients is sufficient to initiate a proper sequence of cell cycle exit and molecular differentiation. Finally, we established an *in vitro* system to show that Wnt and SHH can reciprocally regulate each other and induce DC processes, suggesting a feedback mechanism to ensure coupled levels. This study provides insight into how Wnt and SHH gradients coordinate biological processes in DC formation, which will help guide efforts to recreate DCs to generate organotypic HF models and to promote adult HF regeneration.

0141

A senescent subpopulation of fibroblasts induce inflammation in psoriasis through APOE

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Fibroblasts play a critical role in various inflammatory skin diseases, including vitiligo, atopic dermatitis, and psoriasis; however, the precise mechanisms are not fully understood. Single-cell RNA-sequencing analysis for patients with inflammatory skin diseases and healthy individuals have revealed an increased subpopulation of fibroblasts exhibiting senescent phenotype. This group of fibroblasts demonstrate pro-inflammatory characteristics and show elevated expression of APOE. We hypothesized that APOE$^+$ senescent fibroblasts are a key subpopulation participating in inflammatory skin diseases. In the present study, we found that the number of APOE$^+$ fibroblasts was increased in lesional skin of psoriasis patients as shown by immunofluorescence. We also found that overexpression of APOE in fibroblasts resulted in heightened inflammation, lipid metabolism disorders, and cellular senescence. Mice with fibroblast-specific deletion of APOE exhibited attenuated cutaneous inflammation in imiquimod (IMQ) models, which suggested that APOE$^+$ fibroblasts amplified inflammatory responses. Based on single-cell RNA sequencing and flow cytometry, we found that APOE$^+$ fibroblasts exacerbate psoriasis-like inflammation by recruiting neutrophils through overproduction of CXCL1 and CXCL2. Moreover, lipidomics combined with transcriptomic analysis showed that, overexpression of APOE in fibroblasts leads to a significant increase in prostaglandin E2 (PGE2) levels. And the upregulation of CXCL1 and CXCL2 induced by APOE was reversed by inhibiting the PGE2/EP4/AKT/NF-κB pathway. Moreover, application of ABT-263 eliminated the APOE$^+$ fibroblasts-induced inflammation, which represents a potential strategy for control of skin inflammation. Overall, our study reveals that APOE$^+$ fibroblasts exhibit pro-inflammatory function with senescent phenotype and promote skin inflammation of psoriasis. Targeting APOE$^+$ fibroblasts might be a promising strategy for alleviating skin inflammation.

0142

TWEAK signaling as a central driver of paradoxical reactions: Linking psoriasis to atopic dermatitis-like inflammation.

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Psoriasis (PP) is a chronic skin condition characterized by Th1/Th17-driven inflammation and abnormal keratinocyte proliferation, while atopic dermatitis (AD) is driven by Th2-mediated responses. A subset of PP patients treated with biologics (e.g., TNF-α, IL-17, and IL-23 inhibitors) develop paradoxical reactions (PR), presenting with AD-like inflammation. The mechanisms underlying this shift remain unclear. To investigate PR, we generated a single-cell and spatial transcriptomic atlas of skin biopsies from healthy controls (NL), PP, AD, and PR patients. Analysis of 20 samples (106,331 cells) identified 16 cell types with distinct frequencies across conditions. PR uniquely exhibited enriched interferon responses, leukocyte-mediated immunity, and a Th2-dominant profile. Differential gene expression analysis revealed upregulated immune-related genes (e.g., IFITM3, STAT1, CD74) and pronounced interferon signaling in PR. PR demonstrated the highest number of cell-cell interactions, revealing a pro-inflammatory microenvironment uniquely regulated by TWEAK signaling. Key contributors to this pathway included keratinocytes, myeloid cells, and fibroblasts, with increased expression of TNFSF12 (TWEAK ligand) and TNFRSF12A (receptor). Immunohistochemistry confirmed elevated TNFSF12+ cell densities in PR, mirroring AD patterns. TNFSF12+ keratinocytes were enriched for immune and stress response pathways (e.g., "response to type II interferon"), highlighting their role in inflammation and epidermal remodeling. In contrast, TNFSF12− keratinocytes were associated with differentiation and structural maintenance. Our findings identify TWEAK signaling as a driver of the inflammatory shift in PR, validated by spatial sequencing and immunohistochemistry. Targeting TWEAK signaling offers a promising therapeutic strategy to mitigate PR's effects while maintaining effective PP management, improving outcomes for patients with biologic-induced PR.

0143

Reg3 expression in the skin is influenced by fibroblast-keratinocyte interplay and gut inflammation

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Skin diseases often co-occur with gut disorders and bidirectional crosstalk along the skin-gut axis influences both gastrointestinal and skin health. Our recent findings reveal increased susceptibility to gut inflammation after skin injury with increased expression of Regenerating islet-derived 3 γ (REG3g) in the gut. The functional role of REG3g is not well understood and has previously been suggested to have both antimicrobial and anti-inflammatory functions. Here, we examined the response of the skin to gut inflammation by oral administration of dextran sodium sulfate (DSS) to mice. This intervention caused mice to have more severe infections by S. aureus with an increase in colony-forming units in the skin samples. Furthermore, analysis of the skin during gut inflammation and S. aureus infection showed elevated expression of Reg3g and altered expression of pro-inflammatory cytokines Il-6, Il-1b and TNF-alpha. scRNA-seq data from acute murine skin inflammation induced by topical application of S. aureus(DRA015287) identified fibroblasts as a major source of increased Reg3g expression in skin after S. aureus infection, followed by keratinocytes and myeloid cells. Interestingly, conditioned media from fibroblasts enhanced REG3g expression and protein levels in HaCat cell line of human keratinocytes. Taken together, we show for the first time that gut inflammation modulates Reg3g expression in the skin and alters host defense after S. aureus infection. These data begin to model the impact of intestinal inflammation on the skin host defense system and identify fibroblast-keratinocyte communication as an important factor regulating REG3g. Additional studies to better understand the role of REG3g in the skin and the mechanism for communication between gut and skin are ongoing.

0144

Activation of hippo signaling pathway enhances CCL5 secretion in sebocytes and induces macrophage infiltration in rosacea

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Rosacea is a chronic inflammatory skin disease characterized by the involvement of pilosebaceous units (PSUs) and capillaries. Macrophages constitute a significant portion of the infiltrating cells in rosacea. However, the mechanisms underlying the recruitment of macrophages to rosacea lesions are not well understood, and their interactions with structural cutaneous cells, as well as the precise molecular pathways involved, require further investigation. We investigated macrophage infiltration patterns in rosacea using human biopsy specimens and CX3CR-1GFP knock-in mice. Single-cell RNA sequencing, RNAscope, and ELISA were employed to examine the interactions between sebocytes and macrophages. YAP localization was assessed via immunofluorescence and Western blot to verify the activation of Hippo and AP-1 signaling. Subsequently, we performed *in vivo* blockade of Hippo and AP-1 signaling using verteporfin and SR11302 to explore their regulatory role in CCL5 secretion and macrophage infiltration. In rosacea lesions, macrophages infiltrated in a perifollicular pattern, providing spatial evidence for interactions between PSUs and macrophages. LL37 enhanced the secretion of CCL5 in sebocytes, with the CCL5/CCR5 axis mediating the interaction between sebocytes and macrophages. Transcriptomics results also suggested the activation of Hippo and AP-1 signaling in rosacea, which was confirmed by the increased YAP nuclear localization and upregulation of FOSB protein expression in sebocytes treated with LL37. Meanwhile, the blockade of Hippo and AP-1 signaling reduced macrophage infiltration and attenuated rosacea-like skin inflammation *in vivo*. These findings elucidate that the activation of the Hippo pathway in sebocytes promotes CCL5 secretion and recruitment of macrophages, thereby inducing rosacea inflammation. This underscores the crucial role of sebocytes in the progression of rosacea and provides insights for developing therapies targeting sebocytes.

0145

Serine palmitoyltransferase (SPT) inhibition mitigates IL17A-mediated keratinocyte hyperproliferation through ROS-HIF1α axis.

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Interleukin 17A (IL17A) is pivotal in psoriasis pathogenesis and orchestrates keratinocyte hyperproliferation and the associated metabolic rewiring. Exploring IL17A-mediated lipid metabolic changes in keratinocytes is vital, as several lipids are known to drive this pathogenic proliferative phenotype. Specifically, IL17A increases sphingolipid levels in Human Keratinocytes (HKs) and also enhances the expression of a critical component of the committed step enzyme involved in the sphingolipid synthesis pathway, serine palmitoyltransferase long chain base subunit 2 (SPTLC2). Our study explores the functional relevance of IL17A-induced sphingolipid metabolic alterations in HKs by targeting the sphingolipid biosynthetic pathway. We performed western blotting and immunofluorescence imaging to validate IL17A-mediated upregulation in SPTLC2 levels in HKs. Additionally, immunofluorescence imaging of psoriasis biopsies showed elevated SPTLC2 levels compared to healthy controls (n=6, p<0.05), thus emphasizing its clinical relevance. Further, inhibition of SPT using myriocin not only reduces lipid levels in HKs, but interestingly also attenuates the formation of IL17A-driven cellular and mitochondrial reactive oxygen species (ROS) in HKs. Moreover, flow cytometric analysis showed that myriocin also lowers the IL17A-induced hypoxia-inducible factor 1α (HIF1α) levels in HKs, which is a crucial mediator in the IL17A-ROS-HIF1α axis. Accordingly, myriocin treatment also resulted in abrogation of IL17A-mediated hyperproliferation of HKs orchestrated by this axis. Overall, we uncover a previously unexplored connection between sphingolipid biosynthesis and IL17A-triggered redox imbalance through the ROS-HIF1α axis, which as a consequence, promotes keratinocyte hyperproliferation. Thus, inhibiting sphingolipid biosynthesis may offer a potential strategy for managing IL17A-driven psoriatic pathologies in keratinocytes.

0146

Exploring senescence-related factors to combat skin aging

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Cellular senescence is part of the twelve Hallmarks of aging and is largely addressed nowadays to delay skin aging. The increase of stress and decrease in cell proliferation are recognized as key factors in senescence. Senescence is in part associated with an upregulation of pro-inflammatory cytokines (IL-6 and IL-8), mediated by retinoic-acid-inducible gene-I (RIG-I). Interestingly Klotho, a cofactor of the FGF receptor, has been found to suppress RIG-I-mediated inflammation, suggesting its role as an intracellular anti-inflammatory and anti-aging factor. Besides Progerin, a truncated version of Lamin A, impairs DNA damage repair leading to premature cellular senescence. Targeting these two factors with a natural Dill extract, holds promise as a specific cosmetic approach to delay cell senescence and, consequently, skin aging. *In vitro* experiments involved assessing Progerin synthesis in fibroblasts using ELISA method, with insulin as a positive control. Immunofluorescence was used to evaluate Klotho synthesis in a fibroblast culture, while IL-6 expression was assessed in keratinocytes after LPS stress. Results showed on fibroblasts that Dill extract significantly reduced the accumulation of Progerin by up to 54% and increased the level of Klotho protein by up to +34%. Notably, Dill extract also decreased IL-6 secretion after stress. A clinical study was finally conducted, evaluating the anti-wrinkle effect on crow's feet through digital image analysis, assessing skin biomechanical properties using cutometry, and clinical scoring of skin elasticity and jawline slackness. After three months of applying Dill extract, features of skin aging linked to senescence were significantly improved. These effects were measurable, visible, and perceivable by the volunteers. This study highlights the significance of targeting Progerin and Klotho-related biological pathways to slow-down skin aging and paves the way for new antisenescence targets.

0147

Basophils and pro-inflammatory-fibroblast crosstalk modulates type 2 cutaneous inflammation

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Type 2 skin inflammation is pivotal in pathogen defense and tissue repair but can become aberrantly sustained, leading to inflammatory skin diseases like atopic dermatitis (AD). To identify key cellular interactions and transcriptional profiles driving inflammatory responses, we employed single-cell spatial transcriptomics (MERFISH) and matched scRNA-seq to analyze MC903 and oxazolone murine models, which is reported separately. Basophils crosstalk with pro-inflammatory fibroblasts by producing IL-4 and oncostatin M (OSM), confirmed through re-analysis of scRNA-seq studies. The combination of recombinant IL-4 and OSM synergistically upregulated phosphorylated STAT3 and STAT6 proteins (pSTAT3 and pSTAT6) as well as Cxcl12 and Tnc in primary mouse fibroblasts *in vitro* ($p < 0.01$), while human fibroblasts showed a similar response to recombinant OSM and IL-13. To assess basophil-fibroblast crosstalk *in vivo*, we depleted basophils in the MC903 model using neutralizing antibodies. Basophil depletion reduced type 2 inflammation, skin thickness (~30%, $p < 0.0001$), and pro-inflammatory fibroblast induction, as immunofluorescence revealed a 4-fold decrease in PDGFRA+/pSTAT3+ fibroblasts in basophil-depleted tissues ($p < 0.01$). Bulk RNA-seq and qPCR of fibroblast targets showed downregulation of genes such as Il4ra, Cxcl1, and Tnc. Furthermore, fibroblast-specific conditional Il4ra knockout mice exhibited reduced type 2 inflammation, a ~40% reduction in skin thickness ($p < 0.0001$), and diminished basophil infiltration (~75% reduction, $p < 0.001$), confirming the essential role of IL4RA+ pro-inflammatory fibroblasts in sustaining inflammation. Finally, combined OSM pathway blockade in fibroblast-specific Il4ra knockout mice further reduced inflammation, highlighting a novel therapeutic avenue. These findings demonstrate that basophil crosstalk with IL4RA+ pro-inflammatory fibroblasts is critical for regulating type 2 skin inflammation and offers therapeutic potential.

0148

Dermal fibroblasts are critical mediators of IL-1 function in the skin

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IL-1 is essential for host defense and plays key roles in inflammatory disorders, but its mechanism of action remains incompletely understood. As scRNA-seq revealed several fibroblast subsets highly express Il1r1, and CellChatDB ligand-receptor analysis showed major keratinocyte-fibroblast communication during S. aureus infection, we hypothesized that dermal fibroblasts might have an important role in IL-1-mediated inflammation. To test this hypothesis *in vitro*, human fibroblasts (HPAd) were exposed to conditioned media (CM) from normal human keratinocytes (NHEK). RNA-seq and pathway enrichment analysis showed increased levels of dozens of inflammatory transcripts in NHEK-activated HPAds (fold>2, $p<0.05$). This result was validated by qPCR (e.g., CXCL8: fold=14.3 $p<0.0001$) and multiplex immunoassay (CXCL1/5/8, CCL2/20: fold>4, $p<0.007$). Phosphoproteomic analysis of HPAds also found increased phosphorylation of proteins in several IL-1R-related signaling pathways (e.g., AP-1, NFκB) within 10 minutes of exposure to NHEK-CM. Fibroblast supernatant was then tested in an *in vitro* migration assay, which showed that NHEK-activated fibroblast products preferentially recruited neutrophils and monocytes from bone marrow and blood (fold>2, $p<0.05$). These fibroblast responses were dependent on IL-1R, since NHEK-CM was inactivated by the addition of a neutralizing antibody of IL-1α or a competitive inhibitor of IL-1R (anakinra), and fibroblasts derived from Il1r1-KO mice were nonresponsive to keratinocyte CM. We next developed $Pdgfra^{\Delta Il1r1}$ mice and challenged them with S. aureus to assess the importance of fibroblast IL-1 recognition *in vivo*. The skin of mice lacking fibroblast IL1R1 had reduced inflammatory transcripts (e.g., Csf3: fold=-1.5, p=0.0097), larger infectious lesions, and increased bacterial load (fold=2.8, p=0.0038). These data show that IL-1 can induce inflammatory activity in fibroblasts and that this response is critical to host defense.

0149

Highlights on the communication between dermis and epidermis during aging

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Dermis and epidermis cannot be reduced to two separate and autonomous entities. For several years, new studies have been emerging to analyze the influence of dermal aging on the epidermis, by studying mechanisms of intercellular communication. This study aimed to investigate the impact of aging on the communication systems in place from the dermis to the epidermis. First, a proteomic study was conducted on the secretome of young and aged fibroblasts, enabling the detection of 335 proteins. A bio-informatic analysis reveals that 128 of these proteins are involved in communication paths, with an enrichment in four cellular processes related to communication originating in the dermal compartment (regulation of IGF-1 pathway, signaling of growth factors, signaling of inflammation and cellular interactions). Moreover, our results reveal a deregulation of more than half of these proteins in the secretome from aged fibroblasts. To go further in the investigation of intercellular communication, extracellular vesicles (EVs) were isolated from secretomes. The expression of 9 miRNAs, known as inhibitors of epidermal biological pathways and transported in EVs, was measured in young and aged models. Results reveal a significant increase in their expression with aging, suggesting a communication shortfall that could induce an alteration in epidermal biological functions. To corroborate this hypothesis, old keratinocytes were exposed to aged fibroblasts secretome. This latter significantly decreases keratinocyte proliferation and differentiation, cell cohesion and the anchoring of the dermal-epidermal junction, thus accentuating the impact of aging on the biological functions of the epidermis. Altogether, these results give an overview of the intercellular communication actors deregulated during skin aging. This investigation paves the way to innovative developments allowing to restore the communication systems from the dermis to improve the epidermal functionalities.

0150

Single-cell and spatial transcriptome profiling reveals innate-adaptive crosstalk in alopecia areata

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Alopecia areata (AA) is an autoimmune disorder characterized by immune attack on hair follicles, resulting in non-scarring hair loss. The pathogenesis of this condition is multifaceted and involves T cells, myeloid cells, and innate immune cells. However, the transcriptional profiles of these immune cell types remain inadequately defined, and delineation of aberrant or dysregulated pathways has the potential to identify therapeutic targets. In this study, we created a comprehensive atlas of various immune cells within AA skin lesions in a murine model, achieving single-cell resolution through integrative single-cell analysis, spatial transcriptomics, flow cytometry, and immunofluorescence. We found that macrophage infiltration occurred around the AA hair follicles and correlated with flow cytometry-based data. Significant expansion and transcriptional changes were observed in $CD8^+$ T cells and macrophages within AA skin lesions. We identified two distinct macrophage subpopulations ($Folr2^+$ and $Folr2^-Arg1^+$), each exhibiting unique transcriptional profiles. These subpopulations showed upregulation of genes related to T cell activation as well as pathways involved in leukocyte and myeloid cell differentiation. Additionally, four different subsets of $CD8^+$ T cells revealed heterogeneity in their interactions with macrophages, as demonstrated by ligand-receptor mapping. Spatial transcriptome and flow cytometry imaging data revealed $Folr2^+$ tissue resident macrophages (TRMs) interacted with $CD8^+$ T cells and positively correlated with T cell infiltration. This study examines the roles of macrophages and $CD8^+$ T cells in the recruitment of pathogenic immune cells, as well as the underlying mechanisms involved in AA lesions. Consequently, the findings highlight crucial immunopathogenic characteristics of AA lesions, thereby providing significant insights into the potential immunological alterations associated with this condition.

0151

Lipid aldehydes from senescent cells reshape the ECM and propagate senescence

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Senescent dermal fibroblasts display reactive lipids which are part of the senescence-associated secretory phenotype (SASP). These lipids, such as 4-Hydroxynonenal (HNE) and oxidized phospholipids (OxPAPC), bind covalently to proteins. We investigated lipid-induced collagen modifications and their effects on skin cells, to assess consequences of senescent cells to the microenvironment. Using mass spectrometry and biochemical methods, we identified adducts of SASP lipids to collagen type I, II and IV and cultured skin cells on modified matrices or in skin equivalents containing modified matrices. In fibroblasts, HNE-modified collagen induced redox stress responses (HO1 and HSPA1A), while OxPAPC-modified collagen triggered inflammation. Both modifications increased MMP1 and MMP3 and reduced collagen I and III expression. Fibroblasts on HNE-collagen exhibited reduced proliferation determined by Ki67 expression. Both HNE and OxPAPC modified collagen led to elevated levels of reactive oxygen species (ROS) and further lipid peroxidation. In macrophages cultured on modified collagen the cytokine profiles suggested a modification dependent low grade inflammatory phenotype while Toll-like receptor (TLR4) signaling of the macrophages was impaired. In keratinocytes exposed to lipid-modified basal lamina collagen IV we observed transient stress and inflammatory responses suppressed MMP3/MMP9 expression. In organotypic skin equivalents produced with SASP-modified matrix we observed increased markers of cellular senescence (lower LaminB1, higher H2AX and p16 levels) and disturbed differentiation and parakeratosis induced by OxPAPC modification. We propose that senescent cells cause a long therm modification of the ECM through aldeydic SASP lipids and the modified matrix propagates a senescent phenotype.

0152

IFNg-mediated reprogramming of antigen presenting cell (IMRAPC) behavior in keratinocytes is perturbed in skin cancer

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Keratinocytes (KCs) provide a barrier yet its role for tumor immunosurveillance is not well known. IFNγRa-KO mice exhibit increased tumor formation upon MCA induction. Its ligand IFNγ induces MHC Class II in KCs that is restricted to professional antigen presenting cells (APCs). The findings suggest an IFNg-mediated reprogramming of antigen presenting cell (IMRAPC) behavior in KCs for tumor immunosurveillance that is poorly understood. We determined the transcriptomes of normal KCs (N/TERT) and A431 epidermoid carcinoma KCs upon IFNγ and evaluated its impact in Organotypic Epithelial Raft Cultures (OERCs) with Transepithelial Electrical Resistance (TEER) assays. RNA-seq identified IFNγ induction of CXCL10 and -11 chemoattractant expressions which coincided with MHC Class II (HLA-DRA and -B1) resulting in stable cell surface MHC Class II localization in both cell types (vs untreated) but decreased in A431 ($p<0.001$). However, T cell costimulatory molecule CD58 was compromised in A431 vs N/TERT ($p<0.001$) revealing aberrant IMRAPC reprogramming in A431 cells. IFNγ treatment in N/TERT OERC resulted in KRT14/K1 epidermal thickening and reduced TEER vs untreated N/TERT ($p<0.05$) in contrast to less stratified and undifferentiated epidermis (KRT14 only) and reduction in TEER in A431 OERCs vs untreated A431 ($p<0.05$). Suprabasal expression of CD58 was also dampened in A431. The findings identify IMRAPC remodelling of KCs that compromises barrier function and is aberrant in A431. We sought to further determine the clinical relevance of IMRAPC in skin cancer. We found HLA-DR+CD45- expression in moderate to severe human KRT+ cSCC tumor borders. Our findings identify IMRAPC remodelling in KCs that is compromised in epidermoid carcinoma KCs and tumors and provide opportunities to develop new skin cancer treatments.

0153

What drives menopausal skin changes? A new look through hormone-responsive models

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Despite significant skin changes occur during menopausal period, few models exist to study this hormonal shift. To address this need, we developed three complementary *in vitro* models to specifically target key hormonal aging parameters. Hormonal decline during early menopause leads to a 30% collagen reduction within 5 years due to impaired matrix production and degradation. Reduced sebaceous gland activity causes dryness, while weakened vascular networks impair oxygenation and nutrient delivery, affecting skin vitality. Models on human fibroblasts, sebocytes, and endothelial cells were developed with media using 17β-estradiol, progesterone, dehydroepiandrosterone, growth hormone, and IGF-1 at concentrations mimicking non-menopausal and menopausal serum levels. Dermal atrophy was addressed by quantifying markers of collagen metabolism – procollagen I and MMP-1 – in fibroblasts via ELISA. Sebogenesis activity, reflecting skin dryness, was assessed in sebocytes culture through total lipid content measurement using a BODIPY® probe. Microvascular network formation and integrity in endothelial cells were analyzed with the Angiogenesis Analyzer tool on ImageJ. Under menopausal conditions, fibroblasts showed a 37% ($p<0.01$) reduction in procollagen I content and a 170% ($p<0.01$) increase in MMP-1 secretion, highlighting matrix synthesis and remodeling dysfunction. In sebocytes, menopausal hormonal levels led to a 65% ($p<0.01$) decrease in lipid content, reflecting reduced sebum production contributing to increase skin dryness. Endothelial cells showed microvascular network deterioration, with fewer junctions, segments, and meshes underscoring vascular changes associated with menopause. The developed models, using a physiologically relevant hormonal cocktail, mirror the skin impacts at menopause onset. By leveraging hormone-dependent models, we provide an innovative approach to precisely target skin hormonal aging, enabling to identify active ingredients specifically designed to address the unique needs of menopausal skin, going beyond conventional anti-aging approaches.

0154

GRN-SORT axis exacerbates the inflammatory response in TREM2-macrophage in acne vulgaris.

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The inflammatory response plays a crucial role in the formation and progression of acne vulgaris. However, the dysregulation of inflammation-related genes across acne lesions has not been thoroughly investigated. This study aimed to identify dysregulated genes in acne lesions by integrating single-cell RNA sequencing data from early-stage acne with spatial transcriptomics of acne lesions. Our analysis identified 10 genes, including GRN, IL13RA1, IL4R, FAS, and C3, which were consistently altered in all six acne lesions compared to non-lesional skin. Notably, GRN was predominantly expressed by myeloid cells. The cell-cell communication analysis within acne lesions revealed that GRN exerts its pro-inflammatory effects through its receptor, SORT1, in an autocrine manner within TREM2 macrophages. *In vitro*, treatment of TREM2 macrophages with recombinant GRN protein promoted the expression of pro-inflammatory cytokines (IL-18, IL-1β, TNF-α, IL-6) and chemokines (CCL5, CXCL2). Furthermore, our colony-forming unit killing assays demonstrated that GRN does not exhibit antimicrobial activity or promote the growth of C. acnes, indicating that GRN promotes inflammation through cell-cell interactions rather than directly affecting C. acnes. These findings highlight the critical role of the GRN-SORT1 signaling axis in acne initiation and development, underscoring its potential as a therapeutic target for acne treatment.

0155

Extracutaneous manifestations of keratinocyte ferroptosis-driven chronic psoriatic inflammation.

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It is well-known that keratinocytes (KCs) play a critical role in the initial and chronic phases of psoriasis. However, the mechanism of KC-immune crosstalk which initiates and maintains skin and systemic inflammatory loops in psoriasis has not been established. Recently, we discovered that a prominent feature of psoriasis is an accumulation of pro-ferroptotic oxidized polyunsaturated fatty acid (PUFA)-phosphatidylethanolamine (PE) species (oxPE) in KCs, associated with upregulation of arachidonate 15-lipoxygenase type II (Alox15B or 15-Lox-2, which generates oxPE species) and downregulation of glutathione peroxidase 4 (Gpx4, which reduces oxPE). Strikingly, genetic ablation of Gpx4 in only a small fraction of keratin 14^+ KCs in mouse epidermis (K14/Gpx4 model) produced psoriasis-like skin phenotype and systemic inflammation, including arthritis, closely resembling human disease with characteristic activation of canonical signaling pathways and multi-omics biomarkers. Furthermore, depletion of T lymphocytes, current standard-of-care biological anti-IL-12/IL-23/TNFα therapies, and, most importantly, inhibitors of 15-Lox-2 and oxidized phospholipids (oxPLs) were able to reverse psoriasiform disease in mice. We also found that aged K14/Gpx4 mice develop signs characteristic to psoriatic arthritis in forepaws and hindpaws, including dactylisis, loss of retraction reflexes, significant weakening of grip strength, and demonstrated increased arthritis score. In addition, CT radiography of paws revealed marked bone erosion and proliferation with distal predominance, 'pencil in cup' deformities, ankylosis and phalangeal osteolysis, while histology showed synovial proliferation and bone destruction, dactylitis, and enthesitis. Such arthritis-like extracutaneous inflammation, which occurs after the initial immune responses to KC ferroptosis in the skin, suggests an autoreactive T cell-mediated process which expands from skin to other organs.

0156

Perilla Frutescens leaf-derived exosome-like nanoparticles inhibit ferroptosis in epidermal keratinocytes

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Plant-derived exosome-like nanoparticles (PDEN) are nano-sized particles extracted from plant cells and are generally composed of proteins, lipids, nucleic acids, and other potential signaling components. Recently, various biological functions such as antioxidant, anti-inflammatory, and immune regulation have been reported for PDENs, along with their low toxicity and high safety profiles. Ferroptosis is a recently identified regulated cell death mechanism characterized by iron ion accumulation and lipid peroxidation. The potential involvement of ferroptosis in various skin diseases and aging processes suggests the potential benefits of ferroptosis inhibitors on skin health. In this study, we examined the inhibitory activity of PDENs on ferroptosis in cultured human epidermal keratinocytes (HaCaT). Treatment with RSL3, a potent inhibitor of glutathione peroxidase 4 (GPX4)-induced ferroptosis, induced significant cytotoxicity in HaCaT cells, and among the various PDENs tested, Perilla frutescens PDENs significantly prevented cell death. Further investigation suggested that changes in antioxidant-related factor expression and lipid peroxidation-related enzyme expression underlie the inhibitory effects of Perilla frutescens PDENs on RSL-3-induced ferroptosis. These results suggest that PDENs have potential as natural product-based therapeutics and cosmetic materials for protecting skin cells against ferroptosis.

0157

Interaction between adipocyte lineage cells and mast cells contributes skin inflammation and fibrosis in atopic dermatitis

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Atopic Dermatitis (AD) is a prevalent chronic inflammatory skin disease, hallmarked by type 2 inflammation. Mast cells (MCs) are pivotal in the initiation of type 2 inflammation and skin itching by secreting proinflammatory cytokines. However, the dermal mechanisms underlying MC recruitment, activation, and their impacts on dermal cells are not fully understood. Dermal white adipose tissue (dWAT), composed of highly plastic and immunogenic adipocyte lineage cells (ALCs), can rapidly expand or regress in response to a variety of stimuli. Yet, the contribution of ALCs to mast cell recruitment and activation during AD development is not well defined. Here, by an in-depth analysis of the MC903-induced AD mouse model, we found that mast cell recruitment to the dWAT layer coincided with the area of adipocyte lipolysis and dermal fibrosis during AD pathogenesis. Single-cell RNAseq revealed that ALCs, particularly preadipocytes (pAds) and adipogenesis regulator (AREG) cells, were the prominent cellular source of key mast cell cytokines/ chemokines, including SCF and CXCL. Using *in vivo* mouse models and *in vitro* co-culture systems, we demonstrated that pAds/AREGs effectively induced mast cell migration in a SCF and CXCL-dependent manner. By analyzing MC deficient and adipocyte lineage tracing mice, we found that MC903-mediated mast cell recruitment and degranulation in dWAT led to adipocyte lipolysis and their dedifferentiation into COL1-producing AREGs, thus promoting dermal fibrosis. In summary, our results uncover a previous unrecognized reciprocal interaction between dermal ALCs and MCs, potentially driving skin inflammation and dermal fibrosis in AD. These insights could pave the way for novel therapeutic approaches for atopic dermatitis.

0158

Neutrophils are primed for enhanced inflammasome activation in skin microvasculature during adhesion via E-selectin

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Introduction: Neutrophils play a key role in psoriatic inflammation and recruitment into inflamed skin is initiated by tethering and rolling on E-selectin upregulated on endothelium in the microcirculation. We hypothesized that E-selectin ligation and clustering of L-selectin on the neutrophil membrane signals inflammasome activation that includes release of calprotectin (S100A8/A9), to promote progression of psoriatic plaque formation. Method: Neutrophils were isolated from the blood of healthy adult donors on an IRB from UC Davis. Neutrophils were shear mixed with polymer microspheres coated with recombinant human E-selectin (Eb) to simulate tethering and rolling adhesion. Cells were co-stimulated with LPS, S100A8/A9, or TNFα at 37°C. GMI-1687 is a small molecule antagonist that blocks E-selectin recognition of sLex on L-selectin. Neutrophil suspensions were incubated and shear mixed at 37°C for 20 minutes. FLICA is a fluorescent peptide that reports on Caspase-1 cleavage that initiates activation of the inflammasome and analyzed by flow cytometry. Results: Binding of Eb was a potent agonist of Caspase-1 activation as indicated by increased uptake of FLICA fluorescence. Eb binding to neutrophils increased FLICA by 100% and was blocked to baseline by pretreatment with GMI-1687. Superposition of Eb binding with addition of LPS, S100A8/A9, or TNFα was synergistic, increasing FLICA by 1-fold, 1.7-fold, and 1.5 fold respectively, over Eb alone. Conclusion: Psoriatic neutrophils in circulation are primed for enhanced inflammatory response by elevated b2-integrin binding affinity and calprotectin levels that increase with stimulation via TNFa. Here we report that rolling on inflamed endothelium via E-selectin/L-selectin can trigger inflammasome activation that is enhanced in the presence of calprotectin and TNFα, which may exacerbate the pathogenesis of psoriasis.

0159

Keratinocytes escape cell damage caused by neutrophil extracellular traps

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Neutrophil extracellular traps (NETs) are released by activated neutrophils and are defined as cytotoxic protein-modified DNA-based extracellular reticular structures. The major component of the extracellular reticular structure is decondensed DNA bound to a variety of proteins, including citrullinated histone H3 (cit-H3), neutrophil elastase, cathepsin G, and myeloperoxidase, which are stored in azurophilic granules under normal conditions. Therefore, when examining NETs, it is common to look for reticular structures and the presence of cit-H3. Indeed, reticular structures and cit-H3 were clearly observed when NETs were induced *in vitro* by exposure of circulating neutrophils from healthy volunteers to phorbol 12-myristate 13-acetate (PMA). In contrast, we found that cit-H3 was identified in neutrophils of pustules of neutrophilic pustular dermatoses such as generalized pustular psoriasis, acute generalized exanthematous pustulosis, and palmoplantar pustulosis, but the extracellular reticular structure was absent. Thus, it has been hypothesized that epidermal keratinocytes release molecules that degrade reticular structures or inhibit the formation of reticular structures. To test this hypothesis, neutrophil culture medium was replaced with HaCaT cell culture supernatant, and PMA was added for 5 hours, resulting in the identification of cit-H3 without extracellular reticular structure. Next, culture supernatants were recovered from sub confluent and full confluent normal human epidermal keratinocytes. As a result, disappearance of the extracellular reticular structure was observed only in the latter, suggesting that full confluent or differentiated keratinocytes release molecules that degrade reticular structures or inhibit the formation of reticular structures. Cit-H3-positive neutrophils without reticular structures were also observed in the section of squamous cell carcinoma. Considering that reticular structures of NETs contain many cytotoxic molecules and cause severe cell damage, this process may be a way for keratinocytes to escape cell damage caused by NETs.

0160

IL-17RC signaling in mesoderm-derived stromal cells is dispensable for skin neutrophil recruitment in murine imiquimod-induced psoriasis

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The pathogenesis of psoriasis in humans and the imiquimod (IMQ)-induced mouse model is strongly driven by members of the IL-17 cytokine family which signal not only to keratinocytes but also to dermal stromal cells such as fibroblasts. Signaling occurs through dimeric IL17 receptor (IL-17R) complexes, of which IL-17RA is a common component. It has been described that IL-17RA deletion within either keratinocytes or fibroblasts dramatically reduces neutrophilic inflammation in murine IMQ-induced psoriasis. Dimeric IL-17RA/IL-17RC is thought to be the major receptor complex involved; however, IL-17RA can also dimerize with other IL17R family members. We therefore sought to determine the dependency of neutrophil recruitment on IL-17RA/IL-17RC signaling in dermal fibroblasts using Twist2-driven Cre expression to delete Il17rc in mesoderm-derived tissues. Twist2-cre^{+} and Twist2-cre^{-} littermates, as well as global IL17rc$^{-/-}$ knockout mice were subjected to 5 days of treatment with 5% imiquimod cream, then euthanized for analysis of neutrophilic skin inflammation by flow cytometry. While global IL17rc$^{-/-}$ knockout mice exhibited 10-fold ($p<0.0001$) fewer skin neutrophils relative to Twist2-cre^{-} mice, Twist2-cre^{+} mice displayed equivalent neutrophilic infiltration to Twist2-cre^{-} littermates. These data raise the possibility that alternative IL-17R complexes can fully compensate for the loss of IL-17RA/IL-17RC signaling in dermal fibroblasts to drive neutrophilic inflammation in the IMQ psoriasis model. Future experiments will use *in vitro* and *ex vivo* models of dermal fibroblasts with receptor antibody blockade to isolate the specific IL-17R signaling complexes responsible for neutrophil recruitment to the skin.

0161

Dermal fibroblast expression of transcriptional co-factors YAP/TAZ regulates dermal extracellular matrix homeostasis and fibrotic scar formation in mouse skin

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The collagen-rich dermal extracellular matrix (ECM) provides both mechanical support and a microenvironment crucial for the functions of dermal cells. Dermal fibroblasts play an essential role in this process. We have investigated the function of two homologous transcriptional co-factors, YAP and TAZ, in dermal ECM homeostasis utilizing conditional Cre-LoxP deletion to eliminate YAP/TAZ expression in dermal fibroblasts. We report that deleting YAP/TAZ in dermal fibroblasts three days after birth leads to marked reductions in dermal collagen fibril production, ECM deposition, and ECM organization. The density of the dermal collagen and gene expression of type I collagen were significantly diminished, with reductions of 67% ($p<0.035$) and 88% ($p<0.001$), respectively. Spatial RNA sequencing of the dermis revealed a substantial decrease in the expression of the major collagen genes such as COL1A1 (76% reduction, $p<0.0001$), COL1A2 (73% reduction, $p<0.0001$), COL3A1 (58% reduction, $p<0.0004$), and a negative enrichment of the YAP/TAZ signaling pathway. Further investigations into fibrotic scarring following incisional tail wounding demonstrated that scar formation, measured 4, 8, and 12 weeks after wounding, was significantly attenuated in YAP/TAZ knockout mice. Dermal thickness was reduced by 50% ($p>0.01$) 12 weeks post wounding, compared to age and sex-matched littermate controls. Similarly, in models of bleomycin-induced skin fibrosis, the fibrotic response was significantly reduced (33% reduction, $p<0.01$)in YAP/TAZ knockout mice. These results highlight the critical involvement of YAP/TAZ in fibroblasts in regulating dermal ECM homeostasis and fibrotic scar formation and identify targeting the YAP/TAZ signaling pathway in fibroblasts as a promising approach for ameliorating fibrotic scarring.

0162

Keratinocytes induce neutrophils to acquire antigen presentation capability in sweet syndrome

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Acute febrile neutrophilic dermatosis (Sweet syndrome) is characterized by erythematous plaques with a dense dermal neutrophilic infiltrate. Our prior work identified a molecular trigger to increase recruitment of neutrophils to skin but did not explain their prolonged persistence. We collected skin and blood from 10 Sweet syndrome patients and performed single-cell RNA-sequencing. Sweet syndrome skin was specifically enriched for a non-canonical population of antigen-presenting cell (APC)-like neutrophils (~25% of all neutrophils, p value = 0.0007). These neutrophils expressed canonical APC markers, including MHC-II complex genes, CD80, CD86, and CD40. Notably, this population was absent in Sweet syndrome blood, indicating a tissue-specific local activation. We validated this neutrophil population by immunofluorescence analysis of classical APC markers, including HLA-DPA and HLA-DRB, on 5 additional Sweet syndrome patient skin samples. Using an *in vitro* co-culture system, we demonstrated that keratinocyte-derived serum amyloid A1 (SAA1) binds to formyl peptide receptor 2 (FPR2) on neutrophils, to drive neutrophils to adopt this APC-like phenotype. APC-like neutrophils exhibited extended survival (52% viability at 72 hours versus 5% for conventional neutrophils, p value < 0.0001) and resistance to neutrophil extracellular trap formation. They also stimulated interferon-gamma production from T cells. Finally, established Sweet Syndrome therapeutics, including corticosteroids, reduced the extended survival of APC-like neutrophils. Taken together, we identify a novel keratinocyte-neutrophil pathway that explains the increased persistence of dermal neutrophils and improves our understanding of Sweet syndrome pathogenesis.

0163

Specific targeting of dermal papilla cells with Hhip-Cre

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The dermal papilla (DP) is essential for hair follicle formation and regeneration. Specific and robust Cre-drivers are desirable for a better understanding of the functions of the DP. Hedgehog interacting protein (HHIP) is highly expressed in the DP cells. In this study, we evaluated whether cre recombinase under the control of the Hhip gene can be used as a DP driver. Hhip-IRES-CreERT2 (Hhip-Cre) mice were crossed with ROSA26-LacZ and ROSA26-tdTomato reporter mice. Cre activity was detected in the majority of anagen hair follicles when Cre was induced by tamoxifen during the first hair cycle or after depilation. Thus, this Hhip-Cre is considered a suitable driver for targeting DP cells and a useful tool for gene manipulation in the DP cells.

0164

Spatial transcriptomic analysis identifies markers of neuroinflammation and keratinocyte hyperproliferation in prurigo nodularis

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Prurigo nodularis (PN) is a chronic inflammatory skin disorder characterized by intense pruritus and nodular skin lesions, yet its underlying molecular mechanisms remain poorly understood. Neuroinflammation and epidermal barrier dysfunction are emerging as key contributors to PN pathophysiology. To investigate the spatial expression of relevant genes, we employed spatially resolved RNA sequencing using the Visium Spatial Gene Expression platform (10x Genomics) on lesional and non-lesional skin biopsies from 12 PN patients and 4 healthy controls. Our analysis identified significant upregulation of S100A8, S100A9, GJB2, S100A7, SPRR2G, LCE3D, KRT16, and FABP5 in lesional PN skin compared to healthy controls ($p<0.05$). The S100A8 and S100A9 genes encode calprotectin, a complex implicated in amplifying inflammatory responses via activation of Toll-like receptor 4 (TLR4) and the receptor for advanced glycation end-products (RAGE). Their upregulation suggests a pro-inflammatory milieu contributing to chronic neuroinflammation in PN. Similarly, elevated expression of GJB2 and S100A7, known mediators of epidermal barrier integrity and antimicrobial defense, aligns with impaired barrier function observed in PN. The upregulation of SPRR2G, LCE3D, and KRT16, genes associated with keratinocyte activation and hyperproliferation, highlights epidermal remodeling and stress responses central to PN pathogenesis. Spatial co-expression patterns revealed localization of S100A8/9 and GJB2 within dermal immune clusters, suggesting potential interactions between neuroimmune pathways and keratinocyte signaling. These findings underscore the role of neuroinflammation and keratinocyte hyperproliferation in PN, providing novel insights into its molecular landscape.

0165

Transcriptomic analysis reveals unique neuroimmune, fibrotic, and extracellular matrix remodeling mechanisms in prurigo nodularis compared to atopic dermatitis and psoriasis

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Prurigo nodularis (PN), atopic dermatitis (AD), and psoriasis (PS) are chronic inflammatory skin diseases with distinct yet overlapping immune mechanisms. While AD and PS are classically characterized by Th2 and Th1/Th17 polarization, respectively, PN's molecular landscape remains poorly defined. To address this, we performed transcriptomic analysis of skin biopsies from 26 PN, 26 AD, 15 PS patients, and 12 healthy controls using NanoString 770-gene panel. Differentially expressed genes (DEGs) were analyzed for pathway enrichment and interactions via Ingenuity Pathway Analysis and STRING. Significance was defined as fold change >1.5 and FDR-adjusted $p<0.05$. PN exhibited a unique signature marked by neuroimmune crosstalk, fibrosis, and extracellular matrix (ECM) remodeling compared to AD, PS, and HC. Unique neuroimmune activity was driven by upregulation of S100A10, IL-31 and downregulation of GRIA4, APOE ($p<0.05$), reflecting neural sensitization and chronic itch. ECM remodeling and fibrosis were linked to upregulation of TGFBR1, MMP14, COL6A3, and TIMP1 ($p<0.001$). Enhanced IL-6 signaling (e.g., TGFBR1, MAPK12) further distinguished PN ($p<0.001$), linking immune dysregulation and fibrosis. Compared to AD, PN showed reduced Th2 cytokine expression (IL-13, IL-5) but heightened ECM and fibroblast-related gene expression (MMP14, TGFBR1), indicating chronic reparative responses ($p<0.001$). Compared to PS, PN demonstrated diminished Th17-driven keratinocyte proliferation (STAT3, TGM1) but heightened neuroimmune (IL-31) and pro-fibrotic signaling ($p <0.001$). These findings underscore PN's unique pathophysiology, characterized by interplay between Th1, Th2, and Th17 pathways, neuroimmune mechanisms, and ECM dynamics. Key drivers like TGFBR1, MMP14, and IL6 signaling provide insights into PN pathogenesis and highlight novel therapeutic targets.

0166

LSD1 orchestrates retinoid-immune crosstalk to balance homeostasis and cancer

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Precise regulation of retinoic acid metabolism is critical for tissue homeostasis, yet the context-dependent mechanisms by which this occurs remain incompletely understood. Here, we show that histone lysine-specific demethylase 1 (LSD1, also known as KDM1A) is a previously unappreciated epigenetic brake on retinoid responses in skin. We find that epidermal Lsd1 is essential for embryonic skin development and survival, while deletion in adult epidermis is tolerated, provoking retinoid signaling activation and immune cell infiltration. At the chromatin regulatory level, we show that Lsd1 directly binds to retinoid metabolism and immune chemokine loci in keratinocytes and correspondingly, Lsd1 loss increases H3K4me2 at these same loci. We then leverage single cell resolution spatial profiling and time-course studies to demonstrate that Lsd1 loss leads to early activation of retinoid signaling in certain keratinocyte subsets followed by migration of dendritic cells (DCs) to recruit CD4+ T cells to the skin. Strikingly, topical catalytic Lsd1 inhibition (Lsd1i) recapitulates this phenotype, and we observe that retinoic acid receptor antagonism prevents Lsd1i effects. Finally, we reveal that topical Lsd1i restricts skin tumor growth in two independent cancer models and is associated with enhanced keratinocyte-DC signaling markers. Overall, our data open therapeutic avenues for leveraging this crosstalk observed upon Lsd1i in keratinocyte cancers, the most common of all malignancies.

0167

Impact of insulin resistance in acne vulgaris

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Background: Acne vulgaris is a chronic inflammatory skin disease with multifactorial pathogenesis affecting the pilosebaceous units. The development of acne lesions is strongly associated with metabolic and hormonal disorders. Insulin is a hormone-like myokine with anti-inflammatory, antioxidant, and anti-diabetic effects. It may have a role in the pathogenesis of acne vulgaris and the associated insulin resistance. Aims: We aimed to evaluate serum insulin levels in patients with acne vulgaris to assess its correlation with disease pathogenesis. Method: A cross-sectional observational study was conducted in the dermatology department. Patient's detailed clinical history and necessary parameters like height, weight, body mass index (BMI), etc were recorded in predefined proforma, noting signs and symptoms of underlying IR, along with acne severity calculated by global acne grading system (GAGS) and then analysing using Pearson's correlation test to establish correlation between IR and acne vulgaris. Serum insulin level was measured by an ELISA technique in 86 acne vulgaris patients and 86 healthy controls. Insulin resistance was calculated using the Homeostasis Model Assessment of Insulin Resistance index. A level of 2.5 of HOMA-IR is considered as insulin resistance. Result: Serum insulin level was significantly higher in acne vulgaris patients than in the control group (P < 0.001). It showed a significant correlation with insulin resistance among patients (P 0.000). Moreover, it increased significantly with the increase in disease severity (P 0.000). In acne, raised BMI and severity of acne (GAGs) were positively associated with IR. Conclusions: IR has emerged as an important contributory, if not causative, event in the pathogenesis of severe, resistant acne. These conditions have a great deal of impact on the psychological health of those affected, necessitating different approaches to managing such cases. Our results revealed that serum insulin is not only a biomarker of disease pathogenesis but also a potential prognostic predictor of severity in acne vulgaris.

0168

Quantifying social media's impact on public interest in red light therapy through Google Trends analysis

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Social media platforms, particularly TikTok, have emerged as influential sources of medical information and treatment trends. In early 2024, red light therapy gained substantial attention on TikTok for skincare applications, despite limited scientific understanding of its safety and long-term effects with home use. Here, we quantify the impact of TikTok exposure on public interest in red light therapy and compare interest trends with conventional skincare treatments. We analyzed Google Trends data from November 2019 to November 2024 for red light therapy-related terms ("light therapy", "red therapy", "red light masks", "red therapy benefits", "photobiomodulation", "low level laser therapy") and control terms ("chemical peel", "skin care", "exfoliation"). Statistical analyses included unpaired t-tests comparing pre- and post-February 2024 search volumes, linear regression, Mann-Kendall trend tests, and Chow tests for structural breaks. Search interest for red light therapy terms showed significant increases post-February 2024 ($p<0.001$) compared to the previous year, except for "low level laser therapy" ($p=0.297$). Linear regression revealed significant positive trends for red light therapy terms (slopes ranging from 0.082-0.148, all $p<0.001$), while control terms showed either no significant trends or slight declines. Mann-Kendall tests confirmed strong upward trends for therapy-related terms (Tau=0.384-0.684, all $p<0.001$), contrasting with stable or declining trends for conventional treatments. Chow tests indicated significant structural breaks (all $p<0.001$) between red light therapy and control terms, suggesting distinct pattern changes coinciding with TikTok exposure. TikTok's influence significantly increased public interest in red light therapy, surpassing traditional skincare treatments. These findings highlight social media's role in shaping healthcare trends and underscore the need for healthcare providers to stay informed about viral treatments to address patient inquiries and concerns effectively.

0169

Real world outcomes of patients receiving salvage therapies for immune checkpoint-resistant Merkel cell carcinoma: A baseline for future clinical trials

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PD(L)1 immune checkpoint inhibitor therapy (ICI) provides durable responses in ~50% of patients with advanced Merkel cell carcinoma (aMCC). However, for those who experience disease progression during first-line treatment, salvage therapies such as alternative ICIs, chemotherapy, or radiation can be used. Given the aggressive nature of MCC, assessing outcomes following salvage therapies is critical for improving care. Resistance to ICI may manifest as primary resistance (pR; no initial response) or acquired resistance (aR; loss of response after initial benefit). Here we analyzed real-world outcomes in a prospective cohort of 106 aMCC patients who developed disease progression following first-line ICI, and then received salvage therapy. Primary outcomes were progression free survival (PFS) and disease-specific survival (DSS). In this cohort, 42% had pR, 30% had aR, 21% had an unknown resistance pattern, and 8% had progression following therapy discontinuation. Median PFS from initiation of salvage therapy to next progression was significantly shorter for patients with pR (4.8 months) than for patients with aR (11 months; p=0.004). Median DSS was 12.6 months for pR and was not reached for aR (p=0.002). These results suggest patients with aR receiving salvage therapy have improved survival outcomes compared to those with pR, but outcomes for both remain suboptimal and highlight significant room for improvement. Furthermore, preliminary analyses do not indicate a meaningful difference in clinical benefit between the primary salvage approaches of chemotherapy, radiation therapy or further immune therapy, and point to a major need for new approaches to address this problem. To our knowledge, this study is the largest analysis to date of patients with aMCC and ICI-resistant disease receiving salvage therapy and should help guide future clinical trials.

0170

The impact of age on healing times in radiation dermatitis

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This study investigated the relationship between age and healing times in patients with radiation dermatitis (RD), a common adverse effect of radiation therapy (RT) affecting up to 95% of patients. Slower skin regeneration and immune response in older adults suggest age may influence RD resolution. This retrospective analysis included 21 adult cancer patients treated with RT at the University of California Davis Medical Center (2000–2024), identified via ICD-10 codes. RD healing times were defined as the number of days from RT completion and RD diagnosis to resolution. Patients were stratified by age (≤70 vs. >70 years) and Fitzpatrick skin types (I–VI). Kaplan–Meier estimators and log-rank tests assessed time-to-event outcomes. Patients aged ≤70 years resolved RD significantly faster than those >70 years. Median healing times from RT completion to resolution were shorter in younger patients (p=0.018), as were times from RD diagnosis to resolution (p=0.02). No significant differences were observed among Fitzpatrick skin types I–III, though limited representation of types IV–VI precluded further analysis. These findings suggest that age significantly affects RD recovery, with younger patients experiencing faster healing. Slower epithelial regeneration, collagen production, and immune response in older adults may explain delayed resolution. Future studies should focus on diverse populations and tailored interventions, such as advanced wound care and skin barrier therapies, to improve outcomes for older patients.

0171

Accuracy of administrative codes for hidradenitis suppurativa in the veterans affairs healthcare system

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The positive predictive value (PPV) and negative predictive value (NPV) of a single administrative code for hidradenitis suppurativa (HS) have been reported on in the literature using the general population as a control, but this resulted in no false negative cases. We aimed to assess the diagnostic accuracy of a single ICD code for HS in the Veterans Affairs Healthcare System (VAHCS) using patients with codes for abscess as a control group. Patients with an ICD code for HS from 2011 to 2022 were identified, and 140 were randomly selected for chart review. Additionally, 140 age- and sex-matched controls with a code for cutaneous abscess (without codes for HS) were identified. Two blinded reviewers evaluated charts for HS diagnosis, defined by three Dessau criteria at the date of ICD code entry, HS in the problem list, or evidence of HS on review of recent documentation going back to the date of the ICD code entry. A third blinded reviewer resolved discrepancies. The PPV of a single ICD code for HS was 0.864 (95% CI 0.794-0.914), and NPV was 0.971 (95% CI 0.924-0.991). Sensitivity and specificity were not calculated, as defining cohorts based on the outcomes of the diagnostic test being evaluated (ICD codes) introduces sampling error. Despite using a control cohort with a higher presumed prevalence of HS, our NPV remained high. Limitations include variability in physical exam documentation, which may underestimate HS cases. This method of cohort identification by ICD code entry will be used in planned VAHCS database studies evaluating risk factors for HS progression.

0172

Environmental pollutants and atopic dermatitis: Associations across age groups in a cross-sectional analysis

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The global prevalence of atopic diseases has risen significantly, with evidence suggesting environmental factors as a significant component. We initially explored the association of pollution with any ICD-coded visit, before narrowing our focus to skin disease. This cross-sectional study utilized a model to analyze air and water pollution in relation to skin disease prevalence. We identified associations where beta correlation values exceeded thresholds defined as Mean ± 2×Standard Deviation. We found an association between air exposure to 2-Chloro-1,1,1,2-tetrafluoroethane and potassium bromate and increased atopic dermatitis (AD) diagnoses in the youth population (ages 0–5). Similar to prior reports, the BTEX related compounds catechol and chlorophenol air compounds were linked to higher frequencies of AD among pediatric patients (ages 6–17). Conversely, residing in areas with 1-butanol in the water was associated with decreased odds of AD diagnoses, potentially due to anti-allergic and anti-inflammatory properties demonstrated *in vitro*. These findings suggest that environmental pollution may play a role in the rising prevalence of atopic skin diseases and highlight the need for translational studies to explore the underlying mechanisms and potential interventions.

0173

Clinical profile, treatments, and quality of life of subjects in the Kenya psoriasis registry

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There is a gap in knowledge regarding the demographic and clinical characteristics of individuals with psoriasis (PsO) on the African continent. We have established Kenya's first psoriasis patient registry at Moi Teaching and Referral Hospital (MTRH) in Eldoret, Kenya. We collected patient characteristics including sex, age, race, psoriasis subtype and severity, psoriatic arthritis status, comorbidities, environmental exposures, treatment patterns, itch, pain, sleep, and quality of life. Among the PsO subjects enrolled to date (n=38), the median age of PsO onset was 29 years, and median age of diagnosis by a medical provider was 37 years old. 10.5% of PsO patients reported a positive family history of PsO, and 21.1% of PsO patients reported a diagnosis of psoriatic arthritis. The median psoriasis area and severity index (PASI) was 3.4 and median physician global assessment (PGA) score 3. Regarding treatments, 97.4% of PsO patients have tried moisturizers, 86.8% prescription topical medications, 13.2% crude coal tar, 7.9% phototherapy, 73.7% methotrexate, and 0% biologics. The mean Patient Health Questionnaire (PHQ-9) scores were 3.6 and 0.0 for PsO and healthy controls (n=36), respectively ($p<0.05$). The mean General Anxiety Disorder 7 (GAD-7) scores were 2.3 and 0.0 for PsO and healthy controls, respectively ($p<0.05$). Ultimately, the knowledge gained from this registry will advance our understanding of psoriasis in African and Black populations and will lay the necessary foundation for further research, education, and advocacy for psoriasis in Africa.

0174

A scoping review: Community-based interventions for primary prevention of skin cancer

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Many public health programs aim to reduce skin cancer burden by promoting sun protection habits, but heterogeneity in community-based strategies and outcome methodologies complicates efficacy comparisons. This review aims to summarize intervention strategies for primary skin cancer prevention and the study designs used to evaluate them. A systematic search on sun protection was conducted on July 16, 2023, across PubMed, CINAHL, Embase, Cochrane Library, and PsycInfo. Included articles evaluated sun protection programs, presented original research, and were published in English within the past 10 years. Two reviewers voted on inclusion and exclusion, with a third resolving disagreements. Data extraction focused on study methodologies and intervention strategies. Of 7,342 abstracts, 451 underwent full-text review, and 37 met inclusion criteria: 16 randomized controlled trials, 17 pre-post studies, and 4 non-randomized trials. Twenty-one studies examined school-based interventions, while 16 addressed broader community-based approaches. SunSmart's diffusion of innovations theory and similar frameworks were used in 20 studies to drive early and sustained behavior change. Learning adjuncts, such as facial aging software, mobile apps, text reminders, UV photos, wearable sensors, and interactive exercises, appeared in 24 studies. However, only 7 studies provided concurrent access to sunscreen, highlighting a gap in community-based interventions aimed at improving sun protection accessibility. While many programs emphasize sun safety education to change behavior, lack of access to sunscreen or UV protective clothing may limit adoption. Dermatologists should therefore consider accessibility when making recommendations and incorporate sunscreen as a standard patient resource to encourage adherence.

0175

Semaglutide use for decreasing psoriasis vulgaris resource utilization: A retrospective cohort study utilizing trinetx

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We investigated the impact of semaglutide usage in patients with psoriasis vulgaris (PV) on resource utilization. A retrospective cohort study was performed utilizing the global database TriNetX. Patients with PV were divided based on exposure to semaglutide after their PV diagnosis. This cohort was then matched to a subset of a non-treated cohort prior to the analysis to help ensure the patients compared were of similar demographic makeup. Our primary outcome was a change in the usage of TNF-α inhibitors, calcineurin inhibitors, vitamin-D analogs, IL-17 inhibitors, IL-12/23 and IL-23 inhibitors, traditional systemic therapies, steroids, and the number of emergency room (ER) visits. Risk ratios (RR) were calculated with their associated confidence intervals (CI) to represent the change in usage. After matching, the cohort had 3,242 patients. The results demonstrated that PV patients on semaglutide had a statistically significant decreased use of nearly all measured variables, including TNF-α inhibitors, calcineurin inhibitors, vitamin-D analogs, IL-17 inhibitors, traditional systemic therapies, steroids, and the number of ER visits (RR < 1, CI did not include 1). No significant statistical difference was observed for IL-12/23 and IL-23 inhibitors (RR < 1, CI did include 1). These results are significant and may be suggestive for the use of semaglutide in patients with PV as decreased resource utilization could be indicative of fewer needs and may correlate with a decrease in PV severity. Recognizing the correlation between weight loss and PV, coupled with the growing popularity of weight loss medications, it is crucial to evaluate the effects of these medications on patients with PV.

0176

Evaluating the association between isotretinoin use in acne patients and diabetes risk: A retrospective cohort study.

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Recent reports of new-onset diabetes and worsening insulin resistance in acne patients after starting isotretinoin present conflicting evidence compared to existing cohort studies, which found no association between isotretinoin and insulin resistance. To evaluate whether isotretinoin increases type 1 (T1DM) and type 2 diabetes mellitus (T2DM) risk, we used the TriNetX US Collaborative network (66 healthcare organizations) to identify acne patients 9-40 years old via ICD-10-CM codes and stratified them into 4 treatment cohorts: 1. Isotretinoin; 2. Topical retinoids; 3. Spironolactone; 4. Oral tetracyclines. Cohorts were 1:1 propensity score matched to controls with baseline demographics and potential confounding comorbidities. 2-year Cox proportional hazards models with 95% confidence intervals (CIs) were used to assess risk of T1DM and T2DM development. Compared to topical retinoids, isotretinoin use had no significant difference in T1DM risk (hazard ratio (HR) [95% CI] = 0.98 [0.51, 1.87]) or T2DM risk (HR [95% CI] = 0.73 [0.49, 1.11]). Compared to spironolactone, isotretinoin use had no significant difference in T1DM risk (HR [95%] = 0.39 [0.12, 1.21]) and a significantly decreased risk of T2DM (HR [95% CI] = 0.42, [0.25, 0.71]). Compared to oral tetracyclines, isotretinoin use had no significant difference in T1DM risk (HR [95% CI] = 0.73 [0.40, 1.33]) and a significantly decreased risk of T2DM (HR [95%] = 0.52, 0.35, 0.77]). Sensitivity analyses excluding patients with obesity and PCOS revealed similar results. These findings provide reassuring support that isotretinoin is not associated with an increased risk of T1DM or T2DM in acne patients.

0177

Geographic disparities in dermatologic care access: An analysis of kentucky

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This study utilizes GIS mapping to assess geographic disparities in access to dermatologic care in Kentucky, a state with a known significant rural population and poor national health rankings. Using 2019 Medicare data, the distribution of dermatology providers and utilization rates of dermatologic services were analyzed across Kentucky's 120 counties, classified by urban or rural designation. Geographic mapping revealed vast areas of rural Kentucky with little to no access to dermatologic services, even though 50.4% of the 550,718 fee-for-service (FFS) Medicare beneficiaries reside in rural counties. Despite this, only 13.6% of dermatology providers served these rural areas. Notably, providers offering complex dermatologic procedures were located in 31.4% of urban counties compared to just 4.7% of rural counties ($p<0.001$), while less complex procedures showed similar disparities (37.1% of urban counties vs. 17.6% of rural counties, $p=0.040$). Urban beneficiaries were 8.5 times more likely to access dermatologic services than their rural counterparts. These findings highlight significant epidemiologic disparities in access to dermatologic care, with rural populations facing significant barriers to essential procedures. The findings of these geographic findings further highlight the rural-urban disparity in access to care due to inequitable provider distribution. Policies geared towards investing in improved access to underserved areas can improve dermatologic outcomes for rural populations.

0178

Social media influence on the face of dermatology

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This study investigates how social media influences medical students' perceptions of dermatology as a specialty and career choice. A cross-sectional survey was conducted among 137 students at Cooper Medical School of Rowan University to assess social media usage, engagement with dermatology-related content, and its impact on career interest. The survey revealed that 82% of students engaged with dermatology content, primarily on Instagram and YouTube and that students exposed to this content were more likely to view dermatology positively, with half of those considering a dermatology career citing social media as an influential factor. 55% of students not interacting with such content expressed negative perceptions of the field. While social media exposure often enhanced interest, some participants noted an overemphasis on cosmetic aspects, potentially overshadowing dermatology's clinical scope. These findings highlight social media's dual role in shaping perceptions, emphasizing the need for accurate, professional-driven content to mitigate misinformation. Social media is a powerful tool that can shape the perceptions and career decisions of medical students. However, more effective strategies are needed to mitigate the risk of misinformation, given that most dermatology-related content on social media is not created by medical professionals. Taken together with the results of this study, it is evident that its in the best interest of the medical community to understand this new era of medical decision making.

0179

Exploring erythema differences across racial groups in dermatomyositis: Implications for clinical trial outcome measures

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Two measurement tools are currently used to assess dermatomyositis (DM) skin disease activity: the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) and the Cutaneous Dermatomyositis Investigator Global Assessment (CDM-IGA). As DM studies become more inclusive of cutaneous disease, it is important to utilize a scoring tool that accurately captures changes in skin activity. We aim to assess variability in erythema presentation across DM subtypes and among racial groups to help describe an outcome measure that accurately reflects improvement in DM skin disease. Our cross-sectional study included 464 DM patients enrolled in the Penn Dermatomyositis Database from January 2007 to May 2024. 84.5% of our cohort was female. 89% were White, 6.3% were Black and 3.2% were Asian. Classic (49.1%) and amyopathic (48.3%) subtypes were the most prevalent subtypes. Mean erythema, calculated using the CDASI-Activity total erythema score divided by number of affected areas at first visit, was categorized as "pink" (1.00–1.49) or "red" (≥1.50) as a surrogate for the CDM-IGA score. White (1.29±0.02), Black (1.11±0.05), and Asian (1.14±0.11) patients were all considered "pink" ($p<0.01$), but White patients had significantly increased average erythema compared to Black patients. CDASI severity differed across race: Whites [n=419: 50.4% mild], Blacks [n=29: 72.4% mild], and Asians [n=15: 33.3% mild] ($p=0.026$). However, this difference would not be observed using average erythema scores, as scored by the CDM-IGA, suggesting this measurement tool would not accurately record skin disease activity. With the need to standardize DM trial outcome measures for cutaneous disease, our findings support the use of the CDASI, a composite score which considers features other than erythema, as the primary scoring tool in cutaneous trial outcomes.

0180

Association of dietary sodium intake with IL-17-mediated diseases

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IL-17-mediated diseases (psoriasis, psoriatic arthritis, ankylosing spondylitis, hidradenitis suppurativa, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis) have great global burden. Mechanistic data suggests that excess sodium can trigger IL-17 mediated inflammation, but population-based data on the association between salt intake and IL-17 mediated diseases are limited. We conducted a population-based cross-sectional study using data from the UK Biobank to understand if higher dietary sodium intake is associated with higher prevalence of IL-17-mediated disease. Dietary sodium intake was estimated with urine biomarkers using the International Study of Electrolyte Secretion and Blood Pressure (INTERSALT) equation. A 1-gram increase in estimated daily sodium intake was found to be associated with greater odds of having an IL-17-mediated disease (adjusted odds ratio [OR] 1.08, 95% CI 1.06-1.10) as well as more IL-17-mediated conditions (rate ratio 1.08, 95% CI 1.06-1.10). Sub-analyses showed variable associations of sodium intake with individual diseases. Among dermatological conditions, increased sodium intake was associated with the largest odds of hidradenitis suppurativa (OR 2.07, 95% CI 1.76-2.44). Our findings show that a higher dietary sodium intake was associated with an increased odds of having an IL-17-mediated disease. Prospective studies are needed to confirm these findings and evaluate whether change in dietary sodium intake is associated with disease severity among people with IL-17-mediated conditions.

0181

Clinical characteristics and survival outcomes of primary cutaneous T-cell lymphoma in disaggregated Asian American, Native Hawaiian, and Pacific Islander populations

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Current research on cutaneous T-cell lymphoma (CTCL) commonly aggregates Asian American (AA) and Native Hawaiian and Other Pacific Islander (NHOPI) patients into a single racial category. This restrospective cohort study uses SEER data to explore differences in clinical presentation and disease-specific survival among disaggregated AA and NHOPI populations. We analyzed 168 Chinese, 169 Filipino, 48 Vietnamese, 79 Japanese, 149 Asian Indian or Pakistani (AIP), 39 Korean, 63 NHOPI, and 207 Other Asian patients diagnosed with histologically confirmed primary CTCL, alongside 8,289 non-Hispanic White (NHW) patients for comparison. When disaggregated, AIP patients were more likely to be diagnosed at a younger age (42 years), while Japanese patients were more likely to be diagnosed at an older age (65 years). Rates of distant disease at diagnosis varied significantly among these groups, with Korean patients having the highest rates (18%) and AIP patients having the lowest (5.4%). Regarding survival, Korean patients experienced poorer overall survival (aHR=2.69, 95% CI=1.58–4.57) and higher disease-specific mortality than NHW patients (aHR=2.44, 95% CI=1.32–4.52), whereas Japanese patients exhibited lower disease-specific mortality (aHR=0.45, 95% CI=0.22–0.93). Disaggregating AA and NHOPI populations in CTCL reveals important disparities that are otherwise masked in aggregated analyses. These findings highlight the heterogeneity among AA and NHOPI populations—shaped by differences in genetics, cultural practices, and healthcare use—and emphasize the need for targeted awareness and education efforts, particularly for Korean patients. As AA and NHOPI populations continue to grow in the US, further research is essential to develop interventions that address disparities in CTCL presentation and outcomes.

0182

Use of a questionnaire to assess the perception of women with dermatomyositis in family planning

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Dermatomyositis (DM) is more prevalent in women, often diagnosed during childbearing years, and associated with reduced pregnancy rates and live births, underscoring the need for dermatologists to provide preconception counseling to address family planning (FP) concerns in this population. This study assessed FP concerns in women with DM and explored their relationship with skin severity. We conducted a cross-sectional analysis of women aged 18-45 with DM. Participants completed an English version of a Spanish-validated FP questionnaire developed by Alcantara-Luna. Responses were rated on a 5-point Likert scale (0 = strongly disagree to 5 = strongly agree). We compared responses between two groups: mild DM (CDASI-A ≤14) and moderate/severe DM (CDASI-A >14), two-group t-test, at a significance level of 0.05. 27 patients (19 mild and 8 moderate/severe DM) participated (mean [SD] age, 37.74 [4.8] years). The mild DM group reported significantly greater concern in the following statements compared to those with moderate/severe DM:"The idea that my disease will worsen when I have to withdraw or change the drug before pregnancy worries me."(4.05 vs 2.75;p=0.01), "The idea that my disease will worsen when I have to withdraw or change the drug during breastfeeding worries me."(3.8 vs 2.6;p=0.02) and "I consider that my illness may limit me to adequately caring for a child."(4.1vs 2.5;p=0.001). Unexpectedly, women with mild DM expressed greater anxiety about disease progression related to family planning than those with moderate/severe DM. This may reflect heightened worry among patients with mild disease and a sense of resignation or reduced agency in those with more severe disease, potentially leading them to deprioritize FP due to perceived barriers/priorities. These findings highlight the need for further qualitative research to better understand and address FP concerns in women with DM.

0183

Discordant treatment response between clinicians and patients with skin chronic GVHD and association with mortality

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Both clinician-reported and patient-reported treatment response (CRTR and PRTR) are critical measures of therapeutic efficacy in skin chronic GVHD (cGVHD), however, these outcomes are not always correlated. Identifying factors associated with discordant treatment response between clinicians and patients and comparing the association of CRTR and PRTR with mortality will assist in integration of objective and subjective endpoints in clinical trials and practice. In this multicenter cohort study of adults with skin cGVHD, we identified patient and disease characteristics associated with discordance between CRTR and PRTR, defined as ≥1-point difference on a 3-point scale (improved, stable, worse). The association of CRTR and PRTR with nonrelapse mortality and their prognostic values were assessed. Of 489 adults with skin cGVHD (n=192 [39%] female, median age 55 years [IQR:43-62]), n=321 (66%) had concordance and n=168 (34%) discordance between CRTR and PRTR. Patients with sclerotic cGVHD had greater odds of discordant treatment response in both directions compared to those without sclerosis (adjusted OR (aOR) 2.33 [CI:1.21-4.51, p=0.012] PRTR better than CRTR and aOR 3.42 [CI:1.53-7.65, p=0.003] CRTR better than PRTR). Both CRTR (aHR 2.27 [CI:1.46-3.54, p<0.001]) and PRTR (aHR 1.87 [CI:1.13-3.09, p=0.014]) were associated with nonrelapse mortality in patients with skin cGVHD. In the subset with sclerosis, only PRTR was associated with nonrelapse mortality (aHR 2.13 [CI:1.05-4.30, p=0.036]) and had the highest concordance measure with mortality (Harrell's C: 0.77). Patients with sclerosis are more likely to have discordance between CRTR and PRTR, with PRTR associated and prognostic of mortality. Both CRTR and PRTR should be reported in skin cGVHD clinical trials with endpoint priority dependent on study design and treatment goal.

0184

Single-center case series of cutaneous manifestations of inborn errors of immunity

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Inborn errors of immunity (IEIs) are disorders of the immune system caused by a mutation in a single gene. IEIs can affect aberrant response to self in the form of autoimmunity, autoinflammation and malignancy as well as to non-self in the form of allergy and susceptibility to infection. Clinical findings of immune dysregulation in the skin have an important yet underappreciated role in the diagnosis and treatment of patients with IEIs. To date, over 500 genes have been identified with distinct defects that lead to an IEI. Up to 70% of patients diagnosed with an IEI have reported cutaneous manifestations of disease and as many as 50% of patients have pertinent skin findings when receiving diagnosis of an IEI. The prevalence and early timing of skin involvement in IEIs highlights the importance of an enhanced understanding of skin findings in IEIs so that patient diagnosis, treatment and disease prognosis can be improved. Herein we report the cutaneous manifestations of IEIs across 25 patients from The Mount Sinai Health System. Cases range in age from 17 months old to 50 years old and were chosen based on genetic or biochemical diagnosis of an IEI and clinically relevant skin disease. The most common skin finding among IEI patients were disseminated warts (n = 4 - DOCK8 deficiency, CVID, Hyper IgM Syndrome and NFKB1 deficiency). Recurrent skin infections with Helicobacter (n = 3 - CVID of X-linked Agammaglobulinemia (XLA) was the second most frequent skin finding. Vitiligo (n = 3 - CVID) was the third most common finding. All other diagnoses such as granulomas (CGD), bullous pyoderma gangrenosum, vascular malformations (PIK3CA), fungal infection (XLA), psoriasis (IKZF1) , eczema (WAS), psuedomanas infection (CVID) and candida mucocutaneous candidiasis (STAT1) were detected at least once in our patient group. Additional work is required to better understand the early disease course of IEIs in the skin to warrant immunological assessment.

0185

Systemic therapies in pediatric psoriasis: Impact on liver function in a high-risk population

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This study evaluated the impact of systemic psoriasis treatments on liver function in pediatric patients at high risk for non-alcoholic/metabolic dysfunction-associated fatty liver disease (NAFLD/MAFLD). A cohort of 12 patients (58% female, 58% Hispanic/Latino) with moderate-to-severe psoriasis was followed prospectively from 2010 to 2024, with assessments of liver function (serum hepatic panel and MR imaging), psoriasis severity (by body surface area, BSA), and body mass index (BMI). Nearly all patients (92%, n=11) were overweight or obese and 33% (n=4) were eventually diagnosed with NAFLD/MAFLD. Biologic therapies had variable effects on LFTs. Subjects treated with ustekinumab (n=3; 13–62 months) had ALT levels decline by 62% on average, with normalization (<29 U/L) in one case, and simultaneous improvement in psoriasis BSA (mean 58%) despite a stable BMI. In subjects on secukinumab (n=4; 9–21 months), ALT normalized despite stable BMI in 1 of the 3 subjects with baseline elevations. One patient on guselkumab (n=2; 15–19 months) achieved ALT normalization, but this may have been due to reduced BMI. One patient on adalimumab (n=4; 1–12 months) had normalization of ALT but the remaining subjects had ALT and BSA increases, prompting therapy changes. Etanercept (n=4; 3–44 months) reduced BSA by 52% on average, but improvements in ALT were not observed. Methotrexate (n=7; 3–82 months) achieved a 45% mean BSA reduction but transient ALT elevations occurred in one patient, and 6 patients (86%) required therapy changes due to insufficient psoriasis control. Phototherapy (n=7; 5–100 sessions) resulted in partial improvement in psoriasis symptoms for 4 (57%) of patients; however, logistical challenges limited its practicality, and it lacks the potential to independently mitigate fatty liver risks. These findings suggest biologics like ustekinumab and secukinumab may have the potential to improve both psoriasis and liver function in high-risk populations, but larger studies are needed to validate these results.

0186

Infantile atopic dermatitis and sleep in the first two years of life in a contemporary cohort study

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Atopic dermatitis (AD) is often associated with poor sleep, but many infants/toddlers without AD also have poor sleep. Poor infant sleep places a high burden on parents and can lead to establishment of unhealthy sleep patterns. We aimed to examine the association between AD and sleep in the first 2 years of life within a contemporary multinational cohort. The NiPPeR double-blind randomised trial recruited 1729 UK, Singapore & New Zealand women planning a pregnancy. Participants were allocated to a control (standard micronutrients (folic acid, iodine, calcium, β-carotene, iron) or an intervention supplement (additionally including vitamins D, B2, B6, B12, zinc, myo-inositol, probiotics (L.rhamnosus, B.animalis)). Infant/toddler sleep was assessed using the nurse-led, validated, Brief Infant Sleep Questionnaire (BISQ) at ages 3 & 6 weeks & 3, 6, 12 & 24 months, allowing derivation of the number of awakenings and wake duration after night sleep onset, night sleep duration and day sleep. 553 offspring were assessed at ages 6 and 12 months; AD prevalences (trial secondary outcome, modified UK Working Party Diagnostic Criteria) were 10.8% and 13.0%, respectively. Night time sleep and number of awakenings were similar in infants with AD and those who did not have AD. Infants with/without AD had similar sleep trajectories adjusting for site, sex and breastfeeding (regression analyses examining AD at 6 and 12 months in relation to night sleep at the different timepoints were not significant (p>0.05)). It is encouraging that no associations were seen in our longitudinal data, perhaps due to effective management of AD. This supports guidance for optimisation of AD treatment to minimise effects on infant sleep.

0187

Analysis of race in time to keratinocyte carcinoma in solid organ transplant recipients: Results of a single-institution study.

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Organ transplant patients are at an increased risk of developing keratinocyte carcinomas (KC), including squamous and basal cell carcinomas (SCC/BCC). The risks of developing KCs include type of immunosuppression, years since transplantation, race, male sex, smoking, and age at transplantation. Our study analyzes the timelines and risks of KCs in white versus non-white patients (i.e. Black, Hispanic, Asian, other) utilizing a database of 10,767 solid organ transplant recipients at Mount Sinai Health System. In our cohort, 2.3% (n=248) developed SCC and 2.1% (n=229) developed BCC, with white patients exhibiting increased odds of developing both SCC (OR = 5.75, 95% CI: 4.21-7.79, $p < 0.001$) and BCC (OR = 10.16, 95% CI: 7.09-15.01, $p < 0.001$) when compared to non-whites. These increased odds were seen at all transplant age groups. However, the time to KC diagnosis following transplantation exhibited no significant difference between white and non-white patients. These results were seen in SCC, BCC, and melanoma within our cohort. Our findings suggest that although non-white patients had decreased risk of developing KC overall, they developed them within a similar timeframe as their white counterparts. Thus, these patients should not necessarily undergo different onset or frequency of skin cancer screenings. Future work on understanding intrinsic factors relating to the time course of skin cancer development will help elucidate the frequency and timing of skin cancer screenings.

0188

Jak inhibitor intraclass switch in alopecia areata patients: A retrospective review of cases at an academic center

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Alopecia Areata (AA) is an inflammatory skin condition leading to non-scarring hair loss on the scalp or other hair-bearing areas. Jak inhibitors (JAKi) are used to promote hair growth by blocking the JAK-STAT pathway and down-regulating the inflammatory response. Baricitinib and Ritlecitinib are JAKi approved for the treatment of AA. While there is no significant difference in efficacy between both drugs, there is no data on the switch from one JAKi to another for AA. We analyzed the charts of 16 AA patients at our large academic dermatology clinic between June-2018 and August-2024 for patients prescribed baricitinib and ritlecitinib sequentially. All patients (n=16) were switched from baricitinib to ritlecitinib. On average, patients were on Baricitinib for 414.6 days prior to switch. 6 patients were switched due to primary non-response, while the other 10 were switched after reaching a treatment plateau. The average baseline SALT scores were 81%, with half (n=8) having a score above 95%. The average pre-switch SALT scores were 65%. At the post-switch most recent follow-up visit (average 271 days after switch) SALT scores averaged 52%, with a 20% decrease compared to pre-switch scores and 36% decrease compared to baseline scores. Paired t-tests for difference in SALT scores showed a significant decrease in post-switch scores compared to pre-switch and baseline scores ($p<0.01$). 2 adverse events were noted, one patient developed mild acne on Baricitinib and continues JAKi therapy. The second experienced decreased leukocyte and platelet counts on Ritlecitinib, leading to its discontinuation. While treatment of AA can be challenging, JAKi offer a unique and effective approach for helping patients with hair regrowth. In our cohort, most patients had reached a treatment plateau and following intraclass switch were able to obtain significant improvement in SALT scores. This study is limited by its small sample-size and retrospective nature; however, we have shown positive results in hair growth after intraclass switch.

0189

Ultrasound as a robust tool for lymph node staging in cutaneous T-cell lymphoma: guiding the necessity for invasive biopsy

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Accurate assessment of lymph node (LN) involvement is crucial for determining disease progression and treatment strategies in cutaneous T-cell lymphoma (CTCL). However, the reliance on biopsy for evaluating LN involvement poses risks that limit its widespread application. This underscores the need for non-invasive methods to identify patients who may benefit from biopsy. In the current study, we found that ultrasound detects lymphadenopathy in CTCL patients with high sensitivity and is strongly correlated with disease staging and prognosis in mycosis fungoides (MF), the most common type of CTCL. Key ultrasound parameters, including increased short-axis diameter ($p = 0.0038$) and loss of the echogenic hilum ($p = 0.0376$), were significant indicators of malignant LN involvement. ROC curve analysis revealed that combining short-axis diameter with the echogenic hilum provides superior predictive value for malignant lymphadenopathy. The identified cut-off values offer valuable prognostic insights for MF patients and may help clinicians identify those requiring LN biopsy or more aggressive procedures. This study highlights that ultrasound is an effective, non-invasive tool for detecting and monitoring malignant LN involvement in CTCL, guiding clinicians in determining the necessity of invasive biopsy.

0190

Adalimumab therapeutic drug monitoring in hidradenitis suppurativa

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Hidradenitis suppurativa (HS) is a chronic inflammatory condition. While adalimumab (ADM) is an effective treatment for moderate-to-severe cases, about 50% of patients lose response after 36 weeks. Therapeutic drug monitoring (TDM) optimizes treatment by assessing ADM levels and anti-drug antibodies (ADAs). This observational, single-center study enrolled 46 adult patients with moderate-to-severe HS on ADM therapy from January 2023 to May 2024 at a HS specialty clinic, evaluating serum ADM levels and clinical outcomes after a minimum period of 8 weeks. Most participants were female (60.9%) with a median age of 38. Clinical responses were assessed by changes in lesion count and categorized as: Low (<50%), Partial (50-75%), or High (>75%) improvement. Statistical analyses included Spearman's rank correlation, Pearson's correlation, and the Wilcoxon-Mann-Whitney tests. Serum ADM levels were correlated with clinical response ($r = 0.43$, $p = 0.002$). Low responders had lower ADM level (9.14 vs. 24.6 µg/mL; $p = 0.007$) and higher drug clearance (0.94 vs. 0.37 L/day; $p < 0.001$). ADAs detected in 10 patients, which were associated with lower ADM levels (10 vs. 17 µg/mL; $p = 0.03$) and increased drug clearance (1.048 vs. 0.406 L/day). No ADA-positive patients achieved a high responders. The HLA-DQA1*05 allele was linked to ADA development (83% vs. 19%; $p = 0.001$). High responders showed longer drug survival (146 vs. 45 weeks) and lower hsCRP levels (1.9 vs. 18.3 mg/L). Higher ADM levels and the absence of ADAs are associated with improved outcome in HS patients on maintenance ADM therapy. Elevated ADM levels correlated with better clinical outcomes, lower inflammation, and extended drug survival. However, the presence of ADAs was linked to increased drug clearance, lower ADM levels, and diminished therapeutic efficacy.

0191

Systemic therapy targeting psoriatic inflammation associates with decreased incidence of dementia: An observational retrospective cohort study

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Psoriasis has been implicated in cognitive impairment and dementia. Recent findings indicate systemic inflammation may influence neuroinflammation and subsequent cytokine-driven neurodegeneration, though evidence remains inconclusive. We investigate the relationship between psoriasis and dementia and whether systemic treatments for psoriasis impact this association. Using TriNetX, we conducted a retrospective-cohort-study from 2004-2024. Individuals aged 65-95 without prior history of dementia were included. A control group of individuals without psoriasis [N=5337442] was compared to two experimental cohorts: 1) psoriasis patients receiving systemic therapies [N=14679] and 2) psoriasis patients managed without systemic therapies [N=39601] and matched 1:1 by demographics, BMI, and common risk factors for dementia. Odds Ratios (OR) with 95% confidence intervals were calculated to assess incidence of Alzheimer's disease (AD), vascular, and nonvascular dementia, with sub-analyses based on systemic treatment. Outcomes were assessed over a period of up to 20-years. Psoriasis patients managed without systemic therapy were >49% more likely to develop AD (OR=1.56[1.39,1.75]), vascular (OR=1.56[1.35,1.81]), and nonvascular dementia (OR=1.49[1.39,1.60]) compared to controls. Conversely, psoriasis patients managed with systemic therapy were 31% less likely to develop AD (OR=0.69[0.54,0.86]) and 15% less likely to develop nonvascular dementia (OR=0.85[0.75,0.97]) compared to controls. Though fewer cases of vascular dementia existed amongst treated psoriasis patients compared to controls (105 vs 124), findings were not statistically significant (OR=0.85[0.65,1.10]). Untreated psoriasis is associated with a higher likelihood of dementia compared to non-psoriatic individuals. However, in the presence of systemic therapy, likelihood is markedly reduced. Results of this study warrant further research exploring the impact of systemic therapy on neurocognitive health of psoriasis patients.

0192

Estrogenic effects of 5-alpha-reductase inhibitors in male androgenetic alopecia patients

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Androgenetic alopecia (AGA) is commonly treated with 5-alpha-reductase inhibitors (5ARIs), which inhibit the conversion of testosterone to dihydrotestosterone. However, these medications may shift hormone pathways, potentially increasing estrogen levels and raising concerns about estrogen excess. This study investigates conditions associated with estrogen excess in male AGA patients treated with 5ARIs. TriNetX Research Network was queried for AGA males (ICD-10: L64, L65.8, L65.9) treated with finasteride or dutasteride from 2004–2024, with 5ARI-naïve AGA males used as controls. Propensity score matching was applied based on age, race/ethnicity, obesity/overweight, alcohol use disorder, and hormone replacement therapy. Outcome risks ≥1 day post-5ARI prescription were assessed for gynecomastia (ICD-10: N62), infertility (ICD-10: N46), and erectile dysfunction (ED) (ICD-10: N52). Patients with outcomes prior to 5ARI initiation were excluded. We included 49,937 5ARI-treated and 49,937 5ARI-naïve AGA males. Mean age at index was 39.0 vs. 39.4 years for 5ARI-treated patients vs. controls, respectively, with a majority White identifying (70.9% vs. 69.2%, respectively). Baseline characteristics were clinically similar between cohorts (standardized mean differences <0.04). Compared to controls, 5ARI-treated AGA males had higher risk of gynecomastia (RR: 1.402 [95% CI: 1.218–1.615]) and ED (RR: 1.613 [95% CI: 1.533–1.699]), but no association with infertility (RR: 1.130 [95% CI: 0.976–1.309]) was observed. Our findings indicate increased risk of gynecomastia and ED in 5ARI-treated AGA males, suggesting possible testosterone aromatization contributing to estrogenic effects. The observed associations underscore the need for physicians to consider the potential hormonal side effects when prescribing 5ARIs for male AGA and to discuss these risks with patients as part of shared decision-making.

0193

Predictors of high-quality patient-submitted skin images among the elderly through a teledermatology platform

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Teledermatology benefits older adults by reducing costs, saving time, and increasing access to care. Understanding factors influencing its success is key to improving care for this population. Our prospective, observational study followed 138 patients ≥65 years for 1 year. We collected 1,992 images taken by patients. Patients received a text message with a secure, protected link, making it very easy for them to upload images directly from their phones. The study population was diverse, with 88% of the participants aged ≥65 years and 12% aged ≥80 years. Our study population was 53% female, 53% non-Hispanic white, 17% Hispanic, 9% Black, and 14% Asian. Images were rated by clinicians using a Likert scale that assessed: distance, brightness, focus, background, and adequacy for clinical decision-making (0-lowest; 3-highest for a factor, total 14 points max). We conducted a multivariable-regression analysis to identify predictors for patient-submitted photo quality using a generalized estimating equation model by adjusting for sociodemographic characteristics. Additionally, we also performed a subgroup analysis among those aged 80 and older. While the overall image quality was high (mean 12.8/14.0, SD=2.0), those aged ≥ 80 years (vs 65-79, p=0.0079), of White race (vs Black, p=0.022), or those who were not-married (vs married, p=0.020) showed poorer image quality compared to their counterparts. Among those aged ≥80 years, Asians/Pacific Islanders (vs White, p=0.0098), those with less than high school education (vs bachelor's degree, p=0.0001), or married (vs not-married, p=0.038) showed poorer photo quality. By factors, age ≥80 (distance, decision-making), White race (distance, focus, background), and being not-married (distance, brightness, background) were associated with poorer image quality (p<0.05). Improving accessibility, reducing navigation barriers, and focusing on tailored solutions for underperforming groups will be crucial to achieving more equitable dermatology care through teledermatology.

0194

Qualitative study of patient-reported outcome data collection among clinicians in dermatology at a single academic center

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Patient reported outcomes (PRO) collection helps dermatologists better understand patient perspectives to facilitate shared medical decision-making. One AAD quality metric is to collect quality of life assessments at least once within a 12-month period for patients with chronic skin diseases, but most clinicians do not routinely collect PRO. This semi-structured interview study aimed to elicit key preferences, facilitators, and barriers for routine PRO collection by clinicians in dermatology practices. Clinicians were recruited from Emory Dermatology, which has implemented routine PRO collection. Verbatim transcripts were coded and analyzed deductively using the Theoretical Domains Framework to generate salient themes. We include interview data from nine dermatologists and one APP. Professional roles of all interviewed clinicians aligned with PRO collection. Memory, attention, and decision-making requirements for PRO collection by clinicians were minimized via automation in the electronic medical record (EMR). Skills in navigating EMR were needed to retrieve PRO data. Environmental factors affecting PRO collection included patient MyChart access, IT support for PRO integration into the EMR, institutional interest in PRO collection and research, limited clinician oversight on PRO collection by other staff members, and high patient volume in dermatology clinics. Social support between staff allowed workflow division and maximized opportunities for PRO collection, while survey fatigue and patient skepticism on PRO utility affected PRO collection. This study was limited to clinician perspectives in a single clinic. To broadly implement routine PRO data collection, automation and utilization in the EMR, demonstrating PRO value, establishing institutional support, and streamlining workflow are needed.

0195

Atypical fibroxanthoma: A review of the literature

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Atypical fibroxanthoma (AFX) is a rare, low-grade, dermal neoplasm. The purpose of this article is to review the current literature on AFX as it relates to epidemiology, clinical presentation, histopathology, immunohistochemistry, treatment, and prognosis. An extensive literature review was conducted using PubMed to identify articles related to AFX. AFX typically presents as a red nodule or plaque on the head and neck regions. Etiology is poorly understood, but it is believed that AFX arises from myofibroblasts or fibroblast-like cells and ultraviolet light exposure may play a role in pathogenesis. AFX is more common among the elderly of White race, however it has been reported in other patient populations as well. Skin biopsy is the gold standard for diagnosis, however, AFX has variable histological patterns which may cause AFX to be a diagnosis of exclusion. Histological patterning may include the following: spindle cell, clear cell, keloid-like, rhabdoid, pleomorphic, epithelioid, granular cell, bizarre cell, pseudoangiomatous, inflammatory, and many others. AFX is considered to be a superficial variant of undifferentiated pleomorphic sarcoma (UPS) because it is considered less aggressive with fewer genomic alterations. Further, Immunohistochemistry (IHC) staining may be helpful to exclude AFX from other skin cancers, as AFX can mimic UPS, squamous cell carcinoma, and melanoma. Notably, AFX will stain negative for HMB-45, seen with squamous cell carcinoma, as well as melanoma IHC stains: pan-cytokeratin stains and CD31. Although AFX has an excellent prognosis with low rates of recurrence, Mohs micrographic surgery has become the standard-of-care treatment as it allows for a reconstructive advantage and may decrease recurrence rates even further. Atypical fibroxanthoma is a low-grade tumor which has a favorable prognosis, however a classification system for histologic patterning is needed for a swifter diagnosis.

0196

Levamisole-induced pyoderma gangrenosum case report

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Pyoderma gangrenosum (PG) is one of the neutrophilic dermatoses. While the relationship between PG and systemic diseases is well-established, the association between PG and recreational drugs is less certain. PG in cocaine and heroin users is thought to be due to levamisole, a contaminant which can prolong the euphoric effects of recreational drugs. In this report, we present a case of severe PG in the setting of recent drug use. A 53-year-old man with a history of substance use presented to the ED with a 6-month history of worsening, painful ulcers with purulent drainage that began as pustules. He endorsed ongoing consumption of 3-10 bags of heroin/day. The patient denied any trauma or similar symptoms in the past. Physical examination was notable for ulcers with undermined, erythematous borders and a monomorphic base on the left cheek, back, and extremities. Laboratory workup was notable for a mildly elevated erythrocyte sedimentation rate (40 mm/hr), c-reactive protein (58.1 mg/L), and anti-cardiolipin antibodies (17 U/mL). The patient's history of pustules transforming into ulcers, the classic morphology, and the widespread distribution of symptoms in the setting of recent drug use was consistent with levamisole-induced PG (LIPG). He was started on prednisone 60 mg daily with modest improvement after the first week. Levamisole is well-known to dermatologists given its ability to induce severe vasculitis and vasculopathy. Although it is rarely detected in patients due to its short half-life, LIPG has several unique features that help differentiate cases from classic PG. Patients with LIPG typically have more numerous, diffusely spread lesions with a larger average diameter. Lesions are most prominent on the trunk, while classic PG often presents on the lower extremities. This is consistent with our patient, who had 17 ulcers, the majority on the back, with the largest measuring 10 cm in diameter. This case adds to the existing literature of LIPG and emphasizes the unique distribution of LIPG compared to that of classic PG.

0197

An epidemiologic assessment of FDA-reported complications of cosmetic injections, 2020-2024

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The objective of this study was to examine the data surrounding patient adverse experiences to cosmetic injections using a national database. Data were taken from reports by the FDA's Manufacturer and User Facility Device Experience (MAUDE) database. All entries over a 5-year period (1/1/2020 to 12/31/2024) were included for the following brands: Restylane, Juvéderm, and Sculptra. General etiology (contamination; device failure; off-label use, or user error) of the reported event were assessed. Among specific Juvéderm and Restylane products (when named), G', a measure of elasticity that can be assessed across brand/product, was included along an ordinal scale and analyzed for impact on specific patient outcomes of interest (infection, occlusion, vision-related events, skin necrosis, and anaphylaxis). A total of 2,351 entries were reported and occurred during the specified time period. Overall, the most common brand-specific events were infection (Juvéderm, 37% of all brand-specific adverse events), swelling/edema (Restylane, 38%), and nodules (Sculptra, 47%). The majority of cases of user error occurred among Juvéderm injectors (98%). Among logistic regression analyses, G' level remained negatively associated with infection risk after controlling for brand ($p<0.001$); G' level was similarly positively and significantly associated with likelihood of obstruction event reporting ($p<0.001$) as was the interaction term between G' and brand ($p=0.002$). Product rheology and proprietary, brand specific factors are both implicated in adverse outcomes of cosmetic injections, particularly for risk of infection and vascular obstruction. Given that over 2.5 million soft tissue filler injections are performed annually across the United States and this number continues to rise, vigilant epidemiologic assessment is critical to identify risks of branded product lines in order to ensure safety in dermatologic care.

0198

A new clinical understanding of porocarcinoma

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This study aims to assess the clinical experience and outcomes in managing porocarcinoma, a rare form of skin cancer arising from cutaneous intraepidermal ducts of eccrine sweat glands, historically regarded as an aggressive cutaneous malignancy. A retrospective review of patients treated at UVA diagnosed with porocarcinoma from 2001 to 2024 was conducted with data retrieved from electronic medical records. Sex, age, race, tumor location, size, immunosuppression status, treatments, overall survival rates, recurrence-free survival rates, and disease-specific survival rates were examined. We identified 32 patients diagnosed with porocarcinoma, comprising 19 males and 13 females. Following diagnosis, one patient declined treatment, and two were lost to follow-up, leaving 29 treated patients. At presentation, 7% (2/29) presented with preoperative regional lymph node metastasis. Both patients received wide local excision (WLE) followed by radiation therapy. Among the total cohort, 17% underwent Mohs micrographic surgery alone, and 62% received WLE only. 21% received additional therapies: 14% underwent radiation therapy after surgery, 3% received radiation therapy followed by immunotherapy, and 3% opted for no treatment. Five patients underwent sentinel lymph node biopsy, with one testing positive for metastasis. During follow-up, 10% (3/29) experienced local disease recurrence, and 3% had regional lymph node and distal metastasis. Among those with recurrence, the two patients with local recurrence (67%) were treated with WLE, and the patient with more aggressive disease (33%) received radiation therapy followed by immunotherapy. The overall recurrence-free rate was 90%, with a median follow-up duration of 40 months. Although porocarcinoma has traditionally been regarded as an aggressive disease, our cohort exhibited low rates of short-term recurrence and metastasis. These findings challenge the current perception of the disease and underscore the need for further research to refine clinical approaches and enhance our understanding of porocarcinoma.

0199

Dermatologic care for urgent care patients not referred to dermatology

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Our previous study (DOI:10.1007/s00403-024-03662-1) on urgent care (UC) referrals to dermatology revealed significant discrepancies in diagnoses and treatment plans between UC providers and dermatologists. Surveyed dermatologists identified frequent treatment errors, particularly in corticosteroid and antibiotic prescribing practice. Building on these findings, this study analyzed 511 skin-related encounters from 8 University of Rochester UC sites that did not result in a dermatology referral (9/2022–3/2024). Analyses (Pearson chi-square and ANOVA at α=0.05) focused on diagnostic patterns, corticosteroid and antibiotic usage, and bacterial culture practices. The most common diagnoses were infections of the skin and subcutaneous tissue (27%), followed by rash (17%) and allergic contact dermatitis (ACD, 16%). In our previous study of referred patients, rash and skin infections were most commonly misdiagnosed by UC providers, suggesting the potential for diagnostic inaccuracies within this non-referred population. Oral antibiotics were prescribed in 34% of cases, but only 14% included a culture, with no significant association between antibiotic type and culture acquisition. Oral steroids were prescribed in 25% of cases (mean duration 9.5 ± 4.4 days), of which 9% also received antibiotics, mostly for infections or ACD. Oral steroids were prescribed most often for ACD (52%) and rash (20%). Treatment durations varied by diagnosis ($p<0.0001$), ranging from 12.2 ± 3.3 days for ACD to 4.9 ± 0.9 days for unspecified dermatitis. Overall, management concerns in the non-referred population mirrored those in referred patients, including lack of bacterial cultures with antibiotic prescriptions and frequent use of systemic corticosteroids, often with insufficient dosing when prescribed. These findings highlight the need for standardized treatment protocols and targeted education to enhance the quality of UC dermatologic care.

0200

Odds ratio (OR) or risk ratio (RR): Correct interpretation is key for clinical translation of treatment effectiveness, an example in psoriasis

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The OR is often the default summary measure of choice for dichotomous therapy response outcomes. However, the RR may be more appropriate in cohort studies of real-world effectiveness where risk has a more intuitive interpretation than odds, but requires careful consideration and accurate interpretation. To demonstrate how the OR may not reasonably approximate the RR in cohort studies of psoriasis patients, this study estimated the association between baseline Psoriasis Areas Severity Index (PASI) and PASI75 at 6 months among patients initiating biologic therapy. Adults who initiated a biologic and had a follow-up visit were selected from the CorEvitas Psoriasis Registry (N=5851). Modified-Poisson and logistic regression were used to estimate the RR and OR, respectively, for achieving PASI75 among baseline PASI groups: mild (ref; ≤5, n=2404), moderate (≤12, n=2210), severe (≤20, n=806), and very severe (≤72, n=431). Models were adjusted for age, race, sex, disease duration, psoriatic arthritis, and prior biologics. The percent of patients who achieved PASI75 increased with higher baseline PASI: 43.8 of mild, 59.8 of moderate, 71.0 of severe, and 74.0 of very severe. Adjusted RRs (95% CI) for achieving PASI75 for moderate, severe, and very severe baseline PASI were 1.30 (1.23-1.37), 1.50 (1.39-1.62), and 1.58 (1.48-1.70), respectively, while the corresponding ORs were of higher magnitude: 1.91 (1.63-2.23), 3.23 (2.55-4.10), and 4.16 (3.05-5.66), respectively. Thus, compared to patients with mild baseline PASI, those with very severe baseline PASI had 1.58 times higher risk and 4.16 higher odds of achieving PASI75. In real-world cohort studies evaluating response to therapy, the interpretation of OR estimates as RR is not recommended, as they produce different numerical estimates of the underlying associations. When selecting a measure of association, careful consideration of outcomes and accurate interpretation are necessary for appropriate inference to patient care.

0201

Prevalence and association of cardiovascular comorbidities in prurigo nodularis: A systematic review and meta-analysis

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Prurigo nodularis (PN) is a neuroinflammatory disorder characterized by persistent pruritus and nodular lesions, significantly impairing quality of life. Evidence suggests a potential relationship between PN and cardiovascular (CV) comorbidities, but this relationship remains unclear. We conducted a systematic review and meta-analysis to assess the prevalence of CV conditions in PN patients. Embase, PubMed, Scopus, and Cochrane Library databases were systematically searched for English-language studies (June 2024; PROSPERO CRD42024574854). Studies with ≥20 PN-diagnosed individuals reporting CV comorbidities were included; reviews, and qualitative studies were excluded. Pooled prevalence proportions with 95% confidence intervals (CIs) were estimated using a random-effects model (n≥3 studies). Of 496 abstracts screened, 16 full-text articles were reviewed, and 9 studies were included (pooled n=20,381 PN patients). The pooled prevalence of hypertension was 31.2% [95% CI, 14.0%-48.3%; n=5,616] across 6 studies, with high heterogeneity (I^2 = 99.88%, $p < 0.001$). Congestive heart failure (CHF) prevalence was 8.8% [95% CI, 1.5%-16.1%; n=674] across 5 studies, with similarly high heterogeneity (I^2 = 99.83%, $p < 0.001$). Coronary artery disease, reported in 3 studies (range: 2.0%-21.4%; n=1,008), yielded non-positive confidence intervals and a non-significant pooled prevalence estimate. Our findings suggest PN patients may have a considerable burden of CV comorbidities, particularly CHF, which occurs at rates exceeding global estimates for the general (2%-3%) and elderly (4%-5%) populations. Limitations to this meta-analysis include few studies, retrospective designs, and few control groups, limiting comparisons and risk calculation. However, these results highlight the need for additional prospective studies to clarify disease-specific risks and evaluate the need for CV screening approaches in this population.

0202

Neighborhood-level socioeconomic status and hidradenitis suppurativa severity

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We examined the association between neighborhood socioeconomic status (nSES) and hidradenitis suppurativa (HS) disease severity. In a cross-sectional study, we included adult patients with an initial recorded diagnosis of HS (defined by ICD-10 L73.2 and confirmed with chart review) in the health system during the study period (8/1/2019-5/31/2024), a San Francisco Bay Area residential address, and available Hurley staging. We used a census-tract level measure of nSES derived from 2013-2017 American Community Survey data on income, poverty, housing cost, rental cost, education, occupation, employment; census tracts were assigned quintiles based on Bay Area index value distribution. We developed logistic regression models accounting for clustering by census tract in which the binary outcome was HS disease severity (Hurley stage 1 [mild] vs 2-3 [moderate-severe]), the primary exposure was nSES quintiles dichotomized into lower SES (quintiles 1-2) vs higher SES (quintiles 3-5, ref), and covariates included age, sex, and race-ethnicity. Of 462 patients included (mean [SD] age 35.64 [12.91] years, 72.17% female), 58% had mild, 32.5% moderate, and 9.5% severe disease. In unadjusted models, we found greater odds of worse HS disease among patients residing in lower SES neighborhoods: OR (95%) 1.74 (1.18-2.56), P=0.005. Age, sex, race-adjusted models showed nSES effect attenuation, consistent with possible confounding and/or interaction effects: OR (95%) 1.37 (0.88-2.14), P=0.2. We observed evidence of an interaction between nSES and race-ethnicity (P=0.07) . In age and sex-adjusted models stratified by race-ethnicity, the direction of the effect of nSES was similar within several racial-ethnic groups but statistical differences in smaller groups were not observed. Residing in lower SES neighborhoods may be associated with greater odds of more severe HS disease. Larger studies are needed to examine the apparent complex association between nSES and race-ethnicity.

0203

HS progress: Baseline characteristics and disease impact

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Rigorous clinical characterization of diverse individuals with hidradenitis suppurativa (HS) is lacking, thus limiting understanding of clinical course and therapeutic effectiveness in real-world populations. We report baseline characteristics of the multicenter longitudinal Hidradenitis Suppurativa Prospective Observational REgistry and bioSpecimen repository (HS PROGRESS). Since 2020, HS participants have completed electronic surveys and dermatologic evaluations with validated patient-reported outcomes and HS disease measures. Descriptive statistics are presented. Across 7 U.S. centers, 535 participants (79.4% female; median (IQR) age 35.1 years (28.3-42.9); BMI 33.5 kg/m^2 (27.6-39.8), White 62%, African American 29%, Asian 9%, American Native 5%, Pacific Islander 2%; Hispanic 16%) have been enrolled to date. Median age of onset was 18 years (13-25) and diagnostic delay was 4.5 years (1-10), suggesting increased awareness of HS. Obesity (41.9%), anxiety (41.1%) and depression (33.5%) were common. Moderate and severe disease predominated (Hurley stage I 15.6%, II 57.2%, III 27.2%; median IHS4 of 7 (2-25)). In the last week, pain levels were a median 5 (3-6) on a scale from 1-10 and 52.1% reported very large or extremely large effect on quality of life. 89.6%, 92.3%, and 35.7% reported using topical, systemic, and surgical treatments, respectively. Prior biologic use was limited to 47.8% of participants, suggesting barriers to biologic access. High-fidelity data captured from diverse HS patient in the national HS PROGRESS study will be key to identifying prognostic and therapeutic biomarkers and driving therapeutic development.

0204

Trends of prepubescent and pubescent black and white pediatric patients with hidradenitis suppurativa

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The goal of this research is to compare the differences in prepubescent and pubescent black and white pediatrics patients with hidradenitis suppurativa (HS) to aid in a better understanding of the clinical patterns seen in these cohorts to help clinicians best support pediatric patients. We performed a retrospective chart analysis of 1015 pediatric patients diagnosed with HS. In our study, 104 patients were 11 years old or younger at the time of their HS diagnosis, while 913 patients were 12 years old or older. Nearly 37% of children under 11 were black, while only 27% of children over 12 were black. There were no statistically significant differences between these two cohorts in specialty of the diagnostic provider, use of public or private insurance, or sex. The average BMI of children 11 and under was 29.27, while the average BMI of children 12 and over was 31.94, a value that is significantly higher (p=0.0100). Children under the age of 11 were statistically more likely to be white in comparison to those over age 12 (OR=0.67, p=0.0393, 95%CI=0.4285 to 0.9789), suggesting that white children may have more access to care that facilitates diagnosis at a young age. Importantly, the number of patient hospitalizations due to HS in children 12 and older was significantly higher than those 11 and younger (p<0.00001), indicating that the severity of HS flares increases with age and the onset of puberty. The results of this project suggest that children diagnosed earlier with HS have a higher BMI, but fewer hospitalizations. Black children are less likely to be diagnosed with HS at an earlier age than white children, highlighting the need for greater access to dermatologic care across different minority populations.

0205

Prediction of patterns of persistent problematic atopic dermatitis in childhood

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Patterns of atopic dermatitis (AD) activity and severity vary throughout childhood, and clinicians have limited tools to counsel patients and their families on the likely course of the disease. We developed a clinical risk prediction algorithm for persistent problematic AD through age 14 among 7,406 children utilizing previously identified disease subgroups from a latent class analysis from the Avon Longitudinal Study of Parents and Children birth cohort. A multivariable logistic regression model was fitted to identify variables associated with the outcome of persistent problematic AD (a combination of the 'Severe-Frequent' and 'Moderate-Frequent' AD subtype compared to the 'Moderate-Declining', 'Mild-Intermittent', and 'Unaffected/Rare' subtypes). Known risk factors from early life (up to 42 months) were included, and a stepwise variable selection method identified the most relevant predictors. Fifteen candidate predictors were considered, and seven were retained for analysis. Predictors that were significant in the multivariable analysis ($p < 0.05$) were retained in the final scoring model. The final predictors were child sex, parental AD, food allergy, parent-reported severity of flexural dermatitis (FD) or convexity dermatitis between birth and 18 months, FD severity between 30 and 42 months, and age ≤ 6 months at the first report of dermatitis. Regression coefficients were used to develop a risk score (0–26 points), with children categorized into low (0–4), moderate (5–15 points), and high (16–26) risk groups. The predicted risk of persistent problematic AD ranged from 0.4% (score of 0) to 85.7% (score of 26). The area under the receiver operating characteristic curve was 0.89 (95% CI; 0.88–0.90). This easy-to-use risk score could help predict persistent problematic AD through early adolescence among children up to 42 months and may improve counseling and targeted identification of disease-modifying treatments.

0206

Impact of seborrheic dermatitis on quality of life: a systematic review and meta analysis

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Seborrheic dermatitis (SD) is a common chronic inflammatory skin condition characterized by greasy scaling, erythema, and pruritus, often affecting the scalp, face, and trunk. While traditionally perceived as a benign disorder, its relapsing nature and visible symptoms may significantly affect patient quality of life (QoL), however, the full extent of this impact has not been comprehensively evaluated. To address this gap, we conducted a systematic review and meta-analysis to assess the QoL impairment in SD patients. Searches were performed in Embase, PubMed, Scopus, and the Cochrane Database (up to June 2024) for global, published original research reporting quantitative QoL impact measured in SD patients through instruments such as the Dermatology Life Quality Index (DLQI) and Skindex-29. Following PRISMA guidelines, 26 studies involving 8,384 SD patients met the inclusion criteria. Data were extracted and analyzed using a random-effects model to estimate pooled proportions and means with 95% confidence intervals (CI). Pooled mean DLQI score was 7.2 [95% CI: 6.3–8.1] across 3,812 patients, indicating moderate QoL impairment, with high heterogeneity (I^2 = 97%, τ^2 = 3.7720). Similarly, the pooled mean Skindex-29 score showed moderate impairment (26.0 [16.9–35.1]) also with high heterogeneity (I^2 = 98%, τ^2 = 63.3069), further highlighting functional, emotional, and symptomatic challenges faced by SD patients – with the latter subdomain demonstrating most severe impairment. SD severity showed moderate correlation with QoL impairment (pooled Pearson's r: 0.37 [95% CI: 0.31–0.43]; p=0.03). These findings underscore that SD is more than a dermatological nuisance; it imposes considerable impact on individual QoL, warranting greater clinical attention. Additional studies are needed to prospectively explore comprehensive management strategies to address both physical symptoms and psychosocial health.

0207

Increased risk of hidradenitis suppurativa in tobacco but not cannabis users: A retrospective cohort analysis using a large multicenter database

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Background: Hidradenitis suppurativa (HS) is a chronic inflammatory disease that causes pain and disproportionately affects women and African American patients. There is conflicting evidence that tobacco smoking influences HS development, and the relationship between cannabis and HS is unexplored. Therefore, we assessed the risk of developing HS with tobacco and cannabis use to help counsel patients about potential modifiable risk factors. Methods: TriNetX research database was searched on 11/21/2024 for patients ages ≥18-years who used tobacco only, cannabis only, and both tobacco and cannabis from 2000-2020. Propensity score matching was performed by age, sex, race and ethnicity. Odds ratios of developing HS ≥1 day following tobacco use, cannabis use, or both were calculated. Results: We identified 807,675, 315,695, and 48,442 patients who used tobacco only, cannabis only, or both, respectively. After matching for age, sex, race and ethnicity, patients with tobacco use only and both tobacco and cannabis use had higher odds of HS diagnosis (OR 2.23, 95% CI 2.13-2.33, and 2.11, 1.80-2.48, respectively), but not patients with cannabis use only (0.96, 0.90-1.03). Among patients with tobacco use only, odds of HS diagnosis were higher for females vs. males (2.86, 2.67-3.05) and Black vs. White patients (1.68, 1.56-1.81), whereas odds of HS diagnosis were lower for Asian vs. White patients (0.56, 0.39-0.81). Conclusions: We showed that tobacco use was associated with higher odds of HS diagnosis, which is a relationship that has been controversial in the literature. Our study also found that cannabis use was not associated with increased odds of HS diagnosis, which has not been previously established. Prospective studies are needed to reproduce this data. We recommend that dermatologists obtain tobacco and cannabis use histories for HS patients and counsel on smoking cessation.

0208

Evaluating the incidence and prevalence of perioral dermatitis in the United States: A population-level study.

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Perioral dermatitis has a paucity of epidemiologic data, with prior studies limited by small sample sizes from single institutions. Using the TriNetX US Collaborative Network (69 healthcare organizations), we conducted a multi-institutional, population-based study to estimate the incidence and prevalence of perioral dermatitis from 1/1/2017 to 12/13/2023 in the United States, identifying perioral dermatitis in patients with ≥1 ICD-10-CM code for L71.0. Overall and annualized incidence and prevalence estimates were determined, and 95% confidence intervals were calculated via normal approximation. We identified 135,163 patients with incident perioral dermatitis (incidence proportion (IP) [95% CI] = 0.158% [0.157, 0.159]) and 286,971 patients with prevalent perioral dermatitis (prevalence proportion (PP) [95% CI] = 0.336% [0.334, 0.337]). Patients 0-9 years old had the highest incidence of perioral dermatitis (IP [95% CI] = 0.145% [0.143, 0.147]), followed by patients 30-39 years old (IP [95% CI] = 1.43% [0.141, 0.145]). Patients 50-59 years old had the highest prevalence of perioral dermatitis (PP [95% CI] = 0.308% [0.306, 0.311]). Perioral dermatitis incidence in females (IP [95% CI] = 0.196% [0.195, 0.198]) was higher than in males (IP [95% CI] = 0.080% [0.079, 0.081]), and prevalence in females (PP [95% CI] = 0.420% [0.418, 0.422]) was higher than in males (PP [95% CI] = 0.186% [0.185, 0.187]). Both the annual incidence and prevalence of perioral dermatitis increased overall from 2017 to 2023. Overall, our study provides important population-level data on perioral dermatitis.

0209

How providers navigate systemic therapies in pediatric atopic dermatitis: Qualitative insights and the need for standardized guidelines

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Despite increasing use of biologics and oral JAK inhibitors for atopic dermatitis (AD), guidance on long-term use in pediatric populations is limited. We explored pediatric dermatology providers' approaches to systemic therapies for moderate-to-severe pediatric AD to better understand their perspectives on long-term use. Providers were recruited via email to the Pediatric Dermatology Research Alliance. Semi-structured interviews (n =11) and free-listing techniques were used to identify themes in providers' decision-making. Two researchers independently analyzed interviews using an emergent thematic framework, and a saliency index was applied to free-listing data. Our findings revealed concordance regarding initiation criteria and preferred treatments. Factors contributing to initiating systemics, in descending order of importance, were quality of life, refractoriness to other treatments, and disease severity. Dupilumab was the preferred first-line systemic (saliency index: 0.93). However, variability emerged in preferences for de-escalating therapies after achieving symptom control. Providers emphasized the need for standardized guidelines, as many decisions were perceived to be reliant on individual comfort. Concerns about long-term side effects, parental preferences, and loss of access were factors influencing decisions to discontinue therapy after achieving disease control. Reasons for continuing therapy after adequate control included maintaining therapeutic benefits, preserving quality of life, and preventing relapse. Barriers to systemics included concerns about safety, monitoring requirements, and the mode of administration (e.g., injections). While prior research has examined general approaches to treating AD in children, this study provides a focused lens on systemic therapies, which are increasingly used for moderate-to-severe AD. Our findings highlight the need for standardized, evidence-based guidelines for long-term management of systemic therapies for pediatric AD.

0210

Sociodemographics of patients in a rural psychocutaneous clinic with telemedicine integration

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Our study establishes the sociodemographics of patients seen at a rural psychocutaneous clinic with telemedicine integration in New England and discusses the scalability of such a model. There are few psychodermatology clinics in the United States, with the majority located in urban areas. Literature regarding patient demographics, clinic characteristics, and general feasibility of a rural psychodermatology clinic is therefore extremely limited. A retrospective cohort study of 47 patients seen at our clinic was conducted. All patients who attended the clinic between November 2019 and August 2024 were included in the study. Of 102 patients referred to our clinic, 47 attended for a total of 117 visits. Patients were predominantly female (80.9%); White, and non-Hispanic, with a median age of 54 years. The most common diagnoses were excoriation disorder (51.1%) and delusions of parasitosis (29.8%). More than half had psychiatric comorbidities (55.3%) and dermatological comorbidities (51.1%), and 34.8% had a history of substance use. Telehealth was used for 18.4% of visits. Most patients had private insurance (42.6%), followed by Medicare (36.2%) and Medicaid (19.1%). Only one patient was uninsured. Psychodermatology clinics address an important gap in care that exists for patients with complex psycho-dermatologic conditions requiring integrated treatment. This study demonstrates the feasibility of this model in a rural setting. Telehealth integration provided a valuable means of dismantling barriers to care for patients. Rural healthcare providers may be able to scale this model to establish psychodermatology clinics of their own via collaboration between local dermatologists, psychologists, and psychiatrists, the use of telemedicine, and the utilization of existing local infrastructures.

0211

Characterizing prevalence and impact of dermatologic health among Pakistanis

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Background: Dermatologic conditions, including dermatophytosis, scabies, and skin lightening associated contact dermatitis have been prevalent in certain Pakistani cities. However, the overall burden and age-specific prevalence of dermatologic diseases in Pakistan has not been thoroughly studied. Therefore, our study aims to investigate the prevalence of dermatologic conditions across Pakistan to help provide culturally sensitive care and improve patient outcomes. Methods: The Global Burden of Disease 2021 database was used to analyze the prevalence of skin diseases in the Pakistani population ages 5-94 years. Data was stratified according by condition type, with percent prevalence and contribution to disability-adjusted life-years calculated. Results: The highest prevalence of identified skin diseases included fungal skin diseases (6.12%), scabies (3.50%), acne vulgaris (2.60%), and atopic dermatitis (1.80%). Conditions with the lowest prevalence were alopecia areata (0.18%) and decubitus ulcers (0.002%). Prevalence of skin and subcutaneous diseases was 27.44% in Pakistanis ages 5-19 years, with a decline to 19.44% for people ages 20-24 years. The prevalence then increased steadily with age, ranging between 42.20% and 54.45% in Pakistanis over 80 years old. Conclusions: Our study characterizes dermatologic disease burden across all age groups in Pakistan, with fungal diseases, scabies, acne, and atopic dermatitis being the most prevalent conditions. Communicable diseases may be caused by poor hygiene, communal living, and humid climate, while acne may result from stress and widespread use of skin lightening creams. We recommend that dermatologists be mindful of these conditions when treating individuals from Pakistan. This study provides a basis for future prospective studies to evaluate risk of these conditions over time.

0212

Cardiac comorbidities in patients with erythromelalgia: A retrospective database analysis

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Primary erythromelalgia is a rare condition characterized by numerous dermatologic findings and caused by mutation in the SCN9A gene which encodes the Nav1.7 voltage-gated sodium channel. Given the presence of the Nav1.7 channel in the cardiac system, the potential for alterations in microcirculation in affected areas, and the known association of PAD with adverse cardiac events, our studies aims to assess the relationship between EM and comorbid cardiac conditions. Our study used the All of Us Database (AoUDB) from the National Institute of Health to assess the increased risk for cardiac comorbidities in patients with EM. The AoUDB database returned 88 patients with EM out of the 287,012 patients in the database with EHR data. Cardiac comorbidities queried fell into three categories: conduction abnormalities (heart block and bundle branch block), myocardial infarctions, and angina. Patients with erythromelalgia had significantly higher odds of angina pectoris (OR=2.12; p=0.021), ST-segment elevation myocardial infarction (OR=3.48; p=0.038), and left bundle branch block (OR=2.57; p=0.048). The cohort of EM patients in the AoUDB exhibited significantly higher rates of multiple cardiac events including those with underlying conduction etiologies consistent with current literature supporting that modification of Nav1.7 activity may precipitate changes to autonomic systems. These increased rates underscore the significance of EM as not only an indicator of underlying neuropathy but also potential underlying cardiac abnormalities. The primary limitation of this study is the lack of granularity between primary and secondary EM, potentially dampening the magnitude of the relationship. Nevertheless, our results reached statistical significance for multiple adverse cardiac outcomes in patients with EM.

0213

DMARDs and biologics are protective against alopecia areata in psoriasis patients

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Psoriasis (PsO) is a chronic inflammatory skin disease associated with an increased risk of developing alopecia areata (AA). Case reports and studies have proposed mechanisms linking PsO and AA, suggesting that specific antipsoriatic immunomodulators may trigger AA. However, the relationship between antipsoriatic systemic therapies and AA is underexplored. We used TriNetX, an international EHR database, to evaluate the effects of immunomodulators on AA development in PsO patients. Patients with a PsO diagnosis (ICD-10 L40) and no history of AA (ICD-10 L63) were divided into cohorts based on treatment with disease-modifying antirheumatic drugs (DMARDs) or biologics, versus no systemic therapies. Cohorts were matched by demographics and obesity/overweight diagnosis. DMARDs analyzed included methotrexate, cyclosporine, apremilast. Biologic therapies included TNF-alpha inhibitors (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab), IL-17 inhibitors (brodalumab, ixekizumab, secukinumab, bimekizumab), and IL-12/23 and IL-23 inhibitors (ustekinumab, guselkumab, risankizumab, tildrakizumab). The primary outcome was AA incidence following systemic therapy for psoriasis. Relative to matched controls, psoriatic patients on DMARDS (n= 49,513) had a 55.1% relative risk reduction of developing AA (RR: 0.449; 95% CI: 0.364-0.865). PsO patients on biologics (n= 66,932) had a 64.4% relative risk reduction (RR: 0.354; 95% CI: 0.232-0.540). Among biologics, TNF-alpha inhibitors (n=30,863) and IL-12/23 and IL-23 inhibitors (n=14,311) significantly decreased risk of AA (RR: 0.415, 95% CI: 0.236-0.729 and RR: 0.417, 95% CI: 0.199-0.871, respectively). IL-17 inhibitors (n=7,670) were associated with a non-significant decrease in risk (RR: 0.909; 95% CI: 0.386-2.138). These findings demonstrate the protective nature of DMARDS and biologics, particularly TNF-alpha, IL-12/23, and IL-23 inhibitors, against AA in PsO patients, highlighting the need for further research into shared mechanisms of disease underlying PsO and AA.

0214

Examining the safety of nicotinamide for skin cancer prevention: Review of metabolism, adverse events, and toxic dosages

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Nicotinamide (niacinamide) supplementation for non-melanoma skin cancer (NMSC) prevention has sparked controversy over the past decade due to its inconsistent evidence of chemoprevention and recently challenged safety profile. In this scoping review, we summarize the metabolic mechanisms, adverse effects, and toxic thresholds of nicotinamide and its metabolites to better inform patient recommendations for nicotinamide supplementation. Nicotinamide undergoes hepatic metabolism via three pathways (methylation, oxidation, and hydroxylation) to yield renally excreted end-products: N-methylnicotinamide, 2PY, 4PY, 6PY, nicotinamide N-oxide, nicotinic acid, nicotinuric acid, and 6-hydroxynicotinamide. Reported adverse effects of these metabolites include diarrhea, rash, insulin insensitivity, hepatotoxicity, renal toxicity, thrombocytopenia, anemia, and lymphopenia. Elevated serum levels of nicotinamide metabolites have been correlated with metabolic syndrome, cirrhosis, chronic kidney disease, and bladder cancer. Long-term doses of up to 1g/day have been shown to be well-tolerated. However, patients with impaired nicotinamide elimination (renal failure, cirrhosis, concomitant CYP2E1-metabolized medication) are at higher risk of adverse events. Studies of toxic dosages have been limited to animal studies, and there remains limited research on the toxic threshold of chronic nicotinamide supplementation. Overall, the existing research regarding nicotinamide safety has been largely observational. Until future prospective studies confirm the toxic threshold, we advise that providers limit their recommendation of chronic nicotinamide supplementation for NMSC reduction given the conflicting evidence of its cancer-reducing effect and our incomplete understanding of its long-term toxicities.

0215

Patient-reported outcomes for managing moderate-to-severe pediatric atopic dermatitis: A qualitative study of provider perspectives

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Patient-reported outcomes (PROs) capture patients' perspectives on their symptoms, quality of life, and treatment experiences, serving as critical tools for patient-centered care. Understanding provider perceptions of PROs is essential to identifying challenges and opportunities for effective implementation. This study examined the perspectives of 11 providers, recruited from the Pediatric Dermatology Research Alliance's member listserv, regarding the use of PROs to manage moderate-to-severe pediatric AD. Semi-structured interviews were conducted and independently coded by two researchers using an emergent thematic framework to identify key themes, areas of consensus, and challenges. Providers emphasized the essential role of PROs, recognizing their ability to triage disease severity, generate quality improvement data, and facilitate shared decision-making. They described how PROs align perceptions of symptom progress, address the collateral impact of AD symptoms, and improve family engagement in treatment decisions. PROs were viewed as vital for assessing symptom burden and tailoring treatment plans to meet patient and family needs. However, several barriers to routine PRO use were identified: 1) the lack of PRO integration with electronic medical records (EMRs), 2) the resource-intensive process of collecting PRO data, 3) language barriers and limited health literacy impairing counseling, 4) insufficiently nuanced PRO measurement tools, and 5) discrepancies between parent and patient interpretations of symptoms. Nevertheless, providers supported advancing PRO utilization. In conclusion, these findings underscore the utility of PROs in enhancing clinical care for moderate-to-severe pediatric AD while addressing barriers to their routine use. Streamlining PRO collection, integrating PROs into EMRs, and creating patient-friendly tools that capture nuanced data are critical to overcoming these barriers.

0216

Initial management of infantile atopic dermatitis in primary care settings and predictors of topical steroid potency escalation

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Atopic dermatitis (AD) affects an estimated 15-20% of children worldwide, with most treatment occurring in a primary care setting. Studies from other inflammatory diseases such as psoriasis and rheumatoid arthritis reveal the type and timing of therapy initiation may impact long-term outcomes. Initial management of new onset infantile AD has not been well-characterized. The objective of this study was to describe first-line treatment for AD and investigate changes in topical therapy potency. A retrospective cohort was performed utilizing electronic medical record data from 3053 patients (ages 0-2 years) with a diagnosis of AD and one follow-up visit. The cohort had a mean age of 0.6 years, was majority male (54.4%), with an overall representative distribution of race for the area. Of the 3053 patients, 1015 had at least one additional atopic comorbidity listed in their chart with the most common being asthma, allergy, allergic rhinitis, conjunctivitis, and bacterial infection (28.8%, 33.4%, 34.7%, 41.8%, 6.7% respectively). There were 3043 total individual medications at V1, with the most common being topical corticosteroid (TCS), topical antifungal, oral antihistamine, topical antibiotic, analgesics/antipyretic, and oral antibiotics (48.4%, 4.4%, 4.0%, 2.9%, 2.2%, 2.0% respectively). In the TCS class the potencies at V1 were mostly commonly low (71.5%), medium (27.3%), and high (1.3%). 5.2% (72/1500) of children changed potency of TCS between V1 and V2 showing 5.2% escalating and 1.0% deescalating therapy, while the rest maintained their potency. Multivariate logistic regression identified those who escalated TCS therapy, were significantly more likely to have concomitant atopic comorbidity (OR 3.15, $P < 0.001$) These data suggest children with atopic multi-morbidity may require more aggressive initial therapy and support future studies of early intervention approaches in AD.

0217

Minding the gap: Identifying gaps in skin disease research prioritization as reflected in the cochrane database of systematic reviews

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Skin diseases rank among the leading causes of human disease, yet research prioritization for these conditions remains inadequately characterized. This study examines whether the representation of skin diseases in the Cochrane Database of Systematic Reviews (CDSR) aligns with their global disease burden as quantified by disability-adjusted life years (DALYs) in the most recent Global Burden of Disease (GBD) 2021 Study. In this bibliometric analysis, we evaluated 227 unique CDSR systematic reviews and protocols representing 15 skin disease categories as of November 2024. Representation was assessed relative to DALY metrics from GBD 2021, and linear regression analysis was performed to evaluate correlations between CDSR representation and DALY burden. Changes in CDSR representation from 2014 to 2024 were compared with changes in DALY burden from 2010 to 2021. We found that viral skin diseases were appropriately represented based on DALY metrics, while dermatitis, decubitus ulcer, melanoma, non-melanoma skin cancer, and the "other skin and subcutaneous diseases" category were overrepresented. Psoriasis, acne vulgaris, fungal and bacterial skin diseases, pruritus, leprosy, alopecia areata, urticaria, and scabies were underrepresented. From 2014 to 2024, 13 of 15 disease categories increased in CDSR representation, yet this growth poorly correlated with changes in DALY burden ($R^2 = 0.3953$). Moreover, cumulative CDSR representation through 2024 showed a weak correlation with global DALY burden in 2021 ($R^2 = 0.0876$). Overall, our findings reveal persistent misalignment between dermatologic research prioritization and global disease burden, with 14 of 15 skin disease categories showing disparities. Addressing these gaps will require increased investment in underrepresented, high-burden conditions and a more equitable allocation of research resources to improve evidence-based care and global health equity.

0218

Effect of intravenous immunoglobulin G on mortality among immune checkpoint inhibitor recipients

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Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy, considerably improving patient survival across a wide range of cancers. Immune-related adverse events (irAEs) are common toxicities of ICIs and often require management with systemic immunosuppression, which may negatively impact the therapeutic efficacy of ICIs. Of these, intravenous immunoglobulin (IVIG) is an effective treatment for the most severe irAEs, but little is known about its impact on ICI outcomes. Using the TriNetX Research Network drawing from 105 healthcare organizations across the US and Europe, we conducted a retrospective cohort study to investigate the effect of IVIG exposure on overall survival among ICI recipients. We identified 483 patients who received IVIG post-ICI initiation, who were then 1:1 propensity score matched on baseline demographics (age, sex, ethnicity, race), cancer type, and cancer stage to 483 ICI recipients without IVIG exposure (controls). Patients with hematologic malignancies, autoimmune conditions, or IVIG exposure prior to ICI initiation were excluded. To account for immortal time bias, we used landmark analyses at 3, 6, and 12 months following ICI initiation. Using Cox proportional hazard models with 95% confidence intervals, we found IVIG-exposed patients had a significantly increased risk of mortality at 3- (HR [95% CI] = 1.67 [1.24, 2.25], p=0.001), 6- (1.75 [1.18, 2.57], p=0.004), and 12-month (1.77 [1.08, 2.89], p=0.021) landmarks. Sensitivity analyses using both IVIG and intramuscular immunoglobulin (IG) and stratifying by number of IG treatment cycles showed consistent results. Our findings suggest that administering IVIG to ICI recipients significantly increases their risk of mortality, potentially due to accelerated ICI clearance and negative attenuation of immunotherapy, highlighting the need for careful consideration of alternative management strategies for irAEs in patients on ICIs.

0219

Comparative risk of psoriatic arthritis in psoriasis patients on immunomodulators

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Psoriatic arthritis (PsA) is a progressive arthritis that is difficult to prevent and treat. DMARDs are associated with a decreased risk of developing PsA in patients with psoriasis (PsO), but it is unknown if immunomodulators can decrease the risk of developing PsA. We aim to assess the comparative risk of PsA in PsO patients on immunomodulators approved for PsA. We identified patients with PsO using the TriNetX Research Network between January 1, 2012, and January 1, 2023. The greedy nearest neighbor matching algorithm was used to 1:1 propensity score match PsO patients by demographics and psoriatic arthritis risk factors to a comparator cohort. Index events were identified as a PsO diagnosis and use of only one immunomodulatory agent. We excluded patients who had an outcome of interest before the index event. Cox Proportional-Hazards Models with 95% confidence intervals were assessed to evaluate the three-year risk of PsA. PsO patients had a significantly increased three-year risk of PsA when treated with Adalimumab compared to Ixekizumab, Risankizumab, Guselkumab, Ustekinumab, and Upadacitinib. Infliximab had an increased risk compared to Ixekizumab, Risankizumab, Guselkumab, Abatacept, and Upadacitinib. Ixekizumab had an increased risk compared to Risankizumab and Ustekinumab, and a decreased risk compared to Certolizumab pegol. Secukinumab had an increased risk compared to Risankizumab, Guselkumab, Ustekinumab, Abatacept, Tofacitinib, and Upadacitinib. Golimumab had an increased risk compared to Risankizumab, Abatacept, and Upadacitinib. Certolizumab pegol had an increased risk compared to Risankizumab, Guselkumab, Ustekinumab, Abatacept, and Tofacitinib. Risankizumab had a decreased risk compared to Etanercept and Guselkumab. Etanercept had an increased risk compared to Guselkumab and Ustekinumab. Overall, Risankizumab, Guselkumab, Ustekinumab, and Abatacept have the greatest decreased risk of PsA compared to other immunomodulators.

0220

Multiple comorbidities specifically associated with keloids versus hypertrophic scars: An All of Us case control study.

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Keloid pathophysiology is poorly understood. Identifying keloid comorbidities may reveal mechanistic insights but is complicated by frequent co-diagnosis with hypertrophic scar. We utilized the All of Us program, containing health data from a large representative American population, to identify specific comorbidities that associate with keloids versus hypertrophic scars. Keloid and hypertrophic scar cohorts were defined by SNOMED codes. Demographic makeups were compared with chi-square test, and 568 most reported conditions were tested for associations by both univariate analysis and multivariate logistic regression. 1,397 participants with keloids only and 1,354 participants with hypertrophic scar only were identified. The cohorts differed significantly by age ($p<0.0001$), with the hypertrophic scar cohort having more participants age >65 (34.71% vs 23.84%), but not by race or sex at birth. Univariate analysis revealed 103 keloid-associated conditions (OR >1.5) and 50 hypertrophic scar-associated conditions (OR <0.7). Multivariate analysis, adjusting for demographic categories and all common conditions, revealed 41 keloid-associated and 32 hypertrophic scar-associated conditions (adjusted OR>2 or <0.5, $p<0.05$). Notably, dermatologic conditions such as acne (adj. OR=4.81, 95% CI 3.37-6.85), alopecia (adj. OR=3.58, 95% CI 1.68-7.63), and sebaceous cyst (adj. OR=2.26, 95% CI 1.43-3.56), were associated with keloids. Epidermoid cyst (adj. OR=0.23, 95% CI 0.13-0.38), truncal basal cell carcinoma (adj. OR=0.24, 95% CI 0.12-0.51), and psoriasis (adj. OR=0.47, 95% CI 0.24-0.92) were associated with hypertrophic scars. Non-dermatologic diagnoses associated with keloids included type 2 diabetes mellitus (adj. OR=2.53, 95% CI 1.23-5.18) and uterine leiomyoma (adj. OR=2.26, 95% CI 1.07-4.77). These results, identifying multiple conditions that are specifically associated with either keloid or hypertrophic scar, will help clarify pathophysiologic differences between the two conditions and may lead to more specific and efficacious therapies.

0221

Sunscreen knowledge and practices in dermatology patients: A cross-sectional survey

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Despite increasing recognition of the importance of sun protection, studies report lower rates of sunscreen use and accessibility among patients with skin of color (SOC) compared to White patients in the US. To evaluate the impact of patient demographics on sun protection behaviors and knowledge, we conducted a survey across five dermatology clinics. Among 234 participants, 73 (31.5%) identified as Black, 68 (29.3%) as White, 14 (6.0%) as Asian and 77 (33.3%) were Other/Unknown. The cohort consisted of 166 (71.6%) females and 66 (28.4%) males, with a mean age of 49.36 ± 18.9 years. 160 (69.0%) respondents reported a history of sunscreen/SPF use. Of those, 66 (41.3%) reported wearing sunscreen daily, 22 (13.8%) 3-4 days per week, 5 (3.1%) 1-2 days/week, and 62 (38.8%) sporadically. Multivariate logistic regression identified older age (OR=0.96, 95% CI=0.94-0.98, p=0.001) and male sex (OR=0.15, 95% CI=0.06-0.33, p<0.001) as significant negative predictors of sunscreen use. Although not statistically significant, Black race (OR=0.43, 95% CI=0.15-1.17, p=0.10) had a negative trend towards sunscreen use. Ethnicity, Fitzpatrick Skin Type (FST), personal or family history of skin cancer, and dermatology visit type (medical or cosmetic) did not significantly predict sunscreen use. 55 respondents (34.4%) reported awareness of different sunscreen types (chemical vs. physical blockers). White patients showed a trend towards greater awareness (OR=2.73, 95% CI=0.96-7.95, p=0.060), whereas Black patients (OR=0.38, 95% CI=0.11-1.26, p=0.12) and Hispanic or Latino patients (OR=0.37, CI=0.12-1.10, p=0.080) showed trends towards lower awareness. Race, ethnicity and FST were not significant predictors of preference for chemical vs. physical sunscreen. Our findings show disparities in sunscreen knowledge and practices across different demographic groups and emphasize the need for increased efforts to better inform sunscreen use in SOC patients.

0222

A rare case report of a teenage girl with pemphigus vegetans in Mongolia

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Pemphigus is a group of autoimmune blistering diseases of the skin and mucous membranes characterized by histologically intraepidermal blisters due to the loss of cell–cell adhesion of keratinocytes. In general, it ranges from 0.76 to 5 new cases per million per year. The mean age of onset of a disease is 50 to 60 years old. Pemphigus vulgaris is the most common type of pemphigus, presenting with mucocutaneous bullae, while pemphigus vegetans is the rarest variant, accounting for only 1-2% of cases and typically affecting middle-aged individuals. We report the first child case of the pemphigus vegetans in Mongolia. A 13-year-old girl presenting with mucous erosions, many cauliflower like plaques in the axilla, inframammary, inguinocrural, and intergluteal areas visited the National Dermatology Center of Mongolia. This girl was previously misdiagnosed and mistreated as sexually transmitted disease. We diagnosed the patient with pemphigus vegetans based on skin biopsy results, and positive Dsg1 and 3 results.

0223

Real-world usage of dupilumab in an academic medical center in the southeast.

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Dupilumab has revolutionized the treatment of Atopic Dermatitis. Here, we aim to characterize the real-world usage of dupilumab over 2017-2022 at The Emory Clinic, Atlanta, Georgia, by describing the various diagnoses that necessitated dupilumab, rates of responsiveness as well as rates of discontinuation. Additionally, we examined the time to improvement as well as total duration of therapy, and rates of adverse reactions to medication. We performed a retrospective chart review of male and female patients at The Emory Clinic ages 18-89, on dupilumab between January 1, 2017 to December 31, 2022. Out of 398 adult patients treated with dupilumab, 145 met inclusion criteria. In addition to Atopic Dermatitis (114 patients), dupilumab was prescribed for various diagnoses including Prurigo Nodularis (8) and chronic idiopathic pruritus (18). Interestingly, dupilumab was also prescribed for pruritus associated with other diagnoses (5) including Erythema Annulare Centrifugum, Hypereosinophilic syndrome, Lichen Sclerosus et atrophicus, systemized drug hypersensitivity as well as CD30+ T cell dyscrasia. Patients were on dupilumab for a mean total duration of 2.5 years with a minimum duration of 84 days and maximum duration of 6 years (2164 days). Out of 145 patients, 135 patients demonstrated a reduction in pruritus (94.5%). Ten patients (6.9 %) did not demonstrate an adequate response to dupilumab, and five of these patients were placed on a JAK inhibitor. Eight patients (5.5 %) attempted to taper the dosing interval of dupilumab, and five patients successfully tapered to an injection every 3 to 4 weeks. Twenty-one patients (14.5%) reported adverse reactions to therapy, prompting four patients to discontinue therapy. In summary, we report the real-world usage of dupilumab to treat a variety of causes of chronic pruritus in addition to atopic dermatitis. To our knowledge, this is the first report of usage of dupilumab to treat Erythema Annulare Centrifugum, systemized drug hypersensitivity as well as CD30+ T cell dyscrasia.

0224

Dermatologic outcomes of patients taking semaglutide: A propensity-matched large cohort study

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The rise of GLP-1 agonists as a leading treatment for diabetes, obesity, and many comorbidities has led to increased reports of dermatological events; however, a comprehensive analysis of beneficial and adverse outcomes remains absent in the literature. We performed a 5-year retrospective cohort study using the TriNetX Global Health Research Network comparing two patient cohorts: 1) those with Type 2 diabetes treated with semaglutide (n=13,920) and 2) those with Type 2 diabetes not treated with semaglutide (n=13,920). Cohorts excluded patients already diagnosed with the dermatologic outcome or on other GLP-1 agonists. Patients were 1:1 propensity score matched based on age, sex, race, BMI categories, and HgbA1c. Compared to those not treated with semaglutide, patients on semaglutide had a decreased risk of psoriasis (RR=0.450, 95% CI: 0.310,0.652, p<0.0001), atopic dermatitis (RR=0.632, 95% CI: 0.444,0.899, p=0.010), acne (RR=0.577, 95% CI: 0.391,0.850, p=0.005), pruritus (RR=0.613, 95% CI: 0.511,0.737, p<0.0001), xerosis cutis (RR=0.541, 95% CI: 0.413,0.709, p<0.0001), paresthesia (RR=0.591, 95% CI: 0.496,0.706, p<0.0001), keratinocyte carcinoma (RR=0.641, 95% CI: 0.476,0.865, p=0.003), urticaria (RR=0.674, 95% CI: 0.487,0.934, p=0.017), skin infections (RR=0.576, 95% CI: 0.501,0.662, p<0.0001), intertrigo (RR=0.735, 95% CI: 0.552,0.980, p=0.035), cutaneous candidiasis (RR=0.504, 95% CI: 0.359,0.708, p<0.0001), skin ulcers (RR=0.674, 95% CI: 0.536,0.848, p=0.001), and acquired ichthyosis (RR=0.590, 95% CI: 0.467,0.745, p<0.0001). Semaglutide had no statistically significant association with the risk of developing hidradenitis suppurativa, acanthosis nigricans, xanthelasma, vitiligo, granulomatous skin disease, alopecia, angioedema, bullous pemphigoid, skin vasculitis, erythema nodosum, or diabetic dermopathy. These findings suggest that semaglutide may not be associated with adverse events but rather associated with a decreased risk of dermatologic manifestations of diabetes, as well as decreased risk of inflammatory conditions.

0225

Evaluating the impact of PeDRA's educational initiatives in pediatric dermatology

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The Pediatric Dermatology Research Alliance(PeDRA) has spearheaded efforts to address the shortage of pediatric dermatologists by offering diverse educational resources for medical professionals across various career stages. This study evaluates the scope and impact of PeDRA's educational initiatives. Since 2020, PeDRA has introduced 213 educational programs, drawing 65,658 online views and 23,666 podcast listens. These initiatives were categorized into research (144 [68%]), community (67 [31%]), and mentorship (2 [1%]) topics. Key formats included 59 webinars, 58 Getting to Know You/ Your Research episodes, 33 Points of Discussion podcasts, 16 series-based podcasts, 14 patient-focused podcasts, 11 conference podcasts, 10 Pub Club episodes, and 7 industry-focused podcasts. Among these, series addressing complex dermatologic topics, such as Emerging Mechanisms of Action in the Treatment of Alopecia Areata and Emerging Therapies for Moderate to Severe Atopic Dermatitis, garnered the highest engagement, with a median of 289(IQR 131–310) listens per episode. Similarly, PeDRA's Points of Discussion podcast, which focuses on trending and controversial topics in pediatric dermatology, recorded a median of 186(IQR 97-243) listens per episode. Furthermore, the topics of the episodes were classified under Focused Study Groups(FSGs). The Atopic Dermatitis & Psoriasis FSG had the highest proportion of topics (24% of episodes), followed by Genetics (17%), Acne & Hidradenitis Suppurativa (16%), and Birthmarks (14%). However, Skin of Color & Pigmentary Disorders accounted for only 1% of FSG-relevant episodes, highlighting a need to expand content in this area. To further PeDRA's mission, future initiatives should continue prioritizing educational approaches that respond to audience preferences, broaden content diversity, and address gaps in representation, particularly in Skin of Color educational programming. Leveraging data-driven approaches will enable PeDRA to strengthen its impact, promote inclusivity, and drive innovation in pediatric dermatology education.

0226

The shared genetic architecture between acne vulgaris, hidradenitis suppurativa, and inflammatory bowel disease: A cross-trait analysis

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Acne vulgaris (AV) and hidradenitis suppurativa (HS) are associated with inflammatory bowel disease (IBD), suggesting overlapping pathophysiology. However, the exact mechanisms remain to be elucidated. Genome-wide association studies can be used to identify shared genetic variants and link them to biological pathways, providing insight into the overlapping pathophysiology. We analyzed summary statistics of recent European-based genome-wide association studies (GWAS) for AV, HS, and IBD. To explore the overlap in genetic architectures, we calculated genetic correlations and used the MiXeR method to estimate the number of shared causal variants. To identify specific genetic loci that were shared between AV or HS and IBD, we used the pleiotropic analysis under composite null hypothesis (PLACO) method. These genetic loci were used to map candidate genes and biological pathways using FUMA. AV showed a moderate genetic correlation with IBD (rg = 0.16, p = 0.003), particularly with Crohn's disease (rg = 0.16, p = 0.003), but not ulcerative colitis. HS showed a stronger but non-significant genetic correlation with IBD (rg = 0.22, p = 0.21). We found 21 disease-overlapping genetic loci connecting AV to IBD, including 13 novel loci for AV, and 13 loci between HS and IBD, all novel for HS. These loci implicated over 100 unique biological pathways, 16 of which were shared across AV, HS, and IBD. Key pathways included the JAK-STAT signaling pathway and other immune-related pathways. Our findings reveal genetic correlations and overlapping genetic architectures between AV, HS, and IBD, highlighting novel disease-overlapping loci and biological pathways that may inform future therapeutic targets.

0227

Sun protection awareness through reading in kids (SPARK): A pilot study

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In this pilot study, we created and evaluated a scientifically accurate and inclusive children's book about sun protection, "Sage's Sun-Safe Adventure", and assessed its impact on caregiver knowledge and satisfaction. Our study included 20 caregivers of children aged 4-10 years, who completed pre- and post-intervention surveys. Surveys revealed a significant improvement in sun safety knowledge, with quiz scores increasing from a mean of 4.00 to 4.55 out of 6 (p=0.0312). We also identified common barriers to sun protection, such as, "My child doesn't like wearing sunscreen" (21%) and "Staying in the shade is hard" (26%), highlighting logistical and behavioral challenges facing caregivers. Additionally, we found that while racial differences in the use of sun protection items were not statistically significant, non-white participants were less likely to regularly use sunscreen (14% vs. 38%), suggesting that cultural and socioeconomic factors may influence sun safety practices. Financial constraints, such as the cost of sunscreen, were more commonly reported among non-white participants (29% vs. 0%), highlighting the need for targeted, culturally sensitive, and affordable educational resources and sun protective materials to improve sun safety across diverse populations. These findings suggest that educational children's literature is a promising tool for improving sun safety practices. The book's inclusive and engaging format may be particularly beneficial for children from diverse backgrounds. Future research should explore the long-term effectiveness of such interventions, adapt materials for broader cultural contexts, and conduct larger-scale studies to ensure inclusivity and efficacy across demographic groups. Furthermore, evaluating the potential of multilingual versions and other educational formats may help expand the reach and impact of sun safety messages.

0228

Utility of sentinel lymph node biopsy for acral lentiginous melanoma

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Guidelines on surgical management of clinically localized acral lentiginous melanoma (ALM), including recommendation for sentinel lymph node biopsy (SLNB), are extrapolated from studies with minimal representation of ALM in their cohorts. Additionally, overall survival (OS) outcomes from SLNB-based clinical decision-making are lacking. We sought to understand the relationship between undergoing SLNB and OS in patients with ALM. In this retrospective national cohort study, the National Cancer Database was queried for patients with ALM who met clinical criteria for SLNB (i.e. ≥0.8 mm thick or ulcerated tumors) between 2016 and 2021. The primary outcome was 3-year OS. Of 2409 eligible ALM patients, 1849 (77%) underwent SLNB. On multivariable logistic regression, patients undergoing SLNB were more likely to be younger (adjusted odds ratio [aOR]: 1.05, $p < 0.01$), male (aOR: 1.37, $p < 0.01$), and have ulcerated tumors (aOR: 1.9, $p < 0.01$). On Kaplan-Meier analysis of the overall cohort, patients who underwent SLNB had a 3-year OS rate of 86% vs. 82% for those who did not undergo SLNB ($p = 0.05$). On propensity-matched (PM) analysis, 3-year OS was 86% for the SLNB cohort vs. 85% for non-SLNB ($p = 0.68$). However, on subgroup analysis, PM clinical stage II patients who underwent SLNB had significantly improved 3-year OS (78% vs. 64%, $p = 0.02$). 3-year OS was significantly lower for SLN-positive patients compared to SLN-negative in both the overall (75% vs. 91%, $p < 0.01$) and PM cohorts (75% vs. 90%, $p = 0.02$). SLNB was not associated with improved OS in the overall cohort of ALM patients, though an OS advantage for patients with clinical stage II disease was found. Additionally, SLN-positivity was associated with worse OS, reaffirming the value of SLNB as a prognostication tool for ALM.

0229

Successful bimekizumab treatment for palmoplantar psoriasis in skin of color

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Introduction: Palmoplantar psoriasis (PPP) is a localized form of psoriasis affecting the palms and soles, causing significant itching, pain, and functional impairment. It is characterized by well-defined erythematous plaques with scaling and hyperkeratosis, sometimes with pustules, accounting for 3-4% of all psoriasis cases.This report describes an African American male with refractory PPP successfully treated with bimekizumab, demonstrating its efficacy in managing challenging cases. Case Report: A 78-year-old African American male with a history of hypertension, hyperlipidemia, Type 2 Diabetes Mellitus, and coronary artery disease presented with an eight-month history of worsening itchy, painful, scaly palmoplantar plaques and fissures. Baseline labs were normal. He failed multiple treatments, including topical therapies (triamcinolone .1%, clobetasol .05%, tapinarof, roflumilast), biologics (secukinumab, adalimumab), and four prednisone courses, which provided temporary relief but led to rebound flares once tapered. The patient was started on bimekizumab (320 mg every four weeks), an IL-17A/IL-17F inhibitor. At one month, he reported significant resolution of scaling and cracking skin, near-complete clearance of plaques, marked improvement in itching and joint discomfort, and no adverse effects. Discussion: This case highlights the challenges of managing refractory PPP and the limitations of conventional therapies. In patients with skin of color, subtle erythema complicates the diagnosis, and corticosteroid use can lead to postinflammatory hyperpigmentation. This patient's response to bimekizumab underscores the value of targeting immune pathways in refractory cases and the risks of long-term corticosteroid use. Bimekizumab offers a promising option for refractory PPP, providing symptom relief and a strong safety profile, especially for patients with skin of color who may have unique immune risks.

0230

Relationship between pediatric isotretinoin treatment and adult body height in acne patients

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Given existing reports of premature epiphyseal closure in patients treated with isotretinoin, this research aims to investigate the relationship between pediatric isotretinoin use and adult body height in acne patients and differences in the nature of this relationship by patient sex and age at first isotretinoin treatment. The study uses a retrospective cohort approach, with data obtained from the TriNetX research network. Cohorts of male and female acne patients with a history of treatment with isotretinoin at multiple pediatric age ranges (≤18 years) were obtained and the mean adult body height of each cohort was compared with that of a corresponding doxycycline-treated control cohort. Cohorts included 10,300 male patients with isotretinoin treatment at any age ≤18 years (mean [sd] age, 25 [6] years), 7,462 female patients with isotretinoin treatment at any age ≤18 years (mean [sd] age, 24 [6] years), and 17,153 male (mean [sd] age, 26 [6] years), and 23,696 female patients (mean [sd] age, 26 [6] years) in the respective corresponding control cohorts. Mean (sd) adult body heights of the aforementioned male isotretinoin-treated cohort and its corresponding control cohort were 70.3 (2.92) inches and 70.1 (3.01) inches respectively ($p<.001$), and mean (sd) adult body heights of the aforementioned female isotretinoin-treated cohort and its corresponding control cohort were 65 (2.68) inches and 64.7 (2.8) inches respectively ($p<.001$). Additionally, across all treatment age groups studied, cohorts of patients treated with isotretinoin did not have statistically significantly lower mean body height, and some cohorts had statistically significantly higher mean body height, as compared to controls of the same sex using Welch's t-test. These findings provide evidence against an association between pediatric isotretinoin treatment and decreased adult body height among acne patients and can inform treatment recommendations and shared decision making around isotretinoin use in the pediatric population.

0231

Investigating the relationship between lactose intolerance and doxycycline-induced GI disturbances

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This study aimed to investigate the unexplored role of lactose, an excipient in doxycycline formulations, in exacerbating gastrointestinal (GI) adverse effects (AEs) among lactose-intolerant patients with the goal to improve patient management and treatment adherence. A cross-sectional phone-based survey was conducted on patients prescribed doxycycline for dermatological conditions. Descriptive statistics and a chi-square test were used to analyze the association between lactose intolerance and GI AEs, with an odds ratio (OR) estimating risk. Out of 98 survey respondents, 46 experienced GI AEs. Among the 13 patients who reported lactose intolerance, 8 experienced GI AEs. The odds ratio suggested that lactose-intolerant patients were 1.979 times more likely to report GI AEs than those without lactose intolerance (95% CI 0.598-6.547), although this was not statistically significant (p=0.257). Among patients who experienced GI AEs, 21 (45.7%) made dietary modifications, with seven (33.3%) eliminating lactose. Six patients (13%) discontinued doxycycline due to severe GI AEs, and three of these were lactose intolerant. This study did not find a statistically significant association between lactose intolerance and the incidence of GI AEs in doxycycline users. However, trends suggest that lactose-intolerant individuals may experience more severe GI symptoms. Further research, including larger, randomized studies, is needed to confirm these findings and to investigate whether mitigating factors such as Lactaid use could help reduce GI AEs. Clinicians should remain mindful of lactose intolerance when prescribing doxycycline, especially for patients with known sensitivities, as alternative treatments or dietary recommendations may improve patient outcomes and adherence to therapy.

0232

Asian skincare on social media: Trends, financial bias, and dermatological implications

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Social media is a powerful tool for sharing health information, offering unique insights into patient perspectives. With over a billion users, TikTok helps popularize dermatology content, though most posts are not by medical professionals. The global popularity of Asian skincare has grown through social media, but influencer-driven content and in-app shopping raise concerns about financial bias and product credibility. As little is known about Asian skincare content on social media, this study analyzes TikTok videos on Asian skincare to assess trends and financial incentives. In December 2024, the top 4 Asian skincare-related hashtags on TikTok were identified, and the top 50 videos for each were analyzed. Financial incentives were identified via affiliate links, TikTok Shop tags, or sponsorship disclosures. The top 200 videos averaging 4.77 million views were mostly posted by influencers(83.5%), and only 2.5% by dermatologists. Most videos were promotional(63.5%). Korean products accounted for 70.1% of featured items, with cleansers being the most common item(23.8%). Brightening claims appeared in 26% of posts, alongside Korean beauty trends like “glass skin,” describing crystal-clear, luminous skin (17%). Additionally, 20.5% of posts highlighted products as “viral.” Financial incentives were present in 63% of posts, with 16.4% of affiliate links directing users to third-party sellers. TikTok Shop tags appeared on 10.5% of posts for purchase, with 19.1% linking to official brand stores. Only 31.8% of posts with financial incentives disclosed them. Promotional content on Asian skincare is prevalent in social media, emphasizing aesthetics and “viral” products with limited financial transparency that may mislead consumers and impact skin health. Understanding these trends and biases can help dermatologists improve patient counseling and support more informed patient decisions in an evolving digital world.

0233

Intralesional talimogene laherparepvec for treatment of advanced merkel cell carcinoma

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Merkel cell carcinoma (MCC) is an aggressive skin cancer with rising incidence. While ~50% of patients with advanced MCC respond to immune checkpoint inhibitors (ICIs), those who discontinue ICIs due to side effects or lack of response require alternative treatment options. Talimogene laherparepvec (T-VEC), a modified oncolytic herpes simplex virus, is commonly used for advanced melanoma. However, data on its use in MCC are limited, primarily consisting of case reports with one or two responders, making it challenging to comprehensively evaluate responses and associated clinical features. Here, we report on eight metastatic MCC patients treated with TVEC at two institutions. All had disease progression following ICI or chemotherapy, and two were immunosuppressed due to hematologic malignancies. Five of the eight patients achieved an objective response (OR), with three partial (PR) and two complete responses (CR). The median time to OR was 8 months (range 1.2–14.4). All ORs except one were sustained for at least 10 months after best response. The abscopal effect was minimal. Three patients had non-injectable lesions that either progressed or remained stable in size, at best, throughout T-VEC therapy. Grade 2 and 3 side effects occurred in three patients. Pathological analysis of pre- and post-treatment biopsies were carried out in two patients. Prior to treatment, the responder had more viable tumor content and higher mitotic activity than the non-responder. In the post-treatment biopsies, the responder had more tumor necrosis with prominent lymphohistiocytic inflammation compared to the non-responder. In conclusion, TVEC demonstrates potential as a minimally toxic and salvage therapy that provided meaningful clinical benefit for 5 of 8 patients with therapeutically refractory MCC.

0234

Impact of dupilumab approval on diagnostic coding patterns for atopic dermatitis

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The prevalence of atopic dermatitis (AD) has been increasing, the exact causes of which remain unknown. Estimates of AD prevalence derived from administrative claims or electronic health records data may be affected by changes in diagnostic coding patterns over time due to new drug approvals, among other reasons. To understand the potential impact of dupilumab approval for treatment of moderate-to-severe AD among adults on AD prevalence and ICD-based algorithms for identifying individuals with AD, we evaluated the International Classification of Diseases, Tenth Revision (ICD-10) coding patterns for AD and other dermatitides before and after drug approval. We performed a controlled interrupted time series analysis of Medicare inpatient and outpatient visits with at least one ICD-10 code for dermatitis (L20.0, L20.8x, L20.9, L23.x-L25.x, L30.0, L30.1, L30.5, L30.8, L30.9) between January 2016 and December 2019. The primary outcome was change in monthly proportions of visits associated with the codes L20.8x (other AD); L20.9 (AD, unspecified); L30.0 (nummular dermatitis); L30.8 (other specified dermatitis), and L30.9 (dermatitis, unspecified) before and after dupilumab approval in March 2017. L30.0 served as the reference code due to its low likelihood of being affected by dupilumab approval. Total number of dermatitis-associated visits ranged from 182,801 to 376,927 per month. The total effect (i.e., difference in expected and observed code frequency one year after approval) was positive for specific AD ICD codes L20.84 (intrinsic eczema; 3.26%; 95% confidence interval [2.44%, 4.08%]) and L20.9 (1.46% [1.01, 1.90]) while negative for non-specific dermatitis codes L30.8 (-2.98% [-3.79%, -2.16%]) and L30.9 (-3.26% [-4.72%, -1.80%]). Analyses assessing sensitivity of the results to study time period and modeling choices were consistent for L20.84 but not L20.9 and L30.8. Our study identified increased use of more specific codes for AD and decreased use of non-specific dermatitis codes post-dupilumab approval that may contribute to increasing AD prevalence estimates.

0235

Sarcoidal foreign body reactions and their association with systemic sarcoidosis

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This study investigates the incidence of sarcoidal foreign body reactions (SFBRs) and their association with systemic sarcoidosis (SS) in affected individuals. We conducted a single-center, retrospective chart review of patients 18 years and older with biopsy-proven sarcoidal granulomatous dermatitis (SGD) from 2016 to 2024. Patient demographics, lesion characteristics, histopathological findings, and evaluation for SS were reviewed. Patients with a known history of sarcoidosis preceding their biopsy were excluded. Among 45 cases of SGD, 10 (22%) were associated with foreign materials. Carbon tattoo pigment was most frequently identified (60%), with other materials, including silicone cosmetic filler, asphalt, and anabolic steroid contaminants. Histopathologic evaluation most often revealed granulomatous dermatitis, sarcoidal type, associated with foreign material. Lesions presented as papules, nodules, and plaques and were most frequently located on the arms (41.7%). Of the 10 patients with SFBRs, 8 (80%) were recommended to undergo further work-up for SS, which included bloodwork, chest imaging, and/or referrals to specialists, including pulmonary, cardiology, rheumatology, or ophthalmology. Extracutaneous involvement suggestive of SS was identified in 3 (38%) of these 8 patients. Although sarcoidal granulomatous reactions in response to traumatic inoculation with foreign bodies have been documented, these lesions were primarily limited to the skin. Our findings suggest that SFBRs may represent an initial manifestation of SS and highlight the need for a thorough diagnostic work-up. Given that systemic involvement may present later, longitudinal studies are necessary to further elucidate the association between SFBRs and SS.

0236

Skin cancer anatomic location and future skin cancer risk: A medicare claims cohort study

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Prior studies have found a predominance of KCs occurring at head and or neck anatomic location. To investigate whether the anatomic location of index KC is associated with a higher or lower risk of future melanoma and KCs in the US using a large claims data set. We performed a retrospective cohort study using a de-identified, random sample of 4,999,999 fee-for-service Medicare beneficiaries (2009-2018). We included beneficiaries with at least 1 surgically treated KC, with anatomic locations identified using a previously published method, and we required patients to have at least two years of enrollment between dataset entry and index KC with no ICD code for skin cancer or history of skin cancer. We excluded patients with HIV or organ transplant, patients with >1 KCs on index date with >1 anatomic locations, and patients with ICD codes for melanoma on the date of the index KC. We evaluated the association of index KC anatomic location with future melanoma and with future KC risk using Cox regression, adjusted for age, race, gender and history of actinic keratosis. We identified 2,756,642 patients who met inclusion criteria with at least one surgically treated KC. The mean (SD) age was 77.8 (8.1) years, 56% were women, and 96.3% were non-Hispanic White. Higher risk for future melanoma was observed for patients with index KC of the trunk 1.24 (95% CI 1.10-1.40), upper limb 1.03 (95% CI 0.92-1.14) and lower limb 1.38 (95% CI 1.21-1.58) compared to index KC of the head/neck. Lower risk for future KCs was observed for patients with index KC of the trunk 0.37 (95% CI 0.35-0.38), upper limb 0.52 (95% CI 0.51-0.54), and lower limb 0.58 (95% CI 0.56-0.61) compared to index KC of the head/neck. This study shows an association between anatomic location of an index KC and the risk of future skin cancers, with differing results for future melanomas and for future KCs. Understanding the risks of future skin cancers based on anatomic location of index KC may be useful in improving skin cancer risk factor differentiation and surveillance.

0237

Benefits of minoxidil therapy outweigh potential side effects of hypertrichosis: A systematic review and meta-analysis

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Hypertrichosis, characterized by excessive hair growth, is a recognized side effect of minoxidil, a widely used treatment for androgenetic alopecia. Despite concerns about this side effect, many patients continue therapy due to its proven effectiveness in promoting hair regrowth. This study seeks to quantify the prevalence of hypertrichosis associated with low-dose oral and topical minoxidil use. Additionally, we aim to assess the overall trend of patient adherence to minoxidil despite the occurrence of hypertrichosis, to offer a more comprehensive perspective on this issue and provide reassurance to both clinicians and patients. A systematic review and meta-analysis were conducted, incorporating data from 27 studies comprising 4,294 participants. Eligible studies assessed hypertrichosis in patients using low-dose oral (≤5 mg/day) or topical minoxidil for alopecia. Pooled prevalence of hypertrichosis across studies was calculated as well as overall discontinuation rate. Hypertrichosis was observed in 23% of patients (95% CI: 0.14–0.32, I^2 = 98%), with rates varying across formulations and doses. Oral minoxidil demonstrated higher prevalence rates—10% at 0.25 mg, 15% at 1 mg, and 33% at 1.25 mg—compared to topical formulations, which showed rates of 0% at 2% concentration and 2% at 5% concentration. Notably, only 0.49% of patients discontinued treatment due to hypertrichosis. A significant majority of participants (71.7%) were female, suggesting gender-specific concerns about this side effect. Hypertrichosis is a common but generally mild side effect of minoxidil, with minimal impact on adherence. Clinicians should reassure patients that the benefits of minoxidil therapy for alopecia outweigh the potential for excessive hair growth.

0238

Somatic alterations driving progression in cutaneous squamous cell carcinoma

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Cutaneous squamous cell carcinoma (cSCC) is the second most common cancer in the United States and can cause significant morbidity and mortality in advanced stages. The genetic drivers of disease progression, particularly in metastatic and aggressive (defined as T2b and T3 tumors, based on the Brigham and Women's Hospital Tumor Classification System) tumors, remain poorly understood. This underscores a critical gap in knowledge of its biology and evolution. We conducted whole-exome sequencing on DNA extracted from formalin-fixed, paraffin-embedded tissue of surgically resected primary cSCCs that has aggressive features (agg-cSCC) or went on to metastasize (met-cSCC) and matched normal tissues. Tumor samples were identified from the Kaiser Permanente Genetic Epidemiology Research on Adult Health and Aging cohort using pathology and clinical data. We analyzed 66 tumor-normal pairs, including met-cSCC (n=22) and agg-cSCC (n=44), alongside 59 age-, sex-, and anatomic location-matched non-metastatic or non-aggressive cases. Our analysis revealed a high mutational burden consistent with UV-induced damage. We identified significantly mutated genes using dNdScv and MutSig2CV, considering the intersection of the identified genes as candidate drivers, including NOTCH1, FAT1, NOTCH2, ARID2, HRAS, TP53, CDKN2A, RIPK4, KMT2D, AJUBA, KNSTRN, KRT5, and CHUK, suggesting their pivotal roles in cSCC pathogenesis. In addition, we discovered novel candidate genes, COMMD8 and TMEM222, that warrant further investigation to assess their functional relevance. Our analysis of primary tumors validated known driver genes and identified candidate novel drivers, revealing key alterations associated with cSCC progression and potential clinical targets.

0239

Decreased physical activity in lupus patients, an analysis of biometric data from the All of Us database

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Lupus erythematosus (LE) is a chronic autoimmune disease with variable manifestations, including cutaneous lupus erythematosus(CLE) and systemic lupus erythematosus (SLE). While low physical activity(PA) levels in LE have been reported, prior studies rely on self-reported data, which can introduce recall bias. This study used objective Fitbit data to analyze PA patterns in both SLE and CLE patients, focusing on activity zones, sedentary time, and step counts. Using the All of Us Database, we performed a cross-sectional study to compare patients with Fitbit data and diagnoses of CLE (ICD-10 codes L93.0 and L93.1, representing discoid and subacute cutaneous lupus) and SLE (ICD-10: M32) with age-, race-, and sex-matched controls. PA was categorized by metabolic equivalents (METs): very active (>6 METs), fairly active (3–6 METs), lightly active (1.5–3 METs), and sedentary (<1.5 METs). LE patients (n=91) showed significantly less time in very active (9.9 vs. 16.3 minutes, p=2.25E-06) and fairly active zones (11.4 vs. 16.1 minutes, p=3.58E-05), fewer steps (5,897.5 vs. 7,364.4, p=1.17E-06), and more sedentary time (79.6% vs. 77.9%, p=0.0378) compared to controls. CLE patients (n=25) demonstrated even greater deficits, with higher sedentary time (81.5% vs. 78.1%, p=0.023), fewer steps (6,010.7 vs. 7,474.7, p=0.007), and reduced activity duration. This study confirms that LE patients, particularly those with CLE, engage in significantly less PA than controls, providing unique objective data. In SLE, inactivity is linked to pain, reduced aerobic capacity, and fear of flare-ups, while in CLE, inactivity may stem from skin discomfort, self-consciousness, and mental health challenges. Addressing these barriers is crucial to breaking the cycle of limited activity and worsening health outcomes, ultimately improving lupus management and quality of life in LE patients.

0240

Elucidating medication waste for outpatient clinic procedures with intralesional triamcinolone

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With over 10 million procedures conducted annually in the U.S., single-use intralesional injections performed by dermatology pose significant environmental challenges and contribute to the growing issue of medical waste. At our institution, intralesional triamcinolone is drawn up from a single-use vial into a single-use syringe with the remaining unused medication discarded. This research aimed to quantify the extent of medical waste generated by intralesional triamcinolone injection procedures and to identify areas for minimizing this medical waste. We conducted a retrospective chart review for patients receiving intralesional steroid injections with Kenalog-40 or Kenalog-10 at our academic institution from 01/01/2020–12/31/2023 for the treatment of scars, keloids, or different types of alopecia. Analysis of 650 patients demonstrated that a total of 101.7mL of Kenalog-40 and 171.0mL of Kenalog-10 were used. There were 124.4mL of discarded Kenalog-40, equivalent to 125 vials (1 mL/vial) and 140.6mL of discarded Kenalog-10, equivalent to 29 vials (5 mL/vial). We found that about 60% of Kenalog-40 and 52% of Kenalog-10 were wasted, exceeding the amount utilized. The estimated total carbon footprint from the glass vials alone is 8.6g CO2e per Kenalog-40 and 11.12g CO2e for Kenalog-10, totaling about 1.4kg CO2e. This value does not include waste of the medication itself nor supplies such as gauze, gloves, and syringes used in the procedure which would further compound the environmental impact. Our results highlight an urgent opportunity to reduce unnecessary medical waste from single-use medications and the importance of considering how our daily practice affects our environmental impact. Encouraging sustainable practices such as optimizing medication dosing and preparation, implementing a return program for unused medication, and increasing awareness may help minimize medical waste in dermatology.

0241

Dermatology access in distressed communities: Exploring the impact of community economic hardship on care availability

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This study examines how community economic distress influences access to dermatology care, focusing on three clinic-level factors: clinic operating hours, teledermatology availability, and Medicaid acceptance. The Distressed Communities Index (DCI), a composite measure that combines indicators of economic distress such as income, employment, education, and housing, was used to categorize communities into quintiles, from the most prosperous (1) to the most distressed (5). In this cross-sectional study, 122 medical dermatology clinics in the southern United States were categorized by DCI quintile and contacted for data on operating hours, teledermatology availability, and Medicaid acceptance in August 2024. Clinics in more distressed communities had fewer access opportunities. Operating hours decreased by 1.3 hours per week with each increase in DCI quintile ($\beta = -1.34$, $p < 0.001$), with the most distressed areas operating 5.4 fewer hours weekly than the most prosperous areas (36.1 vs. 41.5 hours, respectively). The proportion of clinics offering teledermatology also decreased by 6.4% per quintile ($\beta = -6.36$, $p = 0.003$), showing a 25.4% decline from prosperous areas (where 54.8% of clinics offered teledermatology) to distressed areas (where only 29.3% of clinics offered teledermatology). Medicaid acceptance did not significantly vary across DCI quintiles ($p = 0.074$). These findings demonstrate how economic distress limits access to dermatology care, particularly in underserved communities. Expanding teledermatology, optimizing clinic hours, and implementing innovative solutions such as mobile units and AI-driven triage systems could help reduce barriers and enhance dermatology healthcare equity in economically distressed regions of the United States and globally.

0242

Staging comparison between merkel cell carcinoma and melanoma in black patients

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Merkel cell carcinoma (MCC) is a rare but highly aggressive skin cancer, with several studies showing an overall higher mortality rate than melanoma. While melanoma has a five-year survival rate exceeding 90% when detected early, MCC's five-year survival rate is significantly lower, with localized cases at 75% and distant metastases at 24%. However, this data across different ethnic groups, especially among black patients, remains underexplored. Therefore, the purpose of this study is to compare the staging between MCC and melanoma in black patients. This retrospective cohort study included black patients diagnosed with MCC and melanoma from 2000 through 2021 in the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. Variables collected included sex, age, and staging. Two-tailed chi-square was used to assess the association between categorical variables. A proportional relative risk ratio was conducted to determine associations between diagnosis and staging. P-values <0.05 were considered significant. A total of 3,853 cases were identified, of which 315 were diagnosed as MCC. No sex predilection was found in MCC patients (48.2% female), whereas there were more females in the melanoma cohort (56.3%, p<0.001). Patients with MCC were older than melanoma patients with higher percentage of patients aged ≥ 70 years (54.9% and 47.1%, respectively; p<0.001). MCC patients were more likely to present with advanced staging than melanoma patients (i.e. Staging: regional and distant; 141 [52.5%] MCC patients vs 1,134 [42.2%] melanoma patients; RR 1.26; [1.12-1.42]; p<0.001). In comparison to black patients with melanoma, black patients with MCC were diagnosed at older age and with more advanced disease stage, suggesting that MCC may not only be more aggressive than melanoma in black patients but also its diagnosis may be delayed in comparison to black patients with melanoma. This disparity underscores the critical importance of early detection and treatment for MCC.

0243

Dermatological injuries linked to topical products: Insights from a decade long national cohort study

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Lotions and moisturizers are widely used for skincare and treating cutaneous conditions. While generally safe, they may occasionally be associated with dermatological injuries requiring emergency department (ED) care. While previous research has focused on their efficacy and side effects, severe lotion-related ED visits remain underexplored. Examining demographics, clinical presentations, and outcomes of these cases may help develop prevention strategies for these injuries. The National Electronic Injury Surveillance System (NEISS), a nationally representative cohort of ~100 U.S. EDs and overlying territories were analyzed. A keyword search of "lotion," "moisturizer," and associated plurals was queried. T-value tests assessed differences across sex (P<0.05). 522 cases were analyzed (mean age: 24, range: 1 month–98 years), with 61.9% female, 28.0% Black. Cases peaked in 2020 at 65 cases. Dermatitis, poisoning, and contusions were the most common diagnoses. Women were significantly less likely to experience accidental ingestion and more likely to experience osseous fractures than men (0.00% vs. 2.01% vs. and 5.57% vs. 2.01%, P<0.05). Lower arm, ankle, and head regions were significantly more impacted in women than men (7.74% vs. 3.52%, 2.48% vs. 0.50%, 7.43% vs. 3.52%, P <0.05), while injuries affecting over 50% of the body were less frequent (21.98% vs. 31.16%, P <0.05). Topical-related injuries represent a significant health burden in the U.S., with women representing the majority of cases (61.9%). The demographic and clinical patterns observed suggest that these injuries are not random but may be influenced by age, gender, and cultural practices. Further study is required to examine the exact cause of these injuries and potential improvements in application instruction and protection.

0244

Evaluating hydroxyurea's photosensitizing effects: A study on cutaneous squamous cell carcinoma risk

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Philadelphia-chromosome–negative myeloproliferative neoplasms (Phl-MPN) are associated with increased risk of cutaneous squamous cell carcinoma (cSCC), potentially due to disease-related immunosuppression. Hydroxyurea (HU), a photosensitizing cytoreductive (CR) agent is used for Phl-MPNs and sickle cell disease (SCD)—a condition not linked to SCC. We evaluate whether HU increases cSCC risk using TriNetX Research Network. Three cohorts were analyzed: (1) Phl-MPN patients receiving HU vs no HU or other CR therapy; (2) SCD patients on HU vs no HU exposure; (3) Phl-MPN patients on HU vs alternative medications (AM) (interferon-α, anagrelide, fedratinib, ruxolitinib, pacritinib, busulfan). Propensity score matching (1:1) controlled for age, sex, race, and ethnicity. Patients with prior cSCC, immunosuppressive treatments or stem cell transplants were excluded. The primary outcome was cSCC incidence after diagnosis and drug exposure, identified via ICD-10 codes. Among 44,122 Phl-MPN patients (22,084 HU-treated, 22,084 no CR agent exposure), cSCC incidence was higher in HU users (460/21,750 vs 314/21,744; RR=1.5, CI:1.3–1.7, p<0.0001). In the SCD cohort (29,910 patients; 14,955 HU-treated, 14,955 no HU), HU was associated with significantly elevated cSCC risk (143/14,192 vs 17/14,948; RR=8.4, CI:5.1–13.9, p<0.0001). In the Phl-MPN cohort comparing HU to AM (8,280 patients; 4,140 in each group), cSCC risk was similar (RR=0.9, CI:0.7–1.2, p=0.5). HU was associated with reduced cSCC in non-sun-exposed areas (anal, hip, trunk, breast) compared to Phl-MPN patients not on CR therapy (RR=0.7, CI:0.5–0.9, p<0.03) and AM (RR=0.5, CI:0.3–1.0, p<0.04). The SCD cohort analysis for non-sun-exposed areas was inconclusive due to limited outcomes. Our findings suggest that HU-associated cSCC may be driven by photosensitization as well as immunosuppressive effects. Highlighting the importance of UV protection for HU users and the need for further research to clarify HU's role in UV-induced cSCC.

0245

Topical minoxidil toxicosis in cats and dogs

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Topical minoxidil, an affordable, over-the-counter treatment for androgenetic alopecia, is widely used but its impact on pets is often overlooked. This study examined topical minoxidil exposure in cats and dogs alongside public interest. Annual poison control report volumes and topical minoxidil exposure cases from the American Society for the Prevention of Cruelty to Animals Animal Poison Control Center (APCC) were collected 2013-2023. Cases involving oral minoxidil or co-exposure to other drugs were excluded. The proportion of yearly reports involving topical minoxidil was calculated relative to the total annual poison control cases. "Topical minoxidil" interest from Google Trends was collected 01/01/2013–12/31/2023. Correlation between normalized proportion of toxicosis reports and normalized topical minoxidil interest was evaluated using Pearson correlation. A total of 488 topical minoxidil toxicosis cases (63.5% in cats) were reported to APCC over the study period, comprising 0.02% of all reports. Most cases occurred in adult animals (71.3%), with oral exposure being the predominant route (92.2%). Exploratory behavior accounted for 68.6% of exposures. Clinical toxicosis was documented in 207 cases (42.4%), with 7 (3.4%) resulting in adverse outcomes, including 3 deaths. The average annual increases in the normalized proportion of topical minoxidil reports and in interest were 5.71 and 7.59, respectively. A strong correlation (R=0.760) was observed between normalized interest in topical minoxidil and proportion of poison control reports linked to it. We found increasing interest in topical minoxidil, strongly correlating with the rise in poison control cases attributed to topical minoxidil. When discussing the potential adverse effects of topical minoxidil with patients, dermatologists should ask about household pets and discuss topical minoxidil's risks to pets, including fatalities. It is important to counsel patients on prevention and prompt veterinary care if exposure occurs.

0246

WITHDRAWN

0247

Antinuclear antibodies and malignancy risk in scleroderma patients: A systematic review and meta-analysis

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Scleroderma is associated with increased malignancy risk. Autoantibodies such as anti-RNA polymerase III (anti-RNAPIII) have been linked to increased cancer incidence in some studies. We conducted a meta-analysis to evaluate malignancy risk in scleroderma patients with anti-RNAPIII, anti-topoisomerase I (anti-Scl70), or anti-centromere antibodies (ACA). Ovid MEDLINE, EMBASE, Cochrane Library, and Web of Science were searched for studies prior to August 15,2023 that evaluated malignancy risk in adult scleroderma patients with anti-RNAPIII, anti-Scl70, or ACA. MOOSE guidelines were followed. Pooled risk ratios (RR) and 95% confidence intervals (CI) were calculated using random-effects models. 20 observational studies and 42,663 patients with scleroderma were included in the meta-analysis. Anti-RNAPIII positivity was associated with a 2-fold increased risk of overall malignancy (RR 2.08; 95% CI: 1.51–2.87), 2.65-fold increased risk of breast cancer (RR 2.65; 95% CI: 1.76–3.98), and 2.13-fold increased risk of skin cancer (RR 2.13; 95% CI: 1.06–4.25) compared to anti-RNAPIII-negative patients. The risk of hematologic cancer did not differ based on anti-RNAPIII status (RR 1.84; 95% CI: 0.72–4.67). The risk of overall malignancy (RR 1.15; 95% CI: 0.88–1.51) or breast cancer (RR 0.62; 95% CI: 0.33–1.15) did not differ based on anti-Scl70 status. ACA positivity was associated with a 4.76-fold decrease in lung cancer risk (RR 0.21; 95% CI: 0.05–0.89) but showed no association with risk of overall malignancy (RR 0.85; 95% CI: 0.69-1.06) or breast cancer (RR 1.05; 95% CI: 0.75–1.48). Although standardized cancer screening guidelines for scleroderma patients are still in development, our findings suggest clinicians can consider earlier screening, especially for breast and skin cancers, in anti-RNAPIII-positive patients. Further studies are required to refine cancer risk prediction and screening strategies in scleroderma patients.

0248

Risk of infections in patients with hidradenitis suppurativa treated with TNF-α inhibitors vs. IL-17 inhibitors: A large-scale cohort study

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Biologic therapies like TNF-α and IL-17 inhibitors have shown promising results in managing Hidradenitis suppurativa (HS) and are increasingly utilized in clinical practice. These immunosuppressive treatments are associated with an elevated risk of infections. Given the microbiome dysbiosis characteristic of HS, there is a potential for heightened susceptibility to infections in this population treated with these immunosuppressive medications. However, there is limited data directly comparing treated-related infection risks in HS patients. This study leverages real-world data from a global cohort to compare the infection risks of TNF-α and IL-17 inhibitors in HS management. Here, we conducted a retrospective cohort study using the TriNetX database from 2003 to 2023, capturing data from de-identified electronic health records across 90-93 healthcare organizations. Patients with HS treated with TNF-α or IL-17 inhibitors were compared after propensity score matching for age and gender. Risk ratios (RR) with 95% confidence intervals (CI) were calculated. The study included 2,076 matched patients per group (mean age: 40.3 years; 68.79% female, 50.96% White, 31.55% Black). TNF-α inhibitors were associated with a higher infection rate (30.83%) compared to IL-17 inhibitors (18.74%) (RR 1.65, 95% CI 1.55–1.75). The most common infections associated with TNF-α inhibitors were urinary tract infection (8.77%), COVID-19 (7.32%), and pneumonia (6.22%), while the most common infections in the IL-17 inhibitor-treated patients were COVID-19 (5.35%), sepsis (4.34%) and urinary tract infections (4.29%). Lastly, all types of infections were more frequent in the TNF-α inhibitor-treated HS patients. The retrospective design and potential underreporting of infections may limit our findings. However, these real-world findings from a diverse patient population offer valuable context for personalized risk-benefit assessments in clinical decision-making for the treatment of HS.

0249

Pruritic papules with keratotic plugs in a patient with end-stage renal disease: Kyrle disease or perforating folliculitis?

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Kyrle disease and perforating folliculitis are rare perforating dermatoses often associated with systemic conditions like diabetes mellitus and end-stage renal disease (ESRD). Differentiating between these entities poses significant clinical and histopathologic challenges due to overlapping features. A 39-year-old female with past medical history of ESRD (on hemodialysis for 12 years), type 2 diabetes mellitus, hypertension, and prior left leg amputation due to gangrene, presented to the emergency department with a 3-month history of worsening pruritic eruptions and poor glycemic control. Lesions began on her legs and spread to her arms and back. Physical examination revealed numerous flesh-colored papules and nodules with central keratotic plugs, predominantly affecting the legs, arms, and back, with koebnerization on the legs. She was admitted for further management. Histopathology from a punch biopsy of the left forearm demonstrated hyperkeratosis with acute folliculitis and dermal parakeratotic material. Differential diagnoses included perforating folliculitis and Kyrle disease. Elastic staining revealed rare elastic fibers entering the epidermis, consistent with Kyrle disease. However, the absence of elastic fibers in the mid to upper epidermis and cornified layer introduced diagnostic uncertainty. This case highlights the diagnostic complexity of perforating dermatoses in patients with systemic comorbidities, emphasizing the importance of integrating clinical, histopathologic, and advanced staining techniques for accurate diagnosis. Recognizing and addressing perforating dermatoses in ESRD patients is critical to improving management and outcomes. Future studies are warranted to refine diagnostic criteria and elucidate pathogenesis.

0250

Systemic therapy associates with a lower incidence of male infertility among psoriasis patients

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Psoriasis is a chronic inflammatory skin disease with severe consequences on quality of life. Existing research indicates systemic inflammation may impair fertility, yet data on whether systemic medications used in the management of psoriasis associate with male infertility remain scarce. We conducted a population-based retrospective cohort study utilizing de-identified data from the TriNetX Global Collaborative Network, between 2004-2024. Male patients diagnosed with psoriasis were included in the analysis. Individuals with a prior history of infertility or known hormonal, genetic, inflammatory or structural causes of infertility were excluded. Using the greedy nearest neighbor algorithm, male psoriasis patients managed with systemic therapy for psoriasis (biologics and non-biologics) were propensity score matched (1:1) to a control cohort of male psoriasis patients managed without systemic therapy. Covariates included demographics, overweight and obesity status, smoking, alcohol use, and body mass index. Male infertility was measured at any time after the index event for up to 20 years or until withdrawal from the TriNetX database. Odds Ratios (OR) with 95% confidence intervals (CIs) were calculated. We identified 26,907 psoriasis patients managed with systemic therapy and 95,305 psoriasis patients managed without, who met the study criteria. Propensity score matching resulted in cohorts of 26,165 patients. The mean age of patients receiving systemic therapy was 48.5 ± 16.8 years, while the mean age of those not receiving systemic therapy was 48.4 ± 17.1 years. Within a 20-year observation window, psoriasis patients managed with systemic therapy were 45% less likely to be diagnosed with male infertility compared to controls (26 vs 47, OR 0.55; 95% CIs: 0.34-0.89). Findings from this large, population-based study suggest male psoriasis patients receiving systemic therapy are less likely to experience infertility compared to those not on systemic therapy.

0251

Comparing teledermatology and in-person dermatology for lichenoid dermatoses

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Given the paucity of research on teledermatology (TD) in the management of lichenoid dermatoses, this study examines its impact on access to care, diagnostic accuracy, treatment protocols, and follow-up compliance compared to in-person (IP) dermatology. A retrospective analysis of electronic medical records at the University of Pittsburgh Medical Center from January 2020 to June 2024 identified 274 patients with lichenoid dermatoses, including lichen sclerosus (60%) and lichen planus (37%). 24% of cases were TD visits. TD significantly improved access to care, with a mean consult submission-to-response time of 14.7 hours. Diagnostic concordance was high between initial TD assessments and subsequent IP dermatology follow-ups (93%) but significantly lower (19%, p <.001) between consulting PCPs and teledermatologists. Teledermatologists demonstrated high adherence to established standards of care for lichenoid dermatoses, screening for HCV infection (91%) and drug-related causes (98%) in lichen planus patients, while prescribing topical corticosteroids as a first-line treatment in 88% of all lichenoid dermatoses cases. Significant demographic disparities were observed, with Black patients comprising 22% of the TD cohort compared to 8% of IP visits (p <.01). These findings emphasize the need for targeted interventions to address disparities in dermatological care among diverse patient populations. Follow-up compliance was lower in TD patients compared to IP patients, particularly among younger eVisit patients (54%, p <0.001). Similarly, compliance with hepatitis C testing was 67% in TD patients with lichen planus compared to 91% in IP patients with the same diagnosis. Contributing factors may include challenges navigating TD systems and difficulties accessing resources without IP support. Our findings suggest that TD can improve access to high-quality dermatologic care for lichenoid dermatoses patients, while demonstrating comparable diagnostic accuracy and disease management to traditional IP care.

0252

Insights from a veteran cohort: Does tumor necrosis factor-alpha (TNF-α) inhibitor use impact COVID-19 breakthrough infection risk in vaccinated dermatology patients?

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This study evaluated whether TNF-α inhibitor use influenced the frequency, timing (relative to last COVID-19 vaccination), or severity of COVID-19 breakthrough infections(BTIs) among dermatology patients in the Veterans Health Administration. Using a nationwide retrospective cohort design, we analyzed data from 20,304 patients receiving TNF-α inhibitors and 115,667 controls not on biologics, systemic steroids, or immunosuppressants. All participants were vaccinated against COVID-19 and received dermatologic care between January 1, 2017, and December 1, 2024. BTI incidence, timing, and severity were assessed using Kaplan-Meier survival analysis and Cox proportional hazards regression. Among TNF-α inhibitor users, 10.8% experienced BTIs compared to 12.7% of controls, with similar times from COVID-19 vaccination to BTI(median: 228 vs. 242 days; mean: 298 vs. 305 days; p = 0.205). BTI severity was milder in TNF-α inhibitor users, with lower 30-day mortality (0.8% vs. 1.6%; p < 0.001). Patients on TNF-α inhibitors were younger (mean age: 61.0 vs. 67.8 years; p < 0.001), more likely female (14.5% vs. 11.4%; p < 0.001), and had fewer comorbidities (Charlson Comorbidity Index 2.14 vs. 2.72; p < 0.001). Psoriasis was the predominant dermatologic condition in the TNF-α inhibitor group (67.4% vs. 12.9%; p < 0.001). After adjusting for race, age, sex, overall health, dermatologic condition, and COVID-19 boosters, the hazard ratio for developing a COVID-19 BTI among TNF-α inhibitor users compared to controls was 0.99 (95% CI: 0.94–1.04; p = 0.6). Kaplan-Meier analysis showed a 50% infection-free survival rate approximately 8 months post-vaccination in both groups (p = 0.18). These findings suggest TNF-α inhibitor use does not increase BTI incidence, timing, or severity in dermatology patients. Both groups experienced waning immunity 8 months post-vaccination, supporting the need for ongoing boosters to sustain protection.

0253

An analysis of ChatGPT recommendations for dressing selection in wound care

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Our study aims to asses the accuracy of wound care recommendations made by ChatGPT, a large language model (LLM), that utizilizes artificial intelligence to generate responses to inquiries, including medical advice. Given its widespread use, the implications of patients querying ChatGPT for medical recommendations, such as wound care, should be reviewed and familiar to the dermatology community. Specifically, this study assesses ChatGPT's accuracy in recommending wound dressings for different wound types, including more general wound types and more detailed descriptions. Data was collected in October 2024 using ChatGPT-4. Inputs and descriptions were derived from Dressings, Chapter 145, of Dermatology and the authors' clinical experience. ChatGPT was queried with wound descriptors, and responses were evaluated for correctness based on established clinical guidelines. ChatGPT's overall accuracy for broad wound categories (e.g., exudative, painful, bleeding, and infected wounds) was 87% (13/15). For specific wound indications, ChatGPT recommended the correct dressing as the first choice 34% (11/32) of the time and within the top three choices 72% (23/32) of the time. The model failed to recommend key dressings for specific wound types including film dressings for skin tears and alginates for venous ulcers. Overall, ChatGPT has suboptimal performance in making wound care recommendations and has increased risk of providing misguidance in wound care to patients. While ChatGPT's performance was high for broader wound categories, its decreased accuracy for specific queries underscores the importance of clinical expertise in wound care decision-making. Algorithmic bias, stemming from training data limitations, may have influenced these results. Further integration with clinical databases and real-world feedback could enhance the model's accuracy in specific wound care scenarios.

0254

Exploring the association between urticaria and risk of type 1 diabetes mellitus: A case-control study

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This global case-control study explores whether an association exists between urticaria diagnosis and increased risk of developing Type 1 Diabetes Mellitus (T1DM). The dataset used was from the TriNetX Research network, comprised of 96 healthcare organizations globally. Two cohorts were defined: Urticaria cohort (n=5,311) included patients with a diagnosis of urticaria (≥2 instances) between 2010 and 2025, followed by T1DM diagnosis (≥1 month post-urticaria). Control cohort (n=617,869) comprised matched controls without urticaria but with T1DM diagnosed in the same timeframe. Propensity score matching was applied to balance baseline characteristics including age, race, sex, and comorbidities, resulting in 5,311 patients per cohort for analysis. After matching, the risk of T1DM was higher in the urticaria cohort (Urticaria cohort, 60.0%) compared to the controls (Control cohort, 56.8%) (Risk Difference: 3.2%; 95% CI: 1.3%–5.1%; p=0.001). The odds of T1DM were significantly greater in the urticaria cohort (OR: 1.142; 95% CI: 1.057–1.233). Urticaria appears to be associated with an increased risk of subsequent T1DM diagnosis. The odds of developing T1DM were 1.142 times greater in the urticaria cohort than in controls. Further research is needed to explore the underlying mechanisms, whether immunologically related or otherwise, which will be important to future diabetes prevention.

0255

Impact of skin disease, interstitial lung disease, and IVIG use on in-hospital mortality in dermatomyositis: A retrospective case control study

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Background: Dermatomyositis(DM) is an autoimmune disorder characterized by muscle inflammation, distinctive skin rashes, and comorbidities such as interstitial lung disease(ILD) and malignancy. Hospitalized DM patients face significant morbidity and mortality, with infection previously identified as a leading cause of death. However, specific factors influencing in-hospital mortality at admission remain poorly defined. Methods: We conducted a retrospective review of 153 adult DM patients admitted to Johns Hopkins Medicine(October 2013–February 2024). Data collected included demographics, disease characteristics, and hospitalization outcomes. Deceased patients were compared to survivors using t-tests, chi-squared tests, and multivariable logistic regression. Results: Among 153 patients (mean age 56.5 years, 73.9% female), 10.5% died during hospitalization. Compared to survivors, deceased patients had a shorter duration of DM (4.08 vs. 7.57 years, p=0.023) and were less likely to be on IVIG at admission (31.3% vs. 61.3%, p=0.041). They were significantly more likely to present with active skin disease (81.3% vs. 34.3%, p<0.001), ILD (87.5% vs. 41.6%, p=0.001), and concurrent rash and ILD (68.8% vs. 11.7%, p<0.001). In adjusted logistic regression, active skin disease (OR 9.71, 95% CI 2.33-56.64, p<0.01) and ILD (OR 8.01, 95% CI 2.04-46.80, p<0.01) remained significant predictors of mortality, while IVIG was protective (OR 0.28, 95% CI 0.09-0.89, p=0.032). All deceased patients experienced respiratory failure, predominantly due to ILD exacerbations (56.3%) or infection (37.5%). Conclusions: Our study is the first to highlight active skin disease as a critical predictor of in-hospital mortality in DM, likely reflecting heightened systemic disease burden. We found that IVIG may confer a protective effect, though disease severity was not accounted for. Clinicians should recognize the association between active skin disease and heightened mortality risk in hospitalized DM patients to guide appropriate management.

0256

Review of the current therapeutic landscape of pemphigus vulgaris: Targeting the type 2 and non-type 2 inflammatory pathways and novel upstream targets

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This study reviews the therapeutic potential of the inhibition of IL-33 and TSLP on type 2 and non-type 2 inflammatory pathways in the pathogenesis of pemphigus vulgaris (PV). Recent advances in biologic therapies have emphasized the role of the type 2 inflammatory pathway in the pathophysiology of PV. Through a review of the literature and analysis, we explore IL-33 and TSLP as important modulators of the type 2 inflammatory pathway via their activity in diseases such as asthma, atopic dermatitis, and bullous pemphigoid. In addition, we describe their impact on non-type 2 inflammation. Our analysis revealed that IL-33 and TSLP have essential roles in the pathogensis of PV, contributing to the activation of type 2 and type 17 T helper cells, eosinophils, and mast cells. In addition to having been implicated in the pathogenesis of PV, targeting of these cytokines can inhibit IL-4, IL-5, IL-13, IL-17, CCL17, CCL22, IFN-γ, and B-cell development. Targeting these cytokines may have a role in being pursued as monotherapy, or in conjunction with existing treatments. First-line therapies for PV, including oral corticosteroids and immunosuppressants, are often associated with systemic side effects and may not be suitable for all patients. Targeting upstream cytokines in PV presents a promising therapeutic avenue to reduce systemic side effects and improve patient outcomes in this chronic disorder.

0257

The association of hidradenitis suppurativa and endometriosis: A cross-sectional study using the All of Us research program

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Hidradenitis Suppurativa (HS) and endometriosis are inflammatory disorders that greatly impact patients' lives. Despite the overlap in inflammatory pathways in HS and endometriosis, the potential relationship between the two has not been well characterized. We sought to examine this association with a cross-sectional study using data from the National Institutes of Health's All of Us Research Program, which focuses on traditionally underrepresented populations in research. Electronic health record and survey data of participants assigned female at birth aged over 60-years-old was used to compare the odds of having endometriosis in patients with HS versus those without via logistic regression and adjusted for demographic factors, smoking, body mass index (BMI) and common comorbidities. In this diverse cohort, 7.0% of those with HS and 2.6% of those without HS had endometriosis (P <0.001). The odds of those with HS having endometriosis was significantly higher than in patients without HS (odds ratio 2.59, 95% confidence interval 1.48-4.23, P < 0.001) even after adjusting for covariates. These findings indicate a positive association between HS and endometriosis and that suggest future research is needed to better understand whether certain therapies may be best for those with both conditions.

0258

Disparities of itch severity in outpatient clinics as measured by the ItchyQuant

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We explored itch severity among demographic populations at a large academic medical center. Itch severity was captured via ItchyQuant, a validated patient-reported outcome measure (PRO) rating itch from 0-10. The ItchyQuant was distributed to every patient via portal 7 days prior to any dermatology encounter except for Mohs surgery as a component of the Standard Dermatology Outcome Measures (SDOM), a panel of five validated skin-related PROs. Of the 21,073 unique patients who completed the SDOM over 1 year, 8,207 (39%) responded to the ItchyQuant. The overall mean itch score was 2.81, with 44% of respondents reporting no itch (itch score 0) and 36% reporting moderate (4-7)-to-severe (8-10) itch. Females reported a higher mean itch score (3.0 vs 2.4) than males and a higher proportion of moderate (26 vs 22%) and severe (14 vs. 9%) itch. Adolescent patients (12-17 years) reported the lowest mean itch score (2.47) with 35% reporting moderate-to-severe itch while patients age 46-55 reported the highest mean itch score (3.05) with 39% reporting moderate-to-severe itch. Black/African American (AA) and Asian patients reported higher mean itch scores than White patients (4.40 and 3.30, respectively vs 2.52), as well as proportion of moderate-to-severe itch (57 and 44% vs 33%). Hispanic patients reported a higher mean itch score (3.2 vs 2.8) compared to Non-Hispanic/Latino patients and proportion of moderate-to-severe itch (44 vs. 36%). Our results corroborate other studies reporting AA with higher itch severity than Whites. Few studies compare itch severity of Asian or Hispanic patients, both of which had a higher proportion reporting higher itch severities than White/Caucasian and non-Hispanic counterparts. These findings, including the gender difference, may be attributed to different diagnoses in these populations. The fact that the oldest patients (>75) were less itchy than younger groups contradicts published conclusions regarding severity of geriatric itch. While more research is needed, our data suggest that itch disparities exist.

0259

Comparison of clinical characteristics and phenotypes of hidradenitis suppurativa by smoking status

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Hidradenitis suppurativa (HS) is a chronic, inflammatory skin condition with smoking as an established risk factor. However, the influence of smoking on disease characteristics and phenotypes remains unknown. This study aims to evaluate the relationship between smoking status and HS phenotypes, demographic characteristics, and clinical features. A retrospective cross-sectional study was conducted with 1,616 HS patients which were stratified by smoking status. Phenotypic distributions, demographic characteristics, and clinical features were compared across groups. A chi-square test was performed to evaluate the independence of HS phenotype by smoking status. Regular phenotype was most common in non-smokers (77.2%) compared to current (56.8%) and former smokers (64.2%). Conversely, scarring folliculitis was more prevalent in current smokers (23.4%) and former smokers (14.8%) than in non-smokers (4.1%) ($p < 0.01$). Other advanced phenotypes, such as conglobata and syndromic HS, were more frequently observed in smokers than in non-smokers. Current smokers showed a higher prevalence of hypertrophic or keloid scarring (8.8%), and honeycomb or cribriform scars (19.8%) compared to former (7.9% and 16.1%, respectively) and non-smokers (6.7% and 8.9%, respectively). Additionally, Hurley stage III was more frequent in current (36.2%) and former (39.4%) smokers when compared to 32.7% in non-smokers. Smokers, both current and former, are more likely to exhibit the scarring folliculitis phenotype and advanced Hurley stages when compared to non-smokers. These findings reiterate the importance of smoking cessation as a potentially critical component of HS management in an effort to mitigate disease progression and severity. Further research is needed to explore the pathophysiological mechanisms linking smoking and specific HS phenotypes and clinical characteristics.

0260

A systematic analysis of meta-analyses: Development of the Meta-Analysis Diversity Index (MADI)

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There are few objective measures of efficacy of a meta-analysis; thus, a systematic review study was conducted to quantify the effect of varying diversity of included studies in meta-analyses published in dermatologic journals. Until December 2024, a comprehensive literature review was conducted, and 123 studies were revised. The 51 included meta-analyses synthesized 943 studies and 28,049,093 participants. Meta-analyses with one predominant study had pooled event rates within the same confidence intervals of that study. A linear regression model was used comparing predominant study event rate to the overall pooled event rate, yielding a positive association ($R^2 = 0.9793$, p= 1.28554E-10). This led to the development of the MADI, which can be calculated using the equation . A MADI score greater than 1.3 predicts greater diversity within the included meta-analyses, indicating novel study. Meta-analyses with less diverse included studies, or one predominant study do not provide new information. Rather, authors should utilize the MADI score and instead perform a replication study with a larger cohort to ensure reproducibility and variability of the predominant study.

0261

Barriers to seeking and obtaining mental health services among atopic dermatitis patients

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Despite an established mental health (MH) burden among atopic dermatitis (AD) patients, there is a gap in diagnosis and treatment, and limited research on the barriers to accessing MH care in the context of AD. Logistic regressions were employed using data from an online survey of adult AD patients and caregivers of children aged 8-17 with AD (October to November 2023) to understand barriers to seeking and obtaining MH services. Among 986 participants, mostly female (68.6%) and White (66.4%), the largest barrier to seeking MH services was discomfort discussing MH (23.9%, 109/456). Structural barriers included uncertainty with how to find a MH provider (18.9%) and assuming/knowing that insurance would not cover MH services (14.5%). Some did not seek care because they thought it would not help (18.9%) or lacked confidence in the MH system (12.1%). Predictors of seeking MH services included race (Black: OR=1.38, p=0.189; Asian: OR=1.18, p=0.494; Other=1.85, p=0.003), sex (Female: OR=1.31, p=0.084), educational attainment (Four-year college, technical, or higher degree: OR=2.29, p=0.029), and the belief that eczema severity affects MH (OR=6.35, p<0.001). Predictors for those who successfully obtained MH services included ethnicity (Hispanic: OR=0.67, p=0.088), sex (Female: OR=1.95, p=0.007), insurance type (Medicaid: OR=0.49, p=0.042; Medicare/Tricare/VA: OR=0.46, p=0.01; Purchased: OR=0.36, p=0.001), and educational attainment (Four-year college, technical, or higher degree: OR=5.55, p=0.017). Participant-reported barriers highlight the role of social determinants of health, structural inaccessibility, and MH stigma in influencing access to MH care. AD providers can normalize MH challenges by educating patients on the AD-MH connection and the utility of MH services, encourage patients to seek MH care, and address structural barriers, which may be especially important for those who are less likely to seek or obtain services.

0262

Patient-reported outcomes for atopic dermatitis in early childhood

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Atopic dermatitis (AD) is the most common chronic skin disease affecting young children and is associated with significant disruptions in sleep and mental health. As AD symptoms are often more burdensome than what traditional clinician-reported disease assessments may capture, patient-reported outcome measures (PROMs) are essential to understanding the full experience of AD in young children and their caregivers. However, few studies have evaluated PROMs for sleep and mental health in early childhood AD. This cross-sectional study thus evaluated the Patient-Reported Outcomes Measurement Information System (PROMIS) Early Childhood (EC) parent-report measures for Sleep Problems, Anxiety, and Depressive Symptoms among 104 children <6 years old seen at Johns Hopkins Hospital between July 2022 and September 2024. PROMIS measure T-scores were standardized to a population mean of 50 (SD 10) and AD severity was measured using the Patient-Oriented Eczema Measure (POEM). Sleep Problems were significantly associated with AD severity, with median T-scores increasing from 51.3 (IQR 43.0–59.7) in children with mild AD (POEM ≤7) to 63.5 (IQR: 57.2–67.3) in those with severe AD (POEM ≥17) (p<0.001). Compared to the general population, sleep was significantly worse among our AD cohort (p<0.001), highlighting the substantial negative impact of early childhood AD on sleep. Though not significantly different by AD severity, anxiety symptoms increased significantly with age, with median T-scores rising from 45.6 (IQR 43.0–56.5) in 1-year-olds to 57.0 (IQR 50.0–61.6) in 5-year-olds (p=0.03). Depressive Symptoms scores were slightly higher in young children with severe AD (median 54.5, IQR 40.5–62.4) but not statistically significantly different from milder AD. Our findings support the use of PROMIS EC measures to assess the burden of AD in young children. Greater attention to AD-related sleep problems and further characterization of when mental health challenges develop in this population would enhance our understanding of the psychosocial impact of early childhood AD.

0263

Sodium-glucose cotransporter-2 inhibitors and vulvovaginal pruritus: Insights from a cox proportional hazards model analysis

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Vulvovaginal (VV) pruritus is distressing with numerous etiologies and has been shown to be more prevalent in individuals with diabetes mellitus (DM).[2] This study investigates the association between sodium-glucose cotransporter-2 inhibitors (SGLT2i) and VV pruritus in patients with type 2 diabetes mellitus (T2DM). Using the TriNetX US Collaborative Network, we identified females with T2DM across 64 healthcare organizations. Cohorts included SGLT2i users (n=832,692) and non-users (n=6,793,437). Patients who developed candidiasis (including VV candidiasis) after starting an SGLTi were excluded. Cox proportional hazards regression, adjusting for demographics, comorbidities, and medications, assessed the primary outcome of vulvovaginal pruritus (ICD-10 code L29.2) within three years. SGLT2 inhibitor use was significantly associated with an increased risk of VV pruritus, with a Hazard Ratio (HR) of 1.9 (p=0.014). Incidence rates were higher among users (0.16%) versus non-users (0.07%), yielding a risk difference of 0.09% (95% CI: 0.05%, 0.13%; p<0.0001). Additionally, patients identifying as white (HR 0.8, p=0.020) and patients taking ACE inhibitors (HR 0.4, p=0.009) had lower rates of VV itch. These findings highlight a notable association between SGLT2i use and VV pruritus, potentially mediated by glucosuria-induced yeast overgrowth and microbiota changes. Given the known association between SGLTi and increased risk of VV candidiasis, it is possible that patients with SGLTi associated pruritis have undiagnosed yeast infections or that the pruritis is mediated through another unknown mechanisms.[4,7] Thus, it is crucial to conduct further prospective studies with evaluation of bacterial and fungal cultures and measurement of VV pH in patients on SGLTi to further elucidate the nature of SGLTi associated pruritis.

0264

25-hydroxyvitamin D_3 mediates the link between heavy metal levels and non-melanoma skin cancer

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The link between combined heavy metal exposure on non-melanoma skin cancer (NMSC) is not well understood. Therefore, we investigated the associations between various metals and NMSC. Data were extracted from the National Health and Nutrition Examination Survey, which included 9,835 participants and measurements of nine urinary metal concentrations: mercury (Hg), cesium (Cs), thallium (Tl), Ionium (Io), cobalt (Co), molybdenum (Mo), lead (Pb), barium (Ba), and arsenic (As). Multivariable logistic regression and weighted quantile sum regression were used to assess the associations of individual and combined metals with NMSC. Additionally, mediation analyses were conducted to explore the mediating role of serum 25(OH)D_3 in these associations. Urinary levels of Hg, Io, Co, and combined metals were positively correlated with NMSC. Serum 25(OH)D_3 exhibited significant associations with NMSC, as did Hg, Cs, Tl, Io, Co, Mo, Pb, Ba, and the combined metals in relation to 25(OH)D_3 levels. Furthermore, the associations between single metals—primarily Hg and Io—and combined metals with NMSC were partially mediated by 25(OH)D_3. These findings suggest that metal exposure increases the risk of NMSC, with a portion of this risk being mediated by 25(OH)D_3.

0265

Social disadvantage and the association between atopic dermatitis severity and cognitive performance in children

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Atopic dermatitis (AD) has been linked to cognitive concerns in children, but the role of socioeconomic factors in this association remains unclear. Thus, this study examined the contribution of social disadvantage to the relationship between AD severity and cognition. In 77 children aged 3-17 years seen for AD at our institution, cognitive performance was assessed via the NIH Toolbox (NIHT) Cognition Battery, and recent AD severity was self-reported (20 mild, 34 moderate, 23 severe). Social disadvantage was approximated by the Area Deprivation Index (ADI), which provides a state decile (sADI) ranking of neighborhoods by socioeconomic disadvantage. sADI was further dichotomized into high or low disadvantage at the median. Participants' age-corrected NIHT Composite Total Cognition Scores (CTCS) were lower (i.e., worse performance) than the normative mean of 100 (median [IQR]: 94 [82-107], p = 0.01), particularly for severe AD (83.5 [80–91], p < 0.001), with scores declining with more severe disease (p for trend = 0.004). When adjusted for sex and sADI, severe AD remained associated with lower CTCS compared to mild AD (β: -12.8, 95% CI [-22.9, -2.6]). In analyses stratified by high vs low ADI, this association between severe AD and lower CTCS remained in both the high ADI subgroup (adjusted β: -13.3, 95% CI [-29.8, 3.2]) and low ADI subgroup (adjusted β: -14.4, 95% CI [-30.0, 1.3]). Tests for statistical interaction between sADI and AD severity showed significance within the high ADI subgroup only (p = 0.04). Our findings suggest that recently severe AD is associated with poorer cognitive performance in children independent of social disadvantage. However, the AD-cognition relationship may also be modified by ADI, whereby greater social disadvantage may interact with severe AD to further impair cognitive performance among individuals living in more disadvantaged neighborhoods. Further research is needed to better characterize the potential interactions between AD severity and individual socioeconomic factors on cognitive outcomes.

0266

Patient perceptions of common invasive therapies in hidradenitis suppurativa: A survey-based analysis

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Background: A variety of invasive treatment options are available for managing moderate to severe hidradenitis suppurativa (HS). However, patients' perceptions of these treatments are not well-studied. This study aims to evaluate patient's perception of common invasive therapies for HS. Methods: A survey was distributed to adult HS patients from a specialized HS clinic between January and August of 2023. Patient demographics were collected, and a 5-point likert scale was used to assess respondents' level of agreement with the statement, "I feel this treatment is good for my skin condition". Results: Of the 62 patients who completed the survey, the median age was 35.5 years (IQR: 30.0-43.0). The majority were female (70.5%), White (64.5%), had Hurley stage II/III disease (88.7%), and 56.4% had prior exposure to biological therapy for their HS. The percentage of patients who agreed or strongly agreed versus disagreed or strongly disagreed were respectively: 30.6% vs. 9.1% for biologics, 27.4% vs. 1.9% for unroofing procedures; 22.6% vs. 5.6% for excision surgeries; 20.9% vs. 19.2% incision and drainage (I&D),and 23% vs. 9.5% for intralesional corticosteroid injections (ILC). The percentage of uncertain patients ranged from 23% (I&D) to 47.2% (ILC). Conclusion: In our study, biological therapies were perceived more favorably compared to other invasive options. However, significant patient hesitancy and uncertainty remains. Addressing these concerns through targeted patient education and support may enhance the acceptance and utilization of these therapies, potentially leading to improved management outcomes for patients with moderate to severe HS.

0267

Circulating igE levels as a biomarker for therapeutic response to dupilumab among patients with prurigo nodularis

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Prurigo nodularis (PN) is a chronic neuroimmune disorder marked by intensely pruritic nodules. Variability in therapeutic response to dupilumab, an IL-4 and IL-13 signaling inhibitor, underscores the need to identify predictive biomarkers. This single-center study evaluated baseline immunoglobulin E (IgE) levels as a potential predictor of treatment response in 15 patients with moderate-to-severe PN treated with dupilumab (2017–2023). Demographics, baseline IgE levels, comorbidities, and pre- and post-treatment Worst Itch Numeric Rating Scale (WI-NRS) scores were analyzed. Patients were grouped based on elevated (>114 IU/mL, n=10) or normal (<114 IU/mL, n=5) baseline IgE levels. The mean baseline IgE levels were significantly higher in the elevated-IgE group (566.3 IU/mL) compared to the normal-IgE group (31.49 IU/mL, p=0.02). Baseline WI-NRS scores were similar between groups (7.7 vs. 9.2, p=0.21), as was treatment duration (7.4 vs. 9.3 months, p=0.34). Common comorbidities included hypertension (60%), anxiety (60%), and obesity (53.3%), with no significant differences between groups. Post-treatment WI-NRS scores were significantly lower in the elevated-IgE group (1.4 vs. 6.0, p=0.004), and a higher proportion of these patients achieved a ≥4-point reduction in WI-NRS (90% vs. 40%, p=0.08). These findings suggest that elevated baseline IgE levels may predict a more favorable dupilumab response in PN, providing a basis for stratifying patients by inflammatory endotypes. Larger prospective studies are needed to validate IgE as a biomarker for tailoring PN management strategies.

0268

Characteristics of registered dermabrasion clinic trials

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This study aimed to characterize the state and current areas of interest for dermabrasion clinical trials. Trials registered in clinicaltrials.gov with "dermabrasion" listed as the intervention were surveyed. 16 dermabrasion trials were found between 2009 and 2024. All 16 studies were interventional in nature and encompassed 315 patients. 50% of these studies have been completed, 13% terminated, 6% recruiting, and 6% withdrawn. The status of 4 studies is unknown. In terms of study design, 75% of studies were randomized. Half of the studies included a single group and half involved parallel groups. 42% of studies were masked. Dermabrasion was studied across several indications. 56% of studies involved patients with vitiligo and 31% examined scar healing. The effects of dermabrasion in healthy volunteers, wound healing, and patients with striae were assessed in 6% of studies each. Repigmentation was the most common primary endpoint, used in 50% of studies. Scar appearance and safety were assessed in 13% of studies each. Colorimetry, time to healing, Jak3 levels, and striae width were assessed in 1 study (6%) each. The endpoint for one study was unclear. Trends in recent clinical trials may elucidate the future role of dermabrasion in clinical practice. Given the high proportion of recent clinical trials examining the role of dermabrasion in treating vitiligo and scarring, these may be directions for larger randomized controlled dermabrasion trials.

0269

The challenge of accurate cardiovascular risk assessment in lupus: A comparative analysis

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Patients with lupus erythematosus (LE) are at an increased risk of clinical events from atherosclerotic cardiovascular disease (ASCVD), yet the accuracy of risk estimation tools in this population remains unclear. Here, we compare the new American Heart Association cardiovascular risk calculator, PREVENT, with the previous ACC ASCVD Risk Estimator Plus (ACC) in a cohort of LE patients, along with investigate the risk of heart failure (HF) estimated by the PREVENT calculator. Utilizing our prospective longitudinal database of patients with LE, we conducted a retrospective chart review to calculate risk scores using both calculators, incorporating optional variables when available. The PREVENT calculator consistently generated far lower estimates of 10-year ASCVD event risk with median risk (2.33% (IQR 0.79%-5.16%)) compared with the ACC calculator (4.65% (IQR 1.30%-11.98%); $p<2.2x10^{-16}$, Wilcoxon signed-rank), consistent with previous studies. Subtype analyses revealed significant differences between the two calculators for CLE-only patients and for CLE+SLE patients as well ($p<2.2x10^{-16}$), although no significant difference was observed within PREVENT-generated scores between these subgroups (p=0.11). A strong correlation was identified between the two calculators ($p<2.2x10^{-16}$). Given literature noting an increased risk of HF in patients with LE, a unique and novel aspect of the PREVENT calculator is the risk calculation for HF (2.01% (IQR 0.59%-5.58%)) and overall cardiovascular disease (3.50% (IQR 1.22%-9.06%)). Given an actual 10-year ASCVD event rate of 13.5% in this cohort (Zhao M et al. 2023), both calculators underestimated risk, with PREVENT underestimating more significantly. These findings highlight the need for caution when using PREVENT in LE populations, because it may be less suitable for certain high-risk patient populations owing to its risk estimates inadequately reflecting their heightened ASCVD risk. This is particularly important for clinical decision-making for LE patients who require tailored risk management strategies.

0270

Outcomes of lumbar punctures in patients suspected of neonatal herpes simplex virus

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Lumbar punctures (LPs) are a necessary measure to diagnosing neonatal herpes simplex virus (HSV); however, their outcomes in suspected neonatal HSV are unknown. When a neonatal patient is suspected of having HSV, dermatologists are typically consulted to identify risk of HSV and guide diagnostic measures. In this study, we aim to understand the outcomes of LPs in patients suspected to have neonatal HSV. We conducted a retrospective cohort study in which we identified neonatal patients who received HSV testing between 01/01/2010 to 12/31/2020 at Rady Children's Hospital in San Diego, California. Data on demographics, presentation, LPs, and treatment outcomes was collected via a chart review. Through this search, 38 patients met the inclusion criteria. Of all the patients who received laboratory testing for HSV, nine were HSV positive while 29 were HSV negative. An LP was obtained in 100% of the HSV positive patients and in 65.52% of the HSV negative patients. Interestingly, several of the HSV negative patients were recommended against obtaining LPs from other consult services such as infectious disease. There were no complications to the LPs performed in either subgroup. Based on these findings, dermatologists can recommend LPs as a useful tool to confirm the diagnosis of neonatal HSV; however, LPs are obtained in the majority of suspected HSV patients despite decreased risk. This is especially important considering the similar presentation of lesions in neonates. While this study has shown no complications with LPs, there should be an effort to identify other clinical indications such as lesion morphology to decrease the rate of LPs in suspected HSV patients that ultimately test negative. Further studies are required to determine specific clinical criteria that dermatologists can utilize to inform hospitalists on LP recommendations.

0271

Assessing the readability of patient education materials on dermatology practice websites: A focus on acne and skin cancer

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Dermatology patients frequently seek medical information online, making accessible and readable patient education materials (PEMs) essential for improving patient understanding. Most dermatology practices established websites that serve as a primary education resource. The American Medical Association (AMA) recommends that PEMs be written at or below a 6th grade reading level. Given that acne is one of the most common dermatological conditions and the importance of skin cancer education in prevention, this study assesses the readability of acne and skin cancer PEMs across dermatology websites. A Google search was performed using "[state] dermatology practice" to identify the 10 most popular dermatology practice websites in 20 states. Duplicate parent websites and sites without relevant PEMs were excluded, resulting in 141 websites for analysis. PEMs were analyzed for readability using the WebFX Readability Tool. Five validated tests were applied to assess readability: Flesch Kincaid Reading Ease (FKRE), Flesch Kincaid Grade Level (FKGL), Gunning Fog Score (GFI), SMOG Index (SMOG), Coleman Liau Index (CLI), and Automated Readability Index (ARI). Mean readability scores for skin cancer PEMs were FKRE (51.18 ± 10.06), FKGL (10.74 ± 1.92), GFI (13.53 ± 2.17), SMOG (10.00 ± 1.65), CLI (12.48 ± 1.78), and ARI (10.51 ± 2.30), with none meeting the recommended 6th-grade reading level. Acne PEMs showed mean scores of FKRE (52.91 ± 11.23), FKGL (10.20 ± 2.24), GFI (12.27 ± 2.47), SMOG (9.13 ± 1.73), CLI (13.34 ± 1.92), and ARI (10.58 ± 2.70). Among the 141 websites, 119 included acne PEMs, and only 2 (1.05%) met the recommended 6th grade guideline. Both skin cancer and acne PEMS were "fairly difficult to read" (mean FKRE) and averaged a 10th-grade reading level (mean FKGL), exceeding the recommended 6th-grade guideline. Advances in artificial intelligence may improve readability of PEMs, though further research is needed to ensure accuracy is maintained.

0272

Immunostimulatory herbal intake and autoantibody positivity in dermatomyositis

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Herbal supplements are popular among the general population, but lab studies have shown that they can activate immune cells and thus precipitate dermatomyositis (DM) onset or flare in susceptible individuals. We sought to assess if real-world autoantibody testing results differ between DM developed with and without prior intake of high-risk herbs. In this retrospective cohort study, patients in the Penn DM database were screened for use of immunostimulatory herbs including alfalfa, ashwagandha, chlorella, echinacea, elderberry, spirulina, and tongkat ali. Autoantibody status was recorded for myositis-associated (MAA), myositis-specific (MSA), and antinuclear (ANA) antibodies. MAA included SSA, Pm-Scl, Ku, U1-RNP, U2-RNP, and U3-RNP. MSA included Jo-1, PL-7, PL-12, EJ, OJ, Mi-2, SRP, TIF-1γ, NXP-2, MDA5, and SAE. Autoantibody positivity rates in patients with and without relevant herbal exposure before DM onset were compared using chi-square and Fisher's exact tests. Out of 286 patients, 36 (13%) were on immunostimulatory herbs prior to developing DM symptoms; the median time from first herbal use to DM onset was 12 months. MSA positivity rate in this herbal group was 22% (8/36) compared to 51% (128/250) in patients without pre-onset herbal intake, p = 0.001. MAA was positive in 13% (4/31) of the patients who took herbs before DM onset vs. 32% (64/202) of those who did not, p = 0.03. ANA positivity rate was also lower in the herbal group (40%, 10/25) than in patients without herbal triggers for their DM onset (61%, 108/176), p = 0.04. Spirulina (22/36) was most commonly taken followed by elderberry (9/36) and ashwagandha (4/36). We found that MSA, MAA, and ANA positivity rates were significantly lower in patients whose DM was potentially triggered by immunostimulatory herbs. Since herbal supplements can lead to new DM onset in the absence of autoantibodies, physicians should consider clinical findings and screen for herbal intake when diagnosing DM.

0273

WITHDRAWN

0274

Maternal microbiota transmission through breastfeeding shapes infant tolerance to skin commensals and protects against dermatitis

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The establishment of tolerance to skin commensals early in life is thought to play a crucial role in the development of dermatitis, but direct evidence remains limited. In this study, we analyzed the skin and fecal microbiome of 102 mother-infant pairs from a high-risk birth cohort for atopic dermatitis (AD), alongside comprehensive blood tests and questionnaires administered during pregnancy, at birth, and at 1, 2, and 6 months of age. From the 769 factors examined, we identified that infants whose mothers routinely wiped their nipples clean before breastfeeding exhibited a higher incidence of AD between 2 and 6 months of age. Comparative microbiome analysis revealed that the maternal nipple microbiota closely resembled the infant's facial microbiota (nose, cheeks, and eyebrows) but differed significantly from microbiota on other infant body sites (e.g., extremities). Furthermore, the nipple microbiota was the only maternal site closely associated with the infant's fecal microbiota, suggesting that mother-to-child bacterial transmission occurs during breastfeeding. We investigated whether maternal nipple-cleaning habits influenced bacterial transmission and found that these habits affected the facial and fecal microbiota of 1- and 2-month-old infants but not those of 6-month-olds. Infants whose mothers wiped their nipples had reduced abundance of certain skin commensals, including Staphylococcus epidermidis, on both facial skin and in feces. This reduction was associated with a higher risk of subsequent dermatitis development. These findings suggest that bacterial inoculation through maternal breastfeeding during the neonatal period may promote tolerance to skin commensals and suppress later skin inflammation in infants, emphasizing the importance of early microbial exposure in preventing AD.

0275

Tanning bed users vs. non-users in the california teachers' study: Characterization of novel at-risk groups

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UV exposure from indoor tanning is a known carcinogen and major risk factor for cutaneous melanoma. Tanning bed use remains prevalent among women despite these known health risks. Identifying characteristics of tanning bed users can inform the need for more public education to reduce melanoma risk in select groups. Data were collected from the California Teachers Study (CTS), a prospective cohort study of over 133,000 female teachers and administrators followed since 1995. Participants who completed baseline questionnaires and provided tanning bed usage data in Questionnaire 5 (n=60,643) were categorized as tanning bed users (ever-used) or non-users (never-used). Differences between groups were analyzed using Chi-squared tests. Tanning bed users (n=5,929) and non-users (n=54,714) had similar characteristics from baseline questionnaires. Tanning bed use was more common among participants with BMI <25, ≥150 minutes per week of moderate/vigorous physical activity, or used sunscreen for more than a year (p<0.0001). Among tanning bed users with more than 20 years of indoor tanning use, 73% and 61% also reported using sunscreen and facial cream with SPF for over 20 years, respectively. Native Americans (n=376) had the highest proportion of tanning bed use compared to other racial groups. CTS tanning bed users reported higher participation in health-conscious behaviors such as moderate/vigorous exercise and sunscreen use. Native American participants had the highest tanning bed usage rates. These findings prompt further research to understand why indoor tanning is more appealing to health-conscious females and why its prevalence may differ among racial groups.

0276

Lichen planopilaris is associated with prior herpes simplex virus, helicobacter pylori, and human papillomavirus in large retrospective cohort

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Lichen planopilaris (LPP) is a scarring cicatrical alopecia type with female predominance. The pathogenesis of LPP is incompletely understood. It has been postulated that infectious agents, may be potential risk factors. Thus, we investigated for potential associations between LPP and viral and bacterial infectious agents using a large database. TriNetX research network was searched for female LPP patients 0-90 and controls without LPP and for female patients with and without prior infections. Cohorts were propensity score matched for age, race/ethnicity. Prevalence of prior infections were collected for LPP vs. control patients. Odds ratios of developing LPP ≥1 day after different infections were calculated. A total of 21,967 LPP and 21,967 matched controls were included. Demographics were similar between cohorts after matching (P>0.05). LPP vs. matched control patients had higher prevalence of prior HSV (2.77% vs. 1.72%, P<0.001), low-risk HPV (1.36% vs. 1.07%, P=0.006), Helicobacter pylori (0.96% vs. 0.34%, P<0.001), high-risk HPV (0.83% vs. 0.56%, P<0.001), HCV (0.37% vs. 0.07%, P<0.001), and syphilis (0.05% vs. 0%, P=0.002). Patients with prior HSV (OR=2.88, 95% CI 2.44-3.41), Helicobacter pylori (2.20, 1.71-2.84), and high-risk HPV (1.80, 1.40-2.30) infections had higher odds of developing LPP vs. matched controls without prior infections. Our study was limited by ICD-10 coding and their accuracy without molecular or histopathological confirmation. We found increased prevalence of prior HCV, Helicobacter pylori, HSV, HPV, and syphilis infections in LPP patients vs. matched controls, and higher odds of LPP with prior HSV, Helicobacter pylori, and high-risk HPV infections. Our findings suggest that prior infectious agents may be a risk factor for LPP.

0277

Bullying in a pediatric alopecia areata population: A survey study

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The California Bully Victimization Scale (CBVS) is a validated self-reported scale that measures bullying, defined as a subset of peer aggression and victimization with victims reporting at least one victimization behavior at least 2-3 times per month and at least one form of power imbalance. The purpose of our study was to assess pediatric bullying in alopecia areata (AA) patients using the CBVS and to compare against population norms. We conducted a single-site, survey study using a modified CBVS. The survey was administered between September 25, 2023 to November 25, 2024 to pediatric patients in grades 5-12 who received a diagnosis of AA from a board-certified dermatologist in the pediatric hair disease clinic. Twenty-four pediatric AA patients were enrolled in our study with the average grade being 5.0. Fourteen (58.3%) respondents reported that they had experienced teasing, name calling, rumors/gossip, being left out/ignored on purpose, being physically hurt, threatened, sexual comments/jokes/gestures, stolen/damaged items, or Internet teasing/rumors/threats in the past month. Teasing/name calling and being left out of a group/ignored on purpose were the most common forms of victimization experienced. Of the 14 children who had experienced these acts in the past month, 25% met the definition of bullying indicated by their aggressor. When asked where and when they experienced victimizations, the most common location and time were in hallways (n=8, 33.3%) and during breaks (n=8, 33.3%), respectively. When asked who knows about these victimizations taking place, 50.0% (n=7) told an adult at home while 12.5% (n=3) told no one. AA is a common autoimmune disease among the pediatric population. Although approximately half of AA pediatric patients reported peer aggression, only 25% met the definition of bullying. Compared to the general population, similar bullying rates were found in this sample of AA pediatric patients.

0278

Whole blood RNA-Seq identifies key pathways linked to TNF-α-inhibitor failure in patients with hidradenitis suppurativa

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Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease often treated with TNF-α inhibitors. However, treatment often fails, and guidance for selecting therapies and predicting response is limited. Differentially expressed genes in the blood of HS patients compared to healthy controls have previously been identified, but the connection between the blood transcriptome and HS treatment response remains underexplored. Here, we analyzed bulk RNA sequencing data from whole blood of patients treated with adalimumab (N=15) and/or infliximab (N=10) for HS, using differential gene expression and Gene Ontology enrichment analysis. Patients who failed adalimumab showed downregulation of genes involved in regulation of the p38 MAPK cascade (p=0.02), which is crucial in Th17 cell differentiation and for the biosynthesis of IL-1β and TNF-α, key drivers of HS. Furthermore, these patients had decreased expression of genes involved in the regulation of epithelial cell proliferation (p=0.02), including NRARP, a known feedback inhibitor of Notch signaling. Notch signaling, particularly when induced by neutrophil extracellular traps (NETs), has been implicated the formation of sinus tunnels. Patients who failed infliximab had downregulation of genes involved in B cell activation (p=0.001), B cell receptor signaling pathway (p=0.002), and B cell differentiation (p=0.0049)—including MS4A1 (CD20). This observation aligns with previous findings that TNF-α inhibitors markedly decrease B cell activation with minimal effect on other inflammatory pathways, and suggests potential differences in B cell migration to skin lesions or reliance on B cell pathways in this subgroup. In summary, this study uncovered blood gene expression differences associated with treatment response in HS, offering insights into the immunopathogenesis of the disease and potential predictive biomarkers for response to TNF-α therapy.

0279

Classic and clinically amyopathic dermatomyositis: Autoantibody positivity

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Dermatomyositis (DM) is subclassified as classic (CDM) and clinically amyopathic (CADM) and can involve myositis-associated (MAA) and myositis-specific (MSA) autoantibodies. Many MSA are associated with specific DM phenotypes, which helps in disease monitoring and prognostication. However, few studies have compared the positivity rates of all commonly tested MAA and MSA in CDM versus CADM. We performed a retrospective cross-sectional review of patients in the Penn DM database who had myositis autoantibody testing between April 2016 and October 2024. MAA included SSA, Pm-Scl, Ku, U1-RNP, U2-RNP, and U3-RNP. MSA included Jo-1, PL-7, PL-12, EJ, OJ, Mi-2, SRP, TIF-1γ, NXP-2, MDA5, and SAE. ANA status was also recorded. The relation between DM subtype and autoantibody positivity rate was assessed using chi-square and Fisher's exact tests. Out of 320 patients, 198 (62%) were CDM and 122 (38%) CADM. MSA was positive in 47% (94/198) CDM vs. 40% (49/122) CADM, p = 0.2. Though typically seen in CADM, anti-MDA5 was comparably positive in CDM (8%) and CADM (10%), p = 0.49. Although anti-NXP2 was more common in CDM (10%) than in CADM (5%), the difference was not statistically significant (p = 0.2). Anti-TIF-1γ was the most common MSA in both subtypes (CDM 17%; CADM 22%). MAA was positive in 29% (48/168) CDM vs. 26% (26/100) CADM, p = 0.65. Anti-SSA was the most common MAA in both subtypes (CDM 21%; CADM 19%). ANA was positive in 63% (90/143) CDM vs. 49% (42/85) CADM, p = 0.045. Of the patients with negative myositis panels, 26/53 (49%) CDM and 13/36 (36%) CADM were ANA positive, p = 0.2. We found that MSA and MAA positivity rates did not differ significantly between CDM and CADM, whereas ANA was significantly more common in CDM. A sizeable portion of DM was ANA positive despite negative MSA and MAA, suggesting that there may be other DM-related autoantibodies not yet discovered. These data reiterate that DM management requires integrating clinical and lab findings and should not rely only on autoantibody status.

0280

Skin cancer risk following bone marrow transplant in patients treated with ruxolitinib compared to other immunosuppressive therapies.

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Ruxolitinib is a Janus Kinase inhibitor commonly used in the treatment of hematologic malignancies and refractory graft versus host disease (GVHD) following bone marrow transplantation (BMT). Limited data exists on the subsequent risk of skin malignancies following BMT compared to other immunosuppressive therapies. This retrospective cohort study utilized the TriNetX Research Dataset. Patients were identified based on a documented BMT followed by exposure to Ruxolitinib and compared to a control cohort in which post BMT exposure could include any immunosuppressive medication except for Ruxolitinib. Cohorts were propensity scored and matched based on age at BMT, sex, race, ethnicity, and hematologic malignancy. Outcomes were measured based on a post-BMT identification of a cutaneous malignancy. A total of 4,948 patients were identified with 50% exposed to Ruxolitinib. Of those exposed to Ruxolitinib, 217 developed skin cancer while 174 of those exposed to other immunosuppressives developed skin cancer (8.771%, 7.033%; respectively). Of those who developed skin cancer, the median number of instances was 4 amongst those exposed to Ruxolitinib compared to 3 in those exposed to other immunosuppressives, though not statistically significant (p-value = 0.1631). The relative risk ratio with Ruxolitinib exposure is 1.247 (95% CI 1.03 - 1.51) with an odds ratio of 1.271 (95% CI 1.032 -1.564). Kaplan-Meier analysis showed a consistently decreased chance of outcome free survival (log-rank p value <0.0001). Overall, Ruxolitinib use is associated with an increased risk of cutaneous malignancies when compared to the use of other immunosuppressants following BMT. Given increased risks amongst both groups, immunosuppressed patients and particularly those on Ruxolitinib should be routinely surveilled by dermatologists for the presence of cutaneous malignancies.

0281

The care gap: Workforce and wait time inequities in comprehensive urgent and cosmetic dermatology

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This study examined disparities in wait times between urgent melanoma care and elective cosmetic procedures, with a focus on comprehensive (consultation plus procedure) and procedure-only wait times. Additionally, the study analyzed the impact of workforce composition, including dermatologists and advanced practice providers (APPs), on access to care. A cross-sectional analysis of 122 dermatology clinics in Alabama collected data on workforce composition and wait times for mole evaluations, cosmetic consultations, melanoma excisions, and dermal fillers from October to December 2024. Wait times were obtained via clinic websites, scheduling portals, and direct phone calls, with independent verification across multiple sources. Descriptive statistics, Wilcoxon signed-rank tests, and multiple linear regression were performed to assess disparities and the role of workforce composition. Comprehensive melanoma wait times (mean: 45.88 ± 29.09 days) were significantly longer than comprehensive filler wait times (mean: 20.34 ± 23.09 days), with 92.9% of clinics reporting longer melanoma wait times ($p<0.001$). Procedure-only wait times for melanoma excisions (mean: 11.23 ± 6.43 days) were also significantly longer than filler procedures (mean: 3.58 ± 13.29 days) in 93.1% of clinics ($p<0.001$). Sensitivity analyses confirmed these findings ($p<0.001$). Regression analyses revealed that APP availability significantly reduced comprehensive melanoma wait times ($B = -0.082$, $p=0.006$), with each additional APP associated with an 18% decrease in wait times. Both APP ($B = -0.098$, $p=0.025$) and dermatologist availability ($B = -0.246$, $p=0.013$) significantly reduced comprehensive filler wait times, but neither significantly influenced procedure-only wait times. These findings highlight disparities in wait times for urgent melanoma care versus elective cosmetic procedures, with the greatest bottleneck at the consultation phase. Given that wait times for cosmetic procedures and consultations are already low, expanding access to these services may not be necessary. Instead, APPs have the most meaningful impact in reducing medical consultation delays and facilitating timely melanoma care, where improved access can directly affect patient outcomes. Therefore, workforce strategies that optimize APP involvement in medical dermatology should be considered to enhance access, particularly for high-risk melanoma patients.

0282

Effect of systemic immunomodulators on incidence of alopecia areata: A retrospective cohort study

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Alopecia areata (AA) is a chronic, autoimmune dermatological disorder characterized by non-scarring patches of hair loss. Patients with autoimmune disorders have an increased risk of developing AA, and these individuals are often prescribed systemic immunomodulatory therapies to manage their primary disease. The relationship between anti-inflammatory immunomodulators, such as disease-modifying anti-rheumatic drugs (DMARDs) and biologics, on AA incidence is unexplored. We sought to determine the effects of immunomodulators on AA incidence compared to a control population. Using TriNetX, we performed a retrospective observational cohort analysis to calculate the relative risks of AA in patients on DMARDs or biologics for any reason versus a healthy control population not on these medications. Cohorts were propensity score matched based on baseline demographics, obesity, rheumatoid arthritis, Sjogren's syndrome, psoriasis, Crohn's disease, ulcerative colitis, and systemic lupus erythematosus. Patients on leflunomide had a decreased risk of developing AA (RR [95% CI] = 0.478 [0.233, 0.981]). Methotrexate (2.192 [1.774, 2.708]), cyclosporine (3.161 [2.376, 4.206]), and rituximab (1.828 [1.162, 2.874]) increased the relative risk of developing AA. Azathioprine (1.38 [0.959, 1.956]), mycophenolate mofetil (1.028 [0.864, 1.224]), apremilast (1.4 [0.6223, 3.151]), etanercept (1.6 [0.726, 3.525]), adalimumab (1.375 [0.915, 2.066]), infliximab (1.1 [0.467, 2.59]), certolizumab pegol (1 [0.416, 2.40]) ustekinumab (1 [0.416, 2.40]), risankizumab (1 [0.416, 2.40]) and secukinumab (1 [0.416, 2.40]) had a similar risk of developing AA as healthy controls. Our findings suggest that leflunomide may offer a protective benefit against AA development, while other immunomodulators may increase the risk. Identifying medications with potential protective benefits for patients at increased risk of AA may impact physicians' therapeutic choices and treatment strategies.

0283

Patient-reported outcomes of glucagon-like peptide-1 agonists on hidradenitis suppurativa severity

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Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition marked by painful, purulent lesions in body fold areas. HS arises from immune activation around terminal hair follicles, causing inflammation, pus, tissue destruction, and scarring. Available data suggest weight loss may reduce HS severity. Glucagon-like peptide-1 receptor agonists (GLP-1-RAs), FDA-approved for diabetes and weight loss, have shown promise in small case studies reporting improved glycemic control and decreased HS severity over short durations. We evaluated the impact of GLP-1-RAs on HS severity using patient-reported outcomes. Adults with HS on GLP-1-RAs, seen in the Department of Dermatology (January 2019-August 2024), were identified using Slicer Dicer. Of 128 patients contacted, 29 completed consents and surveys. Among 21 patients meeting inclusion criteria, 90.5% were female, with a mean age of 45 years. Most were Black (57.1%), non-Hispanic (90.5%), and overweight or obese (Class 1–3) (100%). Active HS was reported by 85.7%, with 76.2% experiencing flares in the preceding 6 months. GLP-1-RAs semaglutide (42.9%), tirzepatide (33.3%), dulaglutide (19.0%), and liraglutide (4.8%) were prescribed for weight loss or diabetes. Mean treatment duration was 18 months. 76.2% reported weight loss, averaging 32 pounds. 71.4% reported improved HS-specific health, including fewer flares (65.0%), new lesions (70.0%), pain (55.0%), drainage (65.0%), and odor (45.0%). 61.9% reported less impact of HS on daily activities. 57.1% indicated they would recommend GLP-1-RAs to other patients. GLP-1-RAs may play an adjunctive role in HS management, particularly given the association between HS and obesity. Though limited by potential recall bias, a strength of this study is its focus on patient experience. It is the largest reported cohort of HS patients on GLP-1-RAs to date. Controlled studies with patient and dermatologist-reported endpoints are needed to confirm these findings and guide clinical practice.

0284

Psychiatric associations of vitiligo by race: A retrospective cohort analysis using a large multicenter database

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Background: Vitiligo is a chronic skin condition characterized by pigment loss. It is known that many vitiligo patients have a psychiatric comorbidity. Since the distribution of psychiatric comorbidities among vitiligo patients across racial groups remains poorly understood, we analyzed these potential associations using a large multicenter database. Methods: TriNetX research database was searched on 12/4/2024 for vitiligo patients ≥18-years (ICD-10 L80). Propensity score-matching by age and sex was performed between each demographic cohort. Odds ratios (OR) of developing psychiatric conditions were calculated by race ≥1 day following vitiligo diagnosis. Results: A total of 101,823 vitiligo patients, including 13,408 Black and 7,106 Asian, were included. Black vs. White vitiligo patients had increased odds of developing schizophrenia (OR 4.31, 95% CI 2.50-7.43), substance use disorder (2.14, 1.63-2.80), bipolar disorder (1.90, 1.43-2.54), suicidal ideation (1.52, 1.16-1.99), and adjustment disorder (1.24, 1.11-1.39). Asian vs. White vitiligo patients had lower odds of developing sleep disorders (0.85, 0.76-0.96), suicidal ideation (0.63, 0.39-0.99), anxiety (0.54, 0.49-0.61), adjustment disorder (0.52, 0.44-0.63), personality disorders (0.45, 0.21-0.96), depressive episodes (0.52, 0.45-0.60), eating disorders (0.37, 0.18-0.76), bipolar disorder (0.29, 0.15-0.56), and substance use disorder (0.27, 0.13-0.54). Conclusions: We found that Black vs. White vitiligo patients had increased odds of having several psychiatric comorbidities, whereas Asian vs. White patients with vitiligo had lower odds. We recommend that dermatologists screen for psychiatric comorbidities in all vitiligo patients, with appropriate referrals to psychiatry.

0285

Psoriasis treatment with adalimumab leading to multiple sclerosis

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Since their introduction in 1999, anti-tumour necrosis factor-alpha (anti-TNF-alpha) therapies have been suspected repeatedly to be associated with the occurrence of central nervous system (CNS) demyelinating disorders, including multiple sclerosis (MS). However, recent publications were restricted to descriptions of monophasic demyelinating events or cases of relapsing–remitting MS (RRMS). We here provide the first case report of primary progressive MS (PPMS) onset upon anti-TNF-alpha therapy. The 51-year old male patient was treated with adalimumab due to psoriasis and psoriatic arthritis. About 18 months after treatment initiation, he developed slowly progressing neurological deficits including gait impairment, paresthesia of the lower limbs, strangury and visual impairment, which led to the discontinuation of adalimumab therapy. Magnetic resonance imaging of the brain and the spinal cord revealed multiple inflammatory lesions and cerebrospinal fluid examination showed slight pleocytosis and positive oligoclonal bands. Thus, PPMS was diagnosed according to the 2017 revision of the McDonald criteria. As PPMS often causes only subtle symptoms in the beginning and early treatment discontinuation of anti-TNF-alpha therapy seems essential to improve the patient's outcome, it is also important to increase the awareness of slowly progressing neurological deficits as a potential adverse event of anti-TNF-alpha therapy among all clinicians involved in the initiation and monitoring of these drugs. In addition, the occurrence of both RRMS and progressive MS upon anti-TNF-alpha therapy might suggest a shared TNF-alpha-mediated pathophysiological mechanism in the evolution of all MS subtypes as an auto-immune event.

0286

Timing of discoid lupus erythematosus onset impacts disease outcomes in systemic lupus erythematosus: A single-center and large, real-world retrospective cohort study

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Discoid lupus erythematosus (DLE) significantly affects a subset of systemic lupus erythematosus (SLE) patients. When DLE precedes SLE, severe systemic manifestations are less common. However, the effects of concurrent or late-onset DLE on long-term SLE outcomes remain underexplored. We conducted two retrospective cohort studies: one using deidentified data from 103 global healthcare organizations in TriNetX and another via chart review of DLE patients with SLE at Johns Hopkins Hospital (2014–2024). Three cohorts were defined: early DLE (>1 year before SLE), concurrent DLE (within 1 year before/after SLE), and late DLE (>1 year after SLE). In TriNetX, cohorts were propensity-matched and univariate regression was performed. At Hopkins, multivariate logistic regression adjusted for demographics, DLE onset timing, smoking, anti-dsDNA positivity, and metabolic syndrome. Risk of 10-year incident outcomes after SLE diagnosis was compared using early DLE as the reference group. We analyzed 3387 patients from TriNetX and 191 from Hopkins. Late DLE was linked to higher odds of CKD/ESRD (TriNetX: $p<0.01$; Hopkins: $p=0.02$) and major adverse cardiovascular events (TriNetX: $p<0.01$; Hopkins: $p=0.02$). In TriNetX, late and concurrent DLE were also associated with increased risk of lupus nephritis ($p<0.01$), malignant neoplasms ($p=0.02$) and hospitalization ($p<0.01$). Hopkins data showed late DLE had higher risk of fractures ($p=0.04$) and osteopenia ($p<0.01$). Among Hopkins patients, 31.3% of late DLE and 71.4% of concurrent DLE cases developed lupus nephritis after DLE, with median times to diagnosis of 8.0 months and 4.5 months, respectively. Our findings reveal worse outcomes in SLE patients with late or concurrent DLE compared to early DLE. Notably, the elevated 10-year incidence of CKD/ESRD and MACE in late DLE was validated in the Hopkins cohort. Late-onset DLE may involve distinct immune dysregulation, requiring vigilant monitoring to mitigate adverse outcomes.

0287

Assessing the risk of pediatric alopecia areata after COVID-19 infection: A population-level study

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COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been linked to various immune-related dermatologic conditions, including alopecia areata (AA). Recent studies highlight new onset, recurrence, or exacerbation of AA after COVID-19 infection. However, reports in pediatric populations are limited. This study aimed to investigate the potential association between COVID-19 infection and the development of AA in pediatric patients. This population-level retrospective cohort study utilized the TriNetX US Collaborative Network to analyze pediatric patients (age 0-18) with a confirmed SARS-CoV-2 infection, identified through the ICD-10-CM Diagnosis Code U07.1. The control cohort comprised pediatric patients (age 0-18) without a COVID-19 diagnosis. Separate analyses were conducted for male and female cohorts to evaluate potential sex-based differences in associations. The two cohorts were matched 1:1 using propensity scores, adjusting for baseline demographics before assessing the development of AA. Female pediatric patients with reported COVID-19 infection conferred a significantly higher risk of AA compared to those without reported infection (HR [95% CI] = 0.455 [0.298-0.696]). In contrast, no significant association was observed between COVID-19 infection and the risk of developing AA in male pediatric patients (HR [95% CI] = 0.771 [0.467-1.273]). The prolonged effects of COVID-19, particularly related to autoimmune disease, are not yet fully elucidated. Our study suggests that there is an increased risk of alopecia areata in female children after COVID-19. Possible mechanisms include molecular mimicry between SARS-CoV-2 and hair follicle autoantigens, cytokine shifting, and bystander activation, but further studies are needed. This retrospective data may help identify pediatric patients at risk of developing or exacerbating AA, ultimately enhancing clinical understanding of this complex, multifactorial disease.

0288

Direct immunofluorescence for oral lichen planus

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Introduction: Oral lichen planus (OLP) is a chronic, inflammatory mucocutaneous disease characterized histologically by lymphocytic lichenoid infiltrate and shaggy fibrinogen depositions near the basement membrane zone with direct immunofluorescence (DIF).[1] There is limited data describing DIF utility in OLP and DIF changes across OLP phenotypes. We aimed to describe the results of DIF in cases of clinically and histologically confirmed OLP. Methods: We retrospectively evaluated OLP cases seen at the University of Utah from 01/2011-07/2023. OLP diagnosis was made via histology and clinical appearance. OLP phenotype, etiology, patient demographics, and DIF data were collected. DIF data was extracted from clinical reports made by experienced dermatopathologists with extensive DIF's experience. Data was analyzed descriptively, and we used logistic regression to compare odds of DIF positivity across OLP phenotypes and etiologies. Results: We identified 122 cases of OLP with DIF were identified (100 idiopathic, 10 allergic contact, 6 drug-induced). 43 were erosive at >50% of visits, 18 had extensive disease (>50% mouth affected), buccal mucosa was most affected (95/122). 95 patients were female, the median age was 62, and 112/122 were white. 75/122 cases were reported as positive and 26/122 were read as negative (sensitivity 61.5%, false negative rate 21.3%). We found no evidence for differences in DIF positivity across OLP etiologies nor disease phenotypes ($p<0.05$). Conclusion: While DIF is critical for ruling out other disease causes, in our cohort it had low sensitivity and a high false negative rate suggesting that DIF should not be relied on for OLP diagnosis. References: Tekin B, Hardway H, Lehman JS, Direct immunofluorescence testing for lichen planus: A retrospective cohort study of 1747 specimens, Journal of the American Academy of Dermatology (2024), doi: https://doi.org/10.1016/j.jaad.2024.06.096.

0289

Comparison of hidradenitis suppurativa (HS) management and risk factors in pediatric HS patients with and without psychiatric comorbidities

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This project aims to compare socioeconomic status and management of hidradenitis suppurativa (HS) between a pediatric HS cohort and a pediatric cohort with both HS and a psychiatric condition such as anxiety or depression. We conducted a retrospective chart review of 1015 patients diagnosed with HS before age 18 within the UPMC electronic medical record. The study included 576 pediatric patients who only had HS, and 439 patients who were diagnosed with HS and a psychiatric comorbidity such as anxiety, depression, or social phobia. There were no significant differences between these two groups in demographics or average age of HS diagnosis. Black patients in both the HS cohort and the HS + psych cohort were more likely than their white peers to be on public insurance instead of private insurance (OR=2.108, p=0.000269; OR=2.0657, p=0.00091). Children with both HS and a psychiatric comorbidity were significantly less likely to have private insurance (OR=0.2194, p<0.0001, 95%CI: 0.168-0.2825), and were significantly less likely to be diagnosed with HS by a dermatologist (OR=0.4982, p<0.0001, 95%CI=0.3816 to 0.6503) than their peers who had only HS. Finally, within the cohort of patients diagnosed with both HS and a psychiatric comorbidity, Black patients were significantly less likely than white patients to be diagnosed with HS by a dermatologist (OR=0.5043, p=0.0091, 95%CI=0.3016 to 0.8434). These findings suggest that pediatric HS patients who also have a psychiatric comorbidity are less likely to have access to care from dermatologists and adequate treatment resources, with black patients in this cohort being more affected. They highlight the need for greater access to both dermatological and mental health care.

0290

Assessing the effect of USMLE step 1 pass/fail grading on dermatology match rates and residency application disparities between institutions with and without home programs

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Prior studies indicate that students without a home dermatology program match at a lower rate compared to those with a home program. A comparative retrospective cohort study was conducted to examine if the change in Step 1 scoring in 2022, intended to increase equity amongst residency applicants, reduced disparities between schools with and without home programs. Match data were collected from the NRMP, medical school, and residency program websites. 109 U.S. MD medical schools with match data for the years 2019, 2022 (numerical Step 1 scores) and 2023, 2024 (Step 1 Pass/Fail) were included. A two-way ANOVA tested the effects of home dermatology programs (1 = yes, 0 = no) and Step 1 scoring format (scored vs. pass/fail) on match rates. Medical schools with home dermatology programs demonstrated a statistically significant improvement in match rates pre/post Step 1 P/F ($p<0.0001$). Pre-transition (2020 and 2022), the match rate was 6.93 matches per school (74%) for schools with home programs compared to 2.32 matches per school (26%) for those without. Post-transition (2023–2024), the match rate was 7.01 matches per school (73%) for schools with home programs and 2.54 matches per school (27%) for those without. While the match rate difference increased, the interaction between the presence of a home program and the scoring period was not statistically significant ($p = 0.34$). The change to Pass/Fail Step 1 did not decrease disparities in dermatology match rates for schools without home programs, possibly due to programs placing greater emphasis on other metrics like Step 2 scores, letters of recommendation, or familiarity with home students.

0291

Investigating the association between proton pump inhibitors and the risk of lupus: A retrospective cohort study of systemic and cutaneous manifestations

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Proton pump inhibitors (PPIs) are among the most prescribed medications in the United States. While short-term use of PPIs is related to mild adverse effects, their use has also been implicated in the development of autoimmune diseases, including systemic (SLE) and cutaneous lupus erythematosus (CLE). However, population-level analyses are limited. A retrospective cohort study was conducted using the TriNetX US Network to evaluate patients in the exposed cohort who were prescribed PPIs, identified by the ATC code classification A02BC. Patients with prior use of comparable treatment modalities, including histamine receptor agonists were excluded. The control cohort consisted of patients who had not been treated with PPIs. Propensity score matching (1:1) was performed based on baseline demographics, including age at index, biological sex, and ethnicity. Stratified analyses were conducted across distinct age groups (0-19, 20-50, 51-70, and 71+) for both male and female populations to assess potential age- and sex- specific variations in associations. The cohorts were then analyzed for incidence of SLE and CLE. The results revealed a statistically significant association between PPI use and the development of SLE in females aged 20-50 ($p<0.001$), 51-70 ($p<0.001$), and 71+ ($p<0.001$), as well as in males aged 20-50 ($p=0.041$) and 51-70 ($p<0.001$). However, no significant association was observed between PPI use and CLE in either group, although there was a limited number of CLE cases in each cohort. These findings suggest that PPI use is associated with an increased risk of SLE in females across multiple age groups (20-50, 51-70, and 71+) and in males aged 20-50 and 51-70. While PPIs showed no association with the development of CLE, larger population-based studies should be performed. As dermatologists are responsible for the management of lupus erythematosus, it is imperative to recognize this potential link between a widely prescribed medication and a life-threatening dermatosis.

0292

It is the era of photography but are we taking enough photographs in our clinical practice?

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We investigated the adequacy of utilization of photographic documentation in our primary care clinic as reliable, standardized photos are critical for patient care, longitudinal disease monitoring and education. A random sample of 50 patient encounters with a dermatologic diagnosis within a 6-month period was studied to determine the frequency of utilization of photographic documentation. Only 30% of the encounters were found to have evidence of photographic documentation. Surveys carried out with medical staff revealed that the major barrier to utilization of photographic documentation is provider unfamiliarity with the process and memory lapse during patient encounters. We aimed to increase the frequency of photographic documentation in our practice from a baseline of 30% to 50% over a 3-month period. A formal didactic session was performed to educate resident and faculty physicians regarding use of HIPPA compliant smart phone application. Laminated cards were strategically placed in clinical workspaces and patient rooms to serve as visual reminders to use and how to use the application. Repeat data analysis at the conclusion of the 3-month period revealed an increase in utilization of photographic documentation from 30% to 70%. Our study reveals that provider education and visual reminders aid in enhancing utilization of photographic documentation for dermatologic conditions.

0293

Regression of primary melanoma without surgery in patients treated with anti-programmed cell death-1 inhibitor therapy: A case series

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The advent of immune checkpoint blockade has significantly improved survival outcomes and the prognosis of advanced melanoma. In the adjuvant setting, immune checkpoint inhibitors (ICIs) have improved recurrence-free and distant metastasis-free survival [1], and neoadjuvant systemic therapy (NAST) with ICIs has emerged as a promising option for patients with palpable stage III melanoma, with several studies demonstrating promising outcomes compared to surgery alone [2]. In this case series we report five cases of locally advanced or metastatic cutaneous melanoma that were treated with ICI monotherapy and demonstrated a full or near-complete resolution of their primary tumor, obviating the need for surgery. Pathologic evaluation of primary lesions demonstrated absence of any tumor in the four patients in which it was obtained. Our experience suggests that in select cases of simultaneous primary and metastatic melanoma, surgical excision of primary tumors may not be necessary, and ICI treatment alone may be sufficient to achieve complete regression of the primary lesion. References: 1. Johnson DB, Nebhan CA, Moslehi JJ, Balko JM. Immune-checkpoint inhibitors: long-term implications of toxicity. Nature Reviews Clinical Oncology 2022; 19 (4):254-267. 2. Amaria RN, Reddy SM, Tawbi HA, Davies MA, Ross MI, Glitza IC, et al. Neoadjuvant immune checkpoint blockade in high-risk resectable melanoma. Nature Medicine 2018; 24 (11):1649-1654.

0294

Symptom influence and diagnostic challenges in vulvar lichen sclerosus

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Vulvar lichen sclerosus (VLS) is a chronic inflammatory condition of the genital area that can cause itching, scarring, and increased risk of squamous cell carcinoma. Prompt diagnosis addresses symptom management and mitigates malignancy risk. However, VLS diagnosis takes 4-5 years on average after symptom onset, potentially due to the overlap of VLS symptoms with other conditions. This study aims to characterize VLS symptoms and examine their influence on diagnostic outcomes. An electronic questionnaire was distributed on the r/lichensclerosus subreddit and the Lichen Sclerosus Support Group on Facebook to collect information on diagnostic experience. Adult English-speaking patients who reported receiving a licensed physician's diagnosis of VLS were considered. Descriptive statistics were used to analyze data. All 82 participants (100%) reported symptoms before diagnosis, with 72/82 (88%) seeking medical care for symptoms. Common symptoms included vulvar itching (n=71, 86.6%), white/shiny scar-like skin (n=56, 68.3%), vulvar irritation/burning (n=51, 62.2%), vulvar fissures or red/inflamed skin (n=46, 56.1%), skin fragility (n=44, 53.7%), change to genital appearance (n=42, 51.2%), vulvar dryness (n=39, 47.6%), vulvar soreness (n=38, 46.3%), and genital pain that occurs just before, during, or after sex (n =38, 46.3%). Multi-variable statistics revealed that participants with vulvar itching were 7.6 times more likely to seek care as compared to other symptoms. This suggests that women may be more likely to perceive itching as abnormal compared to other symptoms. Women reporting pain with sex were 9.8 times more likely to be misdiagnosed compared to other symptoms. These findings highlight the need for improved clinical awareness of VLS symptomatology, especially concerning pain associated with intercourse and other non-pruritic symptoms. Broadening the differential to include VLS when patients present with such symptoms can lead to timelier detection and improve quality of life.

0295

Low incidence of pericardial effusion in alopecia patients taking oral minoxidil: A single center retrospective cohort study

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Oral minoxidil (OM) is commonly used off-label for alopecia, but the risk of pericardial effusion (PEff) is poorly documented. We evaluated the prevalence of PEff in patients prescribed OM for alopecia. We identified patients without pericardial disease who were prescribed OM between January 1, 1979 and June 1, 2024, along with age, sex, race, and ethnicity-matched controls. PEff cases were identified using ICD-9/10 codes. Retrospective chart review confirmed indication, demographics, medical history, and disease course. Statistical analysis used Fisher's exact test and linear regression. Median age was 53 years, with 46% (2054/4501) women and 54% (2445/4501) men. 94% (4238/4501) were initially prescribed 2.5mg. PEff occurred more frequently in patients on OM (2.5%, 110/4501) than controls (0.5%, 41/8841, p<0.001). Of those on OM who developed PEff, 0.2% (10/4501) were prescribed OM for alopecia. Patients on LDOM for alopecia had lower odds of PEff than controls (OR 0.52, 95% CI: 0.23-1.06, p=0.08) and patients taking OM for other indications (p=0.005). A linear relationship was found between PEff incidence and LDOM dosage up to 10mg (R-squared=0.56, p=0.03). All effusions among alopecia patients were small-to-moderate or less (10/10), with 60% (6/10) being incidental and asymptomatic. The remaining 40% (4/10) were symptomatic but attributable to other causes. The odds of PEff on LDOM for alopecia are low and not significantly higher than the general population. Effusions are typically small and incidental. Clinicians should be aware of potential PEff development, especially in patients with comorbidities.

0296

Paving a path for standardized diagnosis: A systematic review and analysis of seborrheic dermatitis diagnostic criteria

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Seborrheic dermatitis (SD) is a chronic inflammatory skin condition that is diagnosed clinically, but there is currently no widely accepted, standardized diagnostic criteria. We performed a systematic review to summarize SD diagnostic criteria across published clinical studies to identify common diagnostic approaches and highlight clinical gaps. A systematic search was conducted in Embase, PubMed, Scopus, CINAHL, and Cochrane databases in June 2024 in accordance with PRISMA guidelines. Original investigations with clinical diagnosis of SD were included after deduplication and screening. Data was extracted and analyzed with descriptive statistics, and quality was assessed with JBI critical appraisal tools. From 5548 deduplicated articles, 209 were included for final analysis (>36,000 SD patients). Among all studies, only 22.0% mentioned the use of any clinical criteria to diagnose SD. Skin examination was described in most of these articles, while dermoscopy and trichoscopy were rarely or never described, respectively. Biopsy was used to aid diagnosis / exclude other entities in 10.5%. Only 7.7% of studies (n=16) explicitly described specific SD diagnostic criteria for SD, with general features of erythema (16), scale (15), and location (14) most frequently mentioned, and symptoms like pruritus infrequently mentioned (3). Among clinical trials (n=122), only 5.7% (7) specified diagnostic criteria for inclusion, most with similar reliance on the erythema, scale, and location. In summary, most SD clinical studies including clinical trials did not specify any diagnostic criteria. Of the small number of articles that provided specific clinical criteria, only a few physical signs (and not symptoms) were consistently described. These results suggest near universal lack of standardization in the approach to SD diagnosis. Future research should focus on development of consensus, uniformly applied diagnostic criteria in clinical studies.

0297

Global prevalence of atopic comorbidities in prurigo nodularis: A systematic review and meta-analysis

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Prurigo nodularis (PN) is a chronic pruritic disorder characterized by neuronal sensitization and dysregulated type 2 inflammation. Clinical evidence suggests that atopic/allergic disorders with shared inflammatory pathophysiology may commonly co-occur with PN, but the extent of their comorbid presence in PN patients remains unclear. Per PRISMA guidelines, we conducted a systematic review and meta-analysis to assess the global prevalence of atopic comorbidities in PN. Embase, PubMed, CINAHL, and Cochrane databases were searched for original studies with clinician-diagnosed PN reporting comorbidities. Reviews and qualitative research were excluded. Pooled prevalence proportions were estimated using a random-effects model for comorbidities reported in ≥3 studies. Of 3,361 abstracts screened, 39 full-text articles were reviewed, and 26 were included (n=33,206 PN patients). The pooled prevalence of AD was 39.1% [95% CI, 27.8%-50.5%] (n=7,788; 26 studies), with high heterogeneity (I^2 = 99.9%, p < 0.001). Pooled prevalence of allergic rhinitis was 30.0% [13.7%-46.2%] (n= 1,775; 12 studies); asthma prevalence was 16.0% [10.2%-21.8%] (n=4,261; 14 studies); chronic urticaria was reported in 3 studies with a pooled prevalence of 4.9% [95% CI, 2.0%-15.4%] (n= 462). Similar high heterogeneity was observed across all analyses. Allergic conjunctivitis (n=72; 4 studies) yielded non-significant results with negative confidence intervals; food allergy was not measured frequently enough to be analyzed. Reference arms were lacking in most studies, preventing calculation of pooled odds ratios of association. These data show that atopic comorbidities, especially AD, allergic rhinitis, and asthma, are quite common among patients with PN. Given an evolving systemic treatment landscape for PN with multiple new and emerging treatments with distinct immunologic mechanisms of action, baseline comorbidity assessment may help guide optimal therapeutic selection.

0298

Managing keratoacanthoma: Watchful waiting as an option

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Keratoacanthoma (KA) is a rapidly growing tumor that often regresses spontaneously. Some classify KA as a variant of squamous cell carcinoma and thus surgical excision is often used as first-line treatment. Our aim was to assess the frequency of spontaneous KA regression. A retrospective chart review was conducted at the San Francisco VA Hospital, of veterans with pathology confirmed KA, 2014-2024. This cohort consisted of 328 patients (39–97y, median 75y IQR=13, 320 male/8 female). In 45 cases the pathology showed complete excision during initial shave biopsy. Among the remaining 283 cases, spontaneous resolution occurred in 216 patients (76%) while in 67 (24%), persistent tumor was seen on pathology after excision. Thus, watchful waiting could be a consideration in the majority of patients. The 328 patients were monitored over 961±864 days, with 5.9±5.9 follow-ups. Recurrences were uncommon (3/328 lesions), with no metastases seen. Of lesions that received surgery (164/283), 2 recurred and of those that spontaneously resolved 1 recurred (1/119). Thus, surgery did not decrease the incidence of recurrence in this cohort (1.2% vs. 0.8%, respectively). Notably, 97/283 (45%) underwent a potentially unnecessary excision (pathology showed scar). Watchful waiting, rather than surgical referral could help avoid the inconvenience, potential morbidity, and cost associated with surgery. KA is a lesion that requires attention, due to its rare potential to exhibit malignant behavior. This review suggests that patients could be offered observation to determine lack of spontaneous regression, before referral for surgery. Surprisingly, surgery did not improve the frequency of recurrence in this cohort. Along with the high incidence of spontaneous regression and lack of metastases observed, these findings suggest that patients can safely be offered watchful waiting as a viable alternative to surgery.

0299

Prevalence and severity of mental health symptoms with seborrheic dermatitis: A systematic review and meta-analysis

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Seborrheic dermatitis (SD) can substantially impact quality of life, though there are conflicting reports about the relationship between SD and mental health symptoms. We evaluated the prevalence and severity of mental health symptoms in SD through systematic review and meta-analysis. Following PRISMA guidelines, we conducted a comprehensive search of PubMed, Scopus, Embase, CINAHL, and Cochrane databases in June 2024. Inclusion criteria included published studies reporting quantitative mental health symptoms in SD patients using scoring instruments such as the Hospital Anxiety and Depression Scale (HADS). Data were extracted and analyzed using a random-effects model to estimate pooled proportions and means in R (v4.4.1). Of 524 deduplicated abstracts that were initially screened, a total of 15 studies (n= 12,668 SD patients) were included following full text review. Depression (8/15 studies) and anxiety (6/15) were the most frequently reported mental health symptoms; others included heightened stress, obsessive-compulsive disorder and alexithymia. The pooled prevalence of depression symptoms among 1,193 SD patients from 6 studies was 21% [95%CI: 8%–47%], with high heterogeneity (I^2=97%; p<0.001). Similarly, the pooled prevalence of anxiety symptoms among 1,065 SD patients (4 studies) was 19% [7%–42%], with similar heterogeneity. Of the 3 studies (n=267) which reported HADS data, total pooled mean HADS-D was 5.9 [5.4-6.2] and HADS-A was 7.6 [7.2-8.1]. These findings highlight a considerable mental health burden in SD patients, with nearly 1 in 5 reporting depression and anxiety symptoms – similar to the observed mental health burden in better studied inflammatory skin diseases. These data suggest a need for more routine evaluation to address the mental health challenges faced by SD patients. Additional prospective studies are warranted to investigate underlying mechanisms and interventions to improve patient outcomes.

0300

The impact of hypertension on mortality in melanoma patients: A matched cohort analysis

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There is limited research on the effect of comorbidities in patients with melanoma. Here, we studied melanoma confounded with hypertension affects mortality rates. Data from the National Institute of Health's AllofUs database was extracted for patients with a malignant melanoma diagnosis. Two groups were then identified: a "treatment" group consisting of patients with melanoma and hypertension, and a "control" group consisting of patients with melanoma but without hypertension. Demographic data and mortality status were collected for all patients. Each "treatment" group patient was then matched to two "control" group patients on the basis of ethnicity, sex, and race. To assess the quality of the matching, standard deviation of the means (SDMs) for all covariates were found, and matching was considered successful if all SDMs were <0.1. Using the matched dataset, 1886 patients were included and mortality rates between the "treatment" and "control" groups were found to be 6.7% and 1.6% respectively. A Chi-squared test was performed and a p-value of <1e-8 was obtained. These results suggest that hypertension may play a role in influencing the course of progression of melanoma and/or compound the severity of the cancer. Additionally, these results underscore the importance of investigating how hypertension may influence responses to melanoma treatments, potentially impacting mortality rates. Ultimately, the strong correlation between hypertension and increased mortality rates in melanoma emphasizes the necessity for clinicians to consider comorbidities when developing treatment plans for melanoma. Further studies exploring the impact of comorbidities on melanoma outcomes are warranted, specifically focusing on the impact they may have on mortality rates and how they may exacerbate health disparities among underserved populations.

0301

Quality of life impairment is present in some but not all patients with frontal fibrosing alopecia

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Frontal fibrosing alopecia (FFA) is a primary cicatricial alopecia associated with psychological distress and reduced self-esteem, with significant impacts upon quality of life (QoL) that are poorly understood and have not been quantified. This single-site validated survey study assessed QoL in participants with FFA versus healthy participants using a modified Dermatology Life Quality Index (DLQI), where participants responded to DLQI questions in relation to their hair rather than skin. Between December 2023 and August 2024, DLQI scores from 15 female FFA participants (mean age=67.7±8.6 years) and 14 female control participants (mean age=59.2±11.0 years) were collected and analyzed. The majority of participants were Caucasian (93.1%). Among FFA participants, 53.3% reported that their hair disease had "no effects on QoL (DLQI=0-1)" compared to 78.6% in the control group. Significantly higher DLQI scores (Mann-Whitney U=57.5, p<0.032) were observed in the FFA group (mean=3.8±6.1) compared to the control group (mean=0.9±1.1). When evaluating individual DLQI scores, only two FFA participants reported hair loss causing a "very large effect (DLQI=11-20)" or "extremely large effect (DLQI=21-30)" on their QoL. This study provides new evidence of the potentially harmful impacts FFA poses on QoL, emphasizing the importance of a multidisciplinary approach to management with psychosocial support to address QoL challenges. Larger prospective studies offer opportunities to further explore the longitudinal psychosocial impacts of FFA and uncover potential correlations between disease severity and quality of life.

0302

Clinical efficacy and endotype changes in Chinese atopic dermatitis patients after abrocitinib treatment

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Phase 3 trials have demonstrated the efficacy and safety of abrocitinib for atopic dermatitis (AD), but real-world evidence remains limited. This prospective study enrolled 117 moderate-to-severe AD patients, and physician- and patient-reported outcomes were evaluated at multiple time points. Blood eosinophil counts, serum IgE, 24 cytokines/chemokines, and blood cell mRNA sequencing were measured. Abrocitinib treatment led to rapid and potent improvements in disease severity. At week 12, 74.3% and 50.5% of AD patients achieved at least 75% and 90% improvement in the eczema area and severity index (EASI), respectively. Compared to dupilumab, abrocitinib showed greater improvement in Itch-NRS at week 2 and a higher proportion of EASI-75 at week 4. Adverse events occurred in 42.7% of AD patients, with gastrointestinal symptoms being the most common (17.1%). No tuberculosis (TB) reactivation was observed in patients who screened positive for TB and received isoniazid prophylaxis during the study period. Lower body mass index (BMI < 24; adjusted OR: 4.01, 95%CI: 1.36–11.73) and no prior dupilumab use (adjusted OR: 5.81, 95%CI: 1.8–18.7) were identified as predictors of a good response. By week 4, blood eosinophil counts and serum IgE significantly decreased. Reductions in Th2-, Th1-, and Treg-related cytokines/chemokines after 4 weeks of abrocitinib treatment, including IL-5, CCL17, CCL18, TNF-α, IL-6, IL-10, and CD25/IL-2Rα, were more pronounced in good responders. Correspondingly, blood transcriptome normalization, including downregulation of Th2, Th1, eosinophil, and an increase in Tr1 cell abundance, rapidly occurred by week 4, with slight rebound by week 12. WGCNA identified an efficacy-related gene module, leading to a five-gene (PLN2, CAT, CLC, RAB44, SMPD3) efficacy-predictive model. In conclusion, Abrocitinib demonstrated robust efficacy and a well-tolerated safety profile in Chinese patients with moderate-to-severe AD in routine clinical practice, accompanied by normalization of elevated blood biomarkers and dysregulated blood transcripts.

0303

Geospatial insights in alopecia quality of life research

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Although alopecia disproportionately affects ethnoracial minorities and significantly impacts quality of life (QoL), the geographical distribution of related research and variations in QoL scale usage remain poorly understood. We examined global patterns in alopecia research and the adoption of QoL measures based on author affiliations and research sites. 90 original peer-reviewed articles on alopecia and QoL were included. Data was extracted on the geographical distribution of author affiliations & research sites and utilization of various QoL scales. Regional trends and differences in scale utilization were analyzed through χ2. The USA (21/90, 23.3%), Turkey (10/90, 11.1%), and Spain (9/90, 10%) led in author affiliations, with Europe (38/90, 42.2%), Asia (29/90, 32.2%), and North America (21/90, 23.3%) dominating at the continental level. Research site distribution followed similar patterns, with the USA (16/90, 17.8%), Turkey (9/90, 10%), and Spain (8/90, 8.9%) as the top countries, and Europe (36/90, 40%), Asia (29/90, 32.2%), and North America (17/90, 18.9%) as the top continents. Significant regional differences were observed in the use of DLQI, which was employed more frequently in studies from Asia (19/29, 65.5%) and Europe (20/36, 55.6%) compared to North America (8/21, 38.1%) ($p = 0.05$). No significant differences were found in the adoption of hair/alopecia-specific scales, SkinDex, other dermatologic scales, and non-dermatologic scales across countries or continents. Overall, this study highlights significant geographical differences in research production and use of DLQI scales in alopecia research. Understanding these regional differences may inform global standardization efforts and improve the cross-cultural applicability of QoL assessments in alopecia, and future research should explore the drivers behind these differences and their implications for patient-centered care.

0304

A model for characterizing anatomical locations of merkel cell carcinoma

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Merkel cell carcinoma (MCC) and melanoma are two of the most common skin cancers, with ultraviolet radiation (UVR) exposure playing a role in the pathogenesis of each. Nearly 50 times more new cases of melanoma are diagnosed annually in the United States compared with MCC, allowing for easier collection and analysis of melanoma data. We sought to examine applicability of a model used for classification of melanoma primary tumor sites to a population of MCC cases. Gordon et al. (2017) characterized primary tumor sites of cutaneous melanoma (n=5,973) using a modified UVR exposure model and a model describing visibility of the lesion upon self-examination. The UVR exposure model consisted of five categories: chronic, moderately intermittent, highly intermittent, rare, or other UVR exposure. Additionally, the primary site of the lesion was classified as either easily or poorly visible upon self-examination. We implemented these models in a smaller MCC cohort (n=105). The highest quantity of MCCs were present in chronically UVR exposed areas (n=45, 42.9%). Most of the MCC lesions were also present in easily visible sites upon self-examination (n=88, 83.8%), emphasizing the importance of awareness and self-examination for earlier detection of this aggressive malignancy. Application of the melanoma model to the MCC cohort did not allow for adequate power to perform survival analysis. This confirmed our expectations that the MCC sample size was too limited for analysis through this model, with the melanoma instrument unable to be directly applied to the small MCC registry size. Dichotomization of variables may be necessary to assess UVR exposure for MCC. A more manageable analysis may result from establishing two distinct groups for UVR exposure of primary sites, rather than several categories. Next steps will explore anatomic determinants through application of the UVR exposure variables in a binary method. Although the adaptation of the instrument from melanoma to MCC was restricted by the rarity of MCC, a binary model may assist with further analysis.

0305

Topical and oral phosphodiesterase-4 inhibitors for refractory seborrheic dermatitis: A systematic review

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Seborrheic dermatitis (SD) is a chronic inflammatory condition characterized by erythema, scaling, and pruritus, primarily affecting sebaceous-rich areas. Treatment typically includes antifungals, corticosteroids, and other anti-inflammatory medications. Recently, Phosphodiesterase-4 (PDE-4) inhibitors emerged as a promising therapeutic option for managing treatment-resistant SD cases. Current literature lacks a summary of this rising therapy option. We present a systematic review summarizing the efficacies and outcomes regarding treatment of SD with topical and oral PDE-4 inhibitors. Of 200 articles screened from three databases, authors included 7 articles describing 638 patients. The most common treatment utilized was topical roflumilast 0.3% applied daily (94.51%). Topical crisaborole 2% (5.02%) and oral apremilast 30mg (0.47%) were also used. Average follow-up time was 1.91 months. A majority of patients, 50.31%, experienced improvement in their condition, 28.37% achieved full resolution, and 21.32% showed no change. Only 16.77% reported adverse effects like nausea and nasopharyngitis. By increasing cAMP levels, suppressing pro-inflammatory cytokines, and promoting anti-inflammatory cytokines (such as IL-10), PDE-4 inhibitors downregulate the skin's inflammatory response. Modulating the immune response is beneficial in SD where immune dysregulation is a key factor. Unlike corticosteroids, PDE-4 inhibitors provide effect without long-term use side effects, such as skin thinning and barrier dysfunction. The use of PDE-4 inhibitors represents a significant advancement in the management of SD, especially in patients needing long-term management, with these results highlighting their efficacy and tolerability. As more clinical data become available, PDE-4 inhibitors are likely to become a cornerstone in the treatment of SD.

0306

Leveraging Google trends to analyze the global impact of Korean skincare on consumer behavior and dermatology practices

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The rise of Korean skincare (K-Beauty) has transformed consumer beauty routines and influenced dermatological practices worldwide. Using Google Trends to analyze global search behavior from 2004 to 2025, this study examines the dissemination and impact of K-Beauty trends over the past decade. Data analysis reveals significant growth in search interest for key K-Beauty terms (e.g., "fermented skincare," "glass skin," "snail mucin"), particularly in North America, Europe, and Southeast Asia. The worldwide rise of social media platforms like TikTok, which became the most downloaded app in 2020, has further enhanced global connectedness and culture sharing, enabling the rapid spread of K-Beauty trends and fostering cross-cultural engagement. During the COVID-19 pandemic, when people spent significantly more time on social media, Google Trends data shows a noticeable rise in interest for "glass skin," shifting from a search interest (relative to peak 2025 search popularity) of below 35% to nearly 50% in early 2020. K-Beauty's innovative concepts, such as fermented ingredients and multi-step regimens, have captured global attention. Fermented ingredients are valued for their enhanced efficacy, while multi-step routines offer customizable approaches to hydration and skin barrier repair. Regional differences highlight diverse consumer priorities, with Western markets favoring anti-aging solutions and Asian markets focusing on barrier repair. Google Trends serves as a valuable resource for dermatologists and industry stakeholders to track emerging trends, understand consumer preferences, and address educational gaps in skincare. Aligning dermatology practices with evolving interests can enhance patient engagement and promote evidence-based regimens. Future studies should incorporate social media analytics and clinical outcomes to further explore the relationship between digital trends and dermatological science.

0307

Developing a skin cancer screening Epic EHR tool to reduce unnecessary skin checks and improve dermatology access

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USPSTF concluded in 2023 that there is insufficient evidence to recommend for or against routine skin cancer screening for those without a history of skin cancer and suspicious moles. There is also no national consensus on skin cancer screening frequency in patients with a history of skin cancer. Therefore, dermatologists and primary care providers are routinely faced with the dilemma of whether to recommend total body skin examinations and at what interval. Our evidence-based skin cancer Epic screening tool was developed to help dermatologists make decisions regarding the need and frequency of complete skin exams (CSEs) for patients depending on their risk factors. Questions within the screening tool are stratified based on patients' personal and family history of melanoma and non-melanoma skin cancer, and other risk factors such as actinic damage, number of nevi, eye and hair color. A user feedback survey utilizing Likert scale, multiple choice, and short answer questions will be distributed to assess ease of use and need for improvements in the screening tool once launched. The goal of implementation is to improve dermatology access and the diversity of patients seen in dermatology clinics without affecting the quality of care. Data collected will assess the impact of this tool on patient access and whether the changing patient demographics better mirror the community served by the clinic. Once optimized, the use of this tool can be broadened to primary care providers to aid in determining which patients should be referred for routine skin cancer screenings and which can be seen as needed for specific complaints. Additionally, physicians may exhibit more confidence in determining an appropriate time between complete skin exams and thus enhance treatment outcomes in their patients.

0308

Building clinical research infrastructure in a dermatology department

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A strong clinical research infrastructure in a dermatology department can advance research goals of faculty investigators, assist trainees in career development, increase departmental research productivity, increase external collaborations, and increase external recognition. We aim to build out specialty clinic observational cohort databases from specialty care clinics in our dermatology department to facilitate clinical investigation. We built out at least one retrospective cohort database to capture the patient panel for each one of 13 specialty clinics. Clinics could have more than one planned cohort study. For each database, we obtained institutional review board (IRB) approval for a minimal risk study, collected data through chart review, and initiated a clinical research work product as either a presentation or publication. This effort was carried out between November 1, 2023 through January 10, 2025 and remains ongoing. Twelve protocols for the specialty clinics were submitted (80.0% n=12/15) and ten were approved as minimal risk studies by our IRB (83.3%, n=10/12). Three (30%, n=3/10) have retrospective databases built out. From these 3 databases alone, there is 1 manuscript in press, 1 manuscript in revision, 3 manuscripts submitted, 2 manuscripts drafted, and 5 national abstracts presented. Seven (70%, n=7/10) databases are still being built and will likely have a similar research output. A projected clinical research output based on these initial results could assume optimally two databases per specialty clinic and three clinical queries per database, resulting in 78 manuscripts within a two year timeline of database development. Strategic alignment between specialty clinic patient panels and clinical research infrastructure can help hasten project initiation for trainees, support research and promotional goals of faculty, and increase research output for an academic medical center. Increased grant and resource support for such an effort can offer educational value, research productivity, and external recognition for an academic dermatology department.

0309

Reduced sensory perception in frontal fibrosing alopecia: A cross-sectional study

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Our study aimed to quantitatively compare sensory function in the affected and unaffected forehead and scalp of patients with frontal fibrosing alopecia (FFA) to healthy control participants. FFA is a scarring hair loss condition involving hairline recession and is frequently accompanied by pain, pruritus, and/or burning. Although idiopathic, dysesthesia suggests potential neural-sensory involvement, possibly linked to small nerve fiber neuropathy. We conducted a cross-sectional study with 29 gender-matched FFA patients (N=15) and healthy control participants (N=14). Each participant completed a single-visit battery of eight quantitative sensory testing (QST) parameters [i.e., cold detection threshold (CDT), warm detection threshold (WDT), cold pain thresholds (CPT), heat pain thresholds (HPT), mechanical detection threshold (MDT), mechanical pain threshold (MPT), wind-up ratio (WUR), and pressure pain threshold (PPT)] following a standardized and validated protocol. The QST protocol was administered at two sites for each participant: the unaffected site (1 cm above the glabella) and the affected site (4 cm above the glabella or above the line of demarcation in FFA participants). FFA patients demonstrated increased mean sensory thresholds at the affected forehead site in seven (i.e., CDT, WDT, MPT, WUR, HPT, CPT) of eight QST parameters compared to control participants. Intra-group analysis of FFA patients showed a statistically significant increase in mean thresholds at the affected site when compared to the unaffected site in WDT ($p=0.002$), CPT ($p=0.02$), HPT ($p<0.001$), PPT ($p<0.001$), and MDT ($p=0.003$) tests. Our QST findings suggest an altered sensory profile (i.e., hypoesthesia) in FFA compared to control subjects. Future research should focus on correlating these findings with nerve structure and disease severity within a large FFA cohort.

0310

Hormonal influence on melanoma outcomes: A retrospective analysis of estrogen and progesterone therapies

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This study investigates the effects of estrogen and progesterone therapies on mortality in melanoma patients, aiming to clarify their influence on outcomes. Using TriNetX, a global database of de-identified patient data, we conducted a retrospective cohort analysis. Adult melanoma patients (≥18 years) exposed to estrogen (n=10,227), progesterone (n=718), or both hormones (n=34,549) were compared to controls without hormone exposure (n=313,691). Propensity score matching adjusted for demographics and common indications for hormone use. Mortality risk was calculated, and Kaplan-Meier survival curves were generated over a 5-year period, excluding patients diagnosed more than 20 years ago. After matching, estrogen-exposed melanoma patients had significantly decreased mortality compared to control melanoma patients not exposed to estrogen (n=9,136; HR 0.645, 95% CI 0.576–0.721, $p=0.039$). Conversely, melanoma patients exposed to both estrogen and progesterone showed significantly increased mortality (n=30,996; HR 1.41, 95% CI 1.339–1.484, $p<0.001$). Progesterone exposure alone showed no significant impact on mortality (n=685; HR 1.158, 95% CI 0.772–1.738, $p=0.950$). To validate melanoma's contribution to mortality, comparisons were made with matched controls without melanoma, confirming higher mortality and reduced survival in melanoma patients across all groups. These findings suggest that estrogen therapy may confer a survival benefit in melanoma patients, while combined estrogen and progesterone therapies are associated with worse outcomes. Preclinical evidence of protective estrogen receptor signaling aligns with our observations, underscoring the complexity of hormonal influences on melanoma. Future studies are needed to elucidate the biological mechanisms and optimize treatment strategies.

0311

Characterization of the racial composition of published alopecia quality of life research

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This study aims to learn about the patient demographics included in alopecia quality of life (QOL) studies, as well as the type of funding involved. We performed a retrospective analysis of 100 published QOL studies on different types of alopecia. For the included studies, the type of alopecia, demographics of study participants, and funding source were all recorded. Studies were significantly less likely to include information on patient race than patient sex (OR=0.2094, p<0.0001, 95%CI=0.1150 to 0.3814). The most common types of alopecia included were alopecia areata (51 studies), androgenic alopecia (33 studies), and alopecia universalis (7 studies). Studies on alopecia areata were significantly less likely to include black patients than any other racial group (OR=0.3321, p=0.018, 95%CI=0.1332 to 0.8280). Twenty-two studies included the patient's race; 18 included Black patients and 20 included white. Studies with black patients included an average of 12.1 patients, significantly lower than studies with white patients, which had an average of 139 (p=0.018). In addition, alopecia QOL studies that included black patients were significantly less likely to receive funding in comparison to patients of other racial groups (OR=0.1765, p=0.0039, 95%CI=0.0543 to 0.5737). This study is significant in highlighting the disparities among different racial groups included in alopecia studies, demonstrating the need for increased funding and research on the impacts of this disease on the quality of life in minority patients.

0312

A survey study on patient perspectives and knowledge of integrative health in the specialty of dermatology

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Integrative dermatology has gained increasing interest for its patient-centered approach to managing and uncovering the root causes of skin conditions. The field combines traditional dermatologic care with complementary therapies, including dietary supplements, herbal remedies, mind-body therapies, and nutritional counseling. Despite its potential benefits, integrative dermatology remains underutilized in practice. A 21-question survey was conducted to understand patient perspectives, knowledge, and attitudes toward integrative dermatology among University of Pittsburgh Medical Center (UPMC) patients. Analysis of 205 completed surveys showed a strong patient preference for integrative care due to its alignment with their health beliefs. Notably, 64.39% of patients would visit an integrative dermatologist, including for acne (60.49%), atopic dermatitis (56.01%), and skin cancer (48.78%). Further, 74.63% of patients wished dermatologists discussed the impact of lifestyle factors on skin, including diet, sleep, exercise, and stress. Patients who felt dermatologists should pay more attention to social support (OR 3.33 (1.33-8.35) p=0.010) and spiritual health (OR 4.56 (1.51-13.71) p=0.007) had a greater likelihood of visiting an integrative dermatologist. If patients believed stress (OR 6.06 (1.45-25.41) p=0.01) or chronic health conditions (OR 2.28 (1.06-4.91) p=0.035) strongly impacted their skin health, they were more likely to visit an integrative dermatologist in the future. Despite the increased readiness of patients for integrative dermatology, 30.24% felt cost may be a barrier due to a lack of insurance coverage for alternative therapies and suspected higher prices compared to conventional medicine. Overall, the findings of this survey highlight potential drivers of patient preferences for integrative dermatology.

0313

Hidradenitis suppurativa in psoriasis patients treated with secukinumab

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Secukinumab (cosentyx), a human monoclonal antibody targeting interleukin (IL)-17, has been demonstrated as an effective and relatively safe treatment for psoriasis by disrupting the IL-17-mediated inflammatory cascade responsible for psoriatic plaques. However, some case reports have suggested an association between secukinumab use in psoriasis patients and the onset of hidradenitis suppurativa (HS). We utilized the TrinetX database to investigate this potential link by analyzing data from 143 healthcare organizations. Patients who were treated with secukinumab after being diagnosed for psoriasis were compared to psoriasis patients who did not receive the treatment. Cohorts were propensity matched for age, sex, ethnicity, and race. Cohorts were matched a second time for additional obesity and tobacco use. Outcomes revealed an increased risk of HS in the secukinumab group (RR: 1.463, 95% CI: 1.143-1.874), corresponding to an absolute risk of 0.709% versus 0.463% in controls. After controlling for known HS risk factors, obesity and tobacco use, risk of secukinumab induced HS remained elevated (RR: 1.357, 95% CI: 1.065-1.728). Absolute risk ratios were 0.739% and 0.545% for secukinumab and control groups respectively. This study demonstrates a relationship between secukinumab treatment for psoriasis and induced HS. Although risk of HS during secukinumab treatment is relatively low, clinicians should be aware of these potential paradoxical symptoms and counsel patients if necessary.

0314

Late ulcerating infantile hemangioma responsive to propranolol

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This study describes an atypical case of a late ulcerating infantile hemangioma (IH) successfully treated with propranolol. A 13-month-old female with no significant medical history presented to our clinic with an ulcerated lesion on the left lateral abdomen, previously diagnosed as an IH. The lesion appeared during her second week of life, grew to 5 x 3 cm, and developed a central ulceration at 12 months, causing considerable pain and discomfort. The patient had been previously treated with topical timolol solution (0.5%) for eight months and metronidazole cream (0.75%) and mupirocin ointment (2%) for one month, all without resolution. Our initial examination revealed a 5 x 2.5 cm erythematous nodule with a 3 x 1 cm central ulceration featuring a yellow, fibrinous base and clear drainage on the left lateral abdomen extending to the back. The patient's topical regimen was changed to gentamicin ointment (0.1%) with Duoderm dressings, but the ulceration and drainage persisted for another two weeks. At 14 months, oral propranolol (1 mg/kg/day, divided twice daily) was initiated. After one week of propranolol therapy, there was already marked improvement, and the dose was increased to 1.5 mg/kg/day. One week later, the central ulceration was largely closed, with only minor superficial erosions remaining. At 16 months, the lesion had evolved into a well-healing, 4.5 x 2.2 cm erythematous plaque with shiny white scars. Propranolol was tapered without re-ulceration. Ulceration of IHs most commonly occurs while they are proliferating in the first 3-6 months of life, when propranolol therapy is thought to be most beneficial. This case highlights the rare occurrence of late ulceration and demonstrates that propranolol remains effective even when initiated later in the disease course.

0315

Caution regarding historical estimates and trends for global burden of AD

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The Global Burden of Disease (GBD) Study is a respected source for standardized estimates of the burden of hundreds of diseases that is frequently used to track disease burden trends over time and inform health policy planning. To address discrepancies in recent publications on trends in the global prevalence of atopic dermatitis (AD) using GBD data, we compared estimates of the global prevalence of AD over the same historical period (1990-2017), using data from the three most recent data releases: GBD2017, GBD2019, and GBD2021. We found marked differences by data release year: Data from both GBD2019 and GBD2021 suggest that AD prevalence decreased since 1990, in contrast to GBD2017, which shows an increasing trend. Overall, AD prevalence estimates across the same three decades are highest using data from GBD2017 (2,746 to 2,787 cases per 100,000 people) and lowest using data from GBD2021 (1,673 to 2,015 cases per 100,000 people). To examine the external validity of each data release, we compared historical estimates to age- and year-matched International Study of Asthma and Allergies in Childhood Phase Three data and found low concordance (Pearson correlation coefficient [PCC] -0.133 for GBD 2021 and -0.130 for GBD 2019). Correlations were lowest for low income and non-European countries. The GBD's modeling tool is designed to incorporate new data. However, it appears that changes in historical GBD estimates are primarily driven by the addition of large insurance claims databases since 2019. Insurance claims databases have limitations for the capture of AD activity and severity and may have limited generalizability, therefore it is important for researchers using GBD data to understand how the employed data sources have changed over time and interpret it with caution.

0316

Epidemiology of skin cancer, dermatological, and associated injuries in U.S. emergency departments: A 10-Year retrospective study

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Emergency departments (EDs) are often the first point of contact for patients with potential skin cancers. With rising skin cancer incidence in an aging population, EDs are uniquely positioned to identify initial skin cancer cases and facilitate timely referrals to dermatologists. Analyzing ED trends may improve understanding of demographics, clinical presentations, outcomes, and may improve equitable prevention pathways. The National Electronic Injury Surveillance System (NEISS) database, representing ~100 emergency departments, was queried using a keyword search of "skin cancer," "melanoma," "squamous cell," "basal cell," "basal cell carcinoma," "squamous cell carcinoma," (including plurals). Descriptive statistics, utilizing T-tests, were performed to identify skin cancer trends regarding age, gender, and race in the EDs. Data in case volume per year and presenting complaints were also analyzed. Among 59 skin cancer cases analyzed (mean age 65 years, range 20–97), 79.7% were White and 3.4% were Black. 64.4% of cases were male, with 50.8% of cases representing White men and 47.5% representing Whites aged older than 65. A seven-fold increase in the average number of cases seen per year from 2014 to 2023. Skin cancer-related ED visits rose 600% from 2014 to 2023, with White patients most at risk and Black and Asian patients presenting the least often. Additionally, men and older patients were diagnosed more frequently than women and younger patients. Further research should examine factors behind racial disparities in ED presentations, including socioeconomic, biological, and environmental influences, and evaluate targeted prevention strategies.

0317

Preoperative and postoperative considerations of micro-arteriovenous fistulas in patients with lower limb lymphedema

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This study aims to explore preoperative and postoperative considerations for managing micro-arteriovenous fistulas (AVFs) in patients with lower limb lymphedema, focusing on optimizing surgical outcomes and long-term care strategies. A comprehensive review of the literature was conducted using PubMed to identify studies addressing the diagnosis, management, and outcomes of micro-AVFs in lower limb lymphedema. The analysis included studies on surgical techniques, perioperative care, imaging modalities, and long-term management. Preoperative considerations emphasize accurate diagnosis through imaging modalities such as Doppler ultrasound and CT angiography, patient risk stratification, and optimization of medical therapy, including compression therapy and infection control. Postoperative care involves rigorous wound care, pain management, and rehabilitation, including manual lymphatic drainage and compression therapy. Studies show that surgical interventions, including ligation of micro-AVFs, result in significant reductions in limb volume and improvements in quality of life. However, outcomes are influenced by patient adherence to postoperative protocols, the severity of preoperative conditions, and comorbidities. Recurrence and persistent edema remain challenges requiring multidisciplinary management. Micro-AVF interventions hold promise for improving outcomes in patients with refractory lower limb lymphedema. Optimizing perioperative care, standardizing protocols, and addressing long-term challenges such as recurrence and complications are critical for enhancing clinical outcomes. Future research should focus on large-scale, standardized trials and the integration of advanced imaging and hybrid techniques to refine patient selection and treatment strategies.

0318

Analysis of sunburn prevalence among US high school students by sex and race/ethnicity (2015-2023)

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Sunburn in adolescents increases skin cancer risk in some and may signal underlying photosensitivity in others. Photosensitivity, resembling sunburn, can indicate increased risk of systemic conditions like lupus erythematosus (SLE), more common in Black female adolescents. Those with perceived higher Fitzpatrick skin types (FSTs) may not be asked about sunburn, leading to under-recognition of sun sensitivity and related risks. This study examined sunburn prevalence trends among U.S. high school students from 2015 to 2023, analyzing variations by sex and race/ethnicity. We conducted a retrospective analysis of data from the 2015-2023 Youth Risk Behavior Surveys. Sunburn history was defined as ≥ one sunburn in the past 12 months. Linear trend analysis using logistic regression was performed to assess prevalence trends. From 2015-2023, sunburn prevalence among U.S. high school students decreased from 55.8% to 54.7% ($p < 0.05$). Among males, prevalence decreased from 61.5% in 2021 to 52.0% in 2023; females decreased from 67.9% in 2021 to 57.9% in 2023. By race/ethnicity, Hispanic/Latino students' prevalence rose from 40.8% in 2015 to 55.2% in 2021, then declined to 41.4% in 2023. Prevalence in White students increased from 72.5% in 2015 to 82.9% in 2021, then decreased to 78.7% in 2023. Black students reported stable rates (15% in 2015, 14.3% in 2023). Black females had higher sunburn rates than Black males across all years. Despite the overall decrease, sunburn remains prevalent and varies significantly by race/ethnicity in high school students. Continued sun safety initiatives are needed to further reduce sunburn rates, especially among individuals with lighter skin phototypes who face higher skin cancer risks. Assessing sunburn history in all individuals, regardless of FST, is essential for identifying photosensitivity in clinical practice. Given their increased risk for SLE, Black adolescents, their families, and clinicians may benefit from tailored interventions addressing the impact of sun-related history on health.

0319

Impact of dupilumab on the atopic march in pediatric patients

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Atopic dermatitis (AD) typically initiates the atopic march, where patients progress to developing asthma and allergic rhinitis. Our study examined whether dupilumab, a targeted immunomodulatory medication available since 2017, could prevent progression of the atopic march in pediatric patients <=18 years old. We conducted a retrospective cohort study using administrative claims data from 2017-2021 in the MarketScan Commercial Claims and Encounters Database. We identified 614 patients with AD who received dupilumab and 168 who received a conventional systemic medication (i.e., methotrexate, cyclosporine, azathioprine, or mycophenolate). The primary outcome was incident asthma or allergic rhinitis diagnosis. The cumulative incidence of atopic comorbidities was greater in the conventional systemics group than the dupilumab group (23.9% vs 12.7%; p<0.001). In proportional hazards models adjusted for age, insurance type, and other medications (e.g., topical calcineurin inhibitors), dupilumab was associated with lower risk of asthma or allergic rhinitis (HR 0.59, 95% CI 0.40-0.89) versus conventional systemics. In secondary analyses, we also compared a cohort of 640 patients who received dupilumab to 4,929 patients who received primarily topical corticosteroids, propensity score matched on age, duration of AD, sex, geographical region, other atopic conditions, history of other AD treatments (i.e. topical calcineurin inhibitors, systemic immunosuppressants, systemic corticosteroids, and phototherapy), and maximum topical corticosteroid strength. The cumulative incidence of atopic comorbidities was similar between the dupilumab and topicals groups (12.8% vs 13.5%; p=0.71); in adjusted models, there was no significant difference in incident asthma or allergic rhinitis diagnosis (HR 1.00, 95% CI 0.79-1.26) between the groups. Our findings suggest that dupilumab may mitigate atopic march progression compared to conventional systemics, but future studies that directly account for AD severity are needed to discern if dupilumab has a protective effect compared to primarily topical therapies.

0320

Antibiotic stewardship in dermatology: An analysis of acne vulgaris prescribing practices

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The purpose of this study is to assess oral antibiotic prescribing trends for acne vulgaris within a dermatology clinic. Guidelines recommend limiting oral antibiotic use to 3–4 months in combination with benzoyl peroxide or topical retinoids to minimize antibiotic resistance. However, discrepancies between guidelines and actual prescribing habits remain a concern. A retrospective chart review analyzed data for patients diagnosed with acne vulgaris from April 2023 to June 2024. Data points included demographics, prescriptions for topical and oral antibiotics, benzoyl peroxide, topical combination therapies, oral isotretinoin, oral contraceptives, spironolactone, and topical dapsone. The primary outcomes analyzed were antibiotic type prescribed and duration of antibiotic prescription to evaluate adherence to current guidelines. Among 168 patients with acne vulgaris, 128 were female and 40 male, with a mean age of 27.24 years (median: 27, range: 11–71). Benzoyl peroxide was used by 55.5% of patients, while 68% were prescribed topical retinoids, and 70% received topical antibiotics. Oral antibiotics were prescribed to 35.1% of patients, with doxycycline being the most common prescribed at 97%, followed by minocycline and sarecycline. The mean duration of oral antibiotic therapy was 7.08 months (median: 5, range: 0.5–36 months). After antibiotic therapy, 28% of patients transitioned to isotretinoin and 24% to spironolactone. The findings of this study highlight the need to re-evaluate prescribing practices for oral antibiotics in the management of acne vulgaris. The mean duration of antibiotic therapy at 7 months exceeds the guideline-recommended duration of 3–4 months, underscoring the importance of aligning practices with stewardship principles. To mitigate the risks of prolonged antibiotic use, future efforts should focus on provider education and the integration of updated guidelines into clinical practice to promote more judicious use of oral antibiotics.

0321

Cardiovascular risk associated with nicotinamide use in keratinocyte cancer patients

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Nicotinamide, a water-soluble form of niacin, has previously been shown to reduce the incidence of new keratinocyte cancers in at-risk immunocompetent persons over a one-year period; however, recent concerns have been raised regarding niacin supplementation and increased cardiovascular risk. This retrospective cohort study evaluated the safety of nicotinamide in patients with a history of non-melanoma skin cancer (NMSC) by studying its association with major adverse cardiovascular events (MACE) using real-world data from the TriNetX platform (2011–2023). Patients with a history of NMSC who received at least three prescriptions for oral nicotinamide (n=1714) were compared to those who never received nicotinamide but were prescribed zinc (n=8858). The index date was defined as the first prescription of either medication. Propensity score matching (PSM) was employed to adjust for potential confounders. MACE was defined by a new diagnosis of ischemic heart disease, transient cerebral ischemic attack, stroke, or cardiac arrest. Both short (3 months to 1 year) and long-term (1-3 years) follow-up periods post-index date were examined. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using Cox proportional hazards models. After PSM, 1671 patients were included in each group. The nicotinamide group did not demonstrate a significantly increased risk of MACE in the short (adjusted HR: 1.18; 95% CI: 0.81-1.72) or long term (1.08; 0.79-1.49) compared to the control group. Our findings indicate oral nicotinamide is not associated with an increased risk of MACE within a 3-year follow-up period and suggest it remains a safe option for skin cancer prevention in those with a history of NMSC.

0322

Retrospective analysis of skin bacterial colonization in patients with cutaneous T cell lymphoma from a tertiary hospital in China

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Primary cutaneous T-cell lymphoma (CTCL) is characterized by the clonal proliferation of neoplastic T lymphocytes within the skin. This study aimed to investigate the risk factors for cutaneous bacterial colonization and to evaluate their impact, along with the administration of systemic antibiotics, on the long-term prognosis of a cohort of Chinese patients diagnosed with CTCL. A total of 113 CTCL patients were included in this research, with a median age at diagnosis of 49 years (interquartile range, 38-58); among them, 49 were male, representing 43.3% of the cohort. The patient demographic comprised 101 individuals with mycosis fungoides (89.4%) and 12 with Sézary syndrome (10.6%). Within this cohort, 85 patients (75.2%) tested positive for bacterial skin colonization, with Staphylococcus aureus (SA) identified in 68 patients (60.2%), and methicillin-resistant Staphylococcus aureus (MRSA) detected in 13 patients (11.5%). Ulcerated lesions significantly increased the likelihood of a positive result in bacterial skin cultures, with an odds ratio of 16.95 (95% CI, 3.95-97.23) according to multivariate analysis. Univariate analysis indicated that advanced stages, the presence of tumors, erythroderma, lymphopenia, and eosinophilia were associated with an elevated risk of positive skin cultures. However, skin bacterial colonization and antibiotic intervention were not correlated with overall survival (OS)—the weighted hazard ratio for the Bacteria+ antibiotics- group was 0.56 (95% CI, 0.10-3.26) and for the Bacteria+ antibiotics+ group was 0.52 (95% CI, 0.07-3.77) after applying inverse probability of treatment weighting. This retrospective study provides data on the prevalence of bacterial skin colonization in Asian CTCL patients, demonstrating a predominance of SA colonization. The findings did not reveal a significant correlation between bacterial skin colonization and worse prognosis for Asian CTCL patients, nor did the administration of systemic antibiotics improve long-term outcomes.

0323

Exploring the impact of ANA positivity on vitiligo: Consequences for disease activity and phototherapy dosage

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Background: Vitiligo is a chronic autoimmune skin disorder with a higher prevalence of antinuclear antibody (ANA) positivity than the general population. ANA-positive vitiligo patients may exhibit differential treatment responses, including potential intolerance to phototherapy based on their skin phototype. The necessity of ANA screening before treatment remains debated. Objectives: This study aims to assess whether ANA-positive vitiligo presents unique treatment challenges, focusing on disease progression control and cumulative phototherapy doses. Methods: Between September 2020 and September 2023, 86 vitiligo patients were recruited from 521 dermatology patients at Guizhou Medical University Affiliated Hospital. Demographic, clinical, and laboratory data were collected, with evaluations at baseline and after six months. Blood samples were obtained for ANA testing, and disease activity was assessed using VIDA scoring. Lesion areas were quantified using the VASI scoring, and pigmentation levels were graded on a four-point scale. Phototherapy doses and responses were recorded at the onset of pink and bright red asymptomatic erythema. Results: Among the cohort, 23 (26.7%) were ANA-positive. A total of 134 lesions were photographed across different anatomical areas. A positive correlation between ANA positivity and the stable phase was observed at the initial visit (Adjusted OR: 7.075, 95% CI: 1.106-45.249), but not at the second visit (Adjusted OR: 5.473, 95% CI: 0.954-31.401). No significant differences were found in cumulative phototherapy doses or the doses required to induce asymptomatic erythema. Nine patients had adverse reactions to phototherapy, including two ANA-positive patients, who developed bright red asymptomatic erythema lasting more than 48 hours. Conclusions: ANA-positive vitiligo patients do not show distinct patterns in disease progression or phototherapy responses, suggesting limited utility of ANA testing in guiding treatment decisions.

0324

Long-term utilization of dupilumab in atopic dermatitis

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Atopic dermatitis (AD) is a chronic inflammatory skin condition affecting millions. Though highly efficacious immunomodulatory medications such as dupilumab have become available, data on long-term treatment utilization in real-world settings remain limited. To investigate dupilumab treatment adherence among patients with AD, we conducted a retrospective cohort study using administrative claims data from 2017-2021 in the MarketScan Commercial Claims and Encounters Database. We identified 2,916 patients (43.7% male) with AD who had received dupilumab. The mean age at dupilumab initiation was 34 years old, with 22.5% of patients being <18 years old. Mean duration of follow-up in MarketScan was 18 (SD 13) months, and mean duration of dupilumab use was 8.5 (SD 8.2) months. We found that 60.1% of patients (1752/2916) had at least one 'short' treatment break lasting <90 days and 7.2% of patients (211/2916) had at least one 'long' treatment break lasting >=90 days. Comparing patients with long treatment breaks to those without any treatment breaks, we found that patients in the long-break and no-break groups were of similar age (34.7 vs 33.9 years old, respectively; p=0.49). There was also no statistical difference in distribution of pediatric vs adult patients between the long-break and no-break cohorts (17.1% vs. 22.9% pediatric; p=0.051). Both cohorts had similar distributions in terms of sex (49.3% vs 43.2% male; p=0.09). Insurance type was also similar between the two groups (p=0.17), with PPO insurance being the most common in both groups. However, patients in the long-break group were more likely to have comorbid asthma than patients in the no-break group (56.4% vs 44.1%, respectively; p<0.001) as well as comorbid allergic rhinitis (73.0% vs 61.1%; p<0.001). In conclusion, interruptions in dupilumab therapy seem to be relatively common; additional research is needed to understand the reasons for these lapses.

0325

Risk of antiepileptic medications inducing drug reaction with eosinophilia and systemic symptoms syndrome

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Aromatic antiepileptic drugs are noted to be a leading cause of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. However, the risk of these medications and general antiepileptics remains unquantified in patients with a history of epilepsy. Utilizing the US Collaborative Network TriNetX and International Classification of Disease (ICD)-10 codes, sixteen cohorts of patients with a history of epilepsy and exposure to antiepileptic medications were created. Each cohort was excluded from exposure to the other measured medications, as well as a history of neuralgia, restless leg syndrome, migraines, and bipolar disorder. The cohorts were matched against a control group, evaluated for the outcome of DRESS syndrome within a 2-8 week period, and a hazard ratio (HR) with 95% confidence intervals (CI) was calculated. When compared to the control group, lamotrigine (HR=3.477, 95% CI [1.416,8.538]), lorazepam (HR=2.033, 95% CI [1.094,3.779), lacosamide (HR=2.836, 95% CI [1.031,7.802], and phenytoin (HR=6.515, 95% CI [1.47,28.868]) showed a statistically significant increased risk for DRESS syndrome. However, the other measured antiepileptics did not show an increased risk. This study highlights the ability of a database study to further support or refute data reported in case report or case series studies. Additional studies evaluating other reported medications associated with DRESS syndrome should be conducted.

0326

Worsened quality of life and increased comorbidity risk associated with multibiologic failure in patients with psoriasis

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Psoriasis is a chronic condition that has a significant physical and mental health burden. Biologic agents that target dysregulated immune pathways have revolutionized the treatment of plaque psoriasis. While many individuals experience effective disease management with single biologic use, some patients experience psoriasis that is refractory to treatment. Cycles of biologics can lead to frustration, poor mental health, and an increased financial burden. Previous research has identified factors like disease severity, genetics, age, and smoking as risk factors associated with biologic failure. This study aims to investigate the differences between 258 individuals who experience multibiologic failure (MBF), defined as the previous or current use of 3 or more biologics, compared to 504 individuals who have only used a single biologic (SB) amongst the All of Us Research Program. Univariate analysis revealed that the MBF and SB cohorts were similar in demographics. Multivariate logistic regression controlling for age, sex, race, and total systemic medications tried revealed that MBF was significantly associated with worse quality of life measures, including increased odds of mild fatigue (ORa = 2.03; 95% CI: 1.13, 3.78) and decreased odds of having very good social satisfaction (ORa = 0.60; 95% CI: 0.37, 0.99) and general mental health (ORa = 0.53, 95% CI: 0.33, 0.85). MBF was also significantly associated with increased odds of comorbidities like obstructive sleep apnea (ORa = 1.47; 95% CI: 1.05, 2.05) and psoriatic arthritis (ORa = 1.76; 95% CI: 1.27, 2.46). These findings underscore the importance of identifying and addressing the significant impact on quality of life and additional health risks of patients who experience MBF.

0327

Variations in prevalence of malignant melanoma across global regions and income levels

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Malignant melanoma exhibits variations in prevalence across global regions and income levels. A comprehensive review of global trends in the disease remains uncommon. Prior work has focused on the incidence of malignant melanoma, especially in the United States, but analyzing prevalence allows us to examine the current burden of disease and evaluate its long-term impact. Using the Global Burden of Disease Study carried out by the Institute for Health Metrics and Evaluation at the University of Washington, data on the prevalence of malignant melanoma across 204 countries and territories as well as from the years 2017 to 2021 was gathered. Classifications were created by the World Bank to group these areas into four tiers by income: low, lower-middle, upper-middle, and high. To determine if there is an overall difference in melanoma prevalence by global income level, a One-Way Analysis of Variance was performed on our data binned into 4 categories, and tested two-sided, two-sample t-tests. There is a statistically significant difference ($p<2e-16$) generally in prevalence for different amounts of global wealth. Looking at pairwise differences, there is a clear, statistically significant monotonic trend: low income regions have a lower prevalence than lower-middle ($p=1.03e-06$), lower-middle lower than upper-middle ($p=1.89e-06$), and upper-middle lower than high ($p=5.41e-09$). The fact that melanoma prevalence increases consistently with income level suggests that individuals from these backgrounds are more likely to be exposed to risk factors such as sun exposure, frequent use of tanning beds, outdoor activities, and may have greater dermatological health resources. This clear trend provides us a global perspective, emphasizing the need to cater to low-income regions where melanoma detection and care may be less accessible, and justifies future prevention and intervention strategies to tackle these disparities.

0328

Spironolactone use in women does not increase the risk of meningioma: A population-based cohort study

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Meningioma pathogenesis is linked to hormonal factors due to its higher prevalence among females during reproductive years and association with progestogen use. Spironolactone, a diuretic with progesterone receptor activity, is commonly prescribed for dermatologic conditions. Given its hormonal receptor affinity, we examined the association between spironolactone and meningioma in females. We conducted a retrospective cohort study using the TriNetX database, including female adults with spironolactone indications. Those with other hormone/antiandrogen therapy use were excluded. Propensity score matching controlled for demographic, socioeconomic, comorbidity, and healthcare utilization factors between spironolactone users and nonusers. Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs). Sensitivity analyses included: 1) adjusting the start of follow-up from 1 to 180 days post-spironolactone prescription to account for cancer induction period, and 2) using eplerenone, a selective mineralocorticoid receptor antagonist, as a comparator. Among 115,184 female spironolactone users (mean age, 54.2±15.5 years) and matched nonuser controls, meningioma incidences were 0.4% for both groups over a mean 5.3-year follow-up. Spironolactone use was not significantly associated with meningioma risk (HR[95% CI], 1.08[0.95–1.22]) overall, nor did it increase the risk of benign (1.09[0.95-1.24]), uncertain (1.14 [0.71-1.84]), or malignant meningiomas (1.05[0.64-1.74]). Sensitivity analyses confirmed these findings. Despite its progesterone receptor affinity, spironolactone does not elevate meningioma risk. This finding is significant when evaluating treatment options for female patients, as meningioma is the most common benign brain tumor.

0329

An analysis of chemotherapeutic treatment avenues for cutaneous and mucocutaneous leishmaniasis: A systematic review and meta-analysis

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Cutaneous and mucocutaneous leishmaniasis, a protozoan parasitic disease characterized by skin and mucosal lesions, is endemic to nearly 100 countries and impacts over 350 million people. Amphotericin B is an intravenous treatment notable for its high efficacy, achieving final cure rates of 74-87%, but presents risks of developing drug resistance, adverse effects, and systemic toxicities. Conversely, orally administered miltefosine has a slightly stronger safety profile and maybe a better treatment option. This systematic review and meta-analysis aim to evaluate the efficacy of amphotericin B compared to miltefosine in patients with cutaneous and mucocutaneous leishmaniasis, seeking to standardize treatment protocols North America as cases may arise due to the accelerating effects of climate change. The primary outcome measures the complete re-epithelialization of lesions, categorized as complete response, partial response, or failure, based on the percentage of re-epithelialization of the ulcer within a standardized timeframe and a secondary outcome measuring adverse effects of the treatments. A comprehensive initial search and manual snowball-method search were conducted across five peer-reviewed databases (PubMed, Medline, Scopus, LILACS, and Cochrane Library) for studies conducted between 2010 and 2024. All stages of screening, extraction, and quality appraisal using GRADE were performed in duplicate by blinded reviewers with a third independent reconciler. Studies focused on old and new world leishmaniasis were included and studies lacking a clear clinical cure outcome were excluded.The findings of this review will comparatively analyze amphotericin B and miltefosine, offering insights to guide future treatment guidelines for managing this disease.

0330

Emotion and behavior in children with atopic dermatitis: Comparing teacher and parent reports

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Atopic dermatitis (AD), affecting up to 20% of children, has been linked to behavioral and emotional problems based on parent- or self-reports. Teachers provide unique insights into school-based challenges, but few studies include their perspective. To address this gap, our study evaluated the association between AD and teacher-reported Strengths and Difficulties Questionnaire (SDQ) scores, a validated tool for assessing emotional and behavioral problems, and examined the concordance between parent and teacher ratings. Data from 11,373 participants in the U.K. Avon Longitudinal Study of Parents and Children birth cohort were analyzed. Longitudinal latent class mixed models identified AD trajectories between 6 months and 7 years old: unaffected/rare (62.9%), early-onset resolving (1.1%), persistent mild (31.4%), moderate-to-severe (0.9%), and worsening (3.7%) AD. SDQ was completed by parents and teachers at age 7 years. In multivariate regression analysis adjusted for sex, gestational age, family socioeconomic factors, and atopic comorbidities, no associations were found between AD trajectories and teacher-reported SDQ scores. However, parent-reported SDQ ratings showed higher emotional problem scores in moderate-to-severe AD (β: 0.47 [95% CI: 0.09-0.85]), persistent mild AD (0.15 [0.07-0.23]), and worsening AD (0.23 [0.04-0.42]) compared to the unaffected/rare group. Total difficulties were also higher in persistent mild AD (β: 0.34, [95% CI: 0.12-0.57]). Parent-teacher concordance measured by intraclass correlation coefficients was low to moderate, ranging from 0.20 (95% CI: 0.17-0.23) for emotional problems to 0.41 (0.38-0.44) for hyperactivity. In sum, AD was associated with worse parent-reported but not teacher-reported SDQ ratings. Low concordance underscores context's role and same-reporter bias, highlighting the importance of multiple informants in assessing behavioral and emotional outcomes in children with AD.

0331

Risk of cardiovascular events among cutaneous T-cell lymphoma patients in the TriNetX database

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We aimed to characterize cardiovascular (CV) comorbidities in Cutaneous T-cell Lymphoma (CTCL), a disease with an unexplored comorbidity risk profile. CTCL has clinical and pathophysiological similarities to benign inflammatory dermatoses (BID), which are associated with elevated risk of CV diseases attributed to systemic inflammation. Data was extracted from the TriNetX database for 23,145 CTCL patients (22,245 w/o concurrent BID), 1,856,614 BID patients, and 11,268,027 healthy controls (HC) (visit w/o abnormal findings, ICD-10: Z00.00). All groups were mutually exclusive, excluding those with CV conditions diagnosed before index CTCL/BID/HC diagnosis. Prevalence of CV disease after CTCL diagnosis was compared to HC/BID using descriptive statistics, Kaplan-Meier analyses, and Cox Proportional (CP) Hazard models with age, sex, ethnicity/race, and prior diagnosis of diabetes mellitus, obesity/overweight, nicotine dependence, or alcohol related disorder as covariates. CTCL patients had higher risk of clots (CPHR=1.95, 95% CI 1.82-2.09), pulmonary embolism (PE) (CPHR=1.62, 1.47-1.79), cardiac arrest-unspecified cause (CA) (CPHR=1.52, 1.29-1.80) and similar risk of acute MI, versus HC. Compared to BID, CTCL patients had greater risk of clots (CPHR=1.84, 1.71 - 1.98), PE (CPHR=1.62, 1.47 - 1.79), CA (CPHR=1.34, 1.13 - 1.59), and slightly lower risk of acute MI (CPHR=0.86, 0.78 - 0.95). Our findings suggest an increased risk of some CV events among CTCL patients, with an almost twofold risk ratio increase for clots, versus those with BID/HC. While recognizing limitations of the TriNetX database, this work represents a novel investigation of CTCL comorbidities in a dataset of this size and prompts further consideration of hypercoagulability screening, prophylaxis, and management strategies in this vulnerable population.

0332

A standardized scoring method for measuring white cast of mineral sunscreens across diverse skin tones

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Mineral sunscreens, using zinc oxide (ZnO) and titanium dioxide (TiO_2) as physical UV filters, are a preferred choice for users with sensitive skin or allergies to chemical UV filters. However, the white cast they can leave on the skin is a significant cosmetic concern. This cosmetic elegance issue often discourages users from applying or using sunscreen correctly, leading to poor sunscreen compliance and a higher risk of developing skin cancer. Despite this, no official method exists to quantify white cast across diverse skin tones. To address the lack of a standardized method for measuring white cast in sunscreen formulations, we developed a validated protocol for measuring and scoring white cast. Our double-blind clinical study on a diverse Individual Typology Angle (ITA°) panel of volunteers combined objective L* measurements (whiteness) taken after sunscreen application with subjective user feedback on formulations containing ZnO concentrations ranging from 0 to 30%. The findings revealed a significantly strong correlation between increasing ZnO percentages and higher L* values ($p < 0.001$), corresponding to a more pronounced white cast. White cast scores for ZnO formulations were consistent across different skin tones, with higher ZnO concentrations leading to unacceptable levels of white cast. This study introduces a validated white cast score protocol as a quantitative tool for evaluating mineral sunscreen formulations in diverse skin tones, allowing the early selection of formulations with a reduced white cast and enhanced cosmetic elegance. These findings can lead to the production of mineral sunscreens that provide an improved user experience and encourage better sunscreen compliance.

0333

Validation of a novel scoring system for skin frailty and its association with age and skin cancer

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Skin frailty is characterized by the decline in the skin's protective mechanisms due to both internal and external factors. A validated assessment tool incorporating clinical signs of skin frailty is currently lacking. Following Stanford Human Subjects' Panel approval and written informed consent, we developed and validated a scoring system to assess skin frailty. Two dermatologist raters assessed digital photographs from 238 adult participants, identifying five reliable skin frailty parameters—purpura, hyperpigmentation, wrinkles, sagging, and skin integrity breakdown—using a 4-point Likert scale, with all parameters demonstrating reliability (Kendall coefficient or Gwet's AC2 > 0.8) both between and within raters. The total skin frailty score (SFS), the sum of the above five parameters, also showed strong reliability (intraclass correlation coefficient = 0.75 for inter-rater, 0.86 for intra-rater). The average SFS (as assessed by two raters, two rounds each) correlated positively with age (Spearman's Rho = 0.74) and was higher in participants with skin cancer history (median 4.00 vs. 2.25, Mann-Whitney U test, $p < 0.001$). Linear regression models identified age, female gender, and skin cancer history as significant independent predictors of higher SFS (beta coefficients 0.13, 0.75, and 0.58, respectively, all $p < 0.05$). The numbers of melanoma and non-melanoma skin cancers were also significantly correlated with SFS (beta coefficients 0.12 and 0.11, respectively, both $p < 0.05$). Logistic regression with skin cancer as the dependent variable showed that higher SFS quartiles were associated with significantly increased odds of skin cancer. Compared to individuals in the first quartile ($0 \le SFS < 2.25$), second ($2.25 \le SFS < 3.50$), third ($3.50 \le SFS < 5.50$), and fourth ($SFS \ge 5.50$) quartiles had respectively 5, 4, and 10 times skin cancer odds (all $p < 0.05$). Our scoring system provides a validated and reliable method for assessing skin frailty and may serve as a valuable tool for evaluating skin cancer risk.

0334

Accelerated biological aging in psoriasis: Findings from the national health and nutrition examination survey

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Psoriasis is linked to systemic disease burden and reduced life expectancy. Previously validated biological age prediction algorithms based on blood chemistry and clinical biomarkers are strong predictors of morbidity and mortality and may serve as markers for more severe forms of systemic inflammatory disease. Using data from the 2003-2006 and 2009-2014 National Health and Nutrition Examination Survey, we conducted a cross-sectional study to analyze differences in biological age using the Phenoage, Klemara-Doubal, and homeostatic dysregulation algorithms. Survey-weighted chi-square, t-tests, and multivariable linear regression models adjusted for sociodemographics were used to assess biological age advancement (difference between biological and chronological age) between individuals with and without psoriasis, across severity levels (measured using body-surface-area), and by quality of life. Our analytical sample included 18,758 adults, with 523 reporting psoriasis (3%). Psoriasis was associated with a 0.789 year greater mean Phenoage advancement compared to healthy individuals (95% CI: 0.197, 1.382), but no significant differences were found for other biological age clocks nor with severity. "Fair/Poor" health status was associated with a greater age advancement compared to those reporting "excellent" health status (Phenoage B= 3.042, 95% CI: 0.873, 5.211; homeostatic dysregulation B=0.329, 95% CI: 0.016, 0.641). More physically unhealthy (Phenoage B=0.089, 95% CI: 0.020, 0.158; homeostatic dysregulation B= 0.016, 95% CI: 0.005, 0.027) and overall unhealthy (homeostatic dysregulation B=0.011, 95%CI: 0.003, 0.019) days in the past month were also associated with age advancement. Our findings suggest that psoriasis is associated with accelerated biological aging and that self-reported QOL may be a sensitive proxy for accelerated biological aging in this population.

0335

A survey and analysis of the presence of allergens in sunscreens in the United States

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Sunscreen is recommended by dermatologists to prevent actinic damage and skin malignancies, whose incidence is steadily rising. However, sunscreen can cause allergic contact dermatitis (ACD). This study evaluates the presence of North American Contact Dermatitis Group (NACDG) core allergens in sunscreens available in the United States. "Sunscreen" was searched on Amazon, Target, Walgreens, CVS, and Walmart. The top 40 products from each site were included with manufacturer websites consulted for ingredient lists as needed. Product characteristics, including chemical/physical blocker, tinted/non-tinted, SPF, cost, and marketing claims were recorded. The most common allergens were fragrance (53.5%), phenoxyethanol (44.5%), ethylhexylglycerin (29.5%), propylene glycol (18%), and methacrylate (17%). Tinted sunscreens had fewer allergens (35.3%) than non-tinted sunscreens (64.6%). Allergen prevalence in chemical and physical 26.2%. Tinted or combination sunscreens had fewer allergens, and can generally be recommended more c sunscreens was similar at 64.5% and 65.9%, respectively, but combination was lower at 26.7%. Market claims of "gentle" (66.7%), "dermatologist recommended" (55.9%), and "allergen-free/hypoallergenic/allergy tested" (52.9%) had the highest allergen prevalence, while "sensitive skin" products had the lowest at onfidently. However, claims such as "gentle", "dermatologist recommended", and "allergen free" are not FDA regulated and may mislead patients, with allergen rates ranging from 52.9-66.7%. "Sensitive skin" labels are more likely to be trustworthy, but should still be scrutinized. As skin cancer incidence rises, dermatologists play a crucial role in eliminating barriers to sun safety. By recommending less allergenic sunscreens, dermatologists can improve compliance, reduce hypersensitivity reactions, and ultimately prevent skin malignancies.

0336

A survey and analysis ChatGPT's generated differential diagnoses utilizing physical exam descriptions from a pediatric dermatology textbook

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With the national shortage of pediatric dermatologists and the evolving field of artificial intelligence (AI), this study was designed to analyze the diagnostic accuracy of ChatGPT 3.5 as it pertains to common pediatric cutaneous pathologies. ChatGPT 3.5 was used to acquire answers to the prompt "diagnosis of [physical exam description]" using standardized physical examination findings from 178 pediatric dermatologic conditions in the Hurwitz Clinical Pediatric Dermatology textbook. Despite the availability of more sophisticated models of ChatGPT that can utilize photo input, ChatGPT 3.5 was specifically used as it is free and the most accessible to parents of patients. Based on inputted physical exam findings, ChatGPT successfully identified 59.30% of pathologies. The inconsistent diagnostic accuracy displays the continued need for pediatric dermatologists and reliable resources to manage pediatric cutaneous disease.

0337

Atopic dermatitis severity and treatment history predict cutaneous T-cell lymphoma outcomes

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We previously demonstrated that a history of atopic dermatitis (AD) impacts cutaneous T-cell lymphoma (CTCL) outcomes. However, the influence of AD severity remains unknown. In this retrospective analysis of 211 CTCL patients with a documented AD history (2011–2024) at a tertiary referral center, we investigated how AD severity, defined by treatment intensity, influenced CTCL outcomes. Mycosis fungoides predominated (90%) over Sézary syndrome (10%) in our diverse cohort (50.7% female; 49.3% White, 47.9% Black, 2.8% Asian; mean age at diagnosis: 54.5 ± 16.3 years). AD severity was stratified based on treatment intensity: mild-to-moderate disease (n=131) managed with topical corticosteroids and/or phototherapy, versus severe disease (n=80) requiring systemic immunotherapy (including corticosteroids, JAK inhibitors, biologics) with or without adjunctive topicals or phototherapy. Multivariate analysis controlled for age at CTCL diagnosis, sex, and race. Patients classified as having severe AD based on prior systemic therapy use had higher odds of advanced-stage CTCL at diagnosis (OR=2.24, 95% CI: 1.16–4.38, p=0.017) and folliculotropic CTCL (OR=2.65, 95% CI: 1.29–5.54, p=0.008). Survival time was reduced by 3.3 years in the severe AD group (95% CI: 2.3–4.2 years, p=0.001). Traditional prognostic markers, including eosinophil counts and lactate dehydrogenase levels, were comparable between AD severity groups, suggesting that other factors such as prior systemic therapy may influence CTCL outcomes. There were no significant differences between severe and mild-to-moderate AD groups in infection-related complications (bacteremia: 19.8% vs 15.3%, p=0.300; cellulitis: 32.1% vs 28.2%, p=0.163; pneumonia: 12.3% vs 20.6%, p=0.695) or comorbidities, including hyperlipidemia (58.0% vs 64.1%, p=0.326) and hypertension (46.9% vs 57.3%, p=0.659). Our findings suggest that AD severity and/or its management may impact CTCL progression and survival. Our ongoing analyses aim to identify specific immune and therapeutic mechanisms driving these outcomes.

0338

An epidemiologic analysis of cutaneous melanomas during 2018-2022: Results from a multicenter health maintenance organization in Northern California

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We aimed to characterize the effects of delayed diagnostics on melanoma stage within distinct demographic groups based on age, sex, and race/ethnicity; by comparing tumor (pT) stage and metastases before, during, and after lockdown periods of the COVID-19 pandemic. This retrospective study analyzed data from the Kaiser Permanente Northern California Regional Cancer Registry to assess cutaneous melanoma incidence trends from 2018 to 2022. For 20 distinct age-sex-race groups, and within each calendar year, we quantified the number and relative proportions of cutaneous melanomas by primary tumor stage (pT0, pT1a, etc.) and pathological stage (0, I, II, III, IV)- defined by regional and distant metastases. There were 14,139 melanomas diagnosed during the study period. Our preliminary analysis reveal no statistically significant differences in the age-adjusted invasive melanoma incidence rates for 2021 (42.7; 95% CI: 40.5–44.8) compared to 2018 (42.8; 95% CI: 40.6–44.9) and 2019 (42.5; 95% CI: 40.3–44.7), as evidenced by the overlapping 95% confidence intervals. In contrast, the age-adjusted incidence in 2022 was significantly higher at 47.6 (95% CI: 45.3–49.9). Within our age group subanalysis, those 75+ had an age-adjusted incidence of 17.3 (95% CI: 15.9-18.9) in 2022 compared to 14.2 (95% CI: 12.9-15.7) and 15.4 (95% CI: 14.1-16.9) in 2018 and 2019, respectively with distinct CIs. No other age groups demonstrated a significant difference in invasive melanoma incidence pre- and post-COVID19. Based on our preliminary results, there was an increase in invasive melanoma incidence in 2022 compared with the preceding four years, which may be driven by the 75+ group. This age group may have been disproportionately affected by disruptions in timely dermatological care during the pandemic. To further evaluate changes in melanoma incidence trends, we plan to estimate the annual percent change (APC) using a joinpoint regression model.

0339

Using the international dermatology outcome measures (IDEOM) clinical framework to streamline psoriatic arthritis screening and assessment

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Due to challenges with psoriatic arthritis (PsA) detection and the risk of irreversible joint damage if inadequately treated, this quality improvement project aims to improve PsA screening, assessment, and rheumatology referral. Our clinical framework integrated the Psoriasis Epidemiology Screening Tool (PEST) and the 12-item Psoriatic Arthritis Impact of Disease questionnaire(PsAID-12) into the electronic medical record system in 26 dermatology clinics. Psoriasis (PsO) patients underwent PsA screening via the PEST. Those scoring ≥3 or already diagnosed with PsA completed the PsAID-12, which guides management. PsAID-12 score >4 indicates an unacceptable symptom state, prompting treatment changes or rheumatology referral[1]. Providers received results in real-time for review. Over 25 months, 7,609 PsO patients were seen by dermatology providers. Of the 6,398 PsO patients without a PsA diagnosis, 36.9% completed the PEST; 12.7% scored ≥3 and completed the PsAID-12. 74.9% of patients who took the PsAID-12 scored ≤4, indicating effective management. Of the 25.1% of patients scoring >4, 26.7% were referred to rheumatology. When comparing the 477 patients who took the PsAID-12 at least twice, an average baseline PsAID-12 score of 2.82 was seen compared to an average most recent score of 2.53, indicating a significant reduction (t-statistic = -3.69, p = 0.044). Of the 50 total patients who received referrals, 62% were seen by rheumatology. Our study demonstrates the feasibility of IDEOM's clinical framework in optimizing PsA screening, assessment, and quality of care. References: 1. Grant C, Perez-Chada LM, Harrison RW, et al. Impact of disease, musculoskeletal symptoms and disease control in the CorEvitas Psoriasis Registry. Clin Exp Dermatol. 2024;49(9):1016-1023. doi:10.1093/ced/llae095

0340

Advanced age as a key risk factor for deep vein thrombosis in patients with lower limb cellulitis: A 10-year retrospective study

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Lower limb cellulitis, a common bacterial infection, can lead to complications such as deep vein thrombosis (DVT). While inflammation and immobility may contribute to thrombosis, specific risk factors in cellulitis patients remain unclear, particularly in Asian populations. We conducted a retrospective study of 158 cellulitis patients treated at our institution between 2013 and 2023. Among these, 36 patients underwent Doppler ultrasound for DVT assessment due to elevated D-dimer levels (≥2.5 μg/mL). Clinical data, including age, BMI, CRP levels, D-dimer, and medical history, were analyzed using univariate and multivariate logistic regression models to identify risk factors for DVT development. Of the 36 patients who underwent ultrasound, 7 (19.4%) were diagnosed with DVT. Univariate analysis revealed that patients aged 70 years or older had a significantly higher odds ratio for DVT (OR: 11.4, 95% CI: 1.2–108.3, p = 0.034). Multivariate analysis confirmed advanced age as an independent risk factor, with an adjusted odds ratio of 13.5 (95% CI: 1.1–165.3, p = 0.049). Other clinical parameters, including CRP levels (mean: 10.5 mg/L in DVT patients vs. 13.1 mg/L in non-DVT patients, p = 0.542), BMI (mean: 25.9 kg/m^2 vs. 30.8 kg/m^2, p = 0.227), diabetes (p = 0.554), malignancy (p = 0.230), and corticosteroid use (p > 0.999), showed no significant associations with thrombosis. Thrombotic events occurred in 43% of cases in the limb affected by cellulitis and in 57% in the contralateral limb. Advanced age (≥70 years) is an independent risk factor for DVT in cellulitis patients, emphasizing the importance of proactive monitoring and prevention strategies, particularly in elderly populations. This study highlights the need for age-specific considerations in cellulitis management and provides a basis for further research into the mechanisms linking cellulitis and thrombosis.

0341

Outcome metrics of intravenous golimumab for hidradenitis suppurativa

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Infliximab (IFX), a chimeric monoclonal antibody targeting tumor necrosis factor (TNF)-α, is a weight-based therapy for hidradenitis suppurativa (HS). However, IFX is contraindicated after IFX-associated-anaphylaxis (IAAx) or when neutralized by IFX-associated antibodies (IAAb). Intravenous (IV) golimumab (GoI), a fully humanized IFX congener, has been proposed for refractory HS. Objective: Examine outcome metrics in a cohort treated with IV-GoI for HS. We surveyed 17 HS patients treated with IV-GoI for 3-months after IAAx or IAAb. Demographic data, HS severity (HS-physician global assessment(HSPGA), numerical rating scale for pain (NRS-Pain) and inflammatory markers (C-reactive protein(CRP), erythrocyte sedimentation rate(ESR), interleukine-6(IL-6) were collected pre- and post-IV-GoI. Study participants were surveyed with standardized questions, grading drainage, mood, sleep quality, mobility, quality of life(QoL), willingness to receive IV-GoI again if discontinued, and overall preference for IV-GoI versus IFX. Mean cohort age was 40 years; 15 female (88%); racial/ethnic distribution: 9 Black, 2 White, 1 Spanish/Hispanic/Latino, 5 Other. There were mean declines (≥3-months) in HSPGA (-1.294) and NRS-Pain (-1.647). All inflammatory markers trended downwards. Neither allergy nor antibodies occurred. Survey participants reported improved or similar lesion status (15[88%]), pain (13[76%]), drainage (13[76%]), mood (16[94%]), mobility (15[88%]), sleep (16[94%]), and QoL (15[88%]) compared to IFX. All reported 'satisfied' or 'very satisfied' with IV-GoI. All were willing to undergo IV-GoI again; 14(82%) preferred IV-GoI over IFX or had no preference. Outcome metrics among HS patients receiving IV-GoI offer a highly promising alternative weight-based (TNF)-α inhibitor in the setting of IAAx and IAAb.

0342

Hidradenitis suppurativa patients experience musculoskeletal symptom burden: A quality improvement project using the IDEOM MSK-Q

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This quality improvement project applies the International Dermatology Outcome Measures (IDEOM) Musculoskeletal Questionnaire (MSK-Q) to assess MSK symptom burden in hidradenitis suppurativa (HS) patients. The MSK-Q is a 9-item tool scored on a 10-point scale, with subscores evaluating MSK symptom severity, impact, and fatigue in the past week[1]. Over 17 months, we distributed the IDEOM MSK-Q to 97 HS patients and collected demographic and clinical data. The mean age was 35.28 +/- 13.06; 37.1% were black or African American, 36.1% other, 18.5 % white, and 6.2% Asian. Average BMI was 31.55 +/- 7.86. 77.1% of patients reported joint pain, swelling, or stiffness, and 30.2% had baseline MSK disorders, most commonly osteoarthritis (n = 6). MSK symptoms were shown to have the greatest impact on daily physical activities (mean impact rating 4.97 +/- 3.59). Spearman's rank-order correlation analysis showed a significant positive relationship between Hurley stage and reported impact of MSK symptoms on daily physical activities (correlation coefficient = 0.033; p = 0.262) and work or school activities (correlation coefficient = 0.015; p = 0.297). Additionally, 55.1% of patients ranked fatigue ≥7/10 (mean fatigue rating 6.17 +/- 3.07), suggesting an inflammatory burden of the skin and/or joints. Our analysis shows substantial MSK symptom burden amongst HS patients. The IDEOM MSK-Q may be a valuable tool for assessing MSK symptoms and impact, highlighting the need for further development and validation in the HS population. References: 1. Zundell MP, Woodbury MJ, Lee K, et al. Report of the Skin Research Workgroups From the IDEOM Breakout at the GRAPPA 2022 Annual Meeting. J Rheumatol. 2023;50(Suppl 2):47-50. doi:10.3899/jrheum.2023-0528

0343

Mental health outcomes of isotretinoin for acne in transgender and gender diverse patients receiving testosterone compared to cisgender patients

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Transgender and gender diverse (TGD) patients receiving testosterone commonly develop acne after starting masculinizing gender affirming hormone therapy (mGAHT). Isotretinoin is highly effective in treating acne, but its use is associated with reports of depression/suicide. TGD patients have a baseline higher risk of depression/suicide, leading to concern about use of isotretinoin in this population. This prospective cohort study evaluated 19 TGD-mGAHT and 16 cisgender adults not receiving testosterone who were starting isotretinoin for acne at Fenway Health between September 2020 to December 2024 and followed for 12 months post-treatment. Mental health was evaluated by monthly Patient Health Questionnaire-9 (PHQ-9) and Dermatology Quality of Life Index (DLQI) surveys. Groups were compared using Wilcoxon (Mann-Whitney) Rank Sum tests, with statistical significance defined as $P<0.05$. Between TGD-mGAHT and cisgender cohorts, there was a significant difference in baseline PHQ-9 scores (medians (interquartile ranges (IQRs)) of 7 (4-10) vs. 2 (1-5), $P<0.01$), but not DLQI scores (medians (IQRs) of 8 (3-12) vs. 6 (4-14), respectively). By treatment end, there was no significant difference in PHQ-9 (medians (IQRs) of 4.5 (2-6) vs. 3 (0.5-5.5) and DLQI scores (medians (IQRs) of 2 (1-4) vs. 1 (0-3)) between TGD-mGAHT and cisgender cohorts, respectively. Difference in PHQ-9 score improvement between the cohorts was statistically significant from baseline to end-treatment ($P=0.01$) but not significantly different for baseline to 12-month follow-up ($P=0.52$). There was no statistically significant difference in DLQI improvement between the cohorts between baseline to end-of-treatment ($P=0.59$) or to 12-month follow-up ($P=1.00$). No patients discontinued isotretinoin due to adverse mental health effects. In conclusion, isotretinoin has similar safety in terms of mental health outcomes in the treatment of acne among TGD patients on testosterone compared to cisgender patients.

0344

Advanced clinical characteristics and survival disparities of patients with primary cutaneous T-cell lymphoma in nonmetropolitan regions in the United States

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The incidence of cutaneous T-cell lymphoma (CTCL) in the United States (US) has been increasing in metropolitan areas, but it remains unclear how survival outcomes in these areas compare to those in nonmetropolitan regions. This retrospective cohort study sought to compare the clinical presentations and disease-specific survival of patients with CTCL residing in metropolitan versus nonmetropolitan regions using SEER data. We identified 12,320 metropolitan and 1,073 nonmetropolitan patients with histologically confirmed primary CTCL diagnosed between 2000 and 2021. Kaplan-Meier survival curves and cumulative incidence functions were utilized to evaluate overall survival and disease-specific mortality. Cox proportional hazard models and Fine-Gray competing risk regression models were used to compare overall mortality and disease-specific mortality. Nonmetropolitan patients were older (63 vs. 57 years) and more likely to present with visceral disease (10.0% vs. 8.5%) than metropolitan patients. Nonmetropolitan patients demonstrated significantly lower 5-year overall survival rates (72.1% vs. 81.5%) and higher 5-year disease-specific mortality rates (15.1% vs. 10.3%) compared to metropolitan patients. These findings remained consistent in both multivariable Cox proportional hazard models and Fine-Gray competing risk regression models. Our study highlights that patients in nonmetropolitan regions were more likely to be diagnosed at an older age and with more advanced disease, with correspondingly worse disease-specific survival compared to patients in metropolitan areas. The reason for this disparity is likely multifactorial, but could result from reduced healthcare access, lower dermatologist density, or environmental exposures. Further research is needed to understand and address these regional survival differences.

0345

Low rate of endocrinology referrals among hyperglycemic hidradenitis suppurativa patients

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Hidradenitis suppurativa (HS) is associated with metabolic comorbidities, including type II diabetes mellitus (T2DM). HS also disproportionately affects socioeconomically and racially diverse populations, raising concerns about potentially underrecognized metabolic risks. Early detection and referral for endocrinologic care may improve outcomes in HS patients; however, the frequency of such referrals remains unclear. This study examined endocrinology referral rates among HS patients with elevated glucose levels, with a focus on potential racial differences. Using the TriNetX database, we performed a 10-year retrospective analysis of de-identified patient records from a broad range of U.S. healthcare organizations, spanning both insured and uninsured populations. We included HS (ICD-10-CM: L73.2) patients with at least two glucose measurements above 120 mg/dL, without a T2DM diagnosis (ICD-10-CM: E11) prior to or within one month of HS onset. Endocrinology referrals were identified using SNOMED and CPT codes associated with referrals to endocrinology. Racial differences in referral rates were also examined. Among 14,740 HS patients meeting the criteria, only 182 (1.24%) received an endocrinology referral. The HS population was further divided into 7974 White patients and 4664 Black patients. Notably, referral rates varied by race, with Black patients having lower referral rates compared to their White counterparts (0.83% vs. 1.29%; p-value: 0.02). These findings suggest a gap in multidisciplinary care for HS patients, underscoring the need for increased awareness and proactive evaluation of metabolic comorbidities. A reason for lower referral rates in Black patients is unknown but may indicate possible disparities in accessing specialized metabolic care. Targeted interventions—such as providing culturally sensitive patient education, and strengthening interdisciplinary care pathways—could help address these disparities, facilitate earlier detection and management of HS, and ultimately foster more equitable health outcomes.

0346

A longitudinal study of periungual fibroma size in adulthood and in response to sirolimus

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A hindrance to assessing changes in periungual fibroma (PF) size in response to therapy has been the lack of a simple method for measurement. PF often appear in adolescence as one of the last skin manifestations of tuberous sclerosis complex (TSC). PF result in nail distortion and may cause pain and bleeding. To assess the natural history of PF size and to determine whether PF size is influenced by treatment with oral sirolimus, we performed a retrospective cohort study analyzing clinical images to obtain ratios of PF area relative to total nail area. PF size was measured over time in 17 patients with TSC, ages 27 to 66 years. A total of 18 PF were from patients not on sirolimus, and 10 PF were from patients on sirolimus to treat lymphangioleiomyomatosis. ImageJ was used to quantify relative PF area at the final visit compared to first visit; defining ratios of 0.7 to 1.2 as similar size, <0.7 smaller size, and >1.2 larger size. Over a median of 3.4 years (range 1.3 to 8.5), 10 of 18 PF maintained a similar size, 5 increased an average of 1.6-fold, and 3 decreased an average of 0.7-fold. In patients treated with sirolimus for a median of 3.5 years (range 1 to 9), 7 of 10 PF maintained a similar size, 1 PF increased 1.3-fold, and 2 PF decreased an average 0.6-fold. In some instances, PF size in patients on sirolimus did not change in area but appeared to flatten. Overall, most PF in patients with TSC are fairly stable in size during adulthood and persist during treatment with oral sirolimus. Oral sirolimus, initiated for systemic indications, does not replace surgical excision of PF when needed for symptomatic lesions. Whether oral sirolimus minimizes recurrence after excision remains to be determined.

0347

Risk of drug-induced alopecia areata in selected drugs: A retrospective cohort study

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Alopecia areata has been reported to be triggered by certain medications. A recent analysis outlined several drugs identified as causing drug-induced alopecia areata via published case reports. This study aims to determine which of these selected medications are associated with the development of alopecia areata in our population. A retrospective cohort study was performed comparing the risk and hazard ratio of alopecia areata diagnosis within five years of starting adalimumab, dupilumab, infliximab, etanercept, alemtuzumab, ribavirin, cyclosporine, golimumab, haloperidol, pembrolizumab, rifampin, or isotretinoin with matched controls. There were no statistically significant differences between alopecia areata risk within five years of starting the above drugs when compared to matched controls. These results support that there is no statistically significant risk of developing alopecia areata after starting the above drugs despite many published case reports of the above drugs as the identified cause of drug-induced alopecia areata.

0348

Adverse event reports of alopecia for sunscreen ingredients and branded products

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As sunscreen use has increased, questions regarding its effects on hair have been raised. Recent reports have demonstrated a correlation between sunscreen use and frontal fibrosing alopecia, yet investigations into specific sunscreen products or ingredient combinations and their association with alopecia are lacking. This study used the FDA Adverse Event Reporting System to examine associations between sunscreen products and reports of general alopecia. Sunscreen ingredients were determined from DrugBank, and sunscreen brands were identified using online product searches. Disproportionality analyses, including proportional reporting ratio, reporting odds ratio, and empirical Bayesian geometric mean were calculated. Of 723 sunscreen products/ingredients, avobenzone/octinoxate/octisalate/octocrylene/oxybenzone had significantly disproportional alopecia reports by all three analytical methods (7 reports, ROR = 22.971 (1.784, 6.018), PRR = 19.832 (1.845, 5.474), EBGM = 19.832 (1.543, 5.777)). No other ingredient combinations or branded products had disproportionate alopecia reports compared to general event reporting. As disproportionality measures do not estimate risks and do not guarantee product safety, future studies should assess temporal associations between sunscreen product use and alopecia development. Meanwhile, the lack of association of many common sunscreen ingredients and combinations (such as preparations containing zinc oxide and titanium dioxide) with reports of alopecia may reassure patients regarding their choices for sun protection despite hair loss concerns.

0349

A longitudinal study of stress and depression in patients with hidradenitis suppurativa

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Hidradenitis suppurativa (HS) is associated with significantly increased anxiety and depression. However, it remains unknown whether these psychosocial effects fluctuate with changes in HS disease activity. We aimed to characterize the association between psychosocial outcomes and disease activity in Hidradenitis Suppurativa in a prospective longitudinal cohort. Patients with HS were recruited from Stanford Healthcare Dermatology clinic between September 2023 and December 2024 (IRB 68654). Patients completed weekly questionnaires for up to 16 weeks, including self-reported measures of lesion count, pain, flare status, HS severity, medications, quality of life measures, stress, and anxiety. Psychosocial outcomes were assessed using the Patient Health Questionnaire 2 (PHQ-2) and Generalized Anxiety Disorder 2 (GAD-2) questionnaires. Ninety-four patients with HS were enrolled in the study (average age: 33 years, range: 18-68, 79.8% female, 16% male, and 4.3% non-reporting). A total of 951 surveys were completed, with 531 self-reporting a flare. 16% of the population reported a GAD-2 score > 3, indicating likely generalized anxiety disorder. 19% of the cohort reported a PHQ-2 score >3, indicating likely major depressive disorder. PHQ-2 scores were 1.44X greater in the flaring group compared to the non-flaring group (2.11 vs 1.47, $p< 0.001$). Similarly, GAD-2 scores were 1.58X greater in the flaring group compared to the non-flaring group (1.76 vs 1.11, $p<0.001$). These findings demonstrate a significant association between HS flares and worsened psychosocial outcomes, including anxiety and depression. This underscores the need for comprehensive management of HS flares to reduce the psychosocial impact in patients with HS. Acknowledgements: Study surveys were collected under a collaborative grant from UCB Pharma, Brussels, Belgium. We would like to thank Helena Andres-Terre, Tanja Tran, Ingrid Pansar, Matladi N. Ndlovu from UCB Pharma for their contributions to this study.

0350

Impact of switching janus kinase inhibitors in the treatment of severe alopecia areata

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Alopecia areata (AA) is an autoimmune condition with limited treatment options for severe cases. Janus kinase inhibitors (JAKis) have improved treatment outcomes for severe AA, but data on switching between JAKis, whether due to lack of efficacy or insurance reasons, is limited. This study evaluated the impact of switching JAKis in patients with severe AA. A retrospective review was conducted on severe AA patients who switched JAKis after at least 6 months of treatment with an initial JAKi. Outcomes were assessed using Severity of Alopecia Tool (SALT) scores. Eight patients (75% female, mean age 45 years) were included, with AA duration of current episode of 6.6 years (1.5–10) and a mean baseline SALT score of 93 (70–100). Patients received their initial JAKi for an average of 24 months (6–65), including baricitinib (n=4), deuruxolitinib (n=1), ruxolitinib (n=1), and tofacitinib (n=2). Six patients switched due to lack of efficacy, and two due to insurance denial. Using SALT ≤20 as a cutoff for response, three patients (37.5%) achieved clinically meaningful improvement after switching JAKis, with a mean SALT reduction of 72. Two patients showed minimal improvement, and one showed no improvement. Notably, two patients worsened after switching JAKis due to insurance denial, despite initial improvement on tofacitinib (SALT 20, 25); their SALT scores increased to 50 and 35 after switching. Of three patients who switched to a third JAKi, none attained a SALT ≤20, though two showed some improvement. This study demonstrates that switching JAKis can benefit some severe AA patients, with 37.5% showing meaningful regrowth. Notably, two patients denied tofacitinib coverage after significant regrowth experienced worsening AA when switched due to insurance restrictions, highlighting the importance of patient advocacy in these cases. Limitations include the small sample size, retrospective design, and severity of AA at baseline. A multi-center study is underway to include a larger, more diverse population.

0351

Decreased incidence of acanthosis nigricans in patients with obesity taking GLP-1 agonists

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This retrospective cohort study evaluates whether patients with obesity taking GLP-1 agonists have decreased incidence of acanthosis nigricans compared to matched controls taking metformin, a common systemic treatment for AN. Insulin resistance and subsequent hyperinsulinemia have been shown to be linked to the epithelial changes characteristic of obesity-associated AN. TriNetX data between 2005 and 2025 was used to analyze the risk of developing AN after an obesity diagnosis and starting an insulin sensitizer, either a GLP-1 agonist or metformin. Metformin has previously been shown to be effective in AN prevention which informed this study's comparison against the newest generation of insulin sensitizers, GLP-1 agonists. Patients were stratified by BMI into obese (BMI 30-40) and severely obese (BMI >40) groups. Analyzed cohorts were propensity matched to control for sex, current age, isotretinoin use, insulin use, and type 2 diabetes diagnosis. Patients diagnosed with AN and with a BMI >=30 were included. Patients with rare diseases that have been demonstrated to lead to AN, with conditions that are contraindicated for GLP-1 agonist use, or with an AN diagnosis prior to starting an insulin sensitizer were excluded. Risk ratios were calculated and evaluated for statistical significance. Patients with BMI 30-40 (n=348,372) showed 38.5% reduced risk of developing AN after starting GLP-1 agonists (RR=0.615, 95% CI=(0.578, 0.654)) and patients with BMI >40 (n=191,456) showed 29.8% reduced risk of developing AN after starting GLP-1 agonists (RR=0.702, 95% CI=(0.655, 0.752)). The ages of each cohort were 54.7±14.8 (BMI 30-40) and 52±17 years (BMI >40). Both sets of cohorts were predominantly female (67-69%). This study demonstrates that GLP-1 agonist use is associated with lower incidence rate of acanthosis nigricans in obese patients compared to matched controls taking metformin. Future studies can further evaluate this association in an experimental setting.

0352

Medical student perspectives on the role of artificial intelligence in dermatology: Implications for specialty choice and ethical concerns

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Artificial intelligence (AI) is playing an increasingly prominent role in healthcare, especially in specialties reliant on visual diagnostics like dermatology. This study explores how medical students perceive AI's role in dermatology, its ethical implications, and its influence on specialty choice. A cross-sectional survey of 230 U.S. medical students gathered perspectives on AI, including perceived risks, benefits, and concerns about bias. Most respondents (95%) had no formal AI education, though 65% agreed all medical students should receive AI training. Despite limited exposure, students were generally optimistic about AI's potential: 91% disagreed that AI will replace dermatologists, and 82% agreed it will augment capabilities and improve efficiency. Importantly, 84% disagreed that AI advancements would deter them from choosing dermatology. However, ethical concerns emerged as a key theme. 48% of students expressed concern about AI's ethical implications in dermatology, and 54% worried AI could exacerbate existing biases, particularly related to race and ethnicity. One student noted, "A lot of technological models that require human samples don't take darker skin tones into account…AI will likely reflect the bias of its developers." Concerns also included AI being used by non-dermatologists, potentially leading to missed diagnoses and poorer patient outcomes. These findings suggest that while students recognize AI's potential to improve dermatologic care, they remain cautious about its ethical implications, particularly regarding bias in diagnosing skin conditions in patients of color. The lack of AI education in medical curricula contributes to this apprehension. Addressing these concerns through AI-focused education can better prepare future dermatologists to identify and mitigate bias in AI tools, ensuring advancements contribute to more equitable and inclusive care.

0353

A dark side of calcium channel blockers: Increased risk of stasis dermatitis

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Stasis dermatitis (SD) is an eczematous condition linked with chronic venous insufficiency. Given the increasing use of calcium channel blockers (CCBs) for hypertension, concerns have emerged regarding their role in exacerbating or inducing SD through peripheral edema. This study investigates the association between CCB use and the development of lower extremity SD in patients with essential hypertension. A retrospective cohort design was employed using the TriNetX database, comparing SD outcomes between CCB users (ATC: C08) and non-users with essential hypertension (ICD-10: I10). To reduce confounding, CCB users were matched 1:1 with controls using propensity score matching, adjusting for age, sex, race/ethnicity, and chronic venous insufficiency risk factors. SD was identified via ICD-10-CM codes for chronic venous hypertension with inflammation (I87.321, I87.322, I87.323). CCB users demonstrated a significantly higher risk of lower extremity SD compared to non-users: right lower extremity (RR: 1.56, 95% CI: 1.236–1.970, p = 0.0002), left lower extremity (RR: 1.24, 95% CI: 1.008–1.523, p = 0.041), and bilateral lower extremity (RR: 1.43, 95% CI: 1.197–1.708, p < 0.0001). One potential mechanism is CCB-induced edema via preferential arteriolar dilation without corresponding venous dilation, leading to venous stasis, inflammation, and subsequent skin changes. If SD develops, management may involve reducing the CCB dose, switching to antihypertensives with a lower edema risk, or adding venodilators like ACEs or ARBs. Limitations include potential ICD-10 misclassification of SD and residual confounding despite matching. Future research should explore whether mitigating venous hypertension in CCB users can reduce SD risk and investigate the timeline for SD improvement after cessation of CCBs.

0354

Clinical outcomes judged by dermatologists, primary care, and a large language model

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Many skin diseases are evaluated qualitatively, complicating efforts to study clinical outcomes. Large language models (LLMs) offer a method to extract outcomes from unstructured medical records. To explore this approach, we developed an online platform to present case histories and associated skin images of 5 different inflammatory and neoplastic skin disease categories at an initial and subsequent visit. For each case, participating VA dermatologists (N=28) and primary care providers (N=51) selected 1 of 5 outcomes (Resolved, Improved, Unchanged Clinically Significant, Unchanged Not Clinically Significant, and Worse), and simulated writing a progress note as if charting the subsequent visit. Participants generated 267 responses spanning 50 distinct scenarios. When the real-life clinical course was used as ground-truth, dermatologists and PCPs correctly assessed the outcome in 62% and 61% of cases, respectively (p=0.9). Accuracies improved to 87% and 83%, respectively, with Unchanged categories combined and Improved/Resolved categories separately combined (p=0.5). A participant's self-assigned outcome was then used as ground-truth to evaluate a commercially available LLM used without additional instructions or training for each simulated progress note. It correctly assigned outcomes to 49% of dermatologists' and 48% of PCPs' notes (F1 scores 0.47 and 0.49, respectively). With Unchanged and Improved/Resolved outcomes separately combined, LLM accuracy on notes by dermatologists and PCPs increased to 68% (F1 = 0.64) and 71% (F1=0.70), respectively. Our results suggest dermatologists and PCPs evaluate outcomes similarly and the zero-shot LLM performance suggests that, with further specific guidance and fine-tuning, LLMs may be effective tools to classify dermatologic outcomes in the medical record.

0355

Genotype-phenotype study of 149 epidermolysis bullosa simplex patients in North America

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Background: Epidermolysis Bullosa Simplex (EBS) is the most common type of EB, with varying severity, from localized blistering on extremities to widespread skin and mucosal wounds. Method: Prospective cohort study of 152 genetically confirmed EBS patients from the Epidermolysis Bullosa Clinical Research Consortium (EBCRC). Results: The mean age of subjects was 11.2 years, 51% were <10 years old. Mean age at diagnosis was 19 days and 55% had a family history. There was an equal number of males: females, 73% were White (12% Hispanic), 9% Black, 4% Asians, 2% Middle Eastern, and 1% American Indian. The most common clinical subtypes were generalized severe or intermediate (22%), localized (20%), and EBS with muscular dystrophy (5%). Most pathogenic variants occurred in KRT5 (28%) and KRT14 (29%), followed by PLEC (15%). 80% were missense, 5% nonsense, and 10% frameshift. Nonsense variants were found in 12% of generalized cases but none in localized EBS (P=0.05). Keratin intermediate filaments consist of 3 domains: a central α-helical "rod" domain flanked by head and tail domains. Almost all KRT14 variants occurred in the α-helical domain (97%), in contrast to KRT5 variants (49%, P=0.001). We found common hotspots (KRT14 p.R125C and p.R125H), but also novel pathogenic variants (KRT14 p.A127P and p.E411G). Nonsense variants frequently lead to severe clinical manifestations; however, for missense variants, the location of the variant plays a more critical role than the specific amino acid change in KRT5 or KRT14. Ongoing genotype-phenotype analyses will enhance our understanding of the underlying genetic mechanisms and may aid in disease prognosis. To our knowledge, this is the largest genotype-phenotype study in a diverse population from North America.

0356

Contact and consequence: Understanding hand and foot dermatitis through patch testing

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Hand and foot dermatitis (HFD) significantly affects quality of life and presents diagnostic challenges due to overlapping features with other dermatitis. Patch testing is essential for identifying allergens, enabling targeted management. This descriptive study analyzed clinico-epidemiological patterns of HFD and correlations with patch test results using standard patch testing kits and additional allergens, including vegetables and detergents, for enhanced diagnostic sensitivity. Seventy patients with HFD were recruited from a dermatology outpatient clinic. Detailed anamnesis, including occupational exposure, and clinical examination were performed to categorize morphological patterns. Patch testing followed standardized protocols, and results were interpreted using International Contact Dermatitis Research Group (ICDRG) criteria. Statistical analyses evaluated correlations between patch test positivity, clinical patterns, and occupational exposure. The study population comprised 55.7% males and 44.3% females, with non-skilled manual labor (40%) as the predominant occupation, followed by homemakers (24.3%). Hyperkeratotic eczema was the most common morphological pattern (40%), followed by housewives' eczema (15.7%). Patch test positivity was observed in 50% of hyperkeratotic eczema and 81.8% of housewives' eczema. The most common allergens were potassium dichromate (11.4%) and detergents (5.7%), reflecting occupational and domestic exposures. No significant correlation was found between test results, occupational category, or morphological pattern ($p > 0.05$). Patch testing is vital for diagnosing hand and foot dermatitis, with potassium dichromate and detergents as key allergens. Expanding allergen panels and enhancing patient education on avoidance can significantly improve outcomes and quality of life.

0357

Identifying the factors that cause vitiligo: The VIGOR study

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Despite a prevalence of 1-2%, the factors that initiate vitiligo are largely unknown. Longitudinal studies of at-risk individuals can be a powerful tool to discover disease processes. However, recruitment, retention, and observation/specimen collection are a challenge, especially with a geographically diverse study cohort. To address this challenge, we have devised a novel siteless longitudinal study called the Vitiligo Genetics of Onset and Relapse (VIGOR) Study. Our first objective was to develop the methodology to allow us to establish a geographically diverse cohort consisting of individuals with vitiligo and their family members without vitiligo. Participation in the study is done at home, using a custom mobile application (app). The app manages recruitment, consent, at-home sample and survey collection, as well as communication with participants. The VIGOR app was launched on June 10, 2024 and has been used to consent 583 participants from 183 families from 42 US States. To study onset and progression of vitiligo, we have collected saliva samples for whole genome sequencing, allowing us to construct accurate family pedigrees. Additionally, regular collection of health surveys, skin/blood samples, and biometric data from FitBit devices is ongoing. Surveys have revealed increased hair dye exposure ($p<0.03$) and strong association with polyautoimmunity ($p<10^{-10}$) in individuals with vitiligo compared to nonaffected relatives. Compliance rates have been high for data collection by sampling devices (95.6%) and surveys (96.6%), giving us confidence that we will be able to successfully monitor environmental triggers and changes in biomarkers to allow us to better predict, and ultimately prevent, vitiligo. Continued enrollment efforts to increase cohort size are underway. In conclusion, we have successfully demonstrated the feasibility of a siteless longitudinal study to identify and monitor factors associated with autoimmunity in the skin.

0358

Inflammatory markers in generalized pustular psoriasis (GPP): An immunohistochemical analysis

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GPP is a rare potentially life-threatening disease characterized by the presence of sterile pustules on erythematous skin. Although clinically different from psoriasis vulgaris (PV) it shares some features of PV such as the spongiform pustule. The cause of GPP is unknown; triggers include infections, corticosteroid withdrawal and genetic factors such as a mutation of the IL-36 RN antagonizing IL36-G and -A. Antibody treatment with the IL-36R antagonist spesolimab has shown efficacy. The role of other inflammatory factors is not well understood. To further elucidate the pathogenesis we performed an immunohistochemical study in 13 patients with GPP and in corresponding skin of 6 healthy control individuals. Skin biopsies were stained with antibodies against HLA-DR, IL-8 recruiting neutrophils, IL-17A, IL-17F, IL-23, IL-36 gamma, the chemokine CXCR3 (CD-183) in IFN-induced inflammation, tyrosine kinase (Tyk) phospho-di-esterase (PDE) 4B, and the T-cell transcription factor FOX-P3 and JAK-3. The stained slides were photographed in 20x enlargement with the Leica DFC 295 microscopic system and digitally analyzed with the ImageJ Plugin-IHC Profiler scanning 82364 square micrometers. Stained cells ranged from 50 to 365 per visual field. The two-sided t-test served for statistical analysis. In GPP compared to healthy controls, we found the following significant increased staining: Fox-P3 ($p<0.00001$), IL-36 gamma ($p<0.001$), IL-17F ($p<0.004$), IL-8 ($p<0.03$). By contrast, there was significantly increased staining for IL-23 in normal skin ($p<0.009$). The remaining differences failed to reach statistical significance. These results indicate that compared to normal skin there is a lack IL-23 in GPP, whereas IL-36 gamma, the transcription factor Fox-P3, IL-17-F and IL-8 are the dominant cytokines in the skin of GPP. Our results provide a basis for successful treatment in generalized pustular psoriasis.

0359

Correlation between psoriasis and urolithiasis:A retrospective and mendelian randomization study

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The study investigated the association using retrospective and Mendelian randomization (MR) study methods. The retrospective study collected data from patients diagnosed with psoriasis vulgaris from November 2024 to the present, and analyzed their clinical manifestations and renal ultrasound characteristics, while the MR study collected data from 483,174 patients with psoriasis and 484,598 patients with urolithiasis from the Genome-Wide Association Studies (GWAS) database, and used the Inverse Variance Weighted (IVW) method to investigate the relationship between psoriasis and urolithiasis. IVW method was used as the main analysis method to evaluate the causal relationship between psoriasis and urolithiasis by P value, odds ratio (OR) and 95% confidence interval (CI) in IVW. Leave-one-out method was used for sensitivity analysis, MR-Egger method for multiplicity analysis, and Cochran Q for heterogeneity detection. The results showed that among the 66 patients included in the retrospective study, 37 were male and 29 were female, with a mean age of 47.21±7.16 years, and the incidence of urolithiasis was 25.82%, which was significantly higher than the incidence of urolithiasis in the healthy population (P<0.05). The results of MR showed that there was a positive causal relationship between psoriasis and urolithiasis (P=0.0357); reverse MR analysis showed that urolithiasis did not increase the risk of psoriasis. The results of the sensitivity analyses were robust, the funnel plots were not biased, and the results were free of heterogeneity, pleiotropy, and reverse causality (all P>0.05). The results of this study provided evidence for a causal relationship between psoriasis and the development of urolithiasis, and that psoriasis might increase the risk of developing urolithiasis, but no evidence was found that urolithiasis leads to an increased risk of psoriasis.

0360

Clinical efficacy of the combination treatment of psoriasis vulgaris with crisaborole ointment in comparison with calcipotriene ointment

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The present study was designed to observe the clinical efficacy and evaluate the safety of the combination of Crisaborole ointment and Captopanol ointment in the treatment of psoriasis vulgaris by self-monitoring. A total of 30 subjects were included in the study, including 16 males and 14 females with a mean age of 42.00±8.94 years. The left upper or lower extremity was designated as the treatment group and the right side as the control group. The control side (control group) was treated with topical Crisaborole ointment both in the morning and in the evening, and the treatment side (treatment group) was treated with topical calcipotriol ointment in the morning and topical Crisaborole ointment in the evening for a total of 4 weeks. Clinical symptoms were scored and adverse reactions were recorded at weeks 1, 2, and 4 of treatment, respectively. The results showed that after 1 week of treatment, the clinical symptom scores of both the control and treatment groups were significantly decreased compared with the pretreatment period (P<0.05), but the difference between the two groups was not statistically significant (P>0.05); the PASI scores of both groups were significantly decreased compared with the pretreatment period after 2 weeks and 4 weeks of treatment (P<0. 05), and the overall therapeutic efficacy of the treatment group (with an effective cure rate of 38.46%) was better than that of the control group (28.91%) (P<0.05); the overall incidence of adverse reactions in the treatment group was lower than that of the control group (P<0.05). The results of the study showed that the efficacy of Crisaborole Ointment combined with Captopanol Ointment in the treatment of psoriasis vulgaris was remarkable, which could effectively alleviate the clinical symptoms and improve the skin condition with good therapeutic effect and safety, and provided a new and effective choice for the treatment of psoriasis.

0361

Chemotherapy-induced alopecia in ovarian cancer patients: A systematic review of platinum-based combination regimens

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Ovarian cancer is the fifth most common cancer among women, with an estimated 19,680 new cases projected in 2024. Chemotherapy with platinum-based compounds (PB), such as carboplatin and cisplatin, remains the standard of care, often combined to other agents to enhance therapeutic efficacy. However, combination regimens significantly increase the risk of side effects, including chemotherapy-induced alopecia (CIA). A systematic review of studies indexed on PubMed investigating PB combination regimens in ovarian cancer cohorts was undertaken, focusing on CIA incidence and severity. Our analysis identified triple combination therapies as causing the most severe alopecia (grade 3-4) with cisplatin, paclitaxel, and Ionidamine leading to severe CIA in 94% of patients. Similarly, the combination of cisplatin with cyclophosphamide and adriamycin, and cisplatin with gemcitabine and paclitaxel, resulted in severe alopecia in 76% and 43.5% of patients, respectively. PB-paclitaxel combinations resulted in CIA (grade 1-4) in as high as 90% of patients, while PB-cyclophosphamide regimens resulted in alopecia in up to 79%. In contrast, PB-gemcitabine combinations resulted in a lower incidence of moderate alopecia (14.3-21.4%), while PB combined to pegylated liposomal doxorubicin exhibited the lowest rate (7-34%). Notably, mild-to-moderate alopecia was reported in all patients treated with docetaxel and PB combination therapy. Further studies should explore alternative dosing strategies, evaluate emerging low-toxicity regimens, and assess supportive care measures aimed at minimizing the severity of alopecia. Ultimately, improving the management of CIA can enhance not only the physical well-being but also the emotional and social quality of life of ovarian cancer patients.

0362

Patient-reported preferences for IL-17 and IL-23 inhibitor dosing frequencies in psoriasis management

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Biologic dosing frequency is a key concern among psoriasis (PsO) patients and physicians, yet dosing optimization remains a challenge. This study evaluates patient dosing preferences for IL-17 and IL-23 inhibitors, risankizumab (RZB) every 12 weeks, guselkumab (GUS) every 8 weeks, and ixekizumab (IXE) every 4 weeks, in managing PsO. This phone survey study evaluated 87 adults on RZB (n=29), GUS (n=35), or IXE (n=23) from 2019 onward at two clinical sites. Patients were assessed for: 1) baseline PsO bothersome severity (0- never bothered to 2-very bothered); 2) current dosing frequency satisfaction (0- very unsatisfied to 4-very satisfied); 3) frequency of PsO flares (0- never to 3- all the time); and 4) preferred doing frequency (0- less, 1- no change, 2- more). Most patients were males (57.5%) with an average age of 54.1 years and an average treatment duration of 19.0 months. At baseline before treatment, 87% were 'very bothered' by their PsO. After treatment, 86% were either '3-somewhat' or '4-very satisfied' with their current dosing schedule, with no significant differences between each drug (p=0.7). Although 39% of IXE users desired less frequent dosing compared to 21% of RZB and 26% of GUS patients, differences in satisfaction were not statistically significant, likely due to the limited sample size (OR 2.36; 95% CI 0.70–8.45; p = 0.2). The higher proportion of IXE patients seeking "less frequent dosing" suggests that injection frequency influences patient comfort and treatment burden. Previous studies report that generally, patients prefer lower frequency dosing schedules which improves adherence and quality of life. While this preliminary study supports those conclusions, further research is required to elucidate the impact of dosing frequency on long term outcomes.

0363

Examining the link between psoriasis and mental health using the U.S 2023 National Health Interview Survey

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Psoriasis (PsO) is a chronic inflammatory skin condition that has been associated with a range of psychiatric disorders including depression and anxiety. Although existing studies have established this association, the availability of national-level data remains limited and outdated. This study aims to utilize recent data from a nationally represented database to elucidate the psychological impact of PsO. This retrospective cohort analyzed the 2023 National Health Interview Survey, consisting of participants with self-reported PsO. Demographic differences among those with and without PsO were analyzed using Wilcoxon rank sum and chi-square tests. Adjusted logistic regression models with outcomes for life satisfaction, depression, anxiety, and use of medication/therapy for mental health reasons were performed. Weighted analysis showed 7,424,788 participants with self-reported PsO. Included participants were equally represented by men (51%) and women (49%) and predominantly identified as White (79%), followed by Hispanic (11%) and Black (3.9%). Compared to those without PsO, those with the condition had over twice the odds of reporting dissatisfaction with life (OR = 2.07 95% CI: 1.52–2.83, p<0.001) and anxiety (OR = 2.06, 95% CI: 1.68–2.53, p<0.001). They were also significantly more likely to experience depression (OR = 1.80, 95% CI: 1.52–2.14, p<0.001) and to use mental health therapy or medication (OR = 1.76, 95% CI: 1.42–2.18, p<0.001). Consistent with previous studies, our national analysis shows that PsO imposes a significant mental health burden doubling the risk for anxiety and life dissatisfaction and increasing the likelihood for depression and mental health treatment use. Therefore, it is important to integrate care methods that address the physical and psychological effects of PsO.

0364

Trends and patterns among influential tape stripping publications (2000–2024)

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Tape stripping is a non-invasive procedure that involves sampling the epidermis with adhesive tape to collect samples for analysis. While numerous studies have been conducted using this method, the patterns and trends within this body of research remain unexplored. This study seeks to address this gap and describe the current state of the literature by analyzing the most influential publications in the field. The top 100 most cited publications from 2000-2024 were identified through the Scopus database using the search term "tape stripping." Categorical factors were evaluated using univariate ANOVA, while continuous variables were analyzed with Pearson correlations in relation to total citation counts. Variables that showed significant results in these initial analyses were then included in a multivariate linear regression model to determine their independent effects on citation counts. Between 2000-2024, the top 100 most cited papers were published in 50 journals, with the most cited papers published 2000-2002. Articles accounted for 92% and review papers accounted for 8% of the publications. There were 49 male and 48 female first authors, whereas there were 75 male and 21 female senior authors. The top 10 most cited papers account for 18.8% of all citations among the top 100 most cited papers since 2000. Factors that significantly influenced citation count included senior author H-index (p=0.0084), year published (p=0.0066), and study focus, particularly stress related (p=0.0011). Our study performed a bibliometric analysis of papers published on tape stripping, shedding light on the growing topic in the literature. Gender disparities were noted among senior authors. Key factors influencing citations included the year published, study focus, and senior author H-index.

0365

Internet-based recruitment for online survey characterizes hidden populations of hidradenitis suppurativa patients

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Hidradenitis suppurativa (HS) is a prevalent, debilitating, inflammatory skin disease. Most HS research is conducted in cohorts that are recruited through clinical services. However, high rates of unemployment and disability among individuals with HS may deter engagement with healthcare services, particularly in the US where health insurance is tied to employment. This calls into question the generalizability of HS research using clinic-based sampling. To address this, we recruited potential participants through Google Adverting to complete an online survey that assessed for potential HS symptoms and comorbidities. Over three months, 2,147 individuals clicked on advertisements directing them to the survey. Of these, 407 matched the inclusion criteria, 109 consented to participate, 106 began the survey, and 73 completed the survey. Among those who completed the survey, 97.3% consented to be recontacted for future research. Eligibility rate was low (18.9%), consent rate was moderate (26.8%), and completion rate was high (68.9%). Analysis of self-reported comorbidity data reveals notable divergence in the prevalence of several comorbidities between internet and clinical cohorts: 24.7% vs 34.3% for hypertension; 50.9% vs. 11.6% for obesity; and 65.8% vs. 4.2% for alcohol consumption, respectively. Additionally, 13.6% of internet respondents assigned female at birth reported polycystic ovarian syndrome, compared to 4.0% in clinic-based cohorts. Limitations include the use of self-reported data without validation, which we are addressing with our current study. These findings suggest a lack of generalizability between clinical and internet cohorts, indicating the need for diverse recruitment methods.

0366

Frequency and characteristics of delayed onset of muscle symptoms in classic dermatomyositis

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Amyopathic dermatomyositis (ADM) is a subset of DM in which cutaneous findings occur without muscle disease for >6 months after diagnosis. However, there is limited data on the mean time to onset of muscle symptoms in classic DM (CDM). Differentiating ADM and CDM may affect treatment, screening for comorbidities including malignancy and interstitial lung disease, and clinical trial inclusion. We performed a retrospective cohort study of adult DM patients at an academic tertiary referral center to determine the mean time to onset of muscle symptoms in CDM and characterize the presentation of patients who develop muscle symptoms >6 months after diagnosis. Patients were reviewed to confirm diagnostic and demographic details, including the timing of muscle symptom onset relative to first cutaneous or pulmonary symptom onset. 223 patients with DM were identified, of which the majority had CDM (172; 77%). 154 CDM patients had a clearly identifiable date of symptom onset. Median time to muscle symptoms was 0 months, with 24 (15.6%) developing muscle symptoms >6 months after first symptom onset. The onset of muscle symptoms in the delayed group ranged from 6.4 months to 42.4 months (median 13.3 months). Those with late onset muscle symptoms did not differ demographically from typical CDM or ADM patients, but they experienced a higher rate of ILD (33%) than either typical CDM (29%) or ADM (18%) patients and lower rate of DM-related death (0%) than either typical CDM (11%) or ADM (5.8%) patients. Our results suggest that even patients diagnosed with ADM should be monitored for muscle weakness and pain. This study sheds further light on a subpopulation of DM patients with potentially disparate outcomes from either CDM or ADM, which could affect counseling, treatment, and clinical trial inclusion.

0367

Exploring diagnostic patterns of physician diagnoses in vulvar lichen sclerosus (VLS)

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VLS is a chronic inflammatory dermatosis of the anogenital region characterized by pruritus and changes to the skin texture that can increase risk of developing squamous cell carcinoma. VLS patients often experience delays in diagnosis and frequent misdiagnoses. This study examined the diagnostic pathways for VLS among patients, highlighting delays and the involvement of different specialties. An anonymous, electronic survey was distributed online to r/lichensclerosus on Reddit and the Lichen Sclerosus Support Group on Facebook. Respondents who were over 18 years old, spoke English, and reported a diagnosis of VLS by a licensed physician were included. From 82 respondents, a majority of patients (55; 67.1%) were diagnosed by gynecologists, followed by primary care providers (PCPs; 17; 20.7%), dermatologists (8; 9.8%), and other specialties (2; 2.4%). 72/82 participants sought medical care for their symptoms while 10/82 had their VLS discovered on a routine exam. Those who had their VLS diagnosed on a routine exam were all diagnosed by either gynecologists (7/10) or PCPs (3/10). 49/82 (59.8%) of respondents consulted more than one physician, with 33/82 (19.5%) seeing at least three different providers before receiving a diagnosis. Notably, of the 8 patients who were diagnosed by dermatologists, 50% saw dermatologists as the 3rd physician or more. The 2 patients who consulted dermatology as the initial provider received an immediate accurate diagnosis. Ultimately, most of our patients received diagnoses of VLS from PCPs or gynecologists, rather than dermatologists. Furthermore, patients are often diagnosed by dermatologists only after seeing additional providers, and none of our patients were diagnosed by dermatologists on routine exams. Our study, therefore, highlights an opportunity for dermatologists to enhance their role in diagnosing and managing VLS and to consider incorporating regular genital examinations into practice to help reduce time to diagnosis and improve patient care.

0368

Swellable microneedle patch for high sensitivity analysis of cytokines in dermal interstitial fluid: Insights from a pilot atopic dermatitis clinical trial

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Atopic dermatitis (AD) is associated with dysregulated T helper (Th) cell responses, particularly Th1, Th2, Th17, and Th22. Although AD is clinically evident in the epidermis, its immunopathogenesis primarily originates in the dermis, which hosts a network of lymphatic and blood vessels and contains the majority of the Th cell populations. Thus, Th cell-derived dermal biomarkers could potentially enhance AD severity assessment when used alongside conventional analyses like SCORAD. However, current sampling methods, such as phlebotomy, fail to capture localized dermal immune changes, while biopsies, though enabling localized sampling, are invasive and hinder participation in trials. To address this, we developed a low-cost swellable microneedle (MN) patch that painlessly collects large volumes of dermal interstitial fluid (ISF). In a pilot study of five moderate-to-severe AD patients, cytokine profiles from lesional (L) and non-lesional (NL) skin collected with MNs were compared to serum (SE) and tape strips (TS) using Luminex MAGPIX to assess 40 biomarkers. Participants reported minimal pain during MN application and removal, with 80% rating it below 2 on a 1-10 scale (average score: 1.4), indicating that MNs (1400 µm height) avoid nociceptor activation. The MNs detected 98% of the tested cytokines and demonstrated superior sensitivity in identifying changes in Th-related cytokines (IL-4, IL-5, IL-10, and IL-17A) from NL to L skin. Notably, only MN-derived profiles from L skin correlated positively with SCORAD scores for Th2 and Th17 cytokines. Conversely, TS showed no positive correlations with SCORAD for any tested cytokine, while only GRO-α, RANTES, and MDC from SE biomarkers correlated positively with SCORAD, highlighting their inability to capture dermal Th cell responses. This study demonstrates that MNs enable high-sensitivity cytokine analysis from dermal ISF, offering a promising approach for AD monitoring and personalized care.

0369

Pressure ulcer closure: Impact of demographics, spinal cord injury, and wound characteristics

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Introduction: Pressure ulcers (PUs) are a significant dermatological concern, particularly in patients with limited mobility. This study analyzed factors influencing PU closure outcomes, focusing on spinal cord injury (SCI) history, demographics, and pre-operative wound characteristics. Methods: In a prospective observational study at a single institution, 38 patients with stage III/IV PUs undergoing surgical debridement and closure were evaluated. Data on wound characteristics, complications, and healing outcomes were collected pre-operatively and at 14 days, 1 month, 6 months, and 1 year post-operatively. Results: Patients with SCI (36.8%) exhibited higher post-operative complications at post-operative day 14 (POD14) (mean 1 vs. 0.36, $p < 0.05$), with wound dehiscence being most common. They also had an increased risk of open wounds at POD14 (relative risk [RR] = 1.4, $p < 0.05$) and 1 month (RR = 2.18, $p < 0.05$), though this was not observed at 6 months or 1 year. Demographic analysis revealed that Black patients (23.6%) had longer initial wound lengths compared to others (7.65 cm vs. 5.12 cm, $p < 0.05$). Additionally, wound location significantly impacted outcomes; sacral wounds had higher complication rates (44% vs. 11% for ischial wounds, OR = 0.16, 95% CI 0.04-0.59) and longer hospital stays (mean increase of 1.7 days, $p = 0.04$). Larger wound volume was associated with lower closure rates at POD14 ($p = 0.006$). Conclusion: These findings underscore the need for personalized dermatological care strategies, particularly for patients with SCI, larger wound volumes, and sacral wound locations. Addressing demographic disparities is crucial to improving PU management and patient outcomes.

0370

Age-dependent sex disparity in cutaneous melanoma: A possible role of androgen receptor

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Comparing to women, men are more susceptible to cancer in general, including higher incidence rates and higher mortality rates. For cutaneous melanoma (CM), this discrepancy is dependent on age. Younger women and older men are more susceptible to CM. The mechanism is not fully understood. Using both epidemiological and molecular biology approaches, we discovered an important role of androgen receptor in CM development and cell proliferation, coordinate with testosterone levels and estrogen levels. Testosterone, in contrast to a general perception, in fact is protective against CM development. This is coordinated with our finding that increased testosterone levels in cell culture can speed up DNA damage repair (8-OxoG and PARP1 as markers). However, once the tumor is initiated, testosterone and AR can stimulate melanoma cell proliferation and even confer drug resistance. Using AR over-expression and an AR-degrading agent we have developed, we demonstrated these roles *in vitro* in melanoma cells. If these results are further validated at molecular levels *in vivo* and at population levels in human cohorts, we can develop specific preventive screening methods and new therapeutic modality.

0371

Summarizing current core assessment domain establishment efforts

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International efforts coordinated by the Core Outcome Measures in Effectiveness Trials (COMET) Initiative have sought to understand what outcomes are critical for adequative assessment in a given setting (clinical trials, etc). One of the initial stages of this process is understanding what domains are important to measure from the perspective of patients and experts. Using COMET-Initiative's database of current efforts we summarized domains evaluated and how recommendations for these varied across patients and clinicians. We identified 25 studies that specifically sought to identify core assessment domains across a broad range of inflammatory and lesional skin conditions. The domains most often assessed included clinical signs/symptoms (19/25), quality of life (16/25), symptoms (15/25), maintenance of effect (14/25), and adverse events (14/25). When comparing patient and expert scoring, patients tended to numerically score mental health and emotional impact-related domains higher. Clinicians numerically scored clinician assessments higher. Common final accepted domains included: quality of life, symptoms, clinical signs/appearance, disease maintenance, global assessments, adverse events, and treatment satisfaction. In the clinical setting, efforts should be made to assess core domains, but these must be efficient and feasible. These summarized data can guide these efforts by highlighting common domains that cross-cut multiple diseases and highly favored by patients and clinicians. Likewise, these may highlight domains that may be of clinical importance but weren't accepted such as psychological well-being which tended to be more recommended by patients than clinicians.

0372

Characterization of skin attributes associated with menopausal stages and fitzpatrick skin types

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Women are known to experience accelerated visible skin aging between their mid-40s to early 60s due to the physiological changes associated with menopause. Understanding these changes is essential for developing strategies to maintain skin health. Here, we examined various skin biophysical parameters across pre-, peri-, and post-menopause women of all Fitzpatrick skin types to characterize these changes. We analyzed 308 women aged 30-65, categorized into pre-, peri-, and post-menopausal groups. Biometric measurements, including Corneometer, TEWL, Sebumeter, and pH probes, were used to assess changes in skin hydration, barrier function, sebum production, and skin pH. Distinct patterns emerged across menopausal stages: an 8% reduction in forehead moisturization between peri- and post-menopausal groups, a 13% reduction in TEWL between peri- and post-menopausal groups, and a 16% reduction between pre- and post-menopausal groups. Additionally, a significant 3% increase in forehead pH was observed between pre- and post-menopausal groups. Forehead sebum decreased notably between stages, with a 16% reduction between pre- and peri-menopausal groups and a 12% reduction between peri- and post-menopausal groups. Fitzpatrick I-III showed a 35% decline in sebum from pre- to post-menopause, whereas Types IV-VI showed no significant changes. These findings underscore the impact of menopausal transitions and skin types on skin aging, highlighting the necessity for targeted skincare strategies that consider both hormonal stages and Fitzpatrick skin types.

0373

VEXAS syndrome: A case of misdiagnosed dermatologic and rheumatologic manifestations in a 77-year-old male

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We present a case of VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) syndrome regarding a 77-year-old Caucasian male. The patient initially presented with widespread dermatitis of unclear etiology with a longstanding history of dermatologic issues for over 10 years. The patient has a history of oral ulcers, diabetes, anemia of uncertain etiology, and lab findings positive for antiphospholipid and double stranded DNA antibodies. Prior visits for his pruritic rashes were suggestive of spongiotic dermatitis or Sweet's Syndrome. Multiple biopsies obtained at separate visits showed findings consistent with both leukocytoclastic vasculitis as well as neutrophilic dermatoses. The patient's symptoms did not resolve despite immunomodulatory and immunosuppressive medications, such as prednisone, dupilumab, and clobetasol. During treatment, the patient was newly diagnosed with relapsing polychondritis, suggestive of VEXAS syndrome. A repeat bone marrow biopsy revealed rare cells with cytoplasmic vacuolization. Such clinical and lab findings led to a diagnosis of VEXAS syndrome, which was confirmed by genetic testing showing a pathogenic mutation in the gene UBA1. The patient was continued on prednisone, hydroxychloroquine, and dupilumab. VEXAS syndrome is a newly described pathological entity that may mimic different systemic rheumatologic disorders associated to myelodysplastic syndrome, such as Sweet's Syndrome. The syndrome has a heterogenous presentation, making diagnosis difficult. Clinical findings of VEXAS syndrome include fever, chondritis, cytopenia, pulmonary infiltrates, neutrophilic dermatosis and vasculitis. As seen in our case, the patient presented with initial vague dermatologic manifestations, but later developed many key findings of the disease.

0374

Skin deep: Unraveling the psychodermatological nexus in psychiatric patients

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Psychodermatology bridges dermatology and psychiatry, examining the relationship between mental health and skin conditions. This study aimed to assess the prevalence and types of dermatological disorders in psychiatric patients and investigate correlations with specific psychiatric conditions. A cross-sectional study was conducted at a tertiary care center with 174 psychiatric patients, comprising 104 males (59.8%) and 70 females (40.2%). Participants underwent dermatological and psychiatric evaluations using standardized diagnostic criteria. The prevalence of dermatological conditions was analyzed alongside psychiatric diagnoses, including schizophrenia, depression, and anxiety disorders. Results revealed that 62% (n=108) of the patients presented with at least one dermatological condition. Infectious skin diseases were noted in 58% (n=50) of patients, with fungal infections comprising the majority (68%, n=34). These infections were prevalent in patients with schizophrenia (38%, n=34, p=0.04), likely attributed to medication side effects, poor hygiene, and self-care deficits. Non-infectious conditions affected 64% (n=56) of the cohort. Eczema was observed in 28% (n=24), while psoriasis accounted for 16% (n=14). Both conditions showed a strong correlation with depression and anxiety (46%, n=40, p=0.01), likely driven by chronic stress-induced immune dysregulation. Psychodermatoses, including delusions of parasitosis, were diagnosed in 22% (n=20), highlighting the interplay of psychological distress and perceived dermatological symptoms. Chronic stress emerged as a key factor exacerbating inflammatory skin conditions. These findings highlight the burden of psychodermatological conditions and underscore the need for integrated dermatological and psychiatric care to enhance patient outcomes.

0375

Racial and facility distance disparities in time to surgical treatment for sebaceous carcinoma

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This study investigates sociodemographic, tumor, and hospital factors associated with delays in time to definitive surgical treatment (TTDS) for sebaceous carcinoma, with the aim of identifying strategies to improve equity in care for this rare but aggressive skin cancer with increasing incidence. This retrospective study analyzed 2004–2021 National Cancer Database, where multivariable logistic regression evaluated characteristics impacting TTDS and multivariable linear regression estimated days contributed to delays. Among 4,496 SC patients identified in the NCDB, 242 (5.38%) were non-Hispanic Black (NHB). NHB patients experienced longer TTDS (10.6 days, P < 0.001) and time to radiation (59.2 days, P < 0.001) compared to non-Hispanic White (NHW) patients, despite living closer to hospitals (P < 0.001). NHB race was associated with higher odds of >90 days TTDS (aOR 1.58; P = 0.022). NHB race, Medicaid insurance, and treatment at academic facilities uniquely contributed 12.70 (p<0.001), 17.72 (p<0.01), and 5.51 (p=0.001) additional days of delay. Distance to the hospital of 40-59 miles and more than 60 miles were also independently associated with 8.97 (p=0.001) and 5.96 (p<0.01) additional days of delay. TTDS disparities for NHB and Medicaid-insured patients highlight inequities in SC care. Novel findings include incorporating facility type and distance when evaluating TTDS. Addressing these disparities through improved transportation programs, outreach to black communities, and increased coordination may enhance timely treatment and SC outcomes.

0376

Retrospective analysis of burn injury trends and outcomes across three African nations using WHO burn registry data

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Burn injuries remain a critical public health issue, particularly in low- and middle-income countries where resources for prevention and management are limited. This study analyzed burn injury characteristics and outcomes in adults aged 18–60 using data from the World Health Organization Burn Registry (2016–2022). Data from Nigeria and Kenya (lower-middle-income countries) and South Africa (upper-middle-income country) were compared to examine burn etiology, mechanisms, management, and the impact of pre-hospital duration on discharge outcomes. A retrospective review evaluated the cause, setting, pre-hospital duration, and discharge condition. Descriptive statistics and ANOVA testing assessed distributions and differences among countries. Flame burns were the most common injury in South Africa (45.3%) and Kenya (38.2%), while electrical burns predominated in Nigeria (42.7%). Most injuries occurred in household settings, with Kenya reporting the highest proportion (62.1%), followed by South Africa (54.8%) and Nigeria (47.5%). Pre-hospital duration varied, with South Africa reporting the longest mean time (7.1 ± 23.8 hours) compared to Nigeria (3.1 ± 9.2 hours) and Kenya (3.9 ± 21.5 hours), showing a trend toward significance (p=0.09). Over 70% of patients across all countries were discharged home without physical impairment. However, longer pre-hospital durations were associated with worse outcomes, emphasizing the need for timely care. This study highlights the influence of economic disparities and healthcare infrastructure on burn care and outcomes. Differences among nations reflect varying healthcare resources and prevention strategies. Targeted interventions, such as improved emergency response systems and burn prevention awareness, are critical to reducing delays and improving outcomes. These findings provide valuable insights for policymakers and global health organizations addressing burn injuries in resource-limited settings.

0377

Clinical studies for lasers in dermatology: A retrospective analysis of spatial distribution and accessibility by race and rurality

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Improving access to dermatological laser clinical studies is essential for driving innovations for an increasingly diverse patient population. However, geographic barriers to access for underserved rural and racial minorities are still prevalent. In this study, the evolving trends in geographic accessibility to dermatological laser clinical studies in the United States in the last two decades were analyzed, particularly on patterns seen among different rural-urban classifications, racial categories, and the post COVID-19 era. Geospatial data on 200 clinical studies extracted from ClinicalTrials.gov was cross-referenced with demographic data from the U.S. Census Bureau. Distances to study sites were computed using the Haversian formula as a measure of geographic accessibility. Trends in accessibility disparities by race and Rural-Urban Commuting Area(RUCA) classification, population coverage, and study count and distribution were analyzed with linear regression analyses and t-tests. Despite an overall incre bhyujhnhhnbhh ase in the number of active clinical studies from 2005 to 2024, y=0.119x-230.267, with x equaling the current year, the analysis revealed significantly greater average distances to the nearest study for rural participants compared to their urban counterparts (p<0.0001). Additionally, Black and American Indians, faced the greatest geographic constraints across all RUCA categories. Geographic accessibility faced a sharp temporary decline in the wake of COVID-19. Barriers to clinical study access disproportionately impacts rural and minority populations, perpetuating existing inequities in healthcare delivery. Strategic clinical trial placement, travel assistance, and telehealth should be implemented to expand and diversify participation among the underserved community. More comprehensive studies are needed to uncover the underlying causes and remedies for disparities in clinical study access.

0378

Population-level analysis reveals increased odds of hypertrophic/keloidal scarring in pemphigus

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The existence of a hypertrophic form of pemphigus, Pemphigus vegetans, has been long appreciated. Moreover, multiple case reports spanning nearly three decades have documented instances of hypertrophic and/or keloidal scarring ("excessive scarring") in individuals with pemphigus. Emerging evidence has implicated the Th2 pathway—long linked to pemphigus pathogenesis—in the development of excessive scarring. Despite these suggestive links, population-level evidence on an association between pemphigus and excessive scarring is lacking. To address this, we conducted a retrospective cohort study using TriNetX's Global Collaborative Network. Our pemphigus cohort was compared to control cohorts identified by the absence of ICD-10 codes for pemphigus and the presence of psoriasis (a non-Th2 disease), atopic dermatitis (AD) (a Th2-mediated disease), or healthy individuals. Comparisons were propensity score-matched for age, gender, race, and ethnicity. The outcome of interest was the ICD-10 code for excessive scarring. Among >12,000 pemphigus patients and >36,000 matched controls, pemphigus patients consistently showed significantly increased odds of excessive scarring when compared to psoriasis (OR=1.645, 95% CI 1.213–2.231), and AD (OR=1.506, 95% CI 1.119–2.026). Compared to healthy controls, pemphigus patients demonstrated a threefold increased odds (OR=3.172, 95% CI 2.155–4.67), suggesting that excessive risk is even higher in pemphigus than other immune-mediated diseases compared to healthy controls. Given that excessive scarring is more frequent among individuals with skin of color (SoC), we stratified our comparison between pemphigus and healthy cohorts by ancestry. We did not find a significant difference (p=0.528) between ancestry-stratified cohorts, however, point estimates modestly preferred elevated risk in SoC patients. Our results underscore a novel, race-independent, link between pemphigus and excessive scarring.

0379

Survival implications of systemic immunosuppression timing, dosage, and duration in immune checkpoint inhibitor therapy: A retrospective multicohort study

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Systemic immunosuppression (sISP) is known to be associated with poor overall survival (OS) in cancer patients treated with immune checkpoint inhibitors (ICIs). This study examined the impact of sISP timing, dosage, and duration on OS among ICI recipients. We identified 13,086 patients from Massachusetts General Hospital, Brigham and Women's Hospital, and Dana-Farber Cancer Institute (MGBD). For independent validation, we included 26,172 patients from the TriNetX network by 1:2 propensity score matching on demographic and cancer-related variables. A computational approach was developed to extract sISP status from medication records and was validated by manual phenotyping. Multivariable survival analyses were performed using Accelerated Failure Time models. Time Ratios (TRs) and 95% Confidence Intervals (CIs) were reported, with TR<1 indicating a shorter OS time. We identified 3,649 (27.8%) and 4,526 (17.3%) sISP patients in the MGBD and TriNetX cohorts, respectively. At MGBD, sISP use within one year of ICI start was associated with worse OS compared to patients without sISP use (TR: 0.71; 95% CI: 0.64-0.79; p<0.0001). This association was accentuated in patients who received sISP closer to ICI start, with those receiving sISP within one month of ICI start having the poorest OS (TR: 0.49; 95% CI: 0.44-0.54; p<0.0001). Increased dosage and duration of sISP were associated with shorter OS. Dosages beyond 80 mg/day had a 55% OS loss, while durations longer than 7 days were associated with a 35% OS loss. These findings were independently validated in the TriNetX cohort. In summary, three key factors associated with significantly worse OS, including sISP use near ICI start, higher dosage of sISP, and longer sISP duration, regardless of indication. These results provide clinicians with valuable information to guide the sISP management in patients receiving ICI therapy.

0380

Regional variations in continuing medical education availability for dermatology grand rounds

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Grand rounds are essential for dermatological education, combining clinical exposure with Continuing Medical Education (CME) opportunities. This study examines regional variations in CME offerings for dermatology grand rounds. US MD schools were identified via the AAMC website and dermatology departments were surveyed. Programs were categorized by AAMC region (Central, Northeastern, Southern, Western). Of 112 departments, 51 (45.5%) responded. Among these, 46 (90.2%) host grand rounds, and 40 (78.4%) offer an average of 1.72 CME credits per session. The Northeastern had the most responses (16, 31.4%) and highest credits (2.58), while the Western had the fewest (11, 21.6%) and lowest (1.18). Central and Southern each had 12 responses, averaging 1.44 credits. Central programs reported hosting grand rounds at 83%, compared to 88%, 91%, and 100% in Northeastern, Western, and Southern regions, respectively. Programs with 1–20 participants averaged 1 CME credit, while those with 61–80 averaged 3.25. Hybrid formats were most common (26, 51%), followed by in-person (9, 18%) and Zoom (3, 6%). Monthly (16, 31%) and weekly (14, 27%) sessions were most frequent. Regional differences in dermatology grand rounds and CME offerings present a clear opportunity to enhance standardization and accessibility. Expanding hybrid formats may bridge regional gaps, ensuring equitable access to dermatology education.

0381

Hidden risks: Exploring the ingredients in top amazon lace wig adhesives

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This study investigated the prevalence of irritating and allergenic ingredients in best-selling lace wig adhesives on Amazon, and it examined their ability to trigger dermatologic reactions, such as atopic dermatitis. Wig adhesive is used to secure many different types of wigs, with lace front wigs being the most common. Lace wig adhesives are widely used in hair camouflage by individuals with alopecia, a condition that predominantly impacts Black women, emphasizing the importance of developing safer formulations to mitigate scalp damage and prevent further hair loss. The ten lace wig adhesives with the highest number of reviews on Amazon were determined, and their individual ingredients were analyzed, with common irritants and allergens identified. In the lace wig glues analyzed, 38 unique ingredients were distinguished and categorized as film-forming agents and polymers, preservatives, water and solvents, conditioning agents and humectants, pH adjusters and stabilizers, fragrances and additives, or adhesives and bonding agents. Each ingredient was determined to be a known irritant or allergen, along with its corresponding side effects. Some ingredients were labeled as common allergens, frequently associated with allergic contact dermatitis and skin sensitization. Other ingredients were severe skin irritants, emphasizing the potential for both acute and chronic dermatological reactions in adhesives. Improved product labeling, consumer education, and further research to develop safe alternatives were considered crucial for lace wig adhesives.

0382

Prevalence, demographics, and comorbidities associated with necrobiosis lipoidica: An analysis of national inpatient sample 2016-2019

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Necrobiosis lipoidica (NL) is a rare chronic inflammatory skin disorder frequently associated with diabetes. Epidemiological data on NL are limited due to its rarity. This study evaluated NL prevalence, gender differences, and its associations with diabetes, vascular, metabolic, autoimmune, and infectious comorbidities. National Inpatient Sample dataset of 36,731,521 patients was analyzed from 2016-2019. NL cases were identified using International Classification of Diseases 10 version (ICD-10) code L92.1, and comorbidities were flagged with corresponding ICD-10 codes. Chi-square tests and logistic regressions with odds ratios (ORs) were used to evaluate the associations between comorbidities in patients with and without NL. NL prevalence was 3.5 cases per million hospitalizations (130 cases out of 36.7 million). Out of the 130 cases of NL, 98 (75.37%) were female, and 32 (24.62%) were male, with a statistically significant association between gender and NL prevalence ($p < 0.0001$). The mean age was 56.69 years (range: 14–90). Type 2 diabetes was present in 39.23% of NL patients, and Type 1 diabetes in 13.85%. Common metabolic comorbidities included dyslipidemia (OR = 1.92, $p = 0.0004$), obesity (OR = 3.11, $p < 0.0001$), and hypothyroidism (OR = 2.17, $p = 0.0003$). Autoimmune conditions, such as rheumatoid arthritis (OR = 6.45, $p < 0.0001$) and systemic lupus erythematosus (OR = 4.54, $p = 0.0042$), were significantly associated with NL. Infectious complications like cellulitis (OR = 10.03, $p < 0.0001$) were markedly elevated. This analysis highlights NL's rarity, its gender disparity, and its associations with diabetes and other comorbidities. These findings indicate that NL is not limited to diabetic patients, highlighting the importance of targeted screening and multidisciplinary care to address associated metabolic, vascular, and autoimmune conditions, especially among high-risk inpatient populations.

0383

Cardiovascular associations with onychomycosis: A global trinetx database analysis

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Onychomycosis is the most common nail condition seen in clinical practice. There are reported associations between onychomycosis and both diabetes and obesity, which are risk factors for cardiovascular conditions. Thus, we hypothesized that there could be an association between onychomycosis and cardiovascular disease and studied these relationships using a large multicenter database. The TrinetX research database was utilized on 1/13/2025 to search for patients ≥ 18 years of age with onychomycosis (ICD 10: B35.1). All patients were propensity-score matched to controls without onychomycosis based on sex, current age, race, ethnicity, diabetes, smoking history, obesity and metabolic syndrome. The odds of developing cardiovascular disease risk ≥1 day following diagnosis of onychomycosis was examined. 537,716 onychomycosis patients and 537,716 propensity-matched controls were included. Cohorts were well matched with a mean age of onychomycosis and control patients of 66.3 and 66.3-years (p=0.8445), and majority male (46.1% and 46.1%, p=0.9306) and White (58.9% and 58.9%, p=0.885), respectively. Patients with vs. without onychomycosis had increased odds of peripheral vascular disease (OR=3.10, 95%CI 3.06-3.14), venous insufficiency (2.76, 2.71-2.81), cardiac arrest (1.45, 1.39-1.51), cerebral infarction (1.43, 1.41-1.45), cardiomyopathy (1.32, 1.29-1.34), cardiac arrhythmias (1.28, 1.27-1.30), acute myocardial infarction (1.24, 1.21-1.26), angina pectoralis (1.23, 1.20-1.25), atherosclerosis (1.19, 1.18-1.20), and chronic ischemic heart disease (1.19, 1.18-1.20). Our study found that onychomycosis was associated with higher odds of cardiovascular comorbidities, suggesting that onychomycosis may be a warning sign for cardiovascular disease.

0384

Chronic spontaneous urticaria and autoimmune comorbidities: A cross-sectional global database analysis

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Chronic spontaneous urticaria (CSU), or idiopathic urticaria, is a mast-cell driven condition, with reported associations with autoimmune diseases. This study assesses risk of autoimmune comorbidities in CSU patients using a multicenter database to guide clinical evaluation. A retrospective study utilizing the TrinetX research database was performed for patients ≥ 18-years of age with CSU diagnosis (ICD-10 L50.1) as of 1/2/2024. CSU patients were propensity score-matched with controls by age, sex, race, and ethnicity. Odds ratios (OR) were calculated for developing autoimmune diseases ≥1 day after CSU diagnosis. A total of 105,187 CSU patients and an equal number of matched controls were included. After propensity score matching, average age for patients CSU patients was 42.1 years, with 66.9% being female and 56.7% being white. Compared to controls, CSU patients exhibited higher odds of developing various autoimmune conditions, including vitiligo (OR=2.619, 95% CI 2.176-3.152), Sjögren's syndrome (2.369, 2.140-2.622), autoimmune thyroiditis (2.200, 2.057-2.353), pernicious anemia (2.154, 1.785-2.599), systemic lupus erythematosus (SLE) (2.084, 1.879-2.310), dermatopolymyositis (2.120, 1.555-2.890), myasthenia gravis (2.001, 1.496-2.678), celiac disease (1.916, 1.700-2.160), Graves' disease (1.879, 1.669-2.115), fibromyalgia (1.864, 1.770-1.963), ankylosing spondylitis (1.831, 1.496-2.241), psoriatic arthritis (1.376, 1.306-1.450), systemic sclerosis (1.348, 1.029-1.766), polymyalgia rheumatica (1.669, 1.399-1.991), inflammatory bowel disease (IBD) (1.440, 1.360-1.524), psoriasis (1.321, 1.232-1.417), rheumatoid arthritis (RA) (1.313, 1.167-1.478), and type 1 diabetes mellitus (DM1) (1.293, 1.191-1.404). The study found an increased risk of developing autoimmune co-morbidities in CSU patients. Future genomic, molecular, and prospective studies are needed to elucidate the underlying mechanisms that drive the association between CSU and autoimmune comorbidities.

0385

Longitudinal study on the efficacy of mixed-method teledermatology in acne management

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Our study aims to evaluate the long-term efficacy of the mixed-method teledermatology approach, combining synchronous (real-time video consultations) and asynchronous (store-and-forward technology) methods, provided through DermCafe, focusing on patient outcomes and satisfaction. We performed a retrospective chart review of patients who received acne treatment through mixed-method teledermatology at DermCafe over the past four years. Our study involved patients who engaged in both synchronous and asynchronous teledermatology sessions. Data was gathered on patient demographics, skin type, genetic background, lifestyle factors, and co-existing conditions. Treatment effectiveness was evaluated through clinical assessments using the Global Acne Grading System. Patient-reported outcomes, including quality of life and treatment satisfaction, were tracked over an extended follow-up period. Preliminary analysis indicated that the mixed-method teledermatology approach results in high diagnostic accuracy and patient satisfaction. Objective measures show a significant improvement in acne severity, as the Global Acne Grading System scores decreased substantially across the patient population. Patient-reported outcomes reflect high satisfaction levels with both convenience and effectiveness of treatment. Acne symptom recurrence was notably delayed, demonstrating the long-term benefits of this approach. This study provides comprehensive insights into long-term outcomes of mixed-method teledermatology for acne management. The findings support the use of this approach for improving patient outcomes and satisfaction, suggesting that mixed-method teledermatology is a viable and effective strategy for acne management. Future research should continue to explore the optimization of these methods to further enhance their efficacy.

0386

Utilizing the VISIA camera for analyzing 5-Fluorouracil treatment efficacy for actinic keratoses

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The VISIA camera is a novel device that captures images of the skin using a rotating camera with both UV and polarized light, assessing the condition of both surface and subsurface skin . It provides patients with an easy-to-understand analysis regarding their skin's problem areas allowing for targeted treatment options. Actinic Keratoses (AKs) are precancerous lesions that are diagnosed through clinical examination and dermoscopy. Incorporating VISIA imaging for AK patients may offer a deeper understanding of sun damage and serve as a tool to encourage adherence to field treatment, such as 5-Fluorouracil (5-FU). In this observational study, we evaluated a male patient diagnosed with diffuse AKs who was prescribed and had consented to go through 5-FU treatment on the scalp. Baseline VISIA photos were taken prior to treatment, and 5-FU was applied twice daily to the scalp for four weeks. Follow-up imaging was obtained one week and three months post-treatment. Analysis using the UV spot filter revealed a reduction in feature count from 706 to 631 and an improvement in the percentile which reduced from 83% to 39%. Spot filter produced the same percentile of 9% for all photos affirming the VISIA's efficacy in detecting UV damage-related areas. These findings demonstrate the VISIA camera's utility for documenting treatment progress while enhancing patient education and motivation for treatment adherence. By illustrating the effectiveness of 5-FU in treating AK's, VISIA serves as a compelling tool for promoting patient understanding and encouraging adherence to future treatment plans.

0387

Mental health consequences of hidradenitis suppurativa: population-level evidence of elevated risk for recurrent major depressive disorder

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Hidradenitis suppurativa (HS) is a chronic inflammatory condition that exerts a substantial psychological toll. HS has been found to be associated with increased risk of anxiety and depression at small sample sizes. Our study provides a novel evaluation of these associations at a population-level. Our retrospective cohort study used TriNetX data between November 2004 and November 2024 to evaluate whether HS patients who had been diagnosed subsequently with major depressive disorder (MDD) (single episode) had a higher risk of developing MDD (recurrent) compared to matched controls without HS and with MDD (single episode). Propensity matching was performed to control for sex, patient current age, age at MDD diagnosis, ethnicity, and race. Risk ratios were calculated and evaluated for statistical significance. HS propensity matched cohorts with initial diagnosis of MDD (single episode) each contained 49,205 patients (mean age 45±15 years) and were 79% female, 27% Black, 9% Hispanic, 56% White, and 1% Asian. HS patients diagnosed with MDD (single episode) were 33% more likely to be diagnosed with recurrent MDD compared to controls without HS (RR=1.328, 95% CI=(1.284, 1.372)), 25% more likely to have anxiety, (RR=1.245, 95% CI=(1.212, 1.279)), 8% more likely to have suicidal ideation (RR=1.078, 95% CI=(1.004,1.153)), and had a lower risk of intentional self-harm (RR=0.892, 95% CI=(0.736, 1.082). This study demonstrates the substantial risk in HS patients for developing anxiety and recurrent MDD. HS-associated lifestyle factors that can explain the results include impaired quality of life leading to social withdrawal and poor self-care. In addition, shared pathobiological pathways include neuroinflammatory processes with aberrant cytokine signaling, such as IL-6, TNF-alpha, and IL-17 that also impact brain function. These findings underscore the importance of early mental health screening and interventions in HS patient care.

0388

Advantages of a virtual collaborative research dermatology laboratory

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The purpose of this investigation is to discuss how the Dunnick/Dellavalle Dermato-Epidemiology Lab, a dual-campus collaboration between the University of Colorado and the University of Minnesota, fosters innovation and enhances medical student access to dermatological research. Currently, there are no publications on this multi-institution research approach in dermatology. This innovative lab structure offers students and researchers unique opportunities to engage in dermatological research and develop professional networks across two leading institutions. By integrating the expertise of faculty, residents, and students across campuses, the lab seeks to foster collaboration to advance dermatological science as well promote equity and inclusivity for all trainees. Through a hybrid model combining virtual and in-person interactions, the lab enables students from over 30 institutions to contribute meaningfully to ongoing projects. Weekly meetings and shared lab project documents maintain continuity and ensure progress, even across geographically dispersed teams. This structure supports diverse perspectives, promoting innovative approaches to complex dermatological issues. This collaborative model highlights the potential for academic institutions to build extensive networks that accelerate scientific discovery. By promoting curiosity and leveraging collective expertise, the Dunnick/Dellavalle Lab creates a new model for how interdisciplinary partnerships can advance dermatological knowledge while equipping future physicians with the skills to thrive in team-based research environments.

0389

Spatial distribution of melanoma clinical studies: A retrospective analysis of trends

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Melanoma stands as the most lethal skin cancer globally. The rising rates in the incidence and prevalence of melanoma underscores the need for an increase in novel therapies. Nevertheless, geographical obstacles impede access to clinical studies. This study looks to measure the geographical inequalities in access to clinical studies that persist amongst patients from various rural-urban commuting areas (RUCAs) and different racial groups. A retrospective study was conducted to assess the geographical accessibility of clinical studies for patients categorized by both RUCA and race, using data extracted from ClinicalTrials.gov. Clinical study data was retrieved on October 31st, 2024. A total of 607 clinical studies were identified. The number of new clinical studies increased significantly from 2005 to 2022 ($R^2 = 0.410$, $p < 0.05$), with a slope of 0.740 trials added per year. It is important to note that during there was a significant decrease in the number of clinical trials in 2020 (87 trials), during the SARS-COV-2 pandemic. Rural areas demonstrated the greatest distance from clinical study sites (>200 km), followed by small town (175 km), micropolitan (160 km) and metropolitan (75 km) areas. All the average distances between the different RUCA categories were significantly different ($p<0.001$). When geographical disparities were analyzed by race, American Indians were located the farthest on average from the nearest clinical trial and Asians were located the closest. There is a great variation in the geographical access to melanoma clinical studies across the mainland United States. Rural areas and American Indian populations face the greatest distance to trial sites. Improving access is important because these groups are known to have higher melanoma-related death rates.

0390

Dermatology residency 2+2 research tracks: A cross sectional survey

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The 2+2 research track dermatology residency model combines two years of clinical training with two years of dedicated research time. These programs are designed to balance comprehensive clinical training with preparing residents for a career in academic research. The objective of this survey study is to analyze the number of current 2+2 programs in the United States and identify factors that influence the success of these programs. A national survey was sent to 141 program directors to assess the number of 2+2 programs and the residents enrolled, key selection criteria for research-track applicants, dedicated clinical and research time distribution and funding mechanisms. Outcomes include career progression, and retention rates. Concurrently, 4 reviewers evaluated residency program websites for advertisement of 2+2 positions. Of the 24 responses, 33% (n=8) reported offering 2+2 research track positions, with an average of 1-2 positions available annually. From a review of residency program websites, only 14 programs advertise 2+2 research track positions. Regarding selection criteria, the majority of the programs (n=7) prioritized research interest followed by interview performance and publication record. 75% of positions are supported by department/division funds. Furthermore, 75-100% of graduates pursued independently funded research post-residency, with retention rates ranging from 25-100% in the 2+2 programs. URM representation showed significant variability across programs, with less than 30% of trainees identifying as underrepresented in medicine. The 2+2 dermatology residency programs are key for training future physician-scientists in dermatology. However, challenges remain in representation and funding. Addressing these gaps may help improve equity in clinical research and strengthen the dermatology research workforce.

0391

Real world safety analysis of boxed warning adverse events for upadacitinib in atopic dermatitis using the FDA adverse event reporting system

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Upadacitinib, an FDA-approved oral JAK-1 selective inhibitor for moderate-severe atopic dermatitis (AD) was issued a boxed warning for serious infections, malignancies, thrombosis, and major adverse cardiovascular events (MACE) based on clinical trial findings. Real-world safety data to guide clinical decision-making remains limited. This study aims to evaluate the incidence and characteristics of adverse events (AEs) in AD patients treated with upadacitinib. AE reports from January 2004 to October 2024 were extracted from the FDA Adverse Event Reporting System (FAERS) using OpenVigil 2.1. Reports identifying upadacitinib as the primary suspect drug in AD patients were categorized using Standardized MedDRA Queries. Disproportionality analysis using reporting odds ratio (ROR) was used to evaluate AEs, with data further stratified by age and sex. 2,903 unique AE reports were identified. Higher reporting was seen in males for opportunistic infections (ROR 3.50), thrombotic events (ROR 7.34), strokes (ROR 5.45) and myocardial infarction (ROR 11.19). Opportunistic infections (ROR 4.89), sepsis (21.93), hematological malignancies (ROR 8.51), thrombotic events (ROR 13.95), strokes (ROR 18.29), and myocardial infarctions (ROR 25.91) reporting peaked in the under-30 age groups. However, solid tumors were primarily reported in the over-50 age group (ROR 6.27). These findings provide critical real-world insights into the safety profile of upadacitinib in AD. Contrasting signals between clinical trials, and our analysis of FAERS' real-world reports highlight the need for vigilant monitoring. The increased reporting in younger age groups may partly reflect the easier attribution of AEs in patients with fewer comorbidities, emphasizing the need for providers to carefully assess individual risks.

0392

Measuring the geographical accessibility of scar and tissue healing clinical studies: A retrospective clinicaltrials.gov study

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Improving functional and cosmetic procedures for patients that have wounds remains a critical area of study. The impact of geographical proximity to scar and tissue healing on participation and diversity in clinical studies for scar and healing is less understood. Therefore, this study focuses on evaluating the accessibility to clinical studies to help inform recruitment strategies. Using the ClinicalTrials.gov API, we extracted clinical study data from 2005-2024 using the keywords "scar and tissue healing". The distances were calculated between zip code populations using K-d tree and the Haversine formula. ZIP codes were categorized as rural or urban using Rural-Urban Commuting Area (RUCA) codes. Racial demographics by ZIP code were analyzed to assess proximity disparities. A total of 596 clinical studies were identified, with an average of 1.85 clinical studies per each ZIP code. From 2005 to 2024, there was a decrease in distance to clinical trial sties over time (slope:-9.04, p=2.71e−03). American Indians had longer average distance to clinical trial sites (43.5 miles, 95% CI: 32.5–44.6) compared to Pacific Islanders (33.0 miles, 95% CI: 31.8–34.3), Whites (32.4 miles, 95% CI: 31.8–33.1), Blacks (21.6 miles, 95% CI: 22.1–22.1), and Asians (16.4 miles, 95% CI: 15.9–17.0) (p<0.0001). A similar trend was prevalent in micropolitan, small town, and rural-areas (p<0.001). Limitations include the study's retrospective design, reliance on publicly available data, and variability in ClinicalTrials.gov updates. Overall, while accessibility to scar and wound studies has improved, certain races continue to face the longest distances to trial sites, highlighting persistent inequities. Addressing these disparities is crucial for equitable clinical trial participation and access to emerging therapies.

0393

Unraveling racial disparities in mycosis fungoides mortality using real-world data

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This study investigates racial disparities in mortality outcomes among Black patients with mycosis fungoides (MF), a form of cutaneous T-cell lymphoma. Previous studies have reported disproportionately poorer outcomes in Black individuals, but these disparities remain unexplained by demographic or disease characteristics.A retrospective analysis was performed in October 2024 using the TriNetX database, which aggregates electronic health records from 66 health systems across the United States. Patients diagnosed with MF were categorized by racial groups (Black and White). Propensity score matching by sex and age generated two balanced cohorts of 682 patients each. Five-year mortality was evaluated using risk analysis and Kaplan-Meier survival curves. Black patients demonstrated significantly higher mortality compared to White patients, even after adjusting for sex and age (hazard ratio 1.37, 95% CI: 1.09–1.72, p=0.007). The odds ratio for mortality was 1.68 (95% CI: 1.15–2.47). Kaplan-Meier survival analysis revealed lower five-year survival probability for Black patients (72%) compared to White patients (81%, p=0.006). These findings highlight persistent racial disparities in MF outcomes, emphasizing the need for further research into potential contributing factors, including diagnostic delays, healthcare access, socioeconomic status, and disease presentation. Targeted interventions addressing these disparities are crucial for improving survival outcomes among Black patients with MF.

0394

Cutis marmorata telangiectatica congenita: Atypical dermatological manifestations and associated comorbidities

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Cutis Marmorata Telangiectatica Congenita (CMTC) is a rare vascular malformation characterized by reticulated, erythematous patches that typically present at birth, often accompanied by skin atrophy, limb asymmetry, and ulceration. These abnormalities can significantly affect patient quality of life, leading to cosmetic concerns, physical discomfort, and functional impairments. Beyond its common dermatologic manifestations, CMTC can present with atypical skin findings and is associated with systemic comorbidities, highlighting the need for multidisciplinary management. To explore these associations, we conducted a comprehensive review of case reports and case series published on PubMed over the past 10 years. Thirty-nine studies met our search criteria, encompassing 48 subjects, of which half presented with either uncommon dermatologic features or comorbid conditions. Dermatologic anomalies, such as phacomatosis pigmentovascularis and infantile hemangioma, were reported in 23% of cases. Ocular conditions, such as glaucoma, retinal nonperfusion, and neovascularization, affected 19% of patients. Systemic conditions, including hypothyroidism and exercise-induced transient edema, along with rare conditions such as Sturge-Weber syndrome and Rubinstein-Taybi syndrome, occurred in 15% of patients. Neurological anomalies, including transient ischemic attacks and learning disabilities, as well as vascular anomalies, such as hypertension and cardiac defects, were observed in 4% of patients. Musculoskeletal defects, such as syndactyly, were only observed in 2% of patients. These findings illustrate the complex nature of CMTC and underscore the importance of comprehensive, multidisciplinary care. Further research is necessary to advance our understanding of this rare condition.

0395

Comorbidities associated with sézary syndrome: A case-control study in the All of Us database

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Sézary syndrome (SS) is a rare aggressive leukemic variant of cutaneous T-cell lymphoma characterized by malignant T-cells in the skin. Its etiology remains unclear. This study aimed to explore the comorbidities associated with SS utilizing All of Us, a database of 413,000 patients. Each case of SS was matched to age-, race-, and sex-matched controls. We identified the most associated conditions in patients with significance and calculated the odds ratios (ORs) with 95% confidence intervals using logistic regression. The All of Us demographics included 49 patients: 51% female, 49% male; 59.2% White, 26.5% African American, and 6% Hispanic/Latino. We identified relevant comorbidities that were most common in patients and with a high odds ratio. Analysis revealed that patients with SS had significantly elevated comorbid conditions. Cardiovascular comorbidities included hypertension (OR: 11.7), cardiac arrhythmias (OR: 6.5), and thrombocytopenic disorders (OR: 13.8). Autoimmune conditions such as IBD (OR: 17.7) and Type 1 diabetes (OR: 5.5) had significant associations. Psychiatric conditions associated with SS include depression (OR: 3.9) and anxiety disorders (OR: 3.7). Significant pulmonary diseases were COPD (OR: 5.4) and acute respiratory infection (5.25). The most common dermatological conditions associated with SS were inflammatory dermatitis (OR: 10.1), psoriasis (OR: 19.8), rosacea (OR: 5.17), and atopic dermatitis (4.78). Significant types of cancers included diffuse Large B-cell lymphoma (OR: 53.4) and Hodgkin's disease (OR: 93.5). The comorbidities presented such as hypertension, Hodgkin's disease, and depression have been published in the literature, but other comorbidities such as psoriasis and rosacea that may be significant were not documented in the literature. This study highlights that SS is associated with a substantial comorbidity burden, including cardiovascular, autoimmune, psychiatric, pulmonary, and dermatologic conditions. Future studies would benefit from including these comorbidities in an analysis of SS.

0396

Associations between skin cancer and psychiatric conditions: A national health interview survey study

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Skin cancer can be life-threatening and impact quality of life due to disfigurement and psychological distress. These challenges are often associated with psychiatric illnesses. However, the prevalence of psychiatric comorbidities after a skin cancer diagnosis remains poorly understood. This study aims to analyze the odds of developing specific psychiatric conditions in skin cancer patients. The 2023 National Health Interview Survey was used to identify participants who reported a prior diagnosis of some form of skin cancer and healthy controls. Survey weights were applied in R (v4.3.3), and demographic data were extrapolated alongside variables corresponding to depression, anxiety, life satisfaction, and receiving mental health treatment. Variables of interest were compared using the Wilcoxon rank-sum test for complex survey samples and chi-squared test with Rao & Scott's second-order correction, followed by adjusted logistic regression. The study included a weighted sample of 8,503,898 participants who reported skin cancer and 237,326,133 who did not. Those with a history of skin cancer were more likely to report depression (OR 1.20, 95% CI 1.05-1.37, $p<0.05$), anxiety (1.36, 1.18-1.57, $p<0.05$), and psychiatric medication use (1.31, 1.07-1.60, $p<0.05$). Specifically, females were more likely to report depression (1.58, 1.49-1.67, $p<0.05$) and anxiety (1.98, 1.85-2.12, $p<0.05$). Black (0.73, 0.65-0.80, $p<0.05$), Asian (0.57, 0.51-0.64, $p<0.05$), and Hispanic (0.58, 0.52-0.63, $p<0.05$) participants were less likely to report depression than White patients. The findings suggest that patients with skin cancer were more likely to experience psychiatric outcomes compared to those without. Racial minority patients were less likely than White patients to have psychiatric outcomes. Mental health screening should be prioritized in dermatology to mitigate the psychiatric burden in skin cancer patients.

0397

The role of skin biopsy in calciphylaxis: Risks, benefits, and controversies

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The purpose of this review is to critically evaluate the role of skin biopsy in diagnosing calciphylaxis, a rare and life-threatening condition characterized by vascular calcification and progressive skin necrosis. While skin biopsy is widely regarded as the diagnostic gold standard due to its ability to provide histopathological confirmation, its use is controversial. Limitations include low sensitivity and specificity, as well as procedural risks such as ulceration and worsening of lesions. A comprehensive review of the literature highlights ongoing debates regarding the reliability of biopsy versus alternative diagnostic strategies, such as clinical evaluation and imaging techniques. Despite its limitations, biopsy remains a commonly used diagnostic tool; however, its risks may outweigh its benefits in some patient populations. This work underscores the urgent need for studies comparing patient outcomes between those undergoing biopsy and those diagnosed via alternative methods. Such research would inform clinical decision-making and encourage dermatologists to weigh the risks and benefits carefully, ultimately optimizing the care of patients with suspected calciphylaxis.

0398

Biologic immune pathway modulators in dermatology: A patent landscape analysis

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Biologic immune modulators, which selectively target key cytokines and signaling pathways, have greatly enhanced the management of inflammatory and autoimmune skin conditions. This study aims to categorize and analyze patents for biologic treatment in dermatology. The Lens database is an open and secure source for all patents. It was used to identify 2,699 granted patents referencing interleukins (IL), Janus kinases (JAK), or tumor necrosis factor (TNF) in conjunction with psoriasis, eczema, atopic dermatitis, seborrheic dermatitis, rosacea, acne, alopecia, hidradenitis suppurativa, urticaria, or lichen planus. After excluding non-dermatological patents, 624 patents for biologics remained which were categorized into six distinct groups (TNF-α, Th2 interleukins, JAK inhibitors, Th17 interleukins, all other IL Pathways, and all other non-IL immunomodulators). Biologics modulating the Th17 axis represented 10% of the patents. Modulation by biologics through the Th2 axis accounts for another 17% of all patents. 22% of patents for biologics fell into those that target and inhibit IL-1/L-2/IL-6/IL-10/IL-11/IL-21, the alternative IL category. 6% of the patents for biologics inhibited the TNF-α pathway. The JAK inhibitor biologics accounted for 15% of all biologics. Finally, all of the other biologic immunomodulators that inhibit pathways not mentioned, including phosphodiesterase inhibitors, account for 30% of all biologics. Collectively, these findings indicate a broad patent landscape for immune pathway modulators in dermatology, covering both well-characterized cytokine pathways and novel therapeutic approaches aimed at inflammatory skin conditions.

0399

An analysis of the most prevalent teledermatology publications: A retrospective scopus database review

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Telemedicine has become increasingly utilized in dermatology across the last decade as a way to improve access to care. In parallel, numerous studies have been performed to assess teledermatology. We sought to analyze trends in literature focused on teledermatology and to understand the different emphases in teledermatology research. SCOPUS was searched for all publications related to teledermatology from 1994 to 2024. The top 100 most cited articles within this time period were extracted and analyzed. Among the top 100 most cited articles, article citation counts, article types, author lists, and journal impact factors were assessed. Additional information regarding country affiliation and the H-index for the first and senior authors was also analyzed. A univariate ANOVA analysis was used for categorical prediction of article type, gender focus of the first and senior authors, study focus, and the country affiliation for the first and senior author. Meanwhile, a Pearson correlation was used for the continuous variable prediction of journal impact factor, year, and the H-index for the first and senior author. The majority of the top 10 most cited articles were published prior to 2015, and the number of published articles peaked in 2020. Article types were predominantly original articles and review articles, and the focus of publications from 2019-2021 was largely centered around patient diagnosis. When modeling predictive variables in a univariate analysis for total number of publication citations, journal impact factor was a significant predictive variable ($p<0.001$), while in the multivariate model, both journal impact factor and review article status were significant ($p<0.001$). These publication trends represent the ongoing interest in telemedicine in dermatology, as well as the importance of review articles and original articles in synthesizing knowledge of teledermatology.

0400

Increased risk of dermatological immune-related adverse events in cancer patients treated with immune checkpoint inhibitors

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Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment but are associated with immune-related adverse events (irAEs), particularly dermatological manifestations. This study evaluates the incidence of dermatological irAEs among ICI-treated versus non-ICI-treated cancer patients. A retrospective cohort analysis used the TriNetX Research Network (2003–2022). ICI-treated patients were compared to non-ICI-treated cancer patients after 1:1 propensity score matching for age, sex, race, ethnicity, BMI, and comorbidities. Dermatological irAEs were identified using ICD-10 codes. Among 234,932 patients (117,466 per cohort), ICI therapy was associated with higher indidence of rash (skin eruptions, lichenoid eruptions, drug-induced hypersensitivity, and pruritus) (17% vs. 3.9%), oral/mucosal conditions (3.5% vs. 0.9%), vitiligo (0.3% vs. 0.0%), and Stevens-Johnson syndrome (0.1% vs. 0.0%; all $p<0.001$), corroborating previous smaller-scale studies. We demonstrated higher incidence of dermatological irAEs in ICI vs. non-ICI treated oncology patients. This large-scale study provides evidence on the dermatological safety profile of ICIs, underscoring the need for multidisciplinary collaboration between oncologists and dermatologists to improve patient outcomes. Further research should explore ICI-related mortality across cancer types.

0401

Integration of thermal imaging and checklist to differentiate cellulitis from pseudocellulitis

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Cellulitis is a skin and soft tissue infection that poses diagnostic challenges leading to substantial healthcare costs and unnecessary hospitalizations. It is the most misdiagnosed disorder in dermatology, highlighting the need for improved diagnostics. This study investigates using thermal imaging (TI) and a clinical checklist to improve accuracy in distinguishing cellulitis from mimickers (pseudocellulitis). TI was used to analyze temperature differentials between affected and unaffected sites in patients with cellulitis symptoms and mimickers. We collected 1165 thermal images from 105 patients with dermatologist-confirmed cellulitis and pseudocellulitis. Patients were enrolled from outpatient clinics, the emergency department, and inpatient unit. Pertinent characteristics were analyzed and a diagnostic checklist was developed from the clinical assessments and TI data. Cellulitis cases showed higher prevalence of tenderness over pruritus 92.2%, confluent erythema over patchy 81.0%, and warmth 90.5% compared to psuedocellultis (tenderness 73.2%, confluence over patchy 43.9%, warmth 50.0%). The distribution of patchy or confluent erythema ($p=0.001$), tenderness or pruritic ($p=0.015$), and warmth ($p<0.0001$) also differed between cellulits and pseudocellulitis. TI showed a temperature difference of 3.1°C between cellulitis affected and unaffected areas. Cellulitis patients also showed higher mean heart rate (81.2±16.5 vs 79.5±13.3 BPM; $p=0.62$) and white blood cell counts (9.5±5.5 vs 7.1±3.4 K/uL; $p=0.03$). This highlights distinct differences in presentation between cellulitis and psuedocellulitis. Integrating TI and a clinical checklist as a point-of-care diagnostic tool shows promise in improving diagnostic precision and lowering cellulitis misdiagnoses, mitigating healthcare costs, reducing unnecessary hospitalizations, and subsequently optimizing patient outcomes.

0402

Tear film insufficiency: Link to ocular inflammatory conditions

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Tear film insufficiency (TFI) is a multifactorial condition characterized by tear prism instability, disruption of the ocular surface homeostasis, tonicity alterations and sensory dysfunction. It includes both aqueous-deficient and hyper-evaporative types, with the latter primarily linked to meibomian gland dysfunction. Despite its high prevalence, the comorbidities and systemic implications of TFI remain understudied. This study utilized the NIH All of Us (AoU) program to explore the associations between TFI and inflammatory eye disorders. A cohort of 21,740 TFI patients was matched with control subjects based on sex, age, race/ethnicity, income, and education. Logistic regression models assessed the odds of having co-occurring inflammatory eye conditions, including chalazion, conjunctivitis, dacryocystitis, episcleritis, hordeolum, keratitis, orbital cellulitis, and uveitis. The results revealed that TFI patients had significantly higher odds of developing these conditions compared to matched controls. Specifically, TFI patients had increased odds of keratitis (OR: 15.99), chalazion (OR: 6.78), and conjunctivitis (OR: 6.33), among others. After adjusting for confounders, these associations remained significant, with strong odds for keratitis (OR: 12.46) and chalazion (OR: 5.83).These findings highlight that TFI is strongly associated with an increased likelihood of inflammatory eye disorders. Recognizing TFI as an early indicator of more severe ocular and systemic conditions can help clinicians adopt a more proactive and multidisciplinary approach to treatment, potentially preventing further complications. Early detection and management of TFI could reduce the risk of developing these associated inflammatory disorders, improving patient outcomes.

0403

Hydroxychloroquine exposure does not affect skin cancer rates in solid organ transplant recipients

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Background: Solid-organ transplant recipients (SOTRs) are at increased risk of developing non-keratinocyte and keratinocyte skin cancers. Chloroquine and its derivative, hydroxychloroquine (HCQ) may play a role in decreasing cancer risk, including skin cancer, via disruption of autophagy (Rangwala et al. Autophagy 2014; Mehnert et al. Clin Cancer Res 2022). Objective: To determine whether HCQ exposure decreases skin cancer risk in SOTRs. Methods: We conducted a retrospective, matched case-control study using chart review data from a single, large academic center. Our patient population included all SOTRs who received a documented transplant before 2020. The population was subdivided by HCQ exposure, defined as HCQ therapy of ≥200mg daily for ≥1 year, and age-, sex-, and race-matched controls identified with 2:1 propensity score matching. We evaluated the development of biopsy-proven skin cancer in SOTRs with HCQ exposure (n=112), compared to HCQ-naïve matched controls (n=247). Results: In the HCQ-exposed cohort, 11.6% developed skin cancer after transplantation compared to 10.1% of HCQ-naïve matched controls. Median time to first skin cancer diagnosis post-transplant was 5.5 years in the HCQ-exposed cohort and 4.1 years in matched controls. Conclusions: Based on these preliminary findings, HCQ exposure does not mitigate the risk of post-transplant skin cancer development. However, further work must be done to better characterize the effect of HCQ exposure on post-transplant skin cancer development after controlling for sociodemographic factors and medical history, particularly autoimmune disease history and prior skin cancer history.

0404

Association between psoriasis and skin cancer: Cross-sectional analysis

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Psoriasis is a chronic autoimmune skin disorder that affects the extensor surfaces, scalp, and lumbosacral region, it is characterized by erythematous plaques with silvery-white scale. Proinflammatory cytokines, including tumor necrosis factor-alpha, dendritic cells, and T-cells, play a crucial role in its pathogenesis and disease progression. The chronic inflammatory dysregulation seen in psoriasis can predispose patients to secondary diseases. The National Institutes of Health's (NIH) All of Us (AoU) program—a nationwide effort aimed to engage underrepresented populations in biomedical research— provides a unique framework for studying the association between psoriasis and skin cancer. Participants with psoriasis (n = 7,377; mean age 63.4 years; 59.2% female) were matched to controls based on sex, age, race/ethnicity, income, and education. Fisher's exact test was applied to analyze categorical variables, and an unpaired t test was used for continuous variables. Logistic regression models were developed to calculate the odds ratio. Results demonstrated a significant increase in the odds of having BCC (OR: 2.18, 95% CI: [2.04, 2.32], $p < 0.01$), SCC (OR: 2.22, 95% CI: [2.02, 2.45], $p < 0.01$), and malignant melanoma (OR: 1.73, 95% CI: [1.52, 1.97], $p < 0.01$) after adjusting for confounders.

0405

Synergy: Empowering medical students in dermatology through observational research collaboration

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Highly talented and motivated medical students compete for access to dermatology clinics to gain 'exposure' to support their applications to residency. By developing self-directed research studies, medical students can give their time in dermatologic clinics a purposeful focus, such as collecting data for observational trials. However, limited clinic availability and insufficient structure for student involvement can hinder meaningful engagement. To address this, we implemented a structured framework that empowers students to develop independent research projects while supporting dermatology clinics in patient recruitment for observational research trials. Our primary outcome was to strengthen student-faculty relationships while improving qualitative metrics such as publication. A secondary outcome is the decreased anxiety of faculty members struggling to find the time to mentor the flood of interested students with heterogeneous research training. In our group, medical students undergo targeted onboarding, including training in observational trial design, ethical data collection, and dermatology-specific foundational knowledge. Students and faculty work together iteratively to create individualized research studies that align with clinical objectives. Individual progress is supported through biweekly office hour sessions and monthly department-wide meetings. Preliminary outcomes highlight increased patient recruitment rates for observational trials and increased student productivity. Furthermore, this model has fostered positive mentorship experiences, reducing faculty workload, while empowering students. This collaborative framework promotes synergy between medical students and dermatology departments, aligning both clinical and research objectives.

0406

Assessing the prior authorization landscape for hidradenitis suppurativa

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Adalimumab, secukinumab, and bimekizumab are approved biologics for moderate to severe hidradenitis suppurativa (HS). However, patients often require off-label therapies after failing first-line treatments or experiencing adverse effects. HS care is fraught with prior authorizations (PA), insurance denials, and appeals, leading to medication delays and administrative burden for clinicians and their staff. This study assessed the administrative burden, PA turnaround times, and approval rates for on-label and off-label HS treatments at a single-center HS specialty clinic. 66 commercially-insured HS patients received biologics between 1/1/23 and 3/31/24. 44 received on-label treatments (adalimumab and secukinumab) and 22 received off-label treatments. PA turnaround times, approval rates, and patient messages were analyzed, and providers and nurses were surveyed about their experiences. The mean PA turnaround time for on-label treatments was 6 days, with a 91% approval rate, compared to 71 days and a 56% approval rate for off-label therapies. On-label medications generated an average of 8 patient messages compared to 22 for off-label medications. Survey responses revealed that 82% of staff reported spending more than half their time managing PAs. Appeal letters, peer-to-peer calls, and communication with insurers were identified as the most time-consuming tasks. This study demonstrated that off-label biologics required nearly 12 times longer for PA appeal decisions, had nearly half the medication approval rates, and generated 3 times the volume of patient messages compared to on-label biologics. Both providers and nurses felt that PAs contributed strongly to burnout among staff and patients, and comprised a substantial portion of inbasket duties. These findings highlight the administrative challenges of managing HS and suggest that private dermatology practices, with fewer resources than academic centers, may face even greater barriers in securing treatment for their patients.

0407

Biologics and patient survival in hidradenitis suppurativa: The Mayo Clinic experience

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Biologics are a mainstay of treatment for hidradenitis suppurativa (HS). To identify whether treatment with biologics was associated with differences in healthcare outcomes, patient demographics, and insurance status, we utilized the Mayo Clinic Platform Discover database, encompassing over 7.3 million patients across Minnesota, Arizona, and Florida. Propensity score matching was conducted to compare HS patients treated with biologics (adalimumab, infliximab, or secukinumab) to those not treated with biologics, controlling for age, sex, race, and ethnicity. Of the 9158 HS patients in the database, 1634 were included after matching. The biologics group and non-biologics group had mean ages of 37.2 and 37.0 years, respectively. Obesity prevalence was similar (39% vs. 43%, p=0.087). However, the biologics group had significantly lower rates of non-insurance (14.8% vs. 27.2%, p<0.0001), Medicaid coverage (21.9% vs. 32.1%, p<0.0001), and government insurance excluding Medicaid and Medicare (15.3% vs. 24.1%, p<0.0001). Biologics were associated with a significant increase in 60-month survival (CI: 1.04–5.96, p=0.034) and a substantial reduction in mortality (1.5% vs. 6.5%, p<0.0001), though hospitalization rates did not differ significantly (41.9% vs. 42.0%, p=0.96). In a sub-analysis of non-white patients, biologics were associated with a significant reduction in hospitalizations (26.3% vs. 38.7%, p=0.028), a group previously reported to face over double the risk of hospitalization. Our findings suggest that biologics improve survival and reduce mortality in HS patients, with notable benefits for non-white populations, who experienced fewer hospitalizations. However, higher rates of insurance and commercial coverage among biologic patients may confound these results, underscoring the need for further research to better understand these associations.

0408

WITHDRAWN

0409

Association of systemic therapies for psoriatic disease with non-fatal major adverse cardiovascular events in older adults: A population-based cohort study

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The cardiovascular effect of systemic treatments for psoriatic disease is uncertain. We estimated the association between treatment classes and non-fatal MACE in a cohort study using population-based health administrative data (2007-2023) from Ontario, Canada. The cohort included residents aged ≥66 years with psoriasis and psoriatic arthritis who initiated systemic therapy between April 2007 and March 2022, categorized as methotrexate, other conventional medications, anti-TNF biologics, IL-17 inhibitors, IL-12 or 23 inhibitors, and tofacitinib. The primary outcome was incident non-fatal MACE (coronary heart disease, cerebrovascular events, heart failure, and peripheral arterial disease). An adjusted Andersen-Gill recurrent event model estimated the relative rate (RR) of MACE for each treatment class compared to time not on that treatment. There were 9,031 new users (median age 71 years [IQR 68-76], 51% female). Analyses showed methotrexate (RR 0.78, 95%CI 0.74-0.83), anti-TNF biologics (RR 0.79, 95%CI 0.72-0.87), and IL-12 or 23 inhibitors (RR 0.76, 95%CI 0.68-0.85) were associated with lower MACE rates, whereas IL-17 inhibitors (RR 0.90, 95%CI 0.79-1.02), other conventional medications (RR 0.96, 95%CI 0.90-1.03), and tofacitinib (RR 0.99, 95%CI 0.71-1.37) were not. This suggests that specific classes of anti-psoriatic therapy may have cardiovascular benefits.

0410

Harnessing artificial intelligence to improve diagnostic precision of CTCL

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Cutaneous T-cell lymphoma (CTCL) may mimic eczema or psoriasis, contributing to diagnostic delay and improper treatments. This retrospective study utilizes natural language processing (NLP) and machine learning (ML) to extract and analyze patient histories from notes prior to diagnosis and develop predictive models for earlier and more accurate CTCL diagnosis. Using electronic health records, unstructured notes were analyzed via NLP to identify terms associated with CTCL versus controls with benign inflammatory skin conditions. Pre-diagnosis notes were reviewed for presentations, treatments, and laboratory results. ML models were then developed using patient histories and laboratory data. Key findings included significantly (p<0.05) higher frequencies of terms associated with failed topical steroids, scaling, patches, plaques, tumors, and history of multiple biopsies in CTCL patients compared to controls. Conversely, xerosis, allergies, and systemic biologic use were significantly (p<0.05) more frequent in controls than CTCL patients. NLP achieved an accuracy of 82.8% at identifying terms in patient notes. ML models distinguishing CTCL patients from controls achieved 73% accuracy (ROC 0.805) with sensitivity (87%) prioritized to minimize false negatives. An interactive tool based on these models was generated for real-time CTCL risk prediction. This study underscores the potential of AI-driven approaches to enhance CTCL diagnosis, emphasizing its utility in cases of treatment failure, inconclusive biopsies, and atypical presentations. Future research should refine these tools, validate their applicability across diverse populations, and integrate them into clinical workflows to improve diagnostic precision and patient outcomes.

0411

Comparison of subsequent malignancies after first diagnosis of merkel cell carcinoma between white and non-white Hispanic patients

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Subsequent malignancies following Merkel cell carcinoma (MCC) have been documented. However, little is known about the trends of subsequent malignancies among ethnic groups, especially in non-white Hispanic (NWH) patients. Therefore, the aim of this study is to describe the differences of subsequent malignancies following the first diagnosis of MCC in NWH patients, taking their white counterparts as control group. This retrospective cohort study included MCC cases diagnosed in white and NWH patients from 2000 through 2021 in the SEER-22 registry. Categorical variables were reported as counts and percentages. Two-tailed Chi-square was used to assess the association between categorical variables. P-values < 0.05 were considered significant. A total of 19,118 MCCs were identified, of which 0.2% (n=39) were in NWH patients. A total of 2,677 subsequent malignancies was found in the white cohort while 5 cases in NWH patients. While melanoma was the most common subsequent malignancy (n=323, 12.0%) in white patients, no subsequent cases of melanoma was registered in the NWH cohort (p>0.05). Furthermore, MCC was the second most common subsequent malignancy in white patients (n=278, 10.4%) followed by lung/bronchus cancer (n=275, 10.3%); no MCC was found as subsequent malignancy in the NWH cohort (p>0.05). The malignancies found in the NWH group included gallbladder/sigmoid colon adenocarcinoma, squamous cell carcinoma of tonsils, angiosarcoma, and breast cancer. Although statistical significance was not achieved, these results carry substantial clinical/ epidemiological relevance. Our findings may suggest that UV radiation could play a bigger role in the development of MCC in white patients than NWH patients since more UV-related malignancies occurred in the white cohort. Despite the small sample size in the NWH group, these observations highlight potential differences in the biological behavior for subsequent malignancies between ethnic groups, warranting further investigation into the role of genetic and environmental factors of MCC and associated cancers.

0412

Discoid lupus erythematosus rapidly responsive to deucravacitnib

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A 41-year-old woman with a history of central centrifugal cicatricial alopecia (CCCA) presented to dermatology with worsening hair loss, itching, and sensations of scalp tightness. Physical exam was significant for broad atrophic hypopigmented plaques with variable central erythema and rims of hyperpigmentation diffusely throughout the scalp, associated with significant scarring of follicular ostia and a few remaining islands of terminal hairs. Although prior presentations were consistent with CCCA, the rapid evolution of the morphology was more consistent with a diagnosis of discoid lupus erythematosus (DLE). The patient began hydroxychloroquine 200mg twice daily, which has a notable slow onset over the course of months. Due to disease severity and the potential for a faster onset of therapeutic action, the patient was also started on deucravactnib 6mg daily. Rheumatology evaluation was significant for negative antinuclear antibodies, positive anti-SSA/Ro antibodies, and normal C3 and C4 levels, thus, not consistent with systemic lupus erythematosus. After one month on hydroxychloroquine and deucravacitnib, the patient endorsed improvement in itch and tightness and reported no further hair loss, which was evident on physical exam with substantial resolution of erythema. At the subsequent two and three month follow up visits, subjective symptoms continued to improve along with almost complete resolution of hypopigmentation throughout the scalp and little change in the number of terminal hairs. The patient reported one mild upper respiratory tract infection on therapy. Deucravacitnib is a selective tyrosine kinase 2 (TYK2) inhibitor with several successful case reports in the treatment of DLE and subacute cutaneous lupus erythematosus. While currently studied for SLE, this case demonstrates evidence that TYK2 inhibition should be further investigated as a potential therapy for cutaneous lupus, especially given the rapid onset noted in this case, to prevent further scarring in DLE.

0413

IL-17 Inhibitors vs. methotrexate in preventing new-onset psoriatic arthritis in psoriasis patients: a retrospective population-level analysis

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Psoriasis increases the risk of psoriatic arthritis (PsA), potentially due to shared inflammatory pathways. This study compares the incidence of new-onset PsA in psoriasis patients treated with IL-17 inhibitors (IL-17i) versus methotrexate (MTX). A TriNetX query identified 1:1 propensity score matched cohorts of 8,531 patients each, controlling for age, race, gender, and comorbidities. Patients treated with IL-17i demonstrated a protective effect against new-onset PsA vs. those on methotrexate. Risk analysis and Kaplan-Meier survival analysis revealed a lower incidence of PsA in the IL-17i group (6.1%) versus the MTX group (7.2%) (p=0.010). Kaplan-Meier analysis showed higher PsA-free survival in the IL-17i group (72.82%) compared to MTX (61.15%) (p=0.003). Hazard ratios confirmed IL-17i's protective effect (HR=1.214, p=0.000). These findings suggest IL-17i as a promising first-line therapy for psoriasis patients at risk of developing PsA. Further longitudinal studies with larger sample sizes and extended follow-up periods are warranted to explore the long-term benefits of IL-17i in PsA prevention.

0414

Evaluating secondary cancer risk among patients receiving extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and/or graft versus host disease

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Extracorporeal photopheresis (ECP) is an effective immunomodulatory therapy used to treat refractory cutaneous T-cell lymphoma (CTCL) and graft-versus-host disease (GVHD). While ECP is thought to have an improved safety profile compared to systemic immunosuppressants, the impact of ECP on long-term cancer risk remains understudied. We aim to evaluate the association between ECP used for treatment of CTCL and/or GVHD and secondary malignancies. Using the multi-institutional TriNetX database, two propensity score-matched cohorts of adult patients with CTCL and/or GVHD were established: those receiving ECP (N=3,244) and those not receiving ECP (N=3,244). Cancer risk and outcomes were evaluated using risk ratios (RR) and Kaplan-Meier survival analyses over a 20-year period. In comparing the cohorts, treatment of CTCL or GVHD with ECP was associated with a higher risk of developing secondary leukemia (RR=1.667, 95% CI: 1.428-1.945, p<0.001) and skin cancer (RR=1.256, 95% CI: 1.101-1.432, p=0.001). Kaplan-Meier analysis revealed significantly lower survival probabilities in ECP patients with secondary leukemias (ECP: 81.55% vs. No ECP:89.48%, p<0.001) and skin cancers (ECP:72.36% vs. No ECP:76.20%, p<0.001). Conversely, ECP was significantly associated with reduced risk for liver (RR=0.081, 95% CI: 0.043-0.155, p<0.001) and pancreatic cancers (RR=0.429, 95% CI: 0.218-0.841, p=0.011). Survival probabilities were also improved in ECP patients with both secondary liver (ECP:99.15% vs. No ECP:93.92%, p<0.001) and pancreatic cancers (ECP:99.22% vs No ECP:98.25%, p=0.015). While ECP therapy is considered an effective treatment for CTCL and GVHD, it may influence patients' likelihood of developing secondary malignancies, particularly leukemia and skin cancer. CTCL ECP guidelines may need to be updated to reflect these risks, and long-term surveillance strategies should be developed for ECP-treated populations.

0415

Spironolactone treatment for dermatologic conditions and blood pressure changes in hypertensive patients on concomitant antihypertensive therapy

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Spironolactone, prescribed off-label for acne, androgenetic alopecia, and hirsutism, is not associated with significant blood pressure (BP) changes. However, its effect when combined with antihypertensives remains understudied. Using the TriNetX Research Network, we retrospectively analyzed 753 hypertensive patients concurrently treated with spironolactone for dermatologic conditions (2004–2024). BP before and after spironolactone initiation was compared using a two-sample T-test. Mean systolic and diastolic BPs decreased overall (134- to 130-mmHg, 82- to 79-mmHg; P<0.001) and for beta-blockers, angiotensin-receptor-blockers, and thiazides. Hypotension diagnoses increased by 1.5%, but absolute hypotension was rare. Subgroup analysis showed BP decreases in White and Black patients. Limitations included retrospective design, unverified adherence, and absence of dose-response analysis. Spironolactone appears safe for most patients on antihypertensives, but individuals with low baseline BP or multiple BP medications may face higher hypotension risk. Therefore, we recommend collaborating with primary care physicians and monitoring baseline and interval BP measurements in this patient population.

0416

Involvement of calcinosis cutis in autoimmune connective tissue diseases

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Calcinosis cutis is commonly seen in conjunction with autoimmune connective tissue diseases (ACTD) and can lead to functional impairment. We sought to complete an in-depth analysis identifying the most commonly affected locations and evaluate the impact and complications varies by the specific underlying ACTD. We used the research patient data registry to identify patients with the diagnosis of calcinosis cutis and connective tissue diseases (SLE, scleroderma, dermatomyositis, etc.) at Brigham Women's Health and Massachusetts General Hospital. 43 patients were identified with the diagnosis of calcinosis cutis adequately documented in their chart. The location of calcinosis was predominantly along sites of trauma in each autoimmune connective tissue disease. 100% of patients with the diagnosis of lSSc described their lesions as painful and functionally limiting, compared to 84.6% of those with dermatomyositis, and 76.9% of those with scleroderma. 54.5% of patients with lSSc, 46.2% of patients with dermatomyositis, and 38.5% of patients with systemic sclerosis indicated ulceration in sites with calcinosis cutis. The most common locations in dSSc/lSSc for painful involvement and ulceration were the fingertips/digits. Our case-series of 43 patients with ACTD resulting in calcinosis cutis demonstrates locations patients are more likely to experience pain and ulceration. Overall, for each connective tissue disease, there was a higher presentation of calcinosis formation and more severe involvement in sites of trauma (digits, knees, elbows, etc.) seen. However, for dermatomyositis, greater involvement was seen in areas such as the thighs, flanks, and gluteal region. It is important to note that many of the provider notes were non-descript in the specific location or size of calcinosis cutis involvement.. This study can help providers in the future counsel patients and guide expectations regarding common locations and resulting pain/ulceration that may develop in the setting of different ACTDs.

0417

Peristomal pyoderma gangrenosum: characteristics, risk factors and, impact on quality of life

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Peristomal pyoderma gangrenosum (PPG) is an uncommon subtype of pyoderma gangrenosum (PG), primarily associated with inflammatory bowel disease (IBD). It is underrecognized and often misdiagnosed, significantly impacting patients' quality of life (QOL). This study describes the clinical characteristics, risk factors, treatment responses, and quantifies the effect of PPG on QOL. In a prospective cohort of PPG patients, data were collected between January 2019 and January 2025, including ulcer characteristics, healing outcomes, recurrences, pain (numerical rating scale), prescription pain medication use, Wound-QOL-14 (WQ14), and Skindex-Mini (SDM) scores. The cohort comprised 28 patients with PPG and 39 peristomal ulcers. The majority of patients were female (75%), with a mean age of 49 years. Twelve patients (42.9%) had IBD (Crohn's disease: 32.1%; ulcerative colitis: 10.7%), six had a known malignancy (21.4%), and five had inflammatory arthritis (17.9%). At least one recurrence occurred in six patients (21.4%), all of whom were female, had a higher mean BMI (37 compared to 28), and 83% had IBD. The mean ulcer size was 25.2 cm^2. Complete healing was achieved in 20 of 39 ulcers, with a mean time to healing of 151.5 days. For non-healers, the mean follow-up duration was 122.9 days. Average pain scores were 4/10, with 12 patients (42.9%) requiring prescription pain medications. Mean WQ14 and SDM scores were 2.2/5 and 3.7/6, respectively. Ulcer size showed a weak positive correlation with pain ($\rho = 0.18$) and WQ14 scores ($\rho = 0.31$). In conclusion, less than half of the patients with PPG had IBD, challenging prior assumptions. PPG was also associated with comorbid malignancy and inflammatory arthritis. Pain and QOL were significantly impacted by PPG, regardless of ulcer size.

0418

Examining atopic dermatitis and its association with non-melanoma skin cancer

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Atopic dermatitis (AD) is a chronic inflammatory skin condition that affects 31.6 million people in the United States. Recent research suggests an association between chronic inflammation, such as in AD, and non-melanoma skin cancer (NMSC); however, large-scale studies examining this relationship remain sparse. This study aims to explore such potential associations through data from the U.S National Health Interview Survey. Utilizing the 2021 U.S National Health Interview Survey, participants with self-reported AD were identified and compared to non-AD participants. Demographic and NMSC outcomes were compared using the Wilcoxon rank-sum test for complex survey samples and chi-squared test with Rao & Scott's second-order correction. An adjusted logistic regression was performed with NMSC as the primary outcome. This study's cohort consisted of 249,877,244 (unweighted = 29,116) participants, in which 18,377,023 (7.4%) reported having AD. The prevalence of NMSC was significantly higher among individuals with reported AD compared to those without (2.8% vs. 2.0%, p<0.05). Adjusted logistic regression showed that individuals with AD were 1.5 times more likely to report NMSC compared to those without AD (OR = 1.53, 95% CI = 1.17–2.01, p<0.05). The study also found that AD was more commonly reported by females (63%) and individuals with private insurance (64%). Additionally, participants with AD were 1.5 times more likely to report having some level of college education (54%) (OR = 1.47, 95% CI = 1.18-1.83, p<0.05) and 2.4 times more likely to hold a professional degree compared to those without AD (OR = 2.41, 95% CI = 1.85-3.13, p<0.05). Our analysis showed a significant association between AD and NMSC. These findings stress the need for targeted cancer screening and preventative strategies to reduce cancer risk in populations with AD, along with putting forth the need for increased dermatologic surveillance and awareness among this population.

0419

Exposure risk of sunburns in the development of keratinocyte carcinoma: A meta analysis

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Ultraviolet exposure is an established risk factor for the development of keratinocyte carcinoma (KC) but quantitative synthesis of published reports is limited. The aim of this study is to evaluate the effect of sunburn exposure on the odds of KC development. PubMed and Embase databases were queried from the period of January 1964 to December of 2023 to identify potential studies for inclusion. Meta-analysis was used to estimate the increase in odds for patients who reported ever having a sunburn during the study period. A dose-response meta-analysis was used to evaluate the effect of an increasing number of sunburns on the odds of developing KC. Of the 35 studies that were included, 31 reported outcomes specific to basal cell carcinoma (BCC) and 15 reported outcomes specific to squamous cell carcinoma (SCC). A total of 1,070,698 persons were analyzed across all included studies. A history of sunburn was associated with an increased odds of BCC and SCC by 53% and 40% (BCC, OR: 1.53, n95% CI: 1.40-1.67, p <0.0001;SCC, OR: 1.40, 95% CI: 1.25-1.55, p <0.0001,) respectively. Ever reported history of sunburn during lifetime (OR:1.60, 95% CI: 1.43-1.70, p = 0.0001), and during pediatric/adolescent periods (OR: 1.43, 95% CI: 1.21-1.69, p <0.0007) was associated with significantly increased odds of BCC and SCC respectively. Each additional sunburn per year increased the odds of developing BCC by 57% (OR: 1.57, 95% CI: 1.40-1.77 , p value <0.0001) and SCC by 44% (OR: 1.44, 95% CI: 1.24-1.66 , p value <0.0001). As a retrospective study, limitations include recall bias and confounding factors such as differences in skin phototype of participants. Furthermore, subgroup analysis was limited by a low number of studies. In conclusion, the odds of BCC and SCC are increased by sunburn exposure and the odds increase per sunburn for most of the periods of life that were studied.

0420

Inflammatory bowel disease comorbidities in patients with basal cell carcinoma: Propensity scored case-controlled study

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Purpose: Basal cell carcinoma (BCC) is the most common skin cancer, influenced by environmental and genetic factors. Emerging evidence suggests an increased incidence of BCC in individuals with inflammatory bowel disease (IBD). This study investigates the association between BCC and IBD using data from the National Institutes of Health's All of Us (AoU) program to explore shared pathophysiological mechanisms. Methods: A cross-sectional analysis was conducted on 9,715 participants with BCC and 38,860 matched controls. Propensity-score matching adjusted for confounders such as age, sex, race/ethnicity, income, and education. Logistic regression models were used to assess the association between BCC and celiac disease, Crohn's disease, ulcerative colitis, and irritable bowel syndrome (IBS). Results: BCC cases exhibited significantly higher prevalence of celiac disease (1.3% vs. 0.7%), Crohn's disease (2.3% vs. 1.1%), ulcerative colitis (2.2% vs. 1.0%), and IBS (9.1% vs. 5.4%) (all $p < 0.01$). Adjusted odds ratios confirmed these associations: celiac disease (OR 1.79, 95% CI [1.45, 2.21]), Crohn's disease (2.04, [1.73, 2.41]), ulcerative colitis (2.20, [1.86, 2.61]), and IBS (1.76, [1.62, 1.91]). Conclusion: This study demonstrates a significant association between BCC and IBD, suggesting shared inflammatory mechanisms. These findings highlight the importance of BCC surveillance in individuals with IBD and call for further research underlying mechanisms and guide prevention strategies.

0421

One-year evaluation of canakinumab's safety and efficacy in Japanese patients with Schnitzler syndrome alongside a parallel exploratory analysis

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Schnitzler syndrome (SchS) is characterized by an urticaria-like rash and monoclonal gammopathy, frequently accompanied by fever and fatigue. No approved treatment currently exists, and its pathogenesis remains unclear. We conducted a multicenter, single-arm, open-label phase II trial to assess canakinumab's safety and efficacy in Japanese SchS patients, based on prior German studies. Previously, we reported results up to 24 weeks; here, we extend findings to 48 weeks, including exploratory analyses. Five active cases with no prior IL-1-targeted treatment were enrolled. scRNA sequencing and spatial transcriptomics identified IL1B-expressing cells in two cases. Canakinumab, given every 8 weeks, continued improving symptoms, lab abnormalities, and quality of life up to 48 weeks, with no new adverse events. Dynamic Time Warping analysis evaluated variations in 32 cytokines/chemokines, 11 complement factors, and clinical symptoms through subjective measures and blood tests. Symptoms correlated strongly with WBC count, neutrophil count, CRP, and SAA levels, while IL-1β and most cytokines/chemokines showed distinct patterns. IgM levels differed from symptom patterns. Although monocytes and mast cells were thought to be primary IL1B-expressing cells, we found neutrophils were predominant in both blood and skin. Notably, blood neutrophil counts decreased post-canakinumab. Thus, canakinumab, targeting IL-1β, showed sustained efficacy and safety in Japanese SchS patients over 48 weeks, suggesting its potential to control peripheral blood neutrophils in SchS treatment.

0422

Allopurinol associated drug reaction with eosinophilia and systemic symptoms (DRESS) in the setting of overlapping cutaneous adverse reactions of toxic epidermal necrolysis (TEN): A case report

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Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) are severe cutaneous adverse reactions that pose significant diagnostic and therapeutic challenges. This case report describes a 73-year-old Indo-Guyanese male patient who developed a complex presentation of DRESS with features of TEN following the administration of Allopurinol for gout. The patient's symptoms included a generalized, painful, pruritic maculopapular rash, fever, and mucosal involvement, which evolved despite initial treatment with corticosteroids and antihistamines. A broad differential for infection with fever and related skin involvement was kept at the forefront, closely monitoring the need for burn unit transfer in the setting of SJS/TEN. Patient initially necessitated in-patient admission to the medicine unit with the impression of DRESS syndrome. Despite aggressive management, the patient's condition progressed, with extensive skin sloughing and mucosal involvement leading to a decision for transfer to a burn unit. The patient's prognosis remains guarded, given the severity of the reaction and the extent of skin involvement (>30% body surface area). The overlap of DRESS and TEN in this patient underscores the importance of early recognition and comprehensive management of drug-induced hypersensitivity reactions. The case highlights the diagnostic challenges and the need for a multidisciplinary approach in managing such patients, including dermatology, infectious disease, and internal medicine consultations. The therapeutic interventions, including the use of intravenous immunoglobulin (IVIg) and corticosteroids, are discussed in the context of current literature to provide insights into effective management for similar cases.

0423

52-week long-term follow-up of non-segmental vitiligo treated with oral abrocitinib and narrow-band UVB phototherapy

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Janus kinase (JAK) inhibitors have begun to be used as investigational therapies in the treatment of progressive non-segmental vitiligo. However, reliable data on the long-term efficacy and safety of oral abrocitinib, a selective JAK1 inhibitor, remains unavailable. We recruited eleven Asian patients with progressive vitiligo who continued to have white patches spreading despite six sessions of intramuscular betamethasone injection. Following the exclusion of contraindications, oral abrocitinib 100 mg once daily was prescribed for 16 weeks. The dosage reduced to 100 mg every other day for an additional 36 weeks. The Vitiligo Area Severity Index (VASI) was used for clinical evaluation. As a result, the mean period from active to stable was 8.0 ± 4.7 weeks. At weeks 24, six patients (54.5%) achieved VASI25, and two patients (18.2%) experienced no improvement. At weeks 52, the number of patients achieving VASI25 increased to eight (72.7%), and only one patient (9.1%) experienced no improvement. At weeks 24, two (28.6%) achieved F-VASI75, two (28.6%) F-VASI50, and one (14.3%) F-VASI25. At weeks 52, two (28.6%) achieved F-VASI90, and three achieved F-VASI50 (42.9%). However, two patients who did not show improvement in F-VASI at weeks 24 still did not repigment at weeks 52. Additionally, when compared to the baseline, serum levels of CCL20 (P = 0.0003) were significantly lower at weeks 24 and 52 although CXCL20 and IFN-γ did not alter significantly. No severe AEs were noted during the 52-week follow-up. In summary, longer-term treatment of non-segmental vitiligo patients with oral abrocitinib in combination with NB-UVB phototherapy demonstrated a favorable benefit-risk profile, with sustained efficacy responses through 52 weeks. Repigmentation on the face, trunk, and even distal extremities may be improved when oral abrocitinib treatment course is prolonged. Nevertheless, patients who developed treatment resistance (with no repigmentation on any part of the body) after 24 weeks would not benefit from an extension of the treatment duration.

0424

Systematic review of lichen planus treatments for pediatric patients

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Although corticosteroids are commonly used as first-line therapy of pediatric Lichen Planus (LP), detailed data on specific agents, dosages, and treatment durations are lacking in the current literature; this systematic review seeks to address literature gaps by synthesizing evidence on topical, systemic, and procedural treatments of pediatric classic cutaneous LP. Article databases were searched for treatments of pediatric LP, following PRISMA guidelines. 934 articles were identified for screening and 32 articles were included in the review. Topical steroids were the most frequently reported treatment. 5 studies reported symptom resolution with 4-8 weeks of clobetasol 0.05%. One study reported symptom improvement in 17 patients with triamcinolone acetonide 0.1% ointment for 8 weeks. One clinical trial of 31 patients reported improvement in 68% of patients with fluticasone propionate 0.005% ointment for 8 weeks. Oral prednisolone was reported in 9 studies with dosages ranging from 5mg to 30mg and durations ranging from 2 weeks to 1 year; 66.6% of these studies reported complete symptom resolution. Tacrolimus was reported in 5 studies, all of which resulted in lesion resolution. UVB phototherapy was reported in 5 studies with duration ranging from 15-17 sessions, and 40% of these studies reported complete response. Immunomodulators were reported in 5 studies, including upadacitinib, cyclosporine, sulfasalazine, and azathioprine. Recently published reviews highlight treatment approaches for LP subtypes like oral, nail, and lichen planus pigmentosus, but current literature lacks a comprehensive review of treatment options for classic LP in children. While topical corticosteroids remain the cornerstone of pediatric LP treatment, emerging modalities like immunomodulators and phototherapy hold promise but require further validation.

0425

Inhibition of the P2X7 receptor is insufficient to mediate disease in hidradenitis suppurativa, but may restore immune exhaustion: Results of a phase 2 randomized controlled trial of AZD9056

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The NLRP3 inflammasome and the upstream P2X7 receptor are upregulated in hidradenitis suppurativa (HS) skin lesions. However, the role of the P2X7-NLRP3 axis in cytokine dysregulation, immune exhaustion, and clinical disease activity in HS remains unclear. To explore the therapeutic potential of targeting P2X7, we conducted a phase 2 randomized, double-blind, placebo-controlled trial of the small molecule inhibitor AZD9056. Five patients with moderate-to-severe HS received AZD9056 (400 mg daily) for 24 weeks, while seven received a placebo for 12 weeks, followed by a 12-week open-label AZD9056 phase. Tissue and plasma samples were collected at baseline, week 12, and week 24 for Luminex assays. Resting cytokine levels were assessed in blood and skin; peripheral blood monocyte (PBMC) immunophenotyping was performed using flow cytometry, and immune exhaustion was evaluated by cytokine production after LPS+ATP stimulation. Clinical data showed no significant impact of AZD9056 on HS disease activity (HiSCR, IHS4). In line with the lack of clinical response, cytokine levels in skin and blood were also unaffected. However, AZD9056 restored LPS+ATP-stimulated cytokine production in PBMCs (restoring IL-13, IL-1β, IL-6, and TNF-α, all $p < 0.05$). Flow cytometry revealed reduced Th1/Th17 axis expression following AZD9056 treatment. In this small study, P2X7 receptor inhibition did not improve HS clinical activity or cytokine dysregulation in HS lesions. Nonetheless, P2X7 inhibition restored cytokine production in PBMCs, reversing immune exhaustion, possibly via reduced Th1/Th17 expression. While it does not address HS clinical activity, it may enhance immune responses, meriting further investigation for its role in immune dysfunction in HS and other autoimmune diseases.

0426

UAZ22-10-01: A Phase IIa single-arm open-label clinical trial of calcipotriene plus 5-fluorouracil immunotherapy for skin cancer prevention in organ transplant recipients

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Squamous cell carcinoma (SCC) significantly increases morbidity and mortality in organ transplant recipients (OTRs); however, effective SCC prevention strategies for OTRs are lacking. In immunocompetent patients, we demonstrated that topical calcipotriene plus 5-fluorouracil (5-FU) induced thymic stromal lymphopoietin and antigen presentation, promoting the induction of $CD4^+$ T helper 2 (Th2) immunity and tissue-resident memory T (T_{RM}) cell formation in actinic keratoses (AKs) leading to AK clearance. Th2-derived cytokines induced interleukin (IL)-24 in malignant keratinocytes, resulting in cytotoxic autophagy and anoikis, a mechanism distinct from $CD8^+$ T cell cytotoxicity potentially harmful for transplanted organs. To assess the activity and safety of calcipotriene plus 5-FU immunotherapy for OTRs, an open-label multi-site Phase IIa trial (NCT05699603) has been initiated. The trial will enroll 56 kidney or lung transplant recipients with 4-15 AKs in 25 cm^2 on the upper/lower extremities, chest, face, and/or scalp with repeated biopsy of AKs and normal skin. Treatment involves one or two courses of topical calcipotriene plus 5-FU given twice daily for six days to evaluate T cell immunity and AK clearance. The primary endpoint is $CD4^+$ T_{RM} cell induction in AKs one day after completing one or two courses of treatment. Secondary endpoints include evaluating T_{RM} cell persistence at 6 months, AK clearance across anatomical sites, and safety. Enrollment began in August 2024 and is ongoing.

0427

Using p63 immunohistochemistry during Mohs micrographic surgery for cutaneous squamous cell carcinoma

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Background: Immunohistochemical (IHC) stains are increasing in use during Mohs micrographic surgery (MMS) when treating high-risk cutaneous squamous cell carcinoma (cSCC). This case series sought to understand the benefits of intraoperative p63 IHC stains during MMS for poorly differentiated cSCC. Methods: Intraoperatively, a staining protocol for AE1/AE3 and p63 IHC staining was implemented for 15 cSCC cases. One additional case used only p63 IHC staining. Stains were reviewed and graded by the Mohs surgeon as either minimal/no staining or strong straining. Results: Upon review, no p63 cases stained strongly for eccrine duct or follicular structures, compared to 67% of AE1/AE3 cases. Additionally, 89% and 50% of cases strongly stained tumor cells with p63 and AE1/AE3, respectively. After a mean follow-up time of 12 months, there have been two local recurrences and two deaths to date. Both deceased patients died of causes unrelated to cSCC. Conclusion: Intraoperative IHC with p63 during MMS for cSCC has not been previously explored in literature. We demonstrate the successful use of p63 IHC in combination with AE1/AE3 IHC in 15 cases with cSCC. The strong staining of adnexal tissue with AE1/AE3 can be visually distracting. IHC with p63 is promising considering the high rate of positivity in cSCC, more intense staining, and minimal staining of adnexal tissue. Interestingly, one case did stain more intensely for AE1/AE3 which is why we continue to use the stains in combination. While larger studies are needed, intraoperative p63 IHC staining in combination with AE1/AE3 IHC staining during MMS is likely beneficial in identifying poorly differentiated cSCC.

0428

Correlates to barrier function before and after dupilumab treatment

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We evaluated the association of transepidermal water loss(TEWL) with S. aureus(SA) abundance, blood biomarkers or atopic dermatitis(AD) severity and compared lesional(L) to nonlesional(NL) TEWL using data from the Atopic Dermatitis Research Network RDBPC dupilumab(DPL) trial. TEWL(Aquaflux) was measured in moderate-severe (IGA≥3) AD adults at Day(D)0 (n=60) and D42 (DPL n=32; placebo [PLA] n=18). Subjects were washed out of all AD treatments. NL site was 4 cm from a lesion; adjacent NL and L sites were swabbed for SA. At D0, TEWL varied widely at NL (median g/m^2/h [IQR]; 15 [12-23]) and L (36 [25-47]) sites. TEWL did not differ by sex or race. Only NL TEWL negatively correlated with age (r=-0.317, p=0.014), and positively correlated with NL SA abundance (qPCR [r=0.308; p=0.017], colony counts/cm^2 [r=0.322; p=0.012]), serum biomarkers (LDH [r=0.318; p=0.014], CCL17 [r=0.285; p=0.028] and s-CD25 [r=0.267; p=0.041]). Neither L nor NL TEWL associated with eosinophil counts or severity (pruritus NRS, EASI, SCORAD). We previously found that DPL significantly reduced L TEWL by D42. We extended that analysis to study the mean D42 L TEWL-D0 NL TEWL difference (controlling for D0 NL TEWL), which was smaller in DPL vs PLA (4.7 vs 16.8, p=0.001). Regardless of treatment, higher D0 NL TEWL was associated with smaller D42 L–D0 NL differences (p=0.006). Barrier function is highly variable in AD subjects and the major drivers of this abnormality remain uncertain, though the strongest associations are seen with NL TEWL. We observed that L approached D0 NL barrier with DPL at D42.

0429

Outcomes of Mohs micrographic surgery versus wide local excision in sebaceous carcinoma: A comparative analysis

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Sebaceous carcinoma (SC) is a rare skin cancer that is treated with both wide local excision (WLE) and Mohs micrographic surgery (MMS). Given its high recurrence rate and metastatic potential, we sought to compare outcomes of both treatment modalities. Using the National Cancer Database, we identified SC cases diagnosed from 2004-2017. Multivariate logistic regression and Cox proportional hazard models were used to identify factors associated with MMS utilization and 5-year mortality, respectively. Our cohort consisted of 3638 patients (MMS [n=697], WLE [n=2657]). Multivariate analysis revealed tumor location on the head/neck was associated with increased MMS use compared to WLE (OR [95% CI] = 2.94 [2.20-4.11]). Treatment at a non-academic facility (0.28 [0.22-0.35]), tumor size over 1cm (0.53 [0.36-0.80]), and TNM stage 4 (0.05 [0.01-0.18]) were associated with decreased MMS use. Independent risk factors for 5-year mortality included age over 65 years (HR [95% CI] = 2.05 [1.63-2.58]), public insurance (1.71 [1.37-2.15]), TNM stage 4 (8.22 [3.94-17.15]), treatment at a non-academic facility (1.23 [1.06-1.44]), and chemotherapy receipt (2.26 [1.23-3.99]). Female patients (0.74 [0.64-0.87]) and radiation therapy (RT) (0.68 [0.52-0.90]) had significantly decreased 5-year mortality risk. We appreciated an insignificant trend towards decreased 5-year mortality with MMS versus WLE (0.85 [0.69-1.04]). To our knowledge, this is the largest comparative analysis of SC treated with MMS or WLE in a racially diverse population. Our analysis highlights use of MMS among small, low stage tumors which likely reflects the lower recurrence rates associated with MMS over WLE. Consistent with prior literature, however, we did not find improved survival among patients treated with MMS over WLE. Finally, the association between RT and decreased mortality is novel and requires further exploration to better define the role of RT in management of SC.

0430

Five year follow up findings testing effectiveness of single ablative fractionated laser resurfacing for the treatment and prevention of actinic neoplasia

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Actinic keratosis (AK) and non-melanoma skin cancer (NMSC) are common human actinic neoplasia associated with chronic exposure to ultraviolet light and aging. Recent studies indicate that a major factor in the enhanced susceptibility of geriatric skin to photocarcinogenesis is due to the lack of the critical fibroblast-derived mediator insulin-like growth factor-1 (IGF-1), and that wounding therapies upregulate IGF-1 levels. This study aims to define the long-term effectiveness of a single wounding of forearm skin with fractionated laser resurfacing (FLR) on precancerous AKs and NMSCs in aged skin. Data was accumulated for up to 66 months from 48 non-diabetic subjects, aged 60 and older. Previously, data from this cohort at 36 months was published. Participants in this randomized clinical trial with at least five AKs on each dorsal forearm/wrist received a single treatment with a 2,790-nm yttrium scandium gallium garnet fractional ablative resurfacing device to one dorsal forearm/wrist. Follow-up appointments occurred every six months, where AKs/NMSCs were counted on both extremities in blinded fashion. FLR treatment reduced AKs present at the time of treatment and decreased AK development for at least 48 months. At 66 months, 34 NMSCs on untreated arms and 7 NMSCs on FLR treated arms were identified, compared to 24 NMSCs on untreated arms and 2 NMSCs on FLR treated arms at 36 months of follow-up. The numbers of NMSC (predominantly SCC) mirrored the numbers of AKs. Data from this cohort recruited suggests a single wounding of geriatric skin with FLR effectively decreases the incidence of AK/NMSC with lasting protection. Patients with a history of multiple NMSC in particular may benefit from this intervention.

0431

Dermatologic adverse events in patients receiving duvelisib single-agent and combination therapies

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Duvelisib is a dual phosphoinositide 3 kinase (PI3K)-g and -d inhibitor, approved for chronic and small lymphocytic leukemia, that is a promising treatment for T-cell lymphomas. Dermatologic adverse events (DAEs) associated with duvelisib have been observed in hematologic malignancy clinical trials and reported in the product's prescribing information, although no in-depth assessment on these has been performed. We retrospectively characterized possible, probable, or definite duvelisib-associated DAEs in all 173 patients treated with duvelisib at our tertiary cancer center from 2000-2024. DAE incidence while on duvelisib was 31.9% (23/72) on single agent duvelisib, 18.6% (8/43) on duvelisib and romidepsin, 17.4% (4/23) on duvelisib and bortezomib, and 5.7% (2/35) on duvelisib and ruxolitinib. Across all regimens, most DAEs were maculopapular rash (n=19, 51.4%), xerosis (n=6, 16.2%), or mucositis (n=3, 8.1%). 24.3% (n=9) were grade 3 DAEs. For single agent duvelisib, median time to DAE onset was 78 days and median duration 29 days. Single agent duvelisib DAEs were managed with topical steroids (56.5%), antihistamines (26.1%) or systemic steroids (34.8%). Most patients (73.9%) continued duvelisib. In addition, 11 patients (6.4%) developed rash only after duvelisib was discontinued for another indication, mostly appearing as maculopapular rash (63.6%) within median 3 days. Our data is consistent with published PI3Ki DAE incidence rates as well as information and management recommendations in the approved labeling for duvelisib. We noted a lower incidence of DAEs (p=.004) and fewer patients with severe DAEs (p=.04), trending towards shorter duration DAE (p=.08), in patients on duvelisib in combination with romidepsin, bortezomib or ruxolitinib compared to patients on duvelisib alone. Further studies are required to delineate the effects of other agents on incidence and severity of PI3Ki-associated DAEs.

0432

Guselkumab pharmacokinetics and immunogenicity in pediatric psoriasis: Phase 3 PROTOSTAR study

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PROTOSTAR evaluated guselkumab (GUS), a selective IL-23p19 subunit inhibitor, in pediatric study participants (pts; ≥6-<18y) with moderate-to-severe plaque psoriasis (PsO; ClinicalTrials.gov: NCT03451851). GUS pharmacokinetics (PK) and immunogenicity were assessed to determine whether PK exposure achieved with pediatric weight-based (WB) dosing was comparable with that established for the approved adult dose regimen. In prior studies, mean steady-state (SS) trough serum GUS concentration in adult PsO pts was approximately 1.2µg/mL. In Part 1 (Weeks [W]0-16), pts were randomized to GUS, placebo, or an open-label etanercept reference arm. At W16 (primary endpoint), Part 1 pts entered GUS withdrawal/retreatment, GUS continuation, or crossover to GUS study periods (W16-52). Part 2 evaluated continuous, open-label GUS treatment in a single arm of pts ≥12y (W0-52). Pts received a WB GUS dose of 1.3mg/kg for pts <70 kg or 100mg for pts ≥70 kg. PK and immunogenicity endpoints (Parts 1&2) included serum GUS concentrations through W16 and W44, and proportions of pts with antibodies (Ab) to GUS, neutralizing Ab (NAb), and Ab titers. In Parts 1&2, 41 and 28 pts received GUS, respectively. In Part 1, mean serum GUS concentrations at W16 were slightly lower in pts aged ≥6-<12y (2.83µg/mL) vs ≥12-<18y (3.61µg/mL); however, ranges largely overlapped. Similar W16 concentrations were observed for the <70 kg and ≥70 kg groups (3.53 and 3.19µg/mL, respectively). In Parts 1&2, SS trough serum GUS concentrations were achieved by W20 and maintained through W44. In Part 2, W20 mean SS trough serum GUS concentrations were 1.50 and 1.54µg/mL for the <70 kg and ≥70 kg groups, respectively. Among 114 GUS-treated pts with available samples through W44, 21 (18.4%) tested positive for Ab to GUS; none had NAb. Ab titers were generally low (80.0% had titers ≤1:160). The development and titers of Ab to GUS did not impact GUS PK or clinical response. The observed PK for GUS in pediatric PsO pts receiving WB dosing was generally comparable with PK in adults with PsO.

0433

JAK inhibitor halts the progression of acute exacerbation of alopecia areata

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JAK inhibitors have been shown to be beneficial for chronic alopecia areata. Their effects on the acute stage of alopecia areata remain uclear. This study aimed to evaluate the efficacy of baricitinib, a Janus kinase inhibitor (JAKI), in halting active hair shedding and promoting hair regrowth in patients with acute alopecia areata (AA) to determine whether early treatment could alter the disease progression. A retrospective review was performed on patients experiencing a new AA episode within three months, with over 30% of the scalp affected by active hair shedding confirmed by a positive hair pull test. All patients were treated with baricitinib (4 mg/day, titrated as needed) for at least three months between November 2022 and July 2024. Baricitinib reduced hair shedding within 2 to 15 weeks (mean 8 weeks), completely halting shedding at 12 weeks. Hair pull tests became negative in all patients by four months, and hair regrowth at an average of 11 weeks. By six months, no patients had a Severity of Alopecia Tool (SALT) score greater than 20. This study showed that JAKI exert beneficial effect on the acute stage of alopecia areata. JAKI, including baricitinib (Olumiant) and ritlecitinib (Litfulo), have demonstrated success in treating chronic AA with extensive hair loss. However, data on their effects in acute active AA remains limited, and whether early treatment with JAKIs can prevent progression to the chronic phase remains to be clarified. While this study suggests that early baricitinib intervention may modify the disease course by rapidly halting hair shedding and promoting regrowth, limitations such as the small sample size, and short follow-up duration warrant further investigation. Future studies should evaluate the broader efficacy of JAKIs in managing acute AA.

0434

Clinical and translational data from a first-in-human study of a novel precision cellular immunotherapy (DSG3-CAART) in mucosal pemphigus vulgaris

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Mucosal pemphigus vulgaris (mPV) is an autoimmune disease caused by autoantibodies to the epithelial adhesion protein desmoglein 3 (DSG3). As a precision medicine approach for mPV, chimeric autoantibody receptor T cell (CAART) technology was developed using an autoantigen-based synthetic immunoreceptor designed to direct T cell cytotoxicity only against anti-DSG3 autoantibody-expressing B cells to avoid global B cell depletion. 23 mPV subjects were enrolled in an open-label phase 1 study of DSG3-CAART, employing 6 dose-escalation cohorts without preconditioning plus 2 cohorts with preconditioning. One subject experienced grade 1 cytokine release syndrome. No dose-limiting toxicities occurred. DSG3-CAART persistence increased linearly across the first 4 cohorts then plateaued; preconditioning with IVIg, cyclophosphamide, +/- fludarabine did not increase post-infusion persistence. After infusion, a decrease in CAAR mean fluorescence intensity was observed in all subjects, associated with enrichment of stem cell memory-like immunophenotypes, little to no IFN-gamma secretion, and no consistent pattern of improvement in clinical disease activity scores or anti-DSG3 antibody titers. In cytotoxicity assays, CAARTs with low CAAR expression demonstrated inferior cytolytic activity compared to those with high CAAR expression. Collectively, these first-in-human data indicate DSG3-CAART is well tolerated, but suggest low CAAR expression post-infusion, potentially due to soluble antibody internalization or inhibition, may impact clinical efficacy.

0435

Exposure - response relationship of icotrokinra effects in participants with moderate-to-severe plaque psoriasis: Phase 2b Frontier 1&2 results

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Icotrokinra (ICO), a targeted oral peptide that binds to the interleukin (IL)-23R to inhibit IL-23 pathway signaling, is in development for moderate-to-severe plaque psoriasis (PsO). Relationships between ICO systemic exposure and clinical response in the Ph2b FRONTIER 1&2 studies were characterized to aid dose selection for Ph3. Population pharmacokinetic (PK) analyses were performed using integrated data from Ph1 (healthy volunteers) and Ph2 (participants [pts] with moderate-to-severe plaque PsO receiving oral ICO 25mg daily [QD]-100mg twice daily [BID]). ICO PK was best described using a one-compartment model with linear elimination and first-order absorption. The relationship between clinical response and population PK-predicted average concentration (C_{avg}) was modeled via ordinal logistic regression. The dataset for exposure-response (ER) analyses included individual PK exposure metrics and PASI/IGA data from 231 pts, including the placebo (PBO) group. Missing clinical response data was treated as missing completely at random and not imputed. Week (W)16 PBO response rates were carried forward to W24 and W52. Among tested exposure metrics, ER analyses showed that C_{avg} is most appropriate to characterize ICO ER relationships. ER modeling suggested the lowest effective ICO dose was 25mg QD and highest clinical response rates were achieved with the 100mg BID dose. As explored by ER, the PBO-corrected PASI and IGA maximal responses for ICO were maintained/increased slightly from W16 to W24 and W52. Model-derived, PBO-corrected maximal PASI 75/90/100 and IGA 0/1 responses at W52 with ICO 200mg QD at the estimated median C_{avg} (1.36ng/mL) were calculated to be 79.8%/69.8%/43.5% and 72.4%, respectively. Estimates from ER models based on C_{avg} indicated that ICO 200mg QD would provide similar clinical response as 100mg BID in moderate-to-severe plaque PsO pts. These findings informed dose selection for the ICO Ph3 PsO program.

0436

Combined phototherapy and systemic treatments for non-segmental vitiligo from 2013 to 2023: A systematic review

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Vitiligo is a disfiguring depigmentation disorder whose treatment remains a serious challenge. While it is generally accepted that phototherapy is helpful for generalized symmetric disease, systemic therapy is often reserved for those with rapid progression. The objective of this study is to evaluate the use of phototherapy combined with systemic therapies for repigmentation. A systematic review was registered in the PROSPERO database and performed under PRISMA guidelines. We searched CENTRAL, ClinicalTrials.gov, Embase, PubMed, and Web of Science from October 2013-2023 for randomized controlled trials (RCTs) using the terms [vitiligo] and/or [treatment] or [intervention]. After exclusion of ineligible reports, 652 studies underwent full-text review. 155 studies met our criteria. The five countries producing the most RCTs for vitiligo were: Egypt, India, Iran, China, and Thailand. We further narrowed our study to RCTs of combination phototherapy and systemic therapy, using vitiligo area scoring index (VASI) as the primary outcome of interest, leading to 9 studies. Interventions included: psoralen (2), afamelanotide, apremilast, minocycline, vitamin D, atorvastatin, vitamin A and E, and prednisone. Eight of nine studies showed statistically significant reduction in VASI after treatment compared to baseline, further supporting the efficacy of phototherapy. Treated versus control subjects showed statistically improved VASI after the following interventions were added to phototherapy: psoralen, minipulsed prednisone, and afamelanotide. In conclusion, UVB remains efficacious in the treatment of vitiligo and some systemic therapies further improved VASI scores. In agreement with previous studies, combination therapy is superior to monotherapy.

0437

Soquelitinib, a selective ITK inhibitor, demonstrates activity in atopic dermatitis (AD) phase 1 clinical trial by a novel mechanism of action

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Interleukin-2-inducible T cell kinase (ITK) is required for the differentiation of naïve helper T cells (Th) into Th2 and Th17 subsets. Given the critical role of these cells in AD, we are evaluating soquelitinib (SQL), an oral, covalent selective ITK inhibitor shown to block Th2 and Th17 differentiation and the production of their associated cytokines such as IL-4, 5, 13, 31, 17, for the treatment of AD. We report interim results of a Phase 1 study evaluating SQL's safety and preliminary efficacy in patients (pts) with moderate to severe AD. The randomized, double blind study design is: 4 cohorts (sequentially enrolled) of 16 pts (12 active to 4 placebo [PBO]); 4 week treatment with additional 30 day follow-up; dosages from 100mg BID, 200mg QD, 200mg BID, to 400mg QD. The 100mg BID and 200mg QD cohorts are fully enrolled. SQL-treated pts demonstrated disease response vs PBO at either dose in terms of mean %EASI reduction at Day 28. EASI 75 or IGA 0/1 was achieved in 25% of pts at 100mg BID dose and in 57% at 200mg QD dose. No PBO pts achieved either measure of response. Serum cytokines including IL-5, 17F, 31, 33 and TSLP were reduced more from baseline to Day 28 in treated responders vs non-responders ($p \leq 0.02$ for each comparison) while PBO pts showed little change in these cytokines. Day 58 safety follow-up showed continued improvement in EASI in the "off period" for SQL-treated pts but not in PBO. Increased circulating FoxP3 +Tregs were found in the blood of SQL treated pts and a reduction in circulating (type 2 innate lymphoid cells) ILC2 cells were seen. In SQL-treated pts, AEs were limited to 1 Gr 1 nausea and 1 Covid 19; all pts received the full course of treatment. This is the first report of selective ITK inhibition for treatment of AD and indicates that this mechanism has the potential for more durable control of AD with an oral agent due to blockade of multiple Th2/Th17 cytokines, induction of Treg suppression and blockade of ILC2.

0438

A randomized controlled trial of a novel skin substitute on epidermolysis bullosa wounds

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Background: Recessive Dystrophic Epidermolysis Bullosa (RDEB) exhibits severe manifestations including extensive areas of wounds, increased risk of squamous cell carcinoma, anemia, skin infections, pain, itch, and early mortality. The topical drugs, beremagene-geperpavec and birch-triterpenes, have been approved for RDEB wound healing but are not curative. We have developed a cell therapy approach utilizing genetically corrected patient-derived stem cells to heal RDEB wounds. Application of cell therapy requires a matrix that can suspend and allow cells to attach to the wound bed. RDEB patient skin is extremely fragile and prone to injury from adhesive dressings. We tested a nano spun polymer spray matrix as a vehicle to ensure safety, tolerability, and wound healing in RDEB wounds. Method: RDEB patients, age 6 years or older with at least six wounds of $10cm^2$ were enrolled at a single site. The primary endpoint was 90% wound closure from baseline to Month 4. Secondary endpoints included wound pain, itch and adverse events (AEs). Results and Discussion: We evaluated 42 wounds in 6 RDEB patients (mean age of 21 years). Wounds were matched by size and location, and were randomized either to Spincare matrix or control. Subjects applied the nano spun matrix weekly and did not report increased blistering, pain, or itch compared with untreated wounds. Importantly, Spincare matrix did not significantly change wound healing over 4 months using monthly evaluations/photos and did not increase wound infection. No AEs were related to Spincare® and its discontinuation. Results from this pilot trial show that Spincare matrix treatment on RDEB wounds is a safe and tolerable cell therapy delivery method for a future Phase 1 trial of gene-edited induced pluripotent stem cells.

0439

3D imaging elucidates neuroimmune dynamics in atopic dermatitis skin treated with ruxolitinib cream

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Atopic dermatitis (AD) is a chronic, inflammatory skin disease with heterogeneous lesions and a complex pathophysiology. The phase 2, open-label SCRATCH-AD study assessed the effects of 1.5% ruxolitinib (RUX) cream (selective JAK1/JAK2 inhibitor) in patients with AD. Adults (N=49) with ≤20% affected BSA applied cream twice daily for 28 days and achieved rapid, sustained itch relief and significant clinical improvement. To explore effects on the AD neuroimmune landscape, 4-mm punch biopsies were collected from lesional and nonlesional skin at baseline and from lesional sites after 28 days of treatment in a subset of 22 patients. Biopsies were stained for nuclei(TO-PRO-3), immune cells (CD45), and peripheral nerves (PGP9.5) and analyzed using Alpenglow Biosciences' Aurora 3Di light-sheet microscope and advanced 3Dm imaging workflows. Machine learning algorithms quantified nerve volume, epidermal thickness, immune cell density, and immune-nerve spatial relationships. Nerve volume did not decrease with treatment, aligning with the observation that nerve fiber density did not differ between lesional and nonlesional skin at baseline. Treatment significantly reduced epidermal thickness and CD45+ immune cells in the epidermis and papillary dermis, with an increased distance between CD45+ cells and nerves observed only in the epidermis. These changes correlated with clinical scores (EASI, IGA). These findings confirm that RUX cream treatment may rapidly transform lesional skin to resemble nonlesional skin, with marked decreases in epidermal thickness and overall immune cell infiltration while leaving nerve fiber volume unchanged. This reinforces the observation that AD lesional and nonlesional skin share similar nerve volume characteristics. By leveraging cutting-edge 3D imaging and machine learning, this study introduces an innovative framework for understanding skin diseases.

0440

Dupilumab for the management of dermatologic adverse events of antibody-drug conjugates

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Background: Antibody-drug conjugates (ADCs) have demonstrated significant efficacy across multiple malignancies. However, ADCs are associated with many dermatologic adverse events (dAEs), which impair patient quality of life and limit treatment adherence. Dupilumab, an IL-4 and IL-13 receptor antagonist, has shown efficacy in managing inflammatory skin diseases and dAEs from immunotherapy. However, its role in treating ADC-related dAEs remains underexplored. Methods: Patients receiving ADCs were identified via retrospective review of dermatology visit notes (January 2020–September 2024). dAE responses were categorized as complete response (CR), partial response (PR), or no response (NR) by manual chart review. Results: The cohort included 11 patients (64% female, 82% White) with a median age of 64 years. Patients received ADC therapy with enfortumab vedotin (82%), sacituzumab govitecan (9%), or ado-trastuzumab emtansine (9%) for genitourinary (73%) and breast (27%) malignancies. Morphologically, dAEs were described as eczematous (54%), morbilliform (46%), vesiculobullous (27%), plaque-like (18%), and lichenoid (9%). Dupilumab was initiated at a loading dose of 600mg followed by 300mg biweekly. Eight patients (73%) achieved CR, and three (27%) achieved PR, with no cases of NR. Median time to first response to dupilumab was 24 days (range=5–74), and median time to best response was 52 days (range=5–287). Eight (73%) patients received systemic steroids previously without clinical response. Dupilumab was well-tolerated, with no adverse events. Conclusions: Dupilumab demonstrates efficacy as a steroid-sparing therapy for ADC-induced dAEs, achieving CR or PR in all patients in this cohort and enabling patients to continue their anticancer therapy. Its favorable safety profile and rapid onset of action suggest a potential future role in mitigating dAEs from ADCs. Prospective studies are needed to confirm these findings and better define the role of dupilumab in this setting.

0441

Effect of oral tranexamic acid on hair melanin in Asian women

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Tranexamic acid (TXA) is an antifibrinolytic agent widely recognized for its efficacy in treating melasma by modulating melanin synthesis in the skin. However, its potential effects on hair pigmentation, a concern often raised by patients, have not been thoroughly investigated. This study aimed to evaluate the impact of oral TXA on hair melanin content and color, providing evidence-based reassurance for its use in clinical practice. A three-month prospective observational study was conducted involving seven middle-aged East Asian women who received 500 mg of oral TXA daily, excluding menstruation periods. Hair samples were collected from ten scalp regions both before and after the treatment. Melanin content was quantified using liquid chromatography-tandem mass spectrometry, while hair color was assessed with a tristimulus colorimeter, allowing precise evaluation of pigmentation changes. After three months, no statistically significant changes were observed in hair melanin content (234.2 ng/mg post-treatment vs. 228.5 ng/mg pre-treatment, p=0.29) or hair color (L*=16.8 post-treatment vs. L*=17.0 pre-treatment, p=0.59). These results were consistent across all participants, irrespective of individual variability in hair growth or baseline pigmentation levels. This study demonstrates that oral TXA at a dosage of 500 mg/day does not significantly affect hair pigmentation, offering valuable reassurance for patients concerned about potential hair whitening during treatment. The findings underscore TXA's selective action on UV-induced skin pigmentation without disrupting hair follicle melanogenesis. By addressing this specific concern, the study enhances patient confidence and supports informed decision-making in the management of pigmentation disorders. Further research is recommended to confirm these findings in larger, more diverse populations, as well as to explore the underlying mechanisms that preserve hair pigmentation during TXA therapy.

0442

Targeting type 2 Inflammation in bullous pemphigoid: Exploring the novel role of upstream tslp and IL-33 as therapeutic targets

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This study explores the theoretical potential of targeting thymic stromal lymphopoietin (TSLP) and interleukin-33 (IL-33) to modulate inflammation in bullous pemphigoid (BP). Conventional therapies such as methotrexate, mycophenolate mofetil, and systemic corticosteroids have limitations in their efficacy and adverse event profile. Recent breakthroughs have demonstrated the importance of type 2 inflammation in bullous pemphigoid. A review of current literature and analysis of cytokine pathways in type 2 inflammatory conditions such as atopic dermatitis and asthma, we evaluated the roles of TSLP and IL-33 in the pathogenesis of BP. The therapeutic targeting of these cytokines in related type 2 diseases underscores their promise in BP. Targeting of TSLP or IL-33 alter the inflammatory milieu to inhibit IL-4, IL-5, IL-13, IgE, CCL17 (TARC), & CCL22 (MDC) production, which have all been implicated in the pathogenesis of BP. These findings highlight the potential for targeting TSLP and IL-33 as innovative therapeutic strategies in BP, offering a novel approach to addressing type 2 inflammation in this disease. Therapeutic targeting of these upstream cytokines result in greater efficacy, lower risk of systemic side effects, and improved patient outcomes in BP versus conventional therapies.

0443

Methotrexate as rescue therapy for hidradenitis suppurativa patients with antibodies against infliximab

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This study investigates the use of methotrexate (MTX) as rescue therapy for patients with Hidradenitis Suppurativa (HS) who have developed antibodies (Abs) against intravenous (IV) infliximab (IFX) therapy. We conducted a single-center, retrospective chart review of patients with HS who were prescribed IFX for HS and initiated on MTX after developing Abs. Patient demographics, comorbid medical conditions, medication regimens, markers of disease severity, and relevant laboratory markers were reviewed. Of the four patients that met the inclusion criteria, 75% were female, 50% identified as Hispanic/Latino, and all were between the ages of 22 and 53. They were managed with varying combinations of infliximab infusions and topical antimicrobials, oral/IV antibiotics, intralesional triamcinolone (ILTAC) injections, or anti-hormonal therapies. Time from infliximab initiation to Ab development ranged from 5 months to 4.5 years. Three patients were started on MTX at the first visit following Ab detection, while one started over two years later. Each patient received a different MTX dose, including 2.5, 7.5, 10 and 15 mg/week. All four patients demonstrated IFX levels ≥1 ug/mL and undetectable Ab levels at the first blood draw following MTX initiation, with time to rescue averaging 53 days. These findings suggest that MTX can be utilized as a rescue therapy for patients with IFX Abs as an alternative to switching therapy altogether. Our findings align with previous literature regarding other inflammatory diseases, in which MTX was shown to be an effective rescue therapy for neutralizing Abs and restoring therapeutic IFX levels. Moreover, the eradication of Abs even at lower doses of MTX or after years of persistent Abs indicates that patients may not always require a high dose of immunosuppression or immediate treatment to achieve a successful response. Due to the retrospective nature and small sample size of our study, further studies of MTX to rescue IFX-refractory HS are needed.

0444

A systematic review of treatments for lupus miliaris disseminatus faciei

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Lupus miliaris disseminatus faciei (LMDF) is a rare granulomatous inflammatory dermatosis with limited cases documented in the literature. At present, there are no established guidelines for treating LMDF making clinical management a challenge. A systematic review of reported treatments for LMDF was conducted using PRISMA guidelines. A total of 486 studies were identified in the literature on initial search. After screening, 86 studies met inclusion criteria. On data abstraction, treatment response was graded on the following scale: complete resolution (CR), significant improvement (SI), partial response (PR), no response (NR), and deterioration (DR). The review included 179 LMDF cases, with gender specified in 176 cases (56.8% male, 43.2% female). Male patients had a mean age of 30.6 ± 10.4 years, while female patients averaged 44.8 ± 16.5 years. Notably, males demonstrated a skewed age distribution with the majority falling into the 20-39 year age range whereas females demonstrated a more standard age distribution. Lesion location was also tracked. Extrafacial lesions of the scalp, abdomen, and back were only reported in male patients. Facial lesion locations were similar across men and women. A total of 296 treatment trials were identified, encompassing 93 unique regimens. The number of cases achieving CR or SI with the following systemic treatments were documented: tetracyclines (39/100, 39%), steroids (39/48, 81.3%), dapsone (32/38, 84.2%), retinoids (17/33, 51.5%), macrolides (12/22, 54.5%), immunosuppressants and DMARDs (7/11, 63.3%), antituberculous drugs (3/8, 37.5%), antimalarials (chloroquines) (4/7, 57.1%), and biologics (6/6, 100%). This study provides a comprehensive review of treatment strategies that have been trialed for LMDF and their respective efficacies.

0445

Amlitelimab reduces atopic dermatitis-related gene expression elevated in lesional skin: An analysis of the phase 2b STREAM-AD study

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Amlitelimab (SAR445229) is a fully human, nondepleting, anti-OX40 ligand monoclonal antibody. In the STREAM-AD phase 2b trial (NCT05131477), amlitelimab, given subcutaneously every 4wks, demonstrated clinically meaningful improvements in patients with atopic dermatitis (AD) and reduced AD-related plasma and cutaneous biomarkers over 24wks compared with placebo-treated patients. This analysis evaluates the effect of amlitelimab on AD-related genes. Differential gene expression analysis was performed between baseline lesional and nonlesional skin biopsies (amlitelimab, n=43; placebo, n=12) and between baseline and on-treatment lesional skin biopsies (amlitelimab, n=27; placebo; n=7) with a specific focus on Th1, Th2, and Th17/22 pathway-associated genes. Normalization of gene expression levels at Wk16 in treated lesional skin toward baseline nonlesional skin was visualized using percent recovery [% recovery= $Log_2FC_{W16vsW0\text{-}LS}$*100/(-$Log_2FC_{LSvNL\text{-}Baseline}$)]. Amlitelimab led to downregulation of Th1 (eg, CXCL9 and CXCL10; P<0.05), Th2 (eg, CCL13 and CCL18; P<0.05), and Th17/22 (eg, S100A8 and S100A9; P<0.05) pathway-associated genes in lesional skin at Wk16 compared with baseline, and a greater % recovery toward nonlesional gene expression levels than placebo. The observed normalization of AD-related genes in lesional skin after 16wks of amlitelimab treatment supports the clinical improvements seen in AD lesions in STREAM-AD.

0446

First insights from phase II, open-label, single-arm study on efficacy of extracorporeal photopheresis (ECP) in early-stage mycosis fungoides

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We aimed to evaluate the efficacy of extracorporeal photopheresis (ECP) therapy among early-stage cutaneous T-cell lymphoma (CTCL) patients with minor peripheral blood involvement using mSWAT, flow cytometry, and quality of life (QoL) questionnaires. ECP has a favorable side effect profile but is currently used for patients with advanced CTCL. Patients received 2 ECP treatments every 2 weeks for at least 3 months, with mSWAT assessed monthly for the first 3 months and then bi-monthly. After 3 months, patients could decrease to monthly ECP treatments. Every 3 months throughout the study, blood involvement was assessed via flow cytometry, and the Skindex-29, FACT-G, and SF-36 QOL questionnaires were completed. Three patients completed the study, with average follow-up time of 14.3 months (range: 12.4 - 18.2 months). Two patients were stage 1A; one was 1B. On enrollment, mSWAT ranged from 1.7 to 11 and the number of CD4+/CD26- cells ranged from 150 to 890. From initial study visit to last follow-up, mSWAT decreased on average by 97% (range: 90%-100%). At three months, mSWAT had decreased by 64% on average (range: -37.7% to -95.45%). Flow cytometry over 9 months showed an average reduction in the number of CD4+/CD26- cells of 44.4% (range: 26.67-69.44%). Over 9 months, FACT-G scores increased on average by 14%, demonstrating slight improvement in overall QoL. Importantly, ECP did not negatively affect patients' QoL. Our preliminary results provide a comprehensive and granular investigation of ECP's effectiveness and impact on quality of life for patients with early-stage disease, suggesting a promising use case for this well-studied and well-tolerated treatment.

0447

Minoxidil for onychodystrophy: Can this hair loss remedy be a nail growth remedy?

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Onychodystrophy, often arising secondary to numerous etiologies, can be idiopathic. In these cases, a nail targeted therapy would be of great clinical utility. This systematic review evaluates the existing literature on minoxidil as a treatment for onychodystrophy. PubMed, Web of Science, and Scopus databases were searched following PRISMA 2020 guidelines using the following strategy: "Minoxidil AND nail." Studies investigating minoxidil treatment of onychodystrophy were included. Background articles, systematic reviews, studies with nonhuman subjects, or articles in languages other than English were excluded. Among 137 articles identified, five were included, yielding 187 patients (51 male, 136 female). Four of five studies evaluated nail growth as an endpoint for minoxidil treatment (n=186), one evaluated nail appearance (n=66), one evaluated nail color (n=1), and one evaluated nail strength (n=66). Three of five studies used 5% topical minoxidil (n=120), one used 2% topical minoxidil (n=1), and one used 1.25 mg oral minoxidil daily (n=66). Topical minoxidil (5%) had significantly greater increases in nail growth at 28 days compared to oral biotin (2.5mg) (p<0.01). Oral minoxidil (1.25 mg) improved nail appearance in 36.4% of patients (n=24), nail growth in 53.0% of patients at month seven (n=35), and nail strength of 37.9% of patients at month eight (n=25). Daily topical minoxidil (2%) resolved nail discoloration within six months (n=1), with no remission at 72 months. All five studies (n=187) demonstrated statistically significant improvement in the measured onychodystrophy outcomes. These outcomes are hypothesized to be linked to increased endothelial growth factors in the area, resulting in improved perfusion to the nail matrix. This review collects all available data on the utility of minoxidil in treating onychodystrophy. While larger and more robust studies are needed to understand optimal dosing and administration regimens, these data are promising for improving nail color, texture, strength, and growth rate. *authors contributed equally

0448

Itching control and long-term remission of atopic dermatitis by TAP1503

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Atopic dermatitis (AD) is a chronic inflammatory disease often causes intense itching. Inflammatory mediators can directly stimulate itch receptors in the skin or sensitize nerve fibers, leading to heightened itch perception. Additionally, persistence of pathogenic resident memory T cells(T_{RM}) , repeated barrier disruption and heightened immune responsiveness in previously affected areas may contribute to lesion recurrence after therapy is discontinued.Tapinarof has been shown to reduce T_{RM} generation and pruritus in inflammatory skin conditions, potentially by activating the aryl hydrocarbon receptor (AhR) and modulating key inflammatory pathways. Through these mechanisms, it may also help stabilize the skin barrier and dampen local immune responses.Here, we report the results from a randomized, double-blind, parallel group, vehicle-controlled Phase III clinical study(CTR20231413), which conducted in more than 30 sites in China. The study evaluated the efficacy and safety of tapinarof(TAP1503) or vehicle applied twice daily for 8 weeks to 272 adults and children 2 years of age and older with moderate-severe AD. Afterward, 43 participants volunteered for a long-term follow-up of 52 weeks, discontinuing medication once their Investigator's Global Assessment (IGA) score reached 0, and resuming treatment if their IGA returned to 2. Itching began to improve on Day 1, with a mean PP-NRS change rate of -5.23%. By Day 2, there was a further, more significant improvement (mean PP-NRS change rate: -8.00%; 95% CI, -16.46% to 0.46%), it was also significantly improved compare with the vehicle-controlled group(p=0.032). During the extended follow-up, approximately 70% of participants in the experimental group did not experience any AD flare-ups after discontinuing treatment, up to the 52-week endpoint. In conclusion, this first and only study in China to use tapinarof (TAP1503) for treating AD-associated pruritus and examining its long-term effects demonstrates that it provides rapid relief and may extend the duration of remission.

0449

Identifying clinical and molecular phenotypes in bullous pemphigoid and immune checkpoint inhibitor-induced bullous pemphigoid: A hierarchical clustering on principal components analysis identifies unique phenotypes and treatment refractory subsets.

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Understanding of disease heterogeneity is limited in classic and immune checkpoint inhibitor (ICI) induced Bullous Pemphigoid (BP); herein, we identify clinical and molecular phenotypes.[1,2] Hierarchical clustering on principal components (HCPC) analysis was performed on 446 patients with a diagnosis of definitive BP (BP=417 & ICI-BP=29) at the Mayo Clinic between 1998-2024. ICI-BP required BP diagnosis during or within 12 weeks of ICI treatment. Four clusters were identified with a difference in treatment refractory and non-treatment refractory cases (N=272 & 174; p=0.040), defined as using two or more systemic treatments. Clusters had similar gender, age, race, ethnicity, smoking, comorbidities, and ICI-BP. Cluster 1 (N=281; ICI-BP=20) had minimal oral involvement (3.6%), highest upper extremity (UE) (92.5%) and trunk (100%) involvement, and highest BP180+/BP230+ (29.5%). Cluster 2 (N=65; ICI-BP=3) had highest lower extremity (LE) (87.7%), and lowest head/neck (10.8%) and trunk (0%) involvement. Cluster 3 (N=27; ICI-BP=2) all had mucosal involvement (100%), highest anogenital (81.5%) and head/neck (48.1%) involvement, and highest BP180+/230- (55.6%). Cluster 4 was the only cluster with eye involvement (12.3%), had lowest UE (9.6%) and LE (16.4%) involvement, and highest BP180-/230- (52.1%). Cluster 3 patients had more refractory treatment (81.5%) compared to cluster 1 (62.6%), cluster 2 (52.3%) and cluster 4 (54.8%). We identified novel phenotypes that have differences in treatment response which further our knowledge for a personalized approach to BP treatment.

0450

Skin transcriptome modulation in Japanese patients with atopic dermatitis treated with rocatinlimab, an anti-OX40 receptor antibody

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Rocatinlimab (AMG 451/KHK4083) is an investigational therapy that inhibits and reduces pathogenic T cells by targeting the OX40 receptor. Rocatinlimab demonstrated efficacy and was generally well-tolerated in moderate-to-severe atopic dermatitis (msAD) in a global placebo (PBO)-controlled, Phase 2b study (NCT03703102). This post hoc analysis in Japanese patients (n=147) explores efficacy and biomarker responses. Patients were randomized to receive subcutaneous rocatinlimab 150 mg every 4 weeks (wks) (Q4W), 600 mg Q4W, 300 mg every 2 wks (Q2W), 600 mg Q2W, or PBO. A double-blind period (to Wk 18) was followed by an active-treatment extension (Wks 18–36; PBO switched to 600 mg Q2W) and an off-treatment follow-up (Wks 36–56). Eczema Area and Severity Index (EASI) and pruritus numerical rating scale (pNRS) scores were evaluated from baseline (BL), and gene expression in non-lesional and lesional skin biopsies were assessed by microarray. Like the global population, greater improvement in EASI score from BL vs PBO was reported as early as Wk 2 with responses maintained through Wk 36 and off-treatment to Wk 56 (Wk 36 LS mean % change in EASI score from BL: -77.81 to -90.15), consistent with improved pNRS scores. Skin transcriptome analysis demonstrated improvement of a meta-analysis derived AD transcriptome at Wks 8, 16, 36, and 52 in lesional and non-lesional skin, consistent with clinical outcomes. Pronounced gene signatures modulated vs BL were related to Th1, Th2, Th17, and Th22 cells, and markers of tissue resident memory T cells and epidermal barrier function (Wk 52, all $p<0.05$). Rocatinlimab induced durable efficacy with acceptable safety and meaningful biomarker responses, demonstrating potential T-cell rebalancing in Japanese patients with msAD.

0451

Phase I/II study of linperlisib plus chidamide in relapsed or refractory cutaneous t-cell lymphoma: A prospective single-center study

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This study aimed to evaluate the safety and efficacy of the combination of linperlisib, a PI3K inhibitor, and chidamide, a histone deacetylase (HDAC) inhibitor, in patients with relapsed or refractory (R/R) cutaneous T-cell lymphoma (CTCL). A prospective, single-center, phase I/II trial was conducted using a "3+3" dose-escalation design. Phase I assessed safety, maximum tolerated dose (MTD), and dose-limiting toxicity (DLT) to determine the recommended phase II dose (RP2D). Phase II primarily evaluated objective response rate (ORR). Linperlisib was administered once daily at escalating doses (40 mg, 60 mg, 80 mg), and chidamide was fixed at 20 mg twice weekly. Between May 1, 2023, and December 31, 2024, 21 patients (12 males, 9 females; median age 43 years) with advanced CTCL, including 18 with mycosis fungoides (MF) and 3 with Sézary syndrome (SS), were enrolled. The median number of prior treatments was 3, and all patients had an ECOG performance status of 0-2. The RP2D for linperlisib was 80 mg, as determined from phase I, with no DLTs observed in the first 9 patients. The most common treatment-related adverse events were nausea (38.1%), pruritus (33.3%), and rash (28.6%), mainly grade 1-2. Grade 3 adverse events included rash and hematologic toxicities (9.5% each). No grade 4 events were reported. In terms of efficacy, the ORR in all patients was 57.1% (12/21): 61.1% (11/18) in MF, 33.3% (1/3) in SS, respectively, with a disease control rate of 85.7% (18/21). 1 patient achieved complete response, and 11 achieved partial response. The median time to response was two months. In conclusion, the combination of linperlisib and chidamide demonstrated a manageable safety profile and promising efficacy in patients with R/R CTCL. This combination may offer a new therapeutic option for advanced CTCL. This trial was registered at www.clinicaltrials.gov as #NCT06037239.

0452

Sunscreen cost inversely associated with sunscreen application amounts

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Sunscreen is a commonly used and accessible form of sun protection, but its cost can present a significant barrier, particularly for individuals requiring regular, year-round use. For these populations, the financial burden may hinder adherence to recommended sun protection practices. To evaluate the relationship between sunscreen cost and application habits, we conducted a study involving 88 participants who used 32 different sunscreen brands, with costs ranging from $0.60 to $36.40/oz and SPF values from 30 to 100. The recommended sunscreen amounts were 2.5 g for the face/neck and 3.0 g for the arm. After adjusting for site, we found that the percentage of the recommended amount applied was inversely associated with sunscreen cost ($p=0.0016$). On average, for every $1/oz increase in cost, the percentage of sunscreen applied decreased by approximately 1%. Participants applied relatively more sunscreen to the arm than to the face/neck. Further analysis revealed that age, gender, and SPF did not significantly influence the amount applied; only price and site of application were significant factors ($p<0.05$). These findings highlight the critical role of affordability in shaping sunscreen usage behaviors. When recommending sunscreen products, healthcare professionals should consider cost as a factor, as patients often rely on their expertise for guidance in skincare and sun protection. Our results suggest that incorporating cost-effective recommendations is optimal to support adherence to sun protection strategies and promote skin cancer prevention.

0453

Therapies for non-anogenital cutaneous warts in immunocompromised patients: A systematic review

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The immune system plays a key role in host recognition and clearance of human papillomavirus-driven cutaneous warts. In immunocompromised patients, warts may be difficult to manage or recalcitrant to first line therapies, raising the risk of progression or malignant transformation. While many interventions exist, there is a lack of comprehensive data on the selection and efficacy of treatments in this patient population. We conducted a systematic review of PubMed, MEDLINE, Web of Science, Scopus, and Cochrane with relevant search parameters for articles published from 1999 to 2024. Of 2,233 articles screened, 46 met the inclusion criteria, with 114 adult and pediatric patients. Among these were 35 case reports, six case series, two retrospective cohort studies, one retrospective observational study, one prospective cohort study, and one open-label clinical trial. The most common immunocompromising condition was organ transplant (58%, n=66), and the least common was iatrogenic immunosuppression (2%, n=2). The most frequent previously failed treatments prior to receiving the studied intervention were cryotherapy, salicylic acid, imiquimod, and 5-fluorouracil. Topical cidofovir exhibited the best response, with 100% complete response (n=7). Pulsed dye laser therapy (PDL), the most frequently studied, showed moderate efficacy (59% partial response, 41% complete response, n=17). Imiquimod had the lowest efficacy (64% no response, 36% partial response, n=14). PDL had the fastest time to clearance at 0.27 months (n=1). Cimetidine had the highest recurrence rate of 29% (n=8). Adverse effects were minimal and did not alter course of treatment. Our review comprehensively synthesizes the existing data over the last 25 years. While several treatments are available, evidence supporting their efficacy remains limited due to small sample sizes and case numbers. Future research directly comparing treatment modalities could help further define the most effective interventions for these challenging lesions.

0454

Artificial intelligence-assisted scribing in dermatology

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Artificial intelligence (AI) assisted scribing, utilizing advanced natural language processing and automatic speech recognition have evolved to generate structured and accurate clinical notes from medical encounters. Additionally, these tools can help with duties traditional scribes may not perform, such as patient follow up, billing, and coding.1 We conducted a review of articles on PubMed using keywords “digital scribe,” “artificial intelligence scribe,” and “artificial intelligence scribe dermatology.” AI technologies have demonstrated high accuracy in diagnosing dermatological conditions, such as skin lesions and melanoma, which suggests that AI scribes could effectively document these findings during clinical encounters. The use of AI in dermatopathology has shown promise in improving diagnostic workflows and supporting education and research. Moreover, AI scribes can enhance teledermatology by facilitating accurate and timely documentation, which is crucial for remote consultations. A pilot study using Dragon Ambient eXperience in a dermatology clinic demonstrated a significant reduction in time spent in EMRs from 90.1 minutes to 70.3 minutes, and a possible saving of $13,000 per year compared to an in-person scribe.2 AI scribes have been demonstrated to save documentation time and help with more accurate charting, however multi-center studies with larger sample sizes are necessary. Research specifically in dermatology is scarce, and the potential integration of visual libraries, such as VisualDx, to assist with diagnosis or patient education should be further explored. 1. Young AT, Xiong M, Pfau J, Keiser MJ, Wei ML. Artificial Intelligence in Dermatology: A Primer. J Invest Dermatol. 2020;140(8):1504-1512. doi:10.1016/j.jid.2020.02.026 2. Cao DY, Silkey JR, Decker MC, Wanat KA. Artificial intelligence-driven digital scribes in clinical documentation: Pilot study assessing the impact on dermatologist workflow and patient encounters. JAAD Int. 2024;15:149-151. doi:10.1016/j.jdin.2024.02.009

0455

Primary localized cutaneous amyloidosis review: An update on immunopathogenesis and therapeutics

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Primary Localized Cutaneous Amyloidosis (PLCA) encompasses a group of disorders characterized by the deposition of amyloid proteins in the skin, with lichen amyloidosis (LA) and macular amyloidosis (MA) being the most common subtypes. These conditions often present with pruritic skin lesions that significantly impact patients’ quality of life. Although PLCA is primarily sporadic, familial cases suggest a genetic predisposition, particularly involving mutations in the oncostatin M receptor-β (OSMRβ) and interleukin (IL)-31RA genes. Recent research has highlighted the IL-31 signaling pathway in PLCA’s immunopathogenesis with IL-31 as a potential target due its role in mediating pruritus. Current treatment options, including topical and systemic therapies, offer varying degrees of efficacy, but there is no standardized treatment protocol. Emerging therapies, such as the aryl hydrocarbon receptor agonist, IL-4Rα inhibitor, IL-13 inhibitors, IL-31RA inhibitor, OSMRβ inhibitor, janus kinase (JAK) inhibitors, and phosphodiesterase 4 inhibitor offer promise in targeting the immunopathogenic mechanisms of PLCA. These novel treatments could potentially transform the management of PLCA, especially in recalcitrant disease refractory to conventional therapies. Further research is warranted to establish the efficacy and safety of these new therapeutic approaches, particularly in PLCA patients without atopic conditions. This review provides an updated overview of the immunopathogenesis of PLCA and explores the expanding therapeutic landscape to improve patient outcomes.

0456

Sarcoidosis: Unveiling a type I interferon driven immunopathogenesis

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Sarcoidosis is a multisystemic granulomatous disease with unclear origins, primarily affecting the lungs, lymph nodes, skin, and eyes. While most patients experience mild symptoms with spontaneous resolution, a subset requires intensive interventions such as lung transplants due to severe respiratory issues. The disease presents a diagnostic challenge due to its heterogeneous triggers and overlapping symptoms with other conditions. Type I interferons (IFNs), previously associated with numerous autoimmune conditions, may be implicated in the immunopathogenesis of sarcoidosis. Plasmacytoid dendritic cells (pDCs), key producers of type I IFNs, are found in sarcoid granulomas, suggesting a role in disease progression. Type I IFNs drive inflammation and also influence macrophage polarization, tipping the balance between the pro-inflammatory M1 and anti-inflammatory M2 macrophages. This modulation may underlie the chronicity of the disease and the formation of granulomas. Moreover, type I IFN-induced signaling pathways, including those involving STAT1 and STAT3, are critical in regulating immune responses and fibrosis, which are central to sarcoidosis immunopathogenesis. Novel therapies targeting type I IFN signaling, including TYK2 inhibitors like deucravacitinib and monoclonal antibodies like anifrolumab, show promise for treating sarcoidosis. This review focuses on the role of type I IFNs in the immunopathogenesis of sarcoidosis and highlights emerging treatments aimed at targeting these pathways. Word Count:

0457

Intradermal influenza vaccination provides an ethical perturbation model for studying cutaneous inflammation in humans

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Comparisons of "snapshot" differences, i.e. cell type composition and cell state, among healthy control, non-lesional, and lesional skin constitute the foundation of known inflammatory skin pathophysiology, yet this design often fails to reveal the dynamical processes that drive disease. Additionally, a rich set of cutaneous stromal cells (keratinocytes, fibroblasts, and endothelial cells) acting as signal amplifiers and immune recruiters are increasingly recognized as critical to inflammatory skin disease pathology. Thus, to better understand the role of stromal cells and their coordinated induction and elicitation of immune responses in human skin so fundamental to inflammatory skin diseases, we have established an intradermal influenza vaccination model to ethically and systematically study the functionality and timing of coordinated immune activity. Through Xenium spatial transcriptomic profiling of skin biopsies from healthy individuals (N=38) before and after intradermally delivered flu vaccine or sham saline, we have identified a dynamic progression of local immune responses involving innate and adaptive immune cells, as well as distinct phenotypic shifts in stromal cell types at the local injection site over time. During early timepoints, there is an initial interferon-STAT1 signature in keratinocytes, fibroblasts, monocytes, endothelial cells and T-cells that rises as early as 2 hours, peaking at day 1 and continues to resolve by day 3. Even 28 days after vaccination, clinically normal appearing skin retains a preponderance of activated monocytes and perivascular T-cells with an effector memory phenotype in the reticular dermis not seen at baseline. This work provides a foundation for future applications in immune cell migration, tissue immune setpoints, and pathogenesis of cutaneous inflammatory disease.

0458

Glucagon-like peptide-1 agonists as an adjunctive treatment for hidradenitis suppurativa: A quality improvement initiative by international dermatology outcome measures (IDEOM)

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This clinic-based quality improvement project aims to assess the effect of glucagon-like peptide-1 (GLP-1) agonists on hidradenitis suppurativa (HS) patient outcomes. Because GLP-1 agonists can reduce systemic inflammation, we hypothesize that their use in HS patients with comorbid diabetes and/or obesity may reduce HS disease severity. Clinical and laboratory assessments were obtained at every patient visit, including vitals, weight, Numeric Rating Scale (NRS) pain score, physical exam, and metabolic parameters. Additionally, patients completed the IDEOM Musculoskeletal Questionnaire (MSK-Q), a 9-item tool validated in psoriasis and exploratory in HS that assesses MSK symptom severity, impact, and fatigue over the past week. The mean age of our 25-patient cohort was 36.4 +/- 13.8; 48.0% African American, 28.0% other, 16.0% white, and 8.0% Asian. Average baseline BMI was 39.6 +/- 7.2, average hemoglobin A1C (HbA1C) was 5.9 +/- 0.5; 24.0% of patients had diagnosed pre-diabetes and 12.0% had diagnosed diabetes. Average responses to the IDEOM MSK-Q showed that MSK symptoms had the greatest impact on daily physical activities (mean impact rating 5.8 +/- 3.5). Due to challenges with insurance approval, only 44.0% of patients received the prescribed GLP-1 agonist. Of these patients, 54.5% had at least one follow-up visit after beginning the medication. Average weight loss was 20 pounds over 19.5 +/- 15.7 weeks. Upon comparing baseline to most recent follow-up visit, three patients achieved HS clinical response (HiSCR). Notably, the mean change from baseline visit to most recent follow-up visit decreased in most questions listed in the IDEOM MSK-Q, abscess and nodule count, NRS pain score, total cholesterol, lipoprotein A, apolipoprotein B, and HbA1C. While our study is ongoing, preliminary data support the use of GLP-1 agonists as an adjunctive HS therapy.

0459

Combination of questionnaire and capsaicin sting test to reliably assess neuron hypersensitivity in sensitive skin population

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Sensitive skin (SS) is a self-perceived condition, characterized by unpleasant sensations (e.g., burning, stinging, itching, etc.). Among the pathophysiological alterations related to skin sensitivity, neuron hypersensitivity is one of the most prevalent symptoms. This study evaluated the feasibility and validity of combining a sensitive skin questionnaire (SSQ) and capsaicin sting test (CST) to identify subjects with neuron hypersensitivity and evaluate skin properties compared to non-sensitive subjects. Additionally, the efficacy of a facial product was investigated. The double-blinded, randomized study was conducted with forty-nine healthy women (Age 28.5 ± 5.6 years old). The responses to the following three items were obtained to segment subjects as Group 1 (Triple negative), Group 2 (Double positive) and Group 3 (Triple positive): 1. A 14-item SSQ, 2. CST on nasolabial areas; and 3. History of diseases. Skin properties including hydration, TEWL, skin pH, and Current Perception Threshold (CPT) and response to CST, were tracked for all three groups, before and after a 4-week usage of an anti-inflammatory product.Groups 2 and 3 subjects displayed significantly higher erythema and discomfort response to capsaicin vs. Group 1 subjects ($p<0.05$). Group 3 subjects depicted significantly lower CPT at 5 Hz ($p=0.0028$) and 250 Hz ($p=0.0015$) compared to Group 1 subjects. At Week 4, both Group 2 and Group 3 subjects demonstrated a significant reduction ($p<0.0001$) in erythema upon CST compared to baseline, with Group 3 subjects showing a more reduction ($p<0.05$) compared to Group 2 subjects. The proposed method was proven effective to identify subjects with neuron hypersensitivity. The applied anti-irritation product improved erythema response upon CST. Based on this data, we suggest that soothing and calming efficacy will be beneficial to the management of symptoms.

0460

Efficacy and safety of once-daily roflumilast foam 0.3% for psoriasis of the scalp and body involving knees/elbows: Subgroup results from the phase 3 arrector trial

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Thick stratum corneum on knees/elbows can complicate topical psoriasis treatment. Roflumilast foam 0.3% (ROF) is approved for seborrheic dermatitis and is being investigated for psoriasis of the scalp and body. In the phase 3 ARRECTOR/NCT05028582 trial, patients aged ≥12 years with psoriasis of the scalp and body (maximum body surface area ≤25%, at least moderate Scalp-Investigator Global Assessment [IGA], and at least mild Body-IGA [B-IGA]) were randomized to once-daily ROF or vehicle(VEH) for 8 weeks. Endpoints included B-IGA success (clear/almost clear plus ≥2-grade improvement), ≥75% improvement in Psoriasis Area and Severity Index (PASI-75), and safety. Outcomes in patients with baseline knee/elbow involvement are described; all P values are nominal. At baseline, 71% (199/281) of the ROF group and 72% (109/151) of the VEH group had knee/elbow involvement. After 8 weeks, B-IGA success was significantly higher with ROF vs VEH (43% vs 18%; $P<0.001$). Significantly higher proportions (each $P<0.001$) of those with knee involvement achieved regional lower-limb PASI-75/100 with ROF(39%/31%) vs VEH(10%/8%); for elbow involvement, significantly higher proportions achieved upper-limb PASI-75/100 (42%/30% vs 19%/13%). Improvements with ROF vs VEH were also observed for individual PASI components. Safety in patients with knee/elbow involvement was consistent with the overall population. Once-daily ROF provided significant improvement across multiple efficacy measures in patients with psoriasis of the scalp and body involving knees/elbows.

0461

Treatment with topical Ruxolitinib is associated with reduced Staphylococcus aureus burden in chronic hand dermatitis

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Chronic hand dermatitis (CHD) is a common debilitating skin condition with complex pathophysiology. Studies have linked CHD severity to increased Staphylococcus aureus (Sa) colonization. Our previous open-label study (NCT05293717) showed significant clinical improvement with topical 1.5% Ruxolitinib (RUX; Jak1/2 inhibitor) in moderate to severe CHD. Here, we examine changes in Sa burden/abundance in this cohort. Participants (n=15) applied RUX twice daily for 12 weeks, with a 4-week post treatment follow-up. Every 4 weeks, skin swabs were taken from a dorsal, non-lesional (NL; 4x4 cm) area, along with assessments of disease severity (e.g. Hand Eczema Severity Index/HECSI and ItchyQuant). Sa abundance was measured by quantitative PCR of the femA gene (rCFU). Analysis used 0.05 significance level (Prism) and data reported as medians [IQR]. Sa abundance was significantly reduced from baseline after 8 weeks of RUX treatment ($p<0.01$, 255.1 [81.1, 2655] vs 42.1 [23.2, 72.3] rCFU) and maintained at week 12 ($p<0.01$, 50.2 [19.6, 85] rCFU). A greater baseline Sa abundance was found in the atopic (n=7) versus the non-atopic (n=8) subtype ($p=0.02$, 2,342 [122.6, 31718] & 161 [0, 756.2] rCFU); the RUX response did not differ between them. Sa abundance moderately correlated with HECSI during RUX treatment ($r=0.41$, $p<0.01$). Notably, there was increased Sa abundance ($p<0.01$, 50 [20, 85] & 72 [25, 1427]), increased itch ($p<0.01$, 1 [0, 2] & 3 [1, 6]), increased HECSI ($p<0.05$, 6 [2, 9] & 12 [6, 32]) at 4-weeks post-RUX compared to week 12. This study highlights the promising role of RUX in CHD management, with clinical improvement associated to reduced Sa burden and a reversed trend after stopping RUX. Further studies are needed to investigate the contribution of Sa burden in CHD as well as the direct or indirect (e.g. inflammatory mediated) mechanism of RUX.

0462

Efficacy and tolerability of roflumilast cream 0.15% for atopic dermatitis: Pooled subgroup analysis of patients with face/eyelid involvement from phase 3 INTEGUMENT-1/2 trials

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Roflumilast cream 0.15% (ROF) was effective and well tolerated in patients with atopic dermatitis (AD) aged ≥6 years in 2 phase 3 trials (INTEGUMENT-1/2; NCT04773587/NCT04773600). Outcomes in patients with face/eyelid involvement included Validated Investigator Global Assessment for AD (vIGA-AD) success (clear/almost clear plus ≥2-grade improvement), ≥75% improvement in Eczema Area and Severity Index for all body regions (EASI-75) and ≥75%/100% improvement for the head region (hEASI-75/100), and safety/tolerability. Of 1337 patients, 567 (42%) had face and 277 (21%) had eyelid involvement at baseline. At week 4, efficacy was greater for ROF versus vehicle (VEH) overall (vIGA-AD success, 31% vs 14%; EASI-75, 43% vs 21%; hEASI-75, 32% vs 22%; hEASI-100, 23% vs 15%) and in those with face (27% vs 10%; 36% vs 14%; 43% vs 23%; 29% vs 13%) and/or eyelid (30% vs 5%; 36% vs 8%; 40% vs 20%; 24% vs 9%) involvement. Improvements in EASI component scores were also greater for ROF versus VEH in all subgroups. Application site pain was reported for ≤2% of patients across treatments and subgroups. In the ROF group, no irritation/minimal erythema and no/mild sensation were reported by physicians and patients, respectively, for ≥97% and ≥81% at all timepoints across subgroups. Roflumilast cream 0.15% was well tolerated and improved outcomes in patients with AD involving the face or eyelids.

0463

Efficacy, tolerability, and accessibility of tapinarof cream 1% in the treatment of atopic dermatitis: Case series

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Tapinarof cream 1% once daily (QD) is novel topical treatment with a unique mechanism of action, recently FDA-approved in 2022 for plaque psoriasis in adults and pending for FDA-approved indication to treat atopic dermatitis in March 2024. The objective of the study was to assess efficacy, tolerability, and accessibility of tapinarof in treating atopic dermatitis. This case series follows 14 patients across an electronic medical record platform, DermCafe, for demographic (age, gender, ethnicity, phototype), severity and spread of atopic dermatitis, and adverse effects. The primary outcome is clinical improvement within interval of treatment and efficacy based on standardized initial and current patient oriented eczema measure (poem) score. Secondary outcome includes financial accessibility including insurance coverage and cost. The sample size limited to 14 patients within Los Angeles, California. Tapinarof cream 1% once daily shows significant clinical improvement given 13 of 14 patients exhibit significant improvement.

0464

Oral lichen planus treated with upadacitinib: A case series

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Oral lichen planus (OLP) is an erosive mucosal subtype of lichen planus characterized by white papules and plaques, reticulated white lines, erythema, and/or ulceration. OLP is often chronic and recalcitrant, and moderate to severe cases frequently require systemic therapies to adequately control the disease. Studies suggest that interferon-γ and its role in activating the JAK-STAT signaling pathway could play a significant part in disease pathogenesis, but little data exists regarding the effect of JAK inhibitors (JAKi) on OLP. We performed a retrospective chart review of patients seen at the University of Utah with biopsy-supported OLP who were treated with upadacitinib. We identified 9 patients, all of whom were female, who had an average age of 67, and 8/9 had erosive disease. Failed medications included hydroxychloroquine, tildrakizumab, and oral immunosuppressants (azathioprine, mycophenolate, cyclosporine). All patients demonstrated insufficient disease control on topical therapy alone. Treatment outcomes were classified as clearance (no erosions, no erythema, no pain), improvement (no erosions, improved erythema, improved reported pain), and no response. The median disease duration before starting upadacitinib was 4 years (IQR: 3-12), and the median number of failed systemic medications prior to upadacitinib was 3 (IQR: 3-7). All patients either improved (n=6, 66.7%) or had disease clearance (n=3, 33.3%), although one patient required increased dosage (30mg/day) to maintain disease control. The average time to complete or partial remission was 1.11 months. These cases suggest that upadacitinib may be a promising option in treating recalcitrant oral lichen planus. More studies need to be done to investigate the use of JAK inhibitors in treating oral lichen planus in larger controlled trials.

0465

Spatial profiling identifies distinct patterns of immune modulation with dupilumab in the dermis and epidermis of atopic dermatitis patients with improved quality of life

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Epidermal and dermal responses in atopic dermatitis (AD) to dupilumab are poorly understood. GeoMx™ Digital Spatial Profiling was undertaken on skin biopsies collected as part of a phase 4, open-label, exploratory study in 31 adults with moderate-to-severe AD receiving dupilumab 300 mg every 2 weeks for 16 weeks and on skin biopsies collected from 10 healthy controls. The SCOring Atopic Dermatitis (SCORAD) index decreased by 75% (90% confidence limits: −83 to −62.3%, P < 0.0001). Spatial profiling highlighted a significant reduction in IL-4R expression in both the epidermis (−6%, P [adj] = < 8.48×10^{7}) and dermis (−4, P [adj] = 0.03), while IL-13Rα significantly decreased in only the epidermis (−6%, P [adj] = 0.0019). There was overlap in PCA transcriptional profiles between the post-treatment and healthy samples, which clustered separately from pre-treatment samples. Gene sets in Notch signaling, interferon signaling, and cell cycle pathways were significantly reduced in the epidermis, while gene sets associated with IL-4, IL-13, cytokine, and chemokine signaling were significantly reduced in the dermis. There were a number of significantly differentially expressed genes associated with changes in itch (Peak Pruritus-NRS) and intraepidermal nerve fiber density. Dupilumab normalizes canonical and non-canonical pro-inflammatory pathways associated with improvement in itch in the epidermis and dermis of AD patients.

0466

Manual fractional carbon dioxide laser for the treatment of xanthelasma palpebrarum: A prospective, multicenter, randomized, split-face controlled trial

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Background: Xanthelasma palpebrarum (XP), the most common form of cutaneous xanthoma, is a benign condition that significantly affects the aesthetic appearance of patients. Although fractional CO2 laser is an effective and safe treatment for XP, the potential of manual fractional CO2 laser, with its added flexibility, remains underexplored. Objective: To compare the efficacy and safety of manual fractional CO2 laser with automated fractional CO2 laser for XP treatment. Methods: A prospective, multicenter, randomized, evaluator-blinded, split-face controlled trial was conducted in 37 patients with symmetrical bilateral lesions who were randomized to receive either a manual fractional CO2 laser or an automated fractional CO2 laser on each side of the face. Treatment efficacy, patient satisfaction, and adverse events were assessed over five treatment sessions at four-week intervals, with follow-up one month after the final session. Results: At the third session, the number of lesions achieving >75% clearance (score, 4–5) was significantly higher in the manual fractional laser group (60.5%) than in the automated group (31.6%, P=0.001). At the final follow-up, 89.5% and 47.4% of the lesions in the manual group achieved >75% and 100% clearance, respectively, compared to 76.3% and 18.4% in the automated group. Both treatments showed excellent safety with mild and transient adverse effects, patient satisfaction was higher with manual fractional laser therapy, and recurrence rates were slightly lower (22.6% vs.28.6%). Conclusion: The manual fractional CO2 laser offers superior efficacy, comparable safety, and greater patient satisfaction, making it a cost-effective option for XP treatment, especially in resource-limited settings.

0467

Oral upadacitinib for the management of refractory immune checkpoint inhibitor-induced lichenoid reaction

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Severe cutaneous immune-related adverse events (cirAEs) often necessitate steroids and biologics. Some cases, however, remain recalcitrant to these systemic treatment modalities. Janus kinase inhibitors (JAKi) are approved for various inflammatory disorders and represent another promising therapeutic option in these instances. A 79-year-old woman with metastatic renal cell carcinoma initially presented with a grade 1 pruritic, papular eruption involving the face, chest, back, and legs starting a few days after her first and only infusion of ipilimumab and nivolumab. Despite treatment with topical steroids and antihistamines, the rash rapidly worsened to a grade 3 erosive lichenoid eruption over 4 days with greater than 90% body surface area involvement. The patient remained afebrile and experienced no new systemic symptoms, such as arthralgia or myalgia. Punch biopsy confirmed lichenoid dermatitis and laboratory findings showed an ANA titer of 1:320, elevated IL-5 and IL-6, and negative SSA/Ro. Following continual worsening of the eruption despite a prolonged course of prednisone, three doses of dupilumab, as well as apremilast 30 mg BID, oral upadacitinib (15 mg daily) was initiated. Within one week, the patient experienced dramatic resolution of the rash with only mild erythema remaining. She is currently not planned for ICI rechallenge. Systemic JAKi have demonstrated efficacy in managing ICI-related hepatitis, myocarditis, and colitis. Although JAKi should be used with caution in all patients, including those with malignancy, they exhibit a favorable safety profile in cancer patients with irAEs and exert a synergistic effect with checkpoint blockade in patients with Hodgkin lymphoma according to a phase I clinical trial. Our case highlights the potential therapeutic promise JAKi have as a steroid-sparing option for severe cirAEs.

0468

Deucravacitinib in the treatment of lichen planopilaris: 28-week analysis of patient-reported outcome metrics

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Lichen planopilaris (LPP) is a form of lymphocyte-mediated scarring alopecia that presents on the scalp as discrete patches with characteristic perifollicular erythema and scale. The pathogenesis of LPPs involves the JAK/STAT pathway. Deucravacitinib is an oral selective inhibitor of tyrosine kinase 2 (TYK2), a member of the Janus kinase (JAK) family. This open-label, single-arm phase II clinical trial (NCT-06091956) included adult patients with biopsy-proven, active LPP. Patients were treated with deucravacitinib 6 mg twice daily for 24 weeks with 4-week safety follow up. Patient-reported outcome measures (PROMs) were assessed by Dermatology Life Quality Index (DQLI), Visual Analogue Score (VAS), Numerical Rating Scale (NRS), and Skindex-16. Patients (N=10) had a mean (SD) age of 61.4 (11.7); 70% were female and 100% were White. Median (range) disease duration was 6.4 (1.67-15) years, with a mean (SD) of 1.7 (1.3) prior systemic treatments. Baseline mean (SD) DQLI, VAS, NRS, and Skindex-16 scores were 3.8 (2.0), 3.4 (2.4), 4.2 (2.4), and 36.3 (18.6) respectively. Mean (SD) NRS score decreased to 2.3 (1.9) at Week 24. Patient-reported 24-hour itch improved from 60% (n=6) reporting mild/no itch at baseline to 100% (n=9) and 77.8% (n=7) at Weeks 16 and 24, respectively. There was significant improvement in mean Skindex-16 score (-22.5, p=0.020) at Week 24 compared to baseline. Deucravacitinib was well tolerated, with no serious treatment-emergent adverse events (TEAEs), or TEAEs leading to discontinuation. This was the first clinical trial to investigate a selective TYK2 inhibitor in LPP. Patients demonstrated improvement across multiple PROMs, including improvements in itch and pain metrics, and significant improvement in Skindex-16 scores at Week 24.

0469

The association between bariatric surgery and improvement in psoriasis: A systematic review

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Obesity, a risk factor for psoriasis, is linked to increased disease severity and frequency, with metabolic syndrome often compounding disease burden and reducing quality of life (QoL). Weight loss in obese patients can improve psoriasis severity, treatment responses, and metabolic health. Metabolic and bariatric surgery (MBS) has emerged as an effective intervention for weight loss. This systematic review evaluates the association between MBS and psoriasis severity. Embase, MEDLINE, and Scopus were searched until October 2024. Search terms included "psoriasis" and "bariatric surgery." Screening by two reviewers yielded 14 studies with 169 patients. The mean age was 46.8 years (range=24-56), with 74.0% female and average BMI of 43.7 kg/m^2. Most patients underwent gastric bypass (75.1%), followed by sleeve gastrectomy (17.8%). Preoperative psoriasis severity was mild (15.6%, PASI<5 or BSA<3%), moderate (76.3%, PASI=5-10 or BSA=3-10%), or severe (8.2%, PASI>10 or BSA>10%). All studies documented notable weight loss (average post-MBS BMI=32.9 kg/m^2, BMI reduction=8-25 kg/m^2) and improved psoriasis severity: 97.2% experienced mild or resolved psoriasis, and only 2.4% reported worsening. While most patients continued psoriasis treatments post-MBS, many required downgraded therapies. Two studies noted Dermatology Life Quality Index improvements, one statistically significant. These findings suggest that MBS facilitates weight loss while improving psoriasis severity and QoL, highlighting its potential role in managing obesity-related inflammatory conditions. Psoriasis improvement may involve early reductions in proinflammatory mediators (e.g., CRP, leptin) following surgery and decreased tumor necrosis factor-α from adipose tissue after weight loss. Limitations include study heterogeneity in design and outcome reporting. Further controlled trials are necessary to validate long-term effects and establish MBS as adjunctive psoriasis therapy.

0470

Clinical study of intratumoral PH-762 targeting PD-1 for cutaneous carcinomas

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Immune checkpoint antibodies directed at PD-1 or PD-L1 block co-inhibitory receptors expressed by anti-tumor T cells, breaking immune tolerance against tumor cells and generating cancer immunity. The INTASYL™ compound PH-762 is designed to silence PD-1 mRNA within the T cells, providing an alternative to an antibody blockade. Structural and chemical modifications ensure an optimized cell and tissue uptake profile with intratumoral (IT) administration. Preclinical pharmacology studies of PH-762 in syngeneic tumor models demonstrated potent *in vitro* silencing of PD-1 associated with T cell activation, and robust, dose-dependent *in vivo* inhibition of tumor growth. In this open-label Phase 1b clinical study (NCT 06014086), escalating dose concentrations of PH-762 (from 1.14 mg/mL through 22.00 mg/mL) are tested serially in cohorts of 3 patients with cutaneous squamous cell carcinoma (SCC), melanoma, or Merkel cell carcinoma (MCC). Patients receive 4 doses of IT PH-762 weekly over a 3-week period prior to surgical excision 2 weeks later. Tumor changes are evaluated per iRECIST criteria and pathological response. Across the initial 2 cohorts, seven patients received IT PH-762 (1.14 or 2.39 mg/mL). No dose-limiting toxicities or serious adverse events were reported. Pathologic response was reported following surgical excision of the tumor or tumor site. Of the 6 patients with SCC, 2 had complete response, 2 had partial response (1 was near complete with <10% viable tumor), and 2 were non-responders. One patient with metastatic melanoma had no response. IT PH-762 has been well tolerated, with no evident safety signals or reported systemic or off-target toxicities. Clinical and histologic evidence of tumor response is encouraging. PH-762 may decrease tumor bulk or provide a non-surgical alternative in specific circumstances, while minimizing systemic exposure and off-target toxicities. Clinical outcomes, coupled with pharmacokinetic and immunologic response data will inform continued clinical development of PH-762.

0471

Assessing high-dose infliximab therapy in recalcitrant hidradenitis suppurativa: A retrospective review

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The utility of infliximab (IFX) at higher dosages (> 10.0 mg/kg) compared to IFX at standard dosages (< 10.0 mg/kg) has not been extensively studied for the treatment of hidradenitis suppurativa (HS). This study aimed to evaluate the efficacy of high-dose IFX in reducing HS disease severity in patients with refractory HS. We performed a retrospective chart review in which 19 HS patients were selected based on inclusion/exclusion criteria. Demographic variables, clinical parameters including HS physician global assessment (HS-PGA) and Numeric Pain Rating Scale (NPRS) scores, and relevant laboratory markers were assessed. 58.0% of patients were female; 58.0% identified as African American and 26.3% identified as hispanic/latino. The mean age was 34.9 ± 10.4, mean BMI was 34.4 ± 8.3, and mean follow-up period was 14.9 ± 7.9 weeks. Compared to the standard IFX dose cohort, patient's on high-dose IFX experienced a decrease in overall HS-PGA from 4.1 to 3.8 ($p<0.02$) and a decrease in the maximum reported NPRS score from 7.0 to 3.8 ($p<0.01$). Additionally, erythrocyte sedimentation rate decreased from 90.0 to 65.1 ($p<0.03$). No statistical differences between our cohorts were observed for maximum and minimum HS-PGA, overall and minimum NPRS, hemoglobin A1C, leukocyte count, C-reactive protein, interleukin-6, serum IFX levels, and levels of detected IFX antibodies. Notably, no patients reported any significant side effects while taking IFX at either dose. High-dose IFX was associated with clinically meaningful reductions in NPRS scores, however all other parameters exhibited no clinically significant changes. Our results suggest that, while safe, IFX dosages above 10mg/kg provide minimal clinical benefit when treating HS. Future research is needed to confirm our findings on a larger scale as well as investigate alternative inflammatory pathways and/or combination treatments that may be more effective for refractory HS.

0472

Topical ruxolitinib 1.5% cream improves immune and barrier dysregulation in patients with moderate-to-severe seborrheic dermatitis

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Seborrheic dermatitis (SD) is a chronic inflammatory skin disease with limited treatment options that presents with scaly, pruritic lesions across the face, scalp, upper trunk, and skinfolds. This open-label trial aimed to assess both the clinical and molecular effects of 4 weeks topical ruxolitinib treatment in SD using tape-stripping, a minimally invasive skin sampling technique. 25 adult patients with moderate-to-severe SD (Investigator's Global Assessment/IGA 3-4) were treated twice daily with ruxolitinib 1.5% cream. Tape-strips were collected from lesional/LS and non-lesional/NL facial skin at baseline, LS after 4 weeks of treatment, and normal facial skin of 20 healthy controls. 20/25 patients achieved IGA 0/1 at week 4. 3939 DEGs/differentially expressed genes (1945 up/1994 down) at baseline between LS and normal skin and 1990 DEGs (1000 up/990 down) between LS and NL skin were evaluated using RNA-seq (fold change/FCH>2 and false discovery rate/FDR<0.05). Ruxolitinib normalized the LS transcriptome towards NL and normal skin, with 82% and 53% respective improvements at week 4. With treatment, there was significantly decreased expression of Th17-related (IL17A/F, IL23A, IL36G, PI3, CAMP/LL-37, STAT3) and Th22-related (i.e. IL22, SERPINB1/4, S100A7A/8/9/12) pathways. Moderate Th1 downregulation (OASL, MX1, STAT1, IL1B) and upregulation of barrier markers (FA2H, ELOVL3/5, CLDN1) markers was also observed (FDR<0.05 for all). These results demonstrate meaningful normalization of the transcriptome in patients with moderate-to-severe SD, supporting the addition of ruxolitinib to the treatment armamentarium. The observed improvement identifies a strafication of complete responders in 4 weeks, suggesting a molecular propensity for treatment response to be further investigated.

0473

Cell-type expression deconvolution of bulk RNA-seq demonstrates an immune response to topical diphencyprone in cutaneous neurofibromas

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Cutaneous neurofibromas (CNs) are benign tumors associated with neurofibromatosis type 1 (NF1) that pose significant psychosocial and physical burdens to patients. There are currently no effective pharmacologic treatments for CNs. Topical diphencyprone (DPCP) is a hapten that induces hypersensitivity reactions in the skin and has been used therapeutically for cutaneous melanoma metastases. In this clinical trial, DPCP was applied to CNs for 10 weeks after a sensitization period. 36 CN samples of biopsies from day 0, 17 (after first DPCP application), and 107 (30 days after final DPCP application) were assessed by RNA-seq and immunohistochemistry. Single-cell RNA sequencing (scRNA-seq) of 7 CNs was performed to deconvolute bulk RNA-seq data. Cell-type-specific expression profiles were leveraged to impute the cellular composition of the bulk samples. Using Wilcoxon signed rank tests, there was a significant increase in the proportion of the population of macrophages and dendritic cells when comparing day 0 (4.1% of cells) to day 17 (8.1%) ($p<0.05$). Immunohistochemistry of CD68 and CD11c, markers for macrophages and dendritic cells, respectively, demonstrated significant increases in intensity of staining from day 0 to day 17 ($p<0.05$). From day 17 to day 107, macrophages and dendritic cells decreased to 4.9%, still higher than baseline ($p<0.05$). There were no significant proportion changes in vascular endothelial cells, keratinocytes, lymphocytes, neuronal/glial cells, or fibroblasts. These findings indicate a strong influx of immune cells after the first DPCP application, which was largely not sustained 30 days after the final application. DPCP is a promising immunotherapy for CNs, but the optimal application schedule is to be determined.

0474

Sensitive skin and low mineralized thermal spring water: Biomechanical and microbiota benefits

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Introduction: The benefits of low mineral content thermal spring water (LM-TSW) on skin diseases have been known for centuries, including effects on cell membrane fluidity, keratinocyte differentiation, antioxidative, anti-inflammatory properties. However, its effects on sensitive skin are not yet studied. Sensitive skin is characterized by sensations like tightness, pruritus, or tingling. Objectives: This study aimed to access the efficacity of LM-TSW on sensitive skin by biomechanical and microbiota analysis. Materials & Methods: A crossover clinical study involved 24 subjects with sensitive skin, randomized into two groups: each group receiving 6 sprays daily of LM-TSW or MR-TSW, on the face for 8 days. Analyses were performed at day 0 and day 8, including clinical scores, biometrological tests, skin biomechanics (atomic force microscopy), intercorneocyte cohesion imaging, microbiota analysis, and user perceptions. Results: After 8 days, LM-TSW improved sensitive skin parameters: cutaneous irritability, redness, tightness, discomfort, and heat sensation. Skin microrelief showed a significant reduction in roughness, indicating a smoothing effect. LM-TSW also improved skin elasticity at the surface and depth of the stratum corneum, and at the cellular level. This biomechanical effect was associated with better corneocyte cohesion, enhancing the skin barrier. LM-TSW was also improved bacterial richness. LM-TSW was improved user perceptions, with subjects reporting significantly softer, more comfortable skin compared to the MR-TSW group. Conclusion: This study demonstrates, for the first time, the clinical efficacy of LM-TSW on sensitive skin by regulating skin biomechanics and bacterial richness, leading to significant improvements in cutaneous symptoms for sensitive skin volunteers.

0475

High-dose UVA-1 therapy improves patient-reported outcomes and clinical scores in patients with sclerosing skin disease

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Sclerosing disease is challenging to treat, and UVA-1 has been proposed as a potential treatment option, but little data exists. Similarly, clinical changes in sclerosing disease are difficult to assess, and patient-reported outcomes (PROs) can provide key supplementary insight on quality of life, symptoms, and functional changes. To evaluate the impact of UVA1 on sclerotic disease, we conducted a prospective, single-center, open-label clinical trial. Twenty-one patients with morphea (n=11) or systemic sclerosis (SSc) with cutaneous involvement (n=10) were given 30 treatments of high-dose UVA-1 therapy. PROs measured included Skindex-16, the Health Assessment Questionnaire-Disability Index (HAQ-DI), and the Patient Reported Outcome Measurement Information System-Physical Functioning (PROMIS-PF) score. Clinical measurements included the modified Rodnan Skin Score (mRSS), the Localized Scleroderma Assessment Tool (LoSCAT) score, the Physicians Global Assessment (PGA), and the Hand Mobility in Scleroderma (HAMIS) score. Outcomes were gathered at baseline and after 30 treatments. Linear mixed models regression was used to model change in PRO and clinical scores over time (baseline to 30 treatment). Nearly all PROs showed improvement after treatment. Skindex-16 demonstrated improvement in the emotional, symptomatic, and functioning domains (β=-16.4 (95% CI: -29.8, -3.07), β=-17.7 (-31.5, -3.92), and β=-11.4 (-21.7, -1.07) respectively). PROMIS-PF scores also demonstrated a small improvement (β=2.34, 0.01, 4.67). In parallel, objective assessments such as the mRSS (β=-6.56, -12.2, -0.90) LoSCAT Activity Index (β=-12.3, -19.0, -5.57), PGA Activity scores (β=-41.4, -55.1, -27.7), and HAMIS scores (β=-2.96, -4.35, -1.58) showed similar improvement. This data supports the efficacy of high-dose UVA-1 therapy in treating localized and systemic scleroderma, but future randomized prospective trials are needed to support this practice further.

0476

Maximal and sustained TYK2 inhibition: The key to higher efficacy with oral allosteric inhibitors

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ESK-001 is a highly selective allosteric TYK2 inhibitor targeting inflammatory cytokine pathways involved in diseases like psoriasis. This study examines whether sustained ESK-001 exposure to achieve maximal TYK2 inhibition impacts clinical efficacy outcomes. Pharmacokinetic (PK) and PD data, including IFNα-induced pSTATs, were collected from Phase 1 healthy volunteers and Phase 2 psoriasis patients. Efficacy data (PASI score) and biomarker data (TYK2-responsive SIGLEC1) were obtained from Phase 2 and Open-Label Extension studies. Data were analyzed for 40 mg QD and 40 mg BID dosing regimens, evaluating the relationship between pSTAT inhibition, SIGLEC1 suppression, and clinical efficacy. ESK-001 demonstrated a strong correlation between exposure and efficacy. At week 12, PASI 75 and PASI 90 responses for the 40 mg BID dose were 14% and 50% higher, respectively, than those for the 40 mg QD dose. Similar efficacy differences were observed during the Open-Label Extension as well. The 40 mg BID dose maintained >24-hour IC90 coverage for IL-12/IL-23 and IFNα pathways. RNA-seq analysis confirmed maximal inhibition of the type I IFN signature and the TYK2 biomarker SIGLEC1 in both Phase 1 healthy subjects and Phase 2 psoriasis patients. The 40 mg BID dose of ESK-001 achieved >24-hour IC90 coverage and complete SIGLEC1 suppression in patients, suggesting that maximal inhibition results in higher efficacy. These findings support 40 mg BID as the optimal regimen for treating psoriasis.

0477

Improvement of facial beauty of elderly panelists by a non-invasive cosmetic approach using a miniprotein

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One of the most easily recognized aspects of beauty is the shape of the face, which can convey age, gender, and attractiveness. In women, an oval facial shape is considered attractive; however, this structure is significantly altered with age due to skin laxity. One solution to preserve or restore an oval face shape is the use of dermal fillers as an invasive aesthetic approach. In our work, we propose a non-invasive cosmetic alternative based on the topical application of a miniprotein. The objective of this work was to demonstrate the efficacy of this miniprotein to preserve and/or restore the aesthetic aspects of the faces of aged panelists. A double-blind, placebo-controlled, split-face clinical trial was conducted on 30 healthy Caucasian women before and after 14 days, 1 month, and 2 months of topical product use. The oval face improvement parameter was determined by volume reduction measurement determined by clinical grading assessment and by 3D image illustrations (Lifeviz Mini).The biomechanical properties of the face skin area were determined by skin stiffness parameter (EasyStiff® device). The study's results confirm the efficacy of the miniprotein in reversing visible signs of skin aging on the face. The clinical grading of oval shape showed that after two months of miniprotein application, the percentage of subjects without an increase in assigned score was higher than the placebo group, and the percentage of subjects that maintained the score was higher in the active ingredient group. These results confirm the ability of the miniprotein to combat the aging process. These outcomes were further substantiated by 3D images. Additionally, biomechanical assessments indicated that the miniprotein led to a consistent enhancement in skin stiffness across all measured time points. The results presented here demonstrates the effectiveness of the miniprotein in enhancing the aesthetic appearance of the facial skin in aged subjects.

0478

Outcomes of oral dutasteride and oral minoxidil for treating endocrine therapy-induced alopecia from breast cancer treatment: A case series

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This case series explores the utility of oral minoxidil and dutasteride for treating endocrine-therapy induced alopecia (EIA) in real life scenarios. Patients with hormone receptor positive breast cancers commonly require long term maintenance treatment with endocrine therapy. The estrogen receptor blockade suppresses estrogen systemically, causing EIA in 15-33% of patients. This pathogenesis closely resembles the hormonally-driven hair loss in androgenic alopecia (AA). There are no FDA-approved treatments for EIA, however, oral minoxidil and dutasteride have shown promising results for AA and may also be advantageous in EIA. Seven patients with EIA were treated with oral minoxidil 1.25 mg (four patients) or dutasteride 0.5 mg (three patients) daily for at least three months. Pretreatment and posttreatment photographs were compared by two independent dermatologist reviewers using the standardized global photographic assessment to quantify change in hair density on a 7-point scale. The average patient age was 62 years (range 48-80) and the average treatment duration was 365 days (range 112-547). All dutasteride patients demonstrated mild-to-moderate improvement in hair density (+1 to +2). Of the minoxidil patients, two had moderate improvement in hair density (+2) and two had mild improvement (0.5 to +1). Oral dutasteride and minoxidil may provide promising treatment options for patients experiencing EIA. Response to oral therapies is likely multifactorial and influenced by age, EIA medication, treatment duration, and other patient factors. Prospective controlled studies exploring treatment efficacy for EIA and patient factors associated with better response to oral therapies are warranted.

0479

Biologics for the treatment of alopecia areata: A comprehensive review of clinical trials

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Alopecia areata (AA) is an autoimmune condition affecting approximately 2% of the global population. Although corticosteroids and JAK inhibitors are effective for treating localized AA, more effective treatments with lower toxicity are needed for advanced disease. Recently, biologics have emerged as promising therapeutic alternatives. This review analyzed clinical trials indexed on PubMed to assess the efficacy of various biologics for the treatment of AA. Studies examining Dupilumab, Secukinumab, Tralokinumab, Abatacept, Alefacept, Efalizumab, and Aldesleukin were identified. Dupilumab, an interleukin (IL)-4 and IL-13 antagonist, demonstrated $SALT_{30}$, $SALT_{50}$, $SALT_{75}$, and $SALT_{90}$ responses in 32.5%, 22.5%, 15%, and 10% of patients (n=40), respectively. Abatacept, a CTLA-4 modulator, resulted in 91% hair regrowth in one patient, partial regrowth (3-25%) in eight patients, and no response in those with alopecia totalis or universalis. A phase II trial of tralokinumab, an IL-13 inhibitor, had a high dropout rate due to poor efficacy, with only 33.75% improvement observed across patients. Secukinumab, an IL-12 and IL-23 inhibitor, showed no response in 71% of the seven treated patients. Aldesleukin, a recombinant IL-2 analog, achieved a 50% SALT reduction in 14.3% of treated patients compared to 9.1% in the placebo group (n=21). Both alefacept and efalizumab were ineffective for AA treatment. Biologics offer a favorable safety profile and hold potential as therapeutic options for AA, although response rates remain inconsistent. Further research is needed to optimize these therapies, identify more effective targets, and determine predictors of clinical response.

0480

Upadacitinib monotherapy for treatment of pyoderma gangrenosum: A case series

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Pyoderma gangrenosum (PG) is a rare inflammatory disorder characterized by sterile neutrophilic infiltration of the epidermis or dermis, leading to painful and often debilitating skin lesions. Rates of disease vary widely, likely due to challenges in diagnosis, but it is estimated to affect approximately 58 people per million in the United States, with a median age of onset at 50 years and a higher prevalence among middle-aged individuals. Diagnosis is challenging due to its variable presentation and lack of definitive diagnostic criteria, while treatment typically relies on off-label drug use and is frequently complicated by relapses. Dysregulation of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway has been implicated in the pathogenesis of PG, and emerging evidence from limited case studies suggests potential efficacy of JAK inhibitors in its management. These medications have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of inflammatory disorders such as atopic dermatitis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and Crohn's disease. In this case series, we report the successful treatment of PG lesions using upadacitinib monotherapy, a second-generation selective JAK1 inhibitor with an improved safety profile compared to conventional therapies. Patients achieved complete reepithelialization of lesions and complete resolution of reported pain, demonstrating the great potential of upadacitinib for the safe and effective management of resistant and recurring PG lesions. These findings underscore the promise of JAK1 inhibitors as a targeted therapeutic option for PG, warranting further investigation in larger clinical trials.

0481

Evaluating recruitment success in skin cancer clinical trials

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Successful recruitment in clinical trials is important to avoid delays, extra costs, and trial termination. While demographics and trail design are known to influence recruitment, their impact on skin cancer trials remains unexplored. This study addresses this gap by examining patterns in skin cancer trials with successful recruitment. Interventional skin cancer trials from ClinicalTrial.gov with completed enrollment data were queried and their estimated enrollment data was scraped. Trials were categorized by sex, age group, phase, presence of a collaborator, and intervention used. Recruitment success was analyzed as a percentage of actual to estimated recruitment. Differences between subgroup recruitment success were analyzed using the Mann-Whitney test. The search yielded 2,522 completed skin cancer trials with estimated enrollment recorded. No significant differences were observed in recruitment success between sex and intervention subgroups. Phase 3 recruitment success was lower than phases 1, 2, and 4 (respective median difference: 33.0, 26.8, 8.8; $p<0.05$). "Older Adults", "Children and Adults", "Adults and Older Adults" achieved higher recruitment success compared to "Adults" (respective median difference: 84.6, 27.2, 16.0; $p<0.05$) and "Children and Adults and Older Adults" (respective median difference: 84.6, 27.2, 16.0; $p<0.05$). Trials with a collaborator also yielded higher recruitment success (median difference: 16.3; $p<0.05$). These results suggest that recruitment in skin cancer trials is more successful when targeting specific age groups and including collaborators. Phase 3 trials represent a challenge for recruitment while sex and the kind of intervention do not play a significant role.

0482

Post-operative radiation therapy in patients with early-stage merkel cell carcinoma: Analyses from an institutional cohort and national data set

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Introduction: Merkel cell carcinoma (MCC) is an aggressive skin cancer. Postoperative radiation therapy (PORT) is employed in the management of stage I-II MCC, especially cases with high-risk features: head and neck site, tumor >1cm, immunosuppression, and lymphovascular invasion present. This study aims to characterize early-stage patients who received PORT and to quantify the effect of PORT on 5-year disease-specific survival (DSS) and recurrence free survival (RFS). Methods: In the institutional cohort (IC), 108 stage I-II MCC patients, diagnosed 2017-2023, were included in demographic and survival analyses. Using SEER, a national cohort (NC) of 2423 stage I-II MCC patients was included in complementary analyses. Results: Patients who received PORT were younger than patients treated with surgery monotherapy (median age 70 years old vs. 75 in the IC, $p=0.026$; and 72 vs. 77 in the NC, respectively). There were no statistically significant differences between treatment groups in terms of gender, tumor site, or immunosuppression status in the IC. DSS was higher for patients treated with surgery monotherapy (95.6% IC; 87.5% NC - stage I) than those treated with PORT (73.2% IC, $p=0.03$; 82.8 NC - stage I). RFS tended to be higher for patients treated with surgery monotherapy than PORT (81.1% vs. 68.0% in the IC respectively, stage I, $p=0.3$). Discussion: The decision to utilize PORT for patients with early-stage MCC requires nuance, and not all stage I-II MCC patients will benefit from PORT. When stage I and II MCC patients were analyzed as single groups, PORT was not associated with improved DSS or local control. It is possible that the use of PORT reflects unmeasured prognostic factors not captured in these datasets, such as postoperative margin status. Regardless, these data suggest that further studies on appropriate use criteria for PORT in early-stage MCC would be helpful.

0483

Hidradenitis suppurativa onset associated with gamma-secretase inhibitor (nirogacestat)

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Hidradenitis suppurativa (HS) is a chronic follicular disorder affecting apocrine-rich areas, characterized by painful nodules, abscesses, and sinus tracts, leading to scarring and impaired quality of life. Previous studies have linked gamma-secretase (GS) complex knockout mutations to HS. Here, we report a case of HS onset temporally associated with gamma-secretase inhibitor (nirogacestat) use. Objective: To describe a rare case of HS onset linked to nirogacestat treatment. A 47-year-old woman presented with a 4-month history of HS symptoms following initiation of nirogacestat for treatment of a right abdominal wall desmoid tumor diagnosed in December 2021. In early 2024, nirogacestat was initiated. After 5 months, inflammatory nodules of HS appeared on the right inner thighs. Concomitant side effects included diarrhea, fatigue, amenorrhea, and daily hot flashes consistent with menopause onset. HS remained localized while flares occurred monthly. Acute lesions were refractory to intralesional triamcinolone, Augmentin, and topical therapies. At presentation to our HS Center, four to five areas of post-inflammatory hyperpigmentation and scarring were observed in the right inguinal crease and upper medial thigh. Topical chlorhexidine wash and clindamycin gel with oral spironolactone 50 mg twice daily led to reduced HS activity. To our knowledge, this is one of the first reports of HS onset associated with a gamma-secretase inhibitor, accompanied by symptoms suggesting androgen excess and menopause, possibly hastened by nirogacestat. Careful monitoring of gamma-secretase inhibitor therapy as a trigger of HS is underscored by this case.

0484

Impact of increased infliximab infusion frequency on disease severity and pain in hidradenitis suppurativa: A retrospective study

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Patients with hidradenitis suppurativa (HS) often experience disease flares in the week preceding scheduled infliximab infusions, raising concerns about whether a shorter interval between infusions may provide relief and clinical benefit. This study evaluated the impact of increasing infliximab infusion frequency from every 4 weeks to every 3 weeks on disease severity and patient-reported outcomes. We conducted a retrospective cohort study of 27 patients who underwent this modified infliximab regimen. Patient demographics included 55.55% male, 51.85% Black, 18.51% Hispanic, and 44.44% with private insurance. The mean age was 34.74 ± 13.74 years, mean BMI was 33.88 ± 7.78, and mean Hurley stage was 2.87 ± 0.34. Patients were followed for a mean period of 734.07 ± 614.39 days. Patient-reported outcomes indicated that 74.07% experienced some to major improvement, while the remainder reported no improvement. Statistically significant reductions were observed in disease severity, with overall HS physician global assessment (HS-PGA) scores decreasing from 3.59 to 2.70 ($p<0.001$), minimum HS-PGA from 3.2 to 2.4 ($p=0.003$), and maximum HS-PGA from 4.72 to 3.92. Pain outcomes showed improvement, with minimum numeric rating scale (NRS) pain decreasing from 1.8 to 0.64 ($p<0.05$), though reductions in maximum NRS pain ($p=0.052$) did not reach statistical significance. No side effects were reported. These findings suggest that increasing the frequency of infliximab infusions from 4 to 3 weeks can significantly improve HS disease severity and reduce pain in many patients, particularly those who report pre-infusion flares. This adjustment may provide a valuable strategy for optimizing infliximab efficacy in patients who report breakout flares in the week leading up to their infusion. Further studies are needed to validate these findings in larger cohorts and explore long-term outcomes.

0485

Filaggrin and paralogs enable resilient intracellular liquid-liquid phase separation dynamics in the skin

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Intracellular liquid-liquid phase separation (LLPS) and related biomolecular condensates govern wide-ranging cellular mechanisms. We recently uncovered that the keratohyalin granules (KGs) of the epidermis are liquid-like condensates whose Filaggrin (FLG)-driven assembly and pH-triggered disassembly propel terminal differentiation during skin barrier formation. Disease-linked FLG truncation potently abrogates intracellular LLPS, providing new insights into the longstanding link between FLG mutations and skin barrier disorders. FLG and its paralogs are gigantic intrinsically-disordered repeat proteins that have long eluded study through conventional genetic and biophysical approaches. Their repeat domains differ at the sequence level but share related LLPS-promoting compositional features. While FLG2 and RPTN are close in composition to FLG, highly-divergent TCHH defies extant LLPS heuristics. Here, applying cutting-edge biomolecular engineering and live-cell imaging approaches to the entire FLG paralog family, we probed the intracellular LLPS of full-length paralogs and intriguing FLG2 variants. Excitingly, we succeeded in cloning full-length TCHH and RPTN and discovered that both readily undergo intracellular LLPS in human keratinocytes. Like KGs, TCHH condensates fused extensively, suggesting that the trichohyalin granules of hair follicles are liquid-like condensates. Both TCHH and RPTN condensates recruited FLG-like proteins, reminiscent of hybrid epidermal granules. FLG2-like proteins also formed liquid-like condensates. Surprisingly, unlike FLG truncation, frequent FLG2 nonsense mutations favored condensate assembly. Tracing this phenotype to the unique two-domain architecture of FLG2, A-type (HRNR-like) repeats potently drove LLPS while B-type (FLG-like) repeats dampened LLPS. Our findings expose resilient mechanisms to impart functional LLPS dynamics across FLG and paralogs, cementing the skin as a prime tissue system to uncover condensate biology.

0486

Hyaluronic acid-like autophagy activation and in vivo benefits of a porphyridium exopolysaccharide.

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As skin ages, hyaluronic acid (HA) production decreases, due inter alia to impaired synthesis by increasingly senescent fibroblasts – and the HA synthesized can show altered structure and impaired functionality. HA has been shown to enhance autophagy and is a key component of the extracellular matrix (ECM), and thus a key player in skin healing, homeostasis, hydration, elasticity, and volume / plumpness – thus as HA levels diminish, skin may lose moisture retention capacity and firmness, and visible signs of aging such as wrinkling will appear. Hyaluronic acid replacement by injection, while often effective, involves high cost and discomfort, and can involve undesirable side effects. Here, we present new results on hyaluronic acid-like pro-autophagic and *in vivo* skin health and beauty benefits of a sulfated exopolysaccharide (EPS) sourced from Porphyridium cruentum, a marine intertidal spray zone microalga. This EPS is key to the algae's survival in its highly challenging natural environment. In aged skin fibroblasts, the EPS was shown to significantly enhance the autophagic flux, suggesting the EPS might contribute to the clearance of impaired tissue components produced under high tissue senescence loads. This indication was borne out by enhanced expression of key autophagy-associated genes in the same model, including ATG7, DNML1, and LAMP2A. The EPS also significantly increased the production of procollagen I in normal dermal fibroblast culture. In a double-blind clinical trial against a placebo control and a benchmark leg comprising a blend of two HA molecular weight grades, 1% EPS in formulation demonstrated strong improvements, equaling or exceeding the HA benchmark, in skin plumpness and hydration, as well as reductions in skin roughness and wrinkling. This data suggests that this EPS has potential as a safe, natural, and possibly superior pro-autophagic alternative to hyaluronic acid in topical treatment.

0487

Therapeutic and microbial aryl hydrocarbon receptor ligands regulate epidermal ceramide biosynthesis

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The aryl hydrocarbon receptor (AHR) is a transcription factor activated by the agonist tapinarof, an approved topical treatment for plaque psoriasis. Ceramides (CER) are critical lipid components of the stratum corneum (SC) and are produced by keratinocytes during differentiation. While much is known about epidermal CER biochemistry and function, very little information exists about the regulation of CER biosynthesis. Integration of RNA- and Chromatin Immunoprecipitation-Sequence (ChIP-Seq) analyses of epidermal keratinocytes identified AHR-responsive genes that were enriched for the KEGG pathway named "sphingolipid metabolism". Following AHR activation, RNA levels of the CER biosynthetic genes SPTLC2, SPTLC3, SPTSSB, CERS3, DEGS2, as well as the CER salvage pathway genes, SMPD3 and SGPP2, increased. Protein levels of the rate-limiting component of the serine palmitoyl transferase complex, SPTLC2, were also elevated. Concordant with these changes in expression, ligand activation of the AHR increased the sphingoid bases, 3-ketosphinganine and sphinganine, and their ensuing metabolites, CERs, dihydroceramides (DCERs) and hexosylceramides (HCERs). ChIP-Seq analysis, electrophoretic mobility shift and luciferase reporter assays identified several of these genes as direct AHR transcriptional targets. Consistent with a physiological role in mice, levels of CERs, DCERs, and HCERs were also decreased in the skin of Ahr-null mice compared to the wild-type. These results indicate that ligand activation of the human epidermal AHR increases CER biosynthesis. Moreover, the increase of ceramides in response to AHR agonists is likely regulated by the AHR, in part, at the level of transcription. Thus, activation of the AHR provides a mechanism for modulating epidermal ceramide levels and provides pharmacological insights into therapeutic and cosmetic applications of AHR ligands.

0488

Systematic evaluation of topical dosage form type and approved indications for dermatologic use

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Suitability of the dosage form (e.g., gel, ointment, etc.) of a drug product for a given indication is important for optimal therapeutic effect and user compliance. We reviewed the current landscape of approved dosage form type and labeled indications for innovator dermatologic products in the United States as of 12/31/2024, to explore whether a trend exists between the dosage form and indication for these products. 360 dermatologic products were identified and comprise of 26 dosage forms and 25 (consolidated) indications. By count, the top five dosage forms are cream, gel, ointment, lotion and solution. The top ten indications are corticosteroid responsive dermatoses, acne, fungal infection, psoriasis, antiseptic use, actinic keratoses, rosacea, pain, atopic dermatitis and viral infection. Most dermatologic products for corticosteroid responsive dermatoses appear to be emulsion-based dosage forms (57%) or ointments (29%), which have emollient effects that may provide better barrier restoration. Antifungal, psoriasis, atopic dermatitis, and rosacea products follow a similar trend. In contrast, acne products appear to be mostly gels (51%) or dosage forms like solutions, swabs, and foam aerosols (18%), which may facilitate application and potentially be less comedogenic than emulsion-based dosage forms. Topical delivery systems (patches) are typically approved for local deep tissue or neuropathic pain. Antiseptic products are mostly solution-based dosage forms that may include a device to assist with the application. In addition, solutions, lotions, oils, foam aerosols, and shampoos are approved for products indicated for scalp use only, as they may offer a more homogenous distribution on the scalp. An obvious trend was not observed for products for actinic keratoses or viral infection. The prevalence of dosage form types approved for topical dermatologic products generally aligns with their indicated treatment needs, supporting the importance of making rational choices related to selection of the dosage form and excipients during development.

0489

Time-course profiling of serine protease activities and inflammatory profiles in netherton syndrome and atopic dermatitis via tape-stripping

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Netherton syndrome (NS) is a rare autosomal recessive skin disorder with ichthyosis, hair abnormalities, and atopic predisposition. It results from SPINK5 mutations, causing LEKTI deficiency. We investigated time-course changes in serine protease activities and cytokine profiles in NS by evaluating a 19-year-old patient with compound heterozygous SPINK5 mutations. Clinical severity was assessed using the Ichthyosis Area and Severity Index (IASI). Tape-stripped scales were analyzed for protease activity and RNA sequencing during erythroderma (IASI=44.4) and stable phases (IASI=18.2). Trypsin-like serine protease activity was persistently elevated compared to atopic dermatitis (AD) patients and healthy controls, independent of skin condition. Chymotrypsin-like activity was also elevated but less dramatically. RNA sequencing revealed increased expression of inflammatory cytokines, including IL-1α, IL-1β, IL-18, IL-36α, IL-36γ, and IL-17C during erythroderma. Additionally, in a separate case series of 5 AD patients, tape-stripping was used to measure serine protease activities before and after treatment with an oral JAK1 inhibitor. Chymotrypsin-like serine protease activity significantly decreased within 2-4 weeks of treatment initiation compared to baseline. These results suggest that serine protease activity in NS is not regulated by inflammation, and that chymotrypsin activity in AD is controlled by inflammation. Our study indicates that serine protease activity is a therapeutic target for patients with NS, and further detailed investigations are needed.

0490

Proteomic analysis reveals sustained improvements in skin composition in pediatric patients treated with dupilumab

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To date, the details about the ongoing proteomic skin changes in pediatric atopic dermatitis (AD) during dupilumab treatment have not been established. PEdiatric skin barrier function and LIpidomics STudy in patients with Atopic Dermatitis (PELISTAD; NCT04718870) was an open-label study in 6-11 year old moderate-to-severe AD patients. Skin tape strips (STS) were collected from lesional/non-lesional skin of 23 AD patients and 18 healthy volunteers (HV) over 28 weeks (wks). STS extracts were examined at baseline, wks 8, 16 on dupilumab treatment and wk 28 off treatment by liquid chromatography mass spectrometry by proteomics. 424 proteins detected in ≥80% of AD and HV skin samples demonstrated significant changes in expression of lesional skin with dupilumab treatment. 155 of these proteins (cluster 1) were inhibited in lesional and non-lesional skin prior to treatment ($p<0.0001$ and $p<0.001$, compared to HV). These included proteins involved in epidermal barrier formation (keratin intermediate filaments, filaggrin processing and lysosomal enzymes). The expression of cluster 1 proteins increased in both lesional and non-lesional skin by 16 wks of treatment ($p<0.0001$ and $p<0.05$, compared to baseline) and was sustained at wk 28. The improvement in AD skin transepidermal water loss (TEWL AUC20) was correlated with changes in expression of cluster 1 proteins (Spearman r=-0.6996, p=0.0002). Longitudinal STS skin proteome analysis established significant improvement in epidermal differentiation in skin samples of pediatric AD patients treated with dupilumab, which was sustained 12 wks off dupilumab therapy.

0491

Multi-modal barrier repair cream: Harnessing the power of the skin's circadian rhythm

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A barrier repair cream (BRC) was formulated to target the symptoms and source of skin barrier dysfunction in dry to very dry and sensitive skin. Containing microbiome, hydrolipid, tight junction, and circadian rhythm technology, the BRC was developed to optimize daytime defense and nighttime regeneration, thereby supporting skin health and resilience. To evaluate the efficacy and tolerability of the BRC, three studies were conducted involving females with dry skin: 1) Corneometer (24-hour; controlled; leg; single application), 2) Tewameter (14-day; randomized; cheek; sensitive skin; twice-daily application), and 3) consumer preference study (BRC vs. competitor barrier creams; randomized/blinded/split-face; self-perceived moderate to severe dry skin; single application). Each study had 35, 22, and 23 subjects complete, respectively. Stratum corneum water content statistically significantly improved through 24 hours, with 70% and 40% increases after 1 and 8 hours, respectively ($p<0.001$). TEWL decreased by 14% after 14 days ($p=0.004$), and 91% of subjects agreed the BRC "alleviates my dry skin" and "my skin is soothed and calmed." The BRC was also well-tolerated and well-perceived. Furthermore, 73% and 58% of subjects preferred the BRC over two competitor creams, respectively. The improvements in skin hydration and barrier integrity are linked to the BRC's comprehensive formulation targeting multiple factors in skin barrier dysfunction, with the skin's circadian rhythm as a key approach. Overall, the BRC is an intensely hydrating barrier repair treatment suitable for dry and sensitive skin that was also preferred over competitor creams targeting the symptoms and not the source of dry skin. This work was funded by the manufacturer of the BRC.

0492

A proposed pathway for small extracellular vesicles derived from human adipose tissue-derived mesenchymal stem cells to ameliorate atopic dermatitis-like skin inflammation

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Epidermal permeability barrier defects are associated with atopic dermatitis (AD). Using an AD mouse model, we previously showed that topically administered small extracellular vesicles derived from human adipocyte stem cells (sEV) ameliorate skin inflammation and normalize barrier function in parallel with increased ceramide (a key barrier lipid) production. To elucidate how sEV alleviates these AD skin abnormalities, we characterized lipids and ceramide metabolic enzymes in sEV vs. donor adipose tissue-derived mesenchymal stem cells. Free fatty acid, ceramide and sphingomyelin, and ceramide synthetic enzymes (serine palmitoyl transferase and sphingomyelinase) and sphingosine-1-phosphate (S1P) (sphingosine kinase) are enriched, and conversely, ceramide (ceramidase) and S1P-hydrolytic enzymes (S1P lyase and S1P phosphatase) are low in sEV vs. donor cells. Thus, ceramide and S1P levels could raise in cells that receive sEV. Next, we found that sEV mediated increases in S1P suppresses pro-inflammatory cytokine production in AD-model keratinocytes (induced by TNFα/IFNγ) (AD-KC). Additionally, decreased keratinocyte (KC) differentiation, assessed by keratin 10, filaggrin and involucrin mRNA expression in AD-KC, was restored by sEV. Blocking S1P synthesis both attenuated restoration of KC differentiation and suppressed basal KC differentiation. Thus, the S1P-mediated pathway should account for KC differentiation, as well as sEV-driven normalization of KC differentiation. In conclusion, cells which endocytose sEV can normalize epidermal permeability barrier function, as well as ameliorate inflammation by stimulating the S1P signaling pathway.

0493

Fibulin-5 is a novel substrate for granzyme B, its degradation causes dysfunction of elastic fiber assembly by ultraviolet irradiation.

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Fibulin-5, an elastin-binding extracellular matrix (ECM) protein acts as an essential factor for elastic fiber assembly. The absence of fibulin-5 alters structure and assembly of elastic fibers, causing a reduction in skin extensibility and elasticity. Granzyme B (GrB), a serine protease, elevated by ultraviolet (UV) irradiation, etc., degrades dermal ECMs and is involved in structural remodeling in the dermis. Structure of elastic fibers is impaired by chronic UV exposure, which not only causes the degradation but also fails the remodeling process of elastic fibers, while the detailed mechanism is not clear. In this study, we identified that fibulin-5 is a novel substrate for GrB. Fibulin-5 fragments cleaved by GrB could not bind tropoelastin and thus failed to assemble elastic fibers. Furthermore, we investigated that UVB irradiation in keratinocytes increases GrB and disrupts fiburin-5 and elastic fibers. The disruptions were rescued by GrB inhibition. These results suggest that the cleavage of fibulin-5 by GrB is likely involved in the dysfunction of elastic fiber assembly by UV exposure.

0494

Transgenic mouse model to explore the pathophysiology in epidermolytic ichthyosis

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Epidermolytic ichthyosis (EI) is a rare genetic skin disorder caused by mutations in the keratin 1 (KRT1) or keratin 10 (KRT10) genes, characterized by severe hyperkeratosis accompanied by erythroderma. Although the genetic basis of EI is well-documented, the mechanisms underlying formation of epidermolytic hyperkeratosis remain poorly understood. We hypothesized that mechanical stress, together with abnormal keratin protein is responsible in the formation of epidermolytic hyperkeratosis, the characteristic feature of EI, and aimed to elucidate its pathophysiological mechanisms. First, we examined two cases of EI with pronounced palmoplantar hyperkeratosis caused by KRT1 mutations (p.Glu180Gly and p.Ile487Thr). Our findings revealed that desmosomal proteins, such as desmoglein 1 and plakoglobin, which are normally localized along the cell membrane, were abnormally distributed within the cytoplasm in KRT1 mutant samples (p.Glu180Gly). Similar abnormalities were observed in cultured keratinocytes expressing the mutant KRT1 (p.Glu180Gly). Secondly, we generated a CRISPR/Cas9-edited transgenic mouse carrying the KRT1 mutation (p.Ile487Thr) to determine whether a single gene mutation could reproduce phenotypes similar to those observed in EI patients. The transgenic mouse exhibited skin erosions and plantar hyperkeratosis, resembling those seen in EI patients. Hematoxylin and Eosin staining of the plantar skin revealed epidermolytic hyperkeratosis, a hallmark feature of EI. Immunohistochemical staining further demonstrated that desmosomal components in the transgenic mouse exhibited localization patterns similar to those observed in EI patients. These findings suggest that the transgenic mouse we created is a valuable model for studying EI pathogenesis and holds significant potential for the development of treatments and drug discovery for this disorder.

0495

Epithelia-derived MPZL3 regulates murine epidermal differentiation and sebaceous gland development

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Previous *in vitro* and *ex vivo* studies have shown that Myelin Protein Zero-like 3 (MPZL3) is an essential regulator of human epidermal differentiation. MPZL3 also likely regulates epidermal differentiation *in vivo*, as Mpzl3 global knockout (GKO) mice show barrier defects and an inflammatory skin phenotype. However, since MPZL3 is expressed in various tissues, extracutaneous changes may have contributed to the skin phenotype. In this study, we investigated the role of epithelia-derived MPZL3 signaling *in vivo*, using Keratin 14 promoter-driven Cre (epiKO). At E17.5, epiKO embryos showed increased toluidine blue dye permeability, suggestive of delayed barrier formation. Although epiKO pups were indistinguishable from control littermates at birth, they showed perturbed epidermal differentiation (increased filaggrin, Sprr4, Lcn2, S100a9 and Cers4 expression) within 2 weeks and subsequent skin inflammation. Flow cytometry detected increased IL-17+ γδ T cells in the lesional skin. The epiKO pups also showed a significant increase in sebaceous gland size and sebum production (by Oil Red O staining), and bulk RNAseq and qPCR analysis detected up-regulation of genes involved in sebocyte differentiation and lipid metabolism (Keratin 79, epigen, Awat, FASN, perilipin 2, etc.). These results demonstrate that MPZL3 is a key regulator of epidermal barrier formation and sebaceous gland development *in vivo*, and barrier defects upon epithelia-specific MPZL3 deletion trigger γδ T cell activation and skin inflammation. Given the functional conservation between murine and human MPZL3, MPZL3 signaling may be targeted therapeutically to restore epidermal barrier function or to treat sebum production disorders.

0496

Particulate pollution acts on epidermis through pathways that are distinct from intrinsic or UV-induced aging

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Epidermal permeability barrier disruption increases not only skin inflammation but also systemic inflammation via skin-derived cytokines such as IL-6 and TNF-alpha. Particulate pollution (PM2.5) is an important source of systemic inflammation, but whether cutaneous exposure to PM2.5 might contribute to systemic effects is, as yet, unknown. Recently, we reported that aged skin suffers from increased PM2.5 penetration without increased transepidermal water loss (TEWL), likely due to larger but more widely spaced stratum corneum defects, which could be reproduced in young mice by occlusion or microneedle application. Using diesel particulate extract (DPE), we first found that DPE's actions on keratinocyte extrinsic aging induce genes that differ from intrinsic aging, as well as differing from aging induced by sequential passaging and aging induced by UV radiation. With bulk RNAseq, we identified known and novel pathways of DPE action, including reactive oxygen pathways and endoplasmic reticulum stress pathways. These findings demonstrate that PM2.5 acts to induce extrinsic skin aging through pathways that differ from intrinsic aging and aging induced by UV, suggesting that increased aged skin permeability may make aged skin more susceptible to DPE effects, and the combination of intrinsic aging and DPE may induce more inflammatory cytokines than either factor alone. Lastly, these findings suggest that ameliorating DPE actions on skin may improve both skin health and systemic health in people exposed to particulate pollution.

0497

Periderm without IRF6: To be or not to be

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Epidermal morphogenesis starts with the delamination of ectoderm-derived epithelial cells from the basal layer to form a flat layer of periderm cells. Subsequent epidermal layers are formed under the periderm, which is shed right before birth after terminal differentiation is completed. Terminal epidermal differentiation is impaired in the absence of the transcription factor Interferon Regulatory Factor 6 (IRF6) as neonatal Irf6-deficient murine embryos lack the granular and cornified layers. These embryos also exhibit oral epithelium defects, with the presence of tissue-tissue fusions due to a presumptive loss of oral periderm/function. Recent examination of the literature reveals conflicting results as to whether the oral periderm is absent, or present and non-functional based on expression of periderm markers Keratin 6 and 17. In this study, we asked whether the loss of Irf6 affects the epidermal periderm. We performed systemic high magnification morphological analysis of the developing epidermis between E12.5 and E17.5 in wildtype and Irf6-null embryos. By transmission electron microscopy, we observe the presence of flat, electron-dense periderm cells in wildtype epidermis. In Irf6-null epidermis, the superficial cells are less elongated and less electron-dense. Expression of K6 and K17 starts between E12.5 and E14.5 in both wildtype and mutant epidermis (timing varies between keratins and genotype). While K6 is restricted to the periderm and K17 to the periderm early then to hair follicles by e17.5 in wildtype, their expression starts in the superficial periderm-like cells in Irf6-null embryos and then expand throughout the entire epidermis (except basal cells for K6). Similar results were observed with K4, a keratin strongly expressed in periderm cluster from scRNAseq of early mouse epidermis. These data demonstrate the presence of periderm-specific keratins in Irf6-null epidermis, suggesting that the periderm may be present after all. The function of epidermal periderm and the role of Irf6 in this function remains to be determined.

0498

Single cell analysis of hidradenitis suppurativa compared to Crohn's disease

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Hidradenitis suppurativa (HS) and Crohn's disease (CD) are chronic inflammatory disorders affecting distinct anatomical regions yet exhibiting shared phenotype. HS manifests as a skin condition characterized by the formation of deep abscesses and tunnel formation in intertriginous areas, while CD primarily affects the gastrointestinal tract. Despite clinical and immunological overlaps, the precise mechanisms driving fistula formation, a hallmark of both conditions, remain poorly understood. Here, we performed single-cell RNA sequencing (scRNA-seq) on inflamed skin biopsies from HS patients (n=16) and intestinal biopsies from CD patients (n=24) to delineate the common pathologic loop underlying fistula generation. Given the systemic nature of both diseases, we further generated scRNA-seq and mass cytometry profiling of peripheral blood mononuclear cells from HS (n=56) and CD (n=32) patients to elucidate the shared immune dysregulation within circulating immune cells. Building on our previous findings that implicate dysfunctional regulatory T cells (Tregs) in early-stage HS pathogenesis, we hypothesize that impaired Treg functionality similarly contributes to the immunopathology of CD. To further validate our findings, we used spatial transcriptomics at single-cell resolution, revealing shared pathogenic mechanisms of immune dysregulation and identifying potential therapeutic targets.

0499

Use of an integrated multi-omics approach to unlock advantage of natural products for tone management: San Bai Decoction as case study

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Increasing concern of skin disorders has resulted in high demand for the development of superior cosmetic products. TCM formulae (consisting of 2 or more medicinal herbs) has been used over thousands of years for maintaining healthy aging, beauty and wellbeing in China. Therefore, it's critical to discover its scientific significances of synergistic effects of TCM formulae and underlying mechanisms from perspective of systems biology. The aim of our study was to demonstrate the importance of the network pharmacology combined with multi-omics analysis in developing cosmeceuticals from TCM by using San Bai Decoction (poria, licorice, peony and atractylodes, SBD) as case study. Firstly, we constructed compound-target map to illustrate the interaction amongst the chemical constituents (n=444) and regulated genes (n=845) based on public domain database, and then overlayed with HPLC fingerprint to identify 72 representative compounds and characterized 22 lead bioactives by LC-MS/MS for SBD. Secondly, we detected the perturbations of whole-transcriptome gene expressions in SBD-treated keratinocytes and melanocytes separately and identified significant changes in SBD-treated 3D skin model under UVB exposure through integrated transcriptomic and proteomic analysis, and then we constructed a signature network, consisting of 5395 genes/142 proteins to illustrate the comprehensive biological basis of the multifaceted skin properties of SBD, including skin development, keratinization, cell adhesion, cell cycle relevant processes and inflammatory response. The outcome provides mechanistic insights into the multiple functions of SBD. Altogether, these results illustrated that the multi-omics paves a way to reduce time and cost of the development of nutraceuticals and pharmaceuticals from TCM formulae.

0500

Mechanisms of the TNF-α signaling pathway in promoting itch and activating central depressive circuits in psoriasis

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The compromised skin barrier plays a crucial role in psoriasis and its associated depressive comorbidities, yet the underlying regulatory mechanisms remain unclear. Existing literature indicates that a disrupted skin barrier leads to increased expression of tumor necrosis factor-α (TNF-α). Through immunohistochemical staining, Western blotting, and other experimental techniques, we observed a significant elevation of TNF-α in psoriasis skin lesions ($p=0.009$). Behavioral tests revealed that psoriasis mice exhibited notable depressive-like behaviors, as evidenced by their reduced preference for sucrose preference test ($p=0.0018$), performance in the tail suspension test ($p<0.001$), and results from the forced swimming test ($p<0.001$). Furthermore, using brain stereotactic injections, optogenetics, and patch-clamp techniques, we identified that central mechanisms of itch and depression are regulated by the PBN➔vlPAG and vlPAG➔LHA neural circuits, respectively. We also noted a significant increase in TNF-α-overexpressing senescent microglial cells in the vlPAG region of the brain ($p<0.001$). Based on these findings, we hypothesize that TNF-α activation contributes to the engagement of central depressive circuits by promoting itch. We propose to investigate the mechanisms through which TNF-α enhances itch and inflammatory mediators in skin lesions, activates the PBN➔vlPAG➔LHA depressive neural circuit, and is modulated by TNF-α-activated senescent microglia. This investigation will employ interdisciplinary approaches from immunology and neurophysiology. Ultimately, we aim to assess the efficacy of drug-delivering microneedles, with the goal of providing a novel therapeutic strategy for managing the comorbidities of cutaneous inflammation and depression in patients with psoriasis.

0501

Keratin 5 knockout dysregulates keratinocyte differentiation and epidermal morphogenesis and reveals potential pathogenic drivers of epidermolysis bullosa simplex

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Epidermolysis bullosa simplex (EBS) is a rare genetic disorder characterized by skin fragility and painful blistering due to shearing of the epidermis. This disease has been linked to a variety of mutations in the keratin genes KRT5 or KRT14, which encode major cytoskeletal components of basal layer epidermal keratinocytes. While the genetic etiology of EBS is well-known, there is currently no cure for this disease and treatments are focused on pain management, infection risk, and wound care. Since KRT5 loss-of-function was not viable in mouse or macaque models, we engineered human *in vitro* cellular and tissue models to determine how KRT5 depletion compromises epidermal integrity and to elucidate the pathogenesis of EBS. Leveraging CRISPR/Cas9, we generated TERT-immortalized KRT5-deficient human keratinocytes and organotypic epidermis. KRT5-deficient cells exhibited irregular morphology and dysfunctional intercellular junctions along with differential expression of epidermal maturation markers. Utilizing a mechanical dissociation assay, we found that KRT5 depletion weakened intercellular adhesion of highly differentiated keratinocyte sheets. Moreover, KRT5-deficient organotypic cultures exhibited stunted epidermal development with basal cell fragility, diminished intermediate layers, and disruption of desmosomal proteins. To delineate the mechanisms underlying this phenotype, we performed RNA sequencing on KRT5-deficient cultures, which revealed altered expression of key regulators of cytokine signaling, epidermal differentiation, and cell stress pathways. Overall, our model indicates that KRT5 is essential for orchestrating proper human keratinocyte differentiation and epidermal morphogenesis. Importantly, we identified multiple druggable pathways that may drive EBS pathogenesis and could represent novel therapeutic targets.

0502

OPN3 regulates keratinocyte function and modulates psoriasis pathogenesis under pathological conditions

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Psoriasis is a chronic immune-mediated inflammatory skin disease characterized by excessive keratinocyte proliferation, immune cell infiltration, and increased angiogenesis, with an unclear pathogenesis. Opsin3 (OPN3), a member of the G protein-coupled receptor (GPCR) family, plays significant roles beyond its classical functions, including cell proliferation, apoptosis, metabolism, adaptive thermogenesis, tumorigenesis, vasodilation, and immunity. However, the role of OPN3 in psoriasis remains unclear. This study aims to investigate the expression patterns of OPN3 in psoriatic and normal skin and explore its relationship with disease severity. We detected OPN3 expression in psoriatic lesions, perilesional skin, and normal skin using immunohistochemistry (IHC), and constructed a psoriasis mouse model along with cell models with lentiviral-mediated OPN3 knockdown and overexpression to explore the relationship between OPN3 and disease severity. IHC results showed that OPN3 expression was decreased in psoriatic lesions compared to normal skin ($p < 0.01$). Interestingly, intradermal injection of lentivirus overexpressing OPN3 alleviated skin thickening and vascularization in an imiquimod-induced psoriasis-like dermatitis mouse model ($p < 0.01$). Furthermore, OPN3 knockdown in keratinocytes reduced cell proliferation ($p < 0.01$) and increased the protein expression levels of the differentiation marker K10. Our study identifies the critical role of OPN3 in maintaining the balance of keratinocyte proliferation and differentiation and in the pathogenesis of psoriasis, suggesting that OPN3 could be a potential therapeutic target for alleviating psoriasis symptoms.

0503

OVOL1-mediated suppression of ID1 coordinately regulates skin barrier maintenance and neutrophil accumulation in atopic dermatitis-like skin inflammation

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Skin is our outer permeability and immune defense barrier against myriad external assaults. Dysregulation of skin barrier maintenance leads to various skin disorders, with atopic dermatitis (AD) being particularly prominent. Human OVOL1 encodes a zinc finger transcriptional repressor and has been identified by genome-wide association studies to be an AD risk locus. However, its role in AD pathology and the underlying mechanisms remain largely unexplored. Here, we identify Ovol1 as an evolutionarily conserved target of the barrier-protecting aryl hydrocarbon receptor pathway and show that its skin epithelia-specific knockout (SSKO) in mice impairs barrier maintenance during homeostasis. Additionally, this knockout exacerbates skin inflammation in an AD mouse model induced by exposure to house dust mites (HDM) and the Staphylococcus aureus-derived toxin, staphylococcal enterotoxin B (SEB), two environmental agents linked to human AD pathogenesis. Mechanistically, Ovol1 binds directly to the promoter region of the inhibitor of DNA binding 1 (Id1) gene, suppressing its expression in keratinocytes. Inhibition of Id1 by the small molecule AGX51 restores skin barrier function and reduces neutrophil accumulation in SSKO mice exposed to HDM and SEB. Notably, AGX51 administration decreases the expression of neutrophil chemoattractants, such as CXCL1 and CXCL2, in *ex vivo* human skin explants from healthy individuals treated with an inflammatory cytokine cocktail. Finally, we observe a reduction in OVOL1 expression and an increase in ID1 expression in the epidermis of human AD skin lesions. Taken together, our study highlights a keratinocyte-intrinsic OVOL1-ID1 regulatory axis that promotes both epidermal and immune homeostasis against skin inflammation, implicating new therapeutic targets.

0504

Super-resolution imaging reveals stretch-induced architecture rearrangement of desmoplakin in desmosomes

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Desmosomes (DSMs) are large intercellular junctions essential for epidermal adhesion. Desmoplakin (DP) anchors DSM plaque proteins to stress-resistant keratins, maintaining tissue integrity under mechanical stress. The three DP splice isoforms differ only in rod domain length and are all expressed in the skin, although their exact roles remain unclear. Clinically, DP mutations are linked to skin fragility disorders such as acantholytic EB, a perinatally lethal condition, highlighting DP's crucial role. However, the effect of stretch on DSM architecture remains poorly understood. Our previous work showed that DP's tail domain shifts position relative to the cell membrane during DSM maturation. In contrast, the head domain remains fixed, suggesting that DP's tail can adopt different arrangements. In this study, we hypothesized that stretch would induce a conformational shift in DP to absorb mechanical strain and maintain adhesion. To test this, we subjected four human cell lines to stretch in the Flexcell system: epidermal keratinocytes (HEKs) and three mEGFP-tagged isoforms (DP1, DP1a, DP2), each individually transfected into DP-KO. Cells were grown on flexible membranes and exposed to either static (control) or 13% uniaxial strain for 30min. Super-resolution dSTORM was utilized to visualize DP architecture with 20nm resolution. Stretch significantly increased the distance between DP tails compared to static controls across all cell lines (HEKs, $p=0.033$; DP1, $p=0.04$; DP1a, $p=0.013$; DP2, $p=0.002$). In contrast, DP head distances showed no change under stretch ($p=0.54$), suggesting DP's tail is the primary site of mechanical adaptation. Furthermore, our results indicate stretch alters the architecture for all DP isoforms. By adjusting its orientation, DP may absorb mechanical load, thereby maintaining epidermal integrity. In summary, this work enhances our understanding of DSM's spatial and biomechanical behavior and their contribution to dermatological health and disease.

0505

Amplifying skin's hydration for skin health and longevity

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Maintaining skin hydration is crucial for overall skin health, particularly in addressing facial skin aging. Hyaluronic acid (HA), a glycosaminoglycan, plays an important role in attracting and retaining moisture, thus supporting skin health and longevity. With age, endogenous HA levels decrease, accompanied by other biological and molecular changes, resulting in compromised skin health and reduced resilience. When applied topically, HA can provide immediate hydration, resulting in a plump and youthful appearance. A limitation of HA for topical delivery is its inability to penetrate deeply into the skin. To achieve both short- and long-term hydration while supporting skin health and longevity, an ultra-light, oil-free Hydration Boosting Serum (HBS) was developed. This formulation combines a unique blend of high- and medium-molecular-weight HA with an anionic polysaccharide resistant to enzymatic degradation in the skin, as well as fruit extracts; watermelon, apple, and lentil and a peptide to support the production of skin's own natural moisturizing factors. An open-label, split-face clinical study evaluated the moisturizing efficacy of the HBS after a single application on 26 females aged 23 – 71 years with dry or mixed facial skin. Subjects were randomized to apply the HBS or untreated to the right or left side. Triplicate corneometer measurements (n=21) were performed at baseline, 15 minutes, and 2-, 6-, 8-, and 10-hours post-product application. Facial hydration mapping was performed via QIMA NEWTONE on 5 subjects. Ten locations per hemi-face were identified, and triplicate measurements were taken at baseline and 15 minutes post-application. A virtual image was then generated utilizing AI technology via Mean Face, using the average corneometer results of 5 subjects. The HBS amplified moisturizing activity of the superficial epidermal layers at post-baseline timepoints. Peak activity was achieved in 15 minutes with a 61% application in skin hydration. At 10 hours, a 40% increase was determined. Facial hydration mapping further validated skin health results.

0506

WITHDRAWN

0507

TNF-α promotes psoriasis-related keratinocytes dedifferentiation by inactivating NOTCH1 signaling

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The pathogenesis of psoriasis remains elusive, yet anti-TNF-α and IL-17A biologics have proven highly effective, highlighting the crucial role of these cytokines. TNF-α exhibits a broader range of responsive gene signatures in keratinocytes, suggesting its significant impact on keratinocyte fate. NOTCH1 signaling, a critical regulator of cell proliferation and differentiation, has not been thoroughly studied in the context of TNF-α interaction in psoriasis. Our study observed inactivated NOTCH1 signaling in psoriasis skin samples and TNF-α-induced mouse epidermis, accompanied by downregulated keratinocyte differentiation markers (KRT1, KRT10). Using a TNF-α-induced NHEK model, we found significant downregulation of differentiation-related genes, including KRT1 and KRT10, and upregulation of the stemness marker CD44. Knockdown of TNFR1 blocked TNF-α's impact on NOTCH1 signaling and differentiation marker expression. Our results further revealed that TNF-α upregulated ADAM8 expression and activated ADAM10 in an ADAM8-dependent manner, leading to NOTCH1 cleavage and NICD1 release. TNF-α also activated TNFR1 signaling, causing ubiquitination-mediated degradation of NICD1, thereby inactivating NOTCH1 signaling. To validate our findings, we employed cell and animal models. Administration of ADAM8 or ADAM10 inhibitors blocked NICD1 degradation, restored KRT1 and KRT10 expression, and alleviated epidermal thickening in psoriasis-like mice. These results suggest that TNF-α inhibits keratinocyte differentiation by inactivating NOTCH1 signaling through ubiquitination-mediated NICD1 degradation. In summary, our study identifies a novel mechanism by which TNF-α regulates keratinocyte differentiation in psoriasis, providing insights into the disease's pathogenesis and potential new therapeutic targets.

0508

Keratin filaments and soluble vimentin interact to organize signal transduction

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The keratin intermediate filament (IF) cytoskeleton provides crucial mechanical support for the epidermis, but the large number of keratin genes and their context-dependent expression patterns suggest additional non-mechanical roles. How individual IF proteins might perform different non-mechanical functions while maintaining the canonical IF mechanical scaffold has not been clear. We recently found that changing keratin expression during skin wound healing triggers a myosin-activating signaling circuit, potentiating wound closure without compromising mechanical stability. We now report that this signal transduction pathway relies on non-filamentous small oligomers of vimentin, the principal IF protein in mesenchymal cells, to shuttle regulatory kinases into transient signaling complexes with myosin organized on keratin 6A-containing filaments. These results highlight two mechanisms by which IF proteins differentially influence cell signaling and cell mechanics. First, through isoform specific interactions, changing keratin expression modulates recruitment of different proteins to the IF cytoskeleton, increasing the likelihood that these proteins interact. This allows the IF cytoskeleton to spatially and temporally organize signal transduction, effectively functioning as a membraneless organelle. Second, largely overlooked non-filamentous pools of even lowly expressed IF proteins can function as signaling shuttles or adapters. Context-dependent cell and tissue regulation, rather than simple mechanics, may therefore explain the size of the IF protein family.

0509

Nanoplastic and microplastic exposure induces epidermal barrier dysfunction and initiates keratinocyte inflammation

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Skin is our most extensive interface with the environment. At this frontier, the epidermal barrier protects us from myriad environmental exposure agents. Among these are nanoplastics and microplastics (NPs/MPs), a relatively recent class of agents found globally in the environment and within organisms. We are continuously exposed to NPs/MPs through contact with the air, water, personal and household care items, and textiles. Yet, despite their prevalence and constant contact with the body, the potential toxic effects of NPs/MPs on the epidermal barrier and skin immune homeostasis is unknown. As such, we sought to identify the effects of a common NP/MP, polystyrene (PS), on barrier function and cytokine expression in epidermis organoids engineered from primary keratinocytes (N=3). Daily topical exposure (4 h) to PS-NPs/MPs (100 nm, 1.1 µm, 3 µm) for 7 days induced a >40% reduction ($p<0.04$) in barrier function measured by TEER at all sizes and doses (1, 10, 100 ppm). These effects were not due to cytotoxicity as constant exposure up to 120 h did not change the growth of keratinocytes in 2D or affect cellular morphology (N=3), despite observing internalized PS. Next, we measured the transcripts of barrier components in organoids chronically exposed to PS. There was a loss ($p<0.01$) in expression of barrier envelope components FLG and LOR and CLDN4 of tight junctions. Agents that damage the barrier often initiate inflammation and cytokine release in keratinocytes, further impairing barrier function. We find heightened ($p<0.05$) transcripts of key inflammatory mediators and known barrier disruptors TNF, IL1β, IFNγ, and IL6 in organoids. Taken together, our new data show that PS-NPs/MPs induce epidermal barrier damage and cytokine production in keratinocytes, indicating that NPs/MPs alter skin function and provoke inflammation. As MPs/NPs are pervasive in the environment with levels that will only continue to increase, understanding the consequence of skin exposure is imperative to our comprehension of how these environmental exposure agents affect humans.

0510

Desmosomes regulate keratinocyte actin dynamics in basal progenitors to promote epidermal development

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Desmoglein 1 (Dsg1), a desmosomal cadherin expressed only in stratified tissues, is necessary for coordinating mechanical and chemical signals to create a multilayered epidermal barrier. We showed that Dsg1 expression *in vitro* in a subset of basal keratinocyte progenitors promotes differentiation by coordinating Erk inhibition with redistribution of cortical actin tension along the plasma membrane, promoting delamination. Consistent with a role for Dsg1 in stratification, Dsg1 knock out (KO) mouse embryos displayed decreased epidermal thickness at E14.5-E15.5, recovering at E16.5. To find pathways involved in stratification, we performed single cell RNA-seq on Dsg1KO and WT embryos at stages E14.5, E15.5, E16.5 and E18.5, building a developmental atlas (62,459 KO, 39,102 WT cells). Using top gene markers, we identified 8 cell types and 6 keratinocyte subclusters. Differential gene expression analysis of the E18.5 basal II and K14+/K10+ transitional populations revealed significant downregulation of actin modulators including the transcription factor, serum response factor (SRF), and downstream effectors like RhoA, Vinculin, Filamin A and Arp3 ($p \leq 0.05$), the latter which we showed to be important for Dsg1-dependent delamination *in vitro*. Towards defining how Dsg1 regulates Arp3, protein interaction studies revealed the SH2/SH3 adaptor and N-WASP activator Nck1 as a Dsg1 binding partner. Silencing N-WASP or Nck1 reduced Dsg1-mediated stratification 3-fold, which expression of a Nck1 binding deficient mutant Dsg1Y1042F was unable to rescue, presumably through inability to activate N-WASP/Arp2/3-dependent actin remodeling. In accordance, Arp3 membrane recruitment by Dsg1Y1042F was decreased 3-fold. These studies support the idea that Dsg1 modulates actin dynamics in basal and transitional populations through transcriptional and post-translational mechanisms to promote epidermal development.

0511

Critical roles of glycolysis in epidermal barrier disruption under mechanical stress in the skin

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The skin, as the outermost organ, is constantly exposed to environmental stimuli, including mechanical stress. While repeated mechanical stress, such as scratching, is known to disrupt the epidermal barrier and lead to inflammation, the mechanisms underlying barrier disruption caused by faint mechanical stress remain unclear. Here, we demonstrate that repeated faint mechanical stress activates the glycolysis pathway in epidermal keratinocytes, playing a critical role in epidermal barrier disruption. Using a tape-stripping model, we found that repeated faint mechanical stress caused significant barrier disruption, as assessed by transepidermal water loss and dye-penetration assays, without triggering notable inflammation. Bulk RNA sequencing of the epidermis revealed an upregulation of metabolic pathways, including glycolysis-related processes, and immunohistochemical analysis confirmed increased expression of Glut1, the primary glucose transporter in keratinocytes. Pharmacological inhibition of Glut1 nearly completely prevented barrier disruption caused by tape stripping. Furthermore, RNA sequencing revealed that inhibition of glycolysis enhanced the expression of barrier-related genes, including Flg and Lor, in the epidermis of tape-stripped skin. Similar findings were observed in normal human epidermal keratinocytes, where glycolysis inhibition increased the expression of these genes and their protein products. These findings highlight the pivotal role of glycolysis in mediating epidermal barrier disruption induced by faint mechanical stress. Interrupting this cycle may offer a novel therapeutic strategy to prevent epidermal barrier disruption as well as subsequent skin inflammation caused by repeated mild mechanical stress.

0512

Loricrin regulates barrier protection and T cell surveillance to influence photocarcinogenesis

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The epidermis functions as both a physical barrier and an environmental sensor, with intercellular communication playing a critical role in facilitating antigen presentation, immunological memory, and tissue repair. Loricrin reinforces this barrier by forming covalent cross-links, providing effective protection against oxidative stress, including ultraviolet B (UVB). However, these cross-links may inadvertently compromise T cell surveillance, which depends on non-covalent interactions. In the loricrin knockout (LKO) epidermis, keratinocyte-T cell interactions were significantly increased, indicated by enhanced actin-CD3 aggregates ($p < 0.005$). Transcriptomic analysis of $CD4^{+}CD25^{high}$ regulatory T cells (Tregs) from draining lymph nodes revealed significant alterations in gene expression associated with the basolateral plasma membrane, antigen presentation, and regulation of T cell-mediated cytotoxicity. Notable changes included upregulation of key immune modulators, such as the epithelial γδ T cell activator coxsackievirus and adenovirus receptor (2.7-fold, $p < 0.05$) and the non-classical MHC class I molecule Qa-1, a $CD8^{+}$ Treg ligand (10.7-fold, $p < 5 \times 10^{-7}$). Despite exhibiting greater UVB-induced damage and apoptosis as early as one hour post-exposure, LKO skin demonstrated accelerated recovery from DNA photodamage, as evidenced by a reduction in cyclobutane pyrimidine dimer-positive cells over the subsequent 96 hours ($p < 0.005$). Intriguingly, 36 weeks of chronic UVB exposure revealed that loricrin sufficiency promoted carcinogenesis, with significantly reduced tumor-free survival rates ($p < 0.005$), likely due to impaired T cell surveillance. These findings highlight the dual role of loricrin in epidermal physiology: maintaining barrier integrity and promoting detoxification through polymerization in its presence, while facilitating tissue repair and enhancing T cell surveillance by enabling access to the local lymphatic circuit in its absence.

0513

Flower directs apically polarized trafficking of lamellar bodies to establish the epidermal barrier

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Apically polarized secretion of lamellar bodies (LBs) by stratum granulosum keratinocytes facilitates delivery of various lipids, structural proteins and enzymes to the stratum corneum for finalization of the epidermal barrier. While LB function is perturbed in numerous disorders of cornification, the molecular mechanisms regulating their formation and secretion are poorly understood. Here, we demonstrate that the Flower isoform, hFWE4, a putative Ca^{2+} channel with no previously described function in the epidermis is critical for biogenesis and Ca^{2+}-dependent polarized transport of these unique organelles. Using Airyscan microscopy, proteomics approaches and epidermal organoid cultures, we find that hFWE4-positive LBs are abundant in human epidermis, originate from the Golgi apparatus and associate with a distinct ensemble of trafficking mediators shared across tissue specific lysosome related organelles. In a process required for maturation of the epidermal barrier, we find that incorporation of hFWE4 into LBs raises cytosolic Ca^{2+} to facilitate the cell surface targeting of these vesicles. Finally, supporting a critical role for hFWE4-dependent trafficking in establishing the epidermal barrier, we demonstrate that this process is dysregulated in Grover's and Darier disease, cornifying disorders that are driven by impairments in keratinocyte Ca^{2+} handling. Our results establish hFWE4 as an important determinant of epidermal barrier function and a novel regulator of LB biogenesis and trafficking.

0514

Direct comparison of molecular effects of PLLA-SCA and CaHA-R in a standardized human 3D skin model containing macrophages

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Modern bio-stimulatory fillers like poly-L-lactic acid (PLLA-SCA; Sculptra) and calcium hydroxylapatite (CaHA-R; Radiesse) induce the synthesis of major structural components of the extracellular matrix such as collagen. However, the underlying molecular mechanisms are not yet fully understood. In a previous study we revealed that PLLA-SCA-induced collagen production in fibroblasts depends on their interaction with macrophages. The aim of the present study was to directly compare the molecular effects of PLLA-SCA and CaHA-R utilizing a previously established standardized human *in vitro* macrophage-containing 3D skin model. According to the clinical manual, both fillers were injected once into the dermal equivalent of the skin model. Histological analysis showed a significant increase in epidermal thickness on days 7, 14, and 21 after injection of both fillers compared to untreated controls. Next generation sequencing analysis showed a similar gene expression pattern on days 7 and 21 after injection of both fillers compared to untreated controls. While these data suggested that both fillers stimulate almost the same molecular signaling pathways, a direct comparison revealed an upregulation of members of the late cornified envelope (LCE) family at day 21 post-injection of PLLA-SCA compared to CaHA-R. In a next step, we investigated the direct effects of both fillers on collagen synthesis using immunohistochemical analysis (collagen I). While the injection of both fillers increased collagen production after 21 days, PLLA-SCA induced a significant increase in collagen synthesis already on day 7 after injection. Our data provide novel molecular insights into the bio-stimulatory effects of PLLA-SCA and CaHA-R on collagen production using 3D skin models comprising macrophages. Due to their special properties, these new *in vitro* models could also be used in future for research into fibrosing skin disorders.

0515

Striatin-Interacting Protein 1 (STRIP1) stabilizes cytoskeletal organizers to ensure barrier formation and planar cell polarity in the skin epidermis

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The skin epidermal keratinocytes undergo cellular rearrangements during development to establish barrier function and organize hair follicles. Cell movement is accompanied by junctional remodeling within and across the layers. Although the executioners of cytoskeletal organization are well-established, their upstream cues that underlie proper epidermal and hair development are largely unknown. We have previously shown that Striatin-Interacting Protein 1 (STRIP1), a core component of the Striatin-Interacting Phosphatases and Kinases (STRIPAK) complex that regulates the activity of PP2A, is essential for actin organization to facilitate cellular migration and intercalation during mouse gastrulation. Here, we hypothesize that STRIP1 is required to mediate the STRIPAK functions in cytoskeletal remodeling during epidermal and hair morphogenesis. Functionally, the epidermal loss of STRIP1 results in a thinner epidermis with less hair follicles and lethality of about half of the mutants due to barrier defects. The granular keratinocytes possess wavy cell borders and reduced mechanical tension in Strip1 mutant epidermis, suggesting perturbed actin-myosin interaction. Interestingly, Strip1 deficiency results in the loss of CTTNBP2NL, and actin organizer and associated member of the STRIPAK, at the protein level both *in vivo* and *in vitro*. Moreover, hair follicles in Strip1 mutant epidermis are misoriented indicating defective planar cell polarity in the absence of STRIP1. Strikingly, DVL2 is destabilized and VANGL2 mislocalized in Strip1 mutant epidermis. Collectively, our data show that STRIP1 regulates cytoskeletal organization to ensure intact barrier formation and planar cell polarity in the epidermis.

0516

SLC7A11 regulates keratinocyte proliferation and inflammatory responses in psoriasis: A metabolic perspective

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Psoriasis, a chronic inflammatory skin disorder, is characterized by aberrant immune activation and excessive keratinocyte proliferation. Although metabolic dysregulation is increasingly recognized as a hallmark of the disease, the role of amino acid metabolism remains poorly understood. Using constitutive and inducible keratinocyte-specific SLC7A11 knockout mouse models, psoriasis-like inflammation was induced with imiquimod (IMQ). Comprehensive functional analyses were also performed in primary keratinocyte cultures. Notably, SLC7A11 expression was significantly upregulated in psoriatic lesions of both human and mouse origin. Deletion of SLC7A11 in keratinocytes resulted in a marked reduction in proliferation and a substantial attenuation of IMQ-induced inflammatory responses. Furthermore, either genetic ablation or pharmacological inhibition of SLC7A11 reduced neutrophil and macrophage infiltration and diminished the secretion of key inflammatory chemokines, including CXCL2, CXCL5, and CCL20, which are instrumental in sustaining the inflammatory environment in psoriasis. *In vitro* experiments confirmed the critical role of SLC7A11 in keratinocyte biology. Silencing SLC7A11 impaired DNA synthesis, arrested cell cycle progression, and disrupted essential intracellular signaling pathways necessary for keratinocyte viability and function. Importantly, the proliferation defects caused by SLC7A11 deficiency were completely rescued by supplementation with N-acetylcysteine, highlighting the pivotal role of cysteine metabolism in keratinocyte homeostasis. These findings identify SLC7A11 as a key metabolic regulator in psoriasis, orchestrating keratinocyte proliferation and the inflammatory response. This study not only advances the understanding of the metabolic mechanisms underlying psoriasis but also positions SLC7A11 as a potential therapeutic target for innovative immunosuppressive treatments aimed at alleviating the chronic inflammation associated with this disease.

0517

scRNA-seq identifies atopic dermatitis development marked by early neutrophils and T cell shifts in filaggrin-null mice with environmental sensitivity

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Filaggrin (Flg) deficiency is a major risk factor for atopic dermatitis (AD) with epicutaneous sensitization and increased permeability shown in filaggrin-null (Flg-/-) mice. Flg loss-of-function variants are semipenetrant for AD suggesting a role for environmental effects. We hypothesize differential AD-like, skin inflammation induced by MC903 in Flg-/- adult mice housed in two different animal facilities. Flg-/- mice in facility A developed normally yet with increased Streptococcus dysbiosis and higher overall rate of MC903-induced inflammation but was not significant (vs. wild-type [wt] mice). Flg-/- mice in facility B exhibited a perinatal flaky tail that resolved yet with a significant increase in the overall rate of MC903-inflammation ($p<0.05$). Flow cytometry revealed neutrophil infiltration in the early (days 1-6) and not in the late phase (days 7-12) with notable TCRb+ cell influx in Flg-/- mice. scRNA-seq of treated ear skin further identified 22 distinct clusters and validated the observed increased neutrophils yet with additional myeloid and lymphoid immune cells in Flg-/- mice in the early and late phases, respectively. Tslp was specific to suprabasal KCs that persisted in both phases whereas IL2/CD101 T cells predominated the early phase and shifted to CD8+, Treg, and Th2 by the late phase with higher inflammation. In summary, our MC903 Flg-/- study identifies environmental sensitivity and longitudinal development of AD with early neutrophil infiltration and late T cell shifts that offers insights into potential therapeutic targets to modulate specific immune cell subsets in treating AD.

0518

Investigating a keratin-endoplasmic reticulum contact site in skin disease

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Keratins are epithelial-specific intermediate filament proteins that provide mechanical resistance to environmental stressors in tissues such as the epidermis. Epidermolysis bullosa simplex (EBS), a skin blistering disease, is caused by mutations in keratins 5 and 14 (KRT5/ KRT14). Prior studies have reported activation of endoplasmic reticulum (ER) stress and inflammatory pathways in EBS cell culture. However, the mechanisms linking keratin dysfunction to activated stress responses in EBS remain poorly understood. We first wanted to determine the association between the ER and keratin using electron and fluorescence microscopy in A431 epithelial cells. We found that peripheral ER tubules are in close proximity to keratin filaments and form paired arrangements at desmosome cell-cell junctions. Focused ion beam scanning electron microscopy (FIB-SEM) reveals intricate associations of ER tubules with keratin filaments at points of contact we term the keratin-ER contact site. Further, fluorescence live-cell microscopy demonstrates that keratin filaments stabilize ER membrane. Disruption of keratin filaments by expression of an EBS-causing aggregation mutant, $KRT14^{R125C}$, leads to changes in ER morphology, converting ER tubules at the cell periphery to ER sheets. Lastly, FIB-SEM datasets reveal that keratin filaments are present within nanometers of ER-mitochondria contact sites. To determine the effects of keratin disruption on mitochondrial organization, we labelled cells with MitoView dye. In $KRT14^{R125C}$-expressing cells, mitochondria are more peripheral, co-localizing with ER sheets, suggesting that ER morphological domains govern mitochondrial positioning. Our results demonstrate that keratin filaments regulate the stability and organization of the ER network in epithelial cells. Further, these studies suggest that keratin disruption in EBS alters the organization of other organelles via its effects on ER morphology, potentially leading to organelle dysfunction.

0519

Involucrin-casein kinase 1e-vitamin D receptor is a functional regulatory axis for human skin evolution and diversity

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We recently discovered that the human skin barrier evolved out-of-Africa. A haplotype for increased involucrin (IVL) expression underwent a near selective sweep in N. European populations in contrast to those in Africa. Ivl positively impacts Vitamin D receptor (Vdr) activity as Ivl-/- mice exhibited a dampened response to Vdr-mediated skin inflammation. Yet the nature and mechanism by which IVL regulates VDR activity that is environmentally sensitive is not known. We examined the significance of this IVL/VDR regulatory axis in primary mouse and diverse human keratinocytes (KCs) using biochemical studies. Ivl-/- mouse KCs exhibited a significant decrease in nuclear Vdr upon vitamin D agonist (MC903) treatment, resulting in decreased Vdr target Tslp, Vdr, and Fos gene expressions. The finding identifies the Ivl-Vdr axis to be cell-intrinsic and transcriptionally active. We further these MC903 studies in dark pigmented, primary human KCs of non-N. European ancestry that also exhibited low IVL and decreased nuclear VDR compared to that of N. European origin of higher IVL, demonstrating functional conservation for this IVL-VDR axis that is calibrated by IVL dosage for human skin barrier evolution and diversity. Multi-omics using ATAC-seq, RNA-seq and LC-MS proteomics in Ivl-/- and wt mouse skin identified Casein kinase 1e (Ck1e) as a putative molecule mediating involucrin's regulation of Vdr. We identify an Ivl/CK1e/Vdr interactome as evidenced by immunoprecipitation of Ivl and Ck1e with Vdr in differentiated KCs. Ck1e inhibition in MC903-treated HaCAT and mouse KCs resulted in a significant decrease in nuclear VDR and TSLP expression, with lower migrating VDR band in human KCs revealing CK1e phosphorylation of VDR that was confirmed by λ phosphatase treatment. Taken together, we identify a functional IVL/CK1e/VDR regulatory axis whose dosage for IVL underlies human skin barrier evolution and diversity out-of-Africa.

0520

Role of IL-33 in modulating filaggrin and acid ceramidase expression for epidermal barrier restoration after tape stripping in mice

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Preserving the epidermal barrier is vital for healthy skin. The stratum corneum depends on ceramides, with ASAH1b being significant due to its link with increased sphingomyelin deacylase activity in atopic dermatitis (AD). Elevated interleukin-33 (IL-33) levels in mice mimic AD-like skin conditions. This study explored IL-33's role in epidermal barrier function using tape stripping to induce skin damage in wild-type (WT) and IL-33 knockout (IL-33KO) mice. Trans-epidermal water loss (TEWL) was monitored over 72 hours, and skin samples were analyzed through tissue staining, immunohistochemistry (IHC), and real-time PCR. Additionally, cultured Ker-CT cells were treated with IL-33 and TNF-α to examine their effects on ASAH1b expression, including experiments with IL-33 knockdown. Tape stripping increased TEWL similarly in WT and IL-33KO mice. However, IL-33KO mice displayed thicker epidermis and a more pronounced granular layer compared to WT mice. IHC analysis showed elevated filaggrin (FLG) protein expression in both groups, with IL-33KO mice showing a greater increase. Tape stripping induced TSLP mRNA expression in WT mice but not IL-33KO mice. Additionally, acid ceramidase (ASAH1 and ASAH1b) expression at protein and mRNA levels was significantly upregulated in WT mice but not in IL-33KO mice after tape stripping. In Ker-CT cells, IL-33 treatment induced ASAH1b mRNA expression in a time- and concentration-dependent manner. TNF-α treatment increased ASAH1b mRNA expression in IL-33-knockdown cells at 16 hours but not 24 hours, while it maintained expression at both time points in WT cells, suggesting IL-33 helps sustain ASAH1b mRNA levels. This study highlights IL-33's critical role in promoting filaggrin and acid ceramidase expression following epidermal barrier disruption, despite no direct effect on TEWL. These findings offer new insights into IL-33's regulatory role in skin barrier maintenance and its implications in atopic dermatitis.

0521

Senescent melanocytes signaling impairs skin barrier function

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Melanocyte senescence primarily occurs in the skin of middle-aged and older individuals, progressively increasing with age. The senescent melanocytes may propagate aging signals to neighboring cells. Our findings reveal that senescent melanocytes contribute to skin barrier dysfunction. Senescent melanocytes-derived conditioned medium downregulated the expression of barrier-associated genes and differentiation markers in keratinocytes and *ex vivo* skin, thereby impairing skin barrier function. The senescent cells showed different secretomes and inhibition of these signaling pathways mitigated skin barrier damage induced by senescent melanocytes. These findings highlight senescent melanocytes and their secretome as promising therapeutic targets for age-related skin barrier disruption.

0522

Sumoylation and neddylation are opposing forces in stratified epithelial homeostasis

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Squamous epithelium stratification involves a coordinated, irreversible differentiation process, that modulates the expression of approximately 3,500 genes. To investigate the less understood post-translational protein modifications governing this process, we employed DIA-MS to map proteome-wide changes during epidermal differentiation. K-εGG-peptide enrichment identified modified peptides in progenitor and differentiated states. A single-cell perturb RNA-seq screen revealed unexpected opposing roles of two ubiquitin-like (UBL) conjugation pathways: Sumoylation was essential for differentiation, while neddylation maintained the undifferentiated progenitor state. These findings were validated through genetic and pharmacologic interventions across multiple stratified epithelia. Epidermal SUMO2 and NEDD8 UBL conditional knockout mice exhibited corresponding perturbations in epidermal homeostasis, with scRNA-seq revealing shifts in epithelial subpopulations and differentiation states. Further investigation of neddylation's role in homeostasis involved examining both canonical modifications and non-canonical mechanisms. DIA-MS analysis of primary keratinocytes treated with various inhibitors revealed overlapping and independent proteome alterations. A genome-wide CRISPR suppressor screen identified 616 genes (FDR<0.05) involved in non-canonical dependencies of neddylation, including pathway components, transcription factors, and epigenetic regulators. This study identifies Nedd8 and Sumo2 as key regulators of epithelial homeostasis through both canonical and non-canonical protein modifications, proposing a model where UBLs exert opposing impacts on the differentiation process.

0523

Choice of dermal scaffold affects molecular differentiation of three-dimensional human epidermal equivalents

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Three-dimensional (3D) skin equivalents (3DSEs) are indispensable tools for modeling human skin biology and disease. Despite advances, systematic comparisons of available models are limited. This study evaluated two approaches to develop 3DSE: one using contracted collagen (CC) that provides a synthetic extracellular matrix and another using acellular devitalized dermis (ACD), which retains native dermal architecture and components. The goal was to determine which model better recapitulates structural and functional characteristics of human skin. Both models showed epidermal stratification, granular layer development, and a mature acellular stratum corneum by day 7 at air-liquid interface. In both, we saw expression of keratin 10 and differentiation markers involucrin and loricrin by day 7. Yet, the ACD model had better restriction of keratin 14 to the basal layer and involucrin to the suprabasal layer than the CC model, where these markers were more widely distributed throughout the epidermis. In addition, invaginations of the basal epidermis into the papillary dermis were only observed in the ACD model, resembling rete ridges found in native human skin. Whole-transcriptome profiling of 3DSEs from multiple time points revealed that both models facilitated increased expression of keratinocyte differentiation markers, but the ACD model had higher expression of stem cell markers and transcription factors essential for maintaining the epidermal progenitor state, including DNMT1, TP63, and CEBPD. Our findings suggest that dermal scaffold choice influences molecular markers of epidermal differentiation in 3DSEs, and that the ACD model may enable formation of a multi-layered epidermis with a basal layer more closely resembling human skin than the CC model.

0524

Cell-associated and tissue-wide reconfiguration of epidermal metabolism by senescent keratinocytes

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Adaptive reconfiguration of metabolic pathways is use by epidermal keratinocyte (KC) as a first line of defense against ultraviolet oxidative and genotoxic damage. Rapid activation of the pentose phosphate pathway (PPP) provides metabolites essential for redox responses and DNA-damage repair. Changes in metabolism are however also a hallmark of aging at the cellular level known as cellular senescence. To investigate senescence related changes in aged skin we used a multimodal tissue cytometry approach. Combining tissue cytometry and image-based in situ zymographic assays we measured the peak activities of glucose 6 phosphate dehydrogenase (G6PD, PPP) and lactate dehydrogenase (LDH) in association with stress, aging and senescence markers in human skin samples and Skin equivalents (SE). In human epidermis we found an age-related increase of LDH and a decrease of G6PD activity, the latter forming an inward out positive gradient of activity in young epidermis, which is lost in aging. While LDH activity correlated to loss of LaminB1 staining, the global decrease of G6PD appeared to be unrelated to senescence markers. We then assessed whether introduction of senescent cells into SE would recapitulate these findings. Indeed, incorporating 5% labelled replicatively senescent KC led to cell associated increased LDH and globally decreased G6PD activity. Our findings suggest that presence of senescent cells contributes to the age-related loss of a potentially protective gradient of G6PD-generated reducing equivalents in the epidermis, and that senescent epidermal cells utilize increasingly LDH for energy production. Targeting these metabolic pathways may help to temporarily restore metabolites needed for cell repair.

0525

Psoriatic lesional skin organ culture replicates therapeutic benefits and reveals short-term responses to IL-23 and IL-17A blockade

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The IL-23/IL-17 axis is crucial in psoriasis pathogenesis, and systemic blockade of IL-23 and IL-17A significantly improves clinical outcomes in moderate-to-severe patients. Here, we evaluated the suitability of the *ex vivo* full-thickness human psoriatic lesional and peri-lesional skin model as a tool to investigate drug efficacy and short-term responses. Histological analysis confirmed the preservation of the lesional psoriatic phenotype in serum-free medium cultured for 96h. Comparative RNAseq analysis between cultured lesional and peri-lesional samples revealed enrichment of psoriasis-related genes and pathways, e.g. T-cell activation, Th17 responses, and (hyper-)keratinization. Among others, increased secretion of ß-defensin-2, CCL20, IL-17A, TNFα, IFNγ, and IL-23 was detected in the medium of lesional compared to peri-lesional skin evaluated by LegendPlex or ELISA. Additionally, quantitative (immuno-)histomorphometry confirmed higher numbers of $CD3^+IL\text{-}17A^+$ T-cells and $CD14^-CD11c^+$ and $CD14^+CD11c^-$ mononuclear phagocytes (MNPs) in lesional skin punches after 72h of culture. Systemic treatment *ex vivo* with αIL-17A (Secukinumab) or αIL-23 (Guselkumab surrogate) antibodies for 48h alleviated the transcriptomic lesional psoriatic phenotype (32% and 36% respectively). While IL-17A blockade did not lead to a reproducible decrease in cytokine/chemokine secretion, αIL-23 administration reduced secretion of IL-1β, CCL20, IL-23 and IL-17A. Furthermore, IL-23 neutralization reduced mRNA expression of IL23A, FCGR1A (CD64), CD40 and CD80 and intradermal $CD3^+IL\text{-}17A^+$ T-cells, $CD14^+CD11c^-$ monocytes, as well activated ($CD40^+$) and psoriatic-relevant ($CD64^+$) $CD14^-CD11c^+$ and $CD14^+CD11c^+$ MNPs. Thus, our human psoriatic lesional skin model replicates clinical therapeutic responses and serves as an excellent pre-clinical tool for investigating psoriasis therapeutics, including topical applications.

0526

Aging human skin shows DNA hypomethylation, which can be reverted by topical melatonin *ex vivo*

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DNA methylation has emerged as a key mechanism in cell and tissue aging. This involves DNA methyltransferases (DNMTs) that add methyl groups to cytosine, creating 5-methylcytosine (5-mC), which typically silences gene expression. Conversely, ten-eleven-translocation (TET) proteins convert 5-mC to 5-hydroxymethylcytosine (5-hmC), potentially reactivating previously suppressed genes. Our study explores if these epigenetic changes occur during human skin aging *ex vivo*, using a "speed aging" organ culture assay of aged, full-thickness female scalp skin (4 healthy donors, aged 43-75 yrs). Quantitative immunohistomorphometry revealed that after 3 days, expression levels of DNMT1, 5-mC and 5-hmC in the epidermis were reduced compared to day 0, showing a progressive DNA hypomethylation observed during "speed aging" *ex vivo*. Moreover, DNA hypomethylation was maximal in skin of the oldest donors (>65yrs), in line with recognized human skin aging characteristics. Topically applied melatonin (200mM) significantly increased epidermal 5-mC, DNMT1, and TET3 protein expression *ex vivo* after 3 and/or 6 days, compared to vehicle-treated control skin. Interestingly, the 5-mC response to melatonin treatment was most pronounced in "middle-aged" skin, while DNMT1 and TET3 expression changes did not differ between age groups. Our pilot data suggest that global DNA hypomethylation is a fundamental feature of human skin aging, which may promote the overexpression of aging-associated genes and suppress anti-aging genetic programs. The high-dose topical melatonin, which circumvents its rapid metabolism in the liver, penetrates the skin barrier and can counteract DNA hypomethylation *ex vivo*. This introduces a new mechanism for how melatonin can be utilized to slow human skin aging.

0527

CAP1 enhances actin dynamics to control epidermal morphogenesis

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Epidermal development relies on precise coordination between the actin cytoskeleton and its associated adhesion structures and polarity complexes. CAP1 (cyclase-associated actin cytoskeleton regulatory protein 1), a multidomain protein known for its roles in actin remodeling and cAMP regulation, is frequently dysregulated in epithelial cancers; however, its role in epithelial development is poorly understood. Here, we identify CAP1 as a critical regulator of epidermal morphogenesis. While CAP1 loss of function did not affect cAMP levels, it significantly increased F-actin content and disrupted actin organization. In-utero depletion of Cap1 in mouse embryos revealed severe epidermal defects, including disorganized adherens junctions (AJs), disrupted apicobasal polarity, and abnormal cell shape. Despite CAP1's profound influence on the structural and molecular organization of junctional actin, CAP1 itself was not enriched at cell junctions. Live imaging demonstrated that CAP1 is essential for maintaining actin dynamics, and pharmacological stabilization of actin filaments confirmed that impaired actin dynamics are incompatible with proper AJ assembly. Moreover, mutational analysis revealed that CAP1's distinct functions in F-actin depolymerization and G-actin nucleotide exchange and CAP1's ability to interact with the actin-severing protein cofilin are essential for AJ integrity and cell shape. These findings position CAP1 as a key modulator of F-actin content, actin dynamics, and junctional organization *in vitro* and *in vivo*, offering novel insights into the cytoskeletal regulation crucial for skin development.

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JAK inhibitors increase sebum production in human sebocytes and facial skin of patients with atopic dermatitis: Implications for JAK inhibitor-induced acne

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Janus kinase inhibitor-associated acne (JAKne) is a treatment-emergent adverse event of JAK inhibitors (JAKi), typically mild to moderate and manageable with topical therapies, though its mechanism remains unclear. Dyslipidemia associated with both non-selective and JAK1-selective inhibitors suggests a potential link to lipid metabolism. This study investigated the effects of the JAK1-selective inhibitor upadacitinib on sebum production in atopic dermatitis (AD) patients and sebocytes to elucidate its role in JAKne. Among 26 AD patients treated with upadacitinib, 8 (30.8%) developed acne. The JAKne group showed significantly higher baseline sebum levels and a greater percent increase in sebum levels compared to the No JAKne group. *In vitro*, upadacitinib (1μM) significantly increased neutral lipid accumulation in SZ95 sebocytes, reversing IL-4/IL-13-induced lipogenesis suppression. Transcriptomic analysis showed upregulation of fatty acid metabolism-related genes (e.g., PPARγ coactivator-1, phospholipase A2) and downregulation of adipogenesis inhibitors (e.g., TGM2). Upadacitinib also counteracted IL-4/IL-13-induced pro-inflammatory gene expressions (e.g., IL-7 and CCL26) and lipogenesis-inhibiting gene expressions (e.g., ERK3/MAPK6, and CCAAT/enhancer-binding protein zeta). In conclusion, upadacitinib increases sebum production in AD patients, particularly those with high baseline sebum levels, implicating lipogenesis as a potential mechanism for JAKne development. These findings provide insight into JAKne pathogenesis and the role of lipid metabolism in JAKi-associated adverse events.

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Protective effect and mechanism of idebenone against UVB-induced photoaging of HaCaT cells

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In this study, we first established a UVB-induced photoaging model for HaCaT cells. After treating HaCaT cells with UVB radiation at 10 mJ/cm^2, 20 mJ/cm^2 and 30 mJ/cm^2, we observed significant changes in the morphology of HaCaT cells, a significant decrease in the viability of the cells as detected by CCK-8, and a significant increase in the positive rate of senescence-associated β-galactosidase (SA-β-gal) staining. Subsequently, we evaluated the protective effects of different concentrations of Idebenone on photoaged HaCaT cells. The results showed that 0.5 nM, 1 nM and 5 nM of Idebenone significantly ameliorated UVB-induced apoptosis of HaCaT cells, reduced UVB-induced reactive oxygen species (ROS) levels, decreased malondialdehyde (MDA) content, increased superoxide dismutase (SOD) activity, restored mitochondrial membrane potential (MMP) levels and intracellular ATP concentration, and enhanced the antioxidant capacity of the cells and the results were concentration-dependent. In addition, Idebenone coukd inhibit the expression of UVB-induced inflammatory factors IL-1β, IL-6 and IL-8, and reduced the activity of matrix metalloproteinase (MMP), thus attenuating the degradation of extracellular matrix. The results suggested that Idebenone had a significant protective effect on UVB-induced photoaging of HaCaT cells, and the mechanism may involve multiple aspects such as antioxidant, anti-inflammatory and protection of mitochondrial function. The present study provided an experimental basis for the application of Idebenone in the treatment of skin photoaging, which was expected to be a valuable ingredient in cosmetic formulations.

0530

Galactomyces ferment filtrate impacts epidermal homeostasis: Spatial localization of gene expression changes involved in differentiation, transcriptional regulation, and cross-talk interconnections.

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Skin is the first line of defense from environmental factors and susceptible to premature aging. Identifying technologies which can repair and slow down aging is dependent upon understanding the mechanistic changes that take place. Galactomyces ferment filtrate (GFF) has been previously shown to impact epidermal differentiation. To understand the impact of GFF on epidermal biology, we used 10x Visium HD spatial transcriptomics profiling to show GFF can impact processes involved in differentiation, structure, and transcriptional regulation. Spatial sequencing discerned multiple epidermal skin compartments including granular, spinous, and basal with both the spinous and basal layer consisting of two distinguishable subtypes. The spatial location of these genes were identified, with S100A9 being upregulated throughout the epidermis whereas HSPB1, EZR and DUSP7 were upregulated in basal and spinous layers. IVL, CDKN1A, and GRHL1 were upregulated in spinous and granular layers. Relative to transcriptional regulation, MAF was downregulated in basal and spinous layers and JUNB was upregulated in the basal layer. MAF and JUNB expression changes with MAFG induction support an alteration in AP-1 dimer structure and regulation. AP1 is a known regulator of differentiation genes and GFF alters those enriched for AP1 binding sites in the basal and spinous layers. These data suggest that GFF alters the AP-1 complex in basal cells, which in turn alters the differentiation trajectory. GFF treatment increased an outgoing crosstalk signal originating from a specific basal cell subtype to neighbouring basal, spinous, and dermal fibroblasts cells. Specifically, GFF increases laminin 332 subunits LAMB3 and LAMC2, suggesting stronger dermal epidermal connections. Our findings provide insights into cellular differences, interconnections, and spatial localization in the epidermis in response to GFF, supporting previous findings that it has a relevant impact on epidermal biology.

0531

Analytical study of skin metabolites changes with ageing

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Metabolites, such as amino acids, sugars or fatty acids detected in the skin originate from multiple sources. In addition to those coming from gland secretion, skin cellular components (e.g., keratinocytes, melanocytes, fibroblasts) or degradation of proteins, there are those brought by exogenous source like lifestyle habits or pollution. While the study of skin metabolites variation induced by both intrinsic and extrinsic factors is already examined as a medical diagnostic tool, the natural aging impact on metabolite skin composition remains little known. Indeed, although the mechanisms of ageing on the structure and functions of the skin have been explained, the study of correlations at the molecular level remains recent. In order to better understand those metabolite changes at dermis and epidermis level we developed this study to establish molecular footprinting of skin at different ages and to target metabolite markers playing an important role in skin ageing. By taking up the technical challenge of high metabolic heterogeneity between individuals the aim of this study was to help identifying new ageing biomarkers. Investigation of ageing impact in metabolic profile has been performed on caucasian skin aged from 20-80 years. After separation of epidermis from dermis, skin biopsies were extracted and then studied in two separated groups (young and aged). Untargeted analysis conducted by gaz chromatography coupled with mass detector allowed to establish global profile of metabolites and then more specific analysis were made by liquid chromatography coupled with UV detector or mass detector. Significant differences appeared between the different age groups highlighting the presence of potential markers such as amino acids, sugars, lipids and organic acids in skin. Those results allowed to characterize skin aging according to its metabolic profile and opened the way to many possibilities, especially in the characterization of the effect of anti-aging cosmetics on the skin.

0532

Skin hydration outperforms other measures in predicting age-related skin barrier changes and systemic inflammation

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Age-related skin barrier decline may contribute to systemic inflammation; however, the best measures of skin barrier function to capture these changes remain unclear. In this cross-sectional study, we compared skin barrier function between young and older adults at the dorsal forearm and upper buttock. Skin barrier function was assessed via transepidermal water loss (TEWL), stratum corneum hydration (SCH), and skin pH. TEWL measurement was repeated after tape stripping in increments of 5 tape strips. The area under the curve (AUC) and slope were calculated from scatter plots of TEWL values against the number of tape strips. Serum inflammatory markers were measured using a 25-plex Luminex assay, and a composite z-score was averaged from standardized z-scores of 9 detectable markers. Thirty healthy participants were included, with 16 young adults (mean age 25.9, SD 3.5 years) and 14 older adults (mean age 79.1, SD 6.8 years). The older adult group showed mixed results regarding skin barrier function. At the forearm, worse barrier function was indicated by lower SCH (unadjusted p=0.021; adjusted p=0.007 for sex, BMI, baseline TEWL, and pH) and a significantly higher baseline TEWL/SCH ratio (unadjusted p=0.026; adjusted p=0.228 for sex and BMI). Baseline TEWL, TEWL AUC, slope, and pH did not differ between the young and older adult groups. At the upper buttock, no significant differences were observed for any measure. Additionally, all participants were divided into two groups based on z-scores, with higher z-scores assumed to indicate higher inflammatory status. At the forearm, participants with higher z-scores exhibited lower SCH (unadjusted p=0.028; adjusted p=0.454 for age, sex, BMI, baseline TEWL, and pH), suggesting worse skin barrier function. However, no significant differences were observed in baseline TEWL, TEWL AUC, baseline TEWL/SCH ratio, slope, or pH. At the upper buttock, no significant differences were found between the lower and higher z-score groups across any measures.

0533

Development of an *ex-vivo* skin explant model for hidradenitis suppurativa

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Hidradenitis Suppurativa (HS) is a chronic, inflammatory skin disease that is not well understood, which is partially due to the lack of an accurate, consistent, and testable model for HS. Current in-vitro experimental models of hidradenitis suppurativa (HS) do not fully capture patient variability and the multiple cell type communication networks involved in this complex disease. Ex-vivo skin explants are advantageous for HS as these models use full-thickness skin punch biopsies, which contain all of the unique architecture and cell types associated with HS skin lesions. While HS skin explants have been used in prior studies, questions arise as to how well the HS skin maintains its characteristic features and cell composition while in culture. Here, we describe a fully validated and reproducible protocol for an HS skin explant culture (n = 18) and therapeutic testing. 8-mm punch biopsies from freshly excised healthy control or HS lesional skin were cultured for 1-7 days after which they were processed for histological analyses of structure (H&E), viability (TUNEL and Ki-67 staining), differentiation (keratin expression), and immune cell composition (immunofluorescence). Explant culture media was also collected at multiple timepoints to evaluate egress of immune cells from the tissue. We found that HS skin explants can be maintained in culture for up to 5 days from severely diseased tissue (HS II/III) with no overt visible loss of viability or tissue architecture. The composition of immune cells was maintained in the tissue throughout culture. These findings establish that our protocol effectively maintains the in-vivo environment of HS skin, thus allowing its use in pre-clinical testing of novel therapeutics to determine their potential efficacy and underlying mechanisms for treating HS.

0534

Whole-genome sequencing identifies risk genes for generalized pustular psoriasis

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Generalized pustular psoriasis (GPP) is a rare, chronic and potentially life-threatening systemic inflammation disorder characterized by widespread pustular rash. Earlier studies reported causative genes for GPP, but they relied mostly on the candidate gene approach with a limited sample size. A non-biased, thorough genome-wide investigation is warranted to capture the comprehensive genetic architecture of GPP. To this aim, we performed a high-coverage (median depth >29×) whole-genome sequencing (WGS) analysis on 121 Japanese patients with GPP recruited through a nationwide collaboration, comparing them with 1,412 common psoriasis cases (PsV) and 3,914 controls without a history of immune diseases. A genome-wide association study analyzing 6,910,328 SNPs identified common genetic variants (minor allele frequency >1%) associated with the GPP risk at the IL36RN and major histocompatibility complex (MHC) loci (Odds ratio [OR] = 5.9 and 4.1, $P = 1.4\times10^{-13}$ and 2.1×10^{-13}, respectively). When comparing GPP and PsV, the IL36RN locus risk was GPP-specific (OR = 4.1, $P = 2.3\times10^{-8}$), while the MHC risk was comparable between the two diseases (P = 0.24). An HLA fine-mapping analysis showed that the strongest associated HLA variant was HLA-A*02:07:01 ($P = 1.6\times10^{-10}$), which was previously reported as a risk HLA variant of PsV in Japanese population. The well-known PsV risk as HLA variant HLA-C*06:02 was independently associated with the GPP risk (P = 0.0030 when conditioned on HLA-A*02:07:01). Finally, utilizing rare variants detected by WGS, we identified GPP risk genes, including IL36RN, in which protein-altering coding variants were significantly enriched in the cases. Our study provides a first comprehensive landscape of genetic determinants of GPP and evidence of the population-level contribution of IL36RN to GPP pathogenesis.

0535

The histone methyltransferase WHSC1 modulates keratinocyte proliferation in wounds via regulation of proliferation and differentiation marker expression

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Keratinocytes are structural cells in the skin that regulate wound repair through proliferation and differentiation, processes that are calcium (Ca)-dependent, with higher Ca levels promoting differentiation and inhibiting proliferation. In pathologic conditions, keratinocyte function is impaired, though the mechanisms remain unclear. Epigenetic chromatin modifying enzymes (CMEs) can control cell functions during tissue repair. Primary murine keratinocytes were cultured in low-Ca (LoCa) medium to isolate a basal subset, or differentiation was induced by switching to a high-Ca (HiCa) medium, and an unbiased epigenetic array was performed. HiCa-differentiated keratinocytes showed significantly decreased expression of WHSC1 ($p<0.001$), a histone methyltransferase that activates gene expression via K36me2 modification. Single-cell RNA sequencing of human wound keratinocytes revealed increased WHSC1 expression in cycling keratinocytes and decreased expression in differentiated keratinocytes, suggesting its role in proliferation. Further analysis of WHSC1-Hi versus WHSC1-Lo expressing cells revealed increased proliferation markers (e.g.,CDC7, E2F7, E2F2, PCNA) in WHSC1-Hi and increased differentiation markers (e.g.,VIM, FLG) in WHSC1-Lo. Further, siRNA and pharmacological inhibition of WHSC1, using siWhsc1 (1 μM) and LEM-14 (150 μM), respectively, in keratinocytes resulted in decreased E2f2, Cdc7 and increased Flg. To examine Ca-dependent regulation of WHSC1, keratinocytes were treated with Ca-sensing receptor inhibitor CalHex-231 (40 μM) and demonstrated increased Whsc1 and decreased Flg following HiCa-induced differentiation. Functionally, WHSC1 inhibition with LEM-14 reduced keratinocyte proliferation (measured via alamarBlue) ($p<0.001$) and decreased wound closure ($p<0.0001$) in scratch assays. Thus, WHSC1 plays a critical role in keratinocyte proliferation and may represent a potential therapeutic target for pathologic processes where keratinocyte function is impaired.

0536

Oncogenic HRAS-driven immune escape in cutaneous squamous cell carcinoma

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RAS mutations are recurrent in skin malignancies and HRAS mutations can be found in approximately 23% of cutaneous squamous cell carcinomas (cSCCs), the second most prevalent type of skin cancer. While RAS activity in various cancer hallmarks is well known, the role of oncogenic HRAS in creating a tumor-promoting microenvironment is less studied. Previous research indicates that oncogenic HRAS causes dose-dependent epidermal activation and inflammation. These mutations may shape the tumor microenvironment and contribute to immune evasion in cSCCs. To understand microenvironmental consequences of oncogenic HRAS signaling in skin, we introduced $HRAS^{Q61}$ and $HRAS^{G12V}$ in healthy human keratinocytes and observed common and disparate effects of these activating mutations. The effects on immunity were contextual. On the one hand, both oncogenic variants induced a high pro-inflammatory response. On the other hand, they promoted expression of genes related to generation of immunosuppressive metabolites and their subsequent production. When investigating mice bearing $Hras^{Q61}$- and $Hras^{G12V}$-mutated skin tumors, we intriguingly observed differential immune infiltration pattern. While neutrophils are a major component of the immune infiltrate in both models, only the G12V-mutated tumors recruited macrophages, suggesting oncogenic variant-specific immune interactions. Importantly, we could disclose that oncogenic HRAS induces NETosis, contributing to further inflammation and immune evasion in the tumor microenvironment. Understanding the interplay between oncogenic HRAS signaling and immune escape provides insights into potential therapeutic strategies that can be translated into improved and personalized treatment, such as targeting NETosis to enhance anti-tumor immunity in mutated HRAS-driven cSCCs.

0537

A rare report of pediatric hailey-hailey disease

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Abstract: Background: Hailey-Hailey Disease (HHD) is an autosomal dominant disorder caused by ATP2C1 gene mutations, leading to recurrent erosions and blisters in flexural areas like the axillae, groin, and neck. Typically manifesting between ages 20-40, we report a case of pediatric-onset HHD in a patient who began experiencing symptoms at 13, highlighting variability in presentation and the importance of recognizing hereditary patterns. Observation: A 15-year-old female with a family history of HHD presented with a two-year history of irritation and hyperpigmentation beneath her breasts, later spreading to the axillae with associated pruritus, pain, and tightness. Initially treated with hydrocortisone ointment, clotrimazole cream, and hygiene counseling, her symptoms persisted. A punch biopsy performed one year later confirmed HHD, revealing acantholytic dermatosis. Treatment was updated to include Tacrolimus 0.1% ointment, Cetirizine, and a three-month course of doxycycline. Maintenance strategies incorporated antiperspirants, zinc oxide paste, and continued Tacrolimus. The patient adhered to the plan, with significant symptom improvement and better quality of life. She was counseled on the chronic nature of HHD and the need for long-term management. Pediatric cases of HHD are rare, with few reports describing patients under 18, making diagnosis in younger patients challenging. In this case, symptoms began at 13, likely contributing to the diagnostic delay despite a positive family history and emphasizing the critical role of family history in diagnosis. Early recognition in patients with a positive family history may facilitate timely diagnosis and treatment. This highlights the importance of a proactive approach to evaluating hereditary conditions in pediatric patients.

0538

Exploring the role of m6A-RNA methylation in severe epidermolysis bullosa simplex

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N6-methyladenosine (m6A) RNA methylation is involved in numerous cutaneous physiological processes, including differentiation, inflammation, immunity, and wound healing. Despite relevance in other dermatoses, m6A's role in epidermolysis bullosa simplex (EBS) remains unexplored. We studied m6A regulation in severe EBS, a rare genetic keratin disorder arising due to abnormalities in either keratin 5 or 14. This manifests as disrupted keratin intermediate filament networks, keratin clumping, basal cytolysis and persistent inflammation that compounds impaired keratin cycling. Consequent skin fragility ensues, exerting considerably morbidity. We studied the overall RNA m6A levels and the gene expression of proteins involved in m6A regulation in a) KEB-7 cells (KRT14 R125P) derived from a severe autosomal dominant EBS patient and b) control NEB-1 cells derived from a healthy donor. Analysis involved mRNA sequencing, quantitative RT-PCR (qRT-PCR), and RNA m6A colorimetry assay. Compared to controls, RNA m6A levels were elevated in KEB-7 cells. On differential gene expression analysis, m6A writer METTL14 and readers YTHDC1, YTHDF2, and YTHDF3 were upregulated, while reader YTHDF1 and eraser FTO were downregulated. Of note, qRT-PCR validated significant METTL14 and YTHDC1 upregulation and FTO downregulation. From the findings of this pilot study, we conclude that dysregulated m6A RNA methylation is one modifier of the genotype-phenotype correlation observed in severe EBS. This conclusion supports existing literature reporting m6A's involvement in inflammatory and immune processes. Future research should explore the use of activators and inhibitors of m6A writers, erasers, and readers as facilitators of clinical improvement in EBS; through exploring their roles on pathological T-cell regulation, keratinocyte migration, and inflammatory response.

0539

Substantial improvement of malnutrition by extensive skin replacement with revertant cultured epidermal autografts following mechanical epidermal stripping in recessive dystrophic epidermolysis bullosa

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Recessive dystrophic epidermolysis bullosa (RDEB) patients with biallelic defects in COL7A1 have little to no anchoring fibrils to hold the epidermis to the dermis, leading to recurrent erosions, malnutrition, and squamous cell carcinoma from APOBEC-induced somatic variations. A study of two RDEB patients, one severe and one intermediate, revealed the presence of revertant skin, measuring several cm^2, in which somatic reversion of a pathogenic COL7A1 allele to wild-type occurred in keratinocytes. A comprehensive approach involving extensive mechanical epidermal stripping under general anesthesia and transplantation of revertant cultured epidermal autografts (CEAs) resulted in successful replacement of the COL7A1-deficient epidermis with revertant. Subsequent generation of CEA (sgCEA) from the revertant CEA-transplanted skin facilitated the expansion of revertant keratinocytes from a limited area to the entire body. Whole exome sequencing revealed no oncogenic variants in either CEA or sgCEA. A total of 78 and 35 CEAs and 27 and 15 sgCEAs, 10 x 8 cm in size, were transplanted at 17 and 18 years of age and at 16 years of age in severe and intermediate RDEB patients, respectively. This resulted in successful epidermal replacement in approximately 80% and 50% of the total skin, respectively, as confirmed by genetic analysis. The patients' weight increased from 28.8 to 44.8 kg over a period of five years from the age of 17 and from 36.7 to 47.2 kg over a period of two years from the age of 16. In conclusion, the mechanical replacement of recurrently eroded epidermis with oncogenic variation-free revertant CEA resulted in substantial and sustained improvements of skin fragility, malnutrition, and quality of life in two RDEB patients, which may also reduce the future risk of carcinogenesis.

0540

LZTR1-associated café au lait macules in a pediatric patient with atypical clinical presentation

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A 3-year-old male presented with numerous café au lait macules (CALMs). Previous genetic testing for NF1 and SPRED1 were negative. Physical examination revealed eight ill-defined, geometrically shaped light brown patches on the trunk, flank, thighs, and arm, some with a surrounding halo. The CALMs were stable in size and number, and the patient was asymptomatic with no significant family history of related syndromes. An ultrasound of the thigh, given the surrounding halo, was performed, which showed no significant findings. Further genetic testing, including the RASopathies and Noonan Spectrum Disorders Panel, identified a variant in the LZTR1 gene (c.1397G>A (p.Arg466Gln)). LZTR1 is associated with LZTR1-related schwannomatosis and Noonan syndrome. LZTR1-related schwannomatosis involves the development of multiple non-intradermal and non-vestibular schwannomas in adulthood, often accompanied by chronic pain. Noonan syndrome is a disorder characterized by cardiovascular abnormalities, short stature, distinctive facial features, café au lait spots, developmental delay, and the development of both benign and malignant tumors. The same variant was detected in the patient's mother but not in the father or sibling. Given the association with schwannomatosis, screening for schwannomas was recommended, including annual clinical evaluations, baseline MRI, and follow-up MRIs every two to three years beginning at age twelve or earlier if symptoms appear. Further genetic testing, including RNA analysis of NF1 and analysis of TSC1/2, PTEN, and NF2, was also recommended. This case brings awareness to considering LZTR1 mutations in patients with multiple asymptomatic CALMs, particularly when more common causes such as NF1 and SPRED1 have been ruled out.

0541

Autosomal dominant SLURP1 variants cause palmoplantar keratoderma and progressive symmetric erythrokeratoderma

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Epidermal differentiation disorders (EDDs) are severe skin conditions characterized by localized or generalized skin scaling and erythema often due to damaging single-gene variants. We performed whole exome sequencing in a large cohort with EDD including palmoplantar keratoderma (PPK) and progressive symmetric erythrokeratoderma (PSEK) phenotypes to identify novel genetic variants. We investigated the consequence of these variants using in silico predictions, assays in primary patient keratinocytes, and high-resolution spatial transcriptomics and quantitative cytokine profiling in affected skin. We identified three unrelated kindreds with autosomal dominant transmission of heterozygous variants in SLURP1 at the same amino acid position (c.65C>A, p.A22D, and c.65C>T, p.A22V) within the signal peptide sequence. One (p.A22V) had isolated PPK, and two others (p.A22D) had a PSEK phenotype. In silico modeling suggested that variants altered the cleavage site of pro-SLURP1, appending two amino acids to the secreted protein, subsequently confirmed with mass spectrometry of secreted mutant protein. Assays in primary patient keratinocytes revealed that differentiation-induced SLURP1 expression and secretion was increased in patient cells compared to healthy control cells. Spatial transcriptomics in affected tissue confirmed increased SLURP1 expression in suprabasal epidermis and showed increased NF-κB signaling and innate immune activity. Our results expand the phenotypic spectrum of EDD due to pathogenic variants in SLURP1.

0542

Variants in KLF4 affecting residue Asp441 cause a novel autosomal dominant syndromic ichthyosis

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Congenital ichthyoses comprise a group of skin scaling diseases with clinical and genetic heterogeneity. Among them, syndromic ichthyoses affect organs beyond the skin. In this study, we enrolled four unrelated patients with a novel form of syndromic ichthyosis to identify the causative gene and its underlying pathogenesis. The patients primarily presented with ichthyosis, palmoplantar keratoderma, hypotrichosis, periorificial keratosis, nail dystrophy, and various extracutaneous features, including sensorineural deafness, lower extremity lymphedema, and developmental defects of internal organs. Whole-exome sequencing identified two de novo heterozygous KLF4 variants, c.1322A>G (p.Asp441Gly) and c.1323T>A (p.Asp441Glu), in these patients, both affecting the Asp441 residue in the second zinc finger (ZF2) motif of KLF4. Structural modeling suggested that these variants destabilize the α-helix of ZF2. KLF4 is a transcription factor widely expressed in various tissues, including the skin. A reduced KLF4 expression in the patients' skin was detected, and dual-luciferase reporter assays revealed impaired transcriptional activity of both variants. Skin organoids harboring the heterozygous c.1323T>A variant displayed defects in epithelial morphogenesis. RNA sequencing of these organoids revealed abnormal expression of keratinocyte differentiation-related genes, including reduced KLK7, a kallikrein-related peptidase crucial for skin desquamation. Consistently, KLK7 expression was downregulated in the patients' skin. In conclusion, loss-of-function variants affecting residue Asp441 of KLF4 are associated with an autosomal dominant syndromic ichthyosis with multi-organ involvement. Our study highlights the essential role of KLF4 in regulating skin keratinization and its broader systemic impact.

0543

Cas9-targeted long-read sequencing of the entire COL7A1 genomic region uncovers revertant mosaicism in recessive dystrophic epidermolysis bullosa

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Revertant mosaicism (RM) is a phenomenon in which disease-causing germline variants are spontaneously corrected in somatic cells. Epidermolysis bullosa (EB) is a group of congenital skin fragility disorders caused by variants in genes encoding epidermal basement membrane zone proteins. Some EB patients develop clinically intact skin spots resulting from RM (revertant skin), which do not show skin fragility, highlighting epidermal autografts derived from these spots as a promising therapeutic option. However, conventional techniques have difficulty confirming RM in these clinically revertant skin spots. Nanopore Cas9-targeted sequencing (nCATS) enables the enrichment and sequencing of specific genomic DNA (gDNA) regions by combining Cas9 cleavage, adapter ligation, and MinION sequencing. Recently, our laboratory confirmed RM in clinically revertant skin from a recessive dystrophic EB (RDEB) patient using this technique. We established an nCATS strategy to enrich the entire 31-kb COL7A1 genomic region for the phasing of its variants. This region was successfully enriched in gDNA obtained from peripheral blood of healthy individuals and RDEB patients. We then applied this method to gDNA extracted from autologous cultured epidermal sheets derived from clinically revertant skin in three RDEB patients. The 31-kb nCATS approach succeeded in phasing the COL7A1 variants and identified RM-induced wild-type allele reads in at least one patient. In contrast, immunofluorescence studies failed to verify RM because COL7 staining was seen in both the clinically revertant skin and the lesional skin. This failure is likely due to leaky protein expression associated with missense or splice-site COL7A1 variants. Our study illuminates nCATS as a feasible strategy for detecting RM and supports the development of epidermal autografts for EB therapy.

0544

Cutaneous features of SDR9C7 mutation in seven patients with autosomal recessive congenital ichthyosis

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Ichthyoses are a heterogeneous group of skin disorders characterized by scaling and erythema. SDR9C7 has been recently recognized as a cause of autosomal recessive congenital ichthyosis (ARCI). Due to the rarity of SDR9C7 mutations in ARCI, there is limited information regarding the associated cutaneous manifestations, comorbidities, and available treatments. We present seven cases of SDR9C7 mutations, detailing their clinical characteristics and management. The genotypes and clinical characteristics of the seven individuals were obtained from the National Registry for Ichthyosis. Among our seven cases, we observe that these individuals exhibited a vulgaris-like phenotype, with fine, white scaling and hyperlinear palms. Notably, common features of ichthyosis, such as ectropion and palmoplantar keratoderma, were absent in this cohort. However, other characteristic features, including hypohidrosis, impaired thermoregulation, and recurrent skin infections, were frequently reported. Topical emollients, particularly those containing ammonium lactate and alpha-hydroxy acids, proved effective in reducing scale, dryness, and pruritus. Regular baths also helped remove scale. Similar to other ichthyoses, the lower extremities demonstrated the most prominent scaling. Recently, SDR9C7 has been identified as a crucial regulator of epidermal barrier function, specifically by facilitating the covalent bonding of ceramides and the formation of the corneocyte lipid envelope. These findings help explain the characteristic clinical features of ARCI in individuals with SDR9C7 mutations, including dry skin, scaling, and hyperkeratosis. Furthermore, SDR9C7's role in vitamin A metabolism – which is essential for epidermal differentiation – underscores the therapeutic efficacy of vitamin A derivatives in treating ichthyosis. This connection also suggests that retinoids could be an effective treatment option for the SDR9C7 subgroup of ARCI patients.

0545

Novel genes and variants associated with vitiligo: A genome-wide association and mendelian randomization meta-analysis

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Vitiligo is a complex autoimmune condition driven by genetic and environmental factors, with few drug targets. This study represents the largest international genome-wide association study (GWAS) of vitiligo to uncover novel genes and variants associated with vitiligo. We conducted a GWAS meta-analysis from the Million Veteran Program (MVP), FinnGen, and UK Biobank databases to identify variants significantly associated ($p < 5 \times 10^{-8}$) with vitiligo. Significant single nucleotide polymorphisms (SNPs) were cross-referenced with the GWAS Catalog, dbSNP, DICE, and prior GWAS studies to assess novelty. Variant-to-gene (V2G) mapping identified the most likely linked genes to these variants. To move from identifying statistical associations to inferring potential causal relationships, we performed Mendelian randomization (MR), applying a Bonferroni-corrected threshold ($p < 2.96 \times 10^{-7}$) based on 169,093 gene-dataset-tissue combinations. The meta-analysis included 3,134 vitiligo cases and 1,383,912 controls, identifying 51 significant GWAS signals. These signals were mapped to 43 unique candidate genes using the V2G pipeline, of which 31 had not been previously associated with vitiligo. MR analysis identified 16 putatively causal genes, including four overlapping with V2G-mapped genes (RNASET2, HLA-A, BACH2, RAB5B). Other putatively causal genes significant in MR included GDF11 (beta: -3.16, $p = 7.56 \times 10^{-9}$) and GABBR1 (beta: +1.57, $p = 2.09 \times 10^{-7}$), both of which demonstrated strong effect sizes. Higher GDF11 levels may reduce vitiligo risk by mitigating oxidative stress through reduced melanin production and improved melanocyte survival. In contrast, increased GABBR1 expression may elevate risk through immune dysregulation. These novel genetic associations enhance our understanding of the pathogenesis of vitiligo and highlight new potential genetic targets for vitiligo.

0546

Genetic insights into hidradenitis suppurativa: A genome-wide association and mendelian randomization meta-analysis

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Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition associated with increased all-cause mortality and is influenced by genetic and environmental factors, though the genetic contributors remain poorly characterized. We performed a case-control genome-wide association study (GWAS) involving patients from the Million Veteran Program to identify genetic markers linked to HS. To identify cases, we used codes for HS from the International Classification of Diseases, Ninth and Tenth Revisions. We then conducted a large-scale meta-analysis with data from UK Biobank and FinnGen, including a total of 3,941 cases and 1,435,603 controls. We identified 24 genome-wide significant variants ($P < 5 \times 10^{-8}$), none of which have been previously reported. Using a variant-to-gene (V2G) analysis pipeline, we mapped these variants to 25 loci and identified HLA-DQ1 ($P = 1.15 \times 10^{-12}$), KLF5 ($P = 1.55 \times 10^{-12}$), and TMEM245 ($P = 9.44 \times 10^{-11}$) as top candidates. A different variant associated with KLF5, a key transcription factor important for neutrophil differentiation and skin barrier function, has been previously linked to HS. Two-sample Mendelian randomization (MR) using expression quantitative trait loci (eQTL) again implicated KLF5 ($P = 4.33 \times 10^{-7}$), in addition to DNAJC1 ($P = 2.45 \times 10^{-7}$), a heat shock protein, NFATC2IP ($P = 9.71 \times 10^{-8}$), a regulator of T-cell differentiation, and SPRN ($P = 4.52 \times 10^{-7}$), a protein with stress-protective activity. MR analysis of protein quantitative trait loci (pQTL) identified MPO ($P = 3.62 \times 10^{-8}$), a key regulator of neutrophil extracellular trap formation previously implicated in familial HS. These results confirm the previously suggested involvement of KLF5 in HS and link the pathogenesis of the disease to new pathways related to immune response, inflammation, and oxidative stress. Our findings may inform potential drug targets for the treatment of HS.

0547

Cell-type specific RNA Pol II activity maps in intact-tissues: Gateway to mammalian gene regulatory mechanisms in vivo

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Accessing ongoing RNA Pol II activity in specific cell-types within intact-tissues can dissect regulatory mechanisms of development. Here, we create Cre-inducible mice for cell-type-specific GFP tagging of endogenous Pol II. Transcriptional run-on on intact-tissue chromatin followed by GFP-immunoprecipitation (our PReCIS-seq method) maps the transcriptionally-engaged Pol II genome-wide on proximal-promoters, gene bodies, and active enhancers. Using keratinocytes of intact-skin as a model, we demonstrate that all transcriptionally regulated functions of a homeostatic transition employ Pol II promoter-recruitment and promoter-proximal pause-release mechanisms. A global Pol II regulatory polarization - enabling contrasting modulation of cellular safeguarding and lineage identity gene expression - is maintained from embryonic development through adult homeostasis. This polarization appears hard-wired in two proximal-promoter structures that distinguish high-paused genes with restricted pause-release from low-paused genes undergoing rapid Pol II firing into productive elongation. PReCIS-seq provides unprecedented *in vivo* access to Pol II regulatory mechanisms in mammalian development, homeostasis, and disease.

0548

Hailey-Hailey disease models reveal impaired cadherin expression and localization along with actin dysregulation as key pathogenic drivers that weaken intercellular adhesion

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Hailey-Hailey disease (HHD) is characterized by painful skin blisters and erosions due to loss of adhesion between epidermal keratinocytes. Despite being linked to ATP2C1 mutations 25 years ago, this disease has no FDA-approved treatments. Understanding HHD pathogenesis has been hampered by the lack of a pre-clinical model as Atp2c1 knockout mice did not replicate HHD. We utilized CRISPR/Cas9 in TERT-immortalized human keratinocytes to ablate ATP2C1, depleting its encoded Golgi calcium ATPase, SPCA1. In a second model, we used drugs to block SPCA1 in normal human epidermal keratinocytes. Leveraging calcium biosensors in live keratinocytes, we found SPCA1 loss did not alter cytoplasmic, ER, or Golgi calcium. However, both genetic depletion and chemical inhibition of SPCA1 impaired the trafficking of adherens junction and desmosomal components to cell-cell contacts and reduced cadherin levels, which compromised the mechanical strength of keratinocyte sheets. Moreover, in organotypic epidermis, we found loss of SPCA1 induced severing of cell-cell junctions (acantholysis), the key pathologic feature of HHD. To identify causes of cell-cell junction disruption in HHD, we performed RNA sequencing of ATP2C1 heterozygous keratinocytes. Gene ontology analysis revealed differential expression of actin regulators including Rho GTPases, in agreement with RNAseq data from HHD biopsies. Further validating a role for actin in HHD, confocal imaging showed impaired actin organization and increased filopodia in SPCA1-deficient keratinocytes; as well, SPCA1-deficient organotypic epidermis and HHD biopsies exhibited impaired cortical actin bundling. These data support our model in which actin dysregulation impairs localization and stability of adhesive proteins in HHD. Importantly, our results point to druggable actin regulators as potential therapeutic targets to restore epidermal integrity in HHD.

0549

Identification of genetic susceptibility to prurigo nodularis in the IL31 gene locus

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The IL31 cytokine is central to the pathogenesis of itch and inflammation in prurigo nodularis (PN). IL31 expression is up-regulated in the skin of individuals with PN and correlates with the intensity of itch. Overexpression of IL31 in animal models leads to skin inflammation and pruritus, and treatment with the IL31 receptor inhibitor nemolizumab has been found to be highly effective in PN. However, the etiology of PN remains unknown. Previous studies (ancestry differences and polygenic risk score) have suggested that genetic factors contribute to PN susceptibility. We therefore conducted the largest GWAS meta-analysis of PN to date (4,239 cases and 583,544 controls) to investigate the genetic mechanisms involved. Our study, combining data from the All of Us research program with the BioVU, FinnGen and Partners biobanks, identified a significant genetic signal ($p=7.5 \times 10^{-13}$, OR=1.17) associated with Prurigo Nodularis (PN) located at the IL31 locus on chromosome 12q24.31; we replicated this result using the Michigan Genomics Initiative (MGI) cohort. Notably, the risk allele frequency for the signal was different between population groups (10 times higher in European than African ancestries), and in linkage disequilibrium (LD) with GWAS signals for other diseases where pruritus is prominent (psoriasis and atopic dermatitis). The IL31 signal is located in a transcription factor binding hotspot, and our functional analyses demonstrate that it acts as an expression quantitative trait locus (eQTL), overlapping chromatin accessibility peaks in T-cells and keratinocytes. These findings represent an important step towards understanding the mechanisms underlying PN predisposition and suggests the PN risk allele could influence IL31 expression levels in relevant skin cells. Our results reinforce PN as a genetic disease, and expand upon the role of IL31 as a central mediator in PN pathogenesis, and its relationship with other pruritic inflammatory skin diseases.

0550

Interplay of oxidative sensitivity and protein glutathionylation in Darier Disease

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The acantholytic phenotype of Darier Disease (DD), a condition caused by heterozygous mutation of the endoplasmic reticulum calcium pump SERCA2, presents during the second decade of life and responds to environmental triggers. Delayed onset, despite lifelong SERCA2 deficiency, suggests that DD cells harbor sensitivities to age-related stressors, such as oxidative damage. The antioxidant glutathione protects certain proteins, including SERCA2, from oxidative damage through reversible glutathionylation. We find that DD keratinocytes (KCs) have an increased level of SERCA2 glutathionylation, as well global protein glutathionylation, and a partially depleted free glutathione pool compared to CTLs. This suggests that SERCA2 deficiency may cause mild oxidative stress that must be buffered at baseline. This theory is supported by our finding that, prior to any apparent adhesion defect, glutathionylation in CTL KCs increases linearly in response to treatment with the SERCA inhibitor thapsigargin. Compared to CTLs, upon the addition of exogenous stress DD KCs generate twice the reactive oxygen species, recruit desmosomal components to junctions 89% less efficiently, and show an 8-fold decrease in adhesion strength via dispase. Desmosomal proteins in DD cells collapse into a perinuclear ring, highly colocalized with the signal for glutathionylation; proximity ligation confirms significantly increased desmoplakin glutathionylation in stressed DD cells. We propose a model whereby SERCA2 heterozygosity causes mild oxidative stress that is buffered by glutathionylation. When subjected to additional external stress, free glutathione is shunted to perinuclear desmoplakin at the expense of SERCA2, rendering the calcium pump vulnerable to irreversible oxidation/inactivation. Lesional flares, then, could represent cases of total SERCA2 inhibition, perturbing intercellular adhesion via ER stress, altered cadherin trafficking, and cytoskeletal disruption.

0551

CRISPR/Cas and dermatology: A new era of skin treatment modalities

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CRISPR/Cas has accelerated gene editing capabilities and holds tremendous potential in dermatology; however, many potential dermatology applications have not been comprehensively explored. This study examines current applications and identifies ideal dermatologic candidates for future CRISPR/Cas therapies. We conducted a literature review of studies involving CRISPR/Cas in dermatology using keywords "[CRISPR]," "[dermatology]," "[gene therapy]," "[genetic skin disease]," "[delivery]," "[skin disorder]," "[caspase]," "[Cas]," "[antimicrobial]", "[virus]," "[CRISPR-Cas9]", "[CRISPR/Cas9]", and "[history]" in the PubMed database. We identified 62 articles relevant to current and potential CRISPR/Cas dermatology applications. Across five monogenic dermatoses, two inflammatory conditions, four cutaneous infections, and two malignancies, CRISPR/Cas has been effective in correcting genetic mutations, reducing inflammation, and disrupting pathogenic processes. It has corrected genetic mutations in multiple forms of epidermolysis bullosa through the DNA repair mechanisms homology-directed repair and non-homologous end joining to restore dermal-epidermal adhesion and inactivate pathogenic alleles. CRISPR/Cas9 has also reduced inflammation in atopic dermatitis and psoriasis by targeting NLRP3 via microneedle patches. CRISPR/Cas knockout has disrupted viral oncogenes in human papillomavirus and Kaposi's sarcoma herpesvirus, reduced tumor growth in cutaneous squamous cell carcinoma, and enhanced immune targeting in metastatic melanoma. Recent CRISPR/Cas innovations, such as lipid nanoparticles for topical delivery and prime editing for precise single-base substitutions, are further broadening the scope of CRISPR/Cas gene editing applications. These findings highlight the significant progress that CRISPR/Cas has made in the field of dermatology. As ongoing research refines its applications and addresses safety considerations, CRISPR/Cas will further transform future treatment possibilities for genodermatoses and a wide range of dermatologic conditions.

0552

Comprehensive characterization of keratinocytes and fibroblasts derived from genetically corrected induced pluripotent stem cells of recessive dystrophic epidermolysis bullosa patients

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Recessive Dystrophic Epidermolysis Bullosa (RDEB) is a hereditary, incurable disease with high morbidity and mortality characterized by severe skin blistering and scarring. RDEB results from mutations in the COL7A1 gene, causing dysfunctional type VII collagen (C7), a key component of anchoring fibrils in the basement membrane. We are developing an induced pluripotent stem cell (iPSC)-based gene therapy for RDEB, which involves combined reprogramming and CRISPR/Cas9 gene correction, iPSC differentiation, and transplantation of genetically corrected iPSC-derived skin cells. Key challenges include ensuring the safety and authenticity of iPSC-derived skin cells for clinical trials. One of the safety challenges stems from the low editing efficiency and off-target effects of CRISPR/Cas9, which risk oncogenic activation and disruption of critical genes. To address this, we adapted the whole-genome CIRCLE-Seq strategy to identify potential off-target modifications in genetically corrected RDEB iPSCs and uncovered 33 potential off-target sites in patient cells. Preliminary analysis of Oxford Nanopore sequencing data in gene edited RDEB iPSCs showed no off-target activity at the top sites with high sequence homology, supporting the safety of our gene editing approach. To confirm complete iPSC differentiation and minimize tumor risks, we performed single-cell RNA sequencing (scRNA-seq) on gene-edited iPSC-derived skin cells at different stages of the manufacturing process. The results revealed distinct clusters of keratinocytes, fibroblasts, mesenchymal stem cells, and melanocytes. These cells are being further characterized by gene and protein expression analyses. Our findings provide critical preclinical safety data for advancing to a clinical trial for RDEB.

0553

Genotype spectrums in 151 patients with pustular psoriasis from China

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Objective: There is a paucity of knowledge on the genetic heterogeneity of pustular psoriasis (PP), this study aims to describe the genetic spectrums. Methods: The analysis of currently known variations in PP-related genes via whole genome sequencing (WGS) was conducted based on a bidirectional cohort research of 151 PP patients. Results: A total of 114 generalized PP (GPP) were identified among 151 PP patients, including 67 GPP-only and 47 GPP+PsV (psoriasis vulgaris). Additionally, 16 patients were diagnosed with ACH (acrodermatitis continua of Hallopeau), and 21 were PPP (palmoplantar pustulosis). IL36RN-positive patients account for 83, including GPP-only (47), GPP+PsV (19), ACH (12) and PPP (5). While the IL36RN-negative patients account for 68, consisting of 20 GPP-only, 28 GPP+PsV, 4 ACH and 16 PPP, among them, 16 were positive for CARD14, and fewer were positive for other pathogenic genes of MPO, AP1S3, SERPINA3 and others. In total, 24.5% (37/151) patients were CARD14-positive, 21.6% (8/37) were homozygous (all of which were c.2458C>T variants), a half of the homozygous were diagnosed with PPP. We further analyzed the genetic variations in PPP patients. 23.8% (5/21) were IL36RN-positive (2 homozygous), while 28.6% (6/21) were CARD14-positive (4 homozygous). Given that tongue abnormalities have been recognized in PP, we analyzed the genetic profiles of 113 patients who underwent tongue examination. 40.7% (48/118) patients exhibited geographic/fissured tongue, including 28 cases of GPP-only, 10 of GPP+PsV, 7 of ACH, and 3 of PPP. The incidence of geographic/fissured tongue was significantly higher in IL36RN-positive patients compared to IL36RN-negative (67.2% vs 10.2%). Conclusions: This study presents the genotype spectrums of PP in the Chinese population, reveals complex genotype-phenotype correlations and provides new insights into the genetic background of PPP.

0554

Expansion of an HSV-1-based gene therapy platform to treat Hailey-Hailey and Darier diseases

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The herpes simplex virus type 1 (HSV-1)-based gene therapy beremagene geperpavec (B-VEC) has been successful in treating the rare genetic skin blistering disease dystrophic epidermolysis bullosa (DEB). The underlying platform technology is being developed to treat additional rare skin diseases, including Hailey-Hailey disease (HHD) and Darier disease (DD). HHD and DD are inherited genodermatoses caused by pathogenic variants in the calcium ATPases ATP2C1 and ATP2A2, respectively, for which Krystal Biotech, Inc. is developing KB111 and KB112. Here, we sought to determine if these vectors are capable of transducing keratinocytes both in culture and in wild-type mice in order to express their encoded ATPases with minimal toxicity. Quantitative PCR (qPCR) and reverse-transcription PCR (RT-qPCR) were used to quantify vector genomes and transcripts, respectively, in clinically relevant immortalized human keratinocytes after transduction; western blotting (WB) was used to verify the production of full-length protein. To evaluate tolerability, Mosmann's Tetrazolium Toxicity (MTT) assay and flow cytometry were used to assess cell viability at multiple timepoints post-dose. Immunofluorescent (IF) staining was employed to observe proper localization of ATP2C1 and ATP2A2 to the Golgi and endoplasmic reticulum, respectively. Experiments were also performed with mice administered either KB111 or KB112 topically or via intradermal injection. Twenty-four hours after administration, skin punches were taken for DNA and RNA quantification, IF, and hematoxylin and eosin staining. *In vitro* and *in vivo* analyses indicated that both KB111 and KB112 are capable of transducing keratinocytes and expressing their encoded ATPases with minimal toxicity both in culture and in murine skin, demonstrating that Krystal's HSV-1-based platform is well-suited for the treatment of both HHD and DD.

0555

Mutational landscape of melanocytic tumors from patients with RASopathies

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RASopathies, including Neurofibromatosis 1 (NF1), Cardio-facio-cutaneous Syndrome (CFC), and Costello Syndrome (CS), are genetic syndromes characterized by germline pathogenic variants in genes of the RAS pathway. They are multi-systemic syndromes and often present with a cutaneous phenotype. Mutations in the RAS pathway also play a critical role in melanoma development, allowing for uncontrolled neoplastic growth. Approximately 80% of melanocytic nevi in the general population harbor the BRAF p.V600E somatic mutation, a common mutation in the RAS pathway. Despite this, the potential for additional somatic mutations of the RAS pathway in melanocytic tumors from RASopathy patients, and its role in melanoma risk, remains unexplored. In this study, we investigated the mutational landscape of melanocytic nevi in patients with NF1, CFC, CS, and controls. Whole exome sequencing was performed with tumor-normal or tumor-only analysis on 58 nevi (32 common, 24 dysplastic, 2 melanoma) from 58 patients (11 NF1, 3 CFC, 1 CS, 43 controls). A BRAF p.V600E somatic variant was found in 66% of the control nevi. In addition, the control nevi had an average of 0.52 somatic variants in the RAS pathway and cancer genes previously reported in melanoma on genomics databases (cBio, COSMIC). In comparison, only 28.6% of the RASopathy nevi harbored a BRAF p.V600E somatic variant. The RASopathy nevi had an average of 2.57 somatic variants in the RAS pathway and cancer genes previously reported in melanoma on genomics databases, compared to 0.52 variants in controls ($p < 0.0003$). This study explored the mutational landscape of melanocytic nevi from patients with RASopathies and controls and found increased somatic mutation burden in RAS pathway genes in RASopathy-associated nevi, leading to more insight into melanoma risk in RASopathies.

0556

SERPINB7 c.796C>T Variant: A genetic risk factor linked to immune dysregulation and skin microbiota alterations in atopic dermatitis

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Atopic dermatitis (AD) is a multifactorial disorder influenced by genetic predispositions and environmental factors. SERPINB7 is a causative gene for Nagashima-type palmoplantar keratosis (NPPK), an autosomal recessive genodermatosis common in East Asia. Here, we demonstrate that the c.796C>T (p.Arg266*) variant in SERPINB7, the most prevalent pathogenic variant for NPPK in East Asians, is associated with an increased susceptibility to AD. Through a combination of whole-genome sequencing and genome-wide association studies in Japanese and Taiwanese populations, the variant exhibited a robust association with AD ($p = 2.06 \times 10^{-9}$, OR = 1.72). To elucidate its phenotypic impact, we analyzed clinical symptoms, peripheral blood markers, and skin microbiome profiles in 283 AD patients. Although the limited sample size precluded statistically significant associations with clinical parameters such as severity and pruritus scores, carriers of the variant showed significantly elevated serum IgE and TARC/CCL17 levels, both of which are established biomarkers of AD. Skin microbiome analysis revealed an increased total bacterial load in carriers and identified specific bacterial species associated with the variant. In conclusion, SERPINB7 c.796C>T (p.Arg266*) variant emerges as a genetic risk factor for AD, likely influencing disease pathogenesis through immune dysregulation and skin microbial alterations. These findings highlight the potential role of SERPINB7 as a critical molecule in AD pathophysiology, paving the way for further investigations into its therapeutic relevance.

0557

Super-enhancer-driven transcriptional program contributes to psoriasis pathogenesis

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Background: Super-enhancers (SEs) are compound regulatory elements that control expression of key cell identity genes. Transcription factor FOSL1 plays a crucial role in cell differentiation, response to environmental stresses, and tumorigenesis. Whether FOSL1 contributes to psoriasis pathogenesis through activating psoriasis related enhancers remain unclear. Methods: RNA-seq and H3K27ac CUT&tag were used to construct enhancers map in psoriasis. CRISPR-based technologies were used to delete SEs. IL-17A, IL-22, oncostatin M, IL-1α, and TNF-α (M5 cytokines) stimulated keratinocytes and Imiquimod induced mice were used as cell and animal models of psoriasis. Results: Global H3K27ac modification levels were elevated in psoriasis lesions and M5-stimulated HaCaT cells, identifying 468 and 254 differentially active enhancers in lesions and cell models, respectively. Pathway enrichment showed that genes regulated by active enhancers were involved in inflammatory pathways. SE inhibitor JQ-1 improved IMQ-induced psoriasis-like dermatitis in mice and inhibited proliferation and promoted apoptosis in M5-stimulated HaCaT cells. Moreover, we identified a SE in IL1 family gene cluster according to the genes expression change and H3K27ac enrichment. IL1-SE knockout in HaCaT cells lead to downregulation of IL1A, IL1B, IL36G, and IL36RN mRNA expression. Motif analysis showed significant enrichment of the transcription factor FOSL1 in SE regions, which was highly expressed in keratinocytes of psoriasis lesions. Combining FOSL1 and H3K27ac CUT&tag data, we found co-localization of FOSL1 and H3K27ac across the genome, and knockdown of FOSL1 reduced H3K27ac occupancy and SE activity. Mechanistically, the upregulation of FOSL1 promotes phase separation, facilitating the aggregation of the EP300 transcriptional complex in IL1-SE. Conclusion: Aberrant upregulation of FOSL1 forms phase-separated liquid condensates with EP300, activating SEs and promoting the transcription of pathogenic genes in keratinocyte of psoriasis.

0558

AlphaMissense (AI algorithm) correctly predicts PTCH1 genomic variants that underlie Gorlin syndrome

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Gorlin syndrome (GS), or basal cell nevus syndrome, is a rare autosomal dominant disease leading to development of numerous BCCs. While GS is commonly driven by variants of tumor suppressor gene PTCH1, exact variants are diverse and not well-characterized. Our study aimed to evaluate the functional impact of PTCH1 variants associated with GS. Using sequencing data from a prior phase 3 clinical trial of Hedgehog pathway inhibitor patidegib, we applied AlphaMissense, an AI-based pathogenicity prediction tool developed by Google DeepMind (2023), to predict pathogenicity of PTCH1 missense variants. Of 131 patients with genomic testing, 118 had PTCH1 variants. These comprised 30 missense, 22 premature termination codons (PTCs), 38 frameshifts leading to PTCs, 10 splice sites, 3 introns, 13 deletions, and 2 duplications. AlphaMissense accurately predicted pathogenicity in 95% of missense variants with established classification on ClinVar (N=20/21). After filtering duplicates, there were 7 missense variants of unknown significance (VUS), and AlphaMissense classified all 7 novel variants as "Likely pathogenic", with pathogenicity scores ranging from 0.860 to 0.999 (scores range from 0-1, higher values indicate higher likelihood of pathogenicity). The scores showed high correlation with other mutation predictors, including PolyPhen-2 (0.984 using Pearson correlation, p-value <0.0001) and MutPred2 (0.890, p-value=0.007). These 7 subjects had many BCCs and other clinical symptoms of GS, confirming the classification of pathogenic variant. AlphaMissense enabled reclassification of novel VUS as pathogenic in patients with clinical GS, highlighting its potential for analyzing and interpreting VUS. While PTCH1 variants are identified in 85% of GS patients, many VUS may currently be misclassified. An enhanced understanding of PTCH1 variants may improve diagnostic and treatment strategies for GS patients.

0559

Integrated transcriptome-epigenome analysis identifies NRIP1, PRDM1, and OSGIN2 as key regulators in skin aging

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Epigenetic modifications are increasingly recognized as critical regulators of the aging process, particularly in skin aging. These modifications can activate or suppress genes associated with collagen production, oxidative stress responses, and inflammation, thereby contributing to the acceleration of skin aging. Here, we performed integrated transcriptome-epigenome analyses (RNA-Seq, ATAC-Seq, and ChIP-Seq) in primary human dermal fibroblasts (HDFs) overexpressing DNMT1. DNMT1 overexpression in skin cells resulted in significant alterations in genes such as NRIP1, OSGIN2, and CRAT. In the promoter region analysis, significant changes were observed in inflammation- and immunity-related genes, including PRDM1. Furthermore, we validated the expression of core genes NRIP1, PRDM1, OSGIN2 (upregulated), and CRAT (downregulated) in ultraviolet (UV)-irradiated HDFs and skin tissues. Knockdown of NRIP1, PRDM1, or OSGIN2 resulted in reduced matrix metalloproteinase (MMP)-1 levels, which are typically elevated following UV irradiation, along with restored procollagen levels. In contrast, overexpression of NRIP1, PRDM1, or OSGIN2 led to a significant increase in the expression of pro-inflammatory cytokines and MMPs. Interestingly, NRIP1 knockdown caused a subsequent decrease in PRDM1 and OSGIN2 expression, whereas NRIP1 overexpression resulted in the upregulation of PRDM1 and OSGIN2 expression. In skin-specific Dnmt1 conditional knockout (cKO) mice, reduced inflammatory cytokines and aging phenotypes were observed upon acute UV irradiation, thereby validating the efficacy of our skin aging model through DNMT1 regulation *in vivo*.

0560

Spatial transcriptomics identifies immunomodulation and vasculogenesis as pathways distinguishing NF1-associated vs a sporadic cutaneous neurofibroma

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Cutaneous neurofibromas (CNs) are benign tumors associated with neurofibromatosis type 1 (NF1). Although the presence of multiple CNs is highly specific for NF1 (NF1-CN), non-NF1-associated, single sporadic CNs (sp-CN) are far more common, and histologically identical. NF1-CN develop secondary to mutations in the NF1 gene, leading to RAS/MAPK pathway overactivation. Whole-exome sequencing studies have identified a different mechanism, KIR2DL5 mutation, leading to the development of sp-CN, suggesting that tailored therapeutic approaches may be required for NF1-CN vs sp-CN. Here, we perform, to our knowledge, the first spatial transcriptomics study of NF1-CN and sp-CN, identifying distinctive molecular processes underlying NF1-CN and sp-CN across over 1 million cells. Five NF1-CN from patients with documented NF1 diagnoses and one sp-CN from an adult male patient with no other signs or symptoms of NF1, were assayed with the Visium HD system (10x Genomics). Unsupervised clustering identified 15 transcriptional clusters, 13 of which were shared between all 6 tumor samples. Two additional B-cell subtype clusters unique to NF1-CN were identified, suggesting greater adaptive immunoreactivity in NF1-CN. Overall, NF1-CNs demonstrated greater immune infiltration (i.e., upregulating C3 (p=1.42e-11) and CXCL14 (p=1.35e-08)) and decreased vasculogenesis (i.e., vascular development, p=2.46x10-19) on pathway analysis. Despite this, NF1-CNs comparatively overexpressed APOD (p=2.49e-18), a known regulator of neurofibroma progression that could underlie the increased growth potential of NF1-CN compared with sp-CN. These data suggest that despite histological similarities, NF1-CNs and sp-CNs may have distinct microenvironments that confer differential susceptibility for vasculogenic and immunomodulatory therapeutics.

0561

Different molecular mechanisms underlie skin fragility in AEC and EEC

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Ankyloblepharon ectodermal dysplasia and cleft lip/palate (AEC) and ectrodactyly ectodermal dysplasia and cleft lip/palate (EEC) are two genetic disorders caused by mutations in the transcription factor TP63. AEC mutations localize to the sterile alpha motif domain, a putative protein-protein interaction domain, while EEC mutations are clustered in the DNA binding domain. Both disorders are associated with severe skin erosions and have no treatment options. Our group is investigating the pathological mechanisms underlying skin fragility. To this end, we developed complementary *in vitro* systems. First, we created a patient-derived induced pluripotent stem cell (iPSC) system with matched gene-corrected pairs that can be differentiated into keratinocytes (iPSC-K). Using the commercially available immortalized keratinocyte line, NTERT, and lentiviral constructs harboring AEC- or EEC-mutant TP63, we generated an additional disease-relevant model. RNA sequencing performed on AEC and EEC iPSC-K, and in silico pathway analysis identified defects to "integrin receptors" and "cell adhesion" in AEC iPSC-K while EEC iPSC-K had a "epidermal differentiation" defect. AEC iPSC-K RNA and protein analysis show reduced expression of desmosomal genes (DSG3, DSC3, DSG1, DSC1), hemidesmosomal (HD) genes (ITGA6, ITGB4, COL17, DST, LM332), and focal adhesion (FA) genes (ITGA2, ITGA3, VINC, PAX, ILK). However, EEC iPSC-K did not show abnormalities to HD or FA genes. Instead, we observed inappropriate expression of genes associated with epidermal terminal differentiation in keratinocytes cultured under proliferating conditions. Upregulated genes included TGM1, DSG1, DSC1, ZNF750, and FLG. EEC iPSC-K also expressed several genes not typically expressed in keratinocytes, including KRT13 and POSTN. The results were confirmed in patient skin. Our findings reveal different pathological mechanisms underlie skin fragility in AEC and EEC. Further understanding of the link between the location of TP63 mutations and different pathological outcomes may facilitate therapeutics for both disorders.

0562

Inborn errors of immunity in hidradenitis suppurativa

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Hidradenitis suppurativa (HS) is an inflammatory skin disease of terminal hair follicles. Despite many unmet needs, its genetic architecture remains understudied. Familial studies have identified four single-gene causes of HS, which belong to a larger class of Mendelian diseases of the immune system known as Inborn Errors of Immunity (IEI). IEI are increasingly diagnosed among adult with common immune-mediated diseases. We hypothesize that IEI are underdiagnosed among patients with HS. In a cohort of 270 ancestrally diverse HS research participants, we performed a diagnostic analysis of IEI genes that share clinical, cellular, or molecular features with HS (N=98). Qualifying variants (QVs) were defined as having a population frequency <0.1%, having genotype distributions consistent with known mode of inheritances, and having predicted protein-alteringe effects. QVs were identified in 29 genes in 87 participants. STAT1 exceeded a Bonferroni adjusted p-value (p=5.1x10-4) and 9 other genes reached a nominal level of significance (p<.05): PIK3R1, CDC42, NCSTN, RELA, NFKB1, FOXN1, TNFAIP3, NLRP1, JAK1. These genes enrich signaling pathways relevant to HS pathogenesis, including NOTCH, PI3K/Akt, TNF, IL17, JAK-Stat, and Leptin signaling. Interestingly, CDC42, RELA, NFKB1, FOXN1, JAK1 cause hair follicle defects in mouse models, while FOXN1 is also a cause of congenital alopecia in humans. Experimental evaluation suggests gain of function variants in STAT1, PI3KR1, or PI3KCD contribute to HS pathogenesis. These results provide preliminary evidence supporting our hypothesis and warrant further investigation.

0563

TRPV3 novel inhibitor KM-023 as a potential oral treatment for keratodermas

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TRPV3, a calcium channel which is predominantly expressed in epidermal keratinocytes and promotes differentiation, hyperkeratosis, and elevated inflammation. Gain-of-function variants in TRPV3 underlie Olmsted syndrome (OS), while its overexpression is associated with various palmoplantar keratodermas. Kamari Pharma is developing potent and specific TRPV3 inhibitors for the treatment of rare skin diseases. KM-023 is an oral drug candidate (IC_{50} ~2nM), which significantly reduced Ca^{+2} flux in OS keratinocytes, as demonstrated by high throughput calcium imaging and calcium flux cellular assay in human epidermal keratinocytes (nHEK) expressing either WT hTRPV3 or G573S hTRPV3 mutated form. The efficacy of KM-023 was tested in several in-vitro studies, including in OS patient derived keratinocytes. Treatment with KM-023 in a 3D skin equivalent model of Pachyonychia Congenita (PC) led to improvement in the impaired skin barrier and normalization of proliferation and differentiation, as assessed by Ki-67 staining, involucrin and loricrin expression and localization. The *in vivo* efficacy of orally administered KM-023 (1-100mg/kg/d for 21 days) was assessed in DS-Nh mice with a 'gain-of-function' Trpv3 mutation. Doses of 10mg/kg and 20mg/kg significantly reduced keratoderma severity ($p < 0.05$) (one of the OS symptoms), while also reduced epidermal thickness and normalized differentiation. These doses were also effective in reducing the frequency of episodes of mouse pruritus. Furthermore, in toxicology studies in rats and minipigs, KM-023 was found to be well tolerated, and non-genotoxic. The results suggest that KM-023 can be potentially used to treat OS, PC and other Keratodermas. A Phase 1 study in healthy volunteers and OS patients is planned to be initiated shortly.

0564

Hidradenitis suppurativa GWAS identifies 12 loci that implicate misdirected keratinocyte migration in pathogenesis

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Hidradenitis suppurativa (HS) is a prevalent inflammatory skin disease. The HS Genetics Consortium facilitates global collaborations for conducting and translating HS GWAS. We report a large diverse HS GWAS meta-analysis with 6,500 HS cases. We identify 12 risk loci, including six new loci and new risk haplotypes at two previously reported loci. In silico functional genomic methods identify a core gene module of 55 genes across 9 loci that share genetic mechanisms, suggesting coordinated regulation in HS pathogenesis. We map these genes to a population of keratinocytes in HS skin that has EMT features and localizes to subsets of epithelial tendrils and tunnels, suggesting that the GWAS gene module is contributing to misdirected keratinocyte migration in HS pathogenesis. Genetic correlation (GC) analyses and PheWAS conducted with individual variants and a multi-ancestry HS polygenic risk score identify new disease comorbidities that have clinical implications for patients, including infection susceptibility. We discover a strong negative GC between HS and IBD, providing an opportunity to improve drug safety.

0565

Enhanced regenerative healing in recessive dystrophic epidermolysis bullosa (RDEB) wounds treated with mesenchymal stem cell-derived extracellular vesicles (EVs): Findings from a phase 1/2a clinical study

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Patients with RDEB suffer from skin fragility, blistering, scarring, and squamous cell carcinoma, resulting from insufficient expression of Collagen VII and disease-associated immunoinflammatory dysregulation. Stem-cell-derived EVs, which deliver a complex mix of proteins, nucleic acids, and basement membrane components, have demonstrated regenerative healing properties in both preclinical and clinical studies. This Phase 1/2a first in human study is a prospective, open label, randomized, multi-center study with intra-subject paired wound control intended to evaluate safety and clinical benefit of topical application of EVs to RDEB wounds persisting ≥ 4 weeks. The treated wounds receive up to 6 EV applications over 10 weeks. The control wound receives standard of care only. Wounds are evaluated for closure and scar quality every 2 weeks for 10 weeks, then every 4 weeks for 12 additional weeks. A 34 year old Caucasian female subject had a chronic atrophic, fibrotic, non-healing wound treated with 5 applications of EVs over 10 weeks. The treated area epithelialized by week 4 and resisted re-opening with evidence of dermal rebuilding in the treated area. This wound demonstrated markedly higher improvement over baseline at 10 weeks versus the control wound in all parameters measured, including POSAS (Patient/Observer Scar Assessment Scale), Wong-Baker Pain, and Quality of Life assessments. The control wound continued to exhibit poor basement membrane function with worsening inflammation by week 10. Data from this first in-human study supports safety and suggests EVs may prove to be a valuable treatment for chronic non-healing RDEB wounds..

0566

Blood gene expression reveals endotypes of atopic dermatitis patients with distinct responses to dupilumab

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Dupilumab (DUP), an IL-4/IL-13 antagonist, reduces Atopic Dermatitis (AD) severity, but its molecular effects and variability in clinical response remain unclear. To identify AD endotypes (eTypes) with distinct gene expression changes in response to DUP, we analyzed bulk RNA-seq data from 47 AD patients pre-and post-DUP treatment (Möbus et al. 2022, GSE208405). Gene Set Variation Analysis (GSVA) using informative gene signatures (Hubbard et al. 2023) identified 3 eTypes via k-means clustering of GSVA scores. eType-1 was enriched in OXPHOS, immunoproteasome, plasma cell (PC), and Treg signatures; eType-2 in GD T cells and T cell signatures; and eType-3 in neutrophil, granulocyte, and monocyte signatures. DUP-induced changes after 3 months varied per eType: eType-1 showed GD T cells (p=0.03), NK cells (p=0.04), and B cells (p=0.00005) upregulated, and PC (p=0.002), immunoproteasome (p=0.004), cell cycle (p=0.001), and LDG (p=0.007) downregulated; eType-2 showed reductions in cell cycle (p=0.03) and IL-1 pathway (p=0.04); eType-3 showed IL-23 complex (p=0.03), GD T cells (p=0.009), and regulatory T cells (p=0.02) upregulated, and cell cycle (p=0.0005), neutrophil (p=0.04), granulocyte (p=0.006), and inflammasome (p=0.01) downregulated. These results show blood gene expression analysis identifies distinct AD eTypes, each with unique responses to DUP manifested by selective changes in cell or molecular pathway signatures. eTypes-1 and 3 exhibited broader immunomodulation in response to DUP across innate and adaptive pathways, whereas eType-2 showed more restricted changes. This study underscores AD heterogeneity and the systemic effects of DUP, emphasizing molecular endotyping's value for personalized AD treatment.

0567

Monogenic etiologies of atopic dermatitis: A comprehensive systematic review of 1165 patients

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Atopic dermatitis (AD) is the most common skin disease in children that affects 10-20% of the general pediatric population and about 10% of adults. It is characterized by inflammation and itching, and is often associated with a history of atopy in patients or their families. AD is a complex disease with mainly multifactorial etiology. However, a small subset of patients has unifactorial etiology caused by a mutation in a single gene that is highly penetrant and afflicts any 1% of the normal population. Recently, the widespread use of genome/exome sequencing made it possible to determine this high-risk Mendelian subset from a larger group of patients with multifactorial etiology. Despite several reported cases of monogenic AD, it is not clear how useful genetic testing is in a clinical setting, and genetic testing is rarely incorporated into clinical assessments. To find out how useful genetic testing is and to encourage broader molecular testing, we conducted a systematic literature review to identify the genotypic and phenotypic spectra associated with monogenic AD. The inclusion criteria were met by 449 of 31,031 articles. In 1165 patients 170 AD-associated genes were identified, including 53, 31, and 82 genes with strong, moderate, and weak evidence for causality, respectively. Autosomal recessive inheritance predominated (57%). AD onset age was 10.18±10.62 months, with an interquartile range of 2 to 12 months. The FLG, DOCK8, CARD11, STAT3, EDA, SERPINB7, SPINK5, and WAS are the most frequently reported AD-associated genes with strong causality. 76 (44.7%) out of 170 belong to a catalog of inborn errors of immunity-related genes. AD has at least 170 monogenic etiologies and a genetic diagnosis is essential for effective management.

0568

UCA1 drives epidermolytic ichthyosis pathogenesis via miR-125a sponging and STAT3 dysregulation

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Epidermolytic ichthyosis (EI) is a rare hereditary skin disorder characterized by scaling, erythema, and an impaired epidermal barrier. Our RNA-seq dataset from biopsied EI skin (GSE192832) was reanalyzed to identify long non-coding RNAs (lncRNAs) that regulate gene expression via microRNA sponging in EI. Among the identified lncRNAs, UCA1 exhibited the highest fold change (3.1-fold, p<0.0001), suggesting a potential regulatory role. We hypothesized that UCA1 suppresses miR-125a to increase STAT3 signaling, promoting inflammation and cell growth in EI, like its role in psoriasis. miR-125a inhibits STAT3 translation by binding its mRNA, while UCA1 sequesters miR-125a, enabling STAT3-driven inflammation and highlighting a key miR-125a/STAT3 axis in EI pathogenesis. Enrichment pathway analysis of miR-125a targets in RNAseq dataset revealed key processes, including immunomodulation, cell proliferation, and the EGFR signaling pathway in EI. Six skin biopsies from patients (15-61 years old) with KRT10 pathogenic variants were collected after IRB-approved consent. RNA and protein were extracted from keratinocytes (KCs) isolated from patient vs. matched controls to study the UCA1/miR-125a/STAT3 axis. qRT-PCR analysis confirmed increased UCA1 expression (2-fold; p<0.05) in EI KCs. TNFA, a STAT3 target gene, was increased in EI samples (1.67-fold, p<0.01), indicating a dysregulated inflammatory response. Additionally, potential STAT3 target genes, FOS (1.2-fold, p<0.05), CCND1 (2.3-fold, p<0.001), CTNNB1 (1.4-fold, p<0.001), and MYC (2-fold, p<0.001), all showed increased expression in EI KCs, suggesting a coordinated disruption of cell cycle regulation, differentiation balance, and inflammatory response. Western blot analysis showed increased total and phospho-STAT3 in EI KCs, linking UCA1 to STAT3 dysregulation in cultured KCs. Our findings indicated that UCA1 may modulate the miR-125a/STAT3 signaling axis in EI, leading to abnormal cell proliferation and inflammatory response, and suggesting a new therapeutic target.

0569

iPSC-derived fibroblasts and keratinocytes from individuals with recessive dystrophic epidermolysis bullosa reveal deficits in early-stage autophagy and lipid accumulation

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Recessive dystrophic epidermolysis bullosa (RDEB) is a recessive congenital skin disease caused by biallelic pathogenic variants in COL7A1, encoding type VII collagen (COL7A1). COL7A1 deficiency results in an unstable dermal-epidermal junction, causing severe blistering and a high risk of aggressive cutaneous squamous cell carcinoma (cSCC) at an early age, suggesting a premature aging phenotype. Whether this is caused by chronic wounding or intrinsic COL7A1 deficiency remains unclear. We hypothesize that COL7A1 deficiency impairs autophagy, promoting senescence and cSCC. Uncorrected ($COL7A1^{-/-}$) and genetically corrected ($COL7A1^{+/-}$) iPSC-derived fibroblasts (iFs) and keratinocytes (iKs) were generated from primary fibroblasts (Fs) through reprogramming, CRISPR/Cas9 gene editing, and differentiation via skin organoids. Analysis of $COL7A1^{-/-}$ and $COL7A1^{+/-}$ iFs and iKs revealed deficits in early-stage autophagy and lipid accumulation. We observed a statistically significant decrease in autophagosome formation in $COL7A1^{-/-}$ iFs relative to $COL7A1^{+/-}$ iFs. Additionally, we observed a statistically significant increase in lipid droplet number, area, and density in $COL7A1^{-/-}$ iFs and iKs relative to $COL7A1^{+/-}$ iFs and iKs. Decreased autophagosome formation and increased lipid droplet accumulation indicate impaired autophagy in COL7A1 deficiency, a hallmark of senescence and potential driver of malignant transformation, metastasis, and aggressive RDEB-associated cSCC. Ongoing studies aim to uncover how COL7A1 deficiency impairs autophagy, which we now speculate may occur through COL7A1 binding partners that stabilize early stages of autophagy. Our findings suggest that targeting autophagy pathways could offer a therapeutic strategy to mitigate accelerated senescence and progression of RDEB-associated cSCC.

0570

Biological mediators of common variant associations discovered in genome-wide association studies of hair traits and disorders.

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Hair plays significant cultural, social, and religious roles, impacting body image, self-esteem, and health. The United States haircare industry is valued at $13.4 billion, representing about 22% of the global beauty market, underscoring the cultural significance of hair. Genome-wide association studies (GWAS) identify common variants that are widely shared among individuals, providing knowledge that has broad population relevance. Here, we systematically perform in silico functional analyses of hair GWAS to identify genes that are responsive to, or have protein-coding changes from, risk variants. We identify 91 genes implicated in two or more hair outcomes, including EDAR, WNT10A, and IRF4, among others. Pathway enrichment analysis identifies several signaling pathways that have been well-established in hair biology (e.g., WNT, Hippo and Notch, etc.), and allows us to functionally organize key genetic regulators. Our analysis reveals how those pathways are differentially utilized within the context of different hair diseases and traits. We next further prioritized genes by cross-referencing them with known Mendelian disease genes from the Online Mendelian Inheritance in Man (OMIM) database. We identify a set of 37 genes that contain both rare pathogenic variants that cause strong biological perturbations and common risk variants with more subtle effects. Our systematic analysis of hair GWAS variants, genes, and pathways not only provides a robust framework for future experimental validation but also paves the way for innovative clinical applications to improve the clinical management of hair disorders.

0571

Linear epidermal nevus caused by a novel mosaic heterozygous PTPN11 variant

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Linear epidermal nevus (LEN) is a rare dermatological condition with skin disease distributed along Blaschko's lines. We present a 3-year-old female case who presented with congenital linear skin lesions on her right side with sharp cutoff at the midline. Physical examination revealed multiple light pink to red papules and hyperkeratotic plaques following Blaschko's lines. Histopathological examination of the affected skin revealed acanthosis, increased capillaries in the papillary dermis, and sparse lymphocytic inflammation. Unaffected skin showed no significant abnormalities. Whole exome sequencing in the affected tissue revealed a heterozygous missense variant (c.C1361T, p.Pro454Leu) in the PTPN11 gene which was absent in saliva and unaffected cultured keratinocytes. Quantitative RNA in situ hybridization did not reveal any changes in IL-17A, IL-13, and IL-36γ levels. Immunofluorescence staining showed increased phospho-S6 Ribosomal Protein levels in the affected skin in both epidermis and capillaries, suggesting upregulated activity of the RAS/MAPK pathway. CD34 staining which labels vascular endothelial cells, was also significantly elevated in the affected skin. Cell proliferation in the basal epidermis of affected skin was increased compared to unaffected skin (36.9% vs. 7.7% Ki-67+ respectively). Our study provides evidence for phenotypic expansion in linear genetic disorders associated with PTPN11 damaging variants.

0572

Characterization of molecular mechanisms in hypermobile Ehlers-Danlos syndrome via transcriptome analysis

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Ehlers-Danlos Syndrome (EDS) is a group of genetic connective tissue disorders characterized by hyperextensible skin, joint hypermobility and cutaneous fragility. Caused primarily by mutations in genes related to collagen and its biogenesis, EDS remains challenging to study due to the lack of reliable *in vivo* and *in vitro* models, particularly for the most common type, hypermobility EDS (hEDS). Genetic causes of hEDS are poorly understood. Therefore, recapitulating the hEDS phenotype in a reliable 3D model opens doors to phenotype characterization and causative mutation validation. We developed an *in vitro* cell-based model of hEDS by generating 3D skin equivalents using hEDS human fibroblasts embedded in thiolated-hyaluronan (HA-SH) fibrin gel scaffolds. These skin equivalents, derived from either primary hEDS fibroblasts or fibroblasts differentiated from hEDS induced pluripotent stem cells, exhibited disorganized collagen fibrils in the extracellular matrix, resembling those in hEDS patient skin biopsies. Spatial transcriptomics of our 3D skin equivalents revealed a distinct biomolecular phenotype of hEDS; including deficiencies in PLOD1 and NFKB2. PLOD1 encodes lysyl-hydroxylase 1 (LH1), essential for fibrillar collagen assembly, while NFKB2 encodes a component of the NFκB complex. Both gene deficiencies were validated via qPCR analysis of fibroblast monolayer cultures from all patients in our cohort (n=18). Immunofluorescent staining has preliminarily validated the deficiency in LH1 on the protein level. Our findings suggest that PLOD1 is regulated via NFκB signaling, and any mutation(s) upstream of this signaling pathway provides a possible link between connective tissue and immunological symptoms of hEDS. CUT&RUN and western blot validations are underway.

0573

The lineage master transcription factor p63 cooperates with FOXK1, a cancer-specific cofactor, to mediate oncogenic 3D chromatin dynamics in squamous cell carcinoma.

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Transcriptional dysregulation by lineage-specific master transcription factors (TFs) is critical in cancer, often altering three-dimensional (3D) chromatin architecture. However, the mechanisms through which master TFs drive these changes remain unclear. Here, we investigate the role of the epidermal master TF, p63, in remodeling 3D chromatin in squamous cell carcinomas (SCCs) compared to normal keratinocytes (KCs). Using a multi-omic approach—integrating chromatin looping, accessibility, transcriptomics, p63 binding, and proteomics—we show that p63 increases connectivity between prognostic genes and cis-regulatory elements (CREs). Gene Ontology term enrichment confirmed a critical role for p63 in regulation of cell proliferation in progenitor KC and SCC, with >67% cancer-specific p63 binding sites enriched for target genes related to the cell cycle pathway. p63-dependent genomic accessibility was also increased in SCC lines and up to 40% was not detected in primary KCs, suggesting p63 may uniquely regulate chromatin architecture in cancer. Integrative analysis of p63 cancer-specific binding, accessibility and looping led to the identification of a unique type of 3D chromatin regulation, termed 'Secondary' mode, where p63 indirectly regulates SCC-specific tumor-promoting genes through an additional CRE lacking direct p63 epigenetic signatures. Proximity proteomics was employed to identify the FOXK1 TF as an SCC-specific p63 cofactor. The p63-FOXK1 interaction was validated in SCC cells, in which FOXK1 loss phenocopied p63 loss, as well in human SCCs. FOXK1 binding was found in 32% of p63-dependent chromatin loops, indicating FOXK1 collaborates with p63 to shape these oncogenic chromatin interactions and drive cell proliferation. These findings uncover the p63-FOXK1 axis as a potential therapeutic target in SCCs.

0574

A rare neonatal case of diffuse capillary malformations in suspected sturge-weber syndrome

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Sturge-Weber Syndrome (SWS), or encephalotrigeminal angiomatosis, is a rare neurocutaneous disorder caused by somatic mutations in the GNAQ gene. It is characterized by a triad of unilateral facial capillary malformations (port-wine stains), leptomeningeal angiomatosis, and glaucoma. Port-wine stains typically involve the ophthalmic (V1) trigeminal dermatome, with diffuse or bilateral presentations associated with an elevated SWS risk. We report a potential case of SWS in a two-day-old full-term neonate presenting with diffuse bilateral capillary malformations of the trigeminal nerve distribution, trunk, and limbs, sparing the left anterior trunk. The lesions appeared as persistent violaceous macules and patches with reticulated patterns. No limb asymmetry, macrocephaly, or neurological symptoms, including seizures, were observed. Ophthalmologic screening for glaucoma, brain MRI, and genetic testing for GNAQ mutations are in progress. Pulsed dye laser therapy is being considered to lighten vascular lesions and address potential psychosocial impacts. While awaiting imaging and genetic results, early evaluation was prioritized to manage potential complications of glaucoma, seizures, and stroke-like episodes. Differential diagnoses of diffuse capillary malformation include Transient Neonatal Harlequin Color Change, Cutis Marmorata Telangiectatica Congenita (CMTC), Klippel-Trenaunay Syndrome, Diffuse Capillary Malformation with Overgrowth (DCMO), and Macrocephaly-Capillary Malformation (M-CM). Given the pertinent negatives, SWS is the favored working diagnosis. This atypical diffuse presentation underscores diagnostic challenges and highlights the importance of timely management to mitigate risks. The uniquely diffuse and mosaic presentation raises the possibility of an early post-zygotic mutation. Further genetic analysis may elucidate novel mutations in GNAQ or other loci that contribute to an aberrant development of diffuse capillary malformations.

0575

Clinical characteristics of recessive dystrophic epidermolysis bullosa patients with collagen VII antibodies

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Patients with recessive dystrophic epidermolysis bullosa (RDEB) have been reported to have collagen VII (C7) antibodies at baseline and after treatments with C7-based therapies. Certain therapies may induce host production of C7 such as gentamicin, exon skipping, and beremagene geperpavec, or patients may be exposed to exogenous C7 such as gene-corrected grafting, intravenous recombinant C7, and bone marrow transplantation. We performed a qualitative study using data from the Epidermolysis Bullosa Clinical Characterization and Outcomes Database (EBCCOD), a North American EB registry, to evaluate clinical characteristics and assess potential predictors of C7 antibodies in RDEB patients. A total of 67 patients were identified in the registry who had C7 titers checked of which 30 patients had elevated C7 titers. Age and sex were not associated with elevated C7 antibody titers compared to RDEB patients with normal titers (p=0.08 and p=0.47, respectively). Patients who were exposed to gene therapies were not more likely to have elevated C7 antibody titers (p=0.15) in this data set. This study includes the largest sample size of RDEB patients that have had C7 antibodies evaluated to date. The pathogenicity of these antibodies and their impact on therapy response in RDEB patients remains unclear and warrants further evaluation. Importantly, understanding C7 antibodies may assist future therapeutic research in RDEB patients.

0576

Altered metabolic responses to stress render darier disease keratinocytes prone to DNA repair abnormalities

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Despite a known role in skin health, calcium dynamics remain underexplored in terms of therapeutics. The heritable acantholytic disorder, Darier disease (DD), arises from well-studied heterozygous variants of the ER calcium pump, SERCA2. Like prior studies, we measured aberrant calcium levels in DD keratinocytes (KCs) but pursued a novel hypothesis. As stress-induced flares characterize DD, we hypothesized that calcium dysregulation could hamper the metabolic response to stress. To test this idea, metabolic profiling of 3 DD patient isolates was conducted. When control KCs were exposed to an oxidative stressor, a set of 44 metabolites showed strong positive Pearson correlations (rho= 0.74 +/- 0.15; mean+/- sd), matched by a negatively correlated group of 27 metabolites (rho= -0.48 +/- 0.23 sd). A coordinated loss of glycolytic products and a surge of pentose phosphate pathway (PPP) metabolites drove these metrics. The correlations collapsed in DD cells (rho= 0.27+/-0.42 and -0.08 +/- 0.31, respectively). DD cells, then, failed to shunt intermediates from glycolysis to the parallel, PPP. Stressed cells normally activate the PPP to replenish antioxidants and produce nucleotides for DNA repair. Western blotting revealed elevated γ-H2AX levels in DD cells, suggesting chronic activation of the DNA repair system and the likelihood of heightened genetic variability. Indeed, publicly available RNAseq reads for 4 control and 4 DD skin samples deviated from the reference genome once every 5681+/-1922 and 862+/-127 exon-mapped bases (p=0.002), respectively. These observations provide a unique perspective on the origin of somatic SERCA2 variants reported to cause type 2 mosaicism in DD and a recently published link to carcinoma. Furthermore, the muted metabolic capacity for protecting genomic integrity highlights a need to consider PPP activation and genoprotective agents in DD therapeutic development.

0577

Unraveling the interplay among skin aging, epigenetic age, sociodemographic and lifestyle factors in Chinese women

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Skin aging results from biological processes and environmental factors. DNA methylation, a key epigenetic modification, is a robust aging biomarker quantifiable through methylation clocks. However, its relationship with skin aging remains unclear. To address this gap, we investigated associations between skin aging, epigenetic age, sociodemographic and lifestyle factors in a cohort of 84 Chinese females (mean age: 50.64 ± 14.91 years). Dermatologists assessed apparent age from facial photographs, and skin aging features were evaluated with a modified SCINEXA scale. Epigenetic age was determined from peripheral blood DNA using targeted bisulfite sequencing of CpG sites in the Horvath and Li clocks. Age acceleration (ΔAge) was defined as the deviation of epigenetic or apparent age from chronological age. Our results demonstrated that apparent age exhibited a strong correlation with chronological age ($p<0.001$), followed by Li epigenetic age ($p<0.001$) and Horvath epigenetic age ($p<0.001$). Importantly, the ΔAge of Horvath and Li epigenetic ages were significantly associated with the ΔAge of apparent age ($p<0.05$), with correlation coefficients of 0.251 and 0.261, respectively. Rhytides, laxity, and dyschromia scores were positively associated with both epigenetic ages ($p<0.001$). Notably, a higher education level was significantly associated with increased ΔAge of both epigenetic ages, whereas menopause and cooking intensity were associated with reduced ΔAge. In conclusion, this study links epigenetic age to skin aging and underscores the impact of sociodemographic and lifestyle factors. Future studies should validate these findings in diverse cohorts and explore personalized strategies for mitigating skin aging and advancing skin health.

0578

m^{6}A-driven epigenetic dysregulation of the tyrosine phosphatase PTPN14 promotes psoriasis progression via YAP signaling

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Psoriasis, a chronic and incurable inflammatory skin disease, poses significant clinical challenges due to its hallmark features of excessive keratinocyte proliferation and persistent inflammation. Despite advances in understanding psoriasis pathogenesis, the precise molecular mechanisms remain incompletely defined. Here, we identify non-receptor protein tyrosine phosphatase 14 (PTPN14), a tumor suppressor known for its role in cellular proliferation and differentiation, as a novel regulator in psoriasis. Analysis of the GEO database and single-cell RNA sequencing demonstrated significantly reduced PTPN14 expression in keratinocytes from psoriatic lesions compared to healthy skin. These results were confirmed by RT-qPCR and immunofluorescence in psoriatic patients and an imiquimod (IMQ)-induced psoriasis-like mouse model. Functional studies revealed that silencing PTPN14 *in vivo*, via topical application of small interfering RNA, exacerbated IMQ-induced psoriasis-like dermatitis. *In vitro* experiments showed that PTPN14 knockdown in human keratinocytes impaired cell differentiation while driving hyperproliferation by activating the YAP signaling pathway. Further investigation into the upstream regulation of PTPN14 uncovered a critical role for m^{6}A methylation. m^{6}A methylation sequencing identified reduced m^{6}A-modified PTPN14 mRNA in psoriatic epidermis in mice, and loss of m^{6}A methyltransferase METTL3 in keratinocytes further suppressed PTPN14 expression. These findings highlight m^{6}A-driven epigenetic dysregulation as a key mechanism underlying PTPN14 downregulation in psoriasis. Collectively, this study unveils a novel m^{6}A-YAP axis involving PTPN14, linking epigenetic dysregulation to keratinocyte hyperproliferation and impaired differentiation in psoriasis. These insights not only deepen our understanding of psoriasis pathogenesis but also identify PTPN14 as a promising therapeutic target for innovative treatment strategies.

0579

Role of miR-214 and miR-382 in regulating key molecular pathways involved in skin aging

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Skin aging is a complex process that is influenced by intrinsic and extrinsic factors, leading to structural and functional skin changes. This study investigated aging-associated microRNAs (miRNAs) and their roles in regulating the molecular pathways involved in skin aging, including epigenetic regulation, mitochondrial function, and extracellular matrix degradation. We performed miRNA-seq and RNA-seq analyses on human skin tissue from young (18–30 years) and aged (>70 years) individuals, identifying miR-214 and miR-382 as significantly altered with age. Human dermal fibroblasts were transfected with miR-214 and miR-382 mimics and inhibitors to validate their roles. Functional assays revealed that these miRNAs significantly affected the expression of histone deacetylases (HDACs), Sirtuins (SIRTs), PINK1, PARKIN, MMP-1, and procollagen, which are critical regulators of histone deacetylation, mitochondrial health, extracellular matrix integrity, and collagen synthesis. Dysregulation of HDACs and SIRTs, which are key players in epigenetic modifications and stress responses, may disrupt cellular homeostasis and accelerate aging. These findings suggest that miR-214 and miR-382 contribute to skin aging by modulating epigenetic regulation, mitochondrial function, and extracellular matrix dynamics, highlighting their potential as therapeutic targets for mitigating age-related skin changes.

0580

Keratin 16 spatially inhibits type I interferon responses in stressed skin: Implications for pachyonychia congenita and chronic inflammatory skin diseases

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Expression of the stress-induced keratin intermediate filament gene KRT16 (protein K16) is spatially restricted to the suprabasal compartment of the epidermis and extensively used as a biomarker for psoriasis, hidradenitis suppurativa and other inflammatory disorders. Pathogenic variants in KRT16 lead to pachyonychia congenita (PC), a rare genetic skin condition in which tissue homeostasis is disrupted in palmoplantar epidermis, oral mucosa, and other epithelial appendages. Despite its importance, the role of K16 in these conditions is not well understood. Here, we report that K16 negatively regulates type-I interferon (IFN) signaling and innate immune responses. *In vivo* studies in mouse skin show that the absence of Krt16 exacerbates imiquimod-induced psoriasiform disease and enhances neutrophil recruitment in a phorbol ester-induced model of sterile inflammation. In KRT16-null NTERT human keratinocytes in culture, the absence of K16 amplifies IFN response to synthetic dsRNA poly(I:C), including increased levels of phospho-IRF7 and ISG15. Mechanistically, K16 interacts with RIG-I-like receptor (RLR) pathway effectors, such as 14-3-3epsilon, and disrupts the 14-3-3epsilon:RIG-I interaction, thereby downregulating IFN activation. Of interest, transcriptomic data from PC patients and PPK-like lesions in Krt16 mouse footpad skin show upregulation of IFN and dsRNA effectors. These findings uncover a new paradigm for keratin-dependent regulation of innate immunity, with clear implications for the pathophysiology of PC and chronic inflammatory diseases.

0581

rhPTH(1-34) regulates PTHCHD1 to restore contact inhibition and modulate keratinocyte proliferation

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The study aimed to investigate whether recombinant rhPTH(1-34) can restore contact inhibition by regulating PTCHD1 and thereby modulating the proliferation of keratinocytes (HaCaT). HaCaT cells were treated with rhPTH(1-34). Western blotting was employed to assess the expression levels of PTCHD1 and the downstream target genes of the Hh signaling pathway, including CCND1, CCND2, CDK1, and CCNB1. Cell adhesion assays were conducted to calculate adhesion indices; DAPI staining was performed to observe nuclear morphology; crystal violet staining assessed cell adhesion under microscopy; and BrdU immunofluorescence was utilized to evaluate cell proliferation capacity. Additionally, PTCHD1 overexpression was induced in HaCaT cells via lentiviral infection, followed by rhPTH(1-34) treatment for 48 hours. Cell viability was evaluated using the CCK8 method, while flow cytometry was employed to analyze the cell cycle. RT-PCR and Western blotting were also performed to detect PTCHD1, CCND1, CCNB1, CCND2, and CDK1 expression. The effects of the treatment on the states of cell adhesion, DAPI staining, crystal violet staining, and BrdU immunofluorescence were observed to assess contact inhibition status following PTCHD1 overexpression. rhPTH(1-34) inhibited the proliferation of HaCaT cells and induced cell cycle arrest in the G1 phase, thereby restoring intercellular contact inhibition. This compound suppressed the proliferation of HaCaT cells by downregulating PTCHD1. Notably, the proliferation capacity and contact inhibition status of PTCHD1-overexpressing cells were reversed upon treatment, with a significant increase in the number of cells arrested in the G1 phase. rhPTH(1-34) inhibits keratinocyte proliferation by regulating the cell cycle and upregulating PTCHD1, ultimately restoring cell contact inhibition.

0582

Dissecting the role of inflammation in the pathogenesis of ichthyosis with confetti

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Ichthyosis with confetti (IWC) is an autosomal-dominant genetic skin condition caused by damaging variants in keratin 1 or 10. Patients with IWC have severely red, scaly skin and develop "confetti spots" of genetically reverted, histologically normal-appearing skin. We aimed to determine whether IWC shares the Th17 immunologic signature shown in other monogenic forms of ichthyosis and whether targeted immune-based therapies could ameliorate inflammation in IWC. Using RNA in situ hybridization, we demonstrated that IWC skin lacked IL-17A+ T cells but had increased levels of IL-36G in the suprabasal epidermis. IL36G elevation was specific to affected skin and at levels similar to psoriasis and atopic dermatitis. We used an inducible transgenic mouse model to express IWC-mutant Krt10 in mice and profiled skin at multiple time points using single cell RNA sequencing. Compared to wildtype controls, suprabasal keratinocytes from IWC mice expressed high levels of epithelial damage markers, antimicrobial calprotectin genes, and IL-36g. Ligand-receptor analysis predicted endogenous products from mutant keratinocytes to activate toll-like receptors on myeloid cells, fibroblasts, and other keratinocytes. Given the demonstrated role of IL-36 ligands in driving psoriasiform dermatitis in mouse models, we crossed IWC mice to IL36 receptor knockout mice. In Krt10-mutant, IL36R knockout-mice, skin pathology (scaling, erythema) remained unchanged and transcripts related to epidermal damage and innate immunity were increased at similar levels to IWC mice. The cellular interactions revealed by our dataset inform our understanding of patterns of inflammation driven by skin barrier dysfunction. Our results indicate that although IL-36 ligands are increased in our mouse model of IWC, inhibiting this inflammatory signal does not ameliorate the skin phenotype.

0583

Generation of novel immortalized keratinocyte lines through overexpression of human telomerase and CRISPR-Cas9 KO of CDKN2A

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Advancements in dermatological research rely heavily on access to robust and diverse cell models. Primary keratinocytes, while valuable, have significant limitations due to their finite lifespan and rapid aging, which hinder long-term studies and complex experimental designs. Immortalized cell lines provide stable and reproducible systems ideal for high-throughput screenings and detailed investigations into gene function and skin disease mechanisms. However, no new keratinocyte cell lines have been introduced in over two decades, with existing and commonly used lines, including HaCaT and N/TERT, originating from male donors. Thus, there is a critical need for diverse cell lines that represent various ages, sexes, and racial ancestry. Addressing this gap is essential for advancing research and refining therapeutic strategies for keratinocyte-related skin diseases. To address these challenges, we have developed a novel method to immortalize primary keratinocytes by combining the overexpression of human telomerase(hTERT) with the knockout(KO) of the cyclin-dependent kinase inhibitor 2A(CDKN2A) gene. hTERT helps maintain telomere length, allowing cells to bypass senescence while CDKN2A KO removes $p16^{INK4a}$, a key tumor suppressor that inhibits cell cycle progression. Using lentiviral transduction, we achieved hTERT overexpression in five primary keratinocyte lines and subsequently performed CDKN2A KO on these cells. The hTERT overexpression was confirmed using quantitative PCR ($p=2.0 \times 10^{-7}$), and CDKN2A KO was validated through Sanger sequencing. The resulting immortalized lines demonstrated a significantly extended lifespan > 12 passages, surpassing typical primary keratinocyte limits. Our findings demonstrate that hTERT overexpression along with CDKN2A knockout effectively eliminates cellular senescence in primary keratinocytes. This approach advances the development of diverse, long-lived keratinocyte models, enhancing our ability to study skin biology, understand disease mechanisms, and refine therapeutic strategies.

0584

Treatment for dystrophic epidermolysis bullosa using an LNP delivery system and an mRNA-based gene editing to correct COL7A1

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Dystrophic Epidermolysis Bullosa (DEB) is caused by COL7A1 loss-of-function variants leading to dysfunctional type VII collagen (C7) and chronic blistering. Fibroblasts (FB) and keratinocytes (KC), which produce C7, differentiate from epidermal stem cells that maintain skin homeostasis. Current treatments offer only temporary wound healing improvements. Our study focuses on a permanent genetic therapy that corrects all proliferative skin cells. We developed efficient gene editing approaches using single-stranded DNA cleavage techniques that avoid homology-directed repair, minimizing indel risks. Our strategies include base editing (BE), prime editing (PE), and a novel technique called eePASSIGE, which integrates whole genes to deliver wild-type COL7A1. By comparing the effectiveness of BE, PE, and eePASSIGE in primary RDEB patient-derived cells, we aim first to create a "gene editing cream" for topical application using lipid nanoparticle (LNP)-mRNA systems. *In vitro* studies have shown 40% to 70% transfection efficiencies in FB and KC. Our best formulation, combining DTDTMA (C14) cationic lipid and DOPE phospholipid (C14/DOPE), achieved 84% correction of the c.5047C>T variant in COL7A1, increasing C7 production while reducing cytotoxicity. Prime Editor PE5bmax showed 43% overall editing efficiency, with 32% variant correction confirmed by Sanger Sequencing. We are currently optimizing the delivery of C14/DOPE-mCherry in 3D organotypics and a novel DEB mouse model while assessing safety and genomic effects through off-target and whole genome sequencing. If successful, our strategy could enable long-term skin regeneration and permanent closure of RDEB wounds.

0585

Revealing the etiology of hypermobile ehlers-danlos syndrome: A method using skin organoids and epigenetics

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Introduction: Ehlers-Danlos Syndrome (EDS) is a group of inherited connective tissue disorders primarily characterized by musculoskeletal manifestations, accompanied by a range of complex comorbidities that severely impact quality of life. The most common form of EDS, hypermobile Ehlers-Danlos Syndrome (hEDS), currently has no known genetic cause and relies on a clinical diagnosis. Estimates of the prevalence of hEDS are around 1 in 3,100, which is likely an underestimate as many patients are without a diagnosis. The complexity of hEDS, stemming from its variable symptom presentation, suggests that its genetic underpinnings are more complex than previously believed, likely consisting of multiple subgroups with individual etiologies. hEDS pathology is likely influenced by polygenic and/or epigenetic factors, which further complicates the characterization of the disorder. Methods: To address this, we have developed a method to investigate DNA methylation changes in skin tissues of hEDS patients, a commonly affected organ of hEDS patients. This method generates skin organoid derived fibroblasts (iFs) from induced pluripotent stem cells (iPSCs) of hEDS patients. During the process of reprogramming cells into iPCS, most of DNA methylation marks are lost. Disease associated marks can be reestablished during differentiation of iFs without background noise of environmental factors, known as episignatures. Results: These hEDS specific-episignatures were identified using Oxford Nanopore Technology (ONT), simultaneously identifying genetic and epigenetic perturbations in hEDS iFs. Differentially methylated regions in hEDS patients compared to both unaffected family members and unrelated controls were evaluated. Episignatures in these genomic regions in hEDS patients provide important insights into the etiology of disorder and allow for further investigations of the molecular underpinnings of hEDS.

0586

Investigating the potential of epigenetic therapeutics to modify epithelial glands

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H3K36 methylation is crucial for maintaining cell fidelity, genomic stability, and proper transcription. To study the role of H3K36 methylation in both cancer and epithelial biology, we generated H3K36 mutant mice (H3K36M), which expressed H3K36M specifically in keratin 14-positive epithelial cells. We previously have shown that H3K36M mice display a significant reduction in body size and an outwardly aged phenotype along with striking hyperplastic glandular formation in the skin (sebaceous), eyelids (meibomian), and tongue (salivary gland) (Ko, et al. Dev Cell. 2024). More recently, we find that mice lacking Setd2 (Krt14-Cre; $Setd2^{fl/fl}$, i.e. "Setd2 KO"), which is the sole methyltransferase for H3K36me3, also exhibit similar phenotypes to H3K36M mice, including sebaceous and meibomian gland abnormalities, albeit more mild. These phenotypes from both H3K36M and Setd2 KO mice are associated with a global loss of H3K36 methylation along with a concomitant genome-wide redistribution of repressive H3K27me3. Together, these results provoke the hypothesis that modulating the epigenome may serve as an effective method to modify epithelial glandular size and/or activity and treat disorders driven by either overactive or underactive glandular activity or development. In this presentation, we will present our results of our *in vitro* and *in vivo* therapeutic studies testing pharmacological modifiers of both H3K36 and H3K27 methylation, as well as new spatial transcriptomic data detailing the underlying mechanisms.

0587

Type VII collagen re-expression and anchoring fibrils formation after systemic delivery of an antisense oligonucleotide inducing COL7A1 exon 73 skipping for RDEB.

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Skipping of the frequently mutated COL7A1 exon 73 using antisense oligonucleotide (ASO) is a promising approach to treat recessive dystrophic epidermolysis bullosa (RDEB), a rare genodermatosis caused by loss-of-function variants in COL7A1 encoding type VII collagen (C7). RDEB is characterized by severe blistering of the skin and mucosae, including oesophageal strictures and corneal blisters. We have developed a palmitoylated tricyclo-DNA ASO which induces efficient exon 73 skipping and C7 re-expression *in vitro* after transfection in primary RDEB keratinocytes and fibroblasts. We grafted reconstructed skin from C7-deficient RDEB patient cells onto an immunodeficient murine model (NMRI-$Foxn1^{nu/nu}$) and demonstrated restoration of C7 expression and formation of mature anchoring fibrils (AF) at the dermal-epidermal junction up to one month after the last injection of either two subcutaneous injections of 500 µg or 1 mg of the ASO beneath the graft, or 4 or 8 weekly intravenous injections at 50mg/kg. This ASO was also injected intravenously in a transgenic murine model ($mCol7a1^{-/-}$; TghCOL7A1) carrying the entire human COL7A1 genomic locus. Transcript analyses of disease relevant tissues (skin, eyes, and oesophagus) revealed variable levels of exon 73 skipping *in vivo*, consistent with ASO biodistribution. No adverse reaction was observed and *in vitro* pre-toxicology studies showed that the ASO does not form homodimers nor activate complement. Overall, our data indicate that systemic administration of palmitoylated tricyclo-DNA ASO restores C7 expression and AF formation by skipping exon 73 of COL7A1 pre-mRNA and holds therapeutic potential for RDEB patients.

0588

Exploring the genetic landscape of alopecia areata: A genome-wide association and mendelian randomization meta-analysis

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Alopecia areata (AA) is a prevalent dermatologic disorder characterized by non-scarring hair loss via autoimmune attacks on hair follicles. We investigated novel markers associated with AA to further understand its underlying genetic mechanisms and uncover potential therapeutic targets. Our study leverages the largest genome-wide association study (GWAS) for AA. Using UK Biobank, Million Veteran Program, and FinnGen datasets for a meta-analysis GWAS, 2,940 cases of AA and 1,460,632 controls were analyzed, and we identified 814 variant SNPs ($p<5e-8$). 518 of the 814 variants were mapped to a total of 364 unique genes using a variant-to-gene (V2G) pipeline. These genes were then examined against data from GWAS Catalog, PheGenI, Ensembl, and prior GWAS studies to assess novelty. We performed Mendelian randomization (MR) analysis (Bonferroni-corrected $p<2.98e-6$) to assess causality, implicating 13 unique genes. Novel V2G-mapped genes included GLP1R ($p=8.32e-12$), HLA-DRB1 ($p=1.01e-10$), and HLA-DRB5 ($p=6.98e-13$). GLP1R, which plays a role in glucose homeostasis, has been a key target in diabetic control and weight loss. It has been previously linked to telogen effluvium, though there are no current links to AA. Notably, HLA-DRB1 and HLA-DRB5 were consistently identified in both the V2G and MR analyses. In addition, CSNK2B ($p=1.40e-06$, $\beta=-6.149043858$) was significantly identified via MR as a causative protective factor against AA through its role in regulating cell growth and proliferation. Our study identified novel genetic determinants associated with AA, providing further steps to explore the functional mechanisms behind the disorder and highlighting potential therapeutic targets for future interventions.

0589

Somatic mutations in NEK9 drive comedogenesis

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Comedogenesis is a process by which keratinaceous debris is produced in hair follicles, leading to follicular occlusion. We previously reported somatic variants in NEK9 cause nevus comedonicus, a rare disorder identifiable at birth featuring severe cystic comedones, but the cause of comedogenesis in acquired disorders has remained less clear. Here we propose somatic mutation as an underlying cause of comedogenesis across different diseases, and a subsequent shared biologic underpinning to comedo formation in these unrelated contexts. To identify possible shared genetic drivers of comedogenesis, we collected fresh tissue from epidermal inclusion cysts (EICs), a common lesion comprised of a single comedo with an underlying cyst. We sequenced saliva and lesional tissue from 14 EICs and identified somatic, rare, damaging variants in the NEK9 gene in 12 samples. Interestingly, 9 of the 12 variants were identical to those reported in nevus comedonicus. The 3 novel variants localized within 19 amino acids adjacent to those previously identified, suggesting a potential specific role for NEK9 function within the hair follicle. It has been proposed that comedogenesis occurs due to dysregulation of specific keratinocyte populations within the follicle, though the driver for such dysregulation has not been identified. We identified ectopic expression of the epidermal differentiation marker Keratin 10 within the cyst wall of EICs, consistent with a loss of follicular specification. The identification of somatic NEK9 variants in 85% of EICs, a postnatally acquired lesion, as well as in nevus comedonicus, a severe comedonal disorder that develops in utero, supports NEK9 variants as robust driver of comedogenesis both during early follicular development and during adulthood, a topic actively under investigation by our group. More broadly, our work highlights the underestimated contribution of mutagenesis to common and acquired dermatologic diseases not previously considered genetic in origin.

0590

Cell-specific genetic effects of topical glucocorticoids in human skin

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Topical glucocorticoids (GCs) are among the most prescribed medications in dermatology, serving as first-line treatments for many inflammatory skin conditions. Despite their widespread use, GCs exhibit variable effects: while they effectively suppress inflammation, they can also lead to resistance, adverse effects such as skin atrophy, and paradoxical exacerbation of inflammation. The biological mechanisms driving these outcomes remain incompletely defined, particularly in the context of intact human skin, where cell diversity and intercellular interactions are preserved. Here, we performed single-cell RNA and ATAC sequencing on paired skin samples from human subjects (n=4), comparing sites treated with clobetasol propionate to vehicle controls. GCs induced distinct, cell-type-specific changes. In immune cells, they suppressed interferon-γ and IL-2/STAT5 signaling, aligning with their established immunosuppressive effects. In fibroblasts, GCs downregulated collagen I and other extracellular matrix components, consistent with their known contribution to dermal atrophy. We observed an unexpected upregulation of NF-κB signaling in both keratinocytes and fibroblasts. This shift may explain why inflammatory skin conditions like rosacea and perioral dermatitis can be exacerbated by topical steroids, as NF-κB activation is known to drive inflammation. We also performed CellChat analysis to examine cell-cell communication. This revealed that GCs induce dynamic changes to intercellular communication, including amplified semaphorin-3a signaling to fibroblasts from melanocytes, adipocytes, and neurons. These intercellular signaling changes highlight the complex cross-talk among resident skin cell types impacted by GCs, shaping their broad biological effects. In summary, our findings define the diverse genetic and intercellular effects of topical GCs *in vivo*, providing new insights into their mechanisms of action and informing strategies to optimize their use.

0591

Clinical and genetic insights into complex lymphatic anomalies for pediatric patients

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The diagnostic journey for patients with lymphatic anomalies can be prolonged and span years before a definitive diagnosis is reached, particularly in cases involving extensive organ involvement and multisystem complications. Despite advancements in medical genetics, there is a lack of recognition and understanding about complex lymphatic anomalies. This study aims to address the gap in genetic testing and management of complex lymphatic anomalies in a pediatric population. Our cohort of 10 pediatric patients at Stanford consisted of four males and six females. Four patients had generalized lymphatic anomaly (GLA), two had central conducting lymphatic anomaly (CCLA), and the remaining patients had Gorham stout disease, overlapping GLA/CCLA features, or Kaposiform lymphangiomatosis. Most patients experienced the onset of symptoms in early childhood at an average age of 1.17 years. However, the average age of diagnosis was 6.18 years. Every patient had additional internal organ involvement such as in the bone, brain, kidney, and spleen, therefore received MRI imaging. Six patients received a biopsy at 5.67 years of age and five patients underwent genetic testing. Two patients had variants of uncertain significance, two results were not diagnostic, and one patient revealed a pathogenic TEK variant. Our results demonstrate that patients received diagnosis and biopsy procedure much later than their symptom onset. Delays for this may include insurance authorization issues or concerns about risks of biopsy procedure. Management varied across the cohort with five patients receiving sirolimus alone or in combination with medications such as rivaroxaban and sildenafil. Our study highlights the heterogeneity in clinical presentation of complex lymphatic anomalies and challenges in discovering underlying pathogenic genetic variants to guide management. By understanding the genetic underpinning in lymphatic anomalies, informed decisions can be made perhaps for medical or surgical treatments.

0592

Ribotag RNA-seq of dermal fibroblasts from Tsc2 cKO mice identifies altered expression of genes that regulate hair cycle and mesenchymal cell differentiation

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Skin tumors in tuberous sclerosis complex (TSC) can display follicular changes associated with loss of TSC2 function in tumor fibroblasts and increased mTORC1 signaling. We developed conditional knockout mice (cKO), with Tsc2 deletion in mesenchymal cells and found increases in dermal thickness, hair shaft diameter, follicular density and hair regrowth. To understand the molecular mechanisms *in vivo*, Tsc2cKO or WT mice were mated with mice carrying a RiboTag allele. RNA sequencing on HA-immunoprecipitated RNA from mice leg skin was done to study changes in expression of translated genes in Tsc2-null or WT dermal fibroblasts (N=3 per group). Libraries were sequenced using the Illumina NextSeq platform. Reads were aligned to mouse transcripts using STAR and expression analysis was performed using DESeq2. We identified 927 differentially expressed genes, including 503 upregulated and 424 downregulated genes in leg skin dermal fibroblasts with Tsc2 deletion ($p<0.05$). In addition to the expected effect on the mTOR signaling pathway, Tsc2cKO also alters the expression of genes involved in hair cycle progression and hair growth, including upregulation of Fgf7, Gas6, Corin, Ctsl, as well as downregulation of Dkk1. Our data show that deep profiling of cell type-specific transcripts *in vivo*, accomplished by sequencing ribosome-associated transcripts, provides insights into molecular changes that may account for observed differences in skin structure and function.

0593

Disseminated keloids in a young man and interdisciplinary management

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Background: Keloids form from aberrant wound healing that leads to disorganized collagen synthesis and persistent inflammation. Widespread keloid formation however is rare and poses significant challenges for management. Clinical course: 28-year-old African American male presents as a new patient in December 2024 with disseminated keloids across his trunk, shoulders, and jaw angle. There is drainage on the chest and shoulders at times. The keloids began in early 2020 and have become larger and itchier in some places this past year. He was managed by Duke before consulting Wake Forest Baptist for a second opinion. Duke prescribed upilumab 600 mg for the first two weeks and then 300 mg every two weeks afterwards starting August 2024. The pruritis is controlled with medical and intralesional triamcinolone and 5-fluorouricil 5% injection therapy, though it recurs just before his monthly appointments. The patient reports less pruritis and drainage from the keloids since starting dupilumab but believes the intralesional injections provide only some improvement. The large keloids on his right thigh were surgically removed. They recurred but have been more manageable. Wake Forest Baptist would like to continue dupilumab, gabapentin 100mg, naltrexone 50mg, and pentoxifylline400mg for pruritis and the benzoyl peroxide 5% cleanser for super infection control. Pre-operative evaluation by Wake plastic surgery confirmed the need for excision and post-operative brachytherapy. Conclusion: Where intralesional injections fail in large keloids, surgical excision is often the next step- though recurrence rates are very common without adjunct therapy. Silicone gel sheets, botulinum toxin A, radiotherapy, cryotherapy, interferon, and bleomycin have all demonstrated efficacy against keloids. W-plasty may provide the best reconstructive outcome in this patient.

0594

Chemical and lipid nanoparticle-siRNA inhibition of GLUT1 rescues in vivo models of psoriasis

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GLUT1 is critical for energy generation, redox homeostasis, and lipid synthesis *in vitro*, but GLUT1-mediated glucose transport is dispensable for normal skin development and barrier function *in vivo*. Because GLUT1 is highly overexpressed in the lesional skin of psoriasis patients, we tested whether it could be inhibited as a novel approach for psoriasis. Previously, we found that mice with an epidermal deletion of GLUT1 were dramatically rescued from mouse models of psoriasiform hyperplasia. To advance the specific targeting of GLUT1 for patients, we tested two novel approaches of inhibiting the GLUT1 transporter *in vivo*. First, novel Selective Organ Targeting (SORT) lipid nanoparticle were formulated and tested for their ability to deliver RNA to skin. Efficient SORT-LNPs were selected and used to deliver siRNAs targeting Slc2a1 (GLUT1) to mouse skin. A single injection of LNP-siGlut1 significantly inhibited GLUT1 RNA and protein expression and significantly rescued imiquimod-mediated psoriasiform dermatitis in mice. In parallel, our prior work demonstrated that small molecule inhibitors of GLUT1 could also ameliorate psoriasis models *in vivo*. Here, we focused on the small molecule phloretin due to its availability as topical cosmeceutical products. Phloretin potently inhibited 2-deoxyglucose transport *in vitro* and improved markers of psoriasiform hyperplasia in skin organoid models. Daily application of phloretin also significantly rescued imiquimod mediated psoriasiform dermatitis in mice. Our findings offer novel, feasible approaches to treat psoriasis. More broadly, our studies advance LNP-siRNA and phloretin as novel therapeutic approaches for a broad range of genetic and inflammatory skin diseases.

0595

The effects of topical antimicrobial-corticosteroid combination therapy in comparison to topical steroids alone on the skin microbiome of patients with atopic dermatitis

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Background: Atopic dermatitis (AD) is a chronic recurrent inflammatory skin disease with a complex pathogenesis including a dysbiosis of both the bacterial and fungal skin microbiome. Treatments for reshaping the skin microbiome may have better therapeutic results, such as antimicrobial drugs and antimicrobial-corticosteroid combination therapy. Objective: We aim to analyze the different therapeutic responses between antimicrobial-corticosteroid combination and corticosteroids alone on improving the skin microbiome and skin barrier of AD patients. Methods: A total 40 patients with mild-to-moderate AD from August 2023 to July 2024 were randomly assigned (1:1) to receive two kinds of treatment. Skin swabs were collected from the lesional sites and nearby nonlesional sites at baseline, after topical medication treatment and 2 weeks post-treatment, and were analyzed by DNA sequencing of the fungal internal transcribed spacer (ITS)1–5 rDNA gene and the V3V4 region of the bacterial 16S rRNA gene. Results: According to our research analysis, both topical steroids alone and combination treatment of steroids and antimicrobials effectively improved the severity of AD and repaired skin barrier. AD lesions were characterized by a decreased sebum level, lower abundance of Cutibacterium and a higher abundance of Staphylococcus. A combined topical treatment with an antimicrobial and steroid showed better responses in increasing skin sebum level and restoring the skin bacterial microbiome, whereas topical steroid alone did not improve skin dysbiosis. Conclusion: A combined therapy with antimicrobial and steroid helps to recover the skin microbiome. Further studies are necessary to explore the therapeutic effects of treatments aiming at balancing the microbiome.

0596

The role of skin dysbiosis in the progression of pediatric atopic dermatitis to asthma

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We aimed to investigate the role of skin dysbiosis and barrier protein expression in the progression of pediatric atopic dermatitis (AD) to asthma. Approximately one-third to one-half of patients with AD characterized by skin dysbiosis and barrier dysfunction, develop asthma. However, the exact mechanisms of AD progression to asthma remain unclear. We utilized a subset of participants with skin metagenomics shotgun sequencing (MSS) data at Visit 1 and an asthma diagnosis at Visit 5 (n = 89) in the Mechanisms of Progression of Atopic Dermatitis to Asthma in Children (MPAACH) cohort. Skin tape samples from non-lesional (NL) skin at Visit 1 were used to analyze the microbial MSS data and expression of barrier proteins including FLG, DSG-1, AHR, and OVOL1. Asthma was diagnosed at Visit 5 via symptoms and spirometry results. We then analyzed microbial alpha and beta diversities, differential species abundance, and barrier protein expression between the asthma and no asthma groups. Alpha (Shannon Index) and beta diversity did not significantly differ between the two groups. The asthma group had 9 bacterial species less abundant than the no asthma group including Streptococcus infantis, Rothia mucilaginosa, and Streptococcus mitis. The asthma group had 2 additional core taxa, including Staphylococcus epidermidis, compared to the no asthma group. There were no differences in the proportion of participants with detectable FLG, DSG-1, AHR, and OVOL1 expression between the two groups. Overall, patients with AD who went on to develop asthma showed a shift in the NL skin microbiome with an increased presence of inflammatory bacteria and a decreased abundance of barrier-protective and anti-inflammatory bacteria compared to those who did not progress to asthma. These findings suggest that the skin microbiome may play a key role in the progression of pediatric AD to asthma.

0597

Candida spp diminish viral susceptibility of human keratinocytes and promote an antiviral state

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We have shown that S. aureus enhances viral susceptibility of keratinocytes (KC). However, little is known about the effect of fungi on KC viral susceptibility. We found that exposure of KC to Candida (C.) albicans (10^4 colony forming units [CFU]) or C. parapsilosis (10^3 CFU) diminished viral susceptibility, whereas Saccharomyces cerevisiae or Malassezia sympodialis exposure had little or no effect, respectively. To extend these findings to additional Candida species (spp) we observed that KC exposed to either C. tropicalis (10^2 CFU) or C. glabrata (10^4 CFU) reduced vaccina virus (VV)-induced cytopathic effect (65±18% decrease, p=0.066; 32±14% decrease, p<0.05, respectively). Collectively, these findings suggest that Candida spp diminish KC viral susceptibility. To understand the molecular changes occurring in Candida-exposed KC that would promote an antiviral response, we quantified gene transcripts associated with antiviral activity from KC following C. parapsilosis or C. albicans exposure (10^4 CFU). We observed an increase in genes related to the inflammasome (NLRP3, 6.2±0.8 fold-increase, p<0.05; IL1B, 21.6±2.1 fold-increase, p<0.0001), antimicrobial peptides (RNASE7, 6.2±2.6 fold-increase, p=0.051; DEFB3, 102.3±73.4 fold-increase, p<0.05) and type 1 interferons (IFNA1, 2.1±0.4 fold-increase, p<0.05; IFNB, 1.5±0.1 fold-increase, p<0.05). Only two genes were significantly upregulated following C. albicans exposure: IL1B (11.9±2.2 fold-increase, p<0.01) and RNASE7 (3.37±0.9 fold-increase, p<0.05). When KC exposed to C. parapsilosis (10^4 CFU), but not C. albicans, were infected with VV for 6 hours, NLRP3 (2.77±1.7 fold-increase), DEFB3 (29.9±15.9 fold-increase), and RNASE7 (3.80±0.8 fold-increase) transcripts remained at higher levels compared to unexposed KC. This research suggests that the composition of the cutaneous microbiome (e.g. presence of specific Candida spp) can dictate human skin viral susceptiblity.

0598

Multiple cell types support productive infection and dynamic translocation of infectious Ebola virus to the surface of human skin.

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Ebola virus (EBOV) transmission occurs through direct contact with an infected individual or their body fluids. In late infection, EBOV virions and RNA are found on the skin's surface. However, the permissive skin cell types and the route of virus egress remain undefined. We report a human skin explant model that robustly supports EBOV infection. Virus inoculated into the medium below explants maintained at the air-liquid interface led to time- and dose-dependent increase in viral load in the dermis and epidermis. EBOV antigen-positive cells included dermal myeloid, endothelial, and fibroblast cells and epidermal keratinocytes. Infectious virus spread temporally from the dermis to the epidermis and was detected on the apical epidermal surface by 3 days post-inoculation (pi). These observations were recapitulated using a BSL2 model virus, rVSV/EBOV GP. Focal viral staining was seen in epidermal keratinocytes and infectious virus was detected on the skin surface by day 8 pi. Additionally, several well-established EBOV inhibitors effectively blocked rVSV/EBOV GP infection of the explants. Finally, purified populations of human fibroblasts and keratinocytes were permissive for both EBOV and rVSV/EBOV GP, and viral entry was mediated by the phosphatidylserine receptor AXL and the endosomal receptor NPC-1, which mediate viral entry in other cell types. Using our infection model, we have demonstrated a route of EBOV transmission through the skin, identified the responsible cell subsets, and shown its utility for antiviral testing. This work is significant because it shows that infectious virus can traverse the skin to the epidermal surface, potentially contributing to person-to-person transmission.

0599

Plastic associated endocrine disruptors reduce nicastrin protein and potentiate inflammation in hidradenitis suppurativa

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Hidradenitis Suppurativa (HS) is an inflammatory skin disorder with poorly understood etiology and few FDA approved treatments. Mutations in gamma secretase (GS), particularly the Nicastrin (NCSTN) subunit, characterize hereditary HS, but the pathophysiology of common acquired HS is unclear, despite associations with obesity and a diet containing ultra-processed foods (UPFs). Consistent with the hypothesis that the phenotypic overlap between acquired and hereditary HS suggests a shared dysfunction of NCSTN, we demonstrate that NCSTN protein is selectively lost in HS dermal fibroblasts ($p<.0001$, n=11 subjects) and primes them for inflammation. In particular, both HS dermal fibroblasts and siNCSTN fibroblasts express more CXCL8 RNA and protein after TNFα stimulation compared to controls ($p<.0001$; $p<.0001$). We further hypothesized the climbing incidence of acquired HS and its hormonal associations suggest Endocrine Disruptor (ED) chemicals as an environmental cause. Given the prevalence of plasticizer bisphenols and phthalates (p-EDs) in UPFs, we tested for their presence in HS skin and impact on NCSTN. p-EDs are elevated in the skin of HS patients but not controls, and persist in *ex vivo* cultured HS fibroblasts but not controls. p-EDs inhibit NCSTN protein expression at nanomolar concentrations in fibroblasts ($p = 0.0004$, $n = 8$), and prime for inflammation as seen in NCSTN siRNA and HS fibroblasts ($p = 0.0002$ overall, $n = 3$ per dose). These results suggest exposure to p-EDs can contribute to disease and the importance of further focus on p-ED research to mitigate HS and possibly other GS related diseases.

0600

Distinct epidermal cell populations and single-cell gene expression signatures are associated with staphylococcus aureus in atopic dermatitis

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Introduction and Aim: Atopic dermatitis(AD) affects 15-30% of children and 5-8% of adults with profound functional, psychological and social morbidity. Staphylococcus aureus(SA) abundance increases in AD and correlates with disease severity, yet its interaction with the host immune system is unclear. We investigated the skin microbiome and single-cell transcriptome to examine the interactions between SA and host in AD. Methods: Skin microbiome swabs and skin biopsies were obtained from lesional and non-lesional skin of adults with AD (n=4 participants, n=8 biopsy and swab samples). SA relative abundance was quantified using shotgun metagenomic sequencing and host single-cell gene expression profile was quantified through single-cell RNA-sequencing. Results: Epidermis cellular proportions are different between SA-high AD (lesional and non-lesional samples with SA relative abundance >35%) and SA-low AD (lesional and non-lesional samples with SA relative abundance <10%), with distinct sub-populations of T-cells as well as basal and differentiated keratinocytes SA-high AD. T-cells in SA-high AD express pro-inflammatory cytokine genes IL-13, IL-22 and IL-26. There are also increased macrophages and dendritic cells expressing the Th2 chemokine gene CCL17 (TARC). Basal keratinocytes in SA-high AD have increased expression of the chemoattractant CXCL14 and reduced expression of aquaporin signaling genes. Differentiated keratinocytes in SA-high AD express increased anti-microbial defense genes including S100A8. Conclusions: These findings show distinct cell populations and cell-specific cutaneous gene expression signatures associated with SA in both lesional and non-lesional AD. In SA-high AD there are increased immune cells expressing pro-inflammatory cytokine genes and increased keratinocytes expressing anti-microbial defense genes, suggesting novel therapeutic targets for SA-host interactions in AD.

0601

A murine model of psoriasis and atopic dermatitis induced with a combination of systemic IL-23 overexpression and topical application of the vitamin D3 analog MC903

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Psoriasis and atopic dermatitis (AD) are autoimmune skin diseases with overlapping features. Psoriasis involves IL-17-producing T cells, while AD is mediated by Th2 cytokines like IL-4 and IL-13. Their comorbid presentation in a subset of patients, suggests shared inflammatory mechanisms. We developed a murine model combining systemic IL-23 overexpression with topical MC903 to mimic the dual disease phenotype and investigate shared pathways. Materials and Methods: Using a single IL-23 minicircle DNA (IL-23MC) injection by hydrodynamic delivery via the tail vein and daily topical application of MC903, we induced significant dermatitis in mice. Groups received single or combined treatments, with assessments on days 5, 10, and 15. Histological analysis, cytokine profiling, and flow cytometry were performed. Dose-response experiments evaluated IL-23MC concentrations, and treatment timing effects were analyzed. Results: Combined treatment with IL-23/MC903 resulted in earlier and more severe lesions than single treatment with IL-23 or MC903 alone, accompanied by increased epidermal thickness and Munro microabscesses. Elevated Th17 (IL-17A, IL-22) and Th2 (IL-4, IL-13, TSLP) cytokines were observed, along with high IL-36G levels. Flow cytometry showed increased infiltration of IL-4+ T cells, γδ T cells, and neutrophils. A dose of 6 µg IL-23MC maximized disease severity, while delayed IL-23MC administration enhanced Th1 and Th2 responses. Discussion: This model reproduces key published features of patients with combined psoriasis and AD, highlighting the interplay of Th1, Th2, and Th17 pathways. IL-36G and IL-33 appear central to the disease phenotype. The model provides a platform for studying combination therapies targeting overlapping inflammatory mechanisms.

0602

Associations between household endotoxin exposure and atopic dermatitis: A cross-sectional U.S.-based population study

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Endotoxin exposure has been shown to be protective against allergic disease in early childhood by promoting a Th1 phenotype. Endotoxins can exacerbate a Th2 immune response and asthma later in life, though research on its effect in adulthood on atopic dermatitis (AD) is limited. The objective of our study was to investigate endotoxin predictors and their allergy-associated outcomes across the lifespan. Using the National Health and Nutrition Examination Survey (NHANES) 2005-2006 dataset, we analyzed data from 7,450 participants aged 1-85 years, including cross-sectional questionnaires and dust sample analyses. Linear and multivariate logistic regression analyses were conducted using R to identify endotoxin predictors and their associations with AD. Demographic analysis revealed that males had 26% lower odds of AD prevalence compared to females (OR: 0.74, 95% CI: 0.57-0.94, p=0.016). Non-Hispanic White and Black individuals showed higher odds of AD prevalence compared to Hispanic individuals (OR: 3.00, 95% CI: 1.59-6.42, p=0.002; OR: 2.67, 95% CI: 1.38-5.80, p=0.007, respectively). The median endotoxin concentration in house dust among AD patients was 42.6 EU/mg, higher than the overall population. Individuals with asthma history exhibited increased odds of AD (OR: 1.78, 95% CI: 1.13-2.72, p=0.010), as did those with hay fever history (OR: 1.64, 95% CI: 1.00-2.61, p=0.043). Interestingly, cockroach presence was associated with 57% lower odds of AD prevalence (OR: 0.43, 95% CI: 0.23-0.75, p=0.005). Endotoxin predictors, including higher house dust endotoxin levels, asthma, and hay fever, were associated with increased AD prevalence, while cockroach presence showed an inverse relationship. In particular, AD prevalence was influenced by factors affecting females and non-Hispanic individuals. These findings highlight the complex interplay of exposomal factors, racial diversity, and age in AD development, emphasizing the need for further research into endotoxins and environmental pollutants to guide targeted prevention strategies.

0603

Bullous pemphigoid-associated S. aureus increases protease activity from keratinocytes and promotes unique BP180 cleavage

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Staphylococcus (S.) aureus has been found to routinely colonize the skin of individuals with bullous pemphigoid (BP). A defining characteristic of BP is subepidermal blistering, which is caused by loss of function of the hemidesmosomal protein BP180. We hypothesized that S. aureus virulence factors facilitate loss of BP180 function from keratinocytes (KC) through diminished expression and/or enhanced cleavage. While host proteases have been shown to cleave BP180, the role of microbiome-associated proteases has not been considered. Adult primary KC from 22-70 years of age were exposed to complex mixtures of virulence factors from S. aureus strains isolated from BP skin, or routinely used in research. We observed that virulence factors from multiple BP-associated S. aureus isolates induced a novel cleavage pattern of BP180 rarely seen in conditions with control strains. A modest association between the ratio of cleaved to full length BP180 and donor age was observed in untreated conditions (n = 14 donors, Spearman R value = 0.4741, p=0.0885). However, when this comparison was conducted on samples exposed to S. aureus virulence factors (BP isolate), this relationship became more robust (n = 9 donors, Spearman R value = 0.6527, p=0.0635). KC exposed to BP-associated S. aureus virulence factors significantly increased expression of the protease MMP9 (2.11 ± 1.43-fold, p≤0.05) and demonstrated elevated protease activity in supernatants (3.26 ± 2.27-fold, p≤0.05). Virulence factors from BP-associated S. aureus strains also uniquely promoted expression of the alarmin IL33 from KC, which was significantly increased (10.84 ± 10.75-fold, p≤0.01) when combined with type 2 cytokines IL-4 + IL-13. These findings suggest an important role for the cutaneous microbiome in BP pathogenesis. We anticipate these observations will lead to novel interventions that improve BP disease, which are desperately needed for this population. For example, targeting specific S. aureus virulence factors directly may provide an efficacious treatment for BP patients.

0604

Akkermansia muciniphila ameliorates imiquimod-induced skin thickening, colitis, and gut microbiota alterations: A metagenome association study

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A decreased abundance of fecal Akkermansia muciniphila (Akk) has been observed in patients with psoriasis and psoriatic arthritis. The potential beneficial effect of Akk in managing psoriasis has been proposed. We aimed to examine the impact of Akk on skin and systemic inflammation, intestinal barrier integrity, and gut microbiota profiles in psoriasis. We conducted a metagenomic association study of the Akk in the imiquimod (IMQ)-mice using whole-genome shotgun sequencing. A dextran sodium sulfate (DSS)- induced colitis experiment and intestinal permeability test were also performed. The association among Akk supplements, skin thickness, circulating inflammatory profiles, fecal microbiota alterations, intestinal epithelium inflammation, and barrier integrity was investigated. The microbiome study was performed using pipelines of phylogenetic analysis, functional gene analysis, and pathway analysis. In IMQ-treated mice, there were increases in skin thickness, splenic weight, and unique fecal microbial profiles compared to controls. Akk supplement ameliorated the IMQ-induced skin thickening, weight loss, spleen weight gain, serum IL-17A and TNF-α levels, and DSS-induced colitis. Akk supplement was associated with a greater fecal microbial diversity and an alteration in the fecal microbiota composition, with the increased prevalence of Muribaculaceae, Bifidobacterium pseudolongum, Desulfovirionaceae, Erysipelotrichaceae, and Alistipes ihumi, which have been involved in Gamma-Aminobutyric Acid (GABA) shunt, cholinergic synapse, cell cycle, and Mitogen-Activated Protein Kinase (MAPK) pathways. Akk may mitigate IMQ-induced skin thickening and DSS-induced colitis associated with reduced IL-17A levels. Akk supplement alters fecal microbiota and metabolism pathways in IMQ-treated mice.

0605

IL-17D-induced metabolic reprogramming empowers inflammatory memory in keratinocytes to promote psoriasis relapse

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Keratinocytes, as the primary cell type in skin epidermis, play a crucial role in the pathogenesis of psoriasis. However, whether keratinocytes acquire inflammatory memory to participate in psoriasis relapse remains elusive. Here we demonstrate that IL-17D-induced lactate accumulation empowers the inflammatory memory of keratinocytes to promote psoriasis relapse. IL-17D enabled keratinocytes to gain inflammatory memory. The deletion of IL-17D in mice alleviated psoriasis relapse, while the restoration of IL-17D rescued psoriasis relapse in Il17d-deficient mice. Mechanically, IL-17D enhanced glycolysis but inhibited OXPHOS to induce lactate accumulation in keratinocytes. Elevated lactate levels promoted histone modifications to facilitate chromosome access at key genes involved in psoriasis pathogenesis. Inhibition of lactate accumulation or histone acetylation and lactylation erased the ability of keratinocytes to recall inflammation and alleviated psoriasis relapse. These data demonstrate that IL-17D-mediated lactate accumulation is a key process enabling keratinocytes to acquire inflammatory memory and promote psoriasis relapse.

0606

Skin microbiota - metabolome signatures in atopic dermatitis associated with staphylococcus aureus and commensal bacteria

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Introduction and Aim: Staphylococcus aureus (SA) skin infections are common in atopic dermatitis (AD) driving flares and chronicity, while commensal bacteria such as Staphylococcus epidermidis (SE) and Corynebacterium are reduced in severe AD. We aimed to identify associations between the skin microbiome and metabolome, to examine metabolite-mediated host-microbiome interactions in AD. Methods: Skin microbiome and metabolome swabs were obtained from adults with mild-severe AD (n=11). Shotgun metagenomic sequencing and nuclear magnetic resonance spectroscopy quantified the microbiome and metabolome, respectively. Machine learning data integration was used to identify interactions between the microbiome and metabolome. Results: Individual variability in microbiome diversity as well as SA, SE and Corynebacterium relative abundance is high in this cohort and no significant differences between lesional and non-lesional AD were observed. However, the skin metabolome profile is altered in lesional AD, with increased glucose metabolism products, proline, alanine and branched chain amino acids (BCAA). In AD samples with high SA abundance, these metabolites are increased further. AD samples with a high abundance of the skin commensals SE or Corynebacterium are both associated with increased natural moisturizing factor (NMF) components urocanic acid, pyroglutamic acid, citrulline and histidine (correlation coefficient >0.55). Conclusions: Distinct metabolic signatures are associated with SA and skin commensal species in AD and may underlie novel host-microbiome interactions. BCAA are important SA nutrients and promote its virulence factors alpha-toxin, hyaluronidase, and Panton–Valentine leucocidin. In contrast the commensal-associated metabolome signature may protect the skin barrier through NMF production.

0607

Comparative analysis of skin immune responses to hematophagous arthropods

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As the outermost barrier facing the external environment, the skin is a potent primary line of defense that employs various strategies against a variety of environmental, microbial, and other biological insults. Importantly, the skin is the first mammalian organ encountered by vectors of human pathogens, providing an avenue for the transmission of vector-borne diseases. In the United States, ticks are the most abundantly encountered vector of human clinical importance. Ticks are hematophagous ectoparasites known for their distinct ability to remain undetected and attached to a host's skin for days, employing a remarkable toolbox of host immunomodulatory strategies to promote successful blood feeding. Our work aims to utilize the biological arsenal utilized by these ancient arthropods to elucidate mammalian immune strategies that facilitate skin immune responses. By leveraging single-cell and spatial transcriptomics in conjunction with animal modeling, we aim to employ a cross-species comparative approach to elucidate species-specific and core immune responses to these salient vectors. Our work reveals differential innate immune responses to each tick bite, suggesting variance in the immune microenvironment generated by these arthropods. We observe conserved macrophage responses and prominent differences in the neutrophil recruitment to the different tick-skin interfaces throughout the duration of tick feeding. Importantly, our understanding of skin immune responses to tick infestation may provide insights into broader skin immune programs, in addition to shedding light on mechanisms that promote pathogen transmission and other diseases states associated with these vectors.

0608

Streptococcus in the skin microbiome of children exacerbates inflammation in atopic dermatitis

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The microbiome in pediatric atopic dermatitis (AD) is unique, containing a marked increase in Streptococcus (Strep) species compared to adults. To better understand this microbial community and its influences on disease, swabs from multiple skin sites were collected from children under 6yo with AD (N=19) and age-matched healthy controls (N=16). Shotgun metagenomics and live culture measurements confirmed a higher abundance of Strep in children than adults and more Strep was found on lesional skin than nonlesional skin (P=0.0071). Furthermore, there was a strong correlation between the abundance of live Strep species, S. aureus, and disease severity (P=0.0036). To understand if Strep-S. aureus coexistence affects the skin barrier, conditioned media (CM) from strains of S. aureus and Strep oralis (a dominant species on children's skin) was added to human keratinocytes. Minimal cytotoxicity was seen if CM from each species was added alone (LDH release =10.7% for 5% S. aureus CM and 1.0% for 15% S. oralis CM), but when as little as 15% CM from S. oralis was added to 5% S. aureus CM, LDH release rose to 62.2%, indicating a strong synergistic cytotoxic effect. This synergy also directly exacerbated inflammation in a mouse model of AD (MC903), where application of both S. aureus and S. oralis each at $5x10^5$ CFU/cm^2 intensified skin barrier disruption and type 2 inflammation compared to applying either species alone at $1x10^6$ CFU/cm^2 (P=0.028). S. aureusstrains lacking phenol-soluble module-α or δ-toxin did not synergize with Strep, and skin inflammation was blocked by a novel antimicrobial strain of Staph hominis (ShC2) that kills both S. aureus and Strep, while a mutant strain of ShC2 lacking the active lantibiotic (ShC2-Δlanti) did not. These findings reveal a previously unknown cooperation between S. aureus and Strep, suggesting that synergy and competition between bacteria likely play an important role in the pathophysiology of AD in children.

0609

Diverse microbial exposure in dirty mice suppresses allergic contact dermatitis

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The translatability of traditional mouse models to humans can be limited. Laboratory mice co-housed with pet store mice, "dirty mice", have been shown to acquire a diverse microbiome and develop a more human-like systemic immune system. Dirty mice have therefore been proposed to better model human disease. We studied the skin's immune system and examined the development of allergic contact dermatitis in this unique model. Dirty mice experienced significant immunity and inflammation during the first month of cohousing, then reached a new steady state immunologically by one month post-cohousing. Despite variable microbial exposure across batches of pet store mice, steady-state dirty mouse skin consistently contained higher numbers of CD4, CD8, and γδ resident memory T cells as well as more neutrophils compared to clean controls. Both mast cells and dendritic cells were reduced in dirty mouse skin at steady state, and there was no difference in regulatory T cell numbers between dirty and clean mouse skin. Comparatively, draining lymph nodes in dirty mice contained higher numbers of dendritic cells, memory T cells, and prominently, regulatory T cells at steady state. Intriguingly, DNFB-induced contact hypersensitivity reactions were markedly dampened in dirty mice compared to clean controls, as demonstrated by less inflamed ears grossly and histologically, and by minimal change in ear thickness measurements. This corresponded to reduced numbers of effector T cells, macrophages, and neutrophils in DNFB-treated dirty mouse ears. Yet, DNFB-treated dirty mice had significantly increased numbers of effector T cells and mast cells in draining lymph nodes above that of DNFB-treated clean control mice. These findings suggest robust sensitization but abrogated elicitation, potentially due to impaired egress of effector populations out of lymph nodes. Overall, the data support that diverse microbial exposure does impact skin immune responses compared to standard laboratory mice and so may be critical to study when modeling human skin inflammation and immunity.

0610

Dynamic role of chromatin remodeler in the regulation of RORγt-mediated type 3 skin inflammation

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The transcription factor RORγt is the master regulator of IL-17 production in T cells. For transcription factors to function optimally, epigenetic modification and chromatin repositioning by chromatin remodelers are essential. Nevertheless, the epigenetic regulatory network involving RORγt in T cells during psoriasis-like skin inflammation remains largely undefined. In this study, we conducted a genome-wide chromatin immunoprecipitation analysis under *in vitro* Th17 cell differentiation conditions. The results revealed that the chromatin remodeler Chd4 is positioned around RORγt binding regions on DNA, including IL-17A and IL-17F, thereby maintaining these regions in a highly epigenetically active state. Chd4 and RORγt were also found in close proximity in γδT cells. We then generated γδT cell-specific conditional knockout (Chd4-gdTcKO) mice and induced type 3 skin inflammation with imiquimod application. Compared to wild-type (WT) mice, Chd4-gdTcKO mice exhibited significantly reduced ear swelling (WT: 263.8±27.5 μm, Chd4-gdTcKO: 215.6±19.4 μm, P<0.0001) and decreased expression of IL-17A and IL-17F. *In vitro*, deficiency of Chd4 in gdT cells resulted in decreased production of IL-17A and IL-17F when activated with CD3/CD28 and IL-23/IL-6/IL-1/TGFb. Furthermore, single-cell analysis of cells infiltrating the ears identified a unique γδ T cell subset by the absence of Chd4. These results demonstrate that Chd4-mediated chromatin remodeling regulates the DNA accessibility and binding of the transcription factor RORγt both physically and functionally, emphasizing the crucial role of Chd4 in IL-17A/IL-17F production in the skin and the development of psoriasis.

0611

Computational insights into streptococcus as a driver of pediatric atopic dermatitis via skin, oral, and nasal cross-transmission

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Pediatric atopic dermatitis affects up to 20% of children globally, yet its pathogenesis remains poorly understood. While Staphylococcus aureus and Staphylococcus epidermidis are established contributors to adult AD, the role of the skin microbiome in pediatric AD remains underexplored, particularly given the distinct microbial composition of infants and young children. Here, we investigate Streptococcus (Strep), a dominant genus in pediatric oral, nasal, and skin microbiomes, and its potential role in AD pathogenesis. Through a multi-omic analysis of 503 16S rRNA sequencing samples and 208 shotgun metagenomes from three independent pediatric cohorts (ages 3 months to 4 years in San Diego, South Africa, and Singapore), we identified a striking enrichment of Strep species on lesional AD skin, with relative abundances exceeding 20% compared to ~10% in non-lesional skin and <5% in healthy controls. Source tracking using FEAST traced the origin of Strep strains on the skin to oral and nasal microbiomes of paired samples, implicating these sites as reservoirs of transmission likely facilitated by frequent hand-to-skin contact. A Random Forest model validated Strep as a discriminatory feature for lesional AD skin, achieving high accuracy in separating lesional, non-lesional, and healthy skin microbiomes. Strain-level analysis revealed shared Strep strains between the skin and oral or nasal microbiomes in children with AD, suggesting cross-microbiome transmission. Metagenomic profiling identified enrichment of protease- and toxin-associated genes in Strep strains isolated from lesional skin, suggesting potential functional adaptations contributing to inflammation and barrier dysfunction. The presence of Strep in the pediatric skin microbiome and its functional potential offer insight into why children are more commonly afflicted with AD and provide microbial targets to improve outcomes for affected families.

0612

STAT3 regulates tissue inflammation by repressing interferon responsiveness of vascular endothelial cells

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Signal transducer and activator of transcription (STAT) 3 is a transcription factor crucial for immunity and tissue homeostasis. Loss-of-function mutations of STAT3 affect multiple cell types and cause autosomal-dominant hyper IgE syndrome (AD-HIES), which features Th17 deficiency, impaired antimicrobial response and wound healing, accompanied by eczematous dermatitis and occasional complication of systemic lupus erythematosus (SLE). To explore the roles of STAT3 *in vivo*, we performed single-cell RNA-sequencing (scRNAseq) on non-lesional (n=7) and eczematous (n=3) skin from 6 AD-HIES patients. Compared to healthy control skin (n=8), keratinocytes, fibroblasts, and vascular endothelial cells (VECs) in eczematous skin commonly upregulated type I and II interferon (IFN) pathways, which were solely enriched in VECs in non-lesional AD-HIES skin. We then generated mice in which ablation of STAT3 was induced in keratinocytes ($Stat3^{\Delta Krt14ERT2}$), fibroblasts ($Stat3^{\Delta Col1a2ERT2}$), or VECs ($Stat3^{\Delta Cdh5ERT2}$). scRNAseq analysis revealed that most differentially expressed genes in targeted cell types were downregulated, consistent with the role of STAT3 in transcriptional activation. Interestingly, type I and II IFN pathways were upregulated in in $Stat3^{\Delta Cdh5}$ VECs, which was in line with AD-HIES skin. $Stat3^{\Delta Cdh5}$ VECs upregulated MHC II and CD74 proteins at baseline, which were further elevated by i.p. injection of poly I:C, a TLR3 agonist. We then applied the TLR7 agonist imiquimod, which is utilized in psoriasis and SLE models. Strikingly, whereas psoriasiform dermatitis was attenuated in $Stat3^{\Delta Krt14ERT2}$mice, it was exacerbated in $Stat3^{\Delta Cdh5ERT2}$ mice. Thus, VECs are central to tissue IFN responses, and STAT3 regulates tissue inflammation by controlling VEC's IFN responsiveness.

0613

Platelet activation in stevens-johnson syndrome and toxic epidermal necrolysis

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Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but life-threatening conditions often triggered by drugs. This study aimed to investigate innate immunity in SJS/TEN. We stimulated HaCat cells with serum from TEN patients or healthy controls (HC) and performed liquid proteomics analysis. A total of 42 altered proteins from 440 targeted were identified, and gene ontology analysis indicated that there were significant differences in platelet degranulation and alpha granules. Our cluster analysis identified platelet factor 4 (PF4/CXCL4) and neutrophil-activating peptide 2 (NAP-2/CXCL7) as notably altered proteins. Then, we enrolled 22 SJS/TEN patients and three times as many healthy controls, measuring serum levels of CXCL4 and CXCL7. CXCL4 levels were 25.93 times higher in SJS/TEN patients (8270±1116 ng/ml) compared to controls (318.9±80.68 ng/ml), while CXCL7 levels were 3.58 times higher (4776±330 ng/ml vs. 1334±272.4 ng/ml). Both CXCL4 and CXCL7 significantly decreased at the recovery stage ($p<0.05$). We found a positive correlation between CXCL4/CXCL7 levels at onset and IL-15 concentration (CXCL4: $r=0.6758$, $p<0.05$; CXCL7: $r=0.5632$, $p<0.05$), a predictor of SJS/TEN severity. Elevated CXCL4 correlated with TNF-α ($r=0.4487$, $p<0.05$) and Granzyme B ($r=0.6484$, $p<0.05$). In a cohort of 42 SJS/TEN patients, we analyzed platelet indices and found significant alterations at onset compared to recovery ($p<0.05$). Furthermore, we injected mice with recombinant CXCL4 (500 ng/mouse), CXCL7 (500 ng/mouse), or both. Inflammatory cell recruitment was assessed by multiplex immunohistochemistry (mIHC). Compared to PBS-treated mice, we observed significant increases in total leukocytes, CD4+ T cells, CD8+ T cells, and neutrophils in the skin of CXCL4-injected mice. Given that these chemokines serve as biomarkers of platelet activation, our findings suggest that platelet activation plays a crucial role in SJS/TEN pathophysiology, warranting further studies using humanized mouse models.

0614

MyD88 restricts dysbiosis-mediated inflammation in filaggrin deficient skin

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Atopic dermatitis (AD) is a chronic inflammatory skin disease associated with immune dysregulation, dysbiosis, and epidermal barrier dysfunction due in part to filaggrin loss-of-function mutations. Although filaggrin loss-of-function mutations are known to alter the skin microbiome in AD patients, the immunological mechanisms that dictate this effect and how this influences pathogenesis are unclear. We and others have previously reported on the importance MyD88-dependent cytokines in orchestrating AD skin inflammation in the context of filaggrin deficiency. Unexpectedly, we discovered that filaggrin deficient mice lacking MyD88 (ft/ft x MyD88) developed spontaneous and persistent skin inflammation that localized around the eyes, which was not observed in ft/ft mice. The ft/ft x MyD88 skin inflammation was associated with increased IgE, epidermal thickness, and eosinophil infiltration compared to ft/ft skin. Furthermore, RNAseq analysis revealed up-regulated IL-17 signaling pathways in the inflamed ft/ft x MyD88 skin, which was associated with increased dermal IL-17-producing γδ T cells compared to ft/ft mice. Using 16S sequencing, we found significant differences in Firmicutes and Actinobacteriota in the skin microbiome between ft/ft x MyD88 and ft/ft mice. Excitingly, treatment of the inflamed ft/ft x MyD88 skin with Neosporin antibiotic ointment attenuated skin inflammation as well as reduced eosinophils and IL-17-producing γδ T cells in the skin compared to vehicle-treated ft/ft x MyD88 mice. Taken together, our findings indicated that MyD88 signaling restricts inflammation mediated by the skin microbiota in the context of filaggrin deficiency, which has implications in the pathogenesis of AD.

0615

Dynamic postnatal tissue adaptation controls functional specification of skin-resident tissue macrophages

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Resident tissue macrophages (RTMs) represent long-lived and stable tissue macrophage populations of prenatal origin found in almost every organ. RTMs in different tissue niches undergo specialized tissue adaptation important in determining their tissue-specific function. However, the adaptation process and subsequent specification of skin RTMs remain poorly understood. Here, by applying time series of postnatal single-cell transcriptome profiling, we show that dermal RTMs undergo dynamic transcriptional shifts during a defined postnatal period that reflect functional differentiation. We found a distinct dermal macrophage subset that appears early in life and exists throughout adulthood, consistent with the long-lived nature of RTMs. Notably, early postnatal RTMs (EpoRTMs) are gradually replaced by transcriptionally distinct major histocompatibility complex class II (MHCII)-high late postnatal RTMs (LpoRTMs) during the postnatal week 2 and 4. Pathway enrichment analysis distinguishes EpoRTMs as metabolically active and LpoRTMs as immunologically active, indicating that postnatal adaptation governs functional changes in dermal RTMs. Upstream analysis predicts a series of cytokines likely to promote postnatal RTM transition, and induction of MHCII expression in LpoRTMs is in part mediated by interferon-γ. Together, our work highlights the time-dependent tissue adaptation of dermal RTMs, which may contribute to regulating skin homeostasis during different postnatal stages.

0616

A critical role for MMP3 during amplification of skin inflammation by psychological stress

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Psychological stress decreases antimicrobial defense and increases susceptibility to S. aureus infection in mice by activating the HPA axis and inhibiting host defense functions of immune-acting fibroblasts. However, in contrast to decreased innate antimicrobial defense, imiquimod (IMQ)-induced skin inflammation is amplified by stress in this model. To understand this dichotomy, RNASeq was performed on mice following restraint-induced stress and topical IMQ. This revealed that stress increased expression in the skin of a spectrum of chemokines associated with immune cell recruitment, notably neutrophil markers (Ly6g, Retnlg, Cd177; fold change > 135) and significantly enriched IL-17 and TNF-α signaling pathways. Notably, upregulation of fibroblast-associated genes (Mmp3, Mmp9) was observed in mice after stress. Analysis of human data sets revealed a similar induction of MMP3 in human psoriasis, with elevated MMP3 mRNA expression in lesional psoriasis ($p = .031$, $n = 67$) and increased MMP3 protein levels in serum ($p = .025$, $n = 23$). To determine if MMP3 expression is directly influenced by inflammation and stress, we treated dermal fibroblasts with a cytokine cocktail to mimic inflammation (IL-17A+TNF-α) and the stress hormone adrenaline. Mmp3 mRNA was induced 17.8-fold by adrenaline, increased 34.5-fold in the presence of IL-17A+TNF-α, and further increased 1.67-fold by the addition of IL-17A+TNF-α+adrenaline. To explore the significance of this response, mice undergoing stress and IMQ treatment were treated with a specific MMP-3 inhibitor (UK356618). This reduced inflammation in stressed mice treated with IMQ to control levels by normalizing epidermal thickness and decreasing neutrophil recruitment ($p < .0001$). In summary, our results reveal the previously unrecognized activation of MMP-3 by stress, and that the action of MMP-3 promotes skin inflammation. These findings further increase understanding of fibroblast function in inflammatory skin diseases and offers potential new therapeutic targets.

0617

Reconstituting systemic immunity with hematopoietic stem cell transplantation remodels the human skin microbiome in DOCK8 deficiency

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The human skin microbiome (bacteria, fungi, viruses) exists in equilibrium with skin immunity. Studies have elucidated microbial influences on immunity, yet understanding how altered immunity perturbs the equilibrium remains limited. We investigated the dual impact of immune deficiency and hematopoietic stem cell transplantation (HSCT) on skin microbiomes in DOCK8 deficiency (n=24), a rare inborn error of immunity with impaired innate and adaptive immunity, eczema, chronic systemic/skin infections, and increased cancer risk. Analyzing 590 shotgun metagenomic and 534 16S rDNA sequencing samples before and after HSCT, we observed disrupted microbiota pre-HSCT (median eukaryotic viruses 67.6% vs. 0.04% in controls), with unique viral compositions and highly diverse human papillomaviruses (HPV) and polyomaviruses – including oncogenic viruses. Specific bacterial species also markedly changed. DNA euk. viral relative abundances markedly decreased (79.7%±28.3% to 4.9%±8.6%; P<0.01) 12 mos. post-HSCT, demonstrating the reconstituted immune system's role in viral control. Recovered microbial communities were relatively stable through 1-year follow-up with clearance of oncogenic HPV and without convergence with transplant donors' microbiomes. Spatial transcriptomics of warts from a patient showed increased immune cell populations and activation of IFN-α/β and IFN-γ pathways post-HSCT, suggesting a robust immune response and decreased viral susceptibility. These results highlight the immune system's critical role in restoring the skin microbial-host equilibrium.

0618

Streptococcal species with high protease activity promote IL-4 expression and correlate with atopic dermatitis severity in infants

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The composition of the human skin microbiome in atopic dermatitis (AD) has been characterized almost exclusively in adults and has mainly focused on staphylococcal species such as S. aureus. While Streptococcus pyogenes commonly causes infections in children, and has been isolated from some children with AD, it has been shown that other streptococcal species are common isolates from the skin and mucosa of children under 6. It is unclear if these non-pyogenes species offer protection against or if they potentially contribute to AD flares. To evaluate this, skin swabs were collected from the face of 19 pediatric subjects with AD and 16 healthy controls. Swabs were then processed and analyzed using culture-based colony counting, qPCR, 16S rRNA community sequencing, and shotgun metagenomics. All techniques showed the absolute abundance of staphylococcal and streptococcal species was higher at AD-lesional skin compared to normal controls (p-value=0.0014). Further, functional analysis of live culture isolates revealed a strong correlation between disease severity and the presence of several different streptococcal species with high protease activity including the Zn-metalloprotease ($gelE^+$) (P=0.0019). In a Balb/c MC903 AD mouse model, the application of streptococcal species with $gelE^+$ activity induced elevated expression of both IL-17A and IL-4 mRNA (75.2-fold increase). In addition, streptococcal species with high $gelE^+$ activity inhibited AMP expression (Camp) (43.6-fold decrease) compared to strains of the same streptococcal species without $gelE^-$ activity. These data suggest that in children, colonization with Streptococcal species other than S. pyogenes may contribute to AD flares by producing a metalloprotease that promotes its own survival, enhances the survival of other streptococcal species, and induces a potent type 2 inflammatory response.

0619

Commensal bacteria negatively regulate skin inflammation by inhibiting proliferation of CD8⁺ Tissue resident memory T cells

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This study explored how commensal bacteria regulate CD8⁺ Tissue-resident memory T cells (Trm) and their role in skin inflammation. Autoimmune and inflammatory skin disorders have complex, immune-mediated pathophysiology, often prone to relapse after drug withdrawal. Trm play a critical role in these relapses. Commensal bacteria on lesional skin differ significantly from those on healthy skin, influencing immune homeostasis. However, the relationship between commensal bacteria and Trm, and their role in skin inflammation, remains unclear. Using a DNFB-induced skin inflammation model in specific pathogen-free (SPF), germ-free (GF), and SPF mice treated with Staphylococcus epidermidis, we analyzed CD8⁺ Trm numbers, distribution, and cytokine secretion. Metabolomics and RNA sequencing investigated potential mechanisms. Skin commensal bacteria alleviated recurrent skin inflammation, reducing ear thickness ($p<0.0001$), epidermal thickening, and dermal edema in Staphylococcus epidermidis-treated mice ($p<0.0001$). Flow cytometry revealed decreased CD8⁺ Trm infiltration in lesional skin ($p=0.0097$). Staphylococcus epidermidis inhibited CD8⁺ Trm accumulation 30 days post-DNFB stimulation, lowering their percentage and count ($p=0.0052$). Bacterial metabolites had similar effects, with metabolomics identifying key substances. Additionally, Staphylococcus epidermidis reduced CD8⁺ Trm IFN-γ secretion ($p=0.0439$) and proliferative capacity ($p=0.0286$), impairing their function and persistence. RNA-seq of CD8⁺ Trm and scRNA-seq of immune cells showed significant downregulation of the PPAR signaling pathway, glutathione metabolism, and fatty acid degradation pathway 3 days post-Staphylococcus epidermidis treatment. This study demonstrates that skin commensal bacteria, particularly through organic acid metabolites, regulate CD8⁺ Trm persistence in skin inflammation. These findings suggest the therapeutic potential of bacterial metabolites in treating inflammatory skin diseases.

0620

Identification of natural killer cells and innate lymphoid cells in human epidermis

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Resident memory T cells and resident memory regulatory T cells have been identified in the human epidermis. Meanwhile, it has been largely unknown whether innate immune cells such as natural killer (NK) cells and innate lymphoid cells (ILCs) are present in the human epidermis. Hence, this study sought to identify them and examine their function. The following three innate immune cells were identified based on the expression of CD94 and CD127: CD94+CD127− NK cells, CD94+CD127+ cytotoxic ILCs (cytoILCs), and CD94−CD127+ conventional ILCs (convILCs). In the CD45+Lin− cells of PBMC, NK cells were the predominant innate immune cells. In the epidermal CD45+CD3− lymphocytes, three populations of innate immune cells were identified. However, unlike PBMC, convILCs were the predominant innate immune cells. A transcriptional factor Eomes is essential for the development, proliferation, and persistence of human NK cells. Additionally, Eomes-depleted human NK cells change the phenotype to ILC. NK cells in PBMC almost completely express Eomes. Epidermal NK cells exhibited higher Eomes expression than cyto ILCs and convILCs. However, its expression rate was only about 20%. These data suggest that under the conditions of the epidermis, the expression of Eomes in NK cells decreases due to some kind of influence, causing a decrease in the number of cells and/or their conversion to ILCs. All three epidermal innate immune cells strongly express skin retention markers such as CLA and CD69. Moreover, the percentage of CD103+CD49a+ cells in CD69+ cells was significantly greater in epidermal innate immune cells compared to those in dermal counterparts. Functionally, epidermal NK cells produced much greater perforin than two ILC populations, however their killing activities were much weaker than those of PBMC NK cells. In summary, we identify innate immune cells in the human epidermis, suggesting that the epidermis is not only endowed with acquired immune cells, but also with innate immune cells like the dermis. However, their function is suppressed.

0621

Bifidobacterium animalis SMUDHYang01 enhances skin barrier function and alleviates atopic dermatitis via acetate secretion

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Dysbiosis in the gut microbiota has been implicated in the pathogenesis of atopic dermatitis (AD). Using faecal shotgun metagenomic sequencing, Bifidobacgterium spp, including B. bifidum, B. breve, B. longum and the B. animalis, were found to be depleted in patients with AD (n = 30) compared with healthy subjects (n =20). Among these, B. animalis was specially shown to alleviate MC903-induced mouse AD. We successfully isolated the B.animalis from healthy human fecal samples, and the strain identification was confirmed through whole-genome sequencing. Notably, the newly isolated strain SMUDHYang01 significantly improved the severity of MC903-induced AD-like lesions in a mouse model, as evidenced by reduced ear thickness, improved epidermal thickness, decreased mast cell infiltration, and lower plasma IgE levels, compared to E. coli MG1655 or BHI-treated mice (All measures, $P < 0.05$, n = 10). Further investigations revealed that both live SMUDHYang01 and its cultured supernatant (CS) effectively alleviated dermatitis. In contrast, heat-inactivation of SMUDHYang01 abolished this effect, suggesting that metabolite(s) derived from SMUDHYang01 contributed to its preventive capacity against AD. Unbiased LC-MS/MS analysis of metabolites identified that acetate was enriched in SMUDHYang01-CS (16.4-fold, $P < 0.0001$), as well as in the gut and skin biopsies of SMUDHYang01-treated mice. Accordingly, administration of acetate alone or oral administration of engineered acetate-producing E. coli significantly inhibited the progression of AD in the murine model. Mechanistically, acetate translocate into the keratinocyte cytoplasm and binds to STAT-6 via Monocarboxylate transporter1 (MCT1) transport, leading to reduced nuclear translocation of p-STAT-6. This further mitigates IL-4-mediated reduction in claudin-1 and claudin-4, thereby restoring skin barrier function. Overall, SMUDHYang01 emerges as a novel prophylactic agent for AD prevention, exerting its skin barrier-protecting effects through gut microbiota modulation and the secretion of acetate.

0622

Altered skin microbiome along with skin barrier changes in cutaneous T cell lymphoma

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Cutaneous T-cell lymphomas (CTCLs) represent a heterogeneous group of lymphoid malignancies arising from skin-homing T cells, with mounting evidence linking their pathogenesis to the host microbiome. However, the specific role of cutaneous microbiota dysbiosis in the development of CTCL remains ambiguous, particularly among Asian populations. In this study, we conducted 16S and ITS sequencing of skin swab samples from 72 CTCL patients and 26 matched healthy controls (HCs) to characterize bacterial and fungal communities. We observed alterations in the skin microbiome among CTCL patients when compared to HCs, with these changes being particularly pronounced in advanced CTCL cases ($P:0.002$). Notably, there was a significant increase in the relative abundances of Staphylococcus aureus (SA, $P<0.0001$) and Mycosphaerella tassiana in advanced CTCL patients, which correlated with elevated mSWAT and pruritus scores, as well as high levels of lactic dehydrogenase. Conversely, we noted a marked decrease in the relative abundances of Cutibacterium acnes($P:0.02$) and Malassezia globosa (0.007) in advanced CTCL patients, which was inversely correlated with the severity of CTCL and the abundance of SA. Furthermore, a random forest model identified the ten most discriminatory species, including the aforementioned four, capable of differentiating advanced CTCL from early CTCL, achieving a mean prediction AUC of 0.752. Additionally, *in vitro* experiments demonstrated that the expression of skin barrier genes, particularly filaggrin and loricrin ($P<0.0001$), was downregulated in HaCaT cells following treatment with the supernatant from CTCL cell lines (Myla and Hut 78). Immunostaining of skin biopsies revealed that decreased expression of filaggrin in the epidermis was associated with increased expression of GATA3 and TOX in malignant T cells (All $P<0.05$). Our findings suggest that the skin microbiome undergoes alterations during CTCL progression, coinciding with an impaired skin barrier, potentially linked to malignant T cells exhibiting a T helper cell-2 phenotype.

0623

Staphylococcus aureus superantigens target sebaceous gland maturation to promote skin pathogenesis and colonization

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Atopic dermatitis (AD) is a chronic, itchy, and inflammatory skin disorder that affects children and adults with increasing prevalence, despite available treatments. AD is associated with abundant Staphylococcus aureus skin colonization, sebaceous gland abnormalities, and sebum lipid alterations. However, the interactions that dictate aberrant S. aureus colonization and sebaceous gland dysfunction to exacerbate AD pathogenesis are understudied. Using a mouse model of AD-like skin inflammation, involving epicutaneous application of S. aureus to the shaved and depilated dorsal skin for 7 days, we found that mice exposed to toxic shock syndrome toxin (TSST) superantigen developed increased epidermal thickening, cutaneous immune cell recruitment, and serum IgE production than mice exposed to TSST-deficient S. aureus. Remarkably, RNAseq analysis of infected skin revealed TSST-mediated suppression of sebocyte maturation and lipid synthesis genes, which was functionally associated with a reduction in mature sebaceous glands and increased S. aureus skin colonization. Excitingly, we observed a similar reduction in mature sebaceous glands in skin exposed to S. aureus deficient in staphylococcal enterotoxin B and staphylococcal enterotoxin C superantigens compared to parent, suggesting a conserved interaction between superantigens and sebaceous glands. Collectively, our data indicated that S. aureus superantigens promote skin colonization via inhibition of sebaceous gland maturation and sebum lipid production pathways. These findings have implications for the development of therapeutics that inhibit S. aureus colonization and restore skin homeostasis in AD and potentially other inflammatory skin diseases with S. aureus involvement.

0624

Cutibacterium acnes induce lipid accumulation and antimicrobial responses in fibroblasts

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The pathogenesis of acne involves complex interactions between Cutibacterium acnes (C. acnes) and various skin cells. Our findings show that C. acnes significantly induce lipid accumulation in fibroblasts, an effect observed in keratinocytes in our prior work. Exposure to 15% C. acnes supernatant increased Oil Red O (ORO) staining, showing a twofold increase by day 2, threefold by day 4, and fivefold by day 8 ($p<0.0001$) in 3T3 fibroblasts, indicating sustained lipid accumulation. Treatment with propionic acid, the main short-chain fatty acid produced by C. acnes, also increased lipid accumulation in 3T3 cells by threefold ($p<0.0001$) in ORO staining. Using differential mobility spectrometry-based shotgun lipidomic analysis and liquid chromatography–mass spectrometry, we observed that exposure to 15% C. acnes supernatant for 4 days significantly induced a twofold increase in ceramides, phospholipids, fatty acids, and triglycerides. In addition to lipid accumulation, C. acnes stimulated the production of antimicrobial factors, including lipocalin-2 (lcn2) and cathelicidin antimicrobial peptide (cramp) in 3T3 fibroblasts. Notably, LCN2 exhibited a bactericidal activity, killing C. acnes at 45 µg/ml. For the first time, we demonstrate that Pdgfra-Cre+/- Camp flox/flox mice exhibit accelerated resolution of acne lesions in an acne model, with lesion resolution occurring twice as quickly. This is associated with a reduction in lipid staining by Bodipy following C. acnes injections combined with squalene application. These findings position fibroblasts as critical players in skin lipid metabolism and immunity, suggesting new therapeutic targets to regulate skin barrier function and immune responses.

0625

Skin as a potential entry point for SARS-CoV-2 virus

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It is well known that the main route of the SARS CoV-2 entry is via respiratory epithelial cells. However, skin cells also express ACE2 and TMPRSS2, critically important for SARS-CoV-2 infection. 1%–20% of COVID-19 patients had dermatological lesions, and viral RNA was detected in skin of COVID-19 patients. Moreover, psoriasis and atopic dermatitis (AD) significantly increased the risk of COVID-19, and ACE2 and TMPRSS2 expression was increased in lesional skin of psoriatic patients. To assess the potential role of skin in SARS-CoV-2 infection, we used 3D human skin organoids (HSO) made from primary African American (AA) and White non-Hispanic (WNH) epidermal keratinocytes. HSO were treated with individual cytokines TNF-α, IL-6, IL-1β, INF-γ, involved in acute/chronic skin inflammation, and with Th1 (TNF-α+IL17) and Th2 (IL4+IL13) cytokine cocktails known to induce pro-psoriasis and pro-AD molecular and morphological changes in HSO. All individual cytokines induced the expression of ACE2 and TMRSS2 at mRNA/ protein level. Interestingly, Th2 cytokine cocktail induced only TMPRSS2 in both AA and WNH HSO. In contrast, Th1 cytokine cocktail mostly induced ACE2, especially in AA HSOs which may correlate with known higher risk of COVID-19 in AA population. We made Spike-pseudotyped lentiviral Tomato reporter (encoding original Spike-protein from wt Wuhan-Hu-1 strain) that similarly to SARS-Cov-2 binds to ACE2. We successfully infected control and cytokine-treated HSO and neonatal skin explants by topical viral application monitored by Tomato fluorescence and expression of Tomato mRNA in epidermis of *in vitro* skin models and showed that cytokines (especially Th1) increased infection efficacy. Further analysis of infected HSOs revealed a decrease of TMPRSS2 in Th1-treated infected rafts, possibly due to endocytosis. These experiments provide proof of principle that skin could be an additional entry port for SARS-CoV-2 virus.

0626

Dissecting the role of sensory neurons in response to skin parasites

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The skin is a vital interface critical in maintaining commensal microorganisms while defending from pathogenic ones. Sensory neurons have been implicated in coordinating immune responses against microbes, but their role in response to parasitic infections remains unclear. In this study, we use the Demodex infection model, a commensal parasite that inhabits mammalian hair follicles, to dissect how this parasite may influence the nervous system. We hypothesized that sensory neurons influence the immune response to Demodex infection by increasing the expression of neuropeptides. We performed bulk RNA sequencing of trigeminal ganglia, which revealed minimal transcriptional changes during early infection despite increased expression of the neuropeptide Calca in the trigeminal ganglia and skin over time. Pharmacological sensory denervation with resiniferatoxin (RTX) or genetic denervation using Trpv1-Cre; R26DTA mice led to modest changes in ILC2 populations. RNA sequencing analysis of the skin identified upregulation of gasdermin C (GsdmC) family proteins and IL-36 cytokines in Demodex-infected skin, implicating increased keratinocyte-mediated inflammation in response to mite colonization. Type 2 immunodeficient mice ($Il4^{-/-}/Il13^{-/-}$ or $Il4ra^{-/-}$), which cannot control Demodex infection, exhibited heightened inflammatory and neuropeptide responses to Demodex, which were mitigated by antiparasitic treatment. Our data highlight potential crosstalk between sensory neurons and keratinocytes in orchestrating localized immune responses to skin-dwelling parasites. These findings suggest that Demodex mites may interact with the sensory neurons to regulate inflammation in a controlled, non-pathologic fashion. This work can help uncover mechanisms underlying neurogenic inflammation in inflammatory skin diseases, offering potential avenues for developing targeted therapies for conditions like atopic dermatitis.

0627

Single-cell analyses of secondary syphilis in skin reveals implications for immune evasion and transmission

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Syphilis is a complex infection where symptomatic stages alternate with phases of latency and, hence, an interesting disease model to study immune evasion. We used single-cell and bulk RNA sequencing along with IHC and assessed immune responses in both blood and keratinocytes to live Treponema pallidum (T. pallidum). For single-cell sequencing, skin biopsies were collected from five subjects with secondary syphilis and four healthy controls. Single-cell data from secondary syphilis skin lesions demonstrated a polymorphous immune infiltrate, which was validated by IHC and demonstrated prominent B cell/plasma cell infiltration with colocalization of T cells, B cells and antigen-presenting cells. Prominent immune-stromal crosstalk was observed, with concomitant pro-inflammatory and regulatory responses, and was accompanied by altered keratinocyte differentiation and decrease in intraepidermal communication, which may provide a niche in the epidermis where T. pallidum can be present. While PBMC immune responses were blunted by T. pallidum, keratinocytes responded with upregulation of type-I interferon responses, that were abolished in MYD88-deficient, but not STING-deficient keratinocytes, suggesting engagement of TLR sensing in skin as a driver of immune responses in syphilitic skin lesions. These data shed light on the mechanisms by which T. pallidum evades immune responses and promotes transmission through the skin.

0628

Unraveling the role of actinotignum schaalii in hidradenitis suppurativa: Genomic and inflammatory perspectives

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Hidradenitis suppurativa (HS) is a debilitating chronic skin disease characterized by recurrent painful lesions, scarring, and malodorous discharge. While microbial dysbiosis is recognized in HS sinus tracts, the contributions of individual microbes to disease progression remain insufficiently explored. This study focuses on Actinotignum schaalii, a Gram-positive facultative anaerobe, and its potential role in HS pathogenesis. Using traditional culture methods, A. schaalii was isolated from severe HS lesions. Whole genome sequencing revealed a suite of virulence-associated genes, including those linked to adhesion, intracellular invasion, antimicrobial resistance, and oxidative stress tolerance. Functional assays demonstrated that ex-vivo infection of human skin with A. schaalii significantly upregulated pro-inflammatory cytokines seen in HS. *In vivo* experiments in murine models confirmed that A. schaalii induces acute abscess formation, mirroring the inflammatory features observed in HS. These findings suggest that A. schaalii actively contributes to the inflammatory milieu of HS and may represent a novel therapeutic target. This research also establishes a scalable methodology for studying additional anaerobic bacteria implicated in HS, advancing our understanding of bacterial-driven mechanisms in disease progression.

0629

Cutibacterium acnes induces skin region-specific innate immune memory events in epidermal keratinocytes

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In immune cells, external insults can cause immune and inflammatory activation. The resulting persistent signaling, metabolic and epigenetic changes can lead to trained immunity, a form of innate immune memory (IIM) in these cells. We investigated whether Cutibacterium acnes (C. acnes) can cause similar changes in human keratinocytes. Normal human epidermal keratinocytes from mammoplasty (NHEK-B) or abdominoplasty (NHEK-A) were trained with C. acnes, followed by a five-day rest period and secondary induction with Pam3CSK4 (TLR1/2 agonist). Immune gene expression (e.g., TNFα, IL-8) revealed regional disparities, signs of innate training-like changes in NHEK-B, and tolerance in NHEK-B cells, compared to untrained, but Pam3CSK4 induced ones. Transcriptome analysis of trained and induced NHEK cells revealed significant differences in the global gene expression patterns. While NHEK-A cells showed changes in gene expressions associated with skin development, NHEK-B cells demonstrated an increased inflammatory response. Region-specific changes in the global genomic 5mC and 5hmC content using ELISA, together with the observed differences in the metabolic changes of NHEK-B and NHEK-A cells in our *in vitro* model system using high-resolution respirometry, are consistent with the IIM changes similar to what happens in immune cells. Based on the results, we propose that epidermal keratinocytes remember their external influences, and the molecular basis of these events is the induction of skin region-specific immune IIM events.

0630

Aryl hydrocarbon receptor knockdown in langerhans cells attenuates psoriatic inflammation by increasing IL-10 but not IDO-1, plausibly through autophagy regulation

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Topical medication targeting aryl hydrocarbon receptor (AhR), an environmental sensor, is approved to treat psoriasis. We have shown that specific AhR ablation in epidermal Langerhans cells (LC) decreases LC numbers while induces Th2/Tr1 polarization in atopic sensitization. However, how AhR in LC regulates pathophysiology of psoriasis remains unclear. We measured AhR expression in LC in human psoriasis. We tested the imiquimod induced psoriasis in langerin-specific AhR knockout mice (Langerin-AhR-/-). In human psoriasis, there are fewer CD207-expressing LC, and most AhR is located in cytosol. Interestingly, these CD207+ cells express LC3b, a marker for autophagy. In imiquimod-induced psoriasis, epidermal thickening was significantly decreased in Langerin-AhR-/- mice. The numbers of bone marrow derived Langerhans cell like cells (BMLC) from Langerin-AhR-/-mice are decreased. BMLC from WT mice treated with AhR inhibitor (CH223191) or from Langerin-AhR-/- showed an increase in IL-10, decreases in IL-1b and IDO-1, with no difference in the IL-23, CGRP, beta-endorphin (by ELISA and real time PCR) and slightly increased expression in the costimulatory markers CD80, CD86, and MHC-II (by flow cytometry). Meanwhile, these BMLC with defected AhR showed attenuated autophagy with late induction of p62. The increased IL-10 and decreased in IL-1b in BMLC from Langerin-AhR-/- or BMLC from WT mice treated with CH223191 are attenuated by treatment with rapamycin, an autophagy inducer. In summary, we showed that AhR blockage in LC showed an attenuated psoriatic inflammation, by increasing IL-10 and decreasing IL-1b (but not IDO-1, an anti-inflammatory mediator), potentially through autophagy mechanisms. AhR may coordinate with autophagy in LC, contributing to the development of psoriasis.

0631

Epigenetic changes associated with Cutibacteriam acnes-induced innate immune memory events in human keratinocytes

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Cutaneous microbiota can transiently activate keratinocytes, leading to innate immune and inflammatory responses that may persist beyond the initial trigger. This phenomenon is referred to as trained immunity or innate immune memory (IIM). We investigated whether Cutibacterium acnes can induce IIM in keratinocytes and to analyze the underlying epigenetic changes. Normal human epidermal keratinocytes from mammoplasty (NHEK-B) or abdominoplasty (NHEK-A) were trained with C. acnes and induced with Pam3CSK4 after five days of rest. The contribution of epigenetic regulation to IIM events was analyzed using pharmacological inhibitors during training, and whole-genome methylation changes were assessed by ELISA. Our results revealed the formation of region-specific immune training(NHEK-B) vs. tolerance(NHEK-A) events, as judged by the significant mRNA expression differences of selected immune effectors (TNFα, IL-8) in trained cells after Pam3CSK4 induction, compared to the untrained ones. Pargyline HCL, a histone deacetylase inhibitor, during training did not modulate the immune effectors. The histone deacetylase inhibitor SAHA resulted in altered mRNA expressions, increased levels in NHEK-B and decreased in NHEK-A, following induction, regardless of training. 5-Aza-dC, a DNA methyltransferase inhibitor, resulted in altered TNFα and IL-8 expression regulation, but only in the untrained cells. The global 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC) reduced in both levels in the genomic DNA of trained NHEK-B compared to NHEK-A cells. These epigenetic differences were supported by region-specific changes in mRNA expression of TET and DNMT genes. Our findings suggest that the cutaneous microbiota induces skin region-specific IIM changes in keratinocytes and that altered epigenetic regulation may be involved in these processes.

0632

Gut microbial signatures associated with uremic pruritus in hemodialysis patients

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The gut microbiota is intricately linked to the gut–skin–kidney axis, yet its role in uremic pruritus remains inadequately understood. This cross-sectional study investigated gut microbial differences in hemodialysis (HD) patients with and without uremic pruritus and aimed to identify potential microbial biomarkers. Stool samples were collected from 93 HD patients, and gut microbiota composition was analyzed using 16S rRNA gene sequencing. Microbial diversity was assessed via alpha and beta diversity metrics, and LEfSe analysis was conducted to identify taxa associated with pruritus. Uremic pruritus was reported in 61.3% of participants, with a median visual analog scale (VAS) score of 4.0. Alpha diversity metrics showed no significant differences between groups, but beta diversity analysis revealed distinct microbial profiles (unweighted UniFrac, p=0.003; weighted UniFrac, p<0.001). LEfSe analysis identified significant enrichment of Pasteurellales, Pasteurellaceae, and Dialister in patients with pruritus, while Corynebacteriales was more abundant in those without pruritus (p<0.05, LDA > 3). These findings highlight significant differences in the gut microbiota composition of HD patients with and without uremic pruritus, suggesting potential microbial biomarkers associated with pruritus. Further research is required to elucidate underlying mechanisms and evaluate microbiota-targeted therapeutic interventions.

0633

Vulval lichen sclerosus and the microbiome

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Female genital lichen sclerosus (FGLSc) is a common, scarring inflammatory dermatosis associated with significant morbidity and a small risk of squamous cell carcinoma. The role of the microbiome in FGLSc has received limited attention. 16S rRNA next-generation sequencing was performed to determine the microbiome of the vulva, vagina and urine of 30 patients with active, untreated FGLSc and 30 healthy controls, and to assess the impact of treatment. Women with immunocompromise and recent (~4 weeks) topical or systemic antibiotics were excluded. Preliminary statistical analyses have demonstrated a reduction in alpha diversity at all three sites for patients with active FGLSc, with significance demonstrated in vulval samples (p=0.041). Permutational multivariate analysis of variance revealed a significant difference in beta diversity between cases and controls in the vulva(p=0.001), vagina(p=0.019) and urine(p=0.021). There was no significant difference in beta diversity between samples before and after treatment of FGLSc. Compared with healthy controls, samples from patients with active FGLSc had a higher abundance of Lactobaccillus, though this did not achieve statistical significance, and a lower abundance of Streptoccus (p=0.01, 0.02 and 0.06 respectively for vulval, vaginal and urine samples). Smaller differences were seen in Corynebacterium (p=0.04) and Staphylococcus (p = 0.05) in vaginal swabs, Actinomyces (p=0.05) and Mobiluncus (p=0.03) in vulval swabs and Mobiluncus (p=0.03) in urine, where abundances of these bacteria were lower in the FGLSc group. These findings demonstrate potential dysbiosis in the FGLSc; further studies to explore causality are justified.

0634

Cutibacterium acnes extracellular vesicles: A new therapeutic target in acne modulated by myrtacine and celastrol

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Introduction: Acne is a chronic inflammatory skin condition involving the sebaceous glands, keratinocytes, skin microbiome, and innate immunity. Cutibacterium acnes (C. acnes), a skin bacterium, is classified into six phylotypes. Phylotype IA1 overgrowth is associated with acne lesions. C. acnes secretes Extracellular Vesicles (EVs) that contribute to skin inflammation. Objectives: This study aimed to assess the effects of Myrtacine® and Celastrol, alone or in combination, on cutaneous innate immunity using human skin models exposed to C. acnes EVs. Materials & Methods: EVs were isolated from two different strains of C. acnes phylotype IA1: T5 (healthy human skin) and A47 (inflammatory acne lesion). These EVs were applied to human keratinocytes (HaCaT cell line) and skin explants. Preventive treatment indicated addition of Myrtacine and Celastrol, alone or combined, to the cells or explants before EV incubation. In curative treatment, the skin models were exposed to EVs before addition of active ingredients. Subsequently, qPCR, ELISA, and immunohistochemistry were performed for select immune markers. Results: A47 EVs, but not T5 EVs, significantly increased proinflammatory and antimicrobial markers at transcript and protein levels. Myrtacine or Celastrol treatment, both preventive and curative, significantly reduced most markers. However, their combination further enhanced the inhibition of the immune response induced by EVs. Conclusion: Preventive and curative treatments with Myrtacine and Celastrol, alone or in combination, significantly decrease immune marker expression, suggesting their potential anti-inflammatory properties for acne therapy.

0635

Granzyme K drives a new pathway of complement activation that contributes to pathology in inflammatory skin disease

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Granzyme K (GZMK) expressing CD8+ T-cells have recently been defined as the predominant CD8+ T-cell population in inflamed tissues in multiple autoimmune diseases. In human psoriasis and cutaneous lupus we see numerous GZMK+ T-cells by immunofluorescence. However, the overall function of GZMK has been relatively undefined. Here, we show that GZMK is a novel activator of the complement cascade. GZMK cleaves C2 to C2b and C4 to C4b to form an active C3 convertase that cleaves C3 into bioactive C3a and C3b. GZMK further forms active C5 convertases that generate C5a and the membrane attack complex, thus generating all key components of the complement cascade. GZMK is continuously released from CD8+ T-cells in an antigen-independent manner. Upon release, GZMK binds to negatively charged surface molecules through electrostatic interactions. Interference of GZMK cell surface binding limits C3b opsonization suggesting that GzmK must be membrane bound to elicit formation of an active C3 convertase. Within tissues, fibroblasts are the major producer of C2, C3 and C4. IFNg and TNFa, cytokines secreted by GZMK+ T-cells, drive fibroblasts to increase synthesis and release of C2-C4. Importantly, in an imiquimod induced dermatitis model, $Gzmk^{-/-}$ mice have less severe erythema, scaling and thickening of skin compared to $Gzmk^{+/+}$ or $Gzmk^{+/-}$ mice. Strikingly, $Gzmk^{-/-}$ mice have markedly less C3d and C4d, products of complement pathway activation at the dermal epidermal junction following IMQ treatment. These data suggest GZMK is activating the complement cascade *in vivo* to drive inflammation. Taken together, we define a new pathway of complement activation independent of the previously well-described classical, alternative, and lectin pathways that is dependent on GZMK and has the potential to drive inflammation in a variety of tissues and disease states.

0636

Staphylococcal scalded skin syndrome imitating Stevens-Johnson syndrome/toxic epidermal necrolysis in adults

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A 60-year-old woman with type 2 diabetes (T2D), chronic kidney disease (CKD), and history of infected spinal hardware presented with a rapidly worsening diffuse rash featuring denudation and superficial desquamation on the trunk, back, and extremities. Extensive antibiotic exposure initially suggested Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), but frozen-section biopsies revealed psoriasiform, spongiotic dermatitis with subcorneal pustules, indicating staphylococcal scalded skin syndrome (SSSS). This diagnosis was further supported by evidence of Staphylococcus aureus infection and the development of acute kidney injury (AKI). In another case, an 81-year-old man with T2D, stage 4 CKD, and a left below-the-knee amputation presented with a worsening stump wound infected by methicillin-resistant Staphylococcus, refractory to antibiotics and complicated by an AKI. After undergoing a left above-the-knee amputation, he developed pustular plaques on the face and chest, along with sloughing and superficial desquamation of the neck, back, face, groin, and chest. Although extensive antibiotic use initially suggested SJS/TEN, a skin biopsy showing a subcorneal split with neutrophils confirmed SSSS. In both cases, development of an AKI on CKD likely caused exfoliative toxin accumulation and SSSS. Both patient's symptoms mimicked SJS/TEN, including cutaneous exfoliation, erythema, and superficial desquamation, necessitating histopathological differentiation. SSSS is characterized by superficial epidermal splitting within the granular layer, sparing mucosal surfaces and showing minimal neutrophilic infiltration; SJS/TEN involves full-thickness epidermal necrosis extending to the dermal-epidermal junction with mucosal involvement. These cases underscore the importance of performing skin biopsies in patients with renal dysfunction who present with SJS/TEN-like symptoms to ensure accurate diagnosis and appropriate management.

0637

Neutrophil extracellular trap induction defines the pathogenicity of Cutibacterium acnes clinical isolates

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Cutibacterium acnes is an anaerobic bacterium implicated in the pathogenesis of acne vulgaris (AV). Variations in virulence factors among C. acnes strains are thought to contribute to differences in their inflammatory potential. Neutrophil extracellular traps (NETs), antimicrobial structures released by neutrophils, play a key role in the inflammatory responses of several infectious and autoimmune diseases. This study investigates the pathogenicity of C. acnes clinical isolates by their ability to induce NETs. With Institutional Review Board approval and written informed consent, clinical isolates were collected from the facial skin of individuals with AV and healthy controls. Among 18 isolates, we identified 8 as phylotype IA1, 6 as IA2, 1 as IB, and 3 as type II. NET release and inflammatory cytokine production were significantly higher in neutrophils exposed to supernatants from certain isolates ($p<0.001$). NET-inducing isolates (NET-C) were more likely to exhibit β-hemolytic activity ($p=0.0392$) and were associated with severe disease in C. acnes-inoculated mice and AV patients. Phylogenetic analysis revealed that NET-C clustered within the camp2 gene, a co-hemolysin linked to virulence. These findings suggest that identifying NET-C isolates could enhance the evaluation and treatment of AV in clinical practice.

0638

Inflammatory skin disease atlas allows disease stratification based on shared and distinctive pathogenic mechanisms

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Inflammatory skin diseases (ISD) represent a large proportion of dermatologic conditions. Prior studies identified dysregulated pathways compared to healthy controls (HC). However, diagnosis of ISD in dermatology is often challenging as clinicians must differentiate between multiple different conditions that may have similar appearances or distribution. Here, we generated bulk-RNA sequencing data from skin biopsies of 753 different patients across 40 different ISD to build a transcriptome atlas. Importantly, we also included five ISD from the scalp, which have not been thoroughly studied. Unsupervised clustering including cytokine and chemokine signatures identified 4 major disease clusters that divided papulosquamous (e.g. psoriasis) from fibrotic (e.g. scleroderma), autoimmune (e.g. lupus) and scalp (e.g. folliculitis decalvans). Interestingly, some samples harbored molecular signatures shared between clusters, highlighting heterogeneity within each disease. We identified shared and distinctive pathways enriched in each cluster and individual disease. Cytokine gene expressions were able to split cases versus HC in most diseases. Importantly, using specific response signatures in keratinocytes, to IL-4, IL-13, type I and II interferons, IL-36, IL-17A, TNFα, and IL-17A+TNF, we stratified ISD across their cytokine signature enrichment. Furthermore, these cytokine signatures were used to train a machine learning prediction model to classify every disease against all the other conditions. Despite unique and shared cytokine responses across many diseases, the majority showed high areas under the receiver operating characteristic curve (AUC >89%), indicating that multidimensional cytokine response signatures can distinguish ISD from each other. In summary, our transcriptome atlas of ISD represents a new resource for dermatologists that can be used for clinical diagnosis, further research, and decision making for targeted treatment based on cytokine signatures.

0639

Sensory nerve-associated, IL-31-secreting M2 macrophages (SNAMs) promote substance P-induced neurogenic inflammation in human skin *ex vivo*

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Sensory-neuron-associated macrophages (SNAMs) are a subset of dermal M2 macrophages that communicate with cutaneous sensory nerve fibers (NFs) through the secretion of cytokines like IL-31, thereby contributing to inflammatory pruritic disorders like atopic dermatitis (AD) and prurigo nodularis (PN). Since the influence of neuropeptides on SNAMs in human skin remains incompletely understood, we have explored this in denervated, organ-cultured, full-thickness, healthy human eyelid skin (3-5 donors) by administering substance P (SP, 10^{-8}M), the key neuropeptide that mediates stress responses and neurogenic skin inflammation, to the culture medium. SP significantly upregulated the expression of the pro-inflammatory pruritogen, periostin, and increased the total number and % of M2 macrophages ($CD68^+CD206^+$), particularly IL-31^+ M2 macrophages. To explore this mechanistically, eyelid biopsies were organ-cultured with either a periostin-neutralizing antibody or the neurokinin-1 receptor (NK-1R) antagonist, aprepitant, in the presence/absence of SP. This showed that aprepitant diminished the SP-induced periostin upregulation, while aprepitant and periostin-neutralization abrogated the SP-induced increase in the number of dermal IL-31^+ M2 macrophages. These *ex vivo* data suggest that SP release from cutaneous sensory NFs propagates neurogenic inflammation in human skin through NK-1R activation, increasing periostin secretion and promoting IL-31^+ M2 SNAMs. This vicious circle aggravates neurogenic skin inflammation, pointing to NK-1R activation (on SNAMs?) and periostin as novel therapeutic targets to break this pathogenic loop; for example, by administering aprepitant to patients with AD or PN.

0640

Integrated proteomic and transcriptomic analyses reveal unique protein composition of Th17 cell-derived extracellular traps in acne vulgaris.

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Extracellular traps (ETs), initially discovered in neutrophils, are now recognized in other immune cells, including T cells. Recent studies report antigen-specific T cells producing extracellular traps, but their protein composition and function remain poorly understood. This study aimed to investigate the protein composition of ETs produced by Th17 cells (TETs) and neutrophils (NETs) in response to different Cutibacterium acnes (C. acnes) phylotypes, to elucidate their roles in acne pathogenesis and identify potential therapeutic targets. We employed integrated proteomics, transcriptomics, and acne biopsy analyses to characterize their protein composition and gene profiles. Proteomic analysis revealed that while NETs exhibited consistent protein profiles across C. acnes phylotypes, TETs demonstrated significant compositional variation, indicating phylotype-specific immune responses. Unique TET-associated proteins, such as GZMM were implicated in bacterial cell wall disruption whereas T cell-associated molecules such as HLA-DRB5, and TAP1, were implicated in T-cell activation, and antigen presentation. Shared proteins between TETs and NETs, including H2BC21, HBD, and HMGN2, were associated with antimicrobial defense, bacterial entrapment, and anti-inflammatory regulation. Spatial transcriptomics further validated the distinct protein profiles of TETs within acne biopsies. These findings provide critical insights into the interplay between skin microbes and ET formation, offering a foundation for developing targeted acne treatments.

0641

Transcription factor ZNF750 recruits histone demethylase KDM1A to manage immune response

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The epidermis provides a physical barrier as well as manages immune responses in the skin. However, how keratinocytes engage in immune sensing or mediates immune tolerance is unclear. Here we uncover that ZNF750, a transcription factor specific to differentiated keratinocytes, recruits the epigenetic regulator KDM1A to silence genes coding for pattern recognition receptors (PRRs). We show that differentiated keratinocytes expressing ZNF750 are resistant to Poly IC stimulation, while undifferentiated cells which don't express ZNF750 generate a robust inflammatory response. Knockdown of ZNF750 in differentiated keratinocytes leads to an enhanced inflammatory response including increased pro-inflammatory cytokines, interferon response genes and PRRs. Epidermis-specific Zfp750 knockout mice exhibit severe and persistent skin inflammation with neutrophil infiltration and psoriasis-like features following UVB-induced damage. In an Imiquimod-induced psoriasis model, Zfp750 knockout skin are also more inflamed with increased neutrophils and Th17 cells in the skin-draining lymph nodes. ZNF750 ChIP-Seq reveal that it binds and inhibits the expression of TLR3, IFIH1, DDX58 and inflammatory genes through its canonical DNA binding motif. Silencing TLR3 in ZNF750 knockdown cells reduces hyperinflammation to Poly IC. Similarly, Zfp750 and Tlr3 double-knockout mice dampen the cutaneous inflammatory response after UVB irradiation. We further determine that ZNF750 recruits KDM1A to repress inflammatory genes by using KDM1A ChIP-Seq and Co-immunoprecipitation. KDM1A siRNA silencing in differentiated keratinocytes also promotes a strong inflammatory response upon PolyIC stimulation and this can be rescued by simultaneously silencing with TLR3. Epidermis-specific Kdm1a mice exhibited similar phenotype as Zfp750 with a hyperinflammatory response following UVB or imiquimod treatment. Overall, we reveal that ZNF750-KDM1A axis is critical for dampening cutaneous inflammatory responses.

0642

Understanding a cutibacterium adaptation to life on humans may help identify infections.

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Over one million indwelling medical device infections occur annually in the USA. Most are due to microbes that live on humans, like Cutibacterium acnes. This microbe is the most common cause of shoulder prosthesis infection and a common cause of neurosurgical shunt infections. C. acnes infections are frequently missed and strategies to quickly identify them are needed. C. acnes secretes the protein RoxP, which might be able to be used as a biomarker to identify these infections. Cutibacteria highly conserve roxP, which is not found in any other genera. Ancestral Propionibacteriaceae acquired this gene after they adapted to human skin, and it is only present in Cutibacterium acnes, modestum, and namnetense. C. acnes requires roxP for wild-type aerobic growth and human skin colonization. Since a better understanding of this protein could improve clinical care and our understanding of host-microbe interactions on human skin, we performed an in-depth analysis of RoxP. In this study, we assessed RoxP sequence space, identified orthologs, biochemically characterized the dominant ortholog, performed in silico analysis that identified conserved molecular surfaces, evaluated conserved surface features in functional experiments, generated anti-RoxP antibodies, and developed anti-RoxP immunoassays. One of these assays is a sandwich enzyme-linked immunosorbent assay (sELISA) with sub-nanogram sensitivity that can detect RoxP in human biofluids (serum, synovial fluid, cerebrospinal fluid) and C. acnes culture media. This sELISA is a promising tool for clinicians who may be able to use it on readily-available clinical samples to rapidly identify C. acnes infections. In addition, the use of this study's findings and assays in future work will help provide new insights into C. acnes biology and Cutibacterium evolution, thereby expanding our understanding of this skin commensal and part-time opportunistic pathogen.

0643

TAK1 regulates langerhans cell homeostasis through MAPK and ER stress-activated autophagic machinery.

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Epidermal Langerhans cells (LCs) are essential for skin homeostasis and the pathogenesis of various diseases. Recent fate-mapping studies have shown that LCs originate prenatally from the yolk sac and fetal liver precursors. These cells undergo self-maintenance throughout life and regenerate from the bone marrow (BM) under stress conditions. While the role of TAK1 in cell survival is well-established, its specific function in LCs and the underlying molecular mechanisms remain unclear. In this study, we aimed to investigate the role of TAK1 in postnatal LC maintenance using $CD11c^{cre}$ mediated TAK1 deletion mice. Our results revealed a significant reduction in steady-state LC number, LC maturation (CD80, CD86, CD40) and antigen uptake function upon TAK1 deletion, highlighting the critical role of TAK1 in both LC maintenance and function. Interestingly, TAK1 deletion had no effect on BM-derived LC repopulation after UVC exposure. Furthermore, TAK1-deleted LCs exhibited increased autophagy (LC3B) and apoptosis (Annexin V), suggesting that TAK1 plays a crucial role in regulating both autophagy and cell death. Mechanistically, this autophagic response is triggered by the induction of ER stress (HSPA5, ERN1, INSIG1, PERK) and the downregulation of MAPK pathways (pP38, pERK, pJNK) and their downstream target (pP65), culminating in the upregulation of autophagy regulatory genes (Uvrag, P62) that mediate cell death. In conclusion, our data suggest that TAK1 regulates ER stress and MAPK-mediated autophagic cell death, thereby maintaining LC homeostasis and function under steady-state conditions. However, TAK1 appears dispensable for BM-derived LC repopulation under inflammatory conditions.

0644

Antiseptic treatment improves response to topical imiquimod therapy in a UVB-induced non-melanoma skin cancer murine model

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Each year, 3.3 million Americans are diagnosed with non-melanoma skin cancers (NMSC). While NMSC lesions are effectively treated surgically, many patients with multiple lesions opt for topical treatments, such as imiquimod (IMQ). These therapies are effective but frequently cause significant inflammatory side effects that result in poor treatment adherence and suboptimal clinical outcomes. Our data shows treatment of UVB-induced lesions in a murine model of NMSC with topical IMQ increases the cutaneous microbial inflammatory index, as reflected by decreased Cutibacterium:Staphylococcus ratios. We hypothesized that antimicrobial treatment decreases the side effects of topical IMQ NMSC therapy by reducing the inflammatory cutaneous microbiome. SKH1-ELITE immunocompetent hairless mice with UVB-induced NMSC were treated with oral antibiotics and daily 70% ethanol skin swabs for 2 weeks and then treated daily for 4 weeks with topical antiseptic and 5% IMQ or vehicle. Antiseptic treatment of IMQ treated mice reduced peak weight loss (3.0% vs. 6.5%) and increased the therapeutic response compared to IMQ alone (44.31% vs. 29.09% tumors decreasing in size; $p<0.0001$). Interestingly, similar trends were observed in vehicle controls. These findings highlight the potential role of the skin microbiome in regulating inflammation in the tumor microenvironment. This work provides a foundation for future research aimed at improving patient outcomes through microbiome-targeted therapies.

0645

The impact of commensal microbiota on dermal matrisome

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As the body's outermost barrier, the skin provides crucial protection against external insults. This protective function is underpinned by the dermis, which constitutes most of the skin's volume and serves as its architectural framework. While the role of commensal microbiota in maintaining skin barrier has begun to gain attention, how the microbiota influences the dermis and dermal fibroblasts remains largely unknown. Here, we demonstrate that microbiota induce distinct patterns of matrisome expression, particularly in the collagen biosynthesis pathway, within the dermis of germ-free (GF) and conventionally-raised (CR) mice. Histological and hydroxyproline analyses revealed lower collagen content and less intricate collagen organization in the dermis of GF mice. A healthy matrisome is crucial as it provides a biophysical scaffold for cell anchorage and migration, while also regulating biochemical signals for cell activation. Indeed, primary fibroblasts derived from GF mice exhibited reduced activation capacity in both transwell migration and *in vitro* wound healing assays. Notably, replacement with CR matrisome restored the activation capacity of GF fibroblasts. These findings suggest that the microbiota contribute to the structural and functional integrity of the skin by modulating dermal matrisome expression.

0646

Impact of polycyclic aromatic hydrocarbons on the skin microbiome and epidermal barrier function

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Polycyclic aromatic hydrocarbons (PAH) are environmental pollutants present in airborne particulate matter, cigarette smoke, and fire smoke. PAHs are known to activate AhR, resulting in ROS production, inflammation and DNA damage after inhalation and ingestion. Research on dermal exposure, particularly the skin microbiome, remains nascent. This study aims to investigate the effects of PAHs on the skin microbiome and to evaluate whether commensals can support epidermal barrier integrity. Human epidermal equivalents (HEEs) were colonized with individual species (S. epidermidis, S. warneri, S .haemolyticus, M. luteus, C. aurimucosum) or with a microbiota consortium of skin bacterial isolates (Flowers Flora 5), simulating a representative model of skin microbiota diversity and function. Bacterial colonization was maintained for 72h, monitored by CFU counting and Gram staining. Colonized and uncolonized HEEs were exposed topically to a multi-component PAH solution. PAH exposure did not affect bacterial growth, as CFU counts remained stable over 72 hours. In contrast, growth assays in TSB revealed a dose-dependent inhibitory effect of PAH on S. epidermidis and S. warneri, highlighting differential bacterial responses in the presence and absence of the host. PAH exposure significantly upregulated CYP1A1 and CYP1B1, indicating AhR activation, while altering key epidermal differentiation markers (KRT10, DSC1, HRNR and IVL), suggesting impaired barrier homeostasis. Notably, bacterial colonization mitigated PAH-induced barrier dysfunction, as evidenced by the restoration of KRT10 and DSC1 in colonized HEEs. Additionally, PAH exposure markedly increased IL1A and IL1B expression. However, colonization with M. luteus significantly suppressed IL-1β release, highlighting an anti-inflammatory effect of commensal bacteria. Overall, our results highlight the potential of leveraging the skin microbiome as a therapeutic target to protect the epidermal barrier from environmental pollutants such as PAH.

0647

Protective immune memory against recurrent methicillin resistant staphylococcus aureus skin infection is enhanced by vancomycin

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Staphylococcus aureus (SA) is the leading cause of skin and skin structure infection (SSSI), a primary portal of entry for invasive infection. Patients with SA SSSI have a high 1-year recurrence. We have previously shown that protective immunity in recurrent SA infection is locally targeted, and involves memory conferred by macrophages (Mf). Mfprimed by SA protected mice against SA SSSI evidenced by decreased bacterial burden in skin and distal organs. Priming potentiated Mf polarization to the proinflammatory M1 phenotype, enhanced opsonophagocytic killing of SA *in vitro*, and their adoptive transfer into naïve skin afforded protective efficacy *in vivo*. However, in the clinical setting, severe bacterial infections are rarely left untreated. The goal of this project is to determine how antibiotics impact protective immune memory to recurrent S. aureus SSSI. We hypothesized that SA exposed to vancomycin would express different antigens that may impact Mf recognition of SA and alter immune memory to future infections. To test this hypothesis, we used a mouse model of recurrent SA SSSI to prime mice with or without vancomycin (primary infection). Six weeks later, the healed mice were reinfected with SA SSSI (secondary infection) and protective immunity assessed. Macrophages isolated from vancomycin treated mice showed greater intracellular killing when challenged with SA *ex vivo*. Together, these data suggest that vancomycin treatment may provide enhanced immune efficacy against recurrent SA SSSI. These insights may provide new targets for vaccine and immunotherapeutic development against MRSA.

0648

Atypical mycobacterium arising in the setting of postscabetic pruritus

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Atypical mycobacterium infections appear to be increasing in incidence with one study demonstrating a threefold increase in incidence from 1980 to 2009. Atypical mycobacterial infections have been shown to be associated with trauma and conditions that disrupt the skin barrier such as prurigo nodularis. Postscabetic pruritus is a common occurrence after scabies treatment and may last weeks to months. This case study highlights the unusual presentation of atypical mycobacterium in a patient with postscabetic pruritus after treatment for scabies. A 54-year-old male, with a history of scabies presented with multiple erythematous papules and erosions bilaterally on his upper and lower extremities. His prior treatment for scabies included 2 courses of ivermectin and 3 courses of permethrin over the span of a year by primary care. At the time of presentation to dermatology, the patient was being treated with oral clindamycin and oral metronidazole due to persistent pruritus. Diagnostic work-up included lower extremity skin biopsies and a PCR assay. The patient was started on oral doxycycline and topical mupirocin 2% ointment mixed with Medihoney twice daily to skin ulcers. While the biopsies did not reveal mycobacteria, the PCR assay identified the presence of Mycobacterium chelonae and Mycobacterium fortuitum. Infectious disease consultation confirmed that doxycycline was effectively managing the atypical mycobacterial infection. This case underscores the importance of considering atypical mycobacterial infections in patients with postscabetic pruritus.

0649

Exploring the gut-skin axis: A comprehensive review of rosacea and its links to inflammatory bowel disease and celiac disease

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This literature review synthesizes findings from 51 peer-reviewed articles examining the relationship between rosacea and inflammatory bowel disease (IBD) and celiac disease. We aimed to identify shared pathophysiological mechanisms, clinical correlations, and potential therapeutic implications based on overlapping risk factors, inflammatory pathways, and microbiome dysregulation contributing to these conditions. Patients with rosacea exhibited significantly higher rates of IBD compared to the general population ($p<0.05$). Shared inflammatory mechanisms, including toll-like receptor activation, elevated pro-inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-17, and dysregulated gut-skin axis signaling, were consistently implicated. Celiac disease was moderately correlated with rosacea, with gluten intolerance and immune dysregulation contributing to the exacerbation of skin symptoms. Gut microbial dysbiosis, characterized by reduced microbial diversity and an overrepresentation of pathogenic species, emerged as a common factor in the systemic inflammation in rosacea, IBD, and celiac disease. These findings highlight the interconnected nature of systemic inflammation and suggest that rosacea may serve as a dermatological marker for underlying gastrointestinal disorders. Targeted therapeutic approaches, including probiotics, dietary modifications, and anti-inflammatory treatments, showed promise in alleviating symptoms in both rosacea and IBD. This review underscores the importance of a multidisciplinary approach to patient management, addressing both dermatological and systemic contributors. Future research should focus on elucidating causative mechanisms, refining gut-targeted interventions, and exploring personalized treatment strategies to improve outcomes for patients with rosacea and gastrointestinal disease.

0650

Dysregulated innate MAIT cells in patients with hidradenitis suppurativa

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Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition characterized by painful and debilitating lesions. Limited studies have examined immune dysregulation in the peripheral blood and skin lesions of HS patients. Mucosal-associated invariant T (MAIT) cells, an innate T-cell subset responsive to bacterial threats, are implicated in autoimmune diseases, cancers, and inflammatory skin disorders. This study investigates the frequency and function of MAIT cells in HS patient blood and lesions. MAIT cells enriched from peripheral blood mononuclear cells (PBMCs) were isolated from HS patients and healthy controls for sc-RNA-Seq analysis. PBMCs and single cells from HS lesions were stained for surface markers (Vα7.2, CD3, CD161, CD4, CD8, MR1 tetramers) and intracellular cytokines (IL-17, TNFα, IFNgama) after stimulation. Flow cytometry analysis showed no change in overall MAIT cell frequency but revealed a significant reduction in IFNgama+ and TNFα+ MAIT cells in peripheral blood of HS patients. Subset analysis identified an increased frequency of CD4+ MAIT cells and a decreased frequency of CD4− MAIT cells in the periphery, with reduced CD4− IFNgama+ and TNFα+ MAIT cells. Additionally, HS lesions showed increased CD4+ MAIT cells and elevated CCL20 and CCL22 expression. These findings suggest that peripheral MAIT cells in HS patients are dysregulated, potentially migrating to skin lesions and contributing to disease pathogenesis.

0651

Gut-skin dysbiosis as a contributory factor in the comorbidity of atopic dermatitis and hidradenitis suppurativa: A systematic review of shared pathways

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Atopic dermatitis (AD) and hidradenitis suppurativa (HS) are chronic inflammatory skin conditions. Recent evidence suggests that gut-skin microbiome dysbiosis may contribute to their development and comorbidity.[1,2] This review examines the role of gut-skin dysbiosis in AD and HS pathogenesis, focusing on immune dysregulation, barrier impairment, metabolic alterations, and systemic inflammation. A literature search on gut microbiome alterations in AD, HS, or their comorbidity was conducted with a focus on microbial composition, inflammatory markers, and proposed mechanisms. Several shared pathways linking gut dysbiosis to AD and HS comorbidity were identified. In both conditions, immune dysregulation with elevated levels of pro-inflammatory cytokines and altered T-cell responses was reported.[3,4] Impaired barrier function due to increased intestinal permeability was found to exacerbate skin inflammation and immune response.[5] Reduced short-chain fatty acid production was also associated with systemic inflammatory response.[6] Inflammatory pathways, including enhanced NF-κB signaling and increased TNF-α expression, were influenced by gut dysbiosis.[7] Microbial shifts were noted, including decreased levels of beneficial Lactobacillus species and increased levels of potentially harmful bacteria.[3,6] Studies have shown that patients with HS have a higher risk of developing inflammatory skin conditions, including AD.[4] Immunomodulatory analysis revealed that HS exhibits increased expression of TH1,2,17 signatures with no prevalent TH signatures, unlike psoriasis (TH1 and17) and AD (TH2).[4] Gut-skin dysbiosis may play a key role in the comorbidity of AD and HS through multiple shared pathways, offering insights into potential therapeutic targets, like prebiotics, probiotics, and microbiome-based therapies.[5,7,8]

0652

The emerging fungal pathogen Candida auris induces IFNγ to colonize mammalian hair follicles

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Public health alarm concerning the worldwide emergence of the fungus Candida auris has been fueled by its high frequency of antifungal drug resistance, including pan-resistance, and its propensity to cause deadly outbreaks. Persistent skin colonization drives transmission and lethal sepsis although its basis remains mysterious. Using a skin colonization model in mice, we compared the behaviors of C. auris and its commensal relative C. albicans. We quantified skin fungal replication/survival and distribution, immune composition, and immune cell positioning. C. auris displays a considerably higher propensity to colonize hair follicles and avidly binds to human hair. While C. albicans triggers an effective sterilizing type 3/17 antifungal immune response driven by IL-17A/F-producing lymphocytes, C. auris triggers a type 1 immune response, including expansion of IFNγ-producing lymphocytes around hair follicles. Rather than promoting fungal clearance, IFNγ promotes C. auris skin colonization by acting directly on keratinocytes. Induced IFNγ impairs epithelial barrier integrity and represses antifungal defense programs in hair follicle keratinocytes. Our data reveal that C. auris exploits focal skin immune responses to create a niche for persistence in hair follicles.

0653
WITHDRAWN

0654
Characterizing racial demographics in mycosis fungoides/sezary syndrome clinical trials

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This study aims to characterize the racial demographics of mycosis fungoides/Sezary syndrome (MF/SS) clinical trials compared to United States (US) census data and explore racial disparities and potential barriers to enrollment. We searched the terms "Mycosis Fungoides/Sezary Syndrome," "Mycosis Fungoides," "Sezary syndrome," "CTCL" and "Cutaneous T-Cell Lymphoma" on clinicaltrials.gov. Interventional trials that were completed with results posted and had at least one trial location within the US were included. Of 316 trials initially identified, 27 trials met the inclusion criteria. A total of 1483 patients were characterized, 154 (10%) of which identified as African American (AA)/Black. Compared to population data from the 2023 US Census, AA/Black patients were significantly underrepresented ($p < 0.001$) in MF/SS clinical trials overall despite 69% of the trial sites occurring in areas with moderate (12.6-49.9%) to high (≥50%) AA/Black populations. Interestingly, substratification revealed that AA/Black patients were significantly overrepresented in phase I clinical trials ($p = 0.013$) and underrepresented in phase III clinical trials ($p < 0.001$). This is consistent with trends previously reported in the literature regarding clinical trials at large: AA/Black patients are more likely to be included in early-phase clinical trials evaluating safety yet excluded from later-phase clinical trials evaluating efficacy. The findings of this study reveal significant racial disparities in MF/SS clinical trial enrollment. Identifying these disparities and investigating barriers to enrollment ensures that MF/SS patients of all racial backgrounds are appropriately represented at each phase of the experimental process.

0655
Limitations of crowdsourced fitzpatrick skin type labeling for dermoscopic images

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Imbalanced skin tone representation in training data may equate to performance disparities among artificial intelligence (AI) skin lesion classifiers. Evaluating the extent of bias is challenging because benchmark datasets often lack skin tone labels. In a prospective, single-center study, we assessed the feasibility of using crowdsourcing to retrospectively assign Fitzpatrick Skin Type (FST) classifications to dermoscopy images. FST was determined by patient-reported photosensitivity during office visits. Dermoscopic images of up to 13 skin lesions per patient were collected using four dermoscopy modes (polarized/nonpolarized & contact/non-contact). Crowdsourced FST annotations were obtained through the DiagnosUS mobile app. Chi-squared and adjusted residual (AR) analyses (threshold ±1.96) were performed. The study included 41 patients, inclusive of all FSTs (I-VI), 361 lesions, and 1,377 images. A total of 210 raters generated 12,470 qualified reads. Overall accuracy was 46.3%, with 31.2% of crowdsourced labels being one FST category away from in-office assessment. Accuracy was highest for FST VI (66.0%) and I (65.0%) but lowest for FST IV (33.6%) and III (33.8%) ($p<0.001$). Non-polarized non-contact images were associated with a tendency toward higher FST labels (AR: +3.9). Sun-exposed regions (dorsal forearm: +2.0) tended to be labeled higher, while non-exposed areas (chest: +3.0, lower back: +2.2) tended to be labeled lower. Overall, there are substantial limitations to retrospective FST labeling using dermoscopic images. Although FST is widely used as a proxy for skin tone, photosensitivity does not always correlate with skin color. Dermoscopic image processing alters coloration, significantly influencing perceived FST. Skin tone also differs by body site due to variable pigment and sun exposure. Validation of alternative skin tone scales and consideration of lighting and body site are needed to improve image-based labeling of skin tone for AI training data sets.

0656
Readmissions and disposition at discharge among persons experiencing homelessness with a dermatologic hospitalization

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Persons experiencing homelessness (PEH) face higher readmission rates, which may be influenced by patient-directed discharges that stem from competing life priorities or healthcare experiences of stigma and discrimination. We sought to examine if discharge patterns among PEH with dermatologic admissions are related to readmissions. This cross-sectional study used the Healthcare Cost and Utilization Project State Inpatient Databases for Florida, Massachusetts, and New York (2014–15) to identify PEH ≥ 18 years hospitalized with a primary dermatologic diagnosis. We developed multi-level mixed effect models where the binary outcome was 30-day all-cause readmission, primary exposure was discharge disposition, and confounders were age, sex, race-ethnicity, Elixhauser comorbidity index (includes mental illness and substance use disorders), insurance status; state as a random effect. Among 2,957 PEH hospitalized for a primary dermatologic diagnosis, the most common causes for admission were skin and soft tissue infection (77.5%), ulcers (8.2%), and venous stasis/lymphedema (4.7%). 20.0% (592) were readmitted within 30 days, with 30.2% (179) having a primary dermatologic diagnosis at readmission. Readmitted patients were older and a greater proportion were male, White, uninsured, and had mental illness ($p<0.01$). Patients with patient-directed discharges were more than twice as likely to be readmitted compared to routine discharges (aOR 2.4, 95% CI 1.8–3.2). Patient-directed discharges showed the highest readmission probability (31%, 95% CI 21.9–41.8), followed by discharge to home health care (24%, 95% CI 16.2–33.9), skilled nursing facility or intermediate care facility (18.7%, 95% CI 12.4–27.2), and routinely (15.7%, 95% CI 11.0–22.0). Addressing factors motivating patient-directed discharges, such as stigma, unmet medical needs, or competing priorities, may help reduce early discharges or convert a patient-directed discharge to routine discharge, enabling time for more robust discharge planning during dermatologic hospitalizations among PEH.

0657

Language-associated disparities in skin biopsy rates

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Language barriers are a recognized obstacle to equitable healthcare, but their role in skin biopsy access and the effectiveness of current phone interpretation services in dermatology remains unclear. This study the effect of language barriers on skin biopsy utilization and evaluates whether phone interpretation services are effective in mitigating these barriers. This retrospective cohort study of 25629 English-speaking and 5019 non-English-speaking patients at Tufts Dermatology between December 2022 and December 2024 compared biopsy rates between English-speaking and non-English-speaking patients. Pairwise comparisons of biopsy rates among non-English-speaking subgroups, including Cantonese, Mandarin, Spanish, Toishanese, Portuguese, Russian, and Vietnamese patients were also conducted. Statistical analysis was performed using R version 4.4.1. A greater proportion of English-speaking patients (9.99%, 2560/25629) received a skin biopsy, compared to non-English-speaking patients (7.83%, 393/5019) ($p<0.001$), with English-speaking patients 1.31x more likely to receive a skin biopsy (Fisher's exact test, $p<0.001$). Among non-English-speaking groups, biopsy rates did not differ (pairwise test of proportions with Holm–Bonferroni correction). There were no disparities in the distribution of languages spoken among those receiving a biopsy for dermatitis, the most common reason for biopsy in this sample ($p=1$). The higher biopsy rate in English-speaking patients may reflect the increased malignancy risk among White patients, most of whom speak English. Notably, the lack of biopsy rate differences between non-English-speaking subgroups and the representative distribution of languages for dermatitis biopsies suggests equitable care across different language-speaking groups. These encouraging findings highlight the effectiveness of on-demand audio interpreter services and suggest that integrating phone interpreter services could help reduce language barriers, ensuring better access to essential diagnostic care.

0658

Cutaneous chronic graft-versus-host disease in skin of color most often presents as lichen planus and dyspigmentation

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Chronic graft-versus-host disease (cGVHD) is a multisystem complication of allogeneic hematopoietic cell transplant (HCT) leading to significant morbidity and mortality. While 80% of cGVHD patients exhibit cutaneous involvement, less than 33% of HCT recipients self-identify as non-white and cutaneous cGVHD in skin of color (SOC) is underexplored. We characterized the clinical features of cutaneous cGVHD in SOC according to 2014 NIH Consensus Criteria. This retrospective study analyzed SOC allogeneic HCT patients (Black/African American, Asian, Hispanic, and/or American Indian/Alaskan Native [AI/AN]) treated at the University of Pennsylvania between 2014-2024. Of 138 SOC patients receiving allogeneic HCT, 25 (18%) had cutaneous cGVHD (11 (44%) Black/African American, 8 (32%) Asian, 3 (12%) Hispanic, 2 (8%) AI/AN, and 1 (4%) Asian-Hispanic). The mean (SD) age at HCT was 46.2 (11.8) years, with cutaneous cGVHD developing mean (SD) 313.0 (169.7) days post-transplant. Biopsy confirmed cutaneous cGVHD in 10 (40%) cases. At diagnosis, 19 (76%) had non-sclerotic cGVHD, while sclerotic (4 [16%]) and combined (2 [8%]) presentations were less common. 16 (64%) patients were classified as having dyspigmentation at the initial cGVHD visit. 23 distinct clinical features were identified at initial or subsequent visits including 22 (88%) hyperpigmentation, 17 (68%) lichen planus, 16 (64%) pruritus, 12 (48%) erythema, 9 (36%) hypopigmentation, and 8 (32%) sclerosis. Like non-SOC populations, lichen planus was the most common diagnostic clinical feature; however, dyspigmentation was the most common overall feature of cutaneous cGVHD in SOC. These findings underscore the importance of differentiating post-inflammatory pigmentary changes from active disease for accurate diagnosis, grading, and management of cutaneous cGVHD in SOC populations.

0659

Improving dermatologic access in shelters: Results from a teledermatology pilot program

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Unhoused populations often lack access to specialized care, including dermatologic services. Partnerships between dermatologists and free clinics may improve access to care for this underserved population. We evaluated the use and outcomes of a teledermatology program designed to expand access to dermatologic care for individuals experiencing homelessness. A student-run dermatologic clinic partnered with general medicine clinics at two shelters to establish a teledermatology referral program. Healthcare providers were instructed to submit a photo with a brief description for each patient case in which they were requesting guidance. Dermatologists had a 72-hour window to respond, with two medical students serving as liaisons to ensure closed-loop communication. Six teledermatology cases were received from March to August 2024. The median age was 49 years, with 67% male and 33% female. All patients were uninsured; 66% preferred English, and 33% preferred Spanish. The median number of prior general medicine visits for dermatologic concerns was 2. The median turnaround time for consults was 0.5 days (IQR 0-1). Reasons for consult were rash (50%) and moles (50%). Diagnoses included bed bugs, nummular eczema, intertrigo, atypical nevus, congenital nevus, and possible basal cell carcinoma. Topical corticosteroids and antifungals were frequently prescribed for rashes, and two patients with mole concerns were referred for in-person dermatology visits; one followed up and was biopsied and diagnosed with a poroid hidradenoma. The pilot teledermatology program was efficient, with most cases addressed within 24 hours. Future improvements include ensuring follow-up for patients with lesions concerning for skin cancer. * HC and AN contributed equally as co-first authors.

0660

Skin cancer incidence and risk in transgender Medicare beneficiaries

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Studies suggest gender minority populations, including transgender individuals, may have increased skin cancer risk due to health disparities and environmental factors. However, less is known about skin cancer epidemiology in this group compared to the general population. We characterized skin cancer incidence and risk in transgender patients using a de-identified, random sample of 4,999,999 Medicare beneficiaries (2009-2018). We used a validated method for identifying transgender patients in claims data using combinations of gender identity disorder and endocrine disorder not otherwise specified diagnosis codes, gender-affirming surgery, and hormone therapy. Our control cohort included cisgender patients matched 8:1 (4 females, 4 males) to transgender patients on age/year at the start of follow-up and race/ethnicity. We calculated age-adjusted incidence rates of skin cancer (basal cell carcinoma, squamous cell carcinoma, and melanoma), identified using diagnosis and procedural treatment codes. To evaluate skin cancer risk we used a Fine-Gray subdistribution hazard model (death as a competing risk) with covariates of age, year at the start of follow-up, race/ethnicity, prior skin cancer and actinic keratosis history, and prior dermatology visits. We identified 1,839 transgender patients. Age-adjusted skin cancer incidence per 100,000 person-years was 18,952 in transgender patients (95% CI 17,510-20,394), 7,351 in cisgender females (95% CI 6,450-7,751), and 17,965 in cisgender males (95% CI 17,329-18,601). Incidence rate ratios of skin cancer in transgender patients were 2.58 [95% CI 2.51-2.65] vs cisgender females and 1.05 [95% CI 1.03-1.08] vs cisgender males. Hazard ratios of skin cancer risk in transgender patients were 1.18 (95% CI 0.98-1.42, $p=0.09$) vs cisgender females and 0.70 (95% CI 0.73-1.03, $p<0.0001$) vs cisgender males. Understanding skin cancer epidemiology in transgender patients is essential to advancing inclusive dermatologic care.

0661

Cutaneous manifestations of atypical mycobacterium chelonae: A case report

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Patient history: A 39 year old Native Hawaiian man was admitted to inpatient care for multiple cutaneous nodules and ulcers of the face and all extremities and gangrene of the toes. His medical history included congestive heart failure (CHF) from nonischemic congenital cardiomyopathy, ventricular tachycardia with an implantable defibrillator. Biopsies: Punch biopsy of a nodule on the right forearm showed positive acid-fast bacilli (AFB) in a pan-dermal, granulomatous and focally neutrophilic infiltrate. Laboratory Data: PCR results did not return until 48 days after collection due to delayed processing. PCR of the right forearm sample demonstrated Mycobacterium chelonae, abscessus group. Diagnosis: Although he was initially suspected to have cutaneous dissemination related to a Staphylococcus Aureus from his implanted defibrillator, the patient was found to have disseminated Mycobacterium chelonae infection, which rarely affects humans. Here, it manifested in a diverse presentation of cutaneous nodules and papular abscesses. This appears to be increasingly prevalent in the last decade. Treatment: The causative organism was not easily identifiable and the patient was initially treated for bacterial sepsis. Initial treatment included prednisone 20 mg BID resulted in significant immunosuppression. Treatment for suspected Staphylococcus aureus sepsis included multiple courses of antibiotics for vancomycin, ceftriaxone, daptomycin, tigecycline, linezolid, imipenem and amikacin. Because tissue culture and PCR confirmation took several weeks, there was delayed identification and treatment of M. chelonae. Although the nodules began to respond to appropriate treatment with minocycline, azithromycin and tigecycline the patient's condition was compromised by CHF and he expired. The state of Hawaii as well as the field of dermatology are both experiencing physician shortages, which has led to poor dermatologic access in the region [1]. This demonstrates multiple cutaneous manifestations of systemic AFB infection.

0662

Rare coexistence of sarcoidosis and atopic dermatitis in an African american female

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We present a rare case of overlapping cutaneous sarcoidosis and AD in an AA female successfully treated with upadacitinib. Sarcoidosis, a chronic inflammatory disorder affecting multiple systems, disproportionately impacts African Americans (AA), who experience more severe disease, higher hospitalization rates, and worse outcomes. Similarly, atopic dermatitis (AD)—a chronic inflammatory skin condition characterized by pruritic and painful lesions—disproportionately affects AA and Latinx patients, contributing to greater disease burden. A 58-year-old AA female with a history of childhood AD, pulmonary sarcoidosis, and hypertension presented with a six-month history of severely pruritic, erythematous, and scaly patches, papules, and plaques. The lesions predominantly involved her scalp, hairline, and eyelids (pruritus NRS 9/10). Previous treatment with topical steroids and tacrolimus failed, and prednisone provided only temporary relief. Shave biopsies from the postauricular hairline and neck revealed overlapping features of spongiotic and granulomatous dermatitis. Routine lab tests were unremarkable. The patient was started on upadacitinib 15 mg daily with excellent tolerance. Upon one-month follow-up, she reported nearly complete resolution of erythema, scaling, and pruritus (pruritus NRS 1/10). The coexistence of cutaneous sarcoidosis and AD is exceedingly rare and undocumented in the literature. It is unclear whether these conditions share a common immune dysregulation or are independent, but both contribute to higher disease burdens in AA patients. Upadacitinib's success in this case highlights its potential in treating complex inflammatory conditions. As a selective JAK inhibitor, it targets immune pathways implicated in both sarcoidosis, driven by type 1 helper T-cells, and AD, induced by type 2 helper T-cells. This case underscores the versatility of JAK inhibitors in managing complex immune-mediated diseases and highlights the importance of personalized therapies for conditions disproportionately affecting minority populations.

0663

Whiteboard-based video provides hispanic patients with melanoma knowledge and retention at 3-month follow-up

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While Caucasians have the highest incidence of melanoma, Hispanics present with higher stage melanoma and have worse survival. Therefore, we aimed to create a whiteboard-based bilingual melanoma educational video and evaluate melanoma knowledge retention at 3 months post-education. Hispanic or Latino individuals identified through Mayo Data Explorer were emailed a link to a five-and-a-half-minute video on melanoma, including risk factors, self-skin examinations, and sun-protective behaviors. The email response rate was 2.2%, and the survey completion rate was 69.6%. Of 1,274 individuals who completed the baseline survey, 813 (63.8%) completed the 3-month follow-up survey. Improvements were seen in melanoma knowledge score between pre-intervention and directly after the intervention (9.50 vs 12.17, $p<0.001$) and at three-month follow-up (9.50 vs 11.28, $p<0.001$). However, there was a decrease in knowledge from directly post-intervention to 3 months post-intervention (12.17 vs. 11.28, $p<0.001$). Improvements were also seen in sun-protective behaviors, including confidence in performing self-skin examinations, wearing protective clothing when outside, and wearing sunscreen when outside at post-intervention and three-month follow-up compared to baseline ($p<0.001$). To the best of our knowledge, this is the largest whiteboard-based bilingual melanoma education developed and shown to improve melanoma knowledge and behaviors in Hispanic patients. Patients were more likely to report wearing sunscreen and sun-protective clothing when outside and conducting self-skin examinations after the intervention. However, these behaviors decreased at three months compared to directly after the intervention, suggesting that ongoing education may be necessary to impact melanoma outcomes long-term.

0664

A decade of hair prosthetic injuries: A review of U.S. emergency department cases (2013-2022)

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Emergency departments (EDs) are often the first point of care for many patients. With rising hair prosthetic injuries, EDs face a growing role in managing these cases and coordinating with dermatology. Given the diverse cultural practices surrounding hair prosthetic use, examining demographics, clinical presentations, and outcomes of these injuries may help promote health equity in the ED. The National Electronic Injury Surveillance System (NEISS) database, representing ~100 EDs, was queried using a keyword search of "wig", "hairpiece", "toupe", "toupee", including plural forms. T-tests evaluated gender and age differences ($P<0.05$). Among 88 hair prosthetic-related injury cases (mean age 34, range 2–84), 53.4% were Black, 10.2% White, and 94.1% female. Cases increased by 56.3% from 2013 to 2022, rising from 7 to 16. The most common diagnoses included dermatitis, lacerations, and contusions. Race documentation was significantly less frequent in patients aged 35+ compared to younger patients (46.3% vs. 25.5%, $P=0.04$). Common diagnoses included dermatitis, lacerations, and contusions. The most frequently injured areas were the head, eyes, and ears, with women experiencing significantly more ear injuries, lacerations, and pain than men (7.2% vs. 0.0%, $P=0.01$; 16.9% vs. 0.0%, $P<0.001$; 6.0% vs. 0.0%, $P=0.02$). Ultimately, hair prosthetic injuries are rising in the US, with Black women representing 53.4% of cases. Expanding culturally competent education on safe prosthetic use is crucial, given the cultural significance and symbolism of hair for women of color. Discrimination and inadequate training may worsen outcomes for this group. Advocacy areas include wig testing, allergy prevention, safe removal practices, and scalp protection measures.

0665

Health care system factors negatively impact Latine patients with hidradenitis suppurativa

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Latine patients with hidradenitis suppurativa (HS) face more severe disease and delayed diagnosis compared to White patients. To identify modifiable factors impacting care, we conducted a multi-method study with English- and Spanish-preferring Latine adults diagnosed with HS by dermatologists. We recruited participants from 2 academic and 2 county hospitals in California. Bilingual Latine team members administered validated measures of acculturation (higher scores nearing 5) and discrimination in medical settings (5-point Likert scale responses to 7 scenarios; experience of discrimination defined as ≥1 response of Sometimes, Most of the time, or Always to ≥1 scenario), conducted semi-structured interviews, and coded transcripts. We used thematic analysis of transcripts to develop themes. We used acculturation and discrimination scales to describe the study population. Among 18 participants, median (IQR) age was 37 (30-44) years, 11 (61%) were female, 5 (28%) were Spanish-preferring, and 15 (83%) had Hurley Stage II or III disease. Participants were mostly bicultural with a median (IQR) acculturation score of 3.4 (3-3.8). 7 (39%) participants experienced discrimination in medical settings for HS care. We developed 5 preliminary themes reflecting challenges in HS care and management due to health care system factors: (1) perceived discrimination leads to delays in seeking care, (2) feeling blamed and unheard by clinicians causes patients to avoid care, (3) absence of clinician recommendations for pain control prompts self-management, (4) inconsistent access to wound care expertise and supplies results in self-directed care, (5) burden of HS management undermines patients' ability to remain in the workforce. Health care system-level interventions are needed to enhance clinician-patient communication, prioritize unmet pain and wound care needs, and streamline processes to implement care plans.

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Global trends in malignant melanoma prevalence: The impact of income and resource access

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Malignant melanoma exhibits variations in prevalence across global regions and income levels. A comprehensive review of global trends in the disease remains uncommon. Prior work has focused on the incidence of malignant melanoma, especially in the United States, but analyzing prevalence allows us to examine the current burden of disease and evaluate its long-term impact. Using the Global Burden of Disease Study carried out by the Institute for Health Metrics and Evaluation at the University of Washington, data on the prevalence of malignant melanoma across 204 countries and territories as well as from the years 2017 to 2021 was gathered. Classifications were created by the World Bank to group these areas into four tiers by income: low, lower-middle, upper-middle, and high. To determine if there is an overall difference in melanoma prevalence by global income level, a One-Way Analysis of Variance was performed on the data binned into 4 categories, and tested two-sided, two-sample t-tests. There is a statistically significant difference ($p<2e-16$) generally in prevalence for different amounts of global wealth. Looking at pairwise differences, there is a clear, statistically significant monotonic trend: low income regions have a lower prevalence than lower-middle ($p=1.03e-06$), lower-middle lower than upper-middle ($p=1.89e-06$), and upper-middle lower than high ($p=5.41e-09$). The fact that melanoma prevalence increases consistently with income level suggests that individuals from these backgrounds are more likely to be exposed to risk factors such as sun exposure, frequent use of tanning beds, outdoor activities, and may have greater dermatological health resources. This clear trend provides a global perspective, emphasizing the need to cater to low-income regions where melanoma detection and care may be less accessible, and justifies future prevention and intervention strategies to tackle these disparities.

0667

Analyzing global differences in acne vulgaris incidence across Africa and the Middle East

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Acne vulgaris remains a common dermatological condition, but its geographic variation across Africa and the Middle East has not been extensively studied. Data on yearly acne vulgaris incidence rates for 66 countries in Africa and the nearby Middle East from 2017 to 2021 was obtained. These metrics were taken from the Institute for Health Metrics and Evaluation at the University of Washington. These countries were grouped into five geographical regions guided by World Health Organizations designations: "North Africa and Middle East", "Central Sub-Saharan Africa", "Western Sub-Saharan Africa", "Eastern Sub-Saharan Africa", and "Southern Sub-Saharan Africa". To ascertain whether there were overall differences in acne vulgaris incidence rates across regions, a One-Way Analysis of Variance was performed, which yielded statistically significant results ($p<2e-16$). Next, a post-hoc pairwise comparison to determine which pairs of regions are likely to experience differences in rates was conducted. Since a total of 10 pairwise comparisons were performed, potentially leading to extremely high probability of making at least one Type I error, a Bonferonni correction was included to maintain the overall error rate at 5%. EEastern Sub-Saharan Africa has significantly higher acne vulgaris incidence compared to North Africa ($p=2.0e-14$) as well as Central ($p=1.3e-08$), Western ($p=4.2e-15$), and Southern ($p=1.7e-13$) Sub-Saharan Africa. However, the other four regions do not seem to have statistically significant differences between them. These findings highlight a notable regional disparity in acne incidence within Africa and the Middle East, warranting further studies into potential environmental, genetic, and socio-economic contributors to this variation. Managing acne vulgaris remains challenging, requiring more targeted interventions to reduce its burden and the health equity gap in less resourced regions.

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Advantages of teledermatology for incarcerated patients: A scoping review

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To address the unique challenges and increasing costs of providing care to incarcerated patients, this scoping review aims to synthesize the documented advantages of utilizing teledermatology in prisons. Article databases were searched for studies on teledermatology for incarcerated populations, following PRISMA guidelines. 43 studies were screened, of which 10 met eligibility criteria. 2417 patient records were evaluated in these studies. Dermatology was the most frequently requested speciality in telemedicines at 50-54% (n=350). Medical transport costs ranged from $700-1000 per day from 1995-1997, an expenditure that has since increased substantially. In one study, telemedicine reduced visit costs to $70 (n=400). Additionally, 84-86.3% (n=387) of patients were successfully managed without requiring an in-person visit and incurring transport costs. 86.7% (n=352) of teledermatology patients had improved by their second visit, and 62.6% (n=254) required only one consultation. Diagnostic accuracy improved with teledermatology as referral/request forms from primary care providers matched post-teledermatology diagnosis in only 57.1% (n=200) of cases. Of the conditions treated, eczematous disorders and infections/infestations were the most frequent diagnoses at 9.3-39% (n=333) and 5.1-42.8% (n=265) respectively. While the current literature on teledermatology in prisons is limited, there appears to be demand and potential benefit for this form of care. Efficacy without the need for in-person intervention, improved diagnostic accuracy, and considerable cost reduction documented in these studies should be further investigated in future studies.

0669

A day in the life of a dermatologist: A guided experiential learning workshop as a modulator of medical career self efficacy among community college premedical students

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Equitable representation in medicine is important, yet dermatology remains one of the least diverse fields. The community college to medicine pathway can help bridge this gap. Using participatory design methods, we piloted a two-hour workshop for community college premedical students modeled after a dermatology encounter. Participants explored five medical careers, learned the ABCDE's of melanoma, and learned biopsy, suturing, and knot tying skills. A convergent parallel mixed methods approach, using pre-/post-surveys and semi-structured interviews, was adopted. Qualitative data was analyzed using a grounded theory approach, with open, axial, and selective coding. 28 students attended 4 workshop sessions. 22 completed pre- and post-surveys and 8 participated in post-workshop interviews. 77% of participants identified as female and 73% as Hispanic. 69% were employed, and 36% reported annual household income below $35,000. Pre-workshop surveys revealed high interest in the five medical careers explored, but low knowledge of their educational paths and low likelihood of pursuing them. 8 participants (29%) had low baseline medical career self-efficacy. Post-workshop surveys showed increased knowledge of educational paths and higher likelihood of pursuing a medical career among all participants, and an increase in medical career self-efficacy among low baseline participants. Qualitative data elucidated four themes: 1) an unmet need for medical extracurricular opportunities, 2) scaffolded learning and individualized guidance as workshop strengths, 3) systemic barriers such as financial constraints and inequitable MCAT accommodations as obstacles, and 4) a change in participants' perceptions of dermatology from a cosmetic field to a medical career that treats skin cancer and other medical skin conditions. Four-year universities can strengthen the pathways to medicine for minoritized groups by partnering with community colleges to allow students to experientially explore a career in medicine.

0670

Acanthosis nigricans in transmasculine patients is associated with cardiometabolic comorbidities and race/ethnicity, but not exogenous testosterone

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Acanthosis nigricans (AN) is a highly visible skin condition associated with metabolic disease and case reports of testosterone (T) usage in men. Transgender patients using T are a growing population, and some transmasculine patients have delayed T usage due to concern for AN, but systematic data on AN in this population is scarce. Here, we assess the factors that associate with AN in transmasculine patients. After IRB approval, we performed a retrospective chart review utilizing the Stanford Research Repository from 2016-2023. Search terms for transmasculine patients were applied with inclusion criteria of age >8 years and older. Exclusions: patients who did not identify as transmasculine per manual chart review. Our analysis cohort consisted of 945 transmasculine patients, with 623 patients on T for ≥2 months (median duration 4.0 years, IQR 2.3-6.5 years). Overall, AN prevalence was 4.6%. Univariate analysis showed AN was positively associated with metabolic syndrome (OR [95% CI]: 25.5 [8.8-73.1]), obesity (18.3 [9.4-37.1]), Native American race (11.2 [3.0-41.9]), type 2 diabetes (9.6 [3.6-24.3]), prediabetes (8.9 [3.7-20.0]), Black race (5.0 [1.8-14.3]), hypertension (4.8 [2.1-10.5]), Hispanic ethnicity (4.5 [2.4-8.3]), and hyperlipidemia (2.3 [1.2-4.6]). Multivariate logistic regression showed that AN associated with metabolic syndrome (5.5 [1.4-22.9]), obesity (10.6 [4.9-23.4]), prediabetes (3.9 [1.3-11.2]), hypertension (3.7 [1.2-10.0]), and Hispanic ethnicity (2.4 [1.1-5.2]). T usage was not associated with AN in transmasculine patients (0.8 [0.4-1.4]) despite >99% power to identify an association between AN and T. Our data suggests that in transmasculine patients, AN is associated with cardiometabolic comorbidities and race/ethnicity, but not exogenous T. Future multicenter, prospective confirmatory studies are needed.

0671

The critical role of early diagnosis, multidisciplinary management, and social determinants in severe eczema herpeticum: a case study of a 24-year-old man

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A 24-year-old male, with a history of atopic dermatitis previously well controlled with dupilumab, presented to the emergency department with a four-week history of painful, pruritic skin vesicles and erosions, which had progressed to crusted plaques affecting his face, neck, chest, arms, and thighs. The patient was homeless, and due to financial constraints had discontinued his dupilumab and topical treatments. Three days prior to symptom onset, the patient had been cleaning rat feces beneath his place of shelter. He had been seen in the emergency department twice prior to this visit, with no definitive diagnosis made. On his third presentation, the patient was febrile with a temperature of 39.2°C, and had a leukocyte count of 14,000 cells/µL. Eczema herpeticum was suspected and he was started on empiric acyclovir 5mg/kg IV every 8 hours. A viral swab with polymerase chain reaction revealed the presence of herpes simplex virus 1, confirming the diagnosis, while a bacterial skin swab identified Pseudomonas aeruginosa and Staphylococcus aureus. Due to periocular impetiginization, ophthalmology was consulted, and mupirocin ointment was applied twice daily to the face. Symptomatic management included cool compresses, emollients, and topical corticosteroids. Within five days, the patient showed clinical improvement, was transitioned to oral valacyclovir, and connected to multidisciplinary outpatient services for continuity after discharge. This case highlights the importance of early recognition and prompt treatment of eczema herpeticum, particularly in the context of social determinants of health, such as homelessness and financial hardship, which contribute to gaps in healthcare access and exacerbate disease burden. Disclaimer: This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

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Evaluation of skin barrier biomarkers in diverse patients with xerosis and atopic dermatitis

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Though patients of color experience higher Atopic Dermatitis (AD) incidence, they show less frequent filaggrin (FLG) loss-of-functions mutations compared to white counterparts, indicating another plausible mechanism contributing to disease prevalence. Deficiency in Natural moisturizing factors (NMF), water-retaining molecules in the stratum corneum, have been found in xerosis, plus are associated with FLG loss-of-functions mutations in AD patients. Given the variations of AD across racial/ethnic groups, here we investigated skin barrier properties of diverse patients with AD & Xerosis in a monocenter single-blinded study. 40 subjects from diverse racial/ethnic backgrounds, aged 3-80 years old and presenting with mild-AD or severe xerosis completed study. After dermatological evaluations, all subjects started using a cleanser and moisturizer skincare regimen for 10 weeks. Evaluations of patients' legs included NMF analysis, corneocyte assessment using scanning electron microscopy, clinical grading and instrumentation at week 0 and 10. Following 10 weeks of skincare regimen, all patients showed significant reduction in severity, increased skin hydration and decreased pH levels on both normal and lesional skin. Tape-stripping analyses of xerosis and AD corneocytes demonstrated significant higher surface isotropy and increased NMF levels following skincare regimen, indicating improvement of skin barrier integrity. Interestingly, sub-analyses comparisons between racial/ethnic groups revealed that xerosis patients of color consistently showed significant lower NMF basal levels compared to white counterparts. Lower NMF levels were also observed only on normal skin of AD patients of color. In summary, our findings suggest that a skincare regimen can effectively decrease AD and xerosis severity and improve symptoms by restoring skin barrier integrity in diverse ethnically patients. Lower NMF levels in patients of color first identified in our study may contribute to racial/ethnic variations in skin-barrier compromised conditions prevalence.

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Barriers to clinical trial access among Black lupus patients

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The purpose of this study was to uncover the most prominent barriers affecting clinical trial access among Black lupus patients in the Philadelphia area. Although Black patients comprise 41% of estimated lupus patients in the US, they make up only 14% of clinical trial enrollees. UPenn has partnered with Lupus Therapeutics in Project CHANGE, a community-based research approach that aims to address challenges that Black lupus patients encounter when accessing clinical trials. We assessed trial access barriers using a REDCap survey accessed via link or QR code. Questions assessed trial knowledge, interest in joining a trial, and barriers affecting participation. Key barriers assessed were transportation difficulties, issues with work leave, distrust, and lack of knowledge. Free response sections evaluated the presence of other barriers and how trial access could be improved. Unique survey QR codes tracked which environments participants were engaging in the survey including social media, community events, support groups, and clinics. 51 patients were included with 30 from clinic, 15 from community events, 5 from support groups, and 1 from social media. 33% had a small interest in joining a trial, 22% were very interested in joining a trial, 22% were unsure due to lack of knowledge, and 8% were not interested at all. For the biggest barrier to joining a trial, 39% said lack of knowledge, 24% said travel difficulties, 16% said no issue, 10% said issues with work leave, and 4% said distrust. 53% had never been approached about a trial before and 78% felt comfortable speaking to their doctor about trials. In free response sections, participants expressed concerns around placebo medications and suggested improvements in transparency, awareness, and financial assistance. Though barriers to trial access are multi-factorial, targeting education and transportation may be helpful in future endeavors to increase trial participation of Black lupus patients in the future.

0674

Neighborhood-level area deprivation influences disease phenotype in adult-onset dermatomyositis

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The impact of neighborhood-level social determinants of health on disease characteristics in adult-onset dermatomyositis (DM) remains unexplored. In this study, we used the area deprivation index (ADI) to identify associations between neighborhood-level disadvantage and cutaneous and extracutaneous DM characteristics. We retrospectively reviewed the medical records of Maryland residents with adult-onset DM who were evaluated by dermatologists at Johns Hopkins Hospital between 2011 and 2024. Data collected included demographic information, smoking history, malignancy status, DM characteristics, and myositis-specific antibody (MSA) profile. State ADI was determined using each patient's documented home address. Univariate and multivariate analyses, adjusted for ADI, race, sex, age at diagnosis, malignancy, and smoking history, were conducted. Ninety-five patients were included in the analysis (mean [SD] age 50.7 [15.4] years; 76 (80%) female; 30 (31.6%) Black; 57 (60%) Non-Hispanic White). Patients residing in areas with a higher ADI were more likely to be Black ($p<0.001$), and to have interstitial lung disease (ILD) ($p=0.003$), myositis ($p=0.01$), and arthritis or arthralgia ($p=0.01$). Conversely, patients in areas with a lower ADI were more likely to exhibit cutaneous manifestations such as V-neck sign ($p=0.02$) and periungual erythema or nailfold changes ($p=0.004$). Additionally, lower ADI was associated with higher peak Cutaneous Dermatomyositis Disease Area and Severity Index Activity scores ($p=0.04$). Following multivariate adjustment, higher ADI emerged as the sole predictor of DM-associated ILD ($p=0.04$) and myositis ($p=0.039$) and remained significantly associated with arthritis or arthralgia ($p=0.037$). Conversely, lower ADI was the only significant predictor of the presence of V-neck sign ($p=0.027$) and periungual erythema ($p=0.004$). Our findings emphasize the importance of considering DM patients' socioeconomic context during evaluation, as ADI emerged as a key factor influencing specific disease outcomes, surpassing race as a determinant after multivariable adjustment.

0675

Health care utilization for melanoma across demographic groups in the United States using the medical expenditure panel surveys (MEPS)

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The purpose of the study is to evaluate demographic disparities in medical expenditures among adults (ages ≥ 18) diagnosed with malignant melanoma in the United States. This is a cross-sectional study using data from the Medical Expenditure Panel Survey from 2014 to 2022. Outcomes examined were medical expenditures including total medical expenditures, office-based visits, outpatient visits, emergency room visits, prescription medicines, dental, home health, and other (vision aids and other medical supplies and equipment). The study analyzed 939 observations from 678 adult patients with malignant melanoma: 638 non-Hispanic White (NHW), 28 Hispanic, and 12 non-Hispanic Black. Mixed-effects linear regression models adjusted for age, marital status, education, income, region, and insurance status were used to analyze differences in expenditures by race/ethnicity, with a random intercept to account for multiple observations per patient. Non-Hispanic Black patients had 3.25 times higher total expenditures compared to NHW patients (95% CI = [1.35, 7.82], p = 0.009), with significantly higher costs for home health and other expenses. No significant differences were observed between Hispanic and NHW patients in total expenditures. Patients aged ≥65 years had 1.47 times higher total expenditures compared to those aged <65 years (95% CI = [1.18, 1.84], p = 0.001). Middle-income individuals reported lower expenditures than low-income individuals (OR = 0.75; 95% CI = [0.59, 0.95], p = 0.015). This study highlights demographic disparities in medical expenditures for malignant melanoma in the United States. These differences signify areas that require further evaluation to address healthcare expenditures and ensure equitable and affordable access to healthcare resources across diverse populations.

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Exploring depression risk in vitiligo across racial and ethnic groups

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Vitiligo is a chronic autoimmune skin condition with significant psychosocial comorbidities. However, clinical variations based on skin tone and unique challenges faced by patients with skin of color (SOC) have limited exploration of racial and ethnic differences in depression risk. This case-control study examined depression prevalence and risk in 1087 vitiligo versus 5435 non-vitiligo patients across racial and ethnic groups from the All of Us database (n = 6522, 1:5 case:control ratio). Adjusted odds ratios (aOR) with 95% confidence intervals (CI) were calculated after multivariable adjustment for relevant covariates. Vitiligo patients had a significantly higher depression prevalence compared to non-vitiligo controls (40.0% vs. 29.2%, $p < 0.01$), with an increased risk of depression (aOR, 1.34; 95% CI, 1.16–1.54). Race-stratified analysis revealed Black vitiligo patients had a significantly higher depression prevalence (52.8% vs. 30.5%, $p < 0.01$), and more than double the risk of depression than Black non-vitiligo patients (aOR, 2.13; 95% CI, 1.55–2.91). White vitiligo patients had a significantly higher depression prevalence compared to White non-vitiligo controls (34.7% vs. 29.4%, $p < 0.05$), but their increased depression risk was not significant after multivariable adjustment (aOR, 1.06; 95% CI, 0.85–1.29). Asian vitiligo patients had similar depression prevalence to Asian non-vitiligo controls (11.1% vs. 12.8%, p = 1.00) and a lower risk of depression (aOR, 0.70; 95% CI, 0.15–2.38). Vitiligo is linked to an increased risk of depression, with Black patients facing significantly higher risk, while White and Asian patients showed non-significant risk after adjustment. These findings reveal racial differences in disease burden and underscore the need for culturally sensitive care. Disaggregating data by race and ethnicity is vital to accurately assess comorbidity risk and address disparities in SOC patients.

0677

Association of Medicaid expansion with time to treatment of melanoma in Hispanic patients: A NCDB analysis

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Patients who are Hispanic are more likely to have delays in cancer treatment compared to non-Hispanic White (NHW) individuals, including melanoma. Treatment delays are likely multifactorial including poor access to care. In 2014, selected states expanded Medicaid to cover more underserved populations. However, its effects on melanoma time to treatment in patients of Hispanic origin is unclear. This hospital-based cohort study used the National Cancer Database (2008-2019) to evaluate differences in time to treatment in patients with melanoma aged 18 to 65 who resided in a state that expanded Medicaid on January 1, 2014. Those who had a time to treatment of zero or unknown were not included. A difference-in-difference (DID) analysis compared multivariate logistic regression and Cox regression models of time to treatment according to time period (pre-expansion [2008-2013] and post-expansion [2014-2019]) and ethnicity (NHW and Hispanic), stratified by insurance type (private vs. Medicaid). A total of 48,720 patients were included, 986 (2.0%) were Hispanic and 3,056 (6.3%) had Medicaid. Mean time to treatment pre-expansion was 32.3 days for NHW and 41.7 for Hispanics, post-expansion was 34.9 for NHW and 46.6 for Hispanics (p-values <0.01). In the Medicaid subgroup, patients who were Hispanic were 2.01 (pre-expansion) and 2.24 (post-expansion) times more likely to have time to treatment greater than 30 days compared to NHW, however adjusted DID analysis showed no significant effect associated with Medicaid expansion (1.06 [95%CI: 0.54-2.07]). Similar results were found for time to treatment greater than 60 and greater than 90 days. Cox regression model demonstrated similar findings (adjusted DID 1.09 [95%CI: 0.80-1.47]). This study reports that patients who are Hispanic have significantly longer time to treatment for melanoma compared to NHW. However, Medicaid expansion did not reduce this disparity.

0678

The role of economic distress in shaping the diversity of dermatology care access

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This study investigates how access to dermatology providers from underrepresented racial and ethnic backgrounds varies across socioeconomically distressed communities in the southern United States. The Distressed Communities Index (DCI), a composite measure of economic distress combining income, employment, education, and housing, was used to categorize communities into quintiles, from the most prosperous (1) to the most distressed (5). We assessed 122 medical dermatology clinics in the southern United States, categorized by DCI quintile, and contacted them for data collection in August 2024. Clinics in less distressed communities (DCI score 0–49.99) had a higher proportion of providers from underrepresented backgrounds (10.64%, 25/235) compared to clinics in more distressed areas (DCI score 50–100), which had lower proportions (6.1%, 10/164). Dermatologists from minority backgrounds in the second most distressed quintile had significantly longer wait times (93.8 days) compared to other quintiles (7.0–35.7 days; p<0.001). In contrast, wait times for racially and ethnically diverse Advanced Practice Providers (APPs) decreased by 3.6 days with each increase in DCI quintile (β = -3.610, p<0.001). While any qualified dermatology provider can offer high-quality, culturally competent care, expanding and diversifying the dermatology workforce—including dermatologists and APPs—could help ensure all communities have equitable opportunities to choose care that aligns with their cultural and personal preferences. Increasing teledermatology services and creating incentives for providers to practice in underserved areas would further support access to care while maintaining the high-quality standards provided by all dermatology professionals.

0679

Dermatology care utilization in transgender and cisgender medicare beneficiaries

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Transgender individuals face discrimination within the healthcare system which may lead to underutilization of specialist care, including dermatology, despite the elevated prevalence of skin conditions in this population. This study investigates dermatology encounters among transgender Medicare beneficiaries compared to matched cisgender controls. We conducted a retrospective cohort study in fee-for-service Medicare data (2009-2018) and used a validated method to identify transgender individuals among 4,999,999 beneficiaries. We excluded individuals with HIV and/or solid organ transplant. We matched 4:1 to two control cohorts (cisgender male, cisgender female) based on race, age, and time in dataset. The primary outcome was any encounter with a dermatology clinician (physicians and advanced practice providers practicing dermatology, identified using a published method). We used multivariate logistic regression adjusted for age, race, census region, median household income, and prior dermatology encounters to evaluate the odds of a dermatology encounter. A total of 1839 transgender cases, 7354 cisgender male, and 7353 cisgender female controls were identified. 45% of transgender individuals had a dermatology encounter (n=818) compared to 49% of males (n=3631) and 45% of female (n=3280) controls. After adjustment, transgender individuals had significantly lower odds of a dermatology encounter compared to males (Odds Ratio [OR]=0.83, 95% CI 0.74-0.94) and to females (OR=0.81, 95% CI 0.72-0.91). These findings suggest a difference in dermatology utilization between transgender and cisgender Medicare beneficiaries. These differences may have implications for the skin health and well-being of this underserved population and emphasize the importance of addressing barriers that hinder healthcare access for transgender patients.

0680

Proteomics identifies blood biomarkers associated with disease severity and genetic ancestry in hidradenitis suppurativa

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Hidradenitis Suppurativa (HS) is a chronic inflammatory skin condition that disproportionately affects individuals of African ancestry and those with a family history, suggesting a genetic basis for the disease. Despite its burden, no clinically validated biomarkers exist to guide treatment or predict outcomes. Previous biomarker studies have been limited by small sample sizes, impeding control for demographic factors such as age, sex, and ethnicity. Identifying robust biomarkers is essential to improve disease management and prognosis. This case-control study employed high-throughput proteomics and whole-genome sequencing (WGS) to address these gaps. Circulating inflammatory proteins were analyzed using Olink high-throughput proteomics in 72 HS patients and 24 age-, sex-, and ethnicity-matched healthy controls (HCs). Genetic ancestry was determined through WGS, and linear regression was used to adjust for demographic variables and identify significant biomarkers. A total of 55 novel inflammatory biomarkers were identified in HS patients compared to HCs, 32 of which were previously unreported. Among these, 26 proteins correlated with disease severity, with IL-6 and MMP1 levels distinguishing between Hurley stages. Genetic ancestry significantly influenced inflammatory profiles: African ancestry was associated with elevated neutrophilic inflammation markers, while European ancestry correlated with increased Th1-related proteins. These findings underscore the interplay between disease severity, genetic ancestry, and inflammatory profiles in HS, paving the way for biomarker-driven, personalized treatment strategies.

0681

Concomitant skin conditions and comorbidities in Black/African American patients with rosacea

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Rosacea is often underdiagnosed in patients with skin of color, leading to symptom progression, hyperpigmentation, and negative impact on quality of life. Systemic comorbidities are also correlated with rosacea, potentially contributing to poor health outcomes. This study investigates concomitant cutaneous conditions and systemic comorbidities in Black/African American patients with rosacea, compared to non-Black/African American patients with rosacea. A retrospective cohort study using de-identified patient data from the TriNetX US-Collaborative Network was conducted. Propensity matching was performed to control for age and sex. Risk ratios were calculated and evaluated for statistical significance. Both propensity-matched cohorts had 13,217 patients each. The mean age for each cohort was 52.4±17.8. Each cohort had 10,687 females (80.8%) and 2,530 males (19.2%). Black/African American patients with rosacea were at higher risk for developing the following concomitant cutaneous conditions than non-Black/African American patients with rosacea, including: postinflammatory hyperpigmentation: RR=5.201, 95% CI=(4.267, 6.339), hidradenitis suppurativa: RR=2.754, 95% CI=(2.092, 3.626), atopic dermatitis: RR=2.152, 95% CI=(1.876, 2.469) and acne: RR=1.457, 95% CI=(1.335, 1.590). Black/African American patients with rosacea were at higher risk for developing systemic comorbidities than non-Black/African American patients with rosacea, including lupus erythematous: RR=2.207, 95% CI=(1.497, 3.254), and type 2 diabetes mellitus: RR=2.006, 95% CI=(1.815, 2.217). Black/African American patients with rosacea face a significantly higher risk of developing concomitant cutaneous conditions and systemic comorbidities, particularly postinflammatory hyperpigmentation, hidradenitis suppurativa, and lupus erythematosus. This underscores the need for greater awareness and timely diagnosis among the African American community.

0682

Serum proteomic characterization of the East Asian and Asian American atopic dermatitis molecular phenotype

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Atopic dermatitis (AD) is a heterogenous disease characterized by universal Th2-skewing and variable Th1, Th17, and Th22 immune activation, and barrier dysfunction, amongst patients of different ancestries. These heterogeneities have suggested that both environmental and genetic factors may contribute to progression and severity of disease suggesting the need for more tailored and individualized treatments. Comparing the American Asian (AA) AD phenotype to the East Asian (EA) phenotype to understand their similarities and differences, with appropriate comparison to a Caucasian American cohort, has not been evaluated, and we aim to bridge this gap. We performed proteomic serum analysis on blood samples from 43 patients with AD (18 EA, 13 AA, 12 White) and 29 ethnicity matched controls (9 EA, 9 AA, 11 White) via the OLINK platform. Differentially expressed proteins (DEPs) were defined as fold change > 1.5 and false discovery rate <.05. Across ethnicities there were common upregulations in Th2 associated genes (CCL13, CCL17), general inflammatory genes (MMP12) and T cell activation (IL18, TNFSF14). However, we found several DEPs between EA and AA. While both EA and AA AD patients demonstrated upregulation of Th1 genes (IL1RA, IL2RA), EA AD showed additional skewing of Th1-related genes (CXCL9/10/11). Th17 activation was also stronger in EA AD patients (CXCL1, CCL20, PI3), while genes related to cellular regulation (NFkB, STAMBP, AXIN1) and apoptosis (SIRT2) were unique to AA. Dysregulation of genes associated with barrier function and atherosclerosis were shared amongst EA and AA AD patients (PI3, EZR, IL16). Our findings expand on the current knowledge of AD profiles. While prior characterizations have not taken into account environmental and migration differences within ethnicities, proteomic profiles of native and corresponding immigrant communities may indicate diverging ancestries and potentiates more targeted and individualized therapies.

0683

Sociodemographic and environmental profiles associated with atopic dermatitis severity among children

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Racial and ethnic disparities in atopic dermatitis (AD) severity exist among children in the United States. The combinations of social and environmental factors contributing to these disparities remain unclear. We aimed to identify population groups and their characteristics (profiles) that are associated with pediatric AD severity. We performed a cross-sectional analysis of children enrolled in the Pediatric Eczema Elective Registry and their associated zip code-based social determinants of health (SDoH) and air pollution (particulate matter [PM] 2.5) data from the American Community Survey and Environmental Protection Agency, respectively. The primary outcome was AD control (poor vs. good). Latent class analysis was used to identify subgroups (latent classes) based on individual and zip code-level demographic, clinical, SDoH and PM2.5 data. Logistic regression evaluated the associations between latent classes and AD control. In total, 5,212 children were included in the study. Mean (standard deviation) age was 7.4 (4.1) years; 52.7% were female; racial/ethnic distribution was 34.4% White, 55.4% Black, 10.2% Hispanic. Six latent classes were identified: Class 1 (socioeconomically advantaged), Class 2 (minoritized and socioeconomically disadvantaged, housing challenged, higher PM2.5 exposure, low atopy); Class 3 (minoritized and socioeconomically disadvantaged, low PM2.5 exposure); Class 4 (multiracial, middle class, immigrant population); Class 5 (White population, lower education, low PM2.5 exposure); Class 6 (minoritized and socioeconomically disadvantaged, higher PM2.5 exposure). Compared to Class 1, Classes 2 and 6 had higher odds of poor AD control (odds ratios [OR] 1.34 and 1.27; 95% confidence intervals [CI] 1.08–1.67 and 1.08–1.50, respectively). Classes 3 and 5 had lower odds of poor AD control (OR 0.62 [CI 0.49–0.77] and OR 0.50 [CI 0.41–0.62], respectively). Our study identifies specific exposure profiles, especially PM2.5 levels, associated with AD severity that can guide interventions to address disparities in pediatric AD outcomes.

0684

Impact of demographic variables on odds of developing autoimmune alopecia

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Frontal fibrosing alopecia(FFA), discoid lupus erythematosus(DLE), and alopecia areata(AA) have all been associated with autoimmunity with various racial predilections. Specifically, FFA has been described as primarily affecting White women and DLE, Black women. Given the known impact of race on socioeconomic status (SES), it is unclear if race is a true driver of disease risk in patients or simply a proxy for SES. The Centers for Disease Control (CDC) has established a level of vulnerability scale (LOV) for every zip code that incorporates SES and other demographic variables to identify areas of affluence. To determine the impact of SES on disease odds, we conducted a retrospective cohort study of patient zip codes to compare LOV in 672 patients with DLE, AA, or FFA treated at Johns Hopkins Hospital over 9 years. Multivariable-adjusted logistic regression and ANOVA were performed. Odds ratios, 95% confidence intervals, and p-values were determined, with $p<0.05$ considered significant. The average age of patients differed across conditions: 45.48 for AA, 61.67 for FFA, 49.48 for DLE ($p<0.001$). Racial distribution also varied, with Whites the most commonly affected racial group with FFA (51.7%) and Blacks the most commonly affected with DLE and AA (76.0%, 51.5%, respectively; $p<0.001$). However, when controlled for race & age, FFA patients were nearly 2x more likely to be from affluent zip codes compared to AA patients (OR: 1.786, $p=0.009$). When controlling for age & SES, race had no impact on the odds of developing FFA (White vs Black $p=0.204$). In contrast, Black race was the strongest predictor of DLE odds when compared to AA(OR: 2.97, $p<0.001$), with SES having no impact ($p=0.446$). While race was a key driver of disease in DLE, it did not influence disease odds in FFA, suggesting its role may be overemphasized in FFA's etiology. Instead, unique environmental exposures that have been associated with higher SES in all races, such as sunscreen use, deserve added focus. Further study is required to understand biological and environmental factors that increase diseases odds of DLE in Black patients.

0685

Acne incidence in transgender adolescents: A multi-center cohort study

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Endogenous puberty, puberty blockers, and gender-affirming hormone therapy may influence acne development in transgender adolescents, but epidemiologic data are scant. This study aimed to examine acne incidence in a validated cohort of transgender adolescents enrolled in Kaiser Permanente Northern and Southern California, Georgia, and Mid-Atlantic States. Transgender adolescents were followed from first documented transgender status (index date) to incident acne (≥1 ICD code) in 1/2006–6/2024. Up to 10 cisgender male (CM) and 10 cisgender female (CF) adolescents matched to each transgender adolescent by age, race/ethnicity, enrollment year, and site were followed from the index date. Incidence rates were compared using negative binomial regression. Subgroup analysis was performed for transmasculine (TM) adolescents receiving testosterone. 5,638 TM adolescents (mean age (SD) 13.6 (2.2) years) and 1,746 TF adolescents (mean (SD) age 12.9 (3.7) years) were matched with 58,718 CM and 56,397 CF adolescents. Mean (SD) follow-up times in TM and TF adolescents were 4.4 (2.7) and 4.9 (3.2) years. Incident acne rates were higher in TM adolescents than CM adolescents (Incidence rate ratio [IRR]=1.1, 95% CI 1.0–1.3; Incidence rates [IR]=43.5 vs 39.8) but similar in CF adolescents (IRR=1.0, 0.9–1.1; IR=44.0 vs 44.4); and similar in TF adolescents than CM adolescents (IRR=1.1, 0.9–1.3; IR=31.8 vs 31.3) and CF adolescents (IRR=0.9, 0.7–1.0; IR=31.6 vs 35.3). 1,979 transmasculine adolescents initiated testosterone at a mean (SD) age of 17.6 (2.3) and had higher incident acne rates than CM adolescents (IRR=2.0, 1.6–2.4; IR=53.5 vs 37.3) and CF adolescents (IRR=1.7, 1.4–2.1; IR=53.7 vs 40.9). This study relied on clinician-diagnosed cases and may not generalize to uninsured patients. Future research should examine how hormone therapy regimens and timing influence acne in transgender adolescents. Clinicians should address acne management in TM adolescents receiving testosterone.

0686

Racial and ethnic disparities in atopic dermatitis medication utilization

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Atopic dermatitis (AD) is an inflammatory skin condition with increasing treatment options, but disparities in its management remain understudied. We examined disparities in the utilization of treatments for AD, specifically dupilumab, crisaborole, topical JAK inhibitors (TJAKIs), and topical calcineurin inhibitors (TCIs). An analysis was conducted using aggregated data from Epic Cosmos, representing over 289 million patient records from over 1600 hospitals and 37,700 clinics. We included patients with an AD diagnosis (ICD-10 L20.*) between 1/1/2021 and 12/31/2023, who received care in the U.S. and had age documented at the encounter. Patients were divided by race, ethnicity, legal sex, and census region. Utilization rates for each treatment were calculated. We identified 1,660,680 AD patients and disparities were observed. Overall, black patients had the lowest rates of each treatment: dupilumab (Asian: 4.8%, Black: 3.9%, Other: 4.0%, White: 4.6%); crisaborole (Asian: 3.9%, Black: 3.6%, Other: 3.4%, White: 3.3%); TJAKIs (Asian: 1.1%, Black: 0.4%, Other: 0.7%, White: 0.8%); and TCIs (Asian: 13.2%, Black: 9.2%, Other: 9.9%, White: 9.6%). Similarly, Hispanic patients had lower rates compared to non-Hispanics (dupilumab: 2.3% vs. 4.7%; crisaborole: 3.1% vs. 3.3%; TJAKIs: 0.4% vs. 0.8%; TCIs: 7.1% vs. 10.1%). Females had higher rates than males (dupilumab: 4.3% vs. 4.1%; crisaborole: 3.4% vs. 3.2%; TJAKIs: 0.9% vs. 0.5%; TCIs: 10.6% vs. 8.2%). Regional differences varied depending on the treatment. For dupilumab and TCIs, the Northeast had the highest rates (dupilumab: 5.5%, TCIs: 12.2%). The rates for TJAKIs were higher in the Northeast and West (both 1.0%) compared to the South (0.6%) or Midwest (0.5%). The rate for crisaborole was highest in the South (5.1%). Limitations include potential classification bias and patients selecting multiple races. These findings suggest significant disparities in AD treatment across demographic groups. Further investigation is needed to identify underlying factors and inform interventions to ensure equitable access to AD therapies.

0687

Permanent hair removal and psychosocial outcomes in transgender and gender-diverse adults assigned male at birth: A cross-sectional study

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Permanent hair removal (PHR) is a medically necessary gender-affirming procedure for transgender and gender-diverse (TGD) individuals. However, data on the impact of PHR on gender dysphoria and quality of life are limited. This study aimed to compare psychosocial outcomes by self-report of PHR receipt in TGD adults assigned male at birth using the nationally representative TransPop Survey 2016-2018. Validated psychosocial outcomes included current and future wellbeing using Cantril Ladder, psychological distress using Kessler-6, and the Satisfaction with Life Scale. Outcomes were compared using linear regression accounting for population-calibrated survey weights and adjusting for gender-affirming hormone therapy or procedure receipt. Among 120 participants (mean (SD) age 40.4 (15.3) years), 39.5% reported having PHR, while 52.1% wanted it someday, 3.0% were unsure, and 6.5% did not want it. Those who received PHR were more likely to report a history of hormone therapy (81.5% vs 47.6%, p=0.005) or gender-affirming procedures (63.0% vs 16.6%, p<0.001) compared to those who desired but did not receive PHR. Compared to those who desired PHR, participants who received PHR reported higher current wellbeing (adjusted β=1.1; 0.2–2.0) and life satisfaction (adjusted β=1.1; 0.2–2.1). Future wellbeing (adjusted β=0.9; -0.1–1.9) and psychological distress (adjusted β=-2.6; -5.2 to 0.1) did not differ significantly by PHR receipt. This study lacked details on the type and location of PHR. Permanent hair removal is associated with multiple positive psychosocial outcomes in TGD adults. Prospective research is critically needed to examine psychosocial outcomes of PHR in gender-affirming care. Clinicians and payers should expand access to medically necessary PHR.

0688

Tape strip transcriptomic profiling of children and adults with mild-to-moderate atopic dermatitis in a Thai population

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Atopic dermatitis (AD) is a heterogeneous disease, with varying clinical and molecular features based on age, severity, ethnicity, etc. While tape strips have characterized many AD endotypes, molecular profiling of mild-to-moderate AD in a Southeast Asian population has never been done. We enrolled Thai children age<12 years with mild AD (SCORAD<25, n=13), moderate AD (25≤SCORAD<50, n=12), and matched healthy controls (HC) (n=8) and included adults with mild AD (n=9), moderate AD (n=7), and HC (n=10) from Thailand. Tape strips were collected from the lesional(LS) and non-lesional(NL) skin of AD patients and HCs for RNAseq analysis. Differentially expressed genes (DEGs) were defined by fold change>1.5 and false discovery rate<0.05. Overall, the LS tape strip transcriptome was significantly more inflamed in moderate vs mild AD in adult (moderate:1348 DEGs, mild:453 DEGs) and pediatric AD (moderate:905 DEGs,mild: 53 DEGs). 7 DEGs were detected amongst all NL samples, suggesting minimal systemic inflammation in this cohort. T-cell and dendritic cell activation products (CD4/ITGAM/ITGAX) were only upregulated in adult moderate AD. Th2 (IL4R/IL13/CCL17) and Th1 (IL1B/CCR1) markers were upregulated in mild-to-moderate AD adult LS skin, but not in children. However, IL5, a Th2 cytokine and eosinophil mediator was elevated only in moderate child AD. The Th17/Th22 axis was enriched across all AD groups, though several Th17 genes (CXCL1/IL6/IL-23A/S100A9) were more elevated in moderate child AD. Barrier alterations were also seen across the entire AD cohort, with several barrier products (GJB3/FA2H/GAL/KRT79) showing greatest decreases in moderate child AD. The tape strip molecular phenotype of Thai patients with mild-to-moderate AD revealed distinct immune and barrier signatures based on age and severity level, identifying potential biomarkers for disease monitoring and therapeutic targeting.

0689

A data driven approach to understand the impact of the social determinants of health in pemphigus

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Social determinants of health (SDoH) are the macro-level conditions that shape health outcomes, such as economic policies, systemic racism, urban design, and education systems. Health-related social needs (HRSNs) are the individual-level, actionable expressions of these systemic factors. Together, these non-medical factors are known to account for up to 50% of all health outcomes. Addressing the burden of unmet HRSNs in a given population first requires a comprehensive characterization of those particular needs. While significant efforts towards this end have been undertaken in the context of other autoimmune diseases such as systemic lupus erythematosus (SLE), no such information is available regarding pemphigus patients. To address this gap, we developed a purpose-fit questionnaire integrating multiple, previously validated instruments to capture a cross-sectional snapshot of the burden of HRSNs in this population. Surveys were distributed in collaboration with the International Pemphigus and Pemphigoid Foundation, with n=165 respondents completing the survey. 97% had ≥1 HRSN, far exceeding reported values among various publicly insured populations (55-57%) and in line with similar estimates among SLE patients (94%). Furthermore, 65% of respondents were found to have a "high" HRSN burden (≥3 needs). The most common HRSNs were those related to mental health (80.8%), physical inactivity (71.9%), and health confidence (36.5%). Our findings reveal a high prevalence of unmet HRSNs among pemphigus patients, mirroring patterns observed in other autoimmune diseases. Associations between unmet HRSNs, poorer self-reported health status, and higher ED dependence, point to critical gaps in care. Integration of HRSN screening and intervention into routine pemphigus care therefore represent a crucial opportunity to improve outcomes in this high-need population.

0690

Sexual and gender minority inclusivity in hidradenitis suppurativa patient reported outcome measures

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Sexual and gender minority (SGM) patients with hidradenitis suppurativa (HS) may have elevated levels of anxiety, depression and suicidality due to HS disease. However, patient reported outcome measures (PROMs) used for HS research and clinical management may exclude or discriminate against SGM populations. To evaluate the inclusivity of SGM content within HS PROMs, we performed a thematic analysis of HS PROMs. Investigators with SGM health expertise amended an existing codebook based on National Institute of Health guides for SGM terminology. The codebook domains included (1) non-assumption of heteronormativity, (2) gender-neutral language, and (3) inclusion of other SGM spectrum topics. Thirty-one PROMs were included in the analysis: five focused on dermatology, five on HS, seven on mental health, and thirteen on general health. Three general health scales assumed heteronormativity (BoQoLI, FSFI-6, IIEF-5) and included phrases asking about "interactions with people of the other sex". Three scales (Arizona Sexual Experience, PSQI, HSPE), including 1 HS-specific scale (HSPE), did not utilize gender-neutral language; an example question asked, "are you male or female?" Four scales (BI-QoLI, FSFI-6, IIEF-5, Arizona Sexual Experience), did not use language that was inclusive of other SGM spectrum topics. Within our study, all dermatology and most HS PROMs met criteria for inclusive language. Notably, there was a lack of inclusive language in PROMs concerning body image and sexual function. Modifying existing instruments to become more inclusive of diverse communities may be a viable option but will require investments of time and resources to ensure they maintain reliability and validity. Nonetheless, the inclusion of diverse patient populations must remain a priority in validating and creating PROMs. To optimize patient care, we must ensure PROMs used in research study methods and clinical management respect and affirm the diversity of the patients we serve.

0691

The disproportionately higher burden of climate change on cellulitis risk factors for marginalized populations: A literature review

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Climate change has been linked to worsening of various skin diseases, including cellulitis. However, it is important to consider the disproportionate burden that marginalized populations may face in these climate-related impacts. A comprehensive review was completed through PubMed to identify relevant literature. Rising ambient temperatures have been linked to a seasonal pattern in cellulitis, with a strong association of disease incidence during the summer. Individuals of low-income and minority communities are at an elevated risk of being exposed to higher temperatures due to persistent housing inequities, in addition to being employed in outdoor occupations that are consistently exposed to high heat. Natural disasters, such as hurricanes and wildfires, are predicted to become more severe with climate change, secondary to rising sea levels and changes in rainfall patterns. Previous research has found that marginalized populations not only live in areas of higher vulnerability to natural disasters, but also face long-term social and financial consequences, which may further limit their ability to receive medical care. The contamination resulting from these extreme weather events also introduces an increased risk of infection, while the disruption of care delivery presents a barrier in receiving care and thereby increases the risk of cellulitis-related complications. Exposure to air pollution, specifically ozone from vehicle emissions and industrial factories, has been associated with an increased likelihood of cellulitis-related emergency room visits. The risk of greater ozone exposure has previously been linked to socioeconomic factors and thus may translate to an elevated risk of cellulitis for low-income communities. This review supports that various environmental factors associated with cellulitis may disproportionately impact marginalized communities. In order to address these disparities, we should prioritize how to target this elevated risk, especially as the effects of climate change may worsen.

0692

Evaluation of clinical scales among populations diagnosed with atopic dermatitis: A scoping review

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This scoping review seeks to determine the availability of current diagnostic scales for atopic dermatitis in skin of colour populations, emphasizing sensitivity, specificity, inter-rater reliability, feasibility, and impact on clinical decision-making. Five peer-reviewed databases were searched for studies published between 2014 and 2024, focusing on quantitative research, including validation and observational studies. Studies on diagnostic scales' effectiveness were considered, excluding those lacking methodological details or focusing solely on treatment outcomes. These studies were screened in duplicate by blinded reviewers with a third independent reconciler. Data extraction and quality appraisal using the GRADE tool and the Covidence platform followed. 1856 articles underwent title/abstract screening, and 360 eligible studies were identified, including hand searches. Data extraction and quality appraisal synthesized findings on diagnostic scale performance in Canada and the United States. Thematic analysis was employed to elucidate trends and disparities in atopic dermatitis diagnosis and management across different demographic groups. Current scale criterium provide unclear descriptions to distinguish signs and symptoms, and were qualitatively assessed. By critically evaluating the current landscape of diagnostic tools for atopic dermatitis, this scoping review aims to validate current tools and inform future research priorities and interventions aimed at reducing disparities in atopic dermatitis outcomes and improving healthcare equity for all individuals, regardless of race or ethnicity. Future studies should evaluate the accuracy of diagnostic tools for skin of colour populations diagnosed with alternate types of dermatitis/eczema skin conditions.

0693

Disparities in care access for pediatric hidradenitis suppurativa patients: A retrospective study

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Nearly one-third of hidradenitis suppurativa (HS) cases affect pediatric patients, yet research on care access disparities within this population remains limited. We conducted a retrospective chart review of 1,015 pediatric HS patients at the University of Pittsburgh Medical Center, identifying the medical specialties that provided initial HS diagnoses and factors associated with differences between populations. Statistics were calculated through $\chi 2$ and ANOVA. Our results found that only 25.26% (72/285) of Black patients were diagnosed by dermatologists, compared with 40.71% (276/678) of White patients. Black patients were more frequently diagnosed in emergency departments (EDs) or urgent care clinics (35/285, 12.28%) than White patients (13/678, 1.92%) ($p < 0.001$). Patients with Medicaid were less likely to be diagnosed with HS by dermatologists (95/289, 32.87%) compared to those with private insurance (236/623, 37.88%) ($p = 0.001$). Conversely, ED or urgent care diagnoses were more frequent among Medicaid patients (25/289, 8.65%) than those with private insurance (19/623, 3.05%) ($p = 0.001$). HS patients with psychiatric comorbidities were significantly more likely to receive their diagnosis from a primary care provider (PCP), with 63.24% (277/438) diagnosed in this setting. In contrast, patients without psychiatric comorbidities were diagnosed by dermatologists (248/576, 43.06%) at rates comparable to those diagnosed by PCPs (263/576, 45.66%) ($p < 0.001$). No significant differences were observed based on sex ($p = 0.45$), age of HS diagnosis ($p = 0.84$), BMI at diagnosis ($p = 0.50$), or age of psychiatric diagnosis ($p = 0.98$). These findings underscore persistent inequalities in access to dermatologic care for pediatric HS patients, highlighting the need for more equitable healthcare delivery.

0694

Investigating the lack of representation of melanoma diagnosis in people of color

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Melanoma is one of the deadliest forms of skin cancer and the prognosis of the patient is dependent on time of diagnosis. It was found that the diagnosis of melanoma for people of color (POC) is typically in advanced stages with lower survival rates. This review investigates the underrepresentation of melanoma in POC and its impact on time to diagnosis. We conducted a systematic review of 3 databases according to PRISMA guidelines. Collected data from 7 studies included study characteristics, correct diagnosis, measurement methods, and source-identifying melanoma. The proportion of ethnicities and skin tones that were represented in each online source was disproportionately lower for images representing POC. The LaRosa study reported that only 16.66% of melanoma depicted in YouTube videos were shown on POC. Of this percentage, only African American, Asian, and Native American ethnicities were shown while no videos depicted melanoma on Hispanic patients. A similar search through Sadur's 2024 study displayed only 13.2% of the images found from online searches of skin cancer were of patients with Pantone C-E or darker skin tones. The diagnostic scores of melanoma diagnosis for skin cancers on darker skin tones displayed that artificial intelligence (AI) has a better probability of correctly identifying skin cancer in patients with Fitzpatrick IV-VI skin tones. In the Lyman study, general practitioners scored 38% and 69% when diagnosing 2 melanoma pictures on "black skin. Schneider's study reported that AI produced 77.78% and 83.33% scores for malignant neoplastic skin conditions. Scheider's study also showed that AI produced scores of 69.57 and 82.61 for benign neoplastic skin conditions. The longer time for melanoma diagnosis for POC can be attributed to limited representation in media sites and online searches. AI may be used to close this disparity by increasing the likelihood of correctly identifying forms of skin cancer on all skin types. Further research is needed to establish a clearer relationship between the lack of representation of POC and its effect on skin cancer diagnoses.

0695

Microdermabrasion in skin of color: A systematic review

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This systematic review aimed to evaluate the frequency and methods of reporting of race-related demographic information in microdermabrasion clinical trials. PubMed and Embase were searched for clinical trials with microdermabrasion as an intervention with filters for clinical and randomized control trials applied. 30 papers involving 695 patients met final criteria. 22 papers reported Fitzpatrick skin type (FST), race, or both. 19 papers (63%) involving 410 patients (59% of total) included some measure of FST. Of these, 1 paper provided an average FST value for participants. 9 papers mention FST as an inclusion/exclusion criterion or report a range of FSTs represented in the study sample. 9 papers provided a participant-level breakdown of FST for 219 participants. In these 9 papers, 5.9% of participants had FST I, 15.5% had FST II, 41.1% had FST III, 28.8% had FST IV, and 7.3% had FST V. 0.5% of participants had intermediate FST between II-III and 0.9% had intermediate FST between III-IV. 4 out of 30 papers encompassing 81 participants (11.7% of total) reported race/ethnicity. 81.5% of these were Caucasian, 13.6% were Korean, 1.2% were Asian, 1.2% were Black/African American, and 2.5% were classified as 'other.' 1 study was conducted in Brazil, 2 in Denmark, 3 in Egypt, 2 in India, 3 in Iran, 1 in South Korea, 1 in Taiwan, and 17 in the United States. Microdermabrasion was studied for healthy skin, acne, actinic keratoses, dyschromia, scarring, rhytides, melasma, photoaging, photodamage, skin cancer, lupus, striae distensae, and vitiligo. This review is significant as it highlights the limited and unstandardized reporting of race-related demographic information in microdermabrasion clinical trials, which leads to poor generalizability of results and inadequate safety information on microdermabrasion for racial groups.

0696

Impact of race on survival of patients with primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders: A longitudinal analysis of the SEER database (1988-2011)

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Introduction: Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders (PCLPD) account for 25-30% of primary cutaneous T-cell lymphomas. Prior studies identified Black race, higher clinical stage, and receipt of chemotherapy as predictors of poor outcome. Data examining differences in racial disparity outcomes are limited. Objective: We aim to examine racial disparities in survival outcome of PCLPD over time. Methods: We examined survival patterns for PCLPD using the Surveillance Epidemiology and End Results database (code 9714/9718) from 1994-2011. Cases were divided into two cohorts based on the year of diagnosis: 2000–2005 and 2006–2011. Univariable and multivariable analyses were conducted to assess for factors associated with overall survival. Nonparametric estimates of survival distribution functions, Kaplan-Meier survival curves, and Cox proportional hazards model were used to examine factors affecting survival time. Results: 294 cases of PCLPD were identified with a median follow-up of 60 months from 1994-2011. The survival of Black patients was not inferior to White ($p=0.7218$) or Asian ($p=0.9919$) from 2000-2005. There was no difference in survival across races ($p=0.9676$) from 2006-2011. The survival of Black patients was not inferior to White ($\chi 2=1.2$, $p=0.8994$) from 1994-2011. Conclusions: We demonstrate that Black race was not correlated with worse survival in PCLPD. This contrasts with previous analysis of mycosis fungoides where Black race was associated with worse survival (Soror et al. Blood 2021). The reason for this is unclear but may be due to a smaller sample size and different disease.

0697

Assessing alopecia in muslim women: A review

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Alopecia is characterized by hair loss and poses unique challenges for hijab-wearing Muslim women. Our study explores the specific etiologies of hair loss in this population. A systematic review was conducted through PubMed using the search terms: "hijab", "alopecia" and "hair loss". Our search populated nine articles meeting the inclusion criteria. It is suggested that the hijab itself does not cause alopecia, but the manner it is worn may contribute. Approximately 82% of hijabi women reported experiencing alopecia but are less likely than non-hijabi women to seek medical attention with only 15.9% of them receiving a formal diagnosis. Approximately 65% of hijabi women regularly wear their hair in a bun, with 66.3% of them reporting subjecting significant tension to their hairline. Consequently, wearing the hijab is associated with an increased incidence of traction alopecia of 10.4% compared to 7.5% in women who do not. Similarly, hijabi women have an increased prevalence of telogen effluvium, and concurrent telogen effluvium with seborrheic dermatitis when compared to non-hijab wearing women (46.4% vs 32.5% and 88.1% vs 11.9% respectively). Many factors contribute may to these secondary manifestations, such as increased traction on the hair root from specific hairstyles, wearing hijab under caps (57.4% of women), and using occlusive hijab materials. Despite the high prevalence of alopecia among hijabi women, there is a notable gap in seeking medical care. The reason for this is unclear, however, a culturally sensitive approach with tailored preventive and therapeutic guidance may be of benefit to this population.

0698

Examining the role of socioeconomic status on severity and outcomes in acral lentiginous melanoma

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Acral lentiginous melanoma (ALM) is a form of cutaneous melanoma (CM) that develops in the palms, soles, and nails. ALM comprises most CM cases in people with skin of color. Further, these populations present with more severe tumors (Breslow thickness, staging, ulceration) and higher melanoma-specific mortality (MSM) rates. Socioeconomic status (SES) has been proposed as a contributor to ALM disparities across racial/ethnic groups, but the evidence is inconclusive. Here, we aimed to identify differences in ALM outcomes across SES groups. We used the SEER 22 database with census tract-level attributes to obtain clinicopathologic and treatment data for patients diagnosed with ALM from 2010-2020. We collected and analyzed age at diagnosis, race/ethnicity (non-Hispanic White (NHW), non-Hispanic Black (NHB), non-Hispanic Asian and Pacific Islanders (NHAPI), and Hispanic), sex, SES quintiles, environment, Breslow thickness, mitotic rate, ulceration, stage, surgery, chemotherapy, and radiation. We then compared clinicopathologic characteristics and outcomes for 2,178 ALM cases across SES quintiles, where the first quintile represents the lowest SES and the fifth represents the highest SES. Patients belonging to SES quintiles 1 and 2 presented with a larger proportion of ulcerated tumors (43% and 40%), as well as a higher median Breslow thickness (2.1 and 1.9 mm) and mitotic rate (2 mitoses/mm^2) compared to patients from SES quintiles 4 and 5. Our multivariate Cox proportional hazard model showed no significant difference in risk for MSM across SES. When stratifying racial and ethnic groups by SES, the risk of MSM was higher among NHB (HR 2.76, p=0.002) and Hispanic patients (HR 1.49, p=0.06) from higher SES (quintiles 3, 4, and 5) compared to those from lower SES (quintiles 1 and 2). Our results show that SES may not contribute to differences in ALM outcomes across minority populations. Further research is needed to elucidate ALM etiology and pathogenesis and to identify the underlying factors driving differences across diverse groups.

0699

Characterization of skin tone in Uganda using subjective and objective methods

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Optical devices (e.g. pulse oximeters) that interact with skin may perform differently depending on skin tone. Regulatory agencies recommend that research and development study cohorts have diverse skin pigmentation. However, definitions for skin pigment have not been adequately validated in global populations and do not fully characterize dark pigmentation, leading to cohorts that may underrepresent people with dark pigmentation. We aimed to characterize the spectrum of skin tone across African populations to ensure representation in common skin pigmentation measurement methods. We conducted a cross-sectional study on healthy adults living in Uganda. The Monk Skin Tone (MST) scale and the Konica Minolta CM-700d spectrophotometer were used (by one operator) to assess pigmentation at the forehead. The CIELAB L*, a*, b* values from the CM-700d were captured in triplicate, and the mean was converted to individual topology angles (ITA). We enrolled 244 participants from 10 African countries. The mean forehead ITA (SD) values for each MST category were: B (4.2°, 13.3), D (-19.0°, 13.7), E (-24.4°, 12.3), F (-41.7°, 8.0), G (-50.1°, 9.2), H (-62.03°, 9.2), I (-68.3°, 6.8), J (-74.2°, 4.6). Approximately 99% of participants had ITA values <10°, 78.9% had mean ITA < -30°, 52.3% had mean ITA < -50°, and 7.2% were <-70°. Currently published ITA cutoffs provide only two categories (< -30 dark° and 10° > ITA > -30° brown) to describe the wide ITA range of 98.8% of study participants. In contrast, four categories exist to describe light skin. Adding additional categories at -10°, -50°, and -70° would provide a more accurate and equitable representation of populations with darker skin tones when using ITA.

0700

Expanding access to dermatologic care for uninsured patients: A retrospective analysis of a free clinic

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Uninsured patients face substantial barriers to healthcare, resulting in poorer outcomes and limited access to specialized services, especially dermatology. The Rhode Island Free Clinic (RIFC) is the state's largest free clinic, with a monthly dermatology clinic for uninsured adults. This study evaluates common dermatologic needs among uninsured patients, the demographics of free clinic patients, and the impact of free dermatologic care. A retrospective chart review of RIFC dermatology visits from March 2018 to May 2024 was conducted. A cost analysis was performed using current procedural terminology codes and Medicare reimbursement rates. A total of 457 patient encounters involving 272 unique patients were recorded. Most patients were female (61.4%), Spanish-speaking (74.8%), Hispanic or Latino (86.0%), and unemployed (55.5%). The wait time for an initial dermatology appointment averaged 55.7 days. Common visit reasons included rashes (48.5%) and lesions of concern (44.5%). Among 586 recorded diagnoses, inflammatory skin conditions were the most prevalent (38.7%), and 9 skin cancers—including squamous cell carcinoma and sebaceous carcinoma—were diagnosed. Estimated Medicare cost savings for office visits totaled $40,650.15 (modeled using code 99213), 594.1 work relative value units (wRVUs), and 1,256.75 total RVUs (tRVUs). Procedural services, excluding benign lesions, added $4,455.51 in savings for the healthcare system, with 34.38 wRVUs and 137.74 tRVUs. This study highlights the vital role of free dermatology clinics in delivering essential care to uninsured, low-income patients, while saving the healthcare system significant costs. High referral rates for suspicious lesions and multiple skin cancer diagnoses underscore the importance of such services. Our results offer key insights into the demographics and clinical needs of free clinic dermatology patients.

0701

Exploring patient preferences for dermatologist gender, race, and training

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The purpose of this study was to assess patient preferences for their dermatology provider's gender, race, and training. This was a cross-sectional survey study. Patients were recruited from an academic dermatology outpatient clinic to complete a survey that inquired about their preferences for their provider's demographic and training level across various indications (e.g. Mohs surgery). No preference was an option for all questions. For questions regarding level of training, patients could choose between physician provider (MD or DO) or non-physician provider (PA or NP). There were 186 survey respondents that completed at least one item. 124 (67.0%) respondents were female and 155 (86.1%) were white. Across all indications, there was a significantly greater proportion (13/25, 52.0%) of non-white respondents who had at least one preference for their dermatologist's race as compared to white respondents (29/153, 19.0%) ($p<0.001$). Of those who had a preference, 100% of non-white respondents preferred a non-white provider, and 75.9% of white respondents preferred a white provider. Most female respondents preferred a female provider for full-body skin exams (72/122, 59.0%), which differed significantly from the proportion of men who preferred a male provider for this indication ($p<0.001$). Most respondents had no preference for their provider's level of training across all indications except for treatment of autoimmune disease where 54.7% of respondents preferred a physician provider. This study underscores the importance of diversity among dermatology providers, as most non-white respondents preferred a non-white provider, and a majority of female respondents preferred a female provider for certain indications. The lack of explicit preference for a physician provider by many respondents may suggest patients are not familiar with the difference between a physician and NP or PA, though additional studies are needed to see if this is the case.

0702

Asynchronous teledermatology as an educational and assistive tool in the brazilian public health system: A pilot project

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This prospective study evaluated the implementation of asynchronous teledermatology in the Brazilian Public Health System to reduce referrals, enhance Primary Care Physician (PCP) education, and assess their dermatological proficiency. Approved by the Ethics Committee, it was conducted in Votorantim, São Paulo, from July to November 2024. Seven PCPs from three Primary Care Units (PCUs) submitted clinical data and photos via a customized platform to three board-certified dermatologists with medical education expertise. Teleconsultations included diagnoses, management recommendations, and educational materials. Dermatologists responded within five business days, compared to several months for traditional referrals. PCPs completed pre- and post-project self-assessment questionnaires on 5-point Likert scales. Thirty-two patients were evaluated, with 27 cases finalized on the platform. Diagnostic concordance between PCPs and teledermatologists showed no significant difference ($p=0.123$), with discordance being most frequent (53.12%). Of the 32 patients, 29 would have been referred for in-person evaluations pre-teleconsultation. Excluding five incomplete cases, referrals were avoided in 18 of 24 cases (efficiency rate: 75%; 95% CI: 53.3%-90.2%). Six cases required in-person referrals for biopsy (4), dermoscopy (1), or rheumatology (1). PCPs unanimously selected "strongly agree" for learning gains from teleconsultations. Pre- and post-study questionnaires showed significant reductions in referrals ($p=0.017$) and diagnostic doubts ($p=0.014$), with improved confidence ($p=0.028$) and teledermatology perceptions ($p=0.045$). Limitations included lack of dermoscopes (except in one PCU) and biopsy access in PCUs. Despite this, the project positively impacted patient care and PCP education, aligning with international studies. Though education wasn't directly measured, improved PCP knowledge during the project may explain the diagnostic outcomes. Further research is needed to evaluate the long-term effects of this model in underserved communities.

0703

Distinct responses of 3D african american and white non-hispanic skin organoids to key pro-inflammatory cytokines

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We recently revealed large transcriptome differences in African American (AA) compared to White non-Hispanic (WNH) adult and neonatal skin including upregulation of pro-inflammatory and cornified envelope genes and discovered the activation of upstream IL1R1/IRAK1/NF-kB/MAPK axis in AA skin. 3D human skin organoids (HSO) made from neonatal epidermal keratinocytes are a well- accepted model to study skin inflammation. Here, we investigated the existence of this proinflammatory signaling axis in control AA HSO and determined whether the molecular landscape of control HSO affects the response to major inflammatory cytokines (TNFa, IL6, IFNg and IL1b) by the changes in transcriptome, activation of NF-kB and MAPK signaling and HSO morphology. Like AA skin, control AA HSO displayed pro-inflammatory signaling at the transcriptome level and activation of NF-kB and ERK1/2. AA HSOs were more sensitive to chronic pro-inflammatory effects of TNFa and IL6 and displayed further activation of NF-kB and ERK1/2 upon treatment, while AA HSO were more sensitive to the pro-inflammatory effects of psoriasis-related IL1b and IFNg. However, only AA HSO displayed large changes in the expression of genes related to keratinization/cornified envelope after exposure to all cytokines. Even more, we observed opposite effects of IL1b and IFNg on the expression of major markers of keratinocyte differentiation in AA and WNH HSO: the expression of FLG, FLG2, LOR, HORN, was increased in AA HSO but was downregulated in WNH HSO. This correlated with increased thickness of stratum corneum and FLG immunostaining in AA HSO. Overall, these results suggest that differential response of healthy AA and WNH skin to the exogenous pro-inflammatory cues may underly the risk disparity of different inflammatory skin diseases in AA and WNH populations.

0704

An analysis of local therapeutic treatments for cutaneous and mucocutaneous leishmaniasis: A systematic review and meta-analysis

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Cutaneous and mucocutaneous leishmaniasis are protozoan parasitic diseases characterized by skin and mucosal lesions. While FDA-approved amphotericin B demonstrates an efficacy rate of 74%, it is an invasive systemic treatment yielding severe adverse effects including nephrotoxicity. Conversely, heat therapies and cryotherapy, while yielding similar outcomes, are cost-effective and have stronger safety profiles. This systematic review and meta-analysis aim to compare the efficacy of amphotericin B with the emerging treatments thermotherapy and cryotherapy in patients with cutaneous and mucocutaneous leishmaniasis. This study seeks to standardize treatment protocols for these underrepresented therapies in clinical trials as leishmaniasis cases may rise in North America attributed to climate change. The primary outcome measures the complete re-epithelialization of lesions, categorized as complete response, partial response, or failure, based on the percentage of re-epithelialization of the ulcer within a standardized timeframe and a secondary outcome measuring adverse effects of the treatments. A comprehensive initial search and manual snowball-method search were conducted across five peer-reviewed databases (PubMed, Medline, Scopus, LILACS, and Cochrane Library) for studies from 2010 to 2024. All stages of screening, extraction, and quality appraisal using GRADE were performed in duplicate by blinded reviewers, with a third independent reconciler. Studies focused on gaps or solutions in current treatment options were included, while studies lacking clear clinical cure outcomes were excluded. Both peer-reviewed and grey literature in English were included. By addressing the current research gap, this review aims to improve treatment options and guide future treatment guidelines for managing this disease.

0705

Bridging gaps throughout a patient's journey with melanoma: A qualitative systematic review

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Malignant melanoma is the deadliest skin cancer, with rising global incidence and mortality. While clinical advancements are crucial, the patient experience also requires attention. Challenges such as anxiety, symptom burden, and limited information affect melanoma patients' well-being. This systematic review aims to identify and analyze the key challenges, barriers, and gaps experienced by melanoma patients throughout their healthcare journey. Studies were identified by applying a search strategy to databases (e.g., Pubmed) with additional hand searching. Included studies focused on melanoma patients' experiences, emphasized gaps or solutions throughout their journey, and were published in English between 2013 and 2023. Screening and extraction were performed in duplicate and independently through Covidence. Data were synthesized around identified themes. Methodological quality was assessed using the GRADE standard. The majority of literature was found to belong to one of four major themes identified and analyzed: intersectionality, treatment, diagnosis/prognosis and quality of life. Positionality-based disparities in the patient journey and other barriers to care were determined; remaining gaps in knowledge were revealed. The introduction of various targeted treatments and immunotherapy 14 years ago has improved survival, but long-term knowledge of clinical outcomes remains nascent. Elucidating knowledge of adverse patient reactions, modality application to rare or advanced melanomas, risk factors/prognosis, and efficacy of various screening methods remain a priority. There remain extensive gaps in a patient's journey with melanoma. Identifying areas of improvement in current practice and knowledge is the first step in determining solutions to improve melanoma patients' quality of life.

0706

Environmental and social factors driving hidradenitis suppurativa

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Hidradenitis Suppurativa (HS) is a chronic inflammatory skin condition influenced by multiple factors. Over the past 30 years, the HS/Psoriasis (PsO) incidence ratio at Hopkins increased from 0.01 in 1994 to 0.23 in 2023, while annual HS-related PubMed citations grew from 12 to 697, with a coincidental abrupt increase after ~2010. To explore the drivers of this rise and contributors to HS prevalence, we analyzed data from Google Search trends, NHANES dietary patterns (N=40,937), a Hopkins prospective cohort (N=40), and a Baltimore City retrospective geospatial cohort (N=6,835). Public datasets revealed strong correlations between HS prevalence and ultra-processed foods consumption both internationally (r=0.83, P<0.0001) and nationally (r=0.82, P<0.0001). In the Hopkins cohort, HS patients consumed more canned beverages (6.7 vs. 2.8, P=0.02), cooked fewer meals at home (8.5 vs. 13.15, P=0.02), and used plastic containers more often (55% vs. 20%, P=0.01). Excessive sweating, especially in groin and abdominal folds, was significantly more common in HS patients (P=0.004, P=0.003). We hypothesize that dietary contaminants may accumulate, be excreted in sweat, and trigger localized inflammation. In Baltimore City, HS prevalence varied widely by ZIP code (P<0.01), and negatively correlated with median household income (r=-0.44, P=0.015), while PsO showed no significant income correlation by ZIP code (r=0.22, P=0.24). Racial disparities were pronounced, with HS predominantly affecting Black individuals (74% vs. 24% in PsO, P=0.02), and PsO more prevalent among Whites (63% vs. 18% in HS, P=0.0001). Gender differences were significant (80% HS females vs. 57% PsO females, P<0.0001). While HS is influenced by multiple factors, the sudden increase of cases, zip code heterogeneity, and survey data of HS suggests environmental exposures, diet, and social determinants intersect to worsen disease burden. Further research is needed to clarify these relationships and address health inequities in HS.

0707

Efficacy of ChatGPT-4o in recognizing and diagnosing skin cancer subtypes in light-skin and skin-of-color based on high-quality clinical images

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Despite the rising popularity of Artificial Intelligence (AI) technology and chatbots such as ChatGPT in the medical community, the accuracy and intrinsic bias of such tools remains unclear. This study aimed to assess the diagnostic accuracy of ChatGPT for skin cancer represented in light-skin (LS) and skin-of-color (SOC). VisualDx, DermNet, and the American Academy of Dermatology website were used to collect clinical images of four skin cancer types: melanoma, squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and Merkel cell carcinoma (MCC). 30 SOC and 30 LS images were obtained per cancer type; for MCC, only LS images were available. ChatGPT-4o was prompted to make a diagnosis based on each image. ChatGPT's overall diagnostic accuracy was 0% (0/90) for Merkel cell carcinoma (MCC), 58.9% (106/180) for melanoma, 42.8% (77/180) for SCC, and 33.3% (60/180) for BCC. For melanoma, ChatGPT had a total diagnostic accuracy of 76.7% (23/30) for LS images after three attempts, which was higher than its accuracy rate of 46.7% (14/30) for SOC images (p = 0.033). Similarly, for BCC, ChatGPT had a total diagnostic accuracy of 56.7% (17/30) for LS images after three attempts, which was higher than its accuracy rate of 23.3% (7/30) for SOC images (p = 0.017). For SCC, ChatGPT had a total diagnostic accuracy of 46.7% (14/30) for LS images after three attempts, which was equivalent to its accuracy of 46.7% (14/30) for SOC images (p = 1.00). Overall, ChatGPT accurately diagnosed skin cancer on just 38.6% of its attempts, showing it was ineffective at diagnosing all types of cancer, regardless of skin color. ChatGPT was unable to diagnose MCC, highlighting a clear knowledge gap. Across the more common skin cancers, ChatGPT was most accurate for melanoma and least accurate for BCC. Lastly, for both melanoma and BCC, ChatGPT had lower accuracy for SOC images, indicating that racial bias may extend to AI tools and limit their validity.

0708

Analyzing acne vulgaris trending treatments, dermatologist prevalence, and content diversity in 2024 on tiktok

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A study by Irfan et al. (2023) found that physicians account for a large portion (38%) of the top "liked" acne vulgaris content on TikTok. We aimed to determine whether this remained true when broadening search parameters to include multiple acne-related hashtags in recently published content. Additionally, we sought to understand the diversity of acne-related content creators, the prevalence of promotional content, and the types of trending products showcased. A researcher input five of the top acne hashtags into TikTok to analyze the top 20 liked videos of each posted from 7/3/24 to 1/2/25. Analyzing these 100 acne-related videos, the majority were inspirational(51%) or promotional(41%), with few educational(8%). Minimal dermatologists (2%) or estheticians (8%) posted this content, as most (90%) was created by layman influencers. Black creators posted 7% of the content, while Hispanic creators posted 11%. Top treatments included niacinamide, salicylic acid, retinol, pimple patches, and diet change. Sunscreen discussions were rare (5%), with 80% of such content focused on international products. In late 2024, a low prevalence of educational content and top acne content was posted by dermatologists, a downward trend from what was found in past literature. Such findings suggest an opportunity for dermatologists to increase the promotion of reliable acne-related medical information on social media. Dermatologists should be aware of acne vulgaris content online to recognize trending information, products sought by online users, and treatments patients may receive outside of clinic.

0709

Wait times for dermatology new patient visits differ by patient sociodemographic and clinical factors

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Existing disparities in access to dermatologic care contribute to health disparities and disproportionately affect minoritized and marginalized populations. To understand potential causes of these disparities, we examined the associations between patient and clinical characteristics and wait times for dermatology appointments. We conducted a cross-sectional analysis of adults scheduled for medical dermatology new patient visits (NPVs) at the University of Pennsylvania between 2017 and 2023. The primary outcome was time from appointment scheduling to visit, categorized as falling within four weeks vs. more than four weeks. Multivariable logistic regression was used to evaluate the associations between patient sociodemographic and clinical factors and the primary outcome. Analyses were stratified by pre-COVID (2017-2020) and post-COVID (2021-2023) time periods to account for post-pandemic scheduling changes. The study cohort included 40,177 patients. Mean (SD) age was 47 (18) years; 62.5% were female; and racial/ethnic distribution was 52.1% White, 27.1% Black, 6.5% Asian, and 4.6% Hispanic. Overall, 47.8% and 76.7% of patients in the pre-COVID and post-COVID time periods, respectively, were scheduled for an NPV within four weeks. In adjusted analyses, malignant visit diagnosis was most strongly positively associated with having an NPV scheduled within four weeks in both time periods (pre-COVID OR: 1.89; 95% CI: 1.19-3.04; post-COVID: 2.38; 1.27-4.95). Medicaid insurance was negatively associated with the outcome in the pre-COVID period only (pre-COVID: 0.74, 0.67-0.82; post-COVID: 1.07, 0.97-1.19). Among patients with NPVs for benign conditions, Black race was negatively associated with the outcome in the pre-COVID period only (pre-COVID: 0.92, 0.85-0.99; post-COVID: 1.23, 1.13-1.33). Our study identified pre-COVID disparities in wait times for dermatology NPVs that were not present following post-COVID scheduling changes.

0710

Racial differences in dermatologic conditions associated with HIV

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Racial differences in dermatoses affecting people living with HIV (PLWH) are understudied, and most research focuses on a Black/White binary. This study used the TriNetX network, a multi-institutional dataset, to compare dermatologic conditions across Asian, Hispanic, Black, and White PLWH. This retrospective cohort study examined dermatologic problems arising after HIV diagnosis in adults. Non-White PLWH were matched to White PLWH by age, sex, socioeconomic status, and comorbidities. Hazard ratios (HR) and 95% confidence intervals were calculated with Cox proportional hazard models. Bonferroni correction was made for multiple testing. A selection of our findings is described here. We identified the following significant racial differences in dermatoses among PLWH. Regarding infectious conditions, Asian, Hispanic, and Black PLWH were at lower risk for verruca vulgaris than White PLWH (HR_{Asian}=0.53, $HR_{Hispanic}$=0.83, HR_{Black}=0.54). In terms of inflammatory conditions, Asian, Hispanic, and Black PLWH had a higher risk of post-inflammatory hyperpigmentation (HR_{Asian}=4.34, $HR_{Hispanic}$=1.78, HR_{Black}=4.24) and pruritus (HR_{Asian}=1.82, $HR_{Hispanic}$=1.32, HR_{Black}=1.37). As it concerns neoplastic conditions, Asian, Hispanic, and Black PLWH had a lower risk of actinic keratosis than their White counterparts (HR_{Asian}=0.11, $HR_{Hispanic}$=0.18, HR_{Black}=0.04). Hispanic PLWH were found to be at higher risk for Kaposi sarcoma (HR=1.34). This study highlights racial differences in dermatoses affecting PLWH. Disparities in access to care may be a contributing factor. Limitations include limited CD4 count and viral load data and reliance on ICD codes for disease identification. Further studies are needed to explore the underlying mechanisms of race-based differences in HIV-associated dermatoses.

0711

Perceived triggers of atopic dermatitis: Differences by disease severity and race/ethnicity

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Inequitable experiences of the environment contribute to existing racial and ethnic disparities in atopic dermatitis (AD) burden. We aimed to identify perceived triggers of AD among adults with the skin disease to guide the patient-centered design of research on environmental exposures relevant to AD. A qualitative study of adults with AD in Philadelphia was performed using freelisting, a technique that identifies how people with shared experiences think about a topic. Participants listed triggers of their AD, and words were grouped into categories. Smith's Salience index (S) was calculated to identify the most important categories; relative salience (RS; a category's S divided by the maximum S among all categories expressed as a percentage) allowed comparisons across AD severity and racial/ethnic groups. The study included 46 adults with AD (15 White, 16 Black, 15 Hispanic). Median (interquartile range) age was 34 (28, 41) years, 72% were female, and 63% had moderate/severe AD. Overall, "weather" (e.g., heat, cold) was the most salient trigger, followed by "allergies & irritants" (e.g., pollen, chemicals; RS 79%), "other exposures" (e.g., water, air quality; RS 59%), and "personal care products" (e.g., lotions, perfumes; RS 44%). Among mild and moderate/severe AD groups, "weather" was the most salient trigger. For moderate/severe AD, "other exposures" (RS 97%) and "allergies & irritants" (RS 96%) were also highly salient. Across racial/ethnic groups, "weather" was a shared highly salient trigger (RS 92%, 100%, 100% for White, Black, and Hispanic adults, respectively). Among White adults, "other exposures" was also salient (RS 100%), while among Black and Hispanic adults, "allergies & irritants" were prominent (RS 75% and 94%, respectively). Our study identified participant-derived AD triggers and differences by disease severity and race/ethnicity that are important to adults living with AD and necessary to inform patient-centered care and research that includes the patient voice.

0712

Proinflammatory and profibrotic transcript profiles are overexpressed in central centrifugal cicatricial alopecia

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Central centrifugal cicatricial alopecia (CCCA) is the most common primary lymphocytic cicatricial alopecia typically affecting women of African descent. While gene expression profiling of CCCA-affected tissue has identified upregulation of profibrotic transcripts, the inflammatory/immune cell landscape of CCCA remains unclear. Further, current clinical practice employs non-specific, broad anti-inflammatory drugs including corticosteroids and oral antibiotics, with minimal targeted therapeutic options. To identify potential therapeutic targets, we used spatial transcriptomics to determine gene expression differences between affected and unaffected follicles in patients with clinically and biopsy confirmed CCCA. Spatial transcriptomics, using the NanoString GeoMx platform, was performed on six biopsies from African American female CCCA patients. A total of 88 follicles, were analyzed of which 61 were affected by CCCA and 27 were unaffected. Gene expression, gene ontology, and gene set enrichment analysis of affected vs unaffected follicles revealed significant upregulation of over 400 genes with multiple genes related to extracellular matrix reorganization (including MMP2, MMP14, VIM, and PDGFRA, adjusted $p<0.01$) and inflammation (including IL32, C1S, and TNFAIP2, adjusted $p<0.01$), and significant downregulation of lipid and fatty acid metabolism (including PLIN4 and APOC1, adjusted $p<0.01$). Additionally, PTGDS, the gene encoding prostaglandin D2 synthase was significantly upregulated (adjusted $p<0.01$). The upregulation of PTGDS suggests involvement of prostaglandin signaling in CCCA, possibly identifying a novel point of therapeutic intervention. These findings highlight a critical shift in the molecular landscape of CCCA-affected follicles, where upregulation of targetable profibrotic and inflammatory genes suggests a pathogenic mechanism which could inform future treatments.

0713

Greater socioeconomic disadvantage associated with delays in Merkel cell carcinoma treatment

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Delayed surgery may worsen the prognosis for cutaneous Merkel cell carcinoma (MCC). The impact of socioeconomic (SE) status on treatment delays and survival has not been studied for MCC. We identified MCC patients treated at a single tertiary medical center (2006-2022). SE status was assessed using the Area of Deprivation Index (ADI), with higher scores correlating to more SE disadvantage. Patients were categorized into two groups using our cohort's median ADI score (group 1: =<50th percentile, group 2: >50th percentile). The primary outcome was the impact of socioeconomic (SE) status on time to surgery (TTS), the number of days from diagnostic biopsy to surgical excision with wide local excision or Mohs micrographic surgery. Secondary outcomes were identifying factors affecting survival and recurrence. Wilcoxon Rank-Sum test assessed differences between the two ADI cohorts. Multivariate analysis evaluated characteristics associated with >4 week TTS, including gender, age, race, ethnicity, ADI group, stage of MCC, type of surgical treatment, and Sentinel Lymph Node Biopsy(SLNB). Cox multivariable hazard model included the same factors to find independent predictors for overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS). 190 MCC patients were included with a median follow-up of 3.62 years (SD:3.51). Median ADI was 31.5 (IQR:18.25-47). TTS was longer in patients with greater ADI (42 days, SD:35) than lower ADI (32 days, SD:14) (p=0.023). Female gender (OR:2.56, CI:1.20-5.65, p=0.017) and having ADI >50th percentile (OR:2.94, CI:1.42-6.34, p=0.005) predicted TTS >4 weeks on multivariate. Controlling for demographic factors, stage, and treatment, ADI was not an independent predictor of OS, DSS, or RFS. However, TTS >4 weeks (HR:1.65, CI:1.03-2.65, p=0.039) put patients at higher risk of recurrence. Greater SE disadvantage can delay MCC care by >a week. This delay in care may affect RFS. Further study is needed to better understand this relationship and address this disparity.

0714

Addressing dermatological needs and risk assessment in Syrian refugees (2021)

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The 2011 Syrian crisis has displaced over 14 million people, with nearly 1 million refugees anticipated to return by mid-2025 amidst a fragile healthcare system. This population faces heightened vulnerability to dermatologic conditions due to poor living conditions and limited access to medical care. This study aims to provide guidance for dermatologists addressing the needs of this population. Data from the Global Burden of Disease (GBD) database revealed that skin and subcutaneous diseases (excluding malignancies) had a prevalence rate of 19.4% among Syrians. Non-communicable dermatologic conditions demonstrated a higher overall prevalence (8.3%) and accounted for a greater proportion of disability-adjusted life years (DALYs) lost (0.70%) compared to communicable conditions (5.8% prevalence, 0.26% DALYs). The most prevalent conditions were acne vulgaris (4.02%), fungal skin diseases (3.12%), and atopic dermatitis (1.34%). Notably, acne vulgaris, atopic dermatitis, and urticaria accounted for over 50% of the dermatologic DALYs, surpassing conditions such as psoriasis, viral skin diseases, contact dermatitis, and scabies. These conditions are not limited to Syria, as studies have found higher rates of communicable diseases among Syrian refugees in Lebanon and Turkey. With the anticipated return of refugees to Syria, the dermatologic disease burden is expected to rise, requiring dermatologists to be well-prepared. Treating symptoms alone is insufficient, as a rapid effort to rebuild healthcare infrastructure is essential to mitigate disease spread and reduce the long-term impact of controllable conditions.

0715

Socioeconomic differences in treatment for immunobullous disorders: An all of us analysis

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Socioeconomic disparities in healthcare have been well-documented across various medical conditions, yet their impact on the management of autoimmune blistering dermatoses remains underexplored. These rare, chronic diseases require complex, long-term therapies, making them particularly susceptible to disparities influenced by social and economic factors. This study aims to address this gap through an analysis of the NIH All of Us Research Program evaluating prescription trends in patients with autoimmune bullous dermatoses, focusing on socioeconomic factors. Multiple multivariate regression models were made assessing various therapeutic treatments (cyclophosphamide, azathioprine [AZA], mycophenolate mofetil [MMF], rituximab, and corticosteroids) with socioeconomic covariates such as race, gender, age, and annual income. The Benjamini-Hochberg correction was used for multiple comparisons. Out of 287,012 patients included in the database, there were 256 patients identified to have an autoimmune bullous dermatosis. Of these patients, the mean age was 70.4 (SD, 14.6) years, and 56.6% were female, 3.9% identified as neither male nor female, 65.2% identified as White, 10.5% identified as Black or African American, 6.3% identified as Asian, and 18.0% identified as another race. After adjusting for covariates, there were no socioeconomic differences in corticosteroid, cyclophosphamide, or rituximab usage. However, individuals in the Asian cohort were more likely to have been prescribed AZA (OR=7.50, p=0.009, 95% CI=1.64-34.24) and MMF (OR=3.92, p=0.038, 95% CI=1.08-14.20). Individuals in the Other Race cohort were more likely to have been prescribed MMF (OR=3.03, p=0.009, 95% CI=1.32-6.93). These findings highlight the potential impact of social and economic factors on treatment disparities in autoimmune blistering dermatoses, especially in the treatment of minority populations and genders. Future research should explore whether these disparities reflect differences in management or influence patient outcomes.

0716

Peripheral blood immunophenotyping in a predominantly African American cohort reveals a role for Type 2 immune dysregulation in hidradenitis suppurativa

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Hidradenitis suppurativa (HS) is a chronic, inflammatory skin disease disproportionately affecting African American (AA) patients. HS is known to be a Th1 and Th17 inflammatory disease and treatments exist targeting these pathways, however the disease is known to have significant heterogeneity. We wanted to investigate the specific role of Type 2 immune responses in HS. We conducted a study including a cohort of primarily African American (AA) HS patients. We analyzed 28 patients with HS, of which 20 patients were African American and primarily Hurley Stage 3. Comprehensive immunophenotyping included whole blood flow cytometry, peripheral blood mononuclear cells (PBMC) cytometry by time-of-flight (CyTOF), and cytokine analysis using the Eve Cytokine Panel on serum samples. Cytokine analysis revealed elevated Th2 markers, including IL-4 ($p<0.01$) and IL-31 ($p<0.05$), in serum from HS patients. Whole blood flow cytometry demonstrated increased circulating basophils ($p<0.0001$), consistent with a Th2-skewed immune response. PBMC CyTOF analysis subsequently identified a marked increase in Th2 cells ($p<0.05$) (CD45+, CD4+, GATA3+). These findings suggest a dysregulated Th2 immune response in African American patients with HS. Our study indicates that African American patients with HS exhibit a heightened Th2 immune profile, as evidenced by increased Th2 cytokines, circulating basophils, and Th2 cell populations, suggesting a need for agents targeting broader immune axes in HS.

0717

Body image is less correlated with cutaneous lupus disease damage over time in skin of color patients

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Cutaneous lupus erythematosus (CLE) disproportionately affects patients with skin of color (SOC), who are more likely to have increased disease damage. Because the effects of disease damage on patient quality of life in CLE patients with SOC are not fully characterized, we performed a prospective study of 131 CLE patients seen in outpatient dermatology clinics at University of Texas Southwestern Medical Center and University of Pennsylvania to compare disease damage and patient-reported outcomes (PROs) over six months between racial/ethnic groups. Damage was quantified via the Cutaneous Lupus Erythematosus Disease Area and Severity Index damage score (CLASI-D), and PROs consisted of quality-of-life domains from the CLE Quality of Life Index. We performed Mann-Whitney tests to compare baseline and final CLASI-D after 6 months between CLE White Non-Hispanic (WNH) and SOC patients. We compared Spearman correlation coefficients between CLASI-D versus PROs at baseline and after six months between WNH versus SOC patients. At baseline, SOC patients had higher CLASI-D scores (n=92, median:15, IQR:10-26, p=0.001) compared to WNH patients (n=39, 7 (2-18)). They had worse associated PROs, including body image (ρ=0.24, p=0.03 vs ρ=0.17, p=0.36), functioning (ρ=0.36, p<0.01 vs ρ=0.13, p=0.42), and symptoms (ρ=0.43, p<0.01 vs ρ=0.37, p=0.02). At six months, damage was higher in SOC patients [25 (17.5-38) vs 23 (9-40.3)] but no longer associated with body image (ρ=0.16, p=0.18) in SOC patients. These findings point to potential adaptation in the perception of damage and associated body image in SOC patients, suggesting that treatment strategies to manage the sequelae of damage, including dyspigmentation and scarring, may be effective to mitigate its effects on quality of life in CLE patients with SOC.

0718

Analyzing the dermatological health needs of venezuelan migrants: A global burden of disease database study

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The ongoing Venezuelan migration crisis has resulted in over 7.7 million people fleeing their homeland due to political and economic instability, malnutrition, and human rights violations. Dermatologic diseases are highly prevalent among refugee populations due to overcrowded living conditions and limited access to healthcare. Despite this, comprehensive data on the dermatologic health burden in Venezuelan refugees remains limited. Therefore, our study assesses the dermatologic health needs of this population by analyzing data from the 2021 Global Burden of Disease (GBD) database to allow for more personalized care to Venezuelan refugees. This study extracted data from the 2021 Global Burden of Disease (GBD) database to evaluate the prevalence and disability-adjusted life years (DALYs) associated with skin diseases in the Venezuelan population. Data were stratified by specific dermatologic conditions and analyzed across age groups. Prevalence percentages and DALY contributions were calculated to assess the dermatologic health burden. The analysis revealed that skin and subcutaneous diseases had a prevalence of 24.53% and contributed to 1.22% of total DALYs among Venezuelans. The most prevalent dermatologic conditions were fungal skin diseases (5.78%), scabies (3.18%), and acne vulgaris (2.48%). The age-stratified data showed a gradual increase in the total prevalence of skin and subcutaneous disease, from adults aged 30-34 years (16.97%) to 90-94 years (58.67%). As Venezuelans seek dermatologic care in clinics worldwide, it is necessary for healthcare providers to understand the prevalence of skin conditions in this population. These findings highlight the need for tailored dermatologic care strategies to improve the quality of life of this population group suffering from migration-related stressors.

0719

Study of dermatological diseases in Iranians using the global burden of disease database

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Previous studies have highlighted the prevalence of infectious diseases such as cutaneous leishmaniasis, scabies, and dermatophytosis in Iran. Nevertheless, the overall burden that dermatologic diseases have on Iranians is relatively insufficiently explored. This study aimed address this gap by analyzing data from the Global Burden of Disease (GBD) database. On 9/24/2024, the GBD database was used to assess the prevalence and disability-adjusted life years (DALYs) associated with dermatological conditionals amongst individuals living in Iran. The Iranian population ages ranged from 5-94 in the study, with all the data categorized based on the specific type of dermatological condition. The most prevalent dermatological conditions identified in the Iranian population were fungal skin diseases (3.40%), acne vulgaris (2.87%) and atopic dermatitis (1.44%). In contrast, decubitus ulcer (0.012%) and cellulitis (0.002%) had some of the lowest prevalence. Notably, 27.23% of skin diseases did not have a classification. Age-stratified total prevalence pattern of all skin diseases increased modestly between the ages 5-9 years (16.63%) and 15-19 years (27.73%). Prevalence continued to increase steadily from 25 years of age to 94 years, with prevalence surpassing 40% in Iranians that were over the age of 80. The study examines the burden of dermatological diseases across all age groups in the Iranian population, with fungal infections, acne vulgaris, and atopic dermatitis having the highest prevalence. We recommend that dermatologists implement culturally sensitive care when treating Iranian immigrants and refugees, with a focus on these common skin diseases and the unique health challenges associated with unstable living conditions. Our findings sets a foundation for future research, including surveys and studies on refugees to better contextualize their health risks, as well as longitudinal studies to assess their risk of developing dermatologic conditions over time.

0720

Breaking barriers for sun safety: Comprehensive tool for equitable protection

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Introduction: Skin cancer prevention requires effective sun protection, but access to sunscreen remains limited, especially for low-income families. Gaps in Medicaid coverage exacerbate financial burdens, with sunscreen costs consuming 1.1–2.3% of disposable income for Medicaid households. This study explores non-insurance initiatives to improve sunscreen access, focusing on community-based programs, tax incentives, employer-sponsored efforts, and public health campaigns. Methods: We conducted keyword-based internet searches and reviewed websites from governmental, nonprofit, and private organizations to identify sunscreen access programs. We evaluated each initiative based on cost, accessibility, implementation feasibility, and sustainability. We identified 80 sunscreen access initiatives. Programs were categorized into four types: 53 community-based sunscreen programs, 3 tax incentive initiatives, 4 employer-sponsored distribution programs, and 20 public health campaigns. Results: Community-based sunscreen programs accounted for 66% of identified initiatives, offering accessibility in public spaces like parks and beaches but required ongoing maintenance and funding. Tax incentives (4%) promoted widespread adoption but had limited immediate benefits for low-income families. Employer-sponsored programs (5%) provided targeted support but excluded broader populations. Public health campaigns (25%) raise awareness but do not address financial barriers to sunscreen access. None of these approaches matched the reach or impact of Medicaid-like programs, highlighting a critical gap in addressing sunscreen accessibility for underserved populations. Conclusion: Current strategies fall short of addressing sunscreen disparities. A centralized, scalable solution involving nonprofits, private entities, and government agencies is critical for equitable skin cancer prevention. Future work will focus on creating a resource to guide policymakers in closing these gaps.

0721

Remote, participant-acquired images for acne research in transgender and gender-diverse individuals: A prospective cohort study

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Transgender and gender-diverse (TGD) patients face a high acne burden, yet remain underrepresented in acne research. Remote participant-acquired photographs may reduce barriers to research participation for TGD individuals, but feasibility data remain limited. This prospective cohort study aimed to describe the feasibility of obtaining participant-acquired photos (frontal, left, and right face, chest, and back) using interim results from an ongoing acne-specific study. Participants were recruited in academic dermatology and endocrinology clinics and a multidisciplinary gender center at a public hospital. At enrollment, participants received equipment and instructions for standardized image collection and secure submission at baseline, 1, 2, and 3 months. Feasibility was defined as the proportion of images deemed acceptable on initial review by trained reviewers who assessed images for blurriness, zoom, and proper labeling. Images requiring corrections were resubmitted. Twenty-two participants were enrolled (mean age 27.6 (6.9) years): 73% self-identified as transgender male or male, 23% as genderqueer or other, and 5% as transgender female. A total of 440 image submissions were made, of which 97% were acceptable upon initial upload. Thirteen images (3%) required resubmission, most commonly due to blurriness (38%) or improper distance (38%). Other resubmission reasons (62%) included filters (38%), missing images (15%), and mislabeling (8%). Left-face images had the highest resubmission rate (31%). Participant-acquired photos proved feasible with adequate quality for prospective remote research or clinical trials in a cohort of transgender and gender-diverse individuals. Study limitations include the single-center design and lack of a validated photo quality assessment. Future studies should evaluate whether participant-obtained photos consistently meet quality standards for reliable clinician assessment.

0722

A rose by any other name: Incidence and implications of donor-named dermatology departments

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This study aims to identify donor-named dermatology programs, their specific donation amounts, and explore how private funding sources shape the field of dermatology. We identified all dermatology residency programs participating in the 2024–2025 application cycle through the Electronic Residency Application Service (ERAS) directory. Two independent reviewers confirmed department names, and discrepancies were resolved by a third reviewer. Literature and internet searches were used to determine donation amounts. We identified 139 ERAS dermatology residency programs. Six were named after a prominent donor or donors. Geographically, three (50%) of these were located in the South and three (50%) in the Northeast. Eight programs were under private ownership without bearing the name of a specific donor. Four (50%) were in the Midwest, two (25%) in the West, and one each in the South (12.5%) and Northeast (12.5%). No privately owned departments disclosed funding. Of programs named after donors, four disclosed donation amounts, on average $9.5 million. The future of dermatology training and research requires diverse funding sources to ensure equity and long-term sustainability. Naming departments after private donors should come with great consideration, as donor objectives may not align with a department's mission. Future studies will investigate implications of named programs, specifically impacts on research, patient populations treated, and clinical training offered.

0723

Worsening trends in disparities of stage of presentation in acral lentiginous melanoma: A national cohort study

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Acral lentiginous melanoma (ALM), the most common histology seen in Black patients, presents with more advanced disease compared to other melanoma microscopic subtypes. The reasons are likely multifactorial and may include decreased awareness of this subtype by both patients and clinicians. We sought to study whether there has been improvement in early detection and presentation stage for ALM over time. This retrospective cohort study used the National Cancer Database to identify melanoma cases from 2010 to 2021, excluding those without staging information. Joinpoint regression was used to determine annual percent change (APC) in the proportion of patients with ALM vs non-ALM who presented with metastatic (AJCC stage III or IV) disease, and, in an independent analysis, the proportion with tumors thicker than 1 mm (T2 or greater). Of 424,903 total cutaneous melanoma patients, 6,543 (1.5%) had ALM and the remaining 418,360 (98.5%) had non-ALM. The median overall age was 64 years; 97.7% of patients were White. The percentage of ALM patients presenting with metastatic disease (Stage III/IV) increased over the study period (24.8% in 2010 to 33.9% in 2021, APC 0.67, p<0.001), as did the proportion of patients with T2 disease or greater (64.2% to 70.5%, APC 0.51, p=0.003). By comparison, for non-ALM patients over the same time period, there was a smaller increase in the proportion of patients with Stage III/IV (12.4% to 15.9%, APC 0.38, p=0.001) or with T2 or greater disease (41.5% to 45.1%, APC 0.28, p=0.001). ALM trends towards worse disease in more recent years seem to outpace overall melanoma trends. These findings underscore the need for effective methods for increasing awareness of and implementation of screening for ALM.

0724

Ethnic disparities in dermatomyositis mortality

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Recent reports have highlighted potential ethnic differences in the presentation and clinical course of dermatomyositis (DM), but mortality data of non-White groups with DM is limited. This retrospective, single-center study presents a review of DM mortality in a diverse patient cohort. Patients seen at UC Irvine Medical Center between Jan 2016 and Dec 2024 with adult-onset DM meeting ACR/EULAR criteria within this timeframe were included. Fisher's exact test and Log-rank test for hazard function analysis were performed. Of the 91 patients identified, 36.2% (33/91) were Non-Hispanic White, 36.2% (33/91) were Hispanic, 24.2% (22/91) were Asian, and 3.3% (3/91) were African American/Black. Documented dates of death were found in 10 of the 91 patients, wherein 60% (6/10) were Asian, 20% (2/10) were Hispanic, and 20% (2/10) were White. Log-rank tests demonstrated higher mortality rates in Asian patients compared to White (p=0.008) and Hispanic (p=0.02) counterparts. Mortality for Asian patients was significantly higher within one year of diagnosis compared to White and Hispanic counterparts (p=0.02). Malignancy was the cause of death for 100% (2/2) of Hispanic patients, 67% (4/6) of Asian patients, and 50% (1/2) of White patients. TIF1-γ was positive in 50% (5/10) of the deceased patients; 3 of these 5 patients were Asian. Autoantibody profiles in DM may vary across ethnicities and are strongly associated with clinical subtypes, such as MDA5 with ILD and TIF1-γ with malignancy. While ILD is recognized as a significant cause of mortality in MDA5+ DM, particularly among Asian patients, we found that our Asian patients cohort experienced higher mortality rates primarily due to TIF1-γ+ DM associated malignancies, rather than MDA5+ ILD. These findings may represent emerging trends that warrant further investigation. In summary, this study suggests differences in mortality rates across ethnicities and highlights the importance of assessing autoantibodies as predictors of disease outcomes. Validation in larger cohorts is needed to better understand these relationships and improve patient management.

0725

Disparities in geographic diversity, enrollment, and reporting trends for hyperhidrosis clinical trials

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The prevalence of hyperhidrosis varies globally, with higher rates documented in Asian populations. Despite its burden and growing therapeutic landscape, limited data exists on the diversity of populations in clinical trials. While the underrepresentation of racial and ethnic minorities in dermatology trials is well-documented, trends in hyperhidrosis trials remain unexplored. This study evaluates the geographic diversity, enrollment, and reporting of racial and ethnic minorities in phase II and III randomized control trials (RCTs) for hyperhidrosis. Completed clinical trials for hyperhidrosis conducted between January 2000 and November 2024 were identified through ClinicalTrials.gov and PubMed. Race and ethnicity demographics were extracted for each RCT. A total of 32 trials with 4,904 participants met inclusion criteria. Majority of the trials (n=22, 68.8%) were conducted in the last decade, with the United States being the most common location (n=22, 62.5%), followed by Germany (n=4, 12.5%), Canada (n=3, 9.4%), and France (n=2, 6.3%). Only 16 (50%) of trials reported race and/or ethnicity data. Of the 4,904 participants, 2,678 (54.6%) were White, 500 (10.2%) were Black/African American, 199 (4%) were Asian, 70 (1.4%) were more than one race, 15 (0.3%) were American Indian/Alaska Native, and 13 (0.3%) were Native Hawaiian/Pacific Islander. The remaining 1,429 participants (29.1%) were unknown or not reported. Furthermore, Hispanic or Latino ethnicity was reported in only 636 (13%) participants. These findings reveal significant gaps in reporting and participant diversity in hyperhidrosis RCTs, with nearly a third of participants lacking demographic. Trials are heavily concentrated in North America and Europe, with minimal representation from other regions. Future trials must expand to underrepresented global regions, improve participant diversity, and mandate standardized reporting of race and ethnicity data to ensure equitable outcomes and better reflect the global burden of hyperhidrosis.

0726

Acne incidence and severity in transgender adults: A multi-center cohort study

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Gender-affirming hormone therapy affects acne incidence in transgender persons, but epidemiologic data are scant. This study aimed to examine acne incidence in a validated cohort of transgender adults enrolled in Kaiser Permanente Northern and Southern California, Georgia, and Mid-Atlantic States. Transgender adults were followed from first documented transgender status (index date) to incident acne (≥1 ICD code) or moderate-to-severe acne (isotretinoin or ≥30 days oral antibiotics post-acne) in 1/2006–6/2024. Up to 10 cisgender male (CM) and 10 cisgender female (CF) adults were matched to each transgender adult by age, race/ethnicity, enrollment year, and site. Incidence rates were compared using negative binomial regression. 11,029 TM adults (mean age (SD) 28.7 (9.6) years) and 9,614 TF adults (mean age (SD) 33.5 (13.2) years) were matched with 149,260 CM and 150,175 CF adults. Mean (SD) follow-up time in TM and TF adults were 4.3 (3.4) and 5.2 (4.1) years. Incident acne rates were higher in TM adults than CM adults (Incidence rate ratio [IRR]=12.6, 95% CI 11.0–14.5; Incidence rates [IR]=29.7 vs 6.1) and CF adults (IRR=2.1, 1.9–2.4; IR=29.8 vs 19.0); and higher in TF adults than CM adults (IRR=3.5, 2.9–4.4; IR=9.8 vs 4.8), but lower than CF adults (IRR=0.6, 0.5–0.7; IR=9.9 vs 14.6). Incident moderate-to-severe acne rates were higher in TM adults than CM adults (IRR=51.6, 34.8–76.4; IR=11.4 vs 2.1) and CF adults (IRR=4.3, 3.2–5.9; IR=11.4 vs 5.0); and higher in TF adults than CM adults (IRR=2.3, 1.4–3.8; IR=2.3 vs 1.5), but lower than CF adults (IRR=0.4, 0.2–0.7; IR=2.3 vs 3.6). This study relied on clinician diagnosis and might not generalize to uninsured patients. Acne more commonly affects transgender adults than cisgender adults. Clinicians should proactively evaluate and manage acne and future research should examine long-term acne outcomes in transgender adults.

0727

Geographic and demographic disparities in chronic spontaneous urticaria clinical trials

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Chronic spontaneous urticaria (CSU) affects populations worldwide, with particularly high prevalence in Asian and Latin American populations. Although therapeutic options are expanding, limited data exists on the diversity of populations in clinical trials. While the underrepresentation of racial and ethnic minorities in dermatology clinical trials is well-recognized, trends in CSU trials remain unexplored. This study evaluates the geographic diversity, enrollment, and the inclusion of racial and ethnic data in phase II and III randomized control trials (RCTs) for CSU. CSU RCTs conducted between January 2000 and November 2024 were identified through ClinicalTrials.gov. Race and ethnicity data were extracted for each RCT. A total of 42 trials comprising of 10,012 participants met inclusion criteria. Most trials (n=32, 76.19%) were conducted within the last decade, with Germany being the most common trial location (n=21, 50.0%), followed by the United States (n=17, 12.5%), Spain (n=15, 35.71%), Canada (n=13, 30.95%), and Japan (n=12, 28.57%). Of the 42 trials included in the analysis, only 27 (74%) did not include race and/or ethnicity data. Of the 10,012 total participants, 55.34% (5,541) were unknown or not reported, 28.06% (2,810) were White, 0.94% (98) were Black/African American, 10.22% (1024) were Asian, .43% (44) were more than one race, 0.69% (70) were American Indian/Alaska Native, and 0.02% (3) were Native Hawaiian/Pacific Islander. Furthermore, only 0.54% (54) were reported as Hispanic or Latino. These findings highlight the urgent need to improve the racial/ethnic and geographic diversity in RCTs for CSU. There is a significant gap in demographic reporting with only a third of trials documenting demographic information. Future trials should expand to underrepresented regions, improve patient diversity, and prioritize the standardized reporting of race and ethnicity data to ensure equitable treatment outcomes and better represent the global burden of CSU.

0728
WITHDRAWN

0729
The dynamic landscape of genomic 5-hydroxymethylcytosine in mycosis fungoides reveals biomarkers for progression and prognosis.

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Mycosis fungoides (MF) is characterized by epigenetic aberrations, notably the loss of 5-hydroxymethylcytosine (5hmC), which serves as an epigenetic hallmark. However, as a key epigenetic marker in DNA methylation, the genomic landscape of 5hmC distribution and its implication MF progression and prognosis remains unraveled. We conducted 5hmC sequencing on a total of 97 skin lesions including 43 early-stage MF lesions, 32 advanced-stage MF lesions and 22 benign inflammatory dermatoses lesions. We found that, in the background of global reduction, 5hmC was enriched in the coding region of genes (gene body) as MF progresses. Gene body 5hmC levels positively correlated with the RNA expression levels of the corresponding genes in paired MF lesions. Gene body 5hmC levels followed the progressive trajectory from early stage to advanced stage MF. Genes with significantly high 5hmC levels in the late pseudotime trajectory were involved in T cell proliferation pathway, cell cycle pathway and central memory T cell phenotype. Among these genes, elevated expressions of central memory T cell marker LEF1 and CD27 were validated by immunohistochemistry staining and proposed as novel biomarkers for clinical prognosis in MF. Potential distal enhancer regions for LEF1 and CD27 were identified by 5hmC level correlation. Motifs of the ETS transcription factor family were significantly enriched in advanced stage, suggesting potential mechanisms driving MF progression. This study depicts a dynamic landscape of genomic 5hmC through MF progression and identifies novel molecular markers associated with prognosis. These findings contribute to the understanding of the epigenetic dysregulation in MF.

0730
Association of common variable immunodeficiency with NMSC: A retrospective case-control study using the trinetx dataset

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Common Variable Immunodeficiency (CVID) is a primary immunodeficiency that is characterized by hypogammaglobulinemia and immune dysfunction, as well as an increased risk of certain cancers. Of these, non-melanoma skin cancers (NMSC) have had conflicting evidence. It has been suggested to occur at elevated rates in certain cohorts, but also had a lack of association in others. Given these differences, this study aimed to explore such an association. This retrospective case-control study utilized the TriNetX (Cambridge, MA) United States network. Of 119,333,537 patients, 30,327 met CVID diagnosis criteria. The case group was defined using the ICD-10 code for individuals diagnosed with CVID. The control population included patients who had undergone at least one general outpatient annual physical examination and had no documented history of CVID, as identified using ICD-10 codes. An adjusted analysis with 1:1 propensity score matching between cohorts for age at index, sex, black and white ethnicity, and race was conducted. 29,529 patients were included after matching to controls. Individuals with CVID were more likely to have a diagnosis of SCC and BCC than those without CVID (SCC: OR: 3.817; 95% CI: 2.926,4.979; p<0.0001) (BCC: OR: 1.515; 95% CI: 1.228,1.868; p<0.0001). The findings suggest an increased risk of NMSC, specifically both SCC and BCC, in CVID patients. It is possible that such an increased risk could be due to the condition's impaired T-cell-mediated immunity. Such patients have a reduced immune surveillance and thus, the body's ability to eliminate pre-malignant cells may be impaired. The finding of increased SCC risk may mimic risks in iatrogenically immunosuppressed patients, such as organ transplant recipients. Additionally, the chronic inflammation, genetic mutations, autoimmune conditions, and infection in CVID may possibly contribute to a carcinogenic environment. Our findings underscore the need to investigate underlying physiology and enhance early detection to improve outcomes in CVID patients.

0731
Malignant T cells undergo metabolic reprogramming by creating a metabolic bypass through glucose-1,6-bisphosphate synthase PGM2L1 in cutaneous T cell lymphoma

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Metabolic reprogramming is a key factor in cancer progression. In cutaneous T cell lymphoma, especially the most frequent subtype mycosis fungoides (MF), elevated lactate dehydrogenase (LDH) levels are associated with poor prognosis, reflecting increased aerobic glycolysis. However, specific metabolic therapeutic targets for MF remain unidentified. In the current study, we identified that Phosphoglucomutase 2-like 1 (PGM2L1), a glucose-1,6-bisphosphate synthase, was highly expressed in the malignant T cells in MF tumors, while its expression is minimal in normal tissues and normal T cells. Moreover, PGM2L1 expression correlates with poor prognosis and elevated LDH levels in clinical data. Functional experiments revealed that PGM2L1 promotes tumor cell survival and resistance to apoptosis, as confirmed by *in vivo* experiments. Using isotope tracing and Seahorse metabolic assays, we demonstrated that PGM2L1 enhances glycolysis. The underlying mechanism involves PGM2L1 facilitating a metabolic bypass: it promotes glycogen consumption, and its product, glucose-1,6-bisphosphate, activates key glycolytic enzymes such as phosphofructokinase and pyruvate kinase, thereby increasing glycolytic flux. Additionally, PGM2L1 inhibits oxidative phosphorylation, reducing ROS production by regulating LDH activity. These findings suggest that PGM2L1 supports MF tumor progression by enhancing glycolysis through glycogen utilization and glycolytic enzyme activation, while suppressing oxidative phosphorylation and ROS-induced cell death. This metabolic reprogramming facilitates malignant T cells' adaptation to unfavorable environmental conditions by altering their metabolic pathways. Consequently, understanding this process is crucial for developing effective therapeutic strategies to target malignant T cells.

0732

Wounding triggers invasive progression in human basal cell carcinoma

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The interconnection between wound healing and cancer has long been recognized, as epitomized by the expression “cancer is a wound that does not heal”. However, the impact of inducing a wound, such as through biopsy collection, on the progression of established tumors remains largely unknown. In this study, we apply spatial, single-cell transcriptomics to characterize the heterogeneity of human basal cell carcinoma (BCC) and identify a wound response-associated gene program as a prominent feature of invasive and therapy-resistant cancer cells. To explore the causal relationship between wounding and cancer progression, we compare human tumors at baseline and one week post-biopsy. Our results demonstrate that biopsy collection triggers, in proximity to the wound, a transcriptional switch in cancer cells and cancer-associated fibroblasts (CAFs) coupled with an invasive morphological pattern. Notably, the wound-induced cancer cell and CAF transcriptional states resemble those found in advanced, therapy-resistant BCC. This study provides evidence that wounding triggers invasive progression of established human tumors and warrants further research on the potentially harmful effects of biopsies and wound-inducing treatments.

0733

Spatial immune landscape of cutaneous squamous cell carcinomas (cSCC) prior to immune checkpoint blockade

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This project aimed to elucidate the spatial relationships and chemokine networks among key immune cells in cSCCs before immune checkpoint inhibition (ICI) therapy. Spatial analyses of baseline tumors (FFPE samples) from patients treated with anti-PD1 therapy was performed, correlating these findings with documented clinical responses to ICI (n=10). Spatial transcriptomics platforms (Merscope and Xenium) were used, targeting over 400 genes focused on immuno-oncology. Probes were selected to investigate immune cell phenotypes, cell-cell communication, and tumor-intrinsic proteins. In responder patients, a significant upregulation of key chemokines, including CCL19, CXCL9-11, and CXCL13 was observed, compared to non-responders. CCL19 and CXCR3 ligands (CXCL9-11) can be secreted by dendritic cells or macrophages, while CXCL13 can be produced by T cells. CCL19 interacts with CCR7, and CXCL9-11 with CXCR3 on T cells. CXCL13, on the other hand, potentially recruits B cells from circulation into the tumor microenvironment. In responder cSCC patients, T cells and APCs were co-localized within the tumor microenvironment. In these cellular neighborhoods, elevated expression of markers associated with tissue-resident memory T cells, such as ITGAE (CD103) and ITGA1 (CD49a), was observed ($p < 0.05$). Additionally, markers such as LAMP3 (a dendritic cell marker) and Flt3-Ligand are were upregulated ($p < 0.05$). Flt3-Ligand can enhance dendritic cell proliferation. In contrast, non-responder patients exhibited upregulation of markers such as TREM2, which has been linked with macrophages and poor prognosis in other cancer cohorts. Overall, these findings suggest a critical role for antigen-presenting cell–T cell interactions in the tumor microenvironment of cSCC responder tissues. The effective recruitment of T cells into the tissue, along with the activation of resident T cells already present within the tissue, may serve as key determinants of therapeutic success.

0734

Differential utilization of superficial x-ray and electron beam radiotherapy for keratinocytic carcinomas: Analysis of patient demographics and tumor characteristics

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Background: Although Mohs micrographic surgery and wide local excision are standard treatments for keratinocytic carcinomas [i.e., squamous cell carcinoma (SCC) and basal cell carcinoma (BCC)], both superficial x-ray radiotherapy (SXRT) and electron beam radiotherapy (EBRT) are viable alternatives. SXRT is typically indicated for tumors up to 5mm in depth, while EBRT can treat more deeply invasive tumors. Objective: To better characterize the clinical utilization of SXRT and EBRT, we analyzed SCC/BCC cases referred to radiation oncology within the Tufts Medicine network from 2009-2024. Results: Of 108 patients seen for consultation, 76% initiated radiotherapy and completed treatment, with radiation dermatitis (76%) being the most common adverse event. Dermatology was the primary referring specialty (79%), followed by otolaryngology (8%). Indications for radiation monotherapy included surgical aversion (46%), surgical contraindications (13%), and failed chemotherapy (1%). Of 97 treated tumors, there were 50 SCCs and 47 BCCs. SXRT and EBRT treated similar proportions of SCCs/BCCs confined to the skin/soft tissue, similarly distributed across high-risk anatomical sites (e.g., face, hands, feet), and had comparable high-risk factors (e.g., perineural and lymphovascular invasion). SXRT was predominantly utilized as monotherapy (77%; n=43), while EBRT primarily served as an adjuvant (59%; n=24) ($p=0.001$). Tumors treated with EBRT were larger than tumors treated with SXRT ($p=0.024$). Limitations: Retrospective study design examining a single healthcare network. Conclusion: Although radiotherapy constitutes a fraction of SCC/BCC treatments compared to surgery, it is a well-tolerated non-invasive therapy that can be used for tumors in challenging anatomical sites and with high-risk features. Dermatologists are pivotal in recognizing eligible patients and optimizing treatments based on specific clinical needs.

0735

Increased expression of SMAD6 contributes to photoaging via suppression of TGF-β signaling pathway

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Photoaging is a skin aging symptom caused by chronic ultraviolet (UV) exposure and it remains a significant unresolved issue. In the dermis of photoaged skin, a decrease or degeneration of elastic fiber is typically observed, contributing to reduced skin elasticity. TGF-β signaling is known to regulate elastin expression, but the effects of long-term exposure to UV on the molecules that mediate this signaling are not completely clear. In this study, we collected sun-protected skins from young and elderly subjects, as well as sun-exposed skin from the elderly ones, for immunohistological analysis. We found that the expression of SMAD6, an inhibitory factor of TGF-β signaling, was increased in dermal fibroblasts of the sun-exposed skin of the elderly subjects compared to the sun-protected skin of the young ones. Based on this finding, we screened plant extracts that inhibit SMAD6 expression using cultured fibroblasts, aiming to develop a new cosmetic technology for anti-photoaging care. Consequently, Geranium thunbergii extract suppressed SMAD6 expression and increased elastin, fibrillin-1 gene expression, and elastic fiber formation. These results suggest that SMAD6 is a novel factor involved in photoaging via suppression of TGF-β signaling and inhibition of SMAD6 by botanical extracts could be a promising strategy to prevent and/or improve photoaging.

0736

Expression of immune checkpoint VISTA in cutaneous squamous cell carcinoma is correlated with T cell infiltration and activation

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Cutaneous squamous cell carcinoma (cSCC) is one of the most common human cancers whose estimated deaths approach or exceed that of melanoma. Blockade of programmed death receptor 1 (PD-1) or its ligand PD-L1, has revolutionized the treatment of cSCC; however, approximately half of the patients still fail to respond. Inhibitory receptor V-domain immunoglobulin suppressor of T cell activation (VISTA), also known as programmed death-1 homolog (PD-1H) functions to control T cell and myeloid cell functions in pre-clinical cancer studies. Current clinical trials using anti-VISTA blocking antibodies for cancer immunotherapy are ongoing. Additionally, VISTA expression can increase within the the tumor microenvironment in response to anti-PD-1 therapy. We sought to determine the extent of VISTA expression in cSCCs and correlate its expression with PD-L1. Using multiplexed quantitative immunofluorescence of primary cSCC tissues (n=76) we found that VISTA is expressed in 48% of cSCCs and PD-L1 is expressed in 58% of cSCCs. We found high VISTA expression, more than PD-L1 expression, was correlated with greater CD3 and CD8 T cell infiltration and activation as measured by proliferation marker Ki-67 and cytotoxic marker Granzyme B. Furthermore, there was no significant correlation between VISTA and PD-L1 co-expression within the same cSCCs, suggesting individual tumors have distinct immunosuppressive microenvironments. These findings provide rationale for targeting VISTA for cSCC cancer immunotherapy. They also suggest that identifying subsets of patients whose tumors express distinct immune checkpoints such as VISTA or PD-L1 and their binding partners may allow for more rationally designed clinical trials and biomarker-driven therapeutic strategies.

0737

Genomic analysis of UV-induced mutations in normal skin cells of dark and light-skinned individuals

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This project aims to investigate how pigmentation influences the earliest stages of skin cancer development by examining the genomic landscape in skin cells across individuals of light and dark skin tones. We obtained punch biopsies from body sites with varying sun exposure. Somatic mutations in melanocytes and keratinocytes were identified through a multi-step process: single cells were expanded into small colonies, their genetic material was extracted and amplified, and the resulting nucleic acids were sequenced at the exome level. In total, we sequenced 67 melanocytes and 25 keratinocytes from 3 African American donors. For comparison, we also analyzed mutations in 237 melanocytes and 131 keratinocytes from 14 white donors. The mutation burdens were, on average, approximately twice as high in melanocytes from white donors after accounting for cell type and anatomic site. These findings suggest melanin may mitigate the effects of UV-induced mutations. We also observed a higher frequency of cytosine-to-thymidine transitions at dipyrimidine sites in skin cells from individuals with lighter skin tones compared to those with darker skin. These mutations are markers of UV radiation-induced DNA damage. Furthermore, we analyzed mutational differences across chronically, intermittently, and minimally sun-exposed regions between the two groups to assess the impact of UV exposure on mutation rates. Our analysis revealed that regions with intermittent sun exposure (i.e., shoulder) exhibit higher levels of DNA damage compared to chronically exposed areas, such as the face. This suggests that DNA repair mechanisms may vary across different anatomical sites. These findings could improve our understanding of skin cancers in all populations, particularly in areas of the body less exposed to the sun or in individuals with lower cumulative UV exposure. Moving forward, we strive to refine early detection methods and create personalized screening guidelines that address the diverse factors contributing to skin cancer risk.

0738

Multiplex immunofluorescent detection of T-cell and myeloid subsets reveals histologic subtype differences in the immunosuppressive landscape of human basal cell carcinoma (BCC)

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BCC is the most diagnosed skin cancer worldwide. Most skin cancers, including BCC, are known to have an immunosuppressive tumor microenvironment, yet little is known about how immune environments differ by BCC histologic subtype. Since histologic subtype correlates with disease aggressiveness, an understanding of immune microenvironmental differences across subtypes may guide treatment decisions. Utilizing the Vectra Polaris multiplex immunofluorescence system from Akoya Biosciences, we designed two staining panels, targeting either T-cells (CD3, CD4, CD8, FOXP3, PD1) or myeloid cells (neutrophil elastase, CD68, CD163, HLADR, CD1c). PanCK and DAPI were included to stain tumor nests and live cells respectively. A series of formalin-fixed paraffin-embedded (FFPE) BCC tumor specimens (n = 30) were analyzed with both the T-cell and myeloid panels. Most immune cells appeared to reside in the peritumoral margin, so we used a boundary zone of 150 µm around tumor nests to determine immuno-phenotypes. A CD8/T-reg ratio and a M1/M2 macrophage ratio of < 0.5 was observed across all BCC specimens, confirming an overall immunosuppressive phenotype. When assessing different histologic subtypes, we found that infiltrative BCC subtypes had a significantly lower proportion of CD8 T cells ($p = .038$) and greater proportions of T-regs ($p = .039$), as well as significantly lower CD8/T-reg ($p = .048$) and M1/M2 ($p = .034$) ratios compared to non-infiltrative subtypes. This indicates that infiltrative BCC subtypes are associated with a more immunosuppressed microenvironment, potentially accounting for their more aggressive nature. Overall, we demonstrate a method to determine T cell and myeloid profiles in fixed (FFPE) tissue of human BCC, to identify immune profile differences. Future studies using this technique will help determine how various treatments can reverse the immunosuppressive nature of BCC, to improve long-term clearance.

0739

Prevention of hev-blue light-induced skin lipofuscin accumulation with a triasorb-containing formulation

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Lipofuscin is a fluorescent pigment made of oxidized proteins and lipids which accumulate during natural or accelerated cell aging. Keratinocytes exposed to UVA and High Energy Blue Light (HEBL) are known to suffer expressive damages in lysosomes and to accumulate lipofuscin. In here, we aim to report whether fibroblasts exposed to UVA and HEBL also accumulates lipofuscin. We also aim to test the efficacy of a TriAsorB-containing formulation (F1) to avoid lipofuscin accumulation in keratinocytes and fibroblasts. Fibroblasts exposed to UVA (356nm; 15 J/cm^2), violet (410nm; 30J/cm^2) or blue (450nm; 110J/cm^2) light shows significant increase in lipofuscin accumulation, as demonstrated by the integration of the intracellular fluorescent signals of lipofuscin pigments (I_{esc}=488nm, I_{emi}>522nm), as well as by Sudan-Black staining. The quantum efficiencies of lipofuscin accumulation in skin fibroblasts exposed, respectively to UVA, violet and blue photons, considering the lipofuscin quantification, and the relatives' photon energies, sun irradiances and skin penetrations, shows the ratio of 1.0:1.1:0.6. So, anti-aging strategies related with sun exposure must offer equilibrated protection in the UVA and visible ranges. Then, we compared the accumulation of lipofuscin in cells whose wells were not protected, with those that were protected with F1 or with placebo formulations. Uncontrolled and placebo showed similar levels of lipofuscin accumulation. F1 formulation protected both keratinocytes and fibroblasts from lipofuscin accumulation. The efficiencies of protection of the F1 formulation varied from 80 to 95%. TriAsorB offers broadband protection extending to the HEV-Blue light range, significantly avoiding the accumulation of lipofuscin and consequently efficiently avoiding the sun-induced photoaging.

0740

Spatial transcriptomics reveals a unique tumor microenvironment distinguishing the invasive region from the premalignant area in early-stage cutaneous squamous cell carcinoma.

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Cutaneous squamous cell carcinoma (SCC) progresses in a stepwise manner, transitioning from healthy skin to premalignant actinic keratosis (AK) and ultimately to malignant SCC. However, the gene expression changes within the tumor microenvironment throughout this progression remain underexplored. In this study, we retrospectively analyzed early-stage cutaneous SCC tissue samples containing both invasive and premalignant regions. Using the NanoString GeoMx Digital Spatial Profiler (DSP), we conducted spatial transcriptomic analyses. Regions of interest (ROIs) were selected from the invasive and premalignant areas within each tissue sample, focusing on three cellular components: tumor cells, immune cells, and fibroblasts. Gene expression patterns were compared between these regions across the 17 selected patient samples. We identified differentially expressed genes (DEGs) in each cellular component: 29 DEGs in tumor cells, 14 in immune cells, and 15 in fibroblasts. The three genes with the greatest differences in expression levels were CCDC88C, GJD3, and COMP in tumor cells; SVEP1, TSLP, and PPP2R5C in immune cells; and SPAG6, PPP1CA, and CCDC68 in fibroblasts. were associated with the development and function of cancer-associated fibroblasts. Functional enrichment analysis revealed significant alterations in various pathways, particularly within tumor and immune cells. Overall, this study highlights distinctive changes in gene expression patterns as premalignant AK evolves into invasive SCC.

0741

Polypodium leucotomos (PL) is ineffective in reducing ultraviolet (UV) induced erythema, edema, or tumor initiation when supplementing a plant-based diet in a mouse model of UV-induced carcinogenesis

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Dietary supplements containing PL are marketed to protect from acute sunburn. PL has been suggested to protect against UV damage through its antioxidant effect. However, the effects of skin-targeting dietary supplements are multifaceted and poorly understood in the acute and chronic photocarcinogenesis setting. The SKH1 mouse model was used to measure the ability of PL to reduce erythema and edema induced by acute UV irradiation with a solar simulator, as well as tumor initiation after chronic UV exposure. In the acute UV studies, SKH1 mice were randomized into PL-containing (n=4) or regular plant-based control diet (n=4) groups, and after 1 week of consuming each diet, the mice were irradiated with escalating doses of UV. The mice were followed for one week after irradiation. In the chronic UV studies, SKH1 mice were fed the PL (n=10) or control diet (n=10) during the 10-week solar simulated UV irradiation period and returned to the control diet after the UV exposure ended. In both studies, mice were regularly photographed to document erythema, edema, tumor formation, and growth. There was no significant difference in erythema, edema, or tumor formation in mice fed the PL diet compared to control (average 6.0 tumors/mouse PL and 3.3 tumors/mouse control p=0.147 analyzed with an unpaired student's t-test). The levels of metabolites detected in the PL diet were 2-fold higher than the control grain-based diet. In similar studies, reduced UV dose led to decreased erythema and edema in the acute setting and significant decreases in tumor formation in the treated areas after chronic UV exposure. These studies provide crucial preliminary data to establish the true efficacy of PL on acute UV response and cancer risk reduction when supplementing a nutritionally complete plant-based diet.

0742

N-MYC amplification as a secondary mutation that promotes basal cell carcinoma progression

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Basal cell carcinoma (BCC) is by far the world's most common cancer. Although these tumors are initiated by mutations that activate upstream Hedgehog signaling—loss of PTCH1 or constitutive activation of SMO—our previous studies have revealed that secondary mutations are also required to drive subsequent tumor progression from microscopic to macroscopic disease. MYCN is recurrently amplified or stabilized in human BCC, and N-Myc is upregulated in mouse BCCs. Here, we show that genetic deletion of Mycn delays tumor progression in a BCC mouse model initiated by loss of Ptch1. Using a newly developed *in vitro* system for culturing numerous mouse BCC cell lines, we further observed that Hedgehog signaling is rapidly silenced *in vitro*, and that inducible expression of N-MYC promotes tumor cell expansion by downregulating differentiation markers such as Keratin 10 and Notch pathway activation. Critically, N-MYC overexpression *in vivo* also downregulates Keratin 10 and Notch signaling in tumors. Finally, RNA-seq and functional analyses suggest that N-MYC can modulate components of the TGFb superfamily. Altogether, our work identifies both N-MYC-dependent and –independent mechanisms that drive BCC progression to malignant disease.

0743

Single-cell RNA sequencing characterization of mogamulizumab-associated drug rash in cutaneous lymphoma patients

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Mogamulizumab is an anti-CCR4 therapeutic antibody approved for relapsed or refractory mycosis fungoides and for Sézary syndrome. During treatment, a subset of patients develops a mogamulizumab-associated drug rash (MAR) that is associated with a better overall survival, but underlying mechanisms remain unclear. In addition, misinterpretation of MAR as CTCL progression can lead to unnecessary drug discontinuation. We performed single-cell RNA sequencing of skin biopsies from 4 patients with MAR, in comparison to untreated erythrodermic CTCL (eCTCL, n=6) and healthy controls (HC, n=4). We found a strongly expanded malignant clone in all eCTCL skin samples (range 29%-79% of all T cells), whereas numbers were significantly lower or even absent in MAR (range 0%-39% of all T cells). As expected, we found a significant decrease in CCR4+ T cells in MAR, together with reduced numbers of FOXP3+ regulatory T cells, compared to both eCTCL and HC samples, in line with the strong pro-inflammatory microenvironment within MAR lesions. Remaining malignant clones in MAR samples showed decreases in the central memory markers SELL and CCR7, as well as the TSLP-receptor component CRLF2 and the lymphoma marker KIR3DL2. We have previously demonstrated that increased B cell counts within the tumor microenvironment are associated with advancing CTCL. Importantly, we found decreases in the B-cell attracting chemokine CXCL13 within MAR lesions, paralleled by reduced numbers of CD19+ B cells. Within polyclonal bystander T cells, we found decreased levels of the exhaustion marker TIGIT in MAR compared to eCTCL, potentially reflecting a more tumor-permissive microenvironment in the latter. In sum, our study provides insights into molecular properties of residual malignant clones within MAR, which show an overall attenuated phenotype.

0744

The vitamin D_3 hormone, 1,25$(OH)_2D_3$, regulates fibroblast growth factor 23 (FGF23) production in human skin cells

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The bone hormone fibroblast growth factor 23 (FGF23) regulates renal phosphate reabsorption and the enzymatic production of active vitamin D_3 (1,25$(OH)_2D_3$). Therefore, FGF23 production in bone cells is closely regulated by 1,25$(OH)_2D_3$ acting via the vitamin D receptor (VDR). Skin cells can produce hydroxyvitamin D_3 metabolites from its precursor D_3 made through UVB-light exposure. Interestingly, expression of Fgf23 has been found in rodent skin, but its expression, regulation, and role in human skin are unclear. Therefore, we investigated whether hydroxyvitamin D_3 metabolites regulate FGF23 in human skin cells. Primary adult and neonatal epidermal keratinocytes (HEKn), melanocytes (HEMn), dermal fibroblasts (HDFn), as well as human melanoma cells, HaCaT, HaCaT VDR KO, and A431 epidermoid cells, were used to assess FGF23 gene expression (qRT-PCR), cellular FGF23 protein (western blot), or secreted FGF23 protein (ELISA) after treatment with hydroxyvitamin D_3 metabolites. HaCaT cells treated with recombinant FGF23 were used to explore its function in skin. Human skin cells can synthesize FGF23. Treatment with 1,25$(OH)_2D_3$ significantly increased FGF23 mRNA levels in HaCaT and HDFn cells, and moderately in HEKn cells, mediated in part by the VDR. It also moderately enhanced mRNA levels of the FGF23-processing enzyme GALNT3 and stimulated secretion of hormonally active FGF23 from HaCaT cells. Treatment of HaCaT cells with FGF23 increased mRNA levels of the cholesterol- and vitamin D-metabolizing enzymes, CYP11A1 and CYP27A1. In conclusion, human skin cells express and secrete FGF23, which is regulated by 1,25$(OH)_2D_3$ acting in part by the VDR. FGF23 affects the expression of cutaneous sterol-metabolizing enzymes

0745

Selective effects of apocynin and diphenyleneiodonium on COL17 expression and cellular aging in keratinocytes

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Background: Apocynin, a potent NADPH oxidase inhibitor, has been reported to induce collagen 17 (COL17), a key protein associated with skin health. UV radiation accelerates cellular senescence via oxidative stress and DNA damage, contributing to skin photoaging, while aging is linked to reduced COL17 expression and increased senescence. This study hypothesized that apocynin induces COL17 through its NADPH oxidase inhibitory effect. Methods: hTert-immortalized keratinocytes (KER-CT) were pretreated with apocynin or diphenyleneiodonium (DPI) (10, 20, and 40 μM) for 24 hours prior to UVB exposure (100 J/m^2). Klotho and wild-type mice were administered apocynin in drinking water (2.5 g/l/kg) for 5 weeks. COL17, p16, and γ-H2AX levels were assessed via immunofluorescence; p16, p21, p53, LaminB1, and PAI-1 were quantified by qRT-PCR; and NOX4, p16, γ-H2AX, pP38, p65, and MMP-9 were analyzed using western blot. Cellular senescence was evaluated through SA-β-gal staining and cell cycle analysis with propidium iodide/RNase. Results: UVB exposure decreased COL17 expression while increasing NOX4, pP38, p65, MMP-9, γ-H2AX, and senescence markers (SA-β-gal, PAI-1), alongside reducing LaminB1 and causing cell cycle arrest. Apocynin reversed these effects by restoring COL17, reducing NOX4, pP38, p65, MMP-9, γ-H2AX, and senescence markers, increasing LaminB1, and alleviating cell cycle arrest may be through oxidative stress reduction. *In vivo*, apocynin upregulated COL17 and reduced senescence markers in Klotho mice. Conversely, DPI reduced DNA damage and p16 expression but did not impact COL17 or other senescence markers. Conclusions: Apocynin induces COL17 expression independently of NADPH oxidase inhibition, suggesting alternative mechanisms of action.

0746

The regulatoryrole of OPN1sw in UVB-induced activation of P53 in human epidermal keratinocytes

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Background: Ultraviolet B (UVB) radiation is a significant factor contributing to DNA damage in skin cells, which can ultimately lead to skin cancer. P53 plays a crucial role in repairing DNA damage, but it is unclear whether photosensitive proteins in the skin transmit light signals to activate P53 and initiate its gene guardian function. Objective: This study aimed to explore whether OPN1sw perceives UVB and regulates P53 activation. Methods: Normal human epidermal keratinocytes (NHKs) were irradiated with UVB, and cell lysates were collected 8 hours later. Western blot (WB) was used to determine the expression of OPN1sw, OPN2, OPN3, OPN4, OPN5, and P53. Immunofluorescence analyzed the co-localization of OPN1sw and P53 proteins in NHKs. Plasmid transfection technology was used to increase OPN1sw levels, and the comet assay measured DNA damage after UVB irradiation. Results: WB showed significant changes in OPN1sw expression among the five opsins after UVB irradiation, with synchronous increases in OPN1sw and P53 expression. Immunofluorescence revealed significant co-localization of OPN1sw and P53 proteins. The comet assay showed significantly lower DNA damage levels in OPN1sw-overexpressing cells compared to the negative control group after UVB irradiation. Conclusion: Our study presents the first evidence that UVB can induce an increase in the expression of OPN1sw in HEKs. The over-expression of OPN1sw in HEKs led to significantly lower DNA damage after UVB irradiation compared to the control group, which might be attributed to OPN1sw enhancing the repair effect of P53 on DNA damage.

0747

The synergistic effects of UVA and DHT in the senescence of dermal papilla cells in hair loss

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Androgenetic alopecia (AGA) is one of the most common forms of hair loss, and recent studies suggest that dihydrotestosterone (DHT)-induced senescence of dermal papilla cells (DPCs) plays a crucial role in its pathogenesis. Clinically, we have observed overlap between areas exposed to ultraviolet (UV) radiation and regions affected by androgenetic hair loss. However, the link between UVA radiation, which penetrates deep into the dermis, and the onset of AGA remains unclear. In this study, we investigate the role of UVA in exacerbating DHT-induced hair loss, with a focus on the potential activation of cellular senescence pathways. We utilized an AGA mouse model and combined it with UVA irradiation to examine the role of UVA in delaying DHT-induced hair growth. To further investigate the mechanisms of the interaction between DHT and UVA, we isolated human dermal papilla cells (DPCs) and performed transcriptome sequencing analysis. UVA accelerates DHT-Induced hair growth delay in AGA mouse model. UVA intensifies DHT-induced cellular senescence in hDPCs. This process is associated with the activation of mTOR pathway. However, rapamycin alleviates this UVA- and DHT-induced cellular senescence by modulating autophagy dysfunction. Furthermore, rapamycin effectively reverses UVA-exacerbated DHT-induced hair loss in AGA mouse model. UVA exposure can affect autophagy levels via mTOR pathway, enhancing DHT-induced cellular senescence in DPCs.

0748

Synergy of TP53 and non-canonical sonic hedgehog pathway in the development of complex basal cell carcinoma

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Basal cell carcinoma (BCC) is the most common cancer, with an incidence of approximately 3.6 million cases annually in the United States. Common BCC arises in chronically UV-induced damaged skin. Although the main driver oncogenes in common BCC include mutations in Sonic Hedgehog (SHH) pathway, a rare subset of aggressive and complex BCCs exhibits mutations in non-canonical pathways in synergy with TP53 mutations, in addition to other well studied oncogenes that are also involved in highly aggressive and potentially deadly pancreatic or renal carcinomas among others. Not only do complex BCC differ from the common ones in clinical presentation, but they also differ in treatment-resistant course of the disease to Hedgehog inhibitors (HHI) due to lack of PTCH mutations, which is the main driver oncogene in common BCC. Although complex BCC stems from the basal layer, hence presenting histologically similar to other BCCs, these patients experience a clinically divergent course of the disease that is complex, destructive, and highly aggressive. This warrants genomically driven and timely personalized or targeted treatment planning to avoid disfiguration and to save lives. Thus was performed a bioinformatic analysis of whole exome genomics of ten complex BCCs acompanied by correlated immunohistochemistry compared with five common BCCs. Our preliminary findings are indicative of a synergistic interplay of TP53, non-canonical SH pathways, with other aggressive driver oncogenes seen in other more deadly carcinomas such as pancreatic and renal. Understanding the genomics in these BCC subsets has guided a more promising treatment plan in presenting patients.

0749

Serine and arginine-rich splicing factor 3 regulates epidermal differentiation in cutaneous squamous cell carcinoma

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Serine/Arginine-rich splicing factor 3 (SRSF3) is one of 12 SRSFs that regulate gene expression via alternative splicing. SRSF3 overexpression is associated with the progression of many different solid malignancies. However, SRSF3 expression in keratinocyte cancers remains uncharacterized and the role of this protein in the skin is unknown. Analysis of RNA-seq data from 279 human skin tissues revealed upregulation of SRSF3 in cutaneous squamous cell carcinoma (cSCC) compared to normal skin. This was mirrored by higher expression of SRSF3 in squamous cancer cell lines in relation to normal primary human keratinocytes. Reduction of SRSF3 with a specific inhibitor, SFI003, resulted in enhanced epidermal differentiation *in vitro* as well as in skin organoid models, with induction of both early (MAF, KRT1) and late (IVL, FLG, LCE3D, CASP14) differentiation markers. Our data suggests that in cSCC, SRSF3 overexpression suppresses cellular differentiation to enable cancer progression. In a clinical setting, patients taking known SRSF3 inhibitors digoxin (n=4,149) and amiodarone (n=9,579) exhibited higher cSCC-free survival compared to a propensity score-matched cohort treated with beta blockers (n=100,000; down sampled). The adjusted hazard ratios (HR) for digoxin (0.57, 95% CI 34-95%) and amiodarone (0.59, 95% CI 40-87%) revealed a lower risk of developing cSCC. Thus, SRSF3 upregulation may be a novel therapeutic target in cSCC that can improve patient prognoses.

0750

Proteomics and transcriptomics profiling define molecular subtypes of advanced cutaneous T cell lymphoma and prognostic biomarkers

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Cutaneous T-cell lymphomas are a heterogeneous group of diseases, with mycosis fungoides (MF) and Sézary syndrome (SS) being the most common subtypes. The disease of advanced stage patients is aggressive, the treatment heterogeneity is great, and the pathogenesis is still unclear. To define molecular subtypes of advanced MF/SS, we perform mass spectrometry-based proteomic and transcriptomic profiling of advanced MF/SS using 33 skin biopsies of tumor cells infiltration obtained with laser capture microdissection. We identified three subtypes of advanced MF/SS with significant phenotypic differences (p=0.001). The function and enrichment pathways of the characteristic proteins in the three subtypes are significantly different, related to intracellular signaling, energy metabolism, and extracellular matrix remodeling, respectively, revealing heterogeneity among advanced MF/SS patients and providing new insights into the pathogenesis of different subtypes. In addition, by comparing the proteomic profiles of patients with different treatment responses and prognosis, we identified biomarkers that may be useful in predicting treatment difficulty and progression, which were validated by immunohistochemical staining.

0751

Association of alport syndrome with NMSC: A retrospective case-control study using the trinetx dataset

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Alport syndrome (AS) is a genetic condition, with predominantly X-linked dominance and autosomal variants in inheritance. It affects up to 60,000 people in the US. It is a disorder with mutations in COL4A3, COL4A4 and COL4A5 that affect type IV collagen, resulting in chronic kidney inflammation, ocular abnormalities, and sensorineural hearing loss. Patients are managed for chronic kidney disease and may undergo kidney transplantation. Systemic inflammation is a key characteristic of the syndrome, yet, to date AS has been associated with diffuse leiomyomatosis and not been investigated for associations with other neoplasms. Given its impact on skin integrity, this study sought to look at the association between AS and non-melanoma skin cancer (NMSC). The TriNetX (Cambridge, MA) US network was utilized to conduct a retrospective case-control study. The case group was defined using the ICD-10 code for individuals diagnosed with AS. The controls included patients who had undergone at least one general outpatient annual physical examination and had no documented history of AS, as identified using ICD-10 codes. We performed adjusted analyses with 1:1 propensity score matching between cohorts for age at index, sex, black and white race and ethnicity. Of 114,251,452 individuals in the US network, 41,939 met AS diagnosis criteria. 37,905 were included after matching to controls. Individuals with AS were more likely to have a diagnosis of SCC and BCC compared to those without (SCC: OR: 4.152, 95% CI: 2.577,6.687, p<0.0001) (BCC: OR: 3.942, 95% CI: 2.954,5.262, p<0.0001). Our results suggest that there is a significantly increased risk of NMSC in patients with AS. No case-control studies have been conducted on this association, making this the largest retrospective study available. It is possible that factors such as chronic inflammation, immunosuppression following transplant and defects in the skin barrier from collagen IV mutation could potentially explain our findings. Further investigation into this association and its underlying mechanism is warranted.

0752

The role of OPN1-SW in regulating UVB induced vitamin D3 metabolism in human epidermal keratinocytes

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Background: Active vitamin D3 is mainly produced by the skin. After UVB irradiation, the accumulated 7-dehydrocholesterol is converted into vitamin D3 precursor by the action of 7-dehydrocholesterol reductase (DHCR7), and then produced through a series of metabolic processes. Opsin, a family of light-sensitive G protein-coupled receptors (GPCR), is widely distributed in the skin and plays an important role in light signal transmission. However, it is currently unclear whether opsin also plays a light regulatory role in the production and metabolism of vitamin D3 induced by UVB. Objective: The aim of this study is to explore in depth the role of shortwave sensitive OPN1SW in UVB induced vitamin D3 metabolism. Methods:Collect cell samples at specific time points after irradiating human epidermal keratinocytes with different doses of UVB. Real time fluorescence quantitative PCR (qRT PCR) and Western blot techniques were used to detect the expression changes of opsins 1-5 and DHCR7 at the mRNA and protein levels. Use high-performance liquid chromatography-mass spectrometry (HPLC-MS/MS) to detect the content of vitamin D3 in cells. Cell immunofluorescence technology was used to detect the expression of OPN1SW and DHCR7 in keratinocytes before and after exposure to UVB light. Results:Compared with other visual proteins, the expression of mRNA and protein levels of OPN1SW increased at a UVB dose of 10mJ/cm^2. Compared with the control group, there was a negative correlation between OPN1SW and DHCR7 expression after UVB irradiation, and the content of vitamin D3 in cells increased. Under a fluorescence microscope, it was observed that compared to the control group, exposure to UVB light increased the expression of OPN1SW and decreased the expression of DHCR7. Conclusion: OPN1SW may have a positive regulatory effect on UVB induced vitamin D3 metabolism, which may regulate the synthesis and metabolism of vitamin D3 by affecting the expression of DHCR7.

0753

IGF2BP1 over-expression and its role in UV-induced skin photoaging

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Skin photoaging, driven by chronic UV exposure, involves complex molecular mechanisms including RNA methylation modifications. While various pathways in photoaging have been identified, the role of RNA-binding proteins remains understudied, particularly regarding insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1). We investigated IGF2BP1, a multifunctional RNA-binding protein known to regulate pro-survival and anti-apoptotic pathways, in human skin aging processes.Our study revealed significant upregulation of IGF2BP1 mRNA and protein expression in UVB-induced senescent human dermal fibroblasts, confirmed by quantitative RT-PCR and Western blot analyses. Immunofluorescence studies demonstrated elevated IGF2BP1 protein expression in sun-exposed skin tissues and cutaneous squamous cell carcinoma (cSCC) compared to controls. Furthermore, IGF2BP1 was found to regulate key cellular senescence signaling pathways activated during skin aging. These findings reveal IGF2BP1 as a critical regulator in UV-induced skin aging, suggesting its potential as a therapeutic target for photoaging management. The connection between IGF2BP1 and RNA methylation in photoaged skin offers new perspectives for therapeutic development.

0754

Single preventative ALA-PDT treatment reduces carcinogenesis in a mouse model of photocarcinogenesis

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Delta-aminolevulinic acid (ALA) photodynamic therapy (PDT) is widely used to treat actinic keratoses and early non-melanoma skin cancer, but its effects on skin cancer prevention are under-studied. ALA incubation times and light delivery vary widely in clinical practice, making it crucial to identify the optimal duration that maximizes therapeutic efficacy and consistency. This study evaluated the optimal ALA incubation time in the SKH1 mouse model and its impact on tumor formation when used preventatively. Mice were incubated with 10% nanoemulsion ALA gel for 0.5,1, and 3 hrs (n=3 per group), followed by red-light PDT (630nm, 37J/cm^2). Protoporphyrin-IX (PpIX) fluorescence was measured in each cohort using a blue light microscope (405nm), and acute PDT response was documented. Although PpIX fluorescence was highest after 3 hours of incubation, the acute response and subacute scabbing were well beyond the accepted human treatment response, thus, in SKH1 mice, 1 hour was the best incubation time to mimic human PDT treatment. To test the effect of a single preventative PDT treatment on the ability to reduce skin tumor formation in SKH1 mice treated for 10 weeks with solar-simulated light treatment (90mJ/cm^2, UVB/UVA=0.048), we treated groups of mice (n=3) with 1-hour incubation ALA-PDT before any visible signs of carcinogenesis and followed tumor development for 12 weeks. PDT-treated areas had a significant 2.2-fold reduction (p=0.0037, one-way ANOVA and post-hoc Tukey testing) of tumors at 12 weeks after PDT compared to untreated controls in the treatment areas. This study presents critical data on PpIX conversion kinetics in SKH1 mice for using the model in PDT efficacy and combination treatment studies. Moreover, we also show the ability of optimally dosed PDT to prevent tumor development even when used well before the first visible signs of photocarcinogenesis.

0755

Designing an improved YAP1/TAZ-TEAD interaction inhibitor

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The Hippo signaling pathway is a main regulator of stem cell proliferation and differentiation in the skin, and mutations in Hippo components can lead to uncontrolled basal cell proliferation, leading to tumor formation. The main effectors of the Hippo pathway are YAP1 and its paralog TAZ, which are co-transcriptional regulators that exert their regulatory and oncogenic functions mainly by interacting with TEAD transcription factors (TF). Developing therapies targeting Hippo-dependent transcription is crucial to advance cancer treatment. As a model to study TEAD-dependent transcription in normal and cancer cells, our group developed a genetically encoded dominant-negative protein that blocks the nuclear interaction of TEAD with YAP1 and TAZ, TEADi. We have proven the specificity and usefulness of TEADi to study YAP1/TAZ-TEAD transcriptional events. To increase the usefulness of TEADi, we improved its design by altering post-transcriptional modification sites in the TEAD binding domains (TBD), creating TEADi version 2 (TEADiv2). Using luciferase reporter assays, we demonstrate that a D93E mutation in the YAP1 TBD of TEADiv2 significantly increases TEADi inhibitory capacity. TEADiv2 provides the greatest inhibition of YAP1 dependent TEAD transcription, however it does not improve TAZ-dependent TEAD transcriptional blockage. We also tested TEADiv2's ability to inhibit each member of the TEAD TF family utilizing a reporter assay. We observe that YAP1 and TAZ dependent TEAD transcription is significantly inhibited for all four TEAD TFs. Protein structure predictions show that TEADiv2 can bind to TEAD in a more stable conformation compared to the original TEADi. Currently, we are utilizing TEADiv2 to study the effect of TEAD inhibition in skin cancer, particularly, by characterizing the proliferation and differentiation gene networks that are regulated by YAP1/TAZ-TEAD transcription.

0756

Cannabidiol as a potential sunscreen additive: A survey of peer-reviewed literature.

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Cannabidiol (CBD), a non-psychoactive phytocannabinoid from Cannabis sativa, has demonstrated antioxidant, anti-inflammatory, and cytoprotective properties, making it a promising candidate as a sunscreen additive. A survey of recent peer-reviewed scientific literature across electronic databases was conducted in 2024 to identify studies for a scoping review of CBD properties. In total, 19 peer-reviewed articles were examined to explore the potential of CBD in preventing UV damage. CBD exhibited antioxidant effects by decreasing reactive oxygen species and free radicals, activating the Nrf2 pathway, preventing lipid peroxidation, and stabilizing lipid membranes. Additionally, CBD reduced inflammation by inhibiting NFκB, while activating PPARγ and the endocannabinoid system. Studies further suggested that CBD may be cytoprotective and modulates apoptosis, while also enhancing melanogenesis through MAPK signaling, thereby strengthening the natural UV-protective barrier provided by melanin. CBD's compatibility with existing mineral and chemical sunscreens could enhance function, offering both primary UV protection and secondary skin repair benefits. Though not a comprehensive search, the assessed literature largely emphasized preclinical studies, with human clinical trials needed to confirm long-term safety, tolerability, and efficacy. Given the recent consumer demand for CBD products and enthusiasm for exploring novel naturally derived compounds in skincare, CBD and its reported properties present important avenues for further research in photoprotection. Subsequent synthesis of quantitative findings and robust meta-analyses could advance CBD research and contribute to innovative strategies in sunscreen development and skin cancer prevention.

0757

Skin oxi-proteome protection against uva/uvb using the vitamin e prodrug delta-tocopherol glucoside

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The aim of this study was to investigate the protective efficacy of the vitamin E prodrug delta-tocopherol glucoside (delta-TG) against oxidative damage induced by UVA/UVB. Using mass spectrometry-based non-targeted oxi-proteomics, we analyzed the oxidation patterns of proteins in keratinocytes after UV irradiation at 1 MED, and the protective effect of delta-TG. After UV irradiation, 273 proteins were significantly oxidized with 12 modification patterns, including carbonylation, tryptophan conversion, and 4-hydroxynonenal modification. Delta-TG treatment significantly protected 44% of these modified proteins from UV-induced oxidation. Analysis of the 120 protected proteins revealed a highly connected network, with subnetworks involved in epidermal structure (e.g., KRT5, KRT14, PLEC), cytoskeleton (e.g., ACTN1, JUP, CTNNA1), collagen chaperones (e.g., SERPINH1, P4HB, THBS1), and mRNA splicing regulation (e.g., HNRPL, HNRPD, PRPF8). These data highlight broad protection by delta-TG, from protein structure to essential tissue functions. Notably, plectin, crucial for epidermal-dermis junctions and a biomarker for several cancers including squamous cell carcinoma, was significantly protected from oxidative damage, as were its interacting proteins like Laminin 332. This study shows that oxi-proteome analysis can guide the development of effective sunscreens, with specific antioxidants to prevent cellular and tissue damage. In conclusion, delta-TG is an excellent candidate for reinforcing skin antioxidants, especially to prevent UV-induced protein oxidation. These results support further research into optimizing suncare formulations with antioxidants like delta-TG.

0758

Dinaciclib impairs mRNA splicing: unlocking new vulnerability in merkel cell carcinoma

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Merkel cell carcinoma (MCC) is a rare, aggressive, and often fatal skin cancer. The majority of MCC cases are caused by Merkel cell polyomavirus (virus-positive, VP-MCC), while a smaller subset is driven by UV-induced mutations (virus-negative, VN-MCC). Immune checkpoint inhibitors (ICI), the current first-line treatment for metastatic MCC, yield durable responses in fewer than 50% of patients, underscoring the need for novel therapies. To explore new treatment options, we employed multimodal high-throughput screening, including pharmacologic and functional genomics screens. Our pharmacologic screen identified dinaciclib, a CDK1/2/5/9 inhibitor, as cytotoxic against MCC cell lines regardless of viral status. In all MCC cell lines, dinaciclib induced apoptosis at 72 hours, and this apoptosis was accompanied by the downregulation of the antiapoptotic factors MCL1, Bcl-xL, and XIAP. Intriguingly, dinaciclib inhibited mRNA splicing within 5 hours of treatment. This splicing inhibition was initially identified through phosphoproteomics and subsequently validated using ribosome-depleted RNA-seq and differential splicing analysis. Interestingly, RNA-seq also revealed dinaciclib increased mRNA degradation, suggesting a dual mechanism affecting RNA dynamics in MCC cells. Functional genomics further confirmed the critical role of mRNA splicing in MCC viability, as knockdown of key splicing factors led to cell death across both VP-MCC and VN-MCC cell lines. In a preclinical xenograft model of MCC, dinaciclib significantly suppressed tumor growth without adverse effects on body weight or other detectable toxicities. Overall, our study positions dinaciclib as a promising therapeutic candidate for MCC while identifying mRNA splicing inhibition as a novel and targetable pathway in the treatment of this aggressive cancer.

0759

Tissue-autonomous cancer resistance of the naked mole-rat epidermis is mediated by highly elevated expression of the tumor suppressor and DNA repair genes in keratinocytes

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Naked mole rats (NMRs, Heterocephalus glaber) are unique long-lived mammals that possess marked resistance to cancer and other age-related pathologies maintaining a sustained healthy life-span for over 30 years. Despite remarkable longevity, there is a lack of any reported skin cancer incidents in NMRs, including basal/squamous cell carcinoma and melanoma. We found that FACS-sorted keratinocytes from normal NMR epidermis show >2-fold and higher expression of 325 tumor suppressor genes including 55 genes regulating DNA repair (Atr, Brca1, Ddx11, Ercc1, Ercc2, Fanca, Fankd2, Mlh1, Mnat1, Neil2, Rad1, Xpc, Xrcc1, Xrcc2) compared to normal mouse epidermal keratinocytes. In chemical skin carcinogenesis (DMBA/TPA) protocol applied to NMRs and FVB mice, as well as in the NMR skin transplanted onto immunodeficient nude mice, NMR skin show remarkable resistance to DMBA/TPA and do not develop papillomas for up to 25 weeks after treatment. Whole exome sequencing revealed that 6.5 weeks after DMBA/TPA treatment NMR epidermis show only 2.6% increase of single nucleotide variants compared to 90.8% increase seen in the mouse epidermis. Robust elimination of DMBA-induced mutations in NMRs was accompanied by significant decrease of gamma-H2AX+ cells in the epidermis 6.5 weeks after DMBA/TPA treatment compared to mice. RNAseq analyses demonstrated that after DMBA/TPA treatment NMR epidermis show upregulation of 21 tumor suppressor genes encoding several components of the DNA repair machinery (Adprh, Cenps, Ddb2, H2AX, Mgmt), inhibitors of cell proliferation (Cdk2ap1, Phb, Rasl10a, Rprm) and decreased expression of 46 oncogenes including Ccnd1, Myc, Pim1, Rel. These data provide evidence that NMR skin possesses unique cancer resistance in a tissue-autonomous manner and serve as a platform for further analyses of the mechanisms regulating highly elevated expression of the tumor suppressor and DNA repair genes in the NMR keratinocytes.

0760

5'-UTR mutation in OXA1L drives cSCC metastasis via tumor dedifferentiation and immune evasion

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The pathogenic role of non-coding mutations in skin cancers is not fully defined. To identify driver mutations in non-coding untranslated regions (UTR), we analyzed 41 metastatic and 57 primary cutaneous squamous cell carcinomas (cSCC). OXA1L, a gene essential for mitochondrial translation, contained the highest incidence of 5'-UTR mutations. We observed more frequent mutations in the 5'-UTR of OXA1L in metastatic cSCC (9/41; 22%) compared to primary tumors (2/57; 3.5%); this 6.3-fold enrichment is higher than that of known metastatic cSCC driver mutations. Functionally, the 5'-UTR mutation in OXA1L was associated with its lower expression in cSCC patients, and primary keratinocytes edited to harbor mutant OXA1L demonstrated decreased OXA1L mRNA stability. OXA1L-mutant cells exhibited accelerated neoplastic invasion in human skin organoid and tumor spheroid models compared to isogenic cells with wild-type OXA1L. Strikingly, tail vein injection in mice with IGR1, a cell line-containing mutant OXA1L, enhanced tumor cell seeding in the lung and spleen compared to CRISPR-corrected IGR1 with wild-type OXA1L. Examination of isogenic tumor spheroids revealed enhanced dedifferentiation and immune evasion in OXA1L-mutant spheroids. Consistent with this, we observed higher T-cell exhaustion in OXA1L-mutant metastatic cSCC patients. As OXA1L maintains mitochondrial function, OXA1L-mutant cells showed altered metabolomics, leading to fructose-1,6-bisphosphate accumulation that reduced aldolase activity and enhanced glutathione activity. Our findings identify a driver recurrent 5'-UTR point mutation in metastatic cSCC and underscore its pathogenic role in promoting cancer hallmarks.

0761

Distinct expression of apoptosis inhibition and cell adhesion genes but not of hypoxia related genes FIH-1, LOX and EGLN in cutaneous squamous cell carcinoma of immunocompetent patients and organ transplant recipients.

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Cutaneous squamous cell carcinoma (SCC) is the second most frequent malignant skin neoplasm in Caucasians with a 60- to 100-fold higher incidence in immunocompromised patients such as organ transplant recipients (OTR). The exact mechanisms leading to the more aggressive behavior of SCCs in OTR are unclear. Hypoxia related genes regulate oxygen dependent molecular pathways and are deemed critical for carcinogenesis in several cancers. We assessed expression of hypoxia related genes as well as ell adhesion and apoptosis related genes by immunohistochemistry in 40 invasive SCCs and 40 actinic keratoses, each in immunocompetent patients (ICPs) and OTRs. We found similar expression of the hypoxia associated proteins FIH-1, LOX and EGLN and its downstream target gene product GLUT-1 in all four groups of cutaneous squamous cell carcinoma in comparison to normal skin. However, we found distinct expression of apoptosis inhibitory proteins hILP, livin and cytoskeleton protein ezrin exclusively in SCC of OTR as compared to SCC in ICP or normal skin. hILP was significantly higher expressed in invasive SCC of OTR compared to ICP ($p<0.05$). Loss of cell-cell adhesion is an important step in tumor invasion and metastasis. We found significantly reduced expression of the cell adhesion molecule galectin-3 in intraepithelial SCC (ICP: IRS 6.28 ± 1.25, OTR: 5.48 ± 0.90, both $p<0.01$) and even greater reduction of expression in invasive SCC (ICP: 4.70 ± 0.32, OTR: 4.33 ± 0.27, both $p<0.005$) compared to normal skin (10.93 ± 0.99). In summary, our data showed an unchanged expression of the hypoxya related genes FIH-1, LOX and EGLN, indicating, that these genes may not be crucial in cutaneous squamous cell carcinogenesis. However, distinct protein expression of the apoptosis inhibitory proteins hILP, livin and cytoskeleton protein ezrin were observed. Further studies are necessary to gain a deeper understanding on a potential mechanistic role.

0762

Inhibition of casein kinase 1α in keratinocytes provides a potential UV protection strategy for melanocortin 1 receptor variants

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Variants in the melanocortin 1 receptor (MC1R) gene generating poor eumelanin formation have been documented with insufficient UV protection and increased risk of skin cancers. We have demonstrated that casein kinase (CK) 1α ablation in keratinocytes increases eumelanin production and melanocyte numbers by activating p53/KitL/c-Kit signaling pathway in wildtype mice. Since CK1α inhibition induced hyperpigmentation is independent of MC1R expression and UV sparing, we hypothesize CK1α inhibition in keratinocytes may serve as a rescue strategy for MC1R defective individuals. The aim of this translational research was to test this hypothesis. We first established the Mc1r-deficient mice $Mc1r^{549del}$, and further established K14-CreERT2-$CK1\alpha^{fl/fl}$; $Mc1r^{549del}$ mice, in which CK1α can be selectively knockout in the keratinocytes of $Mc1r^{549del}$ by tamoxifen. The results showed CK1α inhibition in keratinocytes caused skin pigmentation in $Mc1r^{549del}$ mice with increased eumelanin formation, increased melanocyte numbers in epidermis, and decreased DNA damage during acute UVB exposure. Except skin, the hair color of $Mc1r^{549del}$ became darker with increased eumelanin in hair shafts. To tracing the melanocyte precursors' behavior in hair follicle, we established Fusion Red-labelled-melanocyte reporter mice in $Mc1r^{549del}$ mice and examined the effects of topical CK inhibitor (CKI). Confocal microscopy showed increased numbers of melanocyte precursors in the hair germ and outer root sheath of hair follicle, and in the epidermis. RT-PCR and Western blotting showed up-regulation of p53/KitL/c-Kit/MITF/ tyrosinase signaling pathway in $Mc1r^{549del}$ mice. Treatment of CKI on human keratinocytes showed increased KitL expression; on human skin explants showed up-regulation of p53/KitL/c-Kit/MITF/tyrosinase signaling pathway, too. Thus, CK1 inhibition on skin provides a potential strategy to protect MC1R variants from UV damage.

0763

Keratinocyte-derived tumor necrosis factor-alpha (TNF-a) contributes to more epidermal proliferation induced by UVB exposure at low-irradiance: Novel insights on improving currently available sunscreens.

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The skin exhibits erythema upon exposure to a specific threshold of UVB fluence (mJ/cm^2). Sunscreen application, which extends the duration required for erythema to develop by reducing the irradiance (mW/cm^2) of UVB radiation, is believed to offer protection against the development of skin cancers. Recent studies have highlighted the significant role of UVB irradiance, in addition to fluence, in skin photocarcinogenesis. Following exposure to an equivalent UVB fluence, increased aberrant keratinocyte proliferation has been shown to significantly contribute to the photocarcinogenic potential of low irradiance (LI) UVB compared to its high irradiance (HI) counterpart. However, the underlying mechanisms remain unclear. In this study, we examined the effects of equivalent UVB fluence administered at either HI or LI on epidermal keratinocytes. Our findings demonstrated that, at equivalent fluence, LIUVB induces significantly greater cell proliferation, TNF-a production, and phosphorylated AKT (pAKT) expression in both cellular and animal models compared to HIUVB. UVB-induced AKT signaling played a critical role in the increased cell proliferation. Furthermore, pretreatment with TNF-a inhibitors effectively eliminated the differences in cell proliferation and pAKT expression between HI and LIUVB in both cellular and animal models. In conclusion, compared to its HI counterpart, LIUVB, at equivalent fluence, induces significantly greater aberrant epidermal proliferation through enhanced TNF-a production. Incorporating agents that modulate TNF-a inhibition into sunscreens may improve their efficacy in protecting the skin from UVB-induced damage.

0764

Topical sirolimus prevents cutaneous squamous cell carcinomas by disrupting the balance between differentiation and proliferation

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Topical mTor inhibitors are increasingly being used for several skin disorders. We previously demonstrated in a double-blind study that applying topical sirolimus for 12 weeks effectively reduced the risk of keratinocyte cancers in solid organ transplant recipients, with a significant decrease in the occurrence of intraepidermal carcinomas 24 months post-treatment. To gain deeper insights into the mechanisms of this chemoprevention, patients' skin samples were collected after 12 weeks of treatment (n=10 treated forearm vs. n=10 placebo forearm from the same patient) for Spatial Transcriptomics (10X Visium). We found a significant downregulation of genes involved in the mitosis phase and the G2/M transition, with most keratinocytes arrested in the G1 phase, confirmed by a marked decrease in PCNA expression and reduced p63 synthesis, as confirmed by immunofluorescence. Despite these changes, cell viability remained unaffected, with no increase in apoptosis. Simultaneously and unexpectedly, the differentiation process was also altered, showing downregulation in pathways associated with keratinocyte differentiation. This translated into a significant upregulation of keratin 14 expression, E-cadherin signaling, and integrin regulation as well as an activation of the Hippo-YAP pathway into upper epidermal layers, leading to YAP phosphorylation and restricted cell proliferation. Additionally, NOTCH1 signaling and related reactome pathways were downregulated. To conclude, our findings emphasise the importance of changes in the balance between proliferation and differentiation in the early carcinogenesis process, and the effect of sirolimus in disrupting that balance by controlling excess proliferation despite reduced differentiation.

0765

Rise of the goliaths: Serial imaging of clonal dynamics shows 3 phases of UV-induced carcinogenesis

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While the genetic paradigm of cancer is powerful, it remains incomplete. Although studies demonstrate the presence of high mutational burdens in normal appearing skin, we reveal additional forces governing the eco-evolutionary dynamics of carcinogenesis. Using a UV-driven mouse model of cutaneous squamous cell carcinoma, we tested our central hypothesis that cancer initiation occurs in three phases: 1) tissue disruption and the emergence of unusually large "goliath" clades, 2) clonal selection within a subset of goliaths observed as unusually high local densities of cells ("micro-lumps") with higher mutational burdens, and 3) emergence of macroscopic lesions. We tracked ecological and evolutionary drivers of cancer initiation via in-vivo serial 3-D reconstruction of fluorescently labeled keratinocyte clades, yielding over 25,085 clade measurements. While median and mean clade sizes differed little between UV and non-UV exposure, goliath clades emerged (> 4.2E6 µm3) almost exclusively within UV-exposed skin. Unexpectedly, targeted DNA sequencing revealed very low variant allele frequencies within clades, but substantial differences among clades, suggesting that positive selection for these mutations is superfluous to the development of goliaths early in carcinogenesis. scRNAseq revealed epidermal de-differentiation and immune suppression as early events. Lesions emerged between months 6 and 7, only in UV-exposed skin. Remarkably, 2 of 21 randomly selected goliaths developed into macroscopic lesions. Our adaptation of the Drake equation estimated the probability of this to be <10-6. Taken together, our results support the presence of 3 phases of cancer initiation, the earliest of which presage the acquisition of driver mutations and explains why cancers are rare in relation to the degree of somatic mosaicism present in UV-exposed skin.

0766

BCC development in mice is driven by acquired genomic alterations that increase hedgehog pathway activity

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Constitutive Hedgehog (Hh) pathway activity, driven by loss-of-function PTCH1 mutation or gain-of-function SMO mutation, is a molecular hallmark of basal cell carcinoma (BCC). Both alterations lead to activation of GLI transcription factors in mice and development of microscopic follicular hamartomas, whereas skin-targeted overexpression of GLI2 also drives robust nodular BCC development. Despite widespread expression of GLI2 in K5-Gli2 mice, BCC development is focal and takes 4-5 months, with tumors displaying markedly higher Hh signaling than the background of slow-growing benign follicular hamartomas where they arise. We performed whole exome sequencing on 8 nodular BCCs from K5-Gli2 mice to shed light on the potential molecular mechanism underlying progression from hamartoma to BCC. The BCC genomes were nearly diploid with low tumor mutational burden. Six tumors (75%) carried focal amplification of endogenous Gli2 on Chr 1, and five tumors (63%) had lost all or most of one copy of Chr 19, which includes the Hh pathway repressor and tumor suppressor Sufu. Strikingly, homozygous K5-Gli2 mice developed macroscopic BCCs with shorter latency and markedly higher numbers than heterozygous mice, underscoring the importance of elevated Hh/Gli2 signaling in driving macroscopic tumor development. Our data support the emerging concept that macroscopic BCC development is a multi-step process involving acquired alterations in Hh pathway genes leading to high-level oncogenic Hh signaling, and that follicular hamartomas may be precursor lesions for some BCCs.

0767

Characterizing malignant T cells in CTCL to inform personalized therapy: A scRNAseq study

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Single-cell RNA sequencing (scRNAseq) provides novel insights into cancer biology and cellular interactions, yet its application to cutaneous T-cell lymphoma (CTCL) remains limited. CTCL's overlap between malignant and benign T cells requires strategies to identify and target malignant populations. We analyzed 105,806 PBMCs from 23 CTCL patients with blood involvement (9 UT Southwestern and 14 publicly available) and identified four malignant T-cell phenotypes: central memory/naïve (MTC CM/N), effector memory (MTC EM), regulatory (MTC Reg), and cytotoxic effector memory (MTC CyEM). Malignant cells were defined using transcriptomic, TCR sequencing, and CNV analyses, with benign T-cells as references. Key gene signatures characterized each phenotype. MTC CM/N, the largest subset, upregulated KIR3DL2 (log2FC 1.95), NEDD4L (2.02), and IGFBP4 (1.94), while downregulating FOXP1 (-1.06). MTC EM expressed KIR3DL1 (2.13) and NR4A1 (2.50). HACD1 was shared between MTC CM/N (2.24) and MTC EM (2.10), while EGR1 characterized both MTC EM (2.10) and MTC CyEM (2.49). MTC Reg expressed HMOX1 (2.58) and TWIST1 (2.61), and MTC CyEM expressed FOSB (2.00) and TNF (1.96). Gene set enrichment analysis (GSEA) revealed functional distinctions. MTC CM/N resembled benign T CM/N but with reduced cytoplasmic translation (NES -2.00, FDR 0.07). MTC EM displayed metabolic shifts with decreased oxidative phosphorylation (NES < -1.5, FDR < 0.05). MTC Reg had reduced apoptotic signaling (NES -1.97, FDR < 0.05) and heightened hypoxia responses (NES 1.89, FDR < 0.05). MTC CyEM had inflammatory signatures (NES 2.19, FDR < 0.05) and reduced cellular respiration (NES -1.71, FDR < 0.05). These findings highlight CTCL's malignant T-cell diversity and support personalized therapies. High KIR3DL2 in MTC CM/N supports lacutamab trials, while metabolic and inflammatory pathways in other phenotypes suggest therapeutic targets. Investigation of cell types in the tumor environment is ongoing.

0768

A non-invasive evaluation of DNA photodamage in epidermal keratinocytes subsequent to UV phototherapy for vitiligo

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Objective: To evaluate DNA damage in epidermal keratinocytes subsequent to ultraviolet phototherapy for vitiligo, employing the tape stripping method in a non-invasive manner. Methods: Epidermal cells from multiple stratifications were isolated from the lesions of 11 patients diagnosed with vitiligo, all of whom had undergone six months of phototherapy. Furthermore, epidermal tissue sections were procured from the same region using the suction blister epidermal graft technique. Both hematoxylin and eosin (HE) staining and immunofluorescence staining were applied to the cellular and epidermal tissue samples. A subsequent correlation analysis was performed to assess the expression levels of the epidermal DNA damage marker γ-H2AX between the cellular samples and the epidermal tissue sections. Results: HE staining, along with immunofluorescence staining for pan-cytokeratin (pan-CK), demonstrated the successful collection of nucleated keratinocytes from the deeper layers of the epidermis. The acquisition of these cells was effectively achieved using 20 to 40 consecutive tape strips. The quantity of γ-H2AX positive cells in collected cellular samples demonstrated a positive correlation with those in the corresponding epidermal tissue sections, as determined by Spearman correlation analysis (P=0.034, r=0.639). Additionally, a correlation was observed between the epidermis and granular layer cells at the same site (P=0.014, r=0.711). Conclusion: The tape stripping technique constitutes a non-invasive and reliable method for the effective assessment of epidermal DNA damage marker expression in patients with vitiligo undergoing ultraviolet phototherapy.

0769

Night and day use of stabilized retinol plus broad-spectrum SPF 60+ sunscreen provides enhanced broad-spectrum protection of multiple extra-cellular matrix components

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Retinol, the gold-standard treatment in improving the appearance of aging, helps to clinically delay and reduce signs of skin aging. It has been shown that stabilized retinol formulations can significantly improve numerous signs of photoaging. Additionally, prolonged use of retinol has demonstrated continued improvement as evidenced at the molecular level by an increased expression of type I procollagen, elastin, hyaluronic acid (HA), compared to vehicle in-vitro and in-vivo. Moreover, chronic sun exposure causes photoaging and sunscreens have been shown to provide photo-protection. In this study, skin explants were pre-treated with: (1) a stabilized retinol formulation alone or (2) a PM/AM regimen with a stabilized retinol formulation (PM) followed by SPF60+ sunscreen (AM) before daily UVA+B exposure for 7 days. Explants were assessed for 6 extra-cellular matrix (ECM) components involved in skin aging appearance. As expected, UV treatment caused significant reduction of collagen type 1, 3, 4, elastin and HA, and stimulated matrix metalloproteinase-1. Retinol application protected significantly against UV-induced deleterious effects on all 6 ECM components. Importantly, combined daily use of stabilized retinol (PM) and sunscreen SPF60+ (AM) showed enhanced protection of all 6 ECM components and was significantly superior to the protection provided by retinol treatment alone. This study demonstrated that the combined use of AM broad-spectrum sunscreen SPF60+ with a PM retinol results in enhanced protection of multiple ECM components to protect against skin aging and photodamage and provides further evidence for recommendation of daily use of SPF and retinol regimen as part of a skincare routine

0770

Clonal variation drives heterogeneous necrotic and apoptotic cell death responses to UVB radiation in human keratinocytes

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Ultraviolet B radiation (UVB) is the primary etiological contributor to skin cancer. UVB-induced apoptosis is a non-inflammatory process that suppresses tumor development. However, UVB induces pro-carcinogenic inflammation which may be triggered by necrosis. Necrosis encompasses multiple regulated cell death (RCD) pathways, including necroptosis, pyroptosis, secondary necrosis and PANoptosis. UVB-induced necrotic RCD in keratinocytes is not well understood. We investigated RCD cell fates in HaCaT keratinocytes exposed to 30 mJ/cm^2 UVB after 12 hours by immunofluorescence (IF) staining for phospho-MLKL (necroptosis), cleaved Gasdermin D (pyroptosis), ASC (pyroptosis), and nuclear condensation (apoptosis). Our results showed that individual cells died through different RCD fates including apoptosis, pyroptosis, necroptosis, or PANoptosis. To understand this heterogeneity, twelve HaCaT clonal populations were analyzed by Annexin V/PI flow cytometry and IF, with one population being early apoptotic, two populations necrotic, and nine populations double positive, suggesting either primary or secondary necrosis, similar to the parent HaCaTs. IF staining revealed clones undergoing predominately apoptosis, necroptosis, pyroptosis, or PANoptosis, indicating clonal variation in the parental HaCaT cells. Normal human epidermal keratinocytes (NHEKs) exposed to 30 mJ/cm^2 UVB were also analyzed by IF and found to undergo pyroptosis or apoptosis. The caspase inhibitor zVAD inhibited UVB-induced cleaved Gasdermin D but not ASC clustering, while the RIPK3 inhibitor HS-1371 strongly upregulated pyroptotic markers, indicative of a compensatory RCD cell fate switch. The clonal variation and cell death compensation supports the hypothesis that human keratinocytes exhibit a heterogenic necrotic and apoptotic cell death response upon UVB radiation which is not a stochastic process but regulated by intrinsic cellular properties.

0771

Multi-omic analysis of cutaneous squamous cell carcinoma in patients with recessive dystrophic epidermolysis bullosa

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Recessive Dystrophic Epidermolysis Bullosa (RDEB) is a rare genodermatosis caused by loss-of-function mutations in COL7A1, encoding type VII collagen. RDEB is characterized by severe skin and mucosal blistering, often complicated by the development of life-threatening cutaneous squamous cell carcinoma (SCC), for which no curative treatment exists. To investigate the molecular pathways driving carcinogenesis in RDEB-SCC, we conducted a translational study (NCT04285294) involving 20 RDEB patients. Among them, 5 patients developed aggressive SCC (SCC-AG) with rapid recurrence and/or metastasis, while 15 patients had less aggressive SCC (SCC-NA) with prolonged survival. As controls, 17 individuals from the general population with UV-induced SCC (UV-SCC) were included. Bulk transcriptomic (Limma) and proteomic analyses identified 1810 differentially expressed genes (DEGs) and 114 differentially expressed proteins (DEPs) (fold change >1.5, adjusted p-value <0.05) between RDEB-SCC and UV-SCC, showed enrichment of cell junction, extracellular matrix organization (ECM) pathways, and complement activation cascade (Reactome). Comparative analysis of SCC-AG versus SCC-NA revealed 1124 DEGs and 110 DEPs, downregulation of immune response and ROS detoxification, upregulation of MET signaling and ECM pathways. Single-cell transcriptomic analysis (8 RDEB-SCC, 3 UV-SCC, 3 healthy control skin) revealed differences in cell-type proportions, enriched pathways within clusters (Reactome), and predicted cell-cell interactions (CellChat), identifying specific features of RDEB-SCC, including SCC-AG (n=1). Omic signatures were analyzed through the LINCS drug repurposing database (NIH), identifying 6 potential therapeutic candidates, including rigosertib, which will be tested on primary SCC-AG cells and spheroids. This work aims to advance novel therapeutic strategies for SCC in RDEB patients.

0772

The landscape of alternative splicing in cutaneous squamous cell carcinoma

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Dysregulation of RNA splicing is a feature in many cancers and has been implicated in cancer progression and therapeutic resistance. While alternative splicing events (ASE) have recently been reported in epidermal differentiation and skin homeostasis, little is known about the significance of ASE in cutaneous squamous cell carcinoma (cSCC). In this study, we sought to explore the landscape of ASE in cSCC compared to normal skin, identify candidate events that are associated with tumor progression, and validate the functional impacts of these occurrences. A cohort of 146 cSCC and 73 normal skin samples was investigated to determine ASE using rMATS-turbo. The initial comparison yielded 9,972 ASE (FDR<1%), including 2,535 skipped exon events. Further refinement of these 2,535 skipped exon events was conducted by imposing additional cutoffs for effect size and gene expression and retaining events with 1) opposite directionality in epidermal differentiation or 2) same directionality as observed in cSCC cell lines compared to differentiated keratinocytes. This approach yielded a list of 101 and 70 candidate events, respectively. Prominently, several genes functionally linked to cancer progression such as MAP3K7, EIF4A2, CD44 and FN1 showed alternative splicing in cSCC. Interestingly, exome analysis of 83 cSCC tumors revealed only rare splice site mutations in candidate genes and spliceosome-associated genes were not recurrently mutated in this cohort, suggesting other mechanisms are driving dysregulated splicing in cSCC. Efforts to validate these findings and determine the functional impact of cSCC-associated isoforms are currently underway. Their contribution to proliferation, invasion, and colony formation will provide a first indication of the overall importance of ASE in cSCC progression and novel pathways for cSCC treatment.

0773

Quantifying DNA and extracellular matrix protection from mineral and chemical sunscreens against ultraviolet (UV)-induced epidermal and dermal damage in a human skin explant model

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Sunscreens are recognized as a crucial element of daily skincare routines. Sunscreens, formulated with either mineral or chemical active ingredients, have been shown to protect against sunlight-induced carcinogenesis through prevention of direct epidermal DNA damage. Sunscreens efficacy in protection against DNA oxidative damage or deeper dermal alterations leading to extracellular matrix (ECM) degradation in the process of photoaging have not been extensively characterized. This study investigated the effectiveness of both chemical and mineral sunscreens in preventing total skin damage caused by chronic ultraviolet (UV) exposure *ex vivo*. Broad-spectrum, photostable chemical or mineral sunscreens were applied to human skin explants at doses of 2mg/cm^2 prior to daily UV exposure (30J /cm^2 UVA + 50mJ /cm^2 UVB) for 7 consecutive days. The explants exposed to UV treatment showed >200% increase in DNA damage biomarkers CPD and 8-hydroxy-2 deoxyguanosine (8OHdG), and 35% decrease in key ECM components, Collagen (I, III, and IV), Elastin, and Hyaluronic Acid (HA) as compared to untreated explants. As compared to UV exposed unprotected explants, both types of sunscreens demonstrated significant protection against DNA damage. Protection of 95% and 85% was observed against CPD and 8OHdG damage, respectively. Both types of sunscreens provided over 95% protection of Collagen I, III, IV and HA, and 100% protection of Elastin against UV-induced damage. These results strongly reinforce the importance of daily sunscreen application in maintaining skin integrity for protection against epidermal DNA and deeper dermal ECM damage to help maintain a youthful, healthy appearance.

0774

A tyrosine residue on β4 integrin endodomain plays a key role in epidermal tumorigenesis

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β4 integrin is crucial for squamous cell carcinoma (SCC) tumor formation. However, the mechanisms underlying β4 integrin-mediated SCC tumorigenesis remain unclear. To clarify β4 integrin's functional role in SCC tumorigenesis, we overexpressed mutant β4 integrin cDNAs in β4 integrin null primary junctional epidermolysis bullosa (JEB) keratinocytes and studied the ability of these engineered cells to support SCC tumor formation in immunodeficient mice after Ras/IκB transformation. We also generated β4 integrin knockouts in human SCC line to complement the JEB keratinocyte studies. Phospho-mimic substitution of the tyrosine 1642 residue with aspartic acid (1642D) in β4 null JEB cells after Ras/IκB transformation as well as in human ITGB4 KO SCC cell line promoted hyperproliferation by nuclear translocalization of phospho-JNK and PI3K signaling, resulting *in vivo* human SCC tumor progression. On the contrary Phospho-ablative substitution of the tyrosine 1642 residue with phenylalanine (1642F) demonstrated hypoproliferation, reduced PI3k activity and an almost total lack of tumor growth. β4 integrin AP-MS indicated strong association with Rac1 pathway proteins pointing towards leading pathway for characteristic hyperproliferation and invasion. Further studies with β4 integrin null JEB cells expressing mutant β4 cDNAs demonstrated that EGF stimulation promoted tyrosine 1642 phosphorylation via a signaling cascade which appeared to be regulated by Fyn kinase. Overexpression of a constitutively active PI3K p110 submit mutant restored tumor formation in 1642F expressing JEB keratinocytes following Ras/IκB transformation. Binding of plectin to β4 integrin appeared to antagonize β4 integrin intramolecular association which likely facilitates tyrosine 1642 phosphorylation. These findings identify new mechanisms for β4 integrin dependent SCC tumor progression and point to the β4 integrin 1642 tyrosine phosphorylation as a target for novel cancer therapies.

0775

Impact of age-related dermal microenvironment on keratinocyte skin cancer development

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Keratinocyte skin cancer is common among the elderly, yet the underlying mechanisms driving its development remain poorly understood. Dermal fibroblasts in aged human skin express increased levels of CCN1 (Cell Communication Network family member 1), a multifunctional protein that regulates the homeostasis of the dermal extracellular matrix (ECM). Mice that express CCN1 (Col1a2-CCN1 mice) in dermal fibroblasts exhibit pronounced features of dermal aging, including fragmentation and disorganization of the collagenous ECM and a proinflammatory dermal microenvironment. Given that aging is a significant risk factor for keratinocyte cancers, we have investigated the influence of the age-related dermal microenvironment on keratinocyte skin cancer development in Col1a2-CCN1 mice, compared to matched littermate control mice. At six months of age, Col1a2-CCN1 mice demonstrate significantly increased keratinocyte cancer development in two different cancer models: transformed keratinocyte xenograft ($N=5$, $P<0.001$) and oncogenic HRas expression in keratinocytes ($N=5$, $p<0.01$). RNA-seq analysis of Col1a2-CCN1 mice skin identified substantial enrichments of cancer-related pathways, particularly hepatocyte growth factor (HGF) signaling. Importantly, inhibition of HGF signaling in Col1a2-CCN1 mice, with c-Met inhibitor PHA665752, substantially blocked tumor development following two-stage chemical carcinogenesis ($N=4$, $p<0.01$) or oncogenic HRas expression ($N=3$, $p<0.01$). Furthermore, mice with fibroblast-specific CCN1 knockout (Pdgfra-CreER;$CCN1^{fl/fl}$) displayed reduced tumor development following two-stage chemical carcinogenesis ($N=5$, $p<0.01$) or chronic exposure to ultraviolet irradiation (UV) ($N=6$, $p<0.01$). These findings highlight the critical role of age-related changes in the dermal microenvironment that enable keratinocyte cancer development and advance understanding of the mechanisms involved in the heightened prevalence of skin cancer among older populations.

0776

Environmental polycyclic aromatic hydrocarbons augment UVB systemic immunosuppressive effects via platelet-activating factor and microvesicles

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Humans are subjected to the combination of ultraviolet radiation and pollutants such as polycyclic aromatic hydrocarbons (PAHs), which both exert immunomodulatory and pro-carcinogenic effects. Though the impact of these individual stressors has been extensively studied, a significant knowledge gap exists into the underlying effects and mechanisms of simultaneous exposure to these stressors. Studies, including ours, have implicated a novel pathway involving the potent lipid mediator Platelet-activating factor (PAF) in UVB-mediated acute inflammation and systemic immunosuppression. Of note, PAF appears to exert its effects by leaving the skin by subcellular microvesicle particles (MVP) generated by the enzyme acid sphingomyelinase (aSMase). The current studies determined that pretreatment with the PAH pollutant, benzo[a]pyrene (BaP) alone had no effect, yet augmented UVB-mediated PAF and MVP release selectively in PAF receptor-positive keratinocyte cell lines and mice. Using validated murine models of systemic immunosuppression, topical BaP itself had no effect, yet allowed UVB to be a more potent immunosuppressant as measured by skin contact hypersensitivity testing and surveying murine lymph nodes for immunosuppressive cytokines and Tregs. Use of genetic strategies of mice deficient in PAFR and aSMase and a pharmacologic inhibitor of aSMase confirmed our hypothesis that BaP augments PAF production which then generates PAF-laden MVP via aSMase. In sum, these studies indicate that PAH such as BaP can augment UVB-mediated immunosuppression and could provide an explanation for the increased skin cancer rate in those occupations such as road construction workers who commonly experience both of these environmental stressors simultaneously. These studies also suggest a potential therapeutic strategy involving aSMase inhibitors.

0777

Effect of IGF2BP1 inhibition on Wnt and hedgehog (Hh) signaling in basal cell carcinoma (BCC)

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The insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1) is an RNA-binding protein that we previously identified as a bona fide transcriptional target of the Wnt/β-catenin signaling pathway. We also showed that IGF2BP1 regulates the transcriptional activator of the Hh pathway GLI1 and serves as a mechanistic link in the crosstalk between Wnt and Hh pathways. IGF2BP1 induction has been shown to regulate other genes promoting the development of metastasis. As constitutive activation of the Hh signaling pathway was shown to drive basal cell carcinoma (BCC) development, we hypothesized that inhibition of IGF2BP1 will reduce GLI1 expression and activity and therefore prevent BCC development. To test our hypothesis, we used a mouse model of BCC ($Ptch1^{+/-}$). We also used UW-BCC1 cells to generate xenograft tumors in immunocompromised mice ($Foxn1^{nu}$). We determined the effects of IGF2BP1 inhibition on tumor growth in immunocompromised mice and in the development of BCC-like lesions in $Ptch1^{+/-}$ mice. The expression of Wnt and Hh targets was also assessed. We found that inhibition of IGF2BP1 in UW-BCC1 cells significantly reduced tumor growth in xenograft mice compared to controls ($P<0.05$). In $Ptch1^{+/-}$ mice, skin specific IGF2BP1 knockout significantly reduced the number of lesions in those mice compared to the control mice after their prolonged exposure to 240 mJ/cm^2 UVB irradiation ($P<0.05$). Inhibition of IGF2BP1 also significantly reduced the expression of Wnt and Hh targets analyzed in this study. IGF2BP1 appears to contribute to BCC development and might represent a novel target in the management or treatment of this disease.

0778

Biomarkers of UV irradiated notch-deficient keratinocytes driving neoplasia.

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Actinic keratosis (AK) and squamous cell carcinoma in situ (SCCIS) are precancerous lesions that can progress to cutaneous squamous cell carcinoma (cSCC). To better understand cSCC development, we used omics platforms to a murine skin cancer model and human SCCIS samples to identify biomarkers of disease. We used K14-CreERT2-DNMAML;GFP mice to generate random Notch-deficient keratinocytes which were subjected to UV irradiation or sham followed by *in vivo* fluorescence microscopy to track clone development. UV irradiated Notch-deficient keratinocytes demonstrated both positive and negative selection. Positive selection of large clones, >2000um^2, were significantly increased in irradiated Notch-deficient cells compared to non-irradiated Notch-deficient cells, $p < 0.01$. Notch-deficient keratinocytes showed negative selection manifested by fewer clones in areas of UV irradiated skin compared to unirradiated skin, $p < 0.0001$. UV Irradiated skin containing GFP-labeled clones was subjected to spatial transcriptomics followed by qRT-PCR and RNAscope to identify differentially expressed genes. Twenty-six differentially expressed genes in the Notch-deficient clones including calmodulin isoform CALML3 ($p<4.6x10^{-6}$). To validate this data, RNAscope was performed on human SCCIS and adjacent epidermis. CALML3 was markedly overexpressed in SCCIS (Score 4>) in the lesion compared to adjacent epidermis (Score 1), N=8. To better assess the expression of all six human calmodulin genes in human SCCIS and adjacent epidermis we analyzed expression of all 6 genes using the Xenium platform. Xenium analysis revealed that CALM1 ($p<0.0001$), CALM3 ($p<0.001$) and CALML3 ($p<0.01$) were overexpressed in SCCIS compared to adjacent epidermis. Expression of CALM2, CALML4 and CALML6 did not statistically differ between SCCIS and epidermis. These data confirm that calmodulin genes are biomarkers for human SCCIS and further experiments will determine the mechanism associated with upregulation of these genes.

0779

Topical 5-fluorouracil more effectively eliminates epidermal clonal mutations than photodynamic therapy in a mouse model of early UV carcinogenesis

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Field treatment with topical 5-fluorouracil cream (5FU) and photodynamic therapy (PDT) is frequently used to treat actinic keratoses and early skin cancers. Previous studies by our group demonstrated that PDT effectively reduces the burden of epidermal clonal mutations, particularly those with variant allele fractions (VAFs) below 1%, in both human and mouse models. In this study, we expanded our investigation to include SKH1 mice treated with 5FU. Four weeks after the field treatment, 131 epidermal samples were collected from 9 SKH1 hairless mice treated by PDT (n=5) and 5FU (n=4) following 8 weeks of chronic 3x/week UVB exposure (120mJ/cm^2). A total of 66 samples were from the treated side (38 PDT and 28 5FU-treated), and 75 were untreated samples from the same animals, serving as controls. Ultradeep sequencing (>20,000X) was performed using a custom-targeted panel capturing 251 kb of mouse genomic regions commonly mutated by UV exposure. Of the 25,973 mutations, 87% displayed a UV signature pattern. Both PDT and 5FU treatments significantly reduced mutation burdens in the treated skin (PDT: $p<0.01$, 5FU: $p<0.0001$), with 5FU showing a markedly stronger effect compared to PDT (median mutations per sample: Control = 246, PDT = 173, 5FU = 66). This overall difference was primarily driven by low-VAF (<1%) mutations (median mutations per sample: Control = 237, PDT = 167.5, 5FU = 51, $p<0.0001$) rather than high-VAF (≥1%) mutations (median mutations per sample: Control = 7, PDT = 3.5, 5FU = 3.5). Although the magnitude of the difference is likely model and dose-specific, the current study provides the first objective and quantitative comparison of the early field effect of PDT and 5FU treatments. Our findings indicate that clonal mutations, particularly low-VAF mutations, may help assess early field treatment response and help design treatments to reduce skin cancer risk more effectively.

0780

Evaluating long-term efficacy and patient-specific factors in combination treatments for photoaging

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Photoaging, manifested as wrinkles, loss of elasticity, uneven pigmentation, and rough skin texture, is primarily driven by environmental factors, notably ultraviolet (UV) sun exposure. Despite advancements in treatment options, gaps remain in understanding the most efficacious therapeutic approaches. This study evaluates the long-term efficacy of combination treatments using topical retinoids, antioxidants, and chemical peels to mitigate photoaging's effects. Topical retinoids were found to enhance collagen synthesis, accelerate epidermal turnover, and reduce pigmentary changes by inhibiting tyrosinase activity, leading to improvements in skin texture, fine lines, and pigmentation over prolonged use. Antioxidants play a crucial role in neutralizing reactive oxygen species, reducing oxidative damage, and complementing the reparative actions of retinoids by stabilizing free radicals and enhancing photoprotection, thus maintaining skin integrity. Chemical peels containing glycolic acid, salicylic acid, and trichloroacetic acid resurfaced the skin, improved texture, and reduced hyperpigmentation by promoting controlled exfoliation and stimulating dermal remodelling. The synergistic effects of combining topical retinoids, antioxidants, and chemical peels offer a robust, multifaceted approach to managing photoaging. Personalized treatment plans that consider individual patient profiles are essential for optimizing outcomes and effectively addressing photoaging in clinical practice. Further research is warranted to establish standardized protocols that accommodate the diverse needs of patients.

0781

Cellular and molecular profiling of lymphomatoid papulosis reveals factors associated with indolent vs. aggressive CTCL behavior

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Primary cutaneous T-cell lymphomas (CTCL) comprise a diverse spectrum of neoplastic skin conditions, ranging from self-limiting CD30+ lymphoproliferative disorders such as lymphomatoid papulosis (LyP) to aggressive systemic CTCL. However, mechanisms underlying their specific clinical disease behavior are insufficiently understood. Using single-cell RNA sequencing combined with T cell receptor sequencing, we conducted molecular profiling of skin biopsies from LyP that harbored either a CD4+, CD8+ or TCR-γδ+ clonal phenotype, and compared results to cases of advanced-stage CTCL (CD4+ mycosis fungoides, aggressive epidermotropic CD8+ cytotoxic lymphoma, and TCR-γδ+ mycosis fungoides) with a subsequently lethal disease outcome. Expanded clones of LyP harbored an overall GZMA+GNLY+PRF1+ cytotoxic-like immune phenotype. Importantly, this signature was independent of their CD4, CD8 or TCR-γδ lineage. Advanced-stage CTCL lesions of all subsets, by contrast, showed a transcriptomic pattern that was more reminiscent of helper T cells, but showed a high degree of heterogeneity. Nevertheless, we found that advanced-stage CTCL tumor clones were distinguished by uniform expression of a characteristic panel of 8 genes (LTB, IL32, ISG15, GIMAP5, GIMAP7, MT2A, BATF and SNHG8) across CD4, CD8 and TCR-γδ clones. Within the tumor microenvironment, we detected a unique population of SPP1+ LyP-specific macrophages expressing the M1-associated markers INHBA, IL1B, and FBP1, in line with the more cytotoxic / type-1 associated immune microenvironment in LyP, that was largely absent in all subsets of advanced-stage CTCL. Taken together, we found immune mediators associated with indolent vs. aggressive clinical disease behavior, which might be relevant for future immunomodulatory treatment strategies in CTCL.

0782

MAGT1 deficiency increases polyomavirus susceptibility and risk of early-onset merkel cell carcinoma

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Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine skin cancer, primarily caused by Merkel cell polyomavirus (MCPyV). MCC is a disease of advanced age (median age of diagnosis = 75 years) and is exceedingly rare in individuals under 30. Immune suppression also increases the risk of MCC, with 10% of patients being immunosuppressed. We previously identified three patients with X-linked immuno-deficiency with magnesium defect, Epstein-Barr virus infection, and neoplasia (XMEN) disease who developed advanced-stage, MCPyV-positive MCC before the age of 25. XMEN disease is a rare primary immunodeficiency resulting from pathogenic loss-of-function mutations in the magnesium transporter 1 (MAGT1) gene. To investigate the association between XMEN and early-onset MCC, we analyzed the skin and serum of patients with XMEN. Shotgun metagenomic sequencing of the cutaneous microbiome revealed an elevated MCPyV burden, along with defects in controlling other polyomaviruses in XMEN patients. Consistent with this, XMEN patients exhibited elevated titers of neutralizing antibodies against MCPyV and other polyomaviruses. Remarkably, one patient who underwent allogeneic hematopoietic cell transplant continued to have elevated cutaneous MCPyV levels, even after full engraftment and discontinuation of immunosuppression. Persistently elevated virus in this patient suggests that MAGT1 function in non-hematopoietic cells is necessary for polyomavirus control. Collectively, our findings support the hypothesis that, although immunosuppression increases MCC risk, non-immune risk factors related to MCPyV susceptibility also contribute to the development of early-onset MCC in patients with XMEN.

0783

Cutaneous metastasis of alveolar rhabdomyosarcoma in a young adult: A rare presentation and diagnostic challenges

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We present a 22-year-old woman with a history of metastatic alveolar rhabdomyosarcoma (ARMS) of the left foot who developed progressive skin lesions on the left thigh and back. ARMS is an aggressive subtype of rhabdomyosarcoma (RMS), the most common soft tissue sarcoma in children. Notably, ARMS has a 5-year survival rate of 50-70% for localized cases and 20-30% for metastatic cases. When metastasis occurs, cutaneous sites are exceedingly rare, with only 14 reported cases in the literature to date. However, it is important to recognize these cutaneous findings given that metastasis to the skin indicates advanced disease with a poor prognosis. Despite amputation of her left foot (the primary site of her ARMS) and treatment with multiple chemotherapy regimens, this patient experienced recurrent pulmonary and hepatic metastases. She was admitted for worsening shortness of breath and at that time, our inpatient dermatology team was consulted for evaluation of skin lesions on the left thigh which were worsening over the course of one month. On physical examination, multiple tender, erythematous to pink nodules with red-yellow exudate and central necrotic crust were observed. A punch biopsy confirmed the lesions as metastatic cutaneous ARMS. This case underscores the rarity of cutaneous ARMS and the scarcity of documented physical exam findings in the literature. Cutaneous ARMS metastasis can be an early visible sign of systemic disease and often signifies an advanced disease state, making early recognition crucial for timely intervention and improved patient outcomes, thus highlighting the need for heightened awareness among dermatologists.

0784

Skin of color associated genes with worse outcomes in cutaneous squamous cell carcinoma

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There is a paucity of controlled studies examining racial disparities in treatment and outcome in cutaneous squamous cell carcinoma (cSCC) patients despite being well reported in highly prevalent cancers.[1-3] We previously reported poor cSCC outcomes in skin of color (SOC) compared to non-Hispanic white (NHW) patients and separately reported canonical genes that drive aggressive behavior in cSCC.[4] To elucidate the underlying mechanisms for SOC patient poor outcomes, we performed transcriptomic analysis using a custom cSCC specific 183 Nanostring platform on SOC (N=44) and NHW (N=186) samples. We performed differential and functional enrichment analysis (FEA). We identified 56 differentially expressed genes (DEGs) in SOC and NHW samples. There were 28 DEGs between metastasis and non-metastasis SOC samples including CSMD3, COL25A1, KSR2, PLA2G6, LAMA2, and PCSK1. FEA was performed on the 56 SOC-associated DEGs and identified downregulated pathways of cell cycle/cell division and upregulation pathways of keratinization and metabolism. We performed 2-D unsupervised hierarchical clustering analysis including 3-factors (SOC vs NHW, tumor risk, and metastatic status) on the 56 DEGs and identified 4 distinct clusters. FEA was performed and identified distinct clusters in cell division/differentiation, muscle processes, metabolism, and keratinization. Additionally, we performed FEA on the 28 genes associated with metastasis in SOC samples and identified the down-regulation of metabolic and catabolic pathways. We identified DEGs in SOC cSCC as well as defined enriched pathways of disease. A subset of DEGs were associated with poor outcomes previously reported as predictive of metastasis and survival.[4]

0785

Altered folate and vitamin b12 status in NMSC patients: Insights from the all of us research program

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This study examines the association between folate (B9) and cobalamin (B12) deficiencies or excess and the risk of developing non-melanoma skin cancer (NMSC), including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). A cross-sectional analysis was conducted using data from the All of Us Research Program. Folate and B12 levels were measured in patients within one year of being diagnosed with either basal cell carcinoma (BCC) or squamous cell carcinoma (SCC). Folate deficiency and excess were defined as <4 ng/mL and >20 ng/mL, respectively. B12 deficiency was defined as <200 pg/mL, and excess as >914 pg/mL. Folate deficiency was more prevalent in SCC (3.94%) and BCC (3.07%) patients compared to the U.S. average (~1%, $p<<0.001$). Folate excess occurred in 17.16% of SCC and 21.16% of BCC cases, though national comparisons were unavailable. Vitamin B12 deficiency was less common in SCC (4.40%) and BCC (5.15%) patients compared to the general population (10.06%, $p<<0.001$). However, B12 excess was more prevalent in SCC (24.25%) and BCC (22.11%) patients versus the general population (18%, $p<<0.001$). These findings reveal distinct patterns in folate and B12 levels among NMSC patients. Elevated folate levels, possibly linked to supplementation, may have dual roles in cancer, preventing early development but promoting progression. Higher B12 levels, potentially associated with solid cancers incidence and increased all-cause mortality, also warrant further investigation into the underlying mechanisms. This study emphasizes the need for further research on vitamin B complex levels in NMSC and the potential implications of supplementation in at-risk populations.

0786

DNA sequencing reveals novel subtype of kaposi sarcoma among HIV-negative, immunocompetent, Latin American patients

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We used DNA sequencing of the ORFK1 region to identify a novel subtype of Kaposi Sarcoma (KS) among patients who are HIV-negative, immunocompetent individuals of Latin American origin. After characterizing unique clinical features of this subtype in a cohort of 16 patients, we performed DNA sequencing on the highly variable ORFK1 region of the human herpesvirus 8 (HHV-8) genome. We obtained amplifiable DNA from diagnostic biopsies of 4 patients and sequenced a variable region of ORFK1 using nested PCR. Of the 4 cases amplified, our control (Patient 7) had a presentation consistent with classic KS and corresponded to a C3 strain with 99.68% identity to the C3 reference strains OR829390.1 and KT215122.1. Another patient had a sequence corresponding to A2 with 100% identity to the A2 reference U75698. The other two individuals (Patients 2 and 4) had sequences consistent with an A genotype, with 97.72% and 98.44% identity to the reference strain AF130269.1. Notably, these two patients were slightly more similar to each other than to the reference strains, with 98.4% identity. Two of the sequences, patient 2 and 4 from individuals from the Dominican Republic were highly similar to an ORF-K1 subtype A reference sequence AF130269.1. The reference sequence AF130269.1 is from an isolate IAp1 derived from a classic KS from Italy, that was close to Ic10, an isolate from Iceland. These two subtypes fell within a phylogenetic tree as a separate A subgroup, not classified as A1 through A5 according to a study evaluating the variability and evolution of KSHV strains from Europe and Africa. Our findings provide the first genetic evidence of a novel Kaposi Sarcoma (KS) subtype that may have significant implications for diagnosis, treatment, and understanding the pathogenesis of KS in diverse populations

0787

Lower long-term melasma risk associated with hormonal intrauterine devices compared to combined and progestin-only oral contraceptives

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Previous studies have suggested potential effects of birth control options on chronic dyspigmentation. This study investigated the risk of melasma in patients treated with hormonal intrauterine devices (hIUDs) vs. progestin-only contraceptives (POCs) and combined oral contraceptives (COCs). We conducted a population-based cohort study including U.S. patients aged 18-52 with menorrhagia treated with hormonal contraceptives between January 2001 and October 2024. Patients were classified into those treated with COCs, POCs, hIUDs, and hormone-unprescribed controls. Propensity score matching controlled for demographics, medications, procedures, and comorbidities. Over 1 year of follow-up, compared to controls, no significant difference in melasma risk was observed among patients on COCs (risk ratio [RR]: 1.50; 95% CI: 0.80-2.83), POCs (RR: 1.00; 95% CI: 0.42-2.40), and hIUDs (RR: 1.00; 95% CI: 0.42-2.41). At 3 years of follow-up, COC-treated patients showed a significantly increased risk of melasma (RR: 2.42; 95% CI: 1.57-3.72), while those on POCs (RR: 1.80; 95% CI: 0.96-3.38) and hIUDs (RR: 1.31; 95% CI: 0.64-2.70) did not. At 5 years of follow-up, a significantly increased risk of melasma was observed for COCs (RR: 2.68; 95% CI: 1.86-3.85) and POCs (RR: 1.95; 95% CI: 1.10-3.43), but not hIUDs (RR: 1.59; 95% CI: 0.87-2.92). Findings did not show significant increased melasma risk conferred by hIUDS, whereas there was increased risk at 3 and 5 years for COCs and at 5 years for POCs, suggesting hIUDs may be the safer option for patients at risk of chronic dyspigmentation. Our findings suggest melasma risk may be proportional to systemic hormone absorption, with highest risk in COCs, followed by POCs and hIUDs. Future studies may explore the potential benefits of switching from oral contraceptives to hIUDs as a strategy for management of patients with pre-existing melasma.

0788

Parkin-mediated ubiquitination of DCUN1D1: Implications for CXCL10 regulation in vitiligo

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Vitiligo is a skin disorder characterized by the loss of skin pigmentation resulting from the destruction of melanocytes. Our prior research identified DCUN1D1 as a novel regulator of CXCL10, which is linked to mitochondrial dysfunction. Analysis of RNA sequencing data indicated a reduction in the expression of Parkin, a molecule associated with mitophagy, in patients with vitiligo. Parkin operates as an E3 ubiquitin ligase. In light of these observations, we propose that Parkin ubiquitinates DCUN1D1, thereby modulating CXCL10 levels during the progression of vitiligo. This study evaluated the expression levels of Parkin and DCUN1D1 in both vitiligo patients and mouse models. To investigate their interactions, HaCaT cells were transfected with Flag-DCUN1D1, Myc-PRKN, or HA-Ub, followed by co-immunoprecipitation and Western blot analysis. Mitochondrial activity and mitophagy were assessed following various treatments, including CCCP administration. Additionally, HaCaT cells were transfected with DCUN1D1 or varying concentrations of Parkin to measure CXCL10 levels. The supernatant from HaCaT cells was subsequently incubated with melanocytes for 48 hours, after which apoptosis was evaluated. The findings revealed that DCUN1D1 was upregulated while Parkin was downregulated in both vitiligo patients and mice. Furthermore, Parkin was shown to interact with and ubiquitinate DCUN1D1 at lysine 27 (K27). Elevated levels of Parkin were found to mitigate the decreases in mitochondrial activity and mitophagy induced by DCUN1D1, significantly downregulating CXCL10 levels and reducing melanocyte apoptosis. In conclusion, this study provides compelling evidence that Parkin-mediated ubiquitination of DCUN1D1 plays a critical role in regulating CXCL10 levels in vitiligo, thereby contributing to a deeper understanding of the pathogenesis of this condition.

0789

Hydroquinone-induced vitiligo: A case report

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Introduction: Vitiligo is an acquired skin condition characterized by the loss of melanocytes, leading to depigmented patches on the skin. While the etiology is multifactorial, drug-induced vitiligo has been reported with topical imiquimod, TNF inhibitors, and PD-1 inhibitors. Hydroquinone, a skin-lightening agent, has rarely been associated with vitiligo, with only two prior cases linked to occupational exposure to hydroquinone-containing photographic solutions. Here, we present a rare case of vitiligo induced by topical 4% hydroquinone. Case Summary: A 31-year-old man with no prior history of autoimmune or dermatologic conditions applied topical 4% hydroquinone once daily under his eyes for dark circles. After two weeks of use, he developed a depigmented patch on his chest and white hair (poliosis) on the occipital scalp. Despite discontinuing hydroquinone, depigmentation spread to the chest, upper arm, and back. Examination revealed well-demarcated depigmented patches confirmed by Wood's lamp. Laboratory tests, including thyroid function and autoimmune panels, were normal. A diagnosis of hydroquinone-induced vitiligo was made. The patient declined treatment for depigmentation but avoided further use of hydroquinone. Discussion: This case highlights hydroquinone as a rare but potential cause of drug-induced vitiligo, even with localized application. Unlike classical vitiligo, drug-induced cases can present in both sun-exposed and non-sun-exposed areas, as seen here. Mechanisms such as oxidative stress, melanocyte apoptosis, or immune-mediated cytotoxicity may underlie hydroquinone-induced vitiligo, though further research is warranted. Early discontinuation of the offending agent is critical to minimize progression. This case underscores the need for caution and patient education when prescribing hydroquinone for cosmetic use. Conclusion: Drug-induced vitiligo, though rare, should be considered when evaluating new-onset depigmentation in patients using hydroquinone. Early identification and discontinuation are essential to address this potentially distressing outcome.

0790

Novel siglec probes identify aberrant sialic acid expression linked to immune exclusion and survival in melanoma

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Sialoglycans display aberrant overexpression in a range of cancers, where their interaction with sialic acid-binding immunoglobulin-like lectins (Siglecs) may play a role in facilitating immune evasion and tumor progression. However, Siglec implicated mechanisms of evasion and progression within the tumor immune microenvironment (TIME) remain underexplored, partially due to the limited availability of high-affinity detection probes. In this study, we developed and optimized an immunohistochemistry protocol using novel reagents—HYDRA-3, -7, and -9—to detect Siglec-3, -7, and -9 sialoglycan ligands, respectively. To correlate HYDRA staining patterns with immune infiltration, we analyzed melanoma tissue microarrays (TMAs) constructed using tumor core and tumor-stromal boundary samples from 135 patients with known 5-year survival outcomes. TMAs stained with the three HYDRA reagents were directly compared to TMAs stained with a 6-plex immunofluorescence panel targeting CD8, CD163, FoxP3, PD1, PDL1, and Sox10/S100. Notably, Siglec-3 and Siglec-9 ligand expression negatively correlated with CD8 T-cell infiltration ($r = -0.28$, $p = 0.002$ and $r = -0.29$, $p = 0.001$, respectively), particularly at the tumor-stromal interface ($r = -0.37$, $p < 0.001$ and $r = -0.44$, $p < 0.001$, respectively). Moreover, a high ratio of Siglec-3 and Siglec-9 ligand expression at the tumor-stromal interface relative to the tumor core was associated with reduced overall survival (HR = 2.60, 95% CI 1.31-5.18 and HR = 2.11, 95% CI 1.01-4.41, respectively). These findings suggest that the spatial distribution of Siglec-engaging sialoglycans, rather than total expression, plays a key role in shaping the TIME and influencing patient outcomes, possibly as a result of abnormal sialoglycan overexpression along the tumor-stromal interface promoting an immune excluded environment.

0791

CXCL14 and mast cells: A potential interaction in melanoma

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This study investigates a role of CXCL14 and mast cells in melanoma. CXCL14, a non-ELR CXC chemokine, presents with conflicting pro-tumor and anti-tumor activity depending on tumor type and cellular source of CXCL14. Mast cells, tissue resident innate immune cells, are key modulators of the tumor microenvironment, exerting context specific tumor suppressive or progressive roles depending on tumor type. The role of CXCL14 and mast cells in melanoma remains unclear. By a bioinformatic analysis of TIMER2.0, we identified a positive correlation between CXCL14 and mast cell mRNA expression levels in clinical melanomas ($p<0.05$). By analyzing a public single-cell RNA sequencing dataset of 19 clinical melanomas, we identified that CXCL14 was mainly expressed in cancer associated fibroblasts. We co-stained CXCL14 (in situ hybridization) and various immune cells (immunohistochemistry) and found that the numbers of CXCL14-positive cells and mast cells were correlated both in the peritumoral area ($p<0.01$) and inside tumors in melanoma samples. Furthermore, we identified more CXCL14-positive cells in peritumoral areas of thinner ($p<0.01$) and low-grade ($p<0.05$) melanomas compared with those of thicker and high-grade. At this time, further studies are needed to understand why the numbers of CXCL14-positive cells and mast cells were correlated. Nonetheless, clarifying the role of CXCL14 and mast cells in melanoma pathogenesis would be useful to explore a new therapeutic target.

0792

Polo-like kinase 4 (PLK4) inhibition reverses the loss of primary cilia in human melanoma cells

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Polo-like kinase 4 (PLK4) is the master regulator of centriole biogenesis and its overexpression is associated with centriole overduplication and amplification in melanoma. Centrosomes are responsible for the formation of primary cilia, which are key sensory and signaling hair-like organelles found on the surface of most mammalian cells. Interestingly, primary cilia are frequently lost during melanoma development and progression, which has been shown to enhance pro-tumorigenic WNT/β-catenin signaling. Given the role of PLK4 in centrosome biology, we hypothesized that PLK4 overexpression is involved in loss of cilia in melanocytic cells and its inhibition will reinforce cilia and impart anti-melanoma response. We found that small molecule inhibition of PLK4 (CFI-400945 or centrinone B) or its CRISPR/CAS9 knockout significantly increased the number and length of cilia in A375 and G361 melanoma cells. This was associated with an anti-proliferative response of PLK4 inhibition in-vitro and in-vivo. Further, to identify the mechanisms associated with the observed effects, we employed a human primary cilia specific RT^2 Profiler PCR Array (Qiagen) that contains 84 genes related to ciliary function signaling pathways, on CFI-400945-treated A375 and G361 cells. We found that CDKN1A (p21), IHH, PKHD1, and SHH were significantly upregulated (>1.5-fold) after CFI-400945 treatment, while ARL13B and PTCH1 were significantly downregulated in both cell lines. Taken together, our study suggests that PLK4 is involved in cilia loss in melanoma and its inhibition causes cilia reappearance and an anti-melanoma response. Further functional validation of these targets in PLK4-induced cilia loss in melanoma cells is currently ongoing in our laboratory.

0793

Analysis of the somatic mutational landscape of cutaneous melanoma across racial and ethnic groups

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While racial disparities have been identified in melanoma prognosis, data are lacking on somatic mutational differences between tumors from patients of different racial and ethnic backgrounds. We investigated mutation count, tumor mutational burden (TMB), copy number variations, and known driver mutation prevalence in various racial and ethnic groups by examining two independent sample sets, cutaneous melanomas of any histologic subtype (n=432) and acral melanomas (n=38), available through the cBio Cancer Genomics Portal. For melanomas of any subtype, both mean mutation count and TMB were significantly lower in tumors from Asian, Black, or Hispanic patients than in those from non-Hispanic White patients (287.1 vs 779.1 muts and 9.6 vs 27.3 mut/Mb, respectively; $p<0.001$). Similarly, for acral melanomas, tumors from Black patients had significantly lower mean mutation count and TMB compared to those from non-Hispanic White patients (63.4 vs 238.9 muts and 2.1 vs 7.8 mut/Mb, respectively; $p<0.05$). In all melanoma subtypes, a higher proportion of CDKN2A, KIT, and TERT mutations were found in tumors from non-Hispanic White patients than in those from Asian, Black, or Hispanic patients. Acral melanomas from Black patients had a higher proportion of CCND1 and NF1 mutations compared to those from White patients. Discovery of differences in TMB, unique genetic mutations, or known driver mutation prevalence in specific racial or ethnic groups may enable more personalized and effective treatment options and ultimately reduce melanoma disparities.

0794

Kitl induction in postnatal and adult mice induces epidermal pigmentation via activation of melanocyte stem cells

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Melanocytes (Mcs) determine the color of hair and skin, and their abnormalities cause gray hair, vitiligo, and pigment spots. White hair of receptor tyrosine kinase Kit loss-of-function mutant mice reflects Kit dependency of Mc development. Inversely, overexpression of Kitl, a ligand for Kit, in the epidermis promotes the proliferation and differentiation of developing melanoblasts (Mbs) and maintains Mcs throughout life in the epidermis, where Mcs are not maintained in wild-type mice. Therefore, Kitl-Kit signaling is expected to also be involved in the maintenance of adult melanocyte stem cells (MSCs). Administration of the Kit function-blocking antibody Ack2 ablatesproliferating Mbs, however, quiescent MSCs present in the bulge region of hair follicles are resistant to ACK2 and are maintained independently of Kit signaling. Thus, the exact role of Kit signaling in adult MSCs remains to be further tested. To investigate the impact of Kitl expression in postnatal or adult Mcs, we generated genetically modified mice expressing the Kitl transgene throughout the body in a doxycycline-dependent manner. Doxycycline administration stimulated growth and differentiation of postnatal or adult MSCs. We also generated mice that can transiently induce Kit1 expression only in the epidermis. Even a single pulse expression of Kitl only in the epidermis had long-term effects on MSCs, resulting in pigmentation of the entire epidermis. Intermittent induction of Kitl repeatedly induced pigmented skin. Conditional Kitl overexpression also rescued radiation-induced hair graying in adults. These results indicate that regulation of Kitl signaling is crucial for MSC homeostasis and Mc cell differentiation in postnatal and adult stages.

0795

***In vivo* genome-wide CRISPR screen identifies key factors modulating antigen-specific CD8$^+$ T cells responses to recombinant MVA viral immunotherapy**

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Viral-based cancer immunotherapy represents a novel and versatile platform to modulate the tumor microenvironment (TME) by activating innate and adaptive immune responses. We have previously reported that intratumoral delivery of recombinant MVA (rMVA) deleting cGAS inhibitor E5R and expressing membrane-anchored Flt3L and OX40L generates potent antitumor effects by activating the cGAS/STING DNA-sensing pathway, depleting OX40^{hi} Tregs, and activating CD8$^+$ T cells. In this study, we show that local modulation of the TME by immunogenic viruses is critical for anti-tumor immunity, independent of recruiting antigen-specific T cells from secondary lymphoid organs. Using FTY-720, an inhibitor of T-cell egress, we show that anti-tumor activity induced by intratumoral (IT) rMVA remains intact. Integrated single-cell RNA and TCR sequencing revealed significant reprogramming of CD8$^+$ T cells within injected tumors. Stem-like TCF7-positive cells exhibited the lowest clonality, while greater clonal expansion was observed in effector and proliferating populations. Following rMVA injection, stem-like T cells decreased, while clone proliferation increased in effector and proliferating cells. Interestingly, with FTY-720, T-cell clone proliferation further increased in these populations. These findings underscore the critical role of local TME modulation by rMVA in driving T-cell reprogramming and clonal expansion, independent of T-cell recruitment. An *in vivo* CRISPR screen using antigen-specific OT1 CD8$^+$ T cells expressing Cas9 identified Socs1 and Zc3h12a as top negative regulators and Gpn2 and Adra2A as top positive regulators in response to rMVA therapy. These findings highlight the critical role of local TME modulation by viral immunotherapy and provide insights into mechanisms driving T-cell activation and clonal expansion.

0796

Unveiling the power of tinted sunscreens in reducing melasma hyperpigmentation: A systematic review

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This study investigates the efficacy of tinted versus non-tinted sunscreens in mitigating hyperpigmentation in patients with melasma, focusing on clinical outcomes and patient satisfaction. A systematic review of peer-reviewed studies published from 2010 to 2025 was conducted, including trials evaluating tinted and non-tinted sunscreens in melasma management. Key metrics analyzed included reductions in the Melasma Area and Severity Index (MASI), changes in skin reflectance (ΔL*), and patient-reported outcomes. The results indicate that tinted sunscreens demonstrated significantly greater reductions in MASI scores (30-40%) compared to non-tinted sunscreens (15-25%) over similar treatment durations ($p = 0.027$). Patients using tinted sunscreens also reported higher adherence and satisfaction, attributed to enhanced visible light protection provided by iron and titanium oxides.These findings underscore the superior efficacy of tinted sunscreens in managing melasma, highlighting their potential as a critical component of treatment strategies. This study emphasizes the need for future clinical trials to evaluate long-term outcomes and solidify tinted sunscreens' role in hyperpigmentation therapy.

0797

Histotripsy as a novel adjunct in advanced melanoma treatment

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Advanced melanoma presents significant treatment challenges due to its diffuse nature and complex microenvironment. Current therapies have shown efficacy but are limited by toxicities, resistance, and incomplete tumor eradication.[1,2,3] Histotripsy, a non-invasive focused ultrasound technique, offers a novel approach to tumor disruption and may complement existing treatments.[5,6] Studies investigating histotripsy in melanoma or related cancer models, as well as clinical trials, were reviewed. Data on histotripsy's mechanism, efficacy, safety, and combination therapies were analyzed. Histotripsy utilizes high-amplitude focused ultrasound pulses to mechanically disrupt tumor tissue through nonthermal cavitation.[5,6] Preclinical studies in murine melanoma and hepatocellular carcinoma models have shown histotripsy to induce local tumor destruction and abscopal effects at untreated tumor sites, stimulate systemic anti-tumor response and enhance checkpoint inhibitor immunotherapy.[7,8] A single-arm clinical trial demonstrated histotripsy to be effective in treating primary and metastatic liver tumors with few adverse events, emphasizing its potential as a non-invasive treatment in cases refractory to traditional methods.[9] Primary tumor location and nodal metastasis make histotripsy a candidate for adjunctive treatment of advanced melanoma, as these tumors avoid some of the areas in which histotripsy shows weaknesses (e.g., attenuation of ultrasound energy or bone obstruction).[10] The technique's non-invasive nature and favorable safety profile in early clinical trials support its potential as a complementary treatment. Additionally, its mechanical mode of action bypasses the limitations of systemic therapies, offering a promising adjunct therapy. Exploring histotripsy in combination with checkpoint inhibitors or other immunomodulators may improve advanced melanoma treatment.

0798

Low-grade spitz melanocytoma with novel PTMA: ALK fusion

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Background: Spitz melanocytomas are considered intermediate low-grade melanocytic neoplasms with low malignant potential, but with histomorphologic and/or genetic signatures that place them on the pathway between nevus and melanoma. Recent advances in molecular diagnostics have identified recurrent gene fusions, including ALK (Anaplastic Lymphoma Kinase), as distinguishing features in spitzoid neoplasms. Prothymosin Alpha (PTMA), a nuclear protein involved in transcription regulation and apoptosis, may enhance ALK signaling when fused, contributing to the pathogenesis of melanocytic tumors. We present the first reported case of a Spitz melanocytoma with a PTMA-ALK fusion, offering insights into its clinical presentation, molecular profile, and recommended management strategies. Case Report: An 18-year-old male presented with a pigmented lesion on the right superior flank. Physical examination revealed a well-circumscribed, 1.8 cm dark nodule. Biopsy showed a compound melanocytic proliferation of heavily pigmented, spindled, and epithelioid melanocytes. Cytologic features included pigmented cytoplasm, enlarged nuclei with prominent nucleoli, and occasional nuclear pseudoinclusions. There was focal Ki-67 expression. Immunohistochemistry demonstrated strong Melan-A positivity, retained P16, and negative PRAME staining. Molecular testing identified a novel PTMA-ALK fusion. The lesion was classified as a low-grade Spitz melanocytoma. Conclusion: This case presents the first reported Spitz melanocytoma with a PTMA-ALK fusion. The novel rearrangement emphasizes the potential oncogenic role of ALK signaling in melanocytic tumors, with implications for both prognosis and therapeutic strategies. While ALK fusions in spitzoid tumors are typically associated with low-grade behavior, the intermediate-grade features and incomplete initial excision in this case warranted full-thickness resection with clear margins to reduce recurrence risk.

0799

Targeting UV-induced senescence in the skin microenvironment to prevent melanomagenesis

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Exposure to ultraviolet radiation (UV) and aging are the major risk factors for cutaneous melanoma (CM). The resulting accumulation of DNA damage is necessary but not sufficient for tumor formation, but the mechanisms by which skin aging and photoaging (UV) trigger a tumorigenic skin microenvironment (ME) are largely unknown. Here, we investigated the effects of UVB-induced senescence in non-tumor skin cells on CM progression, and the potential of senolytic drugs as therapeutics. First, we observed that implantation of B16 melanoma cells in mice pre-exposed to UVB yielded larger tumors with shorter latency, and a more suppressive immune infiltrate than in non-irradiated mice. Aging and UVB exposure resulted in similar, molecular and cellular changes in mouse skin, such as accumulation of senescence cells and expression of the senescence-associated secretory phenotype (SASP), increased inflammation and dermal remodeling, which were reverted by the pharmacological or genetic ablation of senescent cells, suggesting similar pro-tumorigenic mechanisms in aging and photoaging. To determine the effect of senescence in the skin on tumor growth, we exposed various mouse and human CM cell lines to the secretome of UV-induced senescent skin-derived keratinocytes and fibroblasts. These secretomes promoted CM cell growth, invasion and migration. Co-implantation of mouse melanoma cells (B16 or YUMM) and senescent dermal fibroblasts resulted in larger tumors compared to cell mixtures with non-senescent dermal fibroblasts. Lastly, the observed UV-related increase in tumor growth and immunosuppressive ME were significantly reduced by the elimination of UV-induced skin senescent cells using the genetic model or senolytics. Our findings suggest that accumulation of SASP expressing senescent cells in UVB-damaged skin promote melanoma growth, and that senolytics may restore a non-tumorigenic skin ME; thus, they may be a promising preventative and therapeutic approach for early intervention in CM.

0800

Pigmentation defects in tissue-engineered skin substitutes are induced by prolonged epithelial cell culture and not cryopreservation

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Severe burn patients can be treated with tissue-engineered skin substitutes (TESs). However, pigmentation is not fully restored after TES grafting, resulting in hypopigmentation with pigmented spots in treated patients. We hypothesized that these defects are caused by the culture conditions. The aim of this project was to evaluate the effect of culture time and cryopreservation of epithelial cells used in TESs production. The subsequent pigmentation of TESs was assessed after grafting onto athymic mice. Briefly, epithelial cells were freshly isolated, minimally amplified over a period of 4 days or for a longer time (12 days) and cryopreserved or not. Epithelial cells were seeded onto a dermal component and the resulting TESs were matured at the air-liquid interface for 12 days before grafting onto athymic mice for 45 days. Our results showed that pigmentation in TES with minimally amplified epithelial cells, cryopreserved or not, appeared 7 days after grafting. Pigmentation then became homogenous 28 days after grafting. In contrast, TES produced with epithelial cells cultured for 12 days, cryopreserved or not, did not show homogenous pigmentation even 45 days after grafting. Histological and immunofluorescence analyzes of the pigmented TESs showed basal epithelial cells presenting nuclear caps of melanin, suggesting that the melanocytes were functional. These results showed that cryopreservation of epithelial cells does not affect TES pigmentation while prolonged culture time causes pigmentation defects. Ultimately, changes in epithelial cell culture conditions, such as reducing the culture time of epithelial cells or modifying the culture medium, could lead to restoration of a homogeneous pigmentation after TES grafting onto severe burn patients.

0801

Sarcopenia is poor prognostic factor in japanese patients with advanced melanoma

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Background&Aims: Sarcopenia is associated with poor immune checkpoint inhibitor (ICI) efficacy in patients with melanoma; however, whether this is true in all populations remains to be explored. The current study aimed to investigate the effect of sarcopenia on overall survival (OS) and progression-free survival (PFS) of patients with advanced melanoma treated with ICI. Methods: We retrospectively collected the clinical data of consecutive patients with advanced melanoma who received ICI as first-line treatment between 2013 and 2024 at our institution. To diagnose insufficient muscle mass, the skeletal muscle index (SMI) at the third lumbar spine was calculated from computed tomography (CT) images, and SMI values < 42 cm^2/m^2 for men and < 38 cm^2/m^2 for women diagnosed sarcopenia. The association of insufficient muscle mass, OS, and PFS with ICI treatment in patients was investigated. Results: 76 patients with advanced melanoma were assessed retrospectively at our institution; 32 were in the sarcopenia group, while 44 were in the non-sarcopenia group. The median OS in patients with and without sarcopenia was 10.6 and 39.0 months (hazard ratio [HR] 3.12, 95% confidence interval [CI], 1.65–5.89; $p < 0.001$) and median PFS was 2.4 and 18.0 months, respectively (HR, 3.10; 95% CI 1.74–5.54, $p < 0.001$). Multivariate analysis showed significantly poor differences in OS (HR, 2.46; 95% CI, 1.20–5.03; $p = 0.01$) and significant differences in PFS independently in the sarcopenia group (HR, 3.10; 95% CI, 1.74–5.54; $p < 0.001$). Conclusions: Sarcopenia may be a poor prognostic factor for advanced melanoma patients treated with ICI.

0802

Identification of risk factors for acral melanoma in veterans

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This study investigates the risk factors associated with acral melanoma (AM) in the veteran population to address the lack of risk prediction models (RPM) for early detection of AM. AM cases were identified in the Veterans Affairs (VA) Cancer Registry (VACR) using ICD-10, ICD-O-3, and primary site codes. A natural language processing pipeline was also developed to identify AM from VA pathology notes. All identified cases were manually reviewed for accuracy. Cases were matched to CM and non-melanoma controls. Phenotypic and putative risk factor data were extracted, and AM associations compared to CM and non-melanoma controls were evaluated using univariate and multivariate logistic regression analyses. 1,304 AM cases were identified. Agent Orange exposure was associated with higher odds of AM (aOR 1.32, 95% CI: 1.08-1.62, $p = 0.007$) compared to non-melanoma controls. Current smoking was inversely associated with AM compared to both CM and non-melanoma controls (aOR 0.75, 95% CI: 0.63-0.89, $p = 0.001$, aOR 0.71, 95% CI: 0.60-0.85, $p < 0.001$). Lower body mass index (BMI) categories (underweight and normal BMI) were inversely associated with AM compared to overweight non-melanoma controls (aOR 0.76, 95% CI: 0.63-0.90, $p = 0.002$). We identified distinct clinical and environmental factors associated with AM in veterans, including increased odds with Agent Orange exposure and reduced odds with current smoking status and lower BMI. We will apply these findings to develop and validate an RPM in civilian populations to improve the early detection of AM.

0803

Mohs micrographic zurgery versus wide local excision for the treatment of melanoma in situ

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The treatment of melanoma in situ (MIS) presents a unique challenge due to the frequent amelanotic spread of tumors arising from the head and neck as well as presentation in cosmetically sensitive areas. Although wide local excision (WLE) is the current standard of care for MIS, Mohs micrographic surgery (MMS) is increasingly being used due to the confirmation of tumor clearance using histopathologic examination of surgical margins and the tissue-sparing approach. This systematic review of the literature evaluates MMS versus WLE in the treatment of MIS. Eligible articles were identified using PubMed, EMBASE, and Cochrane Library. 11 studies were included. Five studies directly assessed the efficacy of WLE versus MMS, five studies assessed MMS only, and one study assessed WLE only. Overall, MMS was similar to WLE regarding both survival and MIS recurrence. Of the three studies that compared survival between WLE and MMS, all reported no statistical difference between the 5, 10, or 15-year survival rates. One study evaluated survival after MMS only and reported zero melanoma-related deaths after a follow-up period ranging from 3 to 30 months. Regarding recurrence rate, the two studies directly comparing WLE and MMS both reported a greater but non-significant rate of recurrence from WLE versus MMS. From the eight studies that evaluated recurrence after MMS, the rate of recurrence ranged from 0% to 17%; however, only one study reported a recurrence rate above 5%. From the four studies that evaluated recurrence after WLE, the rate of recurrence ranged from 0% to 7.3%. One study reported that recurrence after WLE was 3.6 times greater than MMS (95% confidence interval 0.220 - 0.683, P = 0.0008). Overall, WLE cases resulted in similar rates of survival but higher rates of MIS recurrence compared to MMS. MMS is a reasonable option for MIS excision in anatomic locations where tissue sparing is important.

0804

Genetic architecture of income is positively correlated with that of melanoma in situ but not malignant melanoma

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Elegant epidemiological work has identified a potential overdiagnosis of melanoma in situ (MIS). Overdiagnosis is the increased detection of low-risk disease. This occurs more commonly in healthcare-seeking individuals and can result in overtreatment, psychological distress, and increased cost. Evidence for MIS overdiagnosis includes observations that individuals with MIS: have increased disease-specific survival compared to individuals with thin malignant melanomas (MM); have increased overall survival relative to the general population; and are typically of higher socioeconomic status (SES). Income – a proxy for SES – has genome wide association study (GWAS)-significant loci that can be leveraged to investigate the relationship of SES to MIS. Here, we investigate if the genetic architecture of income overlaps with that of MIS and MM incidence. We obtained the most recent publicly available GWAS summary statistics for these traits (MIS and MM – Ingold et al., 2024 and Income – Kweon at al., 2024), standardized them, and then calculated genetic overlap using GNOVA software. As expected, we confirm a significant overlap between the genetic architecture of MIS and MM (genetic correlation: 0.83 [0.72, 0.94]; $p = 3.85 \times 10^{-50}$). We also find a significant overlap between the genetic architectures of income and MIS (genetic correlation: 0.14 [0.06 to 0.21]; $p = 5.55 \times 10^{-04}$) but not income and MM (genetic correlation: 0.05 [-0.01, 0.11]; p = 0.11). The genetic architecture of income can be reasonably assumed to be independent from that of melanoma. Additionally, any confounding or indirect contribution of income's genetic architecture to melanoma etiopathogenesis – for example, through increased risk tolerance leading to more ultraviolet exposure – is likely to impact both MIS and MM equally. Therefore, the difference between MIS and MM in shared genetic architecture with income provides evidence for a causal pathway between income and MIS. This is being further statistically dissected in ongoing work, but the present results support the hypothesis of MIS overdiagnosis.

0805

Melanocytes differential reactivity to prolonged oxidative stress in relation to pigmentation levels: A senescence model

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Understanding how oxidative stress drives melanocyte aging is essential for advancing research on skin aging and its associated disorders. These pigment-producing cells are particularly prone to oxidative damage due to their high metabolic activity and melanin production, which can increase reactive oxygen species (ROS). However, there is limited research on how prolonged oxidative stress affects melanocyte function and senescence, especially regarding the role pigmentation levels might play in their response. This study aimed to develop the SenMel model that induces senescence of human epidermal melanocytes by chronic hydrogen peroxide (H_2O_2) exposure. Melanocytes from three donors with different pigmentation levels underwent six H_2O_2 treatments over two weeks (week 1: 100 µM; week 2: 500 µM). Several parameters were assessed, including cell proliferation (BrdU assay), β-galactosidase (β-gal) activity, melanin content, and the expression of key melanocyte markers at both the gene and protein levels (e.g., MITF, tyrosinase, p16, TRP1, TRP2). Results revealed that chronic exposure to H_2O_2 significantly elevated β-gal activity (up to +95%, depending on the donor) while reducing cell proliferation (up to -75%, depending on the donor) within the SenMel model. Highly pigmented cells showed greater melanin production (+55%), while in medium-pigmented cells trends for inhibition were observed. Interestingly, lightly pigmented SenMel exhibited negligible changes in melanin synthesis. Molecular analysis indicated elevated p16 (up to +50%, depending on the donor) and higher tyrosinase/TRP2 levels in highly pigmented SenMel, though MITF and TRP1 expression remained unchanged across pigmentation groups. These findings emphasize that baseline pigmentation affects melanocyte responses to oxidative stress, positioning this model as a valuable tool for studying senescence mechanisms in melanocytes.

0806

More than skin deep: Understanding the psychosocial impact of living with vitiligo

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The physical manifestations of vitiligo, an autoimmune depigmenting skin disorder, significantly influence the psychosocial well-being of affected individuals. This scoping review explores the historical stigmatization of vitiligo and its subsequent role in perpetuating discrimination and societal exclusion. The study's objective is to investigate the existing research on the psychosocial impacts of this disease, particularly highlighting its association with psychiatric illnesses. Current research demonstrates an almost five-fold increase in depression risk for vitiligo patients. Demographic factors such as female sex and visible lesion locations exacerbate this psychosocial burden. An exploratory review was conducted to examine the complex psychosocial consequences of vitiligo and its subsequent impacts on the quality of life and emotional well-being of individuals in this population. With the Dermatology Quality of Life Index (DLQI), Hospital Anxiety and Depression Scale, and other assessment tools utilized, the burden on quality of life and the significant psychosocial challenges caused by vitiligo could be quantified. Issues related to shame and embarrassment, engaging in social interactions, and clothing-related concerns were among the most significant burdens on daily life highlighted by the DLQI assessment tool. This comprehensive exploration emphasizes the intricate interplay of demographic and disease-related factors, highlighting the necessity for tailored management strategies to address the associated psychological comorbidities of vitiligo, such as depression, anxiety, low self-esteem, social isolation, maladaptive behaviors, stress disorders, and body dysmorphia. The heightened prevalence of mental health conditions, such as depression and anxiety, underscores the need for tailored interventions to address the psychological disorders in individuals with vitiligo.

0807

Skin phototype diversity and representation in melanoma clinical trials from 2000 to 2023: A systematic review

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Although melanoma incidence is lower in skin of color (SOC) than in White patients, the prognosis in SOC is worse. This is often attributed to later stages of presentation in SOC compared to White patients, but even when matched for stage, survival in White patients remains significantly better. Despite the rapid proliferation of melanoma clinical trials, adequate SOC representation remains to be determined. This study aims to characterize the diversity of skin phototypes and their representation in melanoma clinical trials from 2000 to 2023. The PubMed, Embase, Web of Science, and Cochrane Central Register of Controlled Trials databases were searched from January 1, 2000, to December 31, 2023. Articles were included if they were randomized controlled trials (RCTs) in melanoma patients with published original results. Articles were excluded if they were study protocols, abstracts, conference proceedings, updates or subsequent analyses of existing RCTs, contained non-human subjects, or were not written in English. The database searches resulted in 5,766 citations, of which 367 were ultimately included. On average, 41.5% of participants were female, and only one article reported Fitzpatrick skin type (I-III) in the patient demographics. Only 21.8% (n= 80) of articles reported race, with representation limited in diversity and number; for instance, among the 33 studies that included Black patients, they comprised just 1.1% of the total patient population on average. When reported, other races had similar poor representation, with averages of 2.0% for Asian, 1.8% for Hispanic, 0.3% for American Indian/Native Alaskan, and 2.3% for Other. There is poor skin phototype diversity and representation of racial and ethnic minorities in melanoma RCTs from 2000 to 2023. Additional work is needed to help reduce health disparities in melanoma therapies.

0808

Association between UV irradiation exposure by geographic region and stage at presentation in patients with melanoma

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This retrospective cohort study investigated the association between UV irradiation exposure by geographic region of the United States and melanoma stage at diagnosis. We used the National Cancer Database (NCDB) to identify 644,489 patients with primary cutaneous melanoma from 2004 to 2022. Geographic regions were determined by NCDB facility region at diagnosis. Chi-square and Mann-Whitney U tests were used to assess differences by region in sociodemographic variables, comorbidities, body site of the melanoma, and histologic subtype; multivariable ordinal logistic regression was used to assess odds of higher clinical T-stage at diagnosis (categorized as melanoma in situ, cT1-cT2, and cT3-cT4), adjusting for the aforementioned variables. Linear regression was used to model the association between regional UV exposure and odds of higher stage at presentation. Significant regional differences were observed in UV irradiation (ranging from 3,013 J/m^2 in New England (NE) to 4,468 J/m^2 in the Mountain region, p<.001), histologic subtype (67% superficial spreading in the Mountain region to 80% in NE and Pacific regions, p<.001), and stage at diagnosis (12% cT3-cT4 in NE to 19% in the E. South Central region, p<.001). Relative to New England, the E. South Central region had the highest adjusted odds of presenting with more advanced melanoma (aOR 1.68, p<.001), while the Pacific region had the lowest (aOR 1.13, p<.001). Each 1,000 J/m^2 increase in UV irradiation was associated with 22.6% higher odds of more advanced stage (p<.001), although the odds of increased stage at diagnosis were higher than expected for the E. South Central region (p=.030). These findings reveal that regions with increased UV exposure have a higher likelihood of advanced melanoma at presentation, highlighting the need for increased awareness and targeted screening and prevention strategies in high-UV areas.

0809

UV-induced prion-like aggregate seeding of melanosomal proteins is a driver of chronic dyspigmentation

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Cutaneous hyperpigmentation due to triggers such as UV, inflammation, or hormones represents a clinical challenge disproportionally affecting women and people of color. Chronic cases often show melanized dermal deposits which histiocytes, here termed melanophages, are slow to remove for unclear reasons. Interestingly, melanosomes physiologically organize melanin around insoluble PMEL amyloid fibrils which show prion-like self-aggregatory activity. Our work also confirms that alpha-synuclein (aSyn), a component of Lewy body amyloid in Parkinson's disease, is expressed in melanocytes as an MITF target. Using primary human cells and a new aSyn overexpression mouse model, we demonstrate that ROS from sources such as UV exacerbates pathologic aggregation of melanin together with these inherently amyloidogenic proteins, with the skin of these mice developing striking dark macules and dermal melanophage accumulation after exposure. We also use the Real-Time Quaking-Induced Conversion Assay to show that UV increases aSyn and PMEL's prion-like self-aggregation capacity in human skin explants. In parallel we demonstrate that these proteins, upregulated with tanning, are concurrently removed via autophagy activation by MITF, suggesting pigmentation-induced aggregatory toxicity is a routine stress which melanocytes have evolved specific homeostatic mechanisms to manage. For validation, we show that biopsies of hyperpigmentation disorders are enriched in aSyn and PMEL amyloid extracellularly and within melanophages. RNAseq data also suggest that aggregation can trigger cellular senescence, offering a possible explanation for the common clinical co-occurrence of hyper- and hypopigmentation. Ultimately, our data indicate that hyperpigmentation in some ways represents a form of proteinopathy similar to Alzheimer's or Parkinson's disease, suggesting that dissolution of protein aggregates may represent a new strategy to treat chronic dyschromia of multiple etiologies.

0810

Race-specific risk profiles: Vitiligo as a protective factor against cutaneous malignancies

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This study evaluates the relative risk of melanoma and non-melanoma skin cancer(NMSC) in White versus Black individuals with vitiligo, a common depigmenting disorder marked by melanocyte destruction. Despite concerns about increased skin cancer risk due to melanin loss in vitiligo, genetic evidence indicates lower melanoma susceptibility. Epidemiological studies show varied melanoma and NMSC risks in vitiligo patients, potentially linked to autoimmunity, with pigmentation factors individually accounting for less than 1% of skin cancer variance. Using the TriNetX Research database, with electronic medical records from 105 healthcare organizations, White and Black/African American individuals diagnosed with vitiligo were separated into cohorts using specific ICD-10 codes. Comparative analyses of hazard ratios (HR) with 95% confidence intervals(CI) were performed for various cutaneous malignancy outcomes from 1-day post-diagnosis onward. Cohorts were matched for age, ethnicity, and gender using a propensity score model. Statistical significance was defined as p<0.05. White vitiligo patients exhibited significantly higher incidences of the following cutaneous malignancies compared to Black vitiligo patients: All malignant neoplasms of skin: HR [95% CI] = 9.035 [6.539, 12.482], p<0.0001 Melanoma: HR [95% CI] = 7.798 [5.769, 10.54], p<0.0001 Squamous cell carcinoma: HR[95% CI] = 5.743 [2.83, 11.653], p<0.0001 Basal cell carcinoma: HR[95% CI] = 22.509 [8.268, 61.28], p<0.0001 Actinic keratoses: HR [95% CI] = 16.788 [12.241, 23.024], p<0.0001. These findings suggest differing immune effects on melanocytes in White versus Black patients, which may underlie vitiligo's protective role against skin cancer and guide clinical recommendations for skin cancer prevention in individuals with vitiligo.

0811

Telomere lengths in patients with a high burden of melanomas

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Both short and long telomere lengths have been implicated in cancer susceptibility due to its role in genomic stability. While prior studies have found longer blood telomere lengths to be associated with increased risk for melanoma, the role of telomere length in patients with an extreme burden of melanoma remains unexplored. Understanding this relationship can provide insights into mechanisms driving melanoma development in high-burden cases. From 2017 to 2022, 94 patients with an extreme number of melanomas (mean 5.26±2.29, range 3–16) without known germline mutations were enrolled, and genomic DNA from saliva samples were subjected to whole genome sequencing. Telomere lengths were calculated using TelSeq and compared to an age-matched cohort of patients with keratinocyte cancers but no history of melanoma. Contrary to prior findings in melanoma incidence cohorts, these high-burden melanoma patients demonstrated substantially shorter weighted mean telomere lengths compared to controls (0.46 vs 1.24 kb, $p<0.0001$, Wilcoxon Rank Sum Test). This reduction was most pronounced in the shortest telomere fraction (0.32 vs 0.94 kb, $p<0.0001$), though longer telomeres were also decreased relative to controls (0.65 vs 1.62 kb, $p<0.0001$). When separating our high-burden melanoma cohort into groups of patients with 3-4 melanomas versus 5 or more melanomas, we found a non-significant slight trend towards shorter telomeres in patients with 5 or more melanomas compared to those with 3-4 (0.45 vs 0.48 kb, $p=0.303$). These findings challenge the established paradigm of long telomeres in melanoma risk and suggest that telomere shortening, which can lead to genomic instability and compromised DNA damage response, may be a distinct mechanism driving melanoma development in patients with extreme melanoma burden. This suggests that there is a context dependent role for telomeres in melanoma risk.

0812

Characteristics of melanoma among patients with connective tissue disease: A retrospective study

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Pro-inflammatory conditions such as connective tissue disease (CTD) have been associated with an increased risk of malignancy, including melanoma. However, the impact of immunosuppression on cancer risk and tumor presentation remains unclear in this population. To further investigate melanoma characteristics among patients with a history of CTD, this single institution, retrospective study examined all patients with pre-existing CTD who were subsequently diagnosed with melanoma from 2013 to 2023. Our cohort included 151 patients, with 114 (75.5%) in the rheumatoid arthritis (RA) group and 37 (24.5%) in the non-RA group. Non-RA diagnoses included lupus, scleroderma, dermatomyositis, polymyositis, Sjogren syndrome, and mixed CTD. Of 151 patients, the majority were female (60.9%), White (96.7%), non-Hispanic (94.7%), and never-smokers (53.6%). The average time from CTD to melanoma diagnosis was 6 years. Just over half of the melanomas (52.7%) were invasive, mostly located on the head/neck (35.9%) and trunk (25.7%). Although mean Breslow depth was similar in RA and non-RA patients (1.7 ± 2.0 vs. 1.8 ± 2.7 mm), those with RA had more advanced tumor features such as >1 mitoses/hpf (58.3% vs. 38.9%), lymphovascular invasion (5.9% vs. 0.0%), and nodal metastasis (9.7% vs. 0.0%). The most commonly used immunosuppressive medications were high-dose prednisone (45.7%) and methotrexate (39.7%). These findings provide important insights into the clinicopathologic characteristics of melanoma in patients with CTD. Further research is needed to understand why RA patients may face more aggressive disease, including the roles of chronic inflammation and immunosuppressive medications. Future directions include identifying a matched cohort of immunocompetent patients to compare melanoma characteristics across groups.

0813

High fractions of TCF7$^+$ T-cells in tertiary lymphoid structures are associated with improved survival in patients with metastatic melanoma

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Tertiary lymphoid structures (TLS) are ectopic immune cell aggregates that develop in non-lymphoid sites during chronic inflammation. TLS have been shown to be associated with enhanced survival outcomes in metastatic melanoma, yet the underlying mechanism of TLS remains poorly understood. Transcription factor 7 (TCF7) is a marker of stem cell-like T-cells with the ability to proliferate and self-renew and is also associated with improved survival in melanoma. Increased TCF7 expression is theorized to improve immune checkpoint blockade by inducing a robust T-cell response. Thus, this study aimed to investigate varying levels of intra-TLS TCF7$^+$ T-cells and their prognostic potential in metastatic melanoma. Cutaneous metastatic melanomas were evaluated for TLS presence and TCF7 expression by multiplex immunofluorescent histology. CD3$^+$CD8$^-$ (CD4$^+$) and CD3$^+$CD8$^+$ (CD8$^+$) T-cells were enumerated from 15 TLS specimens with Halo software (Indica Labs) and densities of T-cells expressing TCF7 was calculated. The densities of TCF7+ T-cells were then dichotomized into high (TCF7^{high}) and low (TCF7^{low}) groups using the Contal-O' Quigley method. Associations with survival were assessed using log-rank tests. We found that in patients with metastatic melanoma, patients with CD4$^+$TCF7^{high} (Median OS 50.9 vs 11.9 months, $p = 0.005$) and CD8$^+$TCF7^{high} (Median OS 120.5 vs 20.6 months, $p = 0.02$) had significantly prolonged survival compared to patients with CD4$^+$TCF7^{low} and CD8$^+$TCF7^{low}, respectively. These findings suggest TCF7$^+$ T-cells are an important element of TLS that contributes to its survival benefits in metastatic melanoma. TCF7$^+$ T-cells show promise as a valuable prognostic marker and a novel therapeutic target for immunotherapies in the treatment of melanoma and potentially other cancers.

0814

Opsin 3 involved in the regulation of melanoma mitochondria energy metabolism by red light

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Background: Melanoma is one of the most malignant skin carcinoma, and the metabolic reprogramming of melanoma cells is a deep-seated factor that sustains their proliferation and invasion. Red light can interfere with the metabolism of melanoma cells through photobiomodulation, although the specific mechanisms remain unclear. This study aims to determine the regulatory role of opsin in the metabolic processes of melanoma under red light conditions. Objective: To explore the specific molecular mechanisms by which OPN3 participates in melanoma cell metabolism under red light conditions, thereby providing potential targets and strategies for the diagnosis and treatment of melanoma. Method: The expression of CoxIV in melanoma cells was examined by transfecting overexpression plasmids OPN1-5 to screen for the OPN molecule most strongly correlated with CoxIV. Immunofluorescence and immunoelectron microscopy were used to verify whether OPN molecules are localized in mitochondria and to examine changes in ATP levels. The impact of OPN3 on melanoma metabolic capacity was measured using a Seahorse metabolic analyzer, followed by extracellular acidification rate (ECAR) and maximum oxygen consumption rate (OCR) assays after collecting transfected melanoma cells to confirm the metabolic regulation of melanoma by OPN. Results: The results indicate that compared to overexpression of OPN1, OPN2, OPN4, and OPN5, overexpression of OPN3 significantly increased the expression of CoxIV protein. Moreover, melanoma cells overexpressing OPN3 produced significantly more ATP upon red light stimulation, along with increased expression in mitochondria. These findings suggest that OPN3 may be involved in the regulation of red light on melanoma cell metabolism. Additionally, further experiments using a Seahorse system demonstrated that red light increased OCR through Opsin3, while EACR did not show significant changes. It is speculated that OPN3 influences the oxidative phosphorylation process in melanoma through red light. Conclusion: OPN3 participates in the metabolic regulation of melanoma cells through red light.

0815

Spatial clustering and phenol exposure in vitiligo: A cross-sectional analysis of the United States

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Background:Chemical exposure may serve as an environmental risk factor for vitiligo. Most known vitiligo-inducing chemicals are phenols, acting as tyrosine analogs that disrupt melanin production and trigger melanocyte destruction. However, studies examining spatial relationship between phenol exposure and vitiligo are lacking. Methods:We conducted a nationwide cross-sectional study of adults in the 2017-2022 All of Us database. Geographic data was extracted from subjects' 3-digit residential zip code prefixes. Phenol release data from the Environmental Protection Agency was assigned to zip code areas within a 5km radius of phenol-releasing facilities. Exposure levels were classified as none, low(<median), and high(≥median). Poisson-based spatial scan statistics in SaTScan with a 10% maximum cluster size identified geographic clusters of vitiligo cases. Logistic regression examined: 1)the vitiligo clustering effect after controlling for demographics, socioeconomic status, and comorbidities and 2) the association between phenol exposure and vitiligo clusters. Alopecia areata (AA), which shares similar pathogenesis with no known link to phenol, served as a negative control. Results: Of 287012 subjects, we identified 1103 vitiligo cases (prevalence=0.4%). SaTScan identified 4 significant clusters: 1)MA/RI regions (relative risk[RR]=2.13); 2)NJ/NY/PA regions (RR=1.93); 3)OH/KY/WV regions (RR=1.59); 4)IA/MN/WI regions (RR=1.69). The overall clustering effect remains robust after adjusting for individual-level data (odds ratio[OR]=1.77[1.54-2.03]). Cluster residents had higher phenol exposure (65.2% vs 47.4% with any exposure, P<.001) and lower social deprivation index (29.3±5.8 vs 33.9±6.1, P<.001) than non-cluster residents. Vitiligo clusters showed a positive association with phenol exposure (low:OR=2.11[2.07-2.15]; high:OR=2.25[2.21-2.31]) after adjusting for deprivation. Phenol exposure was not associated with AA clusters. Conclusion: Our study characterized vitiligo clustering in the US and demonstrated its association with phenol exposure.

0816

Regulatory T cells inhibit CD8$^+$ T_{RM}-like cells during the early stages of tumor immune escape

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Tissue-resident memory T (TRM) cells have emerged as key players and potential immunotherapeutic targets in antitumor immunity. However, a lack of adequate tumor models has hampered the study of T_{RM} cells within the TME. Cell lines injected subcutaneously lack the same biological cues as tumors arising from the dermis and epidermis, while most other models lack a known tumor-specific antigen to track immune responses. To address this, we modified the Braf/PTEN melanoma model to express OVA as a tumor antigen (abbreviated as BPO). In this novel model, we confirmed a robust endogenous tumor-antigen specific immune response against OVA as measured by IFN-γ ELISPOT, pentamer staining, and OT-I T cell transfer. BPO tumors contained a distinct population of CD8$^+$ T cells expressing CD103, which were not found in cell line-derived subcutaneous tumors. The CD103$^+$ T_{RM}-like subset was unique, showing low PD-1/Tim-3 levels but distinct CD101 expression, unlike CD103$^-$ CD8$^+$ TILs. Longitudinal studies revealed that CD103$^+$ T_{RM}-like cells composed a majority of CD8$^+$ TILs in nascent tumors and co-localized with CD103$^+$ regulatory (Treg) cells. With this data, we hypothesized that Treg-mediated suppression of CD8$^+$ T_{RM}-like cells is important for immune escape at the earliest stages of tumor development. Systemic depletion of Treg cells led to decreased tumor growth, augmentation of the OVA-specific antitumor immune response, a significant increase in CD8$^+$ and CD4$^+$ Foxp3$^-$ TILs, and activation of T_{RM}-like TILs. Blocking T cell trafficking with FTY720 after Treg depletion showed increased TILs were due to infiltration, not local expansion. Finally, Treg depletion specifically at the tumor site (thereby avoiding systemic autoimmunity) induced T cell infiltration, and CD8 T cell deletion prior to Treg depletion blunted CD4 T cell infiltration. Together, these data suggest early tumor immune escape is mediated by Tregs suppressing T_{RM} immunosurveillance and T cell recruitment.

0817

Acetaldehyde metabolism by ALDH2 induces melanocyte activation, transformation, and melanoma initiation

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Despite public health campaigns advocating sun protection, melanoma incidence continues to rise in the U.S., prompting reconsideration of other risk factors. Acetaldehyde (AcAH), a genotoxic metabolite of ethanol (EtOH), is classified as a human carcinogen. We previously demonstrated that aldehyde dehydrogenase 2 (ALDH2), a key enzyme in AcAH metabolism, influences melanoma incidence and prognosis. However, the precise links between ALDH2, EtOH/AcAH exposure, and melanoma development remain unclear. In this study, we used human melanocytes and genetically engineered mice to determine the effects of EtOH and its metabolite, AcAH. We found that melanocytes were significantly less effective at eliminating AcAH than keratinocytes and hepatocytes due to lower ALDH2 activity despite their transiently induced ALDH2 activity upon EtOH exposure. When melanocytes were exposed to EtOH with an ALDH2 inhibitor, they showed enhanced PKA signaling and adenylyl cyclase activity, produced more melanin, extended dendrites, and proliferated. Metabolomic analysis revealed alterations in glycolysis and TCA cycle and elevated oncometabolite levels, along with activation of a one-carbon cycle, in human melanocytes treated with EtOH and ALDH2 inhibitor, suggesting increased DNA methylation and mutagenesis. DNA analysis showed CPD formation and mutations in BRAF, NRAS, CDKN2A, and TP53 in human melanocytes treated with EtOH and the ALDH2 inhibitor. Finally, we cross-bred mouse lines to generate offspring hemizygous for Tg(Tyr-cre/ERT2)13Bos, heterozygous for $Braf^{tm1Mmcm}$, and homozygous for $Aldh2^{tm1kaw}$. When administered tamoxifen to activate the oncogenic driver and treated with EtOH, these mice developed cutaneous melanoma on the trunk and tails within 2 months, whereas water-ingested mice or other genotypes did not develop melanoma. Our findings underscore the critical role of AcAH (i.e., EtOH in the context of ALDH2 inhibition) in melanocyte activation, transformation, and melanoma initiation.

0818

Evaluating the color spectrum of pigmentary disorders

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It is important to establish objective, noninvasive measures of hyperpigmentation. Colorimeters allow for quantitative measurement of skin color and offer insight into the range of color constituting pigmentary disorders, which can be influential in diagnosis and management of these challenging conditions. This prospective pilot study quantifies parameters of color in pigmentary disorders. Patients with a pigmentary disorder were recruited prospectively during appointments at the University of Southern California Keck Medical Center Outpatient Dermatology Clinic. Colorimeter measurements, including erythema index, melanin index, CIE L*a*b*, individual typology angle (ITA), and gloss of affected and unaffected skin and standardized photographs were collected. Among the 25 enrolled patients to date, the majority were female (88%) and Black (72%) with a mean age of 54.32 (SD 18.63). Nine patients were excluded from analysis due to incomplete data. Diagnoses included post-inflammatory hyperpigmentation (PIH) (n=6), melasma (n=5), lichen planus pigmentosus (LPP) (n=4), and maturational dyschromia (n=1). The mean Δerythema index was greatest for maturational dyschromia (-9.04), then PIH (4.1), melasma (3.94), and LPP (-2.38). Mean Δmelanin index was greatest for maturational dyschromia (23.4), then LPP (17.05), PIH (13.64), and melasma (12.62). Mean Δa* (red-green) was greatest for maturational dyschromia (-6.17), then LPP (-2.35), PIH (0.31), and melasma (-0.02). Mean Δb* (blue-yellow) was greatest for maturational dyschromia (-8.23), then LPP (-7.3), PIH (-4.71), and melasma (-3.62). Erythema was greater in PIH and melasma than in maturational dyschromia and LPP with a tendency towards red in a* while melanin was greater in maturational dyschromia and LPP. Preliminary results of this ongoing study demonstrate the varied spectrum of colors composing hyperpigmentation.

0819

Quantifying skin pigment: Comparison of five low-cost devices to the konica minolta CM-700d

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Background: Validated skin-specific colorimeters are typically expensive, and limited data exists about the performance of low-cost colorimeters in quantifying skin color. Our study evaluates multiple low-cost colorimeters in comparison to the Konica Minolta (KM) CM-700d to determine which may be suitable for ensuring diversity of skin pigment in medical device research. Methods: We used four colorimeters, ColorReaderPRO, AMTAST AMT510, WR10QC, Vinckolor ColorMeter Pro ($100-250), and one spectrocolorimeter, X-Rite RM200QC ($2,000) with the KM as reference. Triplicate individual typology angle (ITA) measurements were taken at the forehead (FH) and upper inner arm (UIA) in 38 adult participants and on color swatches from the Pantone SkinTone (PST) Guide. We compared repeatability, inter-operator variability, and ITA measurements by calculating the color difference using deltaE=√(delta(L^2)+delta(a^2)+delta(b^2)). Results: The study population ITA ranged from 47 to -70 (median 17) at FH, and 60 to -62 (median 28) at UIA. The difference in median deltaE across all devices was <0.12 with three operators. With the PST, the difference in median deltaE across devices was <0.1. The RM200QC had the highest median deltaE at both skin sites. At the FH and UIA, all devices had a median deltaE of less than 0.3, except for the RM200QC (0.8 FH, 0.5 UIA). For the PST, the Mann-Whitney U test showed that the ITA values from all devices were not statistically significantly different from the KM. The same was seen with the skin data, except for the WR-10QC. Conclusion: When analyzing inter-operator variability and repeatability, the difference between median deltaEs is likely not clinically significant. Four of five colorimeters tested produced ITA values comparable to the KM, suggesting that they could possibly be used as lower-cost alternatives.

0820

BUB1B germline mutation and predisposition to melanoma and multiple epithelial malignancies

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Although numerous melanoma predisposition syndromes have been identified, many remain genetically unexplained. Whole exome sequencing revealed a novel germline mutation, BUB1B c.2316C>G (p.Tyr772Ter), in a patient with multiple primary malignancies, including melanoma, breast, thyroid, and lung cancers, and an extensive family history of cancer. This truncating mutation likely leads to haploinsufficiency of the spindle assembly checkpoint protein, BUBR1, encoded by BUB1B, supported by reduced protein levels by immunofluorescence in tumor and non-malignant tissues compared with controls ($p < 0.0001$) and evidence of genomic instability, including increased premature chromatid separation in primary patient leukocytes (6.4% vs. normal ≤2%). Somatic mutation analysis of melanoma samples revealed concurrent mutations in established melanoma drivers, such as NRAS and CDKN2A, underscoring the multifactorial nature of tumorigenesis. RNA sequencing highlighted downregulation of genes implicated in the PI3K-Akt pathway and integrin binding, pathways critical to oncogenesis. This study establishes BUB1B as a putative novel melanoma predisposition gene and contributes to understanding the role of mitotic checkpoint defects in hereditary cancer syndromes. Further investigation into BUB1B mutations in cancer predisposition and tumorigenesis may also reveal therapeutic and prognostic insights, enhancing clinical management for at-risk individuals.

0821

Sensory and autonomic innervation of the tumor-draining lymph nodes limit protective anti-tumor immune response.

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Sensory and autonomic nervous systems are critical regulators of cancer progression, acting by direct nerve-cancer interaction as well as via indirect modulation of protective immune responses. The neuro-immune control of cancer progression has been largely investigated by employing either global, whole body, or locoregional surgical, chemical or genetic denervation or gene deletion methods. These approaches are unable to fully capture organ-specific influences of nerves on immunosurveillance. This is particularly true for secondary lymphoid organs, which are critical sites for antigen-driven selection and amplification of protective anti-tumor immunity. Tumor-draining lymph nodes (TDLNs) carry broad clinical significance, acting as the front line for immune response activation and a conduit for malignant cell spread. TDLNs are frequently surgically accessed for cancer staging, determination of prognosis and guidance of therapy. We discovered that selective inhibition of either afferent (sensory) or sympathetic innervation of melanoma TDLNs significantly slowed tumor growth in mouse models. Ablating TDLN innervation also improved protective immune responses to melanoma, characterized by diminished tumor-associated TDLN remodeling, improved cell trafficking and antigen-specific cellular immunity. Our results illustrate that targeting TDLN innervation may provide therapeutic benefit, especially if employed as an immunotherapy adjuvant.

0822

Endothelial progenitors: Unlocking tumor vessel normalization to overcome therapeutic challenges in melanoma

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The formation of new blood vessels is fundamental to melanoma progression, supplying vital nutrients for tumor growth and enabling tumor cell dissemination. However, this process is often disorganized, resulting in immature and leaky vessels that contribute to a pro-tumorigenic and immunosuppressive tumor microenvironment, further compromising therapy response. Our research focuses on endovascular progenitors (EVPs), which are mobilized and infiltrate primary melanoma tumors from very early stages to form new tumor vasculature. These cells express the key transcription factor SOX9, distinguishing them from other endothelial populations. This study investigated how Sox9 deletion in the endothelium affects tumor vascularization, the microenvironment, and metastasis. Sox9 expression was upregulated in tumor endothelial cells of mice with melanomas and human endothelial cells exposed to a melanoma-conditioned medium. Endothelial-specific conditional knockout of Sox9 resulted in significantly reduced tumor growth and metastases. Notably, despite a decrease in CD31+ vessels, there was a significant increase in pericyte coverage, indicating increased maturity of the remaining vessels. These endothelial changes translated into reduced hypoxia, evidenced by decreased GLUT1 and HIF1α expression. RNA sequencing and spatial transcriptomics analysis confirmed reduced hypoxia and demonstrated restored immune cell infiltration, validated by immunostaining. In conclusion, our investigation into Sox9 deletion in the endothelium has yielded promising results. By addressing both the structural and functional aspects of blood vessels to normalize the tumor microenvironment and restore immune cell infiltration, this approach holds significant potential for enhancing immunotherapy outcomes in melanoma.

0823

Application of cutaneous melanoma multiple instance learning model for conjunctival melanoma whole slide images

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While advancements in artificial intelligence have rapidly progressed, there are still many challenges to applying computer vision models to whole slide images (WSIs) in pathology due to their scattered artifacts and large size. Multiple instance learning (MIL) is a type of weakly supervised deep learning that addresses these challenges by dividing WSIs into smaller regions for analysis, while only utilizing slide-level labels. We established proof of concept that MIL models trained on cutaneous melanoma WSIs can be applied to conjunctival melanoma samples, which is particularly important given the smaller number of conjunctival samples. In prior research, we developed several weakly supervised deep learning MIL models (512x512 pixel tiles, extracted 1024-dimensional feature vectors) trained on cutaneous melanocytic lesions and achieved high performance in classifying cutaneous melanoma versus benign lesions. The highest performing model achieved an AUC of 0.96 ± 0.08 using 10-fold cross-validation, using only 82 samples for training, illustrating the applicability of MIL for small, high-resolution datasets. We established proof of concept in the effective application of the cutaneous melanoma models to conjunctival melanocytic lesions. The conjunctival dataset consisted of 53 WSIs across five diagnostic classes: nevus (27), low-grade conjunctival melanocytic intraepithelial lesions (CMIL) (7), high-grade CMIL (4), melanoma in situ (MIS) (6), and invasive melanoma (9). A cutaneous melanoma model performed well in distinguishing conjunctival melanoma versus nevi with an AUC of 0.90 with a sensitivity of 0.944 and a specificity of 0.644. These results demonstrate the generalizability of cutaneous melanoma weakly supervised deep learning models for conjunctival lesions, highlighting their potential to be adapted for diagnosing other lesion types.

0824

Mohs micrographic surgery for intermediate-thickness head and neck melanomas

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Consensus guidelines recommend selective use of Mohs micrographic surgery (MMS) for anatomically constrained T1a melanomas, but MMS is increasingly used for later-stage melanomas. Outcomes data is necessary to validate the growing use MMS for deeper melanomas. This study reports local recurrence-free survival and sentinel lymph node biopsy (SLNB) compliance and performance in a large cohort of consecutive intermediate-thickness head and neck melanomas (HNM) with Breslow thickness (BT) 1.01-4.0 mm treated with MMS at a single institution from 2006-2023. Retrospective review of electronic medical records was performed for patient, tumor, and surgical characteristics, and local recurrence status. Local recurrence (LR) was defined as radial growth phase melanoma arising in the MMS scar. 5-year Kaplan Meier (KM) local recurrence-free survival estimates were calculated. 185 intermediate-thickness HNM were identified with a mean BT of 1.95 mm (median 1.7) and a 25.4% (47/185) ulceration rate. Mean follow-up time was 42.13 months (median 30.9). Two patients (2/135, 1.5%) developed LR at 36.4 months and 76.0 months, and the 5-year KM local RFS was 98.8% (95% CI: 0.920-0.998). SLNB discussion was documented in 98.9% (182/185) and was performed in 77.3% (143/185) of patients. MMS treats intermediate-thickness HNM with a low local recurrence risk and can be coordinated with SLNB at higher compliance rates compared to historical conventional excision cohorts. These data question the rationale of current melanoma consensus guidelines to restrict MMS to in situ and T1a melanomas.

0825

Investigating ruxolitinib's anti-inflammatory and pigmentation-promoting properties in vitiligo skin *ex vivo*

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Vitiligo is a multifactorial autoimmune skin disorder characterized by skin depigmentation due to melanocyte loss. The limitation of available treatment options demands models to explore vitiligo patho-mechanisms and test therapies. This study aimed at assessing the suitability of an optimized vitiligo skin organ culture model for preclinical drug evaluation, while mechanistically evaluating the impact of Ruxolitinib (Ruxo), an FDA-approved JAK1/JAK2 inhibitor. Biopsies from (peri-)lesional (marginal biopsy) and non-lesional skin of vitiligo patients were either freshly embedded for immunofluorescence staining or cultured *ex vivo* with or without Ruxo for 24h (RNA-Seq) or 96h (immunostaining). (Peri-)lesional samples showed reduced melanin content, immature ($SOX10^+$) and mature ($GP100^+$) melanocyte numbers, and increased pathogenic ($CD3^+NKG2D^+$) and memory T cell numbers ($CD3^+CD69^+CD103^-$, $CD3^+CD69^+CD103^+$) compared to non-lesional skin. These findings indicate that the selected (peri-)lesional biopsy sites are ideal to evaluate the characteristic diseased phenotype. Ruxo-treated samples exhibited elevated melanin content, increased percentages and reduced apoptosis of mature/immature melanocytes ($MITF^+$/caspase 3^+), and significantly or tendentially fewer $CD3^+CD69^+$ or $CD3^+CD69^+CD103^+$ memory T-cells, respectively, in the epidermis, compared to vehicle controls. Furthermore, Ruxo decreased pro-inflammatory gene expression of, for instance type I interferon signalling and pro-inflammatory chemo- and cytokines. Ruxo also upregulated genes associated with melanocyte biology, indicating promotion of skin re-pigmentation. This *ex vivo* model highlights the effectiveness of Ruxo in restoring pigmentation and reducing inflammation, which is in concordance with clinical observations, and also reveals preventive changes of Ruxo in non-lesional skin. Therefore, it provides a valuable platform for studying vitiligo pathobiology and to advance therapeutic development.

0826

Impact of theobroma cacao seed extract on photodamage induced by UVs and blue light

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Solar exposition is a major cause of skin aging. Solar spectrum contains the well-known ultra-violet (UV: 100-400 nm), visible light (VIS: 400-770 nm) and infrared (IR: 760-1,000,000 nm) components. Blue light (400-495 nm) represents the highest part of VIS energy and is increasingly described for adverse effects such as free radical production, DNA damage and melatonin alteration. In a previous study we have highlighted the negative effect of blue light on the level of reactive oxygen species (ROS) and opsin photoreceptors. The increase of ROS level, and the decrease of skin opsin induced by blue light on human keratinocytes were counteracted by the application of a Theobroma cacao seed extract (TCE). This TCE was obtained from Nagoya compliant and ethical verified source with white biotechnology to enriched it in natural peptides. Proteomic and artificial intelligence studies allowed to highlight choline acetyl transferase analog peptide in the extract. As this enzyme is implicated in pigmentation, new study was performed with different irradiation stresses (UVA, UVB and blue light) on skin biopsies and on reconstructed epidermis with different melanin levels. These irradiations caused skin damage and hyperpigmentation that were compensated by the 1% TCE application. Bue light and UV exposure impacts were evaluated on opsin 3 and tyrosinase expression in melanocytes and on microsphere ingestion by keratinocytes. The use of TCE counteracted the induced decrease in opsin 3 and increased tyrosinase in melanocytes. It also counteracted the increased absorption of microspheres induced by UV and blue light on keratinocytes. Moreover, the application of 1% TCE increased expression of LC3 autophagy marker in skin biopsies. Thus, the sustainable, ethical, natural extract of Theobroma cacao rich in peptides protects the skin from sun damage by maintaining natural melanin balance control mechanisms.

0827

Defining the development and function of heterogeneous melanoma cell states in time and space

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Tumor heterogeneity plays an important role in metastatic dissemination and therapy resistance. Still, the mechanisms controlling the development of phenotypically and functionally distinctive cancer cell states remain poorly understood. Here, we used a genetically engineered melanoma mouse model to define the emergence of distinctive melanoma cell states and their interactions with surrounding stromal cell types in real-time and transcriptional pseudo-time. Using single-cell and spatial transcriptomics combined with highly multiplexed imaging approaches, we uncover cell state-defining transcriptional networks and cell-cell communication networks in murine models and validate them in tissues of human melanoma patients. We define the occupancy of cell state-defining transcription factors on chromatin in patient-derived melanoma cultures and determine their functions in gene knock-out studies. We also perturb cell state-specific cell-cell communication networks with genetic and pharmacological approaches in mouse and patient-derived models. Collectively, our data provide novel mechanistic insight into the development of specific melanoma cell states and their roles in disease progression.

0828

Preliminary study on the expression and localization of human sebaceous gland melanocytes

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Objective: To investigate the expression and localization of melanocytes in human SGs. Methods: Between December 2023 and December 2024, a total of 123 discarded skin tissue samples were procured from the Cosmetic Surgery Department at the Affiliated Hospital of Guizhou Medical University. Of these, 90 samples containing SGs were selected for further analysis, comprising 60 samples from UV exposed areas and 30 samples from non-UV exposed areas. Immunohistochemical staining for MART-1, TRP-1, TYR, and EMA, alongside immunofluorescence staining for MART-1, TRP-1, TRP-2, TYR, and EMA, were employed to ascertain the localization and functional characteristics of melanocytes in the aforementioned skin samples. Ultrastructural analysis of tissues, cells, and microorganisms located above the skin tissues was conducted utilizing transmission electron microscopy. Results: Multiplex immunofluorescence staining for MART-1 and EMA revealed that melanocytes are localized to the peripheral region of sebaceous glands (SGs). Ultrastructural analysis of skin tissues from UV-exposed areas demonstrated that melanocytes containing stage III and stage IV melanosomes are present in the peripheral region of SGs. In an investigation involving 60 skin tissue samples from UV-exposed areas, the expression rates of SG melanocyte markers MART-1, TRP-1, and TYR were found to be 68.3%, 56.7%, and 15.7%, respectively. Conversely, in 30 skin tissue samples from non-UV-exposed areas, the expression rates of these markers were 50.0%, 43.3%, and 10.0%, respectively. Conclusions: Melanocytes are present in the peripheral region of SGs, and their presence in human SGs may contribute significantly to the skin's defense mechanisms against UV radiation.

0829

SASH1's functions in pigmentation and melanocyte stem cell maintenance in humans and mice

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SASH1 is a novel pigmentation gene in humans, with mutations linked to inherited pigmentation disorders. Understanding the function of SASH1 could provide new insights into pigmentation and melanocyte biology, paving the way for new treatments for melanocyte-related diseases. This study aims to elucidate the role of SASH1 in regulating pigmentation and melanocyte lineage using *in vitro*, human, and mouse models. In cell cultures, wild type SASH1, but not mutated SASH1 (S519N) promotes stem-like characteristics. In humans, individuals carrying SASH1-S519N display accelerated hyper- and hypo-pigmentation in the skin and early hair graying. These results indicate accelerated aging in human melanocyte stem cells, linking both gain and loss of pigmentation to their dysfunction in the same individuals. In B6 mice, knockout of SASH1 results in a persistent dilute coat color from early postnatal stages. The dilute appearance is caused by significantly increased length of unpigmented hair tips ($p<0.01$), leading the animal to appear gray. Histological assessment shows the occurrence of clumped pigment at the hair bulbs, suggesting SASH1's role in melanosome transport. Interestingly, while SASH1 knockout does not accelerate waxing-induced hair graying, acute stress increases the amount of white hair, highlighting SASH1's role in melanocyte stem cell maintenance under specific conditions. Further mechanistic studies with cell culture are ongoing. In conclusion, our studies indicate the importance of assessing hair pigmentation loss in clinical evaluations of hyperpigmentation in human patients. SASH1 is critical for pigmentation and melanocyte stem cell maintenance in both humans and mice.

0830

Nevus-epidermal interactions in halo nevus highlight the role of apoptosis in disease pathogenesis

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Vitiligo, an autoimmune depigmentation disorder driven by CXCR3+ CD8+ T cells recruited by keratinocyte-secreted CXCL9/10 chemokines, remains elusive due to the scarce active lesions and surviving melanocytes. Halo nevus shares phenotypic and pathogenic similarities with vitiligo, offers an alternative model to identify therapeutic targets applicable to both. We aimed to elucidate halo nevus pathogenesis via spatial transcriptomics profiling of nevus and epidermal cells as a vitiligo model. Analysis of 5 pediatric halo nevi and 6 melanocytic nevi controls revealed CXCL9 upregulation in both nevus and epidermal cells. Nevus cells showed increased MHC class I/II genes (HLA-A/B/C, HLA-DPA1), IFNγ-induced genes (IFITM1, IFI27) and oxidative stress genes (SOD2), with enriched pathways in IFNγ response, JAK-STAT3 signaling, and apoptosis. Keratinocytes exhibited stress, apoptosis and immune response with upregulated FOS, HSPB8, MHC class I genes (HLA-B/C) and IFNγ response genes (GBP2, TRIM11). Pathways including MYC/E2F targets, oxidative phosphorylation and MTORC1 signaling were downregulated, reflecting dysfunctional cell growth and metabolism. Cell-cell interaction analysis revealed VEGFC-KDR ligand-receptor pair downregulation, suggesting nevus cell apoptosis, while TNFSF10-TNFRSF10B upregulation suggested keratinocyte apoptosis via FADD and caspases. Keratinocyte death may impair melanocyte homeostasis, increasing apoptotic susceptibility. We propose keratinocyte apoptosis contributes to pathogenesis by releasing melanocyte antigens, facilitating dendritic cell cross-presentation and activating melanocyte-specific immune cells. These findings establish a novel link between keratinocyte apoptosis and autoimmune initiation, highlighting keratinocytes' role in disease progression.

0831

Skin-integrated melanoma organoids to study tumor microenvironment-mediated mechanisms of invasion *in vitro*.

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Resistance to targeted therapies remains a challenge in metastatic melanoma. The tumor microenvironment (TME) is a promising therapeutic target, as it influences cancer progression and drug response. The lack of human *in vitro* 3D models that reproduce the melanoma-TME crosstalk has limited the development of effective therapies. We generated skin-integrated melanoma-TME organoids (mTMEOs) that incorporate key TME components and can serve as a platform for investigating the TME-mediated mechanisms of metastasis *in vitro*. Primary human skin cells were co-aggregated with GFP+ melanoma cells (SK-MEL-28 or A375) under low-adhesion conditions, forming self-assembling melanoma-skin organoids (mSOs) that mimic the skin's structure and cellularity. For the mTMEOs, mSOs were embedded in fibroblast-laden collagen gels simulating the dermal stroma. Tumor invasion rate and migration distances were monitored via fluorescence imaging and quantified using an ImageJ-based pipeline to track GFP+ signals. mSOs recapitulated skin features, including a layered epidermis and dermal-hypodermal core, as well as melanoma-specific traits like pagetoid spread, atypical melanocytes, and spreading. mTMEOs modeled the radial-to-vertical growth phase transition, enabling tumor invasion into the dermis-like gel. Stromal fibroblasts enhanced migration distances and led to fewer but larger melanoma clusters, suggesting the TME's tumor-supportive role by increasing melanoma movement and shift toward collective cell migration, linked to more aggressive metastases. mTMEOs replicate melanoma TME features, including skin architecture, stromal fibroblasts, and collagenous ECM. They provide a tunable platform for studying TME-driven invasion mechanisms and therapy testing. By incorporating patient-derived melanoma cells, these constructs could become a personalized drug-testing tool to improve patient outcomes.

0832

Using machine learning to predict short-term mortality in Icelandic skin cancer patients: A nationwide retrospective cohort analysis

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Early detection and risk stratification remain key challenges in skin cancer mortality. Recent advances in machine learning (ML) have led to success in predicting cancer mortality, including melanoma and Merkel cell carcinoma. Our research aims to similarly develop a model to screen for 5-year mortality in Icelandic patients with skin cancer. The Icelandic Cancer Registry, a nationwide comprehensive database with no loss to follow-up given its design, was used to identify all patients with cutaneous malignancies according to ICD-O-3 codes (n=18300, 1949-2023). An XGBoost-based ML model was developed to predict 5-year mortality in our cohort. The dataset included patient demographics, tumor characteristics, and family history. Preprocessing involved imputation, normalization, and one-hot encoding. A 50:50 class-weighted approach for class imbalance, 4:1 train-test ratio, hyperparameter tuning using grid search, and 5-fold cross-validation were utilized. The ML model achieved an overall accuracy of 98.4% with a ROC-AUC of 0.984. For the majority class (low-risk cases), the precision, recall, and F1 scores were 99.9%, 98.5%, and 99.2%, respectively. Performance for the mortality class yielded a precision of 26.4%, recall of 82.6%, and F1-score of 40%. The balanced accuracy was 90.6%, and specificity reached 98.6%. Feature importance analysis identified Breslow thickness as the most significant predictor, followed by tumor subtype and staging variables. Loss curves showed the absence of overfitting for strong generalization across datasets. The ML model showed excellent discriminatory ability in predicting mortality. To maintain a high recall, lower precision was justified by the low-harm clinical action of recommending increased screening for flagged patients. With minimal cost or risk, the screening tool could utilize health record data to save lives with earlier interventions for high-risk cases and ensure fewer patients with skin cancer go undetected.

0833

Generation of GEMM-derived melanoma cell lines with a defined tumor antigen for the study of antitumor immunity

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Tumor cell lines derived from genetically engineered mouse models (GEMM) have been instrumental in cancer immunity research but often face limitations such as low immunogenicity and the lack of a traceable tumor antigen. To overcome this, we modified the Braf/PTEN melanoma model to express OVA as a tumor antigen (BPO). From enzymatically digested tumors, ~16% (55/328) produced tumor cell lines characterized by continuous growth *in vitro* and condensing of the cell body. Among the lines tested *in vivo*, 7/8 exhibited progressive growth, while one (BPO.1683) was spontaneously rejected, likely due to high (>95%) EGFPOVA expression. In contrast, other lines displayed less EGFPOVA (1-20%), variable T cell infiltration, and response to PD-1 blockade. One caveat of variable EGFPOVA expression is the selection for antigen-loss variants. To address this, we enriched one cell line (891.BPO) to 100% EGFPOVA and passaged them *in vivo*, maintaining expression through cell sorting. After two *in vivo* passages, this line grew progressively *in vivo* and responded to anti-PD-1 therapy, with increased PDL1 expression observed after *in vivo* passaging. Additionally, one line (BPO.653) induced a cachexia-like phenotype, characterized by rapid 10–20% body weight loss within 5–10 days following subcutaneous implantation. This weight loss was independent of tumor burden, as mice with similar or larger-sized control tumors did not lose weight. Food intake decreased at the onset of weight loss, while water consumption remained normal. The phenotype was also observed in Rag1KO mice, suggesting a tumor-derived factor as the cause. In summary, we generated a diverse set of BPO melanoma cell lines with distinct antitumor immune responses, including one producing a cachexia-like phenotype. By passaging *in vivo* and controlling for EGFPOVA expression, we developed a line capable of progressive growth and response to PD-1 blockade, providing a robust tool for studying cancer immunity.

0834

Reduced fiber intake and increased Escherichia abundance in depigmenting vitiligo patients.

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We invited 100 vitiligo patients and controls to fill a dietary questionnaire and donate stool and serum specimens to examine the relationship between diet, the microbiome and autoimmune disease in vitiligo. Participants from the US and Kazakhstan were separated into 3 approximately equal sized groups of individuals with active and stable disease or healthy controls, wherein activity is defined by lesional progression over the past 3 months. There were no significant differences in the healthy eating index among groups, but individual nutrients were significantly underrepresented in the diet of actively depigmenting patients compared to their stable counterparts, including fibers, fats and fatty acids, amino acids including histidine, and zinc. Microbial analysis of the stool showed no difference in alpha or beta diversity among the groups but simultaneously revealed a significant overabundance of the genera Escherichia and Odoribacter in actively depigmenting patients. Metagenome analysis of data further revealed that differences in microbial metabolism between active and stable patients were driven in part by the abundance of Escherichia species. In sera from actively depigmenting patients we found a combination of inflammatory cytokines not seen in stable patients or controls. We propose that dietary deficiencies limit the generation of SCFA and favor an increase in Escherichia in the gut, in turn promoting Odoribacter colonization. Reduced zinc can limit serotonin production, while reduced histidine uptake is not remedied by enhanced production in the gut. Combined with our ongoing studies in vitiligo-prone mice, we find that dietary factors can influence disease progression in vitiligo.

0835

Effects of antibiotic use on survival and immune-related adverse events among patients with cutaneous malignancies receiving an immune checkpoint inhibitor

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The advancement of immune checkpoint inhibitors (ICI) has drastically improved the prognosis of cutaneous malignancies. Nevertheless, despite an average objective response rate to ICIs ranging from 33% to 68%, many patients continue to exhibit a limited or no response. While several retrospective cohort studies have suggested antibiotic (Abx) use as a potential culprit for the variable outcome by disrupting the gut microbiome and subsequently impairing the ICI-mediated antitumor immunity, results have been conflicting. We leveraged a large international deidentified electronic health record database to investigate whether Abx use (e.g., Penicillins, Quinolones, Cephalosporins, and Carbapenems) up to 3 months prior to initiating a single ICI agent would alter survival outcomes among patients with Metastatic Melanoma (MM) or Merkel Cell Carcinoma (MCC). Cohorts were 1:1 propensity matched for covariables of age, sex, ethnicity, smoking status, sites of metastases, and several comorbidities. MM patients who received Abx prior to a PD-1 inhibitor (n=3362) had lower survival at 1 month (96.3% vs 97.3%, log-rank test=0.023) and 3 months (91.9% vs 92.7%, 0.228), but significantly higher survival by 5 years (61.0% vs 56.8%, 0.033). Similar trends were observed for MCC patients who received Abx prior to either a PD-1 or PD-L1 inhibitor (n=113) at 1 month (90.9% vs 93.8%, 0.415) and 3 months (77.2% vs 92.4%, 0.005), with higher, albeit not significant, survival at 5 years (62.6% vs 39.6%, 0.329). Abx use was also associated with a lower hazard ratio for common immune-related adverse events (e.g., Enteritis and Colitis) among MM patients (0.85, 95% CI 0.76-0.99), whereas MCC patients had comparable outcomes. Results of this study highlight the potential temporal impact of Abx usage prior to initiating ICI therapy among patients with certain cutaneous malignancies, potentially eliciting long-term survival benefit.

0836

Endometriosis associated with a decreased risk of melanoma: A retrospective cohort study

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This retrospective cohort analysis investigates whether endometriosis, a hormone-dependent gynecological disorder affecting one in ten women of reproductive age worldwide, influences melanoma risk. Previous studies have suggested an increased melanoma risk in this population, potentially due to shared genetic pathways, including estrogen-mediated photo-carcinogenesis. However, a 2019 meta-analysis of 32 studies found no significant association between the two conditions. Using the TriNetX US Collaborative Network, we identified patients with a nevus diagnosis from approximately 50 million patients and 70 healthcare organizations. We identified 35,194 patients with nevus and endometriosis and 35,194 with nevus without endometriosis. Propensity score matching was used to control for confounding variables, including demographics and melanoma risk factors(e.g., diabetes, chronic kidney disease, alcohol and tobacco use, systemic contraceptives, amiodarone, tranexamic acid, isotretinoin, hydrochlorothiazide, topical retinoids, and non-melanoma skin cancer). Male individuals and those previously diagnosed with the outcome of interest were excluded. Risk ratios and 95% confidence intervals were calculated. We identified 171 females with nevus and endometriosis and 213 females with nevus without endometriosis. Those with endometriosis had a significantly decreased three-year melanoma risk compared to those without endometriosis(RR: 0.81, 95% CI: 0.66–0.98). These findings challenge prior research linking endometriosis to increased melanoma risk. While endometriosis is associated with chronic inflammation that may promote tumorigenesis, it could also inhibit melanocyte proliferation. Additionally, single nucleotide polymorphisms implicated in endometriosis pathogenesis may enhance DNA repair and reduce oxidative stress, lowering melanoma risk. Frequent medical attention in endometriosis patients may also encourage sun-protective behaviors. Further research is needed to reconcile these findings with previous studies and explore molecular mechanisms linking the two conditions.

0837

Clinical patterns and management of melanoma recurrence: True scar, local satellite/in-transit, and nodal presentations

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Melanoma recurrence remains a significant clinical challenge, with approximately 13% of patients with high-risk primary melanoma experiencing recurrence within two years. This case series evaluates distinct presentations of recurrent melanoma and highlights diagnostic and therapeutic approaches guided by the National Comprehensive Cancer Network (NCCN) guidelines. Six cases of recurrent melanoma are presented, encompassing true scar, local satellite/in-transit, and nodal recurrences. True scar recurrence, observed in four cases, was characterized by pigmented lesions within or adjacent to excision scars. These lesions often mimicked benign post-surgical changes, complicating early detection. Local satellite/in-transit recurrence, exemplified by a firm dermal nodule in one case, demonstrated the potential for intralymphatic spread near the primary tumor site. Nodal recurrence, as seen in a patient with cervical lymphadenopathy, highlighted the importance of regional lymph node monitoring, particularly in immunocompromised patients. Across all cases, diagnostic strategies included biopsy, dermoscopy, and imaging, while management encompassed wide local excision, sentinel lymph node biopsy, systemic therapies, and immunotherapy. This series underscores the importance of vigilant follow-up, including routine post-surgical photographs, palpation of excision sites, and patient education on self-examination, to improve early detection of recurrences. Dermatologists play a crucial role in recognizing recurrence types and guiding appropriate treatment, optimizing outcomes in this high-risk population. Despite adherence to guidelines, the persistence of melanoma underscores the need for individualized surveillance and management strategies.

0838

Rare onset of combination immunotherapy induced vitiligo-like depigmentation in patient with metastatic melanoma: A case report

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Background: This case discusses a patient experiencing vitiligo-like depigmentation (VLD) of their eyebrows and eyelashes after the use of T-VEC and pembrolizumab therapy for melanoma. Case Report: A 60 year-old male presented with stage IIC Brag with melanoma in his upper back. A shave biopsy taken on 10/12/2020 of the affected region revealed nodular malignant melanoma with a depth of 10 mm with ulceration and mitotic activity of 7 MF/mm2. A lateral margin biopsy confirmed the presence of microsatellites and neurotropisms. Upon initial diagnosis, the patient began a C3D1 treatment plan until 12/30/21. On 1/20/21, he began combined ipilimumab and nivolumab treatment. Biweekly direct T-VEC injections were added to his treatment plan on 1/28/21 after noting significant lymphadenopathy. 8 weeks into his treatment, he began to notice significant decoloration of his hair, bilateral eyebrows, and bilateral eyelashes. Despite changes made to the regimen, the patient continued to experience progressive lymphadenopathy, showing metastatic melanoma in 8 of 11 affected lymph nodes. Additional neoadjuvant surgery revealed that the melanoma had extended through the soft tissue with resultant ulceration of the overlying skin. On 6/9/21, the pembrolizumab (Q3 weeks) was added alongside continued T-VEC injections. The patient's previously noted depigmentation persisted throughout his hair, eyebrows, and eyelashes. Discussion: Immunotherapies, such as ipilimumab and nivolumab used in our patient, have been previously implicated in VLD. VLD at the site of injection following T-VEC therapy has also previously been documented; this case, however, demonstrates a novel occurrence of VLD, away from the injected melanoma, in the patient's terminal hair after T-VEC and pembrolizumab therapy. T-VEC injections have shown benefits in immunotherapy against melanoma, but further research is necessary to understand the underlying mechanism for the observed depigmentation.

0839

Examining risk profiles of melanoma using the 2021 U.S National Health Interview Survey

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Melanoma is the deadliest form of skin cancer and accounts for over 100,000 new cases annually. While many studies have examined demographic and clinical factors associated with melanoma, none have leveraged the National Health Interview Survey for a national scale association study to support the early detection of melanoma. Responses from 29,482 adults and 8,261 children from the 2021 National Health Interview Survey Questionnaire were analyzed to assess Spearman correlations with melanoma. Correlations greater than 99% were excluded to prevent data leakage. Among sociodemographic variables, the top positive correlations included family income-to-poverty ratio ($\rho = 0.05$, $p < 0.001$), education level ($\rho = 0.04$, $p < 0.01$), highest family education level ($\rho = 0.038$, $p < 0.05$), medicaid coverage ($\rho = 0.04$, $p < 0.01$), and high-deductible health plans ($\rho = 0.05$, $p = 0.001$). Negative correlations with melanoma were observed for Hispanic origin ($\rho = -0.04$, $p < 0.005$), race ($\rho = -0.066$, $p < 0.001$), marital status ($\rho = -0.033$, $p < 0.05$), private insurance ($\rho = -0.032$, $p < 0.05$), and language use in social settings ($\rho = -0.032$, $p < 0.05$). Among clinical factors, positive correlations were identified for BMI ($\rho = 0.04$, $p < 0.005$), weight ($\rho = 0.058$, $p < 0.001$), non-melanoma skin cancer ($\rho = 0.08$, $p < 0.001$), and breast cancer ($\rho = 0.08$, $p < 0.001$). Negative correlations included stomach cancer ($\rho = -0.03$, $p < 0.05$), recent mammogram ($\rho = -0.03$, $p < 0.05$), recent COVID-19 vaccination ($\rho = -0.04$, $p = 0.01$), and taking anxiety medication ($\rho = -0.04$, $p < 0.01$). These results showcase the importance of incorporating both clinical and sociodemographic characteristics into melanoma risk assessments. Identifying these characteristics can help improve melanoma screening protocols and reduce the risk of the condition.

0840

Detecting melanoma in National Health Interview Survey respondents using machine learning

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Melanoma represents the 5th most common cancer in the United States and contributed to over 8,000 cancer deaths nationwide in 2024. Early detection may prevent melanoma metastasis and death. Machine learning (ML) has shown to be successful in the early diagnosis of skin cancer. ML is both an accessible and inexpensive clinical implementation. This study aims to develop an ML model that detects melanoma in respondents from a U.S.-based national survey. Using the 2023 National Health Interview Survey, this study developed an XGBoost-based ML model to predict melanoma. The dataset included 29,522 adult respondents. Preprocessing involved imputation, categorization, and data leakage and class imbalance mitigation. Feature selection employed Spearman correlation analysis to identify significant associations while variables with low variance were removed to prevent data leakage. Moderate predictive performance was observed with an accuracy of 81.25% and ROC-AUC of 0.7932 using our ML model. For the majority class (no melanoma), it achieved a specificity of 81.91%, showing the model's ability to correctly identify negative cases. For the minority class (melanoma), the model yielded a precision of 17.31%, a recall of 69.23%, and an F1-score of 27.69%. The model's balanced accuracy was 75.57%. Cancer-related variables, such as a history of breast cancer and skin cancer, along with demographic factors like Hispanic identity, were observed to be the strongest predictors of melanoma. The ML model showed strong potential for integration with survey responses at a national scale. Therefore, this model has promise in detecting melanoma risk and supporting early screening efforts to reduce the burden of cancer, relying solely on survey data.

0841

GLUT3 regulates Ras signaling and promotes melanoma metastasis

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Melanomas express both GLUT1 and the closely related GLUT3 facilitative glucose transporters. In macrophages, GLUT3, but not GLUT1, is essential for M2 macrophage polarization and function, through a transport-independent role in signal transduction. Here, we explored whether GLUT3 might also possess unique signaling functions in melanoma. Knockdown of GLUT1 in melanoma cells inhibited glucose uptake, energy homeostasis, and cell proliferation. GLUT3 knockdown did not affect glucose transport yet showed even more significant effects on cell proliferation. Principal component analyses of RNA sequencing revealed distinct clustering of GLUT1 and GLUT3 knockdown in melanoma cells, and KEGG pathways analyses highlighted alterations in RAS signaling after GLUT3 knockdown. GLUT3 interacted with RAS, regardless of RAS mutation status. Analysis of RAS downstream signaling pathways revealed that p21 activated kinase (PAK) and signal transducer and activator of transcription 3 (STAT3) were decreased, while extracellular signal-regulated kinase (ERK) was increased, by GLUT3 knockdown in melanoma lines. Overexpression of either constitutively active PAK or STAT3 partially rescued GLUT3 knockdown. In human melanoma cell lines, GLUT3 mRNA expression correlated with metastatic potential, and in patient samples, GLUT3, but not GLUT1, expression was higher in metastases when compared with matched primary tumors. GLUT3 overexpressing cell lines showed greater migration and epithelial-mesenchymal transition marker expression *in vitro* and strikingly higher metastatic potential *in vivo*. GLUT3 expression was increased in BRAF inhibitor–resistant melanomas, and their RAS-related signaling pathways were dependent on GLUT3 expression. We identify a novel role for GLUT3 in regulating RAS signaling in melanoma and demonstrate its critical role in promoting melanoma metastasis.

0842

Dual lineages of langerhans cells cooperate for immune barrier recovery after skin injury

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Tissue-resident immune cells in the skin provide a first line of defense against infections. Langerhans cells (LCs) in the epidermis act as sentinels by surveilling skin and presenting antigens in lymph nodes. While LCs maintain well-organized spatial distribution in healthy skin, the mechanisms governing their de novo reconstitution following tissue damage remain elusive. Through longitudinal tracking of LCs and their progenitor cells in live adult mice, we discovered that most activated LCs near wounds (eLCs) stay local and directly contribute to restoring LCs in injured tissue rather than migrating to lymphatics. Simultaneously, monocytes infiltrate the epidermis during wound repair and differentiate into additional LCs (mLCs) that remain long after healing. While the inhibition of Cxcr2 signaling impairs eLCs contribution, mLCs compensate for this deficiency. Our findings reveal fundamental mechanisms of immune barrier recovery through coordinated repopulation by distinct LC lineages in damaged skin.

0843

N^6-methyladenosine RNA modification promotes keratinocyte proliferation and cutaneous wound repair through regulation of MTOR stability

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N^6-methyladenosine (m^{6}A) plays critical roles in the regulation of various cellular functions, but its functions in the skin remain largely unknown. In this study, we show that keratinocyte proliferation is impaired in the absence of the m^{6}A methyltransferase METTL3 in keratinocytes. Specifically, re-epithelialization of full-thickness excisional wounds was delayed in inducible keratinocyte-specific Mettl3 ablation mice. In addition, the m^{6}A methyltransferase complex activator, MP3C, gained a growth advantage and contributed to re-epithelialization. Mechanistically, m^{6}A disruption in keratinocytes directly leads to the reduction of m^{6}A levels in MTOR mRNAs, thereby decreasing MTOR mRNA stability in an IGF2BP3-dependent manner, resulting in the suppression of the mTOR pathway in keratinocytes. These findings identify m^{6}A modification as an essential player in wound repair through its effect on the mTOR signaling pathway in keratinocytes, and therefore may provide a novel therapeutic strategy for treating wound healing with chemicals that increase m^{6}A abundance, such as MP3C.

0844

Dermal fibroblast-derived thrombospondin 2 orchestrates extracellular matrix organization and influences wound healing

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Thrombospondin 2 (TSP2) is a matricellular protein that modulates extracellular matrix (ECM) dynamics through its influence on collagen fibrillogenesis and tissue remodeling. While global TSP2-null mice display marked skin abnormalities, the fibroblast-specific contribution of TSP2 to skin homeostasis and regeneration remains unknown. Given that PDGFRα labels a progenitor-enriched population of dermal fibroblasts, we utilized a PDGFRαCreER driver to selectively delete TSP2 in these cells. We performed an excisional wound splinting model on TSP2eGFP mice and PDGFRαCreER;TSP2 mice to evaluate wound closure dynamics, scab dissociation, and ECM architecture. Immunofluorescence and Second Harmonic Generation (SHG) imaging were conducted on normal and wounded skin sections to characterize PDGFRα+ fibroblasts,TSP2 expression patterns, and ECM organization. In TSP2eGFP mice, we observed dual PDGFRα+TSP2+ dermal fibroblasts within normal skin. Following injury, TSP2 signal increased significantly at 7 days post injury when compared to uninjured skin. Fibroblast-specific TSP2 deletion in PDGFRαCreER;TSP2 mice revealed a distinct ECM phenotype characterized by significant disorganization of dermal fibroblast alignment in the wound bed. Despite these disruptions, PDGFRαCreER;TSP2 mice exhibited a trend toward accelerated wound closure and earlier scab detachment, recapitulating key features of the global TSP2-null phenotype but revealing distinct, fibroblast-specific ECM defects. Our results indicate that fibroblast-specific TSP2 deletion disrupts normal ECM organization and impacts wound healing dynamics. Ongoing efforts aim to clarify the mechanisms by which TSP2 modulates fibroblast behavior and ECM remodeling, potentially uncovering new avenues for treating fibrotic skin conditions.

0845

Platelet rich plasma for diabetic and leprosy related foot ulcers treatment in low-resource settings: An extended approach to investigate wound healing mechanisms

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Background:Diabetic and leprosy foot-ulcers remain major contributors to morbidity,disability and amputation, imposing a heavy economic burden on healthcare systems.Diabetic-ulcers affect 15-25% of patients globally, while Nepal continues to grapple with endemic leprosy, reporting annual prevalence of 11.8 per 100,000 in 2023,with 6% of cases presenting severe deformities and ulcers. Neuropathic-ulcers associated with leprosy are particularly resistant to conventional therapies.Platelet-Rich Plasma, abundant in growth-factors has shown promise in enhancing wound-healing. Methods:A study was conducted with chronic foot ulcers(16 diabetic,16 leprosy-related two groups). PRP therapy and conventional treatment. Wound healing was assessed using the Bates-Jensen Wound Assessment Tool, dermoscopy and vascular USG before and after treatment. Laboratory parameters included CRP,ESR,HbA1c.USG analyzed blood flow velocity, vascularization patterns and granulation-tissue formation. Results:PRP therapy significantly accelerated healing, with complete epithelialization achieved in 36.7±3 days in the PRP group versus60.6± 3.7 days in the control group($p< 0.0001$).Dermoscopy showed increased vascularization and granulation tissue in the PRP group by the second week. USG findings confirmed improved blood flow and enhanced vascularization in the periwound areas. Inflammatory markers declined more significantly in the PRP group($p< 0.01$).Healing outcomes were consistent regardless of ulcer size,duration, or associated deformities in leprosy patients. Conclusion:PRP therapy demonstrates a significant reduction in healing time and enhanced vascularization, as evidenced by USG and dermoscopy. Its simplicity, safety and cost-effectiveness make it ideal for resource-limited settings.This study underscores PRP's potential as a transformative therapeutic modality for managing chronic diabetic and leprosy-related ulcers,reducing disability and healthcare-costs while improving quality of life in vulnerable populations.

0846

Wnt signaling drives hair follicle regeneration in wounds by attenuating mechanotransduction in the epidermis

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Most wounds heal as scars, which lack hair follicles that serve as crucial reservoirs of stem cells on the skin. However, in the wound-induced hair neogenesis(WIHN) model of skin regeneration, optimal tissue rigidity of the wound allows for hair follicle regeneration. Wnt signaling is needed for WIHN, but whether Wnt serves a potential mechanoregulatory role that allows for regeneration to occur is unknown. Here, we show that Wnt regulates mechanosensitivity at cellular and tissue levels to drive WIHN in mice. Using atomic force microscopy, we found that Wnt attenuates the substrate rigidity response in epidermal keratinocytes but not dermal fibroblasts of healed wounds. Super-resolution microscopy and nanoneedle probing of live human keratinocytes revealed that Wnt-induced chromatin remodeling lowers nuclear rigidity by ~90%, while preserving nucleo-cytoskeletal mechanical coupling—a vital mechanism for relaying mechanosensitive information between the cytoplasm and the nucleus. Our mechanistic studies showed via traction force microscopy and live-cell imaging that Wnt drives massive reorganization of the actin network and recruits adherens junctions(AJs) to form a mechanical syncytium—a cohesive multicellular unit with superb capacity for force coordination. Since AJs anchor actin filaments at cell-cell junctions, the actin network in cells with amplified Wnt exhibited a "hollowed-out" appearance—sparse in the center and rich in the periphery(cell-cell junctions), where junctional actin filaments became highly organized. Overall, our findings revealed Wnt signaling's novel mechanoregulatory function that manipulates the mechanotransduction machinery to drive regeneration.

0847

The addition of collagen scaffolds to human cell therapy to modify skin identity

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Skin identity is controlled by a combination of intrinsic features of the epidermis and dermis as well as crosstalk between the two compartments. The modification of skin identity has clinical potential, such as the conversion of residual limb/stump (Non-volar) skin of an amputee to pressure-responsive palmoplantar (Volar) skin in an effort to enhance prosthesis use and minimize skin breakdown. Features of volar skin, including greater epidermal thickness and dermal papillary elastin expression, likely contribute to its resilience. In our past human clinical trial we demonstrated the efficacy of ectopic volar fibroblasts to partially enhance non-volar epidermis and dermis with volar features. While our past human trial only included cells, we sought to test if the inclusion of extracellular matrix might enhance outcomes. In particular, we hypothesized that collagen, as the principal component of the fibroblast niche, might support ectopic fibroblast engraftment and function. We therefore tested the effects of ectopic volar fibroblasts a unique collagen scaffold on non-volar skin of human volunteers. We observed an increase in volar characteristics in non-volar skin 5 months post-injection, including increased epidermal thickness, skin firmness, and dermal papillary elastin expression. Supporting reprogrammed epithelial-mesenchymal crosstalk, total/single-cell RNA sequencing and Xenium in situ analysis revealed that ectopic volar fibroblasts with collagen had the strongest impact on gene ontology categories related to cornification, limb development, and skin morphogenesis. However, the addition of the collagen scaffold to ectopic fibroblasts also had unexpected effects on human skin, broadly increasing cell density of pan-fibroblasts and immune cells, and modifying keratinocyte differentiation for example through increases in IVL gene expression. This approach highlights the unique effects of extracellular matrix on human skin function and suggests new approaches to regenerative medicine.

0848

Regional and orientation-specific variations in the facial dermis: A comparison of the forehead and nasolabial fold

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The extracellular matrix (ECM) is essential for skin structure, function, and repair. This study investigated regional and orientation-specific differences in ECM components—elastic fibers (EF), collagen fibers (CF), and glycosaminoglycans (GAGs)—in the forehead (FH) and nasolabial fold (NL) to inform strategies for enhancing wound healing and reducing scarring. Skin samples were obtained from cadavers (ages 59–87) and processed histologically. EF, CF, and GAGs were stained with Van Gieson, Trichrome, and Alcian Blue, respectively. ImageJ software quantified ECM components, and a two-way ANOVA with Tukey's post hoc test assessed differences by region and orientation. Regionally, FH exhibited significantly higher levels of collagen compared to NL across vertical orientation ($p < 0.05$). FH demonstrated significantly higher GAG levels than NL across horizontal orientation ($p < 0.0001$). Orientation-specific differences revealed that in FH, GAG levels were lower in vertical sections compared to horizontal sections ($p = 0.0001$), with no significant differences for elastic fibers or collagen. In NL, collagen levels were lower in vertical sections compared to horizontal sections ($p = 0.0041$), while no significant differences were observed for elastic fibers or GAGs. Across collagen, GAGs, and elastic fibers, significant differences were observed with age in both vertical and horizontal orientations for FH and NL. These findings highlight critical region- and orientation-specific ECM variations, offering insights for developing targeted approaches to improve tissue repair and minimize scarring by enhancing collagen deposition and other ECM components.

0849

The mechanotransducer piezo1 coordinates metabolism and inflammation to promote skin regeneration

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The skin has a remarkable ability to grow under constant stretch. To interrogate mechanisms, we established a controlled tissue expansion (TE) system in mice. Through single-cell RNA sequencing (SC-seq), flow cytometry and confirmatory spatial transcriptomics, we identified an enhanced inflammatory-metabolic network in stretched skin. Stretched epidermal cells exhibited heightened cellular crosstalk in CXCL, CCL, TNF, and TGF-β signaling with a significant increase in macrophages and monocytes in stretched skin. Additionally, peripheral blood mononuclear cells showed altered systemic immune profiles after skin expansion. In parallel, genes related to glycolysis, such as Glut1 (Glucose transporter 1) and Aldoa (fructose-bisphosphate aldolase) are significantly elevated. We hypothesize that Piezo1, a mechanically gated calcium ion channel, senses tension in stretched skin, giving rise to these biological responses. The evidence shows that animals with a loss of function in epidermal-Piezo1 showed a decrease in skin growth, tissue weight, tissue thickness, CD68+ macrophages, and glycolysis gene activity. Conversely, animals with a pharmacological Piezo1 gain of function exhibited an increase in these factors. In summary, our findings highlight the coordinating role of Piezo1 for metabolic changes and inflammatory immune cell infiltration in tension-induced skin regeneration.

0850

A novel role for endothelial cell-derived extracellular vesicles in modulating fibroblast behavior in skin wound healing

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An adequate wound healing response requires the coordination of intercellular signals between multiple cell types. Following skin injury, endothelial cells and fibroblasts provisionally replace the site of injury with newly vascularized granulation tissue. Given the spatial and temporal overlap of these two cell types in the healing response, we hypothesize that they likely communicate through the release of endothelial cell-derived extracellular vesicles (ECEVs) that influence fibroblast behavior. Thus, in this study we investigated the effects of ECEVs on fibroblast function both *in vitro* and *in vivo* through a murine skin wound healing model. Uptake of ECEVs by fibroblasts was shown to alter functions and pathways relating to cell division, ECM organization, and fibrosis. This was functionally corroborated through *in vitro* assays, in which fibroblasts demonstrated enhanced proliferation, migration, cell cycle progression, collagen contraction, and altered ECM deposition following ECEV treatment. *In vivo* administration of ECEVs to healing mouse wounds led to greater collagen density and an upregulated fibroblast quantity in the wound bed of scar tissue. Our study highlights a novel role for ECEVs in shifting fibroblasts towards a potentially pro-fibrotic phenotype in the context of wound repair and tissue fibrosis.

0851

Hepatoma derived growth factor (HDGF) is released upon injury and contributes to skin repair in an age-dependent manner

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Connective tissues, including skin and cartilage, utilise several mechanisms to respond to injury. In cartilage, one such mechanism is the release of heparin-bound growth factors (GFs) from the extracellular matrix. These GFs include fibroblast growth factor (FGF)-2 and connective tissue growth factor (CTGF) which are pro-regenerative in both skin and cartilage. Another GF is hepatoma derived growth factor (HDGF), about which little is known. We hypothesized that HDGF, like FGF2 and CTGF, plays a role in tissue injury and repair. Western blots of medium conditioned by either injured skin or cartilage, from both pig and mouse, confirmed the injury-dependent release of HDGF in wild-type (WT) tissues, but not in HDGF-knockout ($Hdgf^{-/-}$). To explore the function of HDGF in tissue repair *in vivo*, we studied its role in skin wounding. A 3-day delay in wound healing was observed in 15- and 26-week-old, but not 10-week-old, $Hdgf^{-/-}$ male mice when compared with age-matched WT animals. Granulation tissue was significantly increased in 15-week-old $Hdgf^{-/-}$ males (unpaired two-tailed t-test, p=0.004) compared to WT at 7 days post-wounding. Wounded $Hdgf^{-/-}$ males developed features of dermatitis, not observed in WT animals. To explore the mechanism of action of HDGF, RNA bulk sequencing of WT and $Hdgf^{-/-}$ cartilage was performed. Among the top 50 differentially expressed genes ordered by adjusted p-value, the most striking difference was observed in the expression of ribosomal genes, both before and after cartilage injury. Skin RNA bulk sequencing and labelled proteomic studies in skin are completed and we are awaiting results. While the role of HDGF in injury is yet to be fully realised, this work demonstrates for the first time the injury-induced nature of HDGF release in skin and cartilage and describes its age-dependent role in tissue repair.

0852

Culture environment affects sweat gland cells' phenotype and their potential to regenerate sweat glands in tissue-engineered skin substitutes

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Severe burns are challenging to treat, and current tissue-engineered skin substitutes (TESs) lack skin appendages like sweat glands, which contribute to wound healing and are essential for thermoregulation and waste excretion. Our project aims to isolate, culture, and integrate sweat gland cells (SGCs) into TESs to restore functional sweat glands. Briefly, SGCs were isolated from human skin biopsies, cultured on feeder layers (2D) or as spheroids (3D), and integrated into TESs. The expression of skin and sweat gland-specific markers, such as aquaporin 5, keratin 5, and α-smooth muscle actin, was characterized by immunofluorescence and flow cytometry. Our findings revealed that 2D culture influenced the differentiation status of SGCs, promoting cell proliferation and a marker expression profile more characteristic of epidermal keratinocytes. In contrast, cell proliferation was limited in 3D spheroid culture, and the expression of markers associated with the glandular phenotype was preserved. Furthermore, 2D-cultured SGCs incorporated into TESs aggregated but did not, however, re-establish glandular differentiation. Conversely, 3D-cultured SGCs retained glandular marker expression for up to 16 days following incorporation into TESs. In sum, our work highlights the impact of the culture mode on the differentiation fate of SGCs and establishes TESs as an environment conducive to the assembly of SGCs and the preservation of their glandular phenotype. Experiments to characterize SGC differentiation factors are currently underway, with a view to optimizing the culture and facilitating the integration of SGCs into TESs. Ultimately, these results could make it possible to produce the first bilayer skin substitute with functional sweat glands that could be used to improve the treatment of burn victims.

0853

Mesoglycan exerts prominent anti-aging effects in photoaged human facial skin

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Novel senotherapeutics are needed to counteract aging-related skin decline. Mesoglycan, a glycosaminoglycan mix that enhances perfusion, angiogenesis, and reduces inflammation, warrants exploration for its synergy with VEGF-A. This pilot study aimed to evaluate the senotherapeutic potential of mesoglycan to inhibit skin aging in old, photoaged human facial skin *ex vivo*, using an organ culture model of accelerated aging. Full-thickness facial skin from 7 women (mean age 72 ± 5 years) was organ-cultured under serum-free conditions for 6 days and treated with topical or systemic mesoglycan (100–300 mg/mL). Skin aging biomarkers were assessed via quantitative immunohistomorphometry. Mesoglycan treatment significantly improved aging biomarkers in old, photoaged female facial skin *ex vivo*. In the epidermis, it counteracted aging-associated changes by enhancing Ki-67, melanin content, gp100+, c-KIT+, and MITF+ cells. Mesoglycan reduced $p16^{INK4A}$ and p-S6 levels while increasing SIRT1, Lamin B1, filaggrin, collagen 17A1, and laminin, indicating improved senescence regulation, nuclear integrity, and epidermal barrier and dermal-epidermal junction function. It also enhanced mitochondrial function by upregulating MTCO-1, PGC1α, and VDAC/Porin, demonstrating efficacy against mitochondrial aging. Mesoglycan boosted skin antioxidant defenses by upregulating NRF-2, HO-1, glutathione reductase, and PRDX. It improved dermal markers, including collagen I and III, fibrillin-1, and CD31+ endothelial cells, and significantly increased VEGF-A expression. As expected, systemic delivery showed greater efficacy than topical application in reducing aging biomarkers, consistent with mesoglycan's limited skin penetration. Our *ex vivo* study demonstrates that both topical and systemic mesoglycan are promising senotherapeutics with significant anti-aging potential for photoaged human facial skin.

0854

Evaluating the efficacy of negative pressure wound therapy in reducing surgical site infections: A systematic review

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Surgical site infections (SSIs) remain significant postoperative complications, impeding wound healing and increasing healthcare burden. In dermatological practice, wound care is critical, especially for chronic wounds and post-surgical healing.Negative Pressure Wound Therapy (NPWT) has emerged as an innovative intervention, minimizing infections, optimizing wound bed preparation, and promoting epithelialization. This systematic review evaluates NPWT's efficacy in managing SSIs and its dermatological applications. A systematic review was conducted following PRISMA guidelines, sourcing data from PubMed, PMC,and Google Scholar using search terms related to NPWT and SSIs. Articles were assessed for quality using the Cochrane Risk of Bias Tool.18,199 articles were identified. After removing duplicates and irrelevant studies, 409 articles underwent screening. Eight high-quality randomized controlled trials(RCTs) involving 1,196 patients were included. The studies focused on adults undergoing NPWT for conditions such as diabetic foot ulcers and post-arthroplasty wounds.NPWT was compared to traditional dressings, with outcomes including infection rates,epithelialization time, hospital stay duration, blister formation, seromas, wound complications, and amputations. NPWT demonstrated significant improvements in reducing infections and accelerating wound healing($p < 0.05$). NPWT has shown remarkable efficacy in reducing SSIs and enhancing wound care outcomes,particularly in conditions frequently encountered in dermatological practice, such as chronic ulcers and complex post-surgical wounds. NPWT fosters a conducive environment for epithelialization and mitigates complications. While these findings underscore its promise, further research focusing on dermatology-specific surgical contexts and patient populations is essential to validate its widespread applicability.

0855

Topological laser delivery induces efficient regeneration via a transient cell network with super activation of hepatocyte growth factor

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Effective tissue regeneration relies on transient activation of cellular signaling networks post-injury. Here, we unveil that fractional CO2 laser treatment induces a quorum sensing-like regenerative response in mammalian skin, orchestrated by macrophage-fibroblast crosstalk. Using optimized laser parameters (3.6 mJ energy, 10% density), we observed synchronized hair regeneration across both ablated and non-ablated regions, triggered by surpassing a critical injury threshold. Transcriptomic analyses identified hepatocyte growth factor/scatter factor (HGF/SF) as a pivotal mediator. Post-laser injury, macrophages act as sensors, secreting HGF/SF to recruit additional macrophages into non-ablated regions and initiating crosstalk with fibroblasts. These interactions stimulate fibroblast to produce more HGF/SF, amplifying macrophage recruitment and further enhancing regenerative signaling (modulator, self-amplifying). Subcutaneous HGF/SF delivery activates telogen-anagen transition of HF stem cells and induce robust hair growth (actuator, when signals are over quorum sensing threshold). Inhibition of the c-Met receptor delayed hair growth. Clinical studies in patients with androgenic alopecia revealed increased hair density (from 90 hairs/cm^2 to 135 hairs/cm^2) following fractional CO2 laser treatment is accompanied by elevated HGF/SF expression from M2 macrophages and fibroblasts. These findings imply that HGF/SF work as a central coordinator, orchestrating macrophage-fibroblast interactions to enable efficient quorum sensing-driven regeneration. This study provides mechanistic insights into fractional laser-induced tissue regeneration and underscores its potential as a minimally invasive therapeutic strategy for alopecic disorders. Targeting HGF/SF-c-Met signaling pathways offers a promising avenue to enhance regenerative outcomes and optimize laser-based clinical interventions.

0856

Developmental origins of fibroblasts determine their scarring potential in wound healing

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Skin wounds at disparate body sites heal with varying degrees of scarring. The location-dependent fibroblast heterogeneity acquired during development points to cell-intrinsic properties determining fibroblasts' scarring potential. To identify fibroblast signaling pathways governing anatomically variant fibrosis, we used a mouse injury model with excisional wounds of facial, scalp, ventral, and dorsal skin. Histological assessment at post-operative day (POD) 14 showed that facial and dorsal skin healed with the least and the most scarring, respectively. Single-cell RNA-seq of POD-14 fibroblasts from these sites revealed that facial fibroblasts highly expressed the neural crest development gene Robo2 and the histone acetyltransferase EP300 inhibitor gene Eid1. Dorsal wound transplantation of fibroblasts with CRISPR-mediated Robo2 or Eid1 overexpression led to reduced scar width, lower collagen deposition, less fibrotic extracellular matrix (ECM) ultrastructure, and increased neural crest marker levels compared to control dorsal wounds. Ep300 knockout in fibroblasts or small-molecule EP300 inhibition phenocopied the reduced scarring features of the transplantation experiments in dorsal wounds, and led to lower fibroblast H3K27 acetylation around ECM genes (e.g., Col1a1, Col3a1, Fbln). Thus, ROBO2-EID1-EP300 signaling underlies the reduced fibrotic potential of facial fibroblasts, and its activation in scar-prone fibroblasts suppresses their fibrotic activity by repressing ECM gene transcription. These data provide a mechanism for anatomically variant scarring, and highlight a novel strategy that manipulates the fibroblast-intrinsic fibrogenic potential for anti-scarring therapies.

0857

Benchmarking human skin organotypic cultures toward high-fidelity excellence

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Over decades, extensive efforts have been devoted to developing *in vitro* 3D skin models, with a particular focus on skin organotypic cultures (OTCs). These models are valued for their cost-effectiveness, straightforward setup, time efficiency, and ability to closely replicate native human skin. Despite significant progress, systematic optimization remains a formidable challenge, and the fidelity of current skin OTC models has yet to be fully defined. In this study, we systematically benchmarked existing skin OTC protocols by evaluating critical parameters, including culture media composition, submerged culture duration, culture inserts, oxygen concentration, culture temperature, and calcium levels. Furthermore, we investigated keratinocytes and fibroblasts derived from diverse sources to identify optimal culture conditions that enhance model performance. To quantitatively assess variation and fidelity in skin organoids, we performed single-cell RNA sequencing (scRNA-seq) on our optimized OTCs and integrated publicly available skin organoid scRNA-seq datasets. Comparative mapping to the human skin atlas identified cell types and states generated *in vitro*, highlighting developmental stage- and anatomical site-specific characteristics. Additionally, we estimated transcriptomic similarities between primary tissues and their organoid counterparts across various skin organoid models. In conclusion, our findings establish a comprehensive framework for evaluating and improving the fidelity of skin OTC models. This work provides critical insights into human skin development and serves as a valuable resource for advancing organoid-based disease modeling and protocol optimization.

0858

Neutrophil recruitment is suppressed by glutamine metabolism in innate immune cells via epigenetic regulation

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Tissue repair requires the resolution of inflammation. However, the molecular mechanisms that attenuate inflammation *in vivo* are not fully understood. Here, we identify that glutamine metabolism suppresses neutrophil recruitment to abrogate inflammation and drive tissue repair. Integrated metabolomic and transcriptional profiling identified glutamine metabolism as a key feature of macrophages during inflammatory resolution. Dietary depletion studies and conditional deletion of glutaminase (Gls), the essential enzyme involved in glutamine metabolism, in innate immune cells in mice reveals an essential role for glutamine metabolism in suppressing inflammation and promoting tissue repair. Genes involved in neutrophil recruitment are upregulated in macrophages lacking Gls and in foot ulcers of diabetic patients. Multimodal single cell transcriptomics and epigenomics reveals that Gls is required for chromatin remodeling of neutrophil recruitment genes in innate immune cells during resolution of inflammation. These findings highlight the role of glutamine metabolism in controlling cellular communication during tissue repair and suppressing neutrophil recruitment to control inflammation.

0859

Endothelial βII spectrin modulates ischemic-diabetic skin wound healing via regulating inflammation

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Impaired lower extremity wound healing due to diabetes is a big burden to our society because up to 25% of diabetic wounds result in major amputation. TGF-β has been well studied in diabetic wound healing research. Although βII spectrin (SPTBN1) is a well-known adapter of SMAD3 in the canonical pathway of TGF-β signaling, the role of SPTBN1 in diabetic wound healing has not been investigated. Single-cell RNA sequencing analysis showed incremental increase of SPTBN1 expression in endothelial cells from non-diabetic skin to diabetic skin and diabetic ulcers, and we discovered that silencing SPTBN1 in human umbilical vein endothelial cells (HUVECs) suppressed endothelial sprouting and tube formation. Taking these together, we hypothesized that SPTBN1 plays an important role in diabetic wound healing via modulating angiogenesis. We generated Sptbn1 endothelial specific conditional knockout ($Sptbn1^{ECKO}$) mice and used a well-established mouse streptozocin-induced diabetic excisional dorsal wound model to study the function of SPTBN1 in diabetic wound healing. Interestingly, although $Sptbn1^{ECKO}$ mice did indeed exhibit delayed wound healing, it was not because of impaired angiogenesis but rather via exaggerated inflammation. Inflammation in $Sptbn1^{ECKO}$ mice persisted at time points when inflammation was resolved in the control group, evidenced by higher numbers of neutrophils, inflammatory monocytes and higher intensity of iNOS staining in the wound beds. $Sptbn1^{ECKO}$ wounds also had significantly lower numbers of fibroblasts in the wound beds in the regenerative phase. Taken together, manipulating βII spectrin in endothelial cells may help understand the healing of chronic diabetic wounds and open doors for future research.

0860

Benfotiamine prevents endotoxin-induced cytotoxicity in human dermal fibroblasts

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Wound healing is a fundamental physiological process involving a complex cascade of cellular events that repair damaged tissue. Impairments in wound healing mechanisms, often exacerbated by conditions such as diabetes, infections, and oxidative stress, highlight the need for novel therapeutic strategies. Oxidative stress, marked by an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, can significantly hinder the repair process. This study investigates the therapeutic potential of benfotiamine, a lipophilic derivative of thiamine (vitamin B1), in preventing lipopolysaccharides (LPS) induced human dermal fibroblasts (HDFs) apoptosis. Benfotiamine is known for its ability to increase thiamine levels in tissues and exert antioxidative effects, thereby potentially countering oxidative stress and its detrimental effects on wound healing. Our study utilizes LPS to induce oxidative stress in HDFs and examined how vitamin B1 derivative counters this. HDFs were treated with LPS in the absence or presence of various concentrations of benfotiamine, and cell viability was assessed. Preliminary results show that cells treated with benfotiamine prevented LPS-induced decrease by 15% (p=0.001) in cell viability. These findings suggest that benfotiamine may mitigate oxidative stress-induced cytotoxicity and apoptosis in HDFs. Future experiments will explore benfotiamine's effects on apoptotic signaling by examining caspase-3 activation, PARP cleavage, and the expression of apoptotic markers. Additional in-vivo studies are planned to determine the therapeutic potential of benfotiamine in improving wound healing.

0861

The Wnt-inhibitor Dkk4 is required for hair follicle initiation and patterning

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Hair follicles (HF) are skin appendages covering the surface of the mammalian body. They arise during embryonic development in regularly spaced patterns through a continuous crosstalk between the epithelium and underlying mesenchyme. Several secreted signaling factors are intricately involved in the determination of HF formation sites. Notably, inhibition of Wnt signaling completely prevents the formation of HF epithelial precursors called placodes (Pc), suggesting that Wnt resides at the top of the hierarchy of Pc initiation. We hypothesized that the interaction of Wnt activators and inhibitors underlies the pattern of HF formation. We focused on the Wnt inhibitor and direct target Dickkopf 4 (Dkk4), which is specifically expressed in Pcs, and generated Dkk4 knockout ($Dkk4^{-/-}$) mice using CRISPR/Cas9. $Dkk4^{-/-}$ embryos show profound disruptions in HF development and patterning, suggesting that Dkk4 plays a crucial role in these processes, likely through its negative feedback interaction with Wnt signaling. To genetically test whether DKK4 acts as an inhibitor of the Wnt pathway during HF formation, we crossed $Dkk4^{-/-}$ mice with the BAT-GAL line, a canonical WNT reporter mouse. $Dkk4^{-/-}$; BAT-GAL embryos showed abnormal Wnt activity pattern, suggesting that the loss of DKK4 disrupts the balance of Wnt inhibitors and activators. To further characterize the role of Dkk4 in HF formation and patterning, we generated and used Dkk4-Cre knockin mice and performed lineage tracing analysis to test whether entire HFs are derived from Dkk4-expressing cells. Our data showed that not all Pc cells originate from Dkk4-Cre expressing cells, and instead mature HFs show a broad and patchy distribution of Dkk4-derived cells. Overall, we propose that Dkk4 is initially expressed in the skin to mark the position of HFs and modulate Wnt activity for a refined regular pattern.

0862

A diabetic foot consortium study: Evaluation of tissue biomarkers for predicting DFU healing

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Diabetic foot ulcers (DFUs) are a major clinical problem characterized by high morbidity, disability, amputations and mortality. A key challenge to the early use of advanced therapies for DFUs is lack of predictive biomarkers to guide therapeutic decisions. Thus, we conducted the first multicenter observational study of the recently established NIDDK Diabetic Foot Consortium (DFC) to test if either of the two previously identified tissue biomarkers, c-myc and phosphorylated-glucocorticoid receptor (p-GR), could predict complete healing after week 12 follow-up in 107 participants. Originally aiming for 213 participants, the study was stopped early due to slow enrollment and lack of biomarker significance in interim analyses. Wound edge tissue was collected from the DFU edge at the initial visit, using biopsy and debridement methods. Nuclear presence of c-myc and p-GR was quantified by immunohistochemistry, our recently developed SANDD algorithm and correlated to clinical outcomes at week 12. Complete healing was observed in 42/107 (39%) of participants, and 65/107 (61%) were considered non-healers. The distributions of baseline c-myc and p-GR between healed and not-healed DFUs by week 12 were not significantly different (p>0.025). Although the two tested biomarkers lacked significant predictability, this first DFC study, involving a national consortium of DFU centers, successfully created a unique resource of wound-related biomaterials and clinical outcomes, providing a platform for future biomarker discovery and validation.

0863

The new frontier: Microgravity research on the international space station shows impairments in human wound healing

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Understanding wound healing in microgravity and space-flight conditions is imperative for the health of all space-travelers and could improve healing on Earth. Previous studies have used mouse models and 0G simulations to explore this effect. We have recently performed the first of its kind study using human 2D and 3D cutaneous wound models and lab-on-a-chip technology (SpacePharma). Samples launched on SpaceX's 27th mission were kept on the International Space Station (ISS). Primary cells were maintained in microfluidic chips with automated media and oxygen/CO2 flow. Cultured and wounded primary human keratinocytes and fibroblasts in 2D and 3-D equivalents were exposed to microgravity for 7 days at ISS, then fixed in PFA prior to return to Earth. A parallel control experiment, using the same biological material was conducted on Earth. RNA isolation was performed post-crosslinking, and the effects of spaceflight, microgravity and space radiation were analyzed using Nanostring's nCounter technology for differential gene expression. The experiment was successful. The wound healing response including the epithelial-to-mesenchymal transition, is attenuated in response to space stressors, with genes including ADPGK, GLI1, BLK, F5 and IGF5 found suppressed a MPTPS2, CASP3, PTCH1, MYLK, IRS1 induced. In addition, key fibrotic genes including HIF1A, RBX1, PTNPN11, HMGCS2 and VCAM1 were found activated in space. The data suggests microgravity disturbs wound healing signals, highlighting the impact of space travel on skin and its barrier repair. This and future studies are vial for advancing regenerative medicine and space-specific wound treatments.

0864

Preliminary outcome of enhancing hair regeneration through macrophage polarization in mice model: The therapeutic potential of cuban oregano

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Hair loss has become a significant concern, with recent studies highlighting the vital role of M2 macrophages in tissue repair and hair regeneration. In our study, we evaluates the preliminary outcome of cuban oregano extract in promoting hair regeneration by enhancing macrophage polarization. A preclinical model using 33-week-old male and 7-week-old male C57BL/6 mice and different ages mice were divided into two treatment groups which receiving topical applications of the herbal extract compared to control group. Hair density and follicle condition were observed via dermoscope, with quantitative analysis conducted using Image J software. In 33-week-old mice, the treated groups showed significant improvement in hair growth in treated groups compared to control group, with higher dosage group demonstrating the highest efficacy (Day 13 hair density: 99.15 vs. 93.20% in the lower dosage group and 92.76% in controls). In 7-week-old mice also observed similar result as above. We hypothesize that the mechanism is attributed to enhanced M1/M2 macrophage polarization, increased secretion of growth factors, and activation of dermal papillae. These findings suggest that the mechanism of increasing M2 macrophages through cuban oregano can effectively enhance hair growth, offering a novel therapeutic approach for hair loss. Further research will need to investigate the underlying molecular pathways and explore clinical applications for patients with hair loss conditions.

0865

Porcine fallopian tube stem cells exosomes and hyperbranced polymerdots with laser treatment therapy for nude mice wound healing

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Eepithelial-to-mesenchymal transition(EMT), where epithelial cells acquire mesenchymal characteristics, is crucial in wound healing. Porcine Fallopian Tube Stem Cell(PFTSC)-derived exosomes and nanomaterial polymer dots(PDs) are known to promote EMT. Meanwhile, picosecond 755 nm laser-induced optical breakdown(LIOB), initially used in cosmetic treatments, has shown promise in wound repair and photodamage recovery. Fifteen mice were assigned to five groups: (1)control, (2)exosomes, (3)exosomes + PDs, (4)laser + exosomes, and (5)laser + exosomes + PDs (combination group). Wounds were created on the mice's backs and analyzed using Image-J. Biomarkers such as ERK1/2, VEGF, EGF, CD31, collagen1/3, and pro-collagen 1/3 were assessed via ELISA, immunostaining, and Masson trichrome staining. Exosomes enhanced ERK1/2 and EGF levels, with PDs further increasing EGF expression (1.6% vs. 0.5% in controls, p<0.01). Laser treatment delayed ERK expression and slowed early proliferative phase wound healing. However, the combination group exhibited superior angiogenesis (VEGF: 18% vs. 4%, p<0.0001; CD31: 17% vs. 5%, p<0.05), improved skin barrier restoration (filaggrin: 11% vs. 6%, p<0.05), and faster wound closure (wound size: 13% vs. 33%, p<0.0001). The combination also demonstrated higher collagen quality (pro-collagen 3 and collagen 1) and dense, organized scar tissue (MT staining: 39% vs. 19%, p<0.0001). Vimentin and E-cadherin co-expression was observed during the proliferative phase in the combination group. We suggest that the combination of exosomes, PDs, and laser therapy effectively induces partial EMT, accelerates wound re-epithelialization, enhances angiogenesis, and improves scar quality. While laser therapy promotes collagen deposition and angiogenesis, it may impede early proliferative phase healing. This combination strategy offers a promising therapeutic approach for wound repair and regeneration.

0866

Role of transcriptional elongation in dermal fat development

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Dermal white adipose tissue (dWAT) is vital for skin regeneration, wound healing, and tissue repair. It supports hair follicle regeneration, fights infections, and regulates extracellular matrix through free fatty acid signaling. Dermal fibroblasts (dFbs) maintain dWAT by generating adipocyte precursors and playing a key role in adipogenesis. PDGFRA+ fibroblasts contribute to adipocyte progenitors and can differentiate into adipocytes, but the mechanisms of their transition to dWAT remain unclear. dWAT development may involve gene expression regulation via transcription elongation, a process controlled by the negative elongation factor (NELF) and RNA Polymerase II (Pol II). NELF stabilizes paused RNA Pol II, preventing premature termination. Phosphorylation of NELF, Pol II CTD Ser residues, and DSIF promotes Pol II release, enabling transcription elongation. To determine whether transcriptional elongation plays any role in dWAT development or maintenance, we generated Nelfb deficient mice by deleting Nelfb in PDGFRA+ dermal fibroblasts. Loss of Nelfb led to no dermal fat formation, perinatal lethality, and reduced adipogenic regulators. Nelfb promotes adipogenesis by binding to the transcription start site of regulators that promote adipocyte differentiation such as Pparg, Cebpa, Krox20, and Stat3 to turn on their expression (CUT&Run assay). Its loss destabilizes RNA Pol II at those regions and causes chromatin closure resulting in silencing of key adipogenic genes. Notably, retroviral expression of Pparg in Nelfb deleted cells could restore adipocyte differentiation suggesting that Nelfb regulates Pparg expression, a critical mediator of adipogenesis. In addition, treatment of Nelfb deficient mice with PPARG agonist (Rosiglitazone) restored dWAT formation and increased their lifespan. These findings highlight Nelfb's critical role in promoting the expression of Pparg, Cebpa, Krox20, and Stat3 which are necessary for adipogenesis and dWAT formation.

0867

The role of schwann cell - macrophage interactions in keloid pathogenesis

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Emerging evidence indicates that the interaction between Schwann cells and M2 macrophages plays a pivotal role in the initiation and/or progression of keloids, a fibrotic skin disorders characterized by an excessive production of extracellular matrix (ECM). To study this process, we developed a three-dimensional *in vitro* model utilizing the self-secreted ECM of dermal cells derived from keloids or healthy skin. Models generated from keloid-derived cells exhibited increased production of ECM and a greater degree of collagen fiber alignment compared to those established with cells from healthy skin. Subsequently, we integrated differentially polarized macrophages into the *in vitro* models to evaluate their effects on Schwann cells and the reciprocal influence of Schwann cells on macrophages. Schwann cells exerted minimal, if any, influence on macrophages. In contrast, macrophages significantly affected Schwann cell gene expression in a phenotype-dependent manner, as revealed by RNA sequencing. Co-culture of Schwann cells with monocytes produced only minor effects. Co-culture with M1 macrophages induced a pro-inflammatory phenotype in Schwann cells and gene expression associated with antigen presentation. Conversely, co-culture with M2 macrophages resulted in increased expression of ECM components and factors involved in TGFβ signaling. Overall, our *in vitro* model replicates changes comparable to those observed *in vivo* in keloids, providing a valuable platform for studying the pathology and testing potential therapeutic interventions. The cross-talk of Schwann cells and M2 macrophages in keloids may represent an important mechanism, leading to increased matrix deposition, which could therefore contribute to the infinite growth of keloids.

0868

CRISPR/dCas9-mediated activation of SOX18 reprograms human dermal fibroblasts into dermal papilla cells

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A major contributing factor to the failure of cell-based human hair follicle (HF) regeneration is the lack of highly specialized and inductive mesenchymal fibroblasts, located in the HF dermal papilla (DP). Thus, there is great demand to derive a sufficient amount of inductive DP cells (DPCs) from small amounts of tissue. Dermal fibroblasts (DFs) are abundant and can be isolated and expanded easily, making DFs an ideal cell source for HF engineering. Bioinformatic analysis identified five major transcription factors (TFs) central to DP phenotype and inductivity. Via CRISPR activation, each TF was enriched in DFs and their extent of reprogramming compared. Among them, SOX18-overexpressing DFs (SOX18-DFs) were the only transduced DFs that induced the expression of alkaline phosphatase (ALPL) at a level comparable to DPCs. In hydrogel and 3D spheroid culture, SOX18-DFs exhibit colony-forming behavior and maintain significantly higher ALPL expression for longer time than other TF-overexpressing DFs, comparable to passage 5 DPCs. RT-qPCR showed SOX18-DFs express DPC signature genes ALPL, FGF2, FGF7, FGF10, CTNNB1, and LEF1 significantly higher than control DFs ($p < 0.05$). We have previously shown that DPCs but not DFs interact with human epidermal keratinocytes (KCs) to form hair germ-like structures in organoid culture. Following this method, reprogrammed DFs were seeded in mixed suspension with keratinocytes for 3D co-culture. Among the TF-overexpressing DFs and controls, only organoids constructed with SOX18-DFs exhibit strong ALPL-positivity and advanced structure formation comparable to those constructed from DPCs. Application of the organoids to micropatterned engineered skin substitute showed that SOX18-DF organoids continue to develop *ex vivo*. Our findings demonstrate that genetic reprogramming of human DFs, including with SOX18, is a feasible approach to overcome the key bottleneck in HF engineering: generating human DPCs with sufficient activity and quantity.

0869

Development of an original in vivo model to investigate real-time dynamics of skin repair

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Wound healing is a highly regulated process starting with re-epithelialization and concomitant immune cells recruitment, followed by tissue remodeling. Among animal models that should shed light this process, zebrafish is suitable thanks to its thin epidermis and dermis structures combined with its transparency, enabling live imaging. This study aimed to investigate the involvement and dynamics of the extracellular matrix in the various steps of skin repair using 4 days-post-fertilization zebrafish larvae. Transgenic fluorescent zebrafish lines were used. The larvae allowing the visualization of the basal keratinocytes' plasma membrane and/or their cytoplasm, were crossed with lines in which neutrophils and macrophages are highlighted. Then, a laser-ablation technique was implemented to induce controlled wounds. Regardless of the lesion type, the re-epithelialization process exhibits 5 distinct phases. Real-time observations reveal actin-based cell movement of leader cells, cryptic lamellipodia formation in following cells, and a noticeable shift in cell-cell and cell-matrix contacts over distance. This is followed by the recruitment of neutrophils and macrophages at the injury site. Results reveal that Collagen XIV, a basement membrane-associated component, is also expressed by basal keratinocytes. Interestingly, lack of its expression in mutant fish impairs neutrophils recruitment at the injury site while increasing wound closure, revealing that extracellular matrix actively influences the immune response. Finally, immunostaining show that the dermis at the injury site contains disorganized collagen I fibrils and tenascin C extra-deposits, reminiscent to the granulation tissue formation. Hence, this original study highlights that zebrafish larvae, in conjunction with laser ablation and live imaging, provides a reliable model for investigating skin repair dynamics and drug testing while operating outside the scope of animal testing legislation.

0870

Improving the stability of retinol: Overcoming obstacles through solid lipid particle technology.

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Retinol, while powerful in anti-aging skincare, is known for its instability due to oxidation, its poor bioavailability and its potential to cause skin irritation. To tackle these challenges, we developed an innovative specific Solid Lipid Particle(SLP) technology. SLPs offer distinct advantages over other particle types by effectively protecting active ingredients while facilitating the release of the encapsulated molecules. To prove the efficacy of this specific SLP technology regarding retinol, we evaluated its stability formulated in a cream in a real-life study (product opened every day, for 4 months) versus a market benchmark(closely related particle technology). The bioavailability of encapsulated retinol was evaluated through the measurement of collagen I (immunostaining) on skin explants vs non-encapsulated retinol. Additionally, irritation potential was monitored by measuring pro-inflammatory response (IL-8 by Elisa) on fibroblasts. After 4 months of real-life use, the SLP formulation achieved an 83% retinol retention rate, significantly surpassing the 46% of the benchmark. Retinol is also bioavailable as collagen I was increased by 43% after SLP application, matching the level of non-encapsulated retinol. Furthermore, retinol irritation potential was avoided with the SLP technology. No stimulation of Il-8 secretion was observed with encapsulated retinol whereas the non-encapsulated retinol (free Retinol and empty solid lipid particles in solution) significantly induced IL-8 by 47% vs untreated control. In conclusion, the SLP encapsulation technology effectively addresses the main drawbacks of retinol by enhancing its stability, bioavailability, and minimizing skin irritation. This ultimate encapsulation solution enables the use of retinol without any formulation and packaging constraints. This advancement better addresses consumer demand for effective retinol formulations that provide visible anti-aging benefits.

0871

Skin longevity breakthroughs and targets for cellular age reversal: Sirtuins, key epigenetics regulators

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In longevity research, Sirtuins have been demonstrated to extend cellular lifespan, but even more importantly, to extend healthspan as they have been shown to address impact all hallmarks of aging. Sirtuins are a family of 7 proteins. They are also epigenetic regulators that are located in strategic organelles in cells to respond to any attacks by reducing damage and optimizing cellular repair. Inspired by the potential of these Sirtuin proteins, we have undertaken more than 15 years of research to understand their impact on skin cell lifespan and healthspan and helping skin cells fight aging. Here, we show our discoveries on the importance of Sirtuins on overall skin cell healthspan and longevity and how breakthrough technologies can support Sirtuins, resulting in skin cells acting younger, thereby moving anti-aging to cellular age reversal.

0872

Reserve transit-amplifying cells contribute to rapid tissue regeneration in nails

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Tissue homeostasis is maintained by stem cells (SCs). In many tissues, SCs produce differentiated cells through transit-amplifying cells (TACs), enabling them to recover quickly after minor injuries in which a large portion of the TACs are preserved. However, the mechanisms that foster fast tissue regeneration after more extensive damage in which a significant portion of TACs are lost remain unelucidated. We here demonstrate not only the existence of injury-reactive reserve SCs in the digit ventral skin but also that pre-existing TACs produced by these reserve SCs before injury contribute to fast tissue repair. Through fate mapping experiments, we discovered that both keratin 6 $(K6)^+$ $K15^+$ SCs and $K6^+$ $K15^-$ TACs in the ventral digits gain the ability to produce nails upon injury. In contrast to complete nail regeneration after a single injury, repeated wounding induced migration of the reserve SCs into the TAC region, resulting in irreversible nail dystrophy. Wnt signaling was activated in the TACs during nail regeneration, and Wnt inactivation upon single injury induced nail dystrophy, recapitulating the changes observed after repetitive wounding. Prospective clinical research revealed the formation of $K6^+$ dystrophic nails in humans after therapeutic nail removal, suggesting the presence of SC sources other than nail matrix. Our study highlights new roles of TACs in tissue homeostasis and regeneration.

0873

Modeling junctional epidermolysis bullosa using tissue-engineered skin substitutes

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Junctional epidermolysis bullosa (JEB) is a rare genetic skin disorder with currently no curative treatment. It causes skin fragility and separation at the dermal-epidermal junction (DEJ) following minor trauma. Tissue-engineered skin substitute(s) (TES) produced with the self-assembly approach represent a useful model to study epidermolysis bullosa and, in combination with *ex vivo* gene therapy, could lead to the development of a treatment for JEB wounds. We believe that TES can be used to model the JEB phenotype *in vitro*. The objective of this study was to cultivate JEB skin cells and characterize the adhesion strength at the DEJ of TES produced with these human cells. We isolated and cultivated keratinocytes and fibroblasts from a JEB patient with a mutation in the gene of type XVII collagen (COL17A1). We produced TES with JEB cells or with healthy cells, and we measured the DEJ adhesion strength. Finally, we evaluated type XVII collagen expression in JEB keratinocytes and in TES by immunofluorescence labeling. TES with JEB keratinocytes had a low DEJ adhesion strength, regardless of whether fibroblasts were JEB (0,84mN/mm) or healthy (0,89mN/mm). TES produced with healthy keratinocytes had a high DEJ adhesion strength, with both healthy (5,54mN/mm) or JEB (6,13mN/mm) fibroblasts. Type XVII collagen was not expressed by JEB keratinocytes in 2D, or in TES with JEB keratinocytes. In conclusion, TES reproduced well the JEB phenotype, with a low DEJ adhesion strength and detachments at the DEJ. Our results indicated that only keratinocytes are involved in the production of the type XVII collagen at the DEJ. Therefore, the targeting of keratinocytes should be sufficient for the development of a gene therapy for JEB.

0874

TGF-β signaling-mediated wound healing is required for hair follicle neogenesis

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Mammalian adult skin wounds typically end in fibrosis and fail to regenerate skin appendages, such as hair follicles (HFs). Our previous studies demonstrated that new HFs regenerate in the center of large full-thickness wounds of mice following wound healing. However, it remains unclear how the initial wound healing mechanisms are linked to the later HF neogenesis (HFN). Transforming growth factor-β (TGF-β) is a pivotal mediator in wound healing, promoting myofibroblast differentiation and extracellular matrix deposition, including collagen, in the wound dermis. We aimed to understand HFN-competent tissue state, specifically focusing on TGF-β signaling-mediated wound healing. Using multiple genetically modified mouse models, we depleted TGF-β signaling to explore its role in wound-induced HFN. Conditional knockout of TGF-β receptor 2 in wound fibroblasts before but not after re-epithelialization inhibited HFN and reduced myofibroblast differentiation and collagen deposition. These results suggest that TGF-β signaling during wound healing is critical for HFN. Further, conditional knockout of collagen type I in wound fibroblasts also inhibited HFN, which was rescued by the activation of the Sonic hedgehog (Shh) signaling. Spatial transcriptomic analysis further revealed that the absence of TGF-β signaling disrupted macrophage infiltration and chemoattractant expression, major players in wound healing and HFN, as well as Shh signaling activation in the wound dermis. Collectively, our results suggest that TGF-β signaling orchestrates wound healing process by sufficient collagen deposition and macrophage recruitment in the wound dermis, which may provide the regenerative microenvironment to initiate HFN.

0875

Taxane chemotherapy induces premature aging and epigenetic changes in human hair follicles

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Taxane chemotherapy damages human scalp hair follicles (HFs) and their epithelial stem cells (eHFSCs) on multiple levels (e.g., excessive apoptosis, mitotic disruption, DNA damage, pathological EMT induction). Yet it is unclear if taxanes also promote premature HF aging. To explore this, we treated organ-cultured human anagen scalp HFs from 4 donors with paclitaxel (PTX, 100nM, 6 days). Quantitative immuno-histomorphometry revealed that PTX significantly decreased the protein expression of nuclear Lamin B1 in the peripheral rim and SIRT1 and PGC1α within the hair matrix epithelium, indicating premature HF aging/senescence. PTX also reduced the number of gp100+ cells in the hair matrix, thus facilitating premature greying. In the bulge, the number of K15+ eHFSCs and expression of collagen XVIIa1 were significantly reduced in PTX-treated HFs. Given that aging is also associated with epigenetic alterations, we next evaluated the global methylation patterns of PTX-treated HFs. This showed decreased levels of DNA methylation markers (5-methylcytosine, DNA-Methyltransferase 1) in eHFSCs, and elevated 5-hydroxymethylcytosine expression in hair matrix keratinocytes, documenting enhanced global DNA demethylation. Thus, taxanes trigger premature HF aging, also at the level of epigenetic changes, both in maximally proliferating hair matrix keratinocytes and in quiescent eHFSCs, thereby reducing the HF's regenerative capacity and facilitating the development of permanent alopecia. The taxane-induced global DNA hypomethylation favors the expression of normally silenced genes, which may include aging-promoting ones. We are currently exploring in scalp skin organ culture if topical treatment with melatonin protects against the taxane-induced HF damage reported above.

0876

Tsc2 deletion in mesenchymal cells improves distal digit regeneration

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Digit regeneration is limited in mammals. After distal amputation, undifferentiated blastema cells may drive complete regeneration or pro-inflammatory cells may induce a fibrotic, non-regenerative scar. We hypothesized that deletion of Tsc2 in mesenchymal cells would support nail regeneration after amputation, based on our previous work showing that loss of this gene altered skin morphogenesis and regeneration. Tsc2 conditional knockout (cKO) mice were generated from a cross between mice with a conditional Tsc2 allele and mice containing the cre recombinase transgene possessing a Prrx1 enhancer, deleting Tsc2 on both alleles in limb bud mesenchyme. The middle three hindpaw digits from 11 control and 10 Tsc2 cKO mice were amputated by cutting through the most distal phalanx (P3). Digit tip regeneration was scored visually as complete, partial, or none. At 28 days after amputation, digits were harvested and histological sections were analyzed to quantify P3 bone length and percent regeneration. From visual inspection, 54 of 60 digits in the cKO group showed complete regeneration indicating full digit elongation and nail regrowth compared to 11 out of 62 digits in the control group ($p < 0.005$). P3 bone length measured in amputated digits from the cKO group was 690 ± 290 μm, significantly greater than 430 ± 260 μm in the control group ($p < 0.005$). In summary, our data demonstrates Tsc2 deletion in mesenchymal cells within a mouse model improves bone digit regeneration and regeneration of the nail. Understanding signaling pathways relevant to Tsc2 deletion in mesenchymal cells can open new avenues to improve digit regeneration after amputation.

0877

Activated wound phenotype and microbial dysbiosis are driven by AhR suppression in hidradenitis suppurativa tunnels

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Tunnels drive advanced disease in hidradenitis suppurativa (HS); however, dysregulation in tissue repair and the microbiome within these intradermal structures remains poorly understood. We characterized the cellular phenotypes and microbiome of HS tunnel tissue and explored the role of microbiome-sensing AhR pathway as a mechanistic mediator. Comparative gene ontology (GO) and Ingenuity pathway analysis (IPA) were performed using bulk RNAseq and scRNAseq data from tunnel and peri-lesional tissue, complemented with16s rDNA microbiome profiling from tunnel tissue. Furthermore, we isolated and isolated keratinocytes (HK), fibroblasts (FB), and bacteria from the above tissues and validated omics data using *in vitro* assays, immunohistochemistry (IHC), and qPCR. Controls from peri-lesional skin and location/age/gender matched skin. GO analysis showed enrichment in acute wound healing processes in tunnel tissue, confirmed by "wound activated" keratin 17 uniquely expressed in tunnel and not peri-lesional epidermis as confirmed by IHC and qPCR. Tunnel HK also showed faster migration compared to peri-lesional HK, an effect modulated by AhR active drugs. IPA revealed decreased AhR signaling in tunnel HK, including suppression of CYP1A and CYP1B, aligning with the reduced abundance of commensal bacteria in tunnels, including Cutibacterium and Lactobacillus species. In addition, tunnel FB showed increased contractility in our 3D HS tunnel organotypic, mimicking activated wound phenotype. Using multiple omics approaches and validation, we show that the persistent activated wound cellular phenotype and unfettered inflammation in HS tunnels correlate with dysbiosis and suppression of AhR signaling. Our data complements previous studies showing that skin microbiota mediate cutaneous barrier repair through AhR signaling. We provide novel insights into HS pathogenesis and rationale for therapeutic targeting of AhR in HS tunnels.

0878

Aging impairs cutaneous healing through miR-133 mediated inhibition of regenerative pathways and increased cell senescence

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The skin serves a critical role in the protection of our body from the outside world, yet our ability to restore this barrier after injury greatly declines with age. Despite understanding the pathways influencing cutaneous regeneration, there is still a knowledge gap in how these factors change with age and whether they can be targeted therapeutically. To answer this, we used a wound-induced hair neogenesis (WIHN) mouse model to quantify regeneration. WIHN is a phenomenon where adult mammals undergo embryonic-like regeneration in large cutaneous wounds via the development of neogenic hair follicles (HFs) and functional, non-scarred skin. Young (4-week) and aged (91-week) C57BL/6J mice were given full-thickness dorsal cutaneous wounds of 1.25x1.25cm and 1.5x1.5cm, respectively. Aged mice took twice as long to re-epithelialize wounds ($p<0.0005$) and had a 20-fold decrease in neogenic HFs ($p<0.0005$). mRNA sequencing and qPCR of re-epithelialized wounds showed that young mice had an increase in pro-regenerative markers LGR6, Wnt7B, SHH, and TLR3 ($p<0.005$ for all). Conversely, aged mice had a 7-fold increase in senescence marker p53 ($p <0.001$) and an 3-fold increase in p16 ($p<0.0005$). miRNA sequencing revealed a 16-fold ($p<0.0005$) increase of miR-133 in aged mice. Treatment of human keratinocytes with miR-133 partially phenocopied aging through reduced expression of regenerative markers LGR6 ($p<0.005$), Axin2 ($p<0.05$), and TLR3 ($p<0.0005$), while increasing expression of senescence markers p53 ($p<0.0005$) and p16 ($p<0.0005$). Treatment of young mice with miR-133 resulted in a 5-fold decrease in neogenic HF formation ($p<0.0005$) as well as a decrease in the expression of LGR6 ($p<0.05$), Wnt7B ($p<0.005$) and an increase in p16 ($p<0.05$). Inhibition of miR-133 in aged mice resulted in a 3-fold increase ($p<0.005$) in neogenic HFs.These results elucidate the molecular pathways of wound healing that change with aging and provide a potential therapeutic target through miR-133 to improve the regenerative capacity of the skin.

0879

Potent complex optimized with tripeptide-32 to increase key proteins and address periorbital skin lifting

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Research shows that the skin around the eye ages earlier than other sites on the face. Why is it aging faster? This skin is unique and distinct from other areas on the face. Periorbital skin is the most sensitive and delicate skin in our face; it is 40% thinner and as we age, it becomes even thinner due to a natural decrease in protein production. In addition, the skin around the eyes has very few oil glands and therefore it lacks natural moisture. It is also more prone to inflammation and irritation. And finally, the periorbital skin is constantly moving. Blinking (~10,000 times/day) and repetitive facial expressions create fine lines and “crow’s feet”, or lines that appear at the outer corner of the eyes. Therefore, periorbital skin requires specific treatment. In this study, to fight periorbital skin aging by lift this delicate skin, we address key proteins such as elastin, fibrillin, collagen and fibronectin and optimize the treatment result by aligning skin cell functions with the natural circadian rhythm. Ex-vivo skin was treated with different technologies and complexes. After 5 days, treatment with a complex of exclusive Adansonia digitata seed extract+ hexapeptide+algae extract+whey protein (complex 1) did not show significant elastin increase. However, after adding our exclusive tripeptide-32, previously shown to help synchronize skin cell activity with natural circadian rhythm, to this complex, elastin increased by more than 100%, showing once again the importance of synchronization. Results continued to improve: after 10 days, the full complex (complex 1 + tripeptide-32) showed an elastin increase by more than 230% and a fibrillin increase by more than 60%. In addition, in-vitro treatment with the full complex on normal human adult dermal fibroblasts showed an increase in collagen by 113% and fibronectin by 80% after 3 days. We show that the full complex including our exclusive tripeptide-32, is very efficient in increasing key proteins essential to counter periorbital skin sagging.

0880

Novel synthetic melanin nanoparticles modulate CXCL1/CXCR2 axis in skin wound healing

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CXCL1/CXCR2 axis play an important role in recruiting immune cells to sites of injury and modulating inflammatory responses. CXCL1 signaling acts as a potent chemoattractant for neutrophils, driving their migration to inflamed or injured skin. Neutrophil infiltration contributes to the resolution of injury but also exacerbates tissue damage if dysregulated. Previously we had shown that topical treatment with synthetic melanin nanoparticles (SMP) significantly improve skin wound repair. Based on our findings, we synthesized SMPs with modified characteristics (SMP_{mod}) designed to improve the interactions of the SMPs with the surface of stratum corneum. We found that SMP_{mod} decreased edema ($p<0.01$; n=6-9 mice/group) and reduced eschar detachment time in mouse chemical injury skin model. SMP_{mod} significantly downregulated Cxcl1 gene expression compared to the control group ($p=0.026$; n=5-9 mice/group). Following this, we performed flow cytometric analysis of injured mouse skin treated with SMP_{mod} as well as of spleen and blood samples (n=4-7 mice/group). Topical SMP_{mod} treatment significantly reduced the frequencies of CXCL1 expressing eschar-infiltrating non-inflammatory monocytes ($p=0.0008$) and macrophages ($p=0.02$), as well as CXCR2 expressing inflammatory-, and non-inflammatory monocytes ($p=0.01$; 0.001), neutrophiles ($p=0.00002$) and dendritic cells ($p=0.03$). Besides, SMP_{mod} treatment significantly enhanced IL-10+ ($p=0.04$) while reducing iNOS+ ($p=0.00003$) eschar-infiltrating neutrophils. A concomitant reduction of splenic antigen presenting cells was observed in SMP_{mod} treated mice, with significant amelioration in CXCR2 expressing neutrophils ($p=0.002$). In contrast to the eschar and spleen, frequencies of macrophages and mDCs were increased in the blood of SMP_{mod} treated mice. Our data demonstrate that topical application of SMP_{mod} nanoparticles modulate CXCL1/CXCR2 axis, and that chemical modification of SMP characteristics leads to the activation of different signaling pathways

0881

Persistent PTEN signaling underlies the non-healing phenotype in venous leg ulcers

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Venous leg ulcers (VLUs) are common chronic wounds with only 44% healing rate with standard of care. This highlights the need for better understanding of their molecular and cellular pathology to improve treatment. In this study, we investigated the mechanisms that influence the clinical progression of VLU healing. We performed single-cell and bulk RNA sequencing on VLU samples and compared them with human acute wounds (AW) using Ingenuity Pathway Analysis. Validation was done through immunostaining, qPCR, flow cytometry, and proteome arrays. Additionally, a murine wound model was used for pharmacological confirmation of findings. Our single-cell analysis showed impaired immune and lymph-endothelial functions in VLUs. Comparison of healing versus non-healing VLUs revealed that healing VLUs exhibited immune responses similar to acute wounds, while non-healing VLUs had suppressed inflammation and lymph-angiogenesis. This inadequate inflammatory response in non-healing VLUs was linked to impaired cell processes, including reduced transmigration, egression and chemotaxis, and decreased immune recruitment. Furthermore, signaling pathways involving AKT, ERK, SRC, STAT, and PDGFR were suppressed in non-healing ulcers. Upstream regulator analysis identified PTEN as a critical negative regulator of these pathways. Consistently, PTEN protein expression was significantly higher in non-healing VLUs, indicating its central role in driving the non-healing phenotype. PTEN inhibition in murine wound model accelerated wound closure, enhanced granulation tissue formation, and promoted inflammatory response. Our findings position PTEN as a critical regulator of non-healing VLUs, offering potential targets for new therapeutic interventions to improve healing outcomes.

0882

Patterning and regional specification of hairy skin

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Mechanisms controlling regional variation of hair follicle development and other skin characteristics such as innervation and epidermal thickness and how these have adapted during mammalian evolution, are poorly understood. To begin to unravel these questions we carried out scRNA-seq on hairy, poorly haired, and hairless regions of mouse embryonic and human fetal skin. These experiments revealed differential expression of members of several families of secreted factors that inhibit Wnt and/or IGF signaling. While the IGFBP family member IGFBP3 was more highly expressed in developing less hairy skin in both mouse and human, other IGFBP family members, the secreted Wnt inhibitor DKK2, and the Wnt and BMP inhibitor SOSTDC1 showed species-specific differential expression. Mice lacking DKK2 develop ectopic hair in the normally hairless plantar region of mouse hindfeet. Genetic loss of function experiments revealed that combined homozygous loss of DKK2 and SOSTDC1 exacerbated ectopic plantar hair follicle development compared with the phenotype of Dkk2-null mice and caused a new phenotype of hairy ears that was not observed in either single-null mutant. Thus, DKK2 and SOSTDC1 act together either to dictate development of hairless and less-hairy skin in mice. Combined deletion of DKK2 and IGFBP4 resulted in expanded Wnt activity in the developing mandible and formation of ectopic incisor teeth that was absent in either single mutant, indicating that these factors can act synergistically to suppress Wnt signaling. These data show that secreted inhibitors of Wnt and IGF signaling are differentially expressed in less haired versus hairy skin and that specific secreted Wnt inhibitors and IGFBP family members can function together to control the pattern of appendage development. Our data further suggest that expression of a subset of secreted Wnt inhibitors and IGFBP family members has been adapted during evolution to allow for species specific patterns of appendage development.

0883

Chronic facial abscess mimicking cervicofacial actinomyces from dermal filler migration

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Dermal fillers are widely used for facial aesthetics, offering a minimally invasive solution for volume loss, wrinkles, and facial asymmetry. Composed of materials such as hyaluronic acid, calcium hydroxylapatite, and polymethylmethacrylate (PMMA), these fillers provide long-lasting results with minimal recovery time. While complications like filler migration and granulomatous reactions are well-documented, the development of a chronic filler reaction mimicking a cervicofacial actinomycetoma as a result of filler migration is rare and has not been described to our knowledge. A 56-year-old female presented with a chronic draining sinus on the right cheek, persisting for approximately three years. Initial diagnostic concerns included chronic infections such as actinomyces, cervicofacial fistulous abscess, nocardia, or a chronic fungal wound. Tissue culture was negative for bacterial, fungal, and atypical mycobacterial growth. Pathology revealed foreign body granulomas with reactive lymphoid tissue, consistent with PMMA microspheres and hyaluronic acid, components typically found in semi-permanent fillers like Bellafill or Artefill. The patient underwent excision of the foreign material, with complete removal of the affected tissue. The post-operative course was uneventful. This case highlights the importance of early recognition and consideration of rare side effects of iatrogenic procedures such as filler injections. It also denotes the long-term risks of semi-permanent fillers and the inclusion of iatrogenic factors in the differential diagnosis of facial abscesses. Treatment for PMMA-based filler reactions relies on adequate excision as noted in this case, but may respond to intralesional steroids. Although PMMA-fillers are not widely used, the need to consider reactions to these could provide valuable insight into the recognition and management of chronic, non-healing wounds of the head and neck.

0884

Mis-relocation of mesenchymal niche leads to permanent radiotherapy-induced alopecia from stem cell exhaustion due to failed new stem cell formation

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Permanent radiotherapy-induced alopecia (pRIA) is a type of scarring alopecia featured by loss of the entire hair follicle structure. Similar to most scarring alopecic diseases, how hair follicles (HFs) become absent in pRIA remains unknown and effective treatments are lacking. Using an animal model, we found that radiation induced premature entry into catagen (dystrophic catagen) with retraction of the growing HF epithelium, which was immediately followed by HF loss. Early in this dystrophic process, the dermal papilla fibroblast niche became disconnected from the receding HF epithelial strands due to protracted apoptosis and suppressed regenerative cell proliferation from prolonged p53 activation. In the absence of the mesenchymal niche, HFs failed to generate new epithelial HF stem cells (eHFSCs) and HFs became lost from stem cell exhaustion. We demonstrated that enhancing regenerative epithelial proliferation by boosting hedgehog signaling prevented HF loss by maintaining the dermal papilla-epithelial connection to support new HFSC formation. Our work highlights the essential role new HFSC formation during catagen in the maintenance of normal hair cycling. Preserving the mesenchymal niche to support new HFSC formation is a promising strategy to prevent pRIA and possibly other types of scarring alopecic diseases.

0885

The androgen-THY1 axis mediates sexual dimorphism in dermal adipogenesis and fibrosis

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Sexual dimorphism manifests in human development and diseases, with the skin being one of the most sexually differentiated tissues. Dermal white adipose tissue (dWAT, also known as dermal fat) plays a crucial role in various skin processes including hair cycling, tissue regeneration and defense against bacterial infection. However, the sex differences in dermal fat and the underlying mechanism remain poorly understood. In this study, we analyzed the dynamic changes in dWAT during skin maturation and found that male dWAT volume were rapidly lost by 2 months of age, whereas female dWAT was relatively resistant to these age-dependent changes. Single-cell RNA sequencing identified dermal fibroblasts (dFBs) as the most sex-biased cell type. Specifically, female dFBs expressed elevated level of Thy1, while male dFBs exhibited increased expression of fibrotic-associated genes. Gonadectomy surgeries and fibroblast-specific androgen receptor (AR) knockout mice revealed that activation of AR signaling in dFBs contributed to the sexual dimorphism in dermal fat and downregulation of THY1 expression in dFBs. Next, we generated Thy1 knockout (KO) mice, and found that Thy1-KO skin exhibited a thinner fat layer and extensive collagen deposition compared to control skin. Mechanistically, Thy1 deficiency in dFBs led to increased susceptibility to TNF-mediated P38 phosphorylation and upregulation of fibrotic genes. In a large wound-induced skin fibrosis mouse model, deletion of Thy1 blocked the regeneration of dWAT layer and promoted ECM accumulation, whereas inhibiting AR signaling in dFBs restored THY1 expression and promoted skin regeneration in male mice. Together, our results show that androgen-driven loss of THY1 in dermal fibroblasts inhibits adipogenesis, promotes skin fibrosis, and prevents regeneration, providing a better understanding of skin sexual dimorphism under homeostatic and fibrotic conditions.

0886

Setting the standard: developing a calciphylaxis wound scoring tool

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This study uses the modified Delphi method to develop a validated wound scoring tool for assessing progression of calciphylaxis ulcers. Calciphylaxis is a rare and life-threatening disease caused by calcification and thrombosis of microvasculature, most often affecting patients with end-stage renal disease. Resultant necrosis of the surrounding tissue can manifest with painful and slow-healing skin ulcers. The presence of ulceration signals poor prognosis, with mortality rates rising to over 80%. Sepsis from wound infection is the leading cause of death in patients with calciphylaxis, highlighting the necessity for effective wound management. However, current treatment options lack evidence from prospective randomized controlled trials. One major challenge for therapeutic investigations is the lack of formal assessment tools to risk-stratify patients and evaluate improvements in both disease progression and wound healing. Existing systems such as the Bates-Jenson Wound Assessment Tool are not designed to reflect the unique features of calciphylaxis. This new calciphylaxis wound scoring tool was informed by expert opinion, validated utilizing a standardized patient database, and scored for interrater reliability. Development of a validated and reliable calciphylaxis wound scoring tool will standardize the surveillance of clinical improvement and treatment efficacy in much-needed prospective research on calciphylaxis.

0887

Long-lived and genetically-diverse skin organoids derived from murine adult hair follicle stem cells

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3D *in vitro* skin models provide a convenient mechanism to study skin structure and function. However, these models are largely created from cell lines or neonatal keratinocytes, which may not be reflective of adult skin *in vivo*. To overcome the limitations in the current 3D skin model platforms, we developed Matrigel-supported skin organoids from stem cells present in whole skin samples of adult mice (9-12 wks old). We have also successfully established organoid lines from older adult and elderly mice (up to 89 wks old) using our protocol. Organoids developed via this method each represent a genetically unique and physiologically relevant primary tissue. Once established, they are as convenient to work with as a cell line: they can be viably frozen and thawed, passaged >20 times, and maintained in culture >3 months. When allowed to mature without single-cell dissociation for passaging, our skin organoids begin to show "buds" typical of more established epithelial organoids derived from other tissues. They also express hair follicle-associated markers such as EpCAM and pan-cytokeratin, as well as CD34 and keratin 15 (stem cell markers of the hair follicle bulge). To determine the stem cell of origin of our model, we established skin organoids from transgenic lineage-tracer mice for three distinct hair follicle stem cell populations: Lgr5+ cells from the bulge, Lgr6+ cells from the isthmus, and Lrig1+ cells from the infundibulum. Interestingly, our results show the skin organoids are derived from all three stem cell populations. To our knowledge, these are the first skin organoids developed from adult stem cells that can be biobanked and indefinitely passaged while still retaining hair follicle stem cell markers. Our optimized skin organoid methodologies will be an exciting new resource to the field for future studies of skin homeostasis, regeneration, and pathology.

0888

Developing vascularized immune-competent skin organoids for advanced dermatological research

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A large amount of research has been devoted to developing skin equivalent for studying developmental pathways, modelling diseases, or regenerative medicine purposes. Despite progress, the field remains far from creating fully structured skin, including appendages like hair follicles and sweat glands, and lacks vascularization. Here, we present a pioneering approach for engineering stratified skin layers with their appendages using human induced pluripotent stem cells (hiPSCs)-derived skin organoids (SKOs) from multiple distinct hiPSCs lines. Comprehensive cellular and molecular analyses confirm that mature SKOs contain skin stem/progenitor populations, including dermal papilla cells, and can develop sebaceous glands, sweat glands, fat, and touch-receptive Merkel cells, highlighting their complexity and fidelity to native human skin. However, skin's vascularization, vital for homeostasis, remains an unmet challenge. Thus, to further enhance physiological relevance of SKO, we investigate the vascularization of human SKO using hiPSCs-derived vascular organoids. This approach results in developing fully vascularized SKOs, sustaining hair follicle formation and demonstrating the integration of CD45+ immune cells, like *in vivo* skin microenvironment. Generation of both immune cells and vascular components within the complete-appendage SKO mimics the structure of *in vivo* skin setting a new benchmark for translational skin research. The human immune-competent vascularized skin organoids demonstrate substantial translational potential and could be used as valuable platforms for advancing dermatological research, understanding skin development, modelling diseases, and advanced regenerative solutions and personalized medicine.

0889

Increased stem cell quiescence underlies the decreased proliferation in aged human epidermis

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There is a decrease in cell proliferation in the human epidermis with age. While in some tissues aging has been associated with a decrease in stem cell (SC) number, no decrease has been seen in the hematopoietic system and skin. In both mammary and epidermal SCs there is a decrease in asymmetric stem cell self-renewal with age (associated with decreased P53 expression), expected to result in a decrease of committed progenitors (transit-amplifying cells). To help account for the decreased proliferation with age, we hypothesized that aging is associated with an increase in keratinocyte SC quiescence (a decrease in the number of SCs actively dividing). Tissue sections from formalin-fixed paraffin-embedded human aged (81y, n=5) and adult (21-37, n=6) skin surgical discard samples were studied. P21, a CDK1 inhibitor, was used to indicate quiescence. Ki67, associated with the cell cycle, was used to indicate active/cycling SCs. Sections were incubated with anti-p21 antibody and anti-ki67 antibody and then analyzed under a fluorescence microscope. Cells that were cycling (Ki67+) in the basal layer were considered SCs or early CPs. Cells in the basal layer that were quiescent (P21+) were considered quiescent SCs. The number of quiescent (P21+) basal cells was increased in aged vs. adult (0.6±0.30 vs 0.19±0.12, P=.015). The number of actively cycling (Ki67+) basal cells was decreased in aged vs. adult (1.7±1.1 vs 3.9±1.9, P=.05). The total numbers of quiescent and cycling basal keratinocytes was unchanged (2.3±1.1 vs 4.1±1.9, NS). Our study demonstrates that the decrease in stem cell self-renewal in aged adult human epidermis is associated with an increase in quiescent SCs. Furthermore, this study did not detect a change in total SC number. A more granular understanding of the hypoproliferation of aging is key to developing therapeutics targeting aging keratinocytes and restoring skin homeostasis.

0890

Human skin rejuvenation via mRNA

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Aging is characterized by a gradual decline in function, partly due to accumulated molecular damage. Human skin undergoes both chronological aging and environmental degradation, particularly UV-induced photoaging. Detrimental structural and physiological changes caused by aging include epidermal thinning due to stem cell depletion and dermal atrophy associated with decreased collagen production. Here, we present a comprehensive single-cell atlas of skin aging, analyzing samples from young, middle-aged, and elderly individuals, including both sun-exposed and sun-protected areas. This atlas reveals age-related cellular composition and function changes across various skin cell types, including epidermal stem cells, fibroblasts, hair follicles, and endothelial cells. Using our atlas, we have identified basal stem cells as a highly variable population across aging, more so than other skin cell populations such as fibroblasts. In basal stem cells, we identified ATF3 as a novel regulator of skin aging. ATF3 is a transcriptional factor for genes involved in the aging process, with its expression reduced by 20% during aging. Based on this discovery, we have developed an innovative mRNA-based treatment to mitigate the effects of skin aging. Cell senescence decreased 25% in skin cells treated with ATF3 mRNA, and we observed an over 20% increase in proliferation in treated basal stem cells. Importantly, we also found crosstalk between keratinocytes and fibroblasts as a critical component of therapeutic interventions, with ATF3 rescue of basal cells significantly enhancing fibroblast collagen production by approximately 200%. We conclude that ATF3-targeted mRNA treatment effectively reverses the effects of skin aging by modulating specific cellular mechanisms, offering a novel, targeted approach to human skin rejuvenation.

0891

RGR modulates angiogenic sprouting under mild heat stress *in vitro*

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Objective: To elucidate the impact of the retinal G protein-coupled receptor (RGR) on angiogenic sprouting under MHS conditions. Methods: The expression profile of RGR in human umbilical vein endothelial cells (HUVECs) was examined utilizing immunofluorescent staining techniques. Quantification of RGR mRNA and protein levels was conducted through real-time quantitative PCR and Western blot analysis under varying MHS conditions (37°C, 39°C, 41°C and 43°C). Additionally, the expression and subcellular localization of RGR in HUVECs were detected under laser scanning confocal microscopy. The pro-angiogenic properties under different MHS conditions (37°C and 41°C) were identified using spheroid-based angiogenesis and tube formation assays. Lentiviral transfection techniques were employed to achieve overexpression or suppression of RGR in HUVECs. The effects of RGR overexpression or suppression on angiogenic sprouting in HUVECs under different MHS conditions (37°C and 41°C) were assessed through spheroid and tube formation assays. Results: Co-immunostaining analysis of RGR and CD31 revealed that RGR was localized to the cell membrane and nucleus of HUVECs, with a predominant expression in the cell membrane. Upon exposure to heat stress at temperatures of 37°C, 39°C, 41°C, and 43°C for one hour, a progressive increase in RGR mRNA and protein levels was detected. Significantly, cellular damage was observed in the group exposed to 43°C, whereas no cellular damage was detected in the other groups. Significantly enhanced angiogenic sprouting and tube formation were observed at 41°C for one hour, in comparison to the 37°C group. This enhancement effect was modulated by the overexpression and knockdown of RGR, respectively. Conclusions: RGR is capable of modulating angiogenic sprouting under various MHS conditions *in vitro*.

0892

Role of TET-mediated DNA demethylation in wound healing

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DNA methylation and the subsequent oxidation of 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC) are key epigenetic mechanisms that regulate organ development, stem cell maintenance, and differentiation in mammals. TET enzyme family (TET1, TET2, and TET3) catalyzes the oxidation of 5mC, an essential step in DNA demethylation. Accumulating evidence shows that Tet proteins are essential in diverse biological processes, including development, regeneration, and cellular reprogramming. However, the role of Tet-mediated DNA demethylation in controlling gene expression in keratinocytes during wound healing remains unknown. In this study, we assess the dynamics of gene expression and chromatin accessibility in epidermal keratinocytes during wound healing using a mouse tail model. Our results show that the epigenetic landscape in keratinocytes is altered during regeneration, with DNA methylation changes occurring in gene regulatory regions. RNA-seq of wounded keratinocytes reveals dysregulation of genes involved in epidermal development, proliferation, motility and cytokine production. Similar to unwounded skin, we found that TET2 and TET3 protein expression predominated over TET1 in keratinocytes isolated from the wound epithelium. Both TET2, TET3, and 5hmC were expressed in proliferating and migrating keratinocytes of the regenerating epithelium. To study the role of TET2 and TET3 in epidermal regeneration, we generated conditional K14-Cre-driven Tet2/Tet3 double-knockout (DKO) mice. DKO mice exhibited significant delays in wound healing, which were associated with reduction of expression of genes that control the cell cycle, cytoskeleton organization, and cell migration in regenerating wound epithelium. These data provide a platform for further research towards pharmacological modulation of wound healing by targeting DNA methylation/demethylation enzymes in regenerating tissues.

0893

Investigation into the promotive effects of extracellular vesicle from human transformed skin-derived precursors on hair growth *in vitro* and *in vivo*

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Background: The exploration of stem cells and their paracrine factors represents a cutting-edge approach for treating alopecia. However, there is a paucity of research on the efficacy of human skin-derived precursors (ht-SKPs), which are most closely related to hair follicle locationally and functionally, in treating hair loss. We established a novel stem cell culture system and investigated the role and mechanism of extracellular vesicle (EV) from ht-SKPs in hair growth. Methods: ht-SKPs-EV was obtained by three-dimensional (3D)-directed induced transfer culture system based on chemical small molecule induction with poly-hema coated plates and ultra-high speed centrifugation. Subsequent intervention experiments of human DPCs /HFSCs, human *in vitro* hair follicles and mice alopecia model of hair cycle were performed for ht-SKPs-EV. Protein mass spectrometry and miRNA sequencing were conducted to identify differentially expressed protein or miRNAs for further similar *in vitro* and *in vivo* investigation. CCK8, scratch assay, immunofluorescence, HE staining, immunohistochemistry staining, dermoscope, dual luciferase reporter assays, PCR and Western blotting were employed for above study. Results: ht-SKPs-EV promoted the proliferation of human DPCs and HFSCs by regulating the Wnt signaling pathway, which in turn facilitated hair follicle growth both *in vitro* and *in vivo*. It is worth mentioning that miR-221-3p, which was identified through sequencing data and introduced via miRNA transfection vectors, was found to downregulate the expression of DKK2, activate the Wnt pathway, and induce hair follicles to enter and maintain the anagen phase both *in vitro* and *in vivo*. Conclusion: ht-SKPs-EV containing miR-221-3p effectively downregulate DKK2 expression in dermal papilla cells. Consequently, the Wnt signaling pathway is activated, exerting a favorable effect on the hair follicle growth cycle. This significant discovery may herald a promising novel therapeutic target for the treatment of alopecia in the realm of regenerative medicine.

0894

Characterization of cellular senescence in complex engineered skin constructs using spatial transcriptomics

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Cellular senescence is a biological state that despite intense research efforts in the field is not completely characterized. Skin is the first target of environmental stressors, such as ultraviolet radiation (UV), which contribute to extrinsic cellular senescence. In addition, the constant need for self-renewal in the skin progressively leads to replicative (intrinsic) senescence. Due to the biological differences between human and animal models, notably the lifespan of the organism, engineered human tissues allow for a more faithful recapitulation of certain features observed in human senescence. We recently developed complex Human Skin Constructs (HSCs), with pigmentation and vasculature, to model intrinsic and extrinsic senescence in human skin. We introduced high-passage growth-arrested cells to recapitulate intrinsic senescence, and irradiated whole HSCs with UV-B to induce extrinsic senescence. We first characterized the senescent cells in the HSCs using two 8-marker Opal multiplex immunofluorescence (IF) panels, detecting both known senescence markers (e.g., p16, p21, HMGB1, pH2A.X, caveolin-1 and lamin-b1), and lineage markers (i.e., K14 for keratinocytes, TRP2 for melanocytes, and CD31 for the endothelium). We then performed spatial transcriptomics analysis using the Visium HD platform, staining each section with p16, p21 and lamin-b1 (IF) antibodies, and hematoxylin & eosin, before proceeding with probe hybridization and sequencing. We observed enrichment of different subpopulations of senescent cell in our models, identified by cell type-specific and intrinsic vs extrinsic senescence markers. The development of these HSCs enables mechanistic studies of cellular senescence and aging *in vitro*, and has the potential to aid the near-term development of senolytic therapies.

0895

Combined topical rapamycin and melatonin improve biomarkers of aging/ senescence in aged human scalp skin *ex vivo*

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Given the multifactorial nature of human skin aging, we tested whether the combined topical application of two agents with well-known, but quite distinct anti-aging effects improves core biomarkers of skin aging/senescence aged human scalp skin: the endogenous indoleamine neurohormone, melatonin (MT), which inhibits human eyelid skin aging *ex vivo*, and the immunosuppressive mTOR inhibitor, rapamycin (RPM), which can stimulate repigmentation in gray/white human hair follicles, after addition to the culture medium. Topical MT application circumvents rapid MT metabolism by the liver, while topical RPM reduces the risk of systemic immunosuppression. Combined MT (1 mM) and RPM (2uM) was applied every other day topically to aged, organ-cultured, full-thickness human scalp skin from 5 healthy male donors (age range: 42-63y-o) for 6 days in a PEG/isopropanol vehicle. Quantitative immunohistomorphometry revealed that topical MT+RPM significantly decreased $p16^{INK4}$, mTORC1 activity (reduced S6 phosphorylation), and MMP1 protein expression in the basal and granular layers of the epidermis compared to vehicle-treated skin. Instead, MT+RPM significantly increased the epidermal protein expression of SIRT-1, PGC1a, and Lamin B1. Instead, no changes were seen in VEGF-A, and MTCO1 protein expression in the epidermis and fibrillin-1, and collagen 1&3 in the dermis of MT+RPM skin compared to control. Our study provides proof-of-principle that the combined topical application of two established, well-tolerated, anti-aging actives, MT and RPM, unfolds potent, interindividually reproducible anti-ageing/-senescence properties in aged male scalp epidermis *ex vivo*. This encourages subsequent *in vivo* testing of this senotherapeutic combination in skin aging trials.

0896

Regulation of feather length: FGF and IGF signaling and Notch/YAP modulation of progenitor cell topology

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Understanding organ size regulation is a fundamental biological question. Bird feathers of the same bird exhibit incremental length changes which are important for their function and present a good model to study the mechanism of organ size. This study examines how feather length is controlled in chickens in short contour versus long sickle feathers. We also examined Phoenix chicken variant known for their exceptionally long sickle feathers. We observed the length can be controlled by growth rate and growth period. At cellular level, the collar bulge stem cell zones differ in size from small to long feathers. IGF and FGF are initially highly expressed, while BMP and WIF1 levels rise as growth concludes. Functional assays indicate that IGF and FGF signaling promote feather elongation through tyrosine kinase receptor pathways. Single-cell RNA sequencing (scRNA-seq) reveals that keratinocyte differentiation occurs more rapidly in short contour feathers compared to long sickle feathers. In Phoenix chickens, the exceptionally long main sickle feathers possess specialized stem cell zones with increased Delta-like 1 (DLL1) expression and expanded intermediate-layer cell clusters. These clusters exhibit dynamic interactions involving Notch/DLL, YAP1, and Wnt signaling within progenitor zones in the proximal follicle. Perturbation experiments resulting in shorter feather phenotypes arrested at various stages provide insights into the versatile regulatory mechanisms governing feather length. The work suggest that growth rate relies on IGF/FGF signaling, while growth period relies on the duration in which collar progenitor cells are active. The topological arrangement of progenitor cells in collar region set up a cellular platform for Yap / Notch/ Dl1 circuit to work as sensor and actuator of length control. This research enhances our understanding of feather length control and offers potential avenues for manipulating length of skin appendages.

0897

Novel automatically stratified fibrotic 3D cutaneous spheroids for studying fibrotic mechanisms in hypertrophic scars

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Background: Hypertrophic scarring (HTS) is marked by excessive fibrosis and structural disorganization. Traditional 2D scar models fail to mimic the structural and biological complexity of HTS. Recent 3D bioprinted models are innovative but labor-intensive, limiting their practicality for fibrosis studies. Methods: Fibroblasts, keratinocytes, and vascular endothelial cells were co-cultured in a multicellular model using Molecular Assembly-based Macromolecular Crowding (MAMC) technology. This approach enabled stratified spheroid formation with a dermal core and epidermal layer, inducing myofibroblast differentiation. Fibrotic features and multicellular interactions were analyzed using TEM, qPCR, and Western blot. Results: MAMC-derived spheroids displayed key HTS features, including a 100 µm-thick epidermal crust and increased collagen/SMA accumulation in the dermal core. Surface keratinocytes exhibited tight connections, replicating the HTS's mechanical microenvironment. Gene analysis revealed elevated TWIST and SNAIL levels during fibroblast activation, highlighting their role in multicellular interactions driving fibrosis. The dermal core showed more complex fibril structures and increased fibril diameter, validating the model's accuracy in simulating pathological conditions. Conclusion: This novel 3D cutaneous spheroid model, featuring automatic stratification, offers a scalable and biologically relevant platform for studying HTS pathology with a focus on multicellular interactions. By incorporating three cell types, it more accurately replicates the scar's mechanical microenvironment than single-cell-type models. qPCR results highlight its utility in exploring fibrosis mechanisms and its potential value for research.

0898

Smad7-based biologic targets neutrophil NETosis in diabetic wound models

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Neutrophils are crucial in the early phase of wound healing but can impair healing when excessive neutrophil extracellular traps (NETs) are formed. In diabetes, neutrophils are primed for NETosis, a process that exacerbates tissue damage and chronic inflammation, hindering wound healing. This study explored the mechanisms of diabetic wound healing defects and evaluated a Smad7-based therapeutic intervention. We engineered Tat-PYC-Smad7, a biologic comprising the PY motif and C-terminal domain of human Smad7 fused with a cell-penetrating Tat tag for topical application. Tat-PYC-Smad7 accelerated wound closure and improved extracellular matrix (ECM) remodeling in diabetic mouse and pig models. RNA sequencing revealed that the top pathways targeted by Tat-PYC-Smad7 are related to neutrophil functions and NET formation. Mechanistic studies revealed that Tat-PYC-Smad7 inhibits histone 3 citrullination, a critical step in NETosis, by directly binding to and suppressing myeloperoxidase (MPO) activity. This suppression reduced elastase release and tissue damage while promoting keratinocyte survival and ECM deposition. These findings highlight the pivotal role of NETosis in diabetic wound pathology and the potential of Smad7-based biologic for therapeutic intervention.

0899

Advancing cosmetic dermatology and wound healing: The synergy of laser therapies and artificial intelligence

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Recent advancements in laser therapies and artificial intelligence (AI) are innovating cosmetic dermatology and wound healing. Laser treatments such as fractional resurfacing, intense pulsed light (IPL), low-level laser therapy (LLLT), and high-intensity laser therapy (HILT) effectively promote collagen production, enhance skin texture, and accelerate wound healing. These lasers use specific wavelengths to target different stages of the wound healing process, improving cellular functions like angiogenesis, epithelialization, and collagen synthesis while modulating inflammation and boosting microcirculation. Artificial Intelligence is playing an increasingly significant role in shaping the field of cosmetic dermatology, especially in wound healing. This review explores how AI enhances treatment personalization and optimizes outcomes, complementing the advancements provided by laser therapies. By integrating AI, laser treatments can be dynamically adjusted based on real-time data, improving precision and reducing the risk of adverse effects. This synergy between laser therapies and AI opens new possibilities for personalized care, where algorithms can adapt treatments based on individual responses, ensuring more efficient and targeted results. Ongoing research is improving cosmetic dermatology and regenerative skincare, offering patients more effective, accessible, and personalized solutions. Future directions emphasize the integration of AI in cosmetic dermatology and wound healing procedures and its role in enhancing the overall patient experience. This review emphasizes the modernizing potential of combining laser therapies with AI, showcasing how their integration can advance wound healing and skin rejuvenation, offering patients more effective and efficient treatment options.

0900

Loss of Mrgprd+ sensory nerves delays wound healing by suppressing keratinocyte migration and exacerbating inflammatory states in fibroblasts and immune cells

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The role of sensory neuronal subsets in the wound healing impairment of type 2 diabetes (T2D) is poorly understood. We have noted reduced Mrgprd+ nerve afferents in skin of diet-induced T2D mice, leading to our hypothesis that this nerve subset participates in normal wound healing. Mice with diphtheria toxin-ablated Mrgprd+ nerves (Mrgprd-) had a 25% reduction in histological wound closure ($p<0.01$) at 5 days after wounding, correlating with reduced keratinocyte (KC) migration from the proliferating wound edge (0.8 vs. 1.6 mm, $p<0.05$) ($r=0.68$, $p<0.01$). KC proliferation was unaffected. Wound healing was similarly reduced when the Mrgprd receptor was genetically deleted from the intact nerve ($p<0.01$). Single-cell RNAseq (scRNAseq) of unwounded skin from Mrgprd-ablated mice had fewer follicular stem cells (SC) (7.1% of total cells vs. 10.8%) and more immune-responsive fibroblasts (5.7% vs. 9.4%) than wildtype littermates ($p<0.001$). Analysis of wounded skin by scRNAseq with a focus on immune cells showed persistence of the M1-like macrophage population at day 5 post-wounding, with these cells having upregulation of genes ($\geq$log 2-fold change, $p<0.05$) associated with inflammatory responses and delayed wound healing, among them Hif1a, Ldha, Mct4, Nos2, Arg2, Tnf, Il1b, and Ccl2 (all $p<0.001$). There were also increases in neutrophils ($p<0.01$), as well as reductions in M2-like and monocyte-derived dendritic cells (MoDCs) (both $p<0.001$) when compared to control littermate wounds. Our findings suggest a key role for Mrgprd+ afferents in wound healing, with Mrgprd loss leading to reduced KC stem cells, impaired fibroblast activation, and increased recruitment of inflammatory immune populations.

0901

Tissue-engineered skin substitutes preserve the potential of epithelial cells to differentiate into sebaceous glands

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Sebaceous glands maintain skin hydration by producing sebum, a lipid mixture secreted by sebocytes. To date, human tissue-engineered skin substitutes (TESs) have limited capacity to regenerate sebaceous glands. This study investigates the cell sources that promote sebaceous differentiation in TESs produced by the self-assembly method. Bilayered TESs were produced using epithelial cells and fibroblasts from scalp, foreskin, and breast tisssues. Epithelial cells were cultured on fibroblast sheets for 10 days at the air-liquid interface to promote maturation, then grafted onto athymic mice for 21 days. Biopsies were analyzed by histology, immunofluorescence, and transmission electron microscopy (TEM). Before grafting, sebocyte clusters were observed in TESs epidermis made with scalp epithelial cells. After grafting, glandular structures were seen only in these TESs, suggesting that *in vitro* clusters developed into sebaceous glands *in vivo*. TEM revealed lipid droplets and tonofilaments typical of sebaceous glands. Oil Red O staining showed an excretory duct connecting the structures to the skin surface, suggesting functionality. Immunofluorescence confirmed the presence of early and mature sebocytes (keratin 7, mucin-1) and the human origin of the sebaceous gland-like structures. Notably, the fibroblast origin did not affect this process. We developed a human model enabling the de novo formation of sebaceous-like glands in TESs and we highlighted the importance of epithelial stem cell origin for sebaceous differentiation. Future research will focus on identifying key molecular and cellular signals involved. These results provide new insights into sebaceous gland development in tissue-engineered substitutes, potentially enhancing their therapeutic use in treating burn patients.

0902

Impaired early neutrophil response and wound closure in diabetic injury is associated with loss of ecrg4 expression

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Diabetic patients have dysfunctional neutrophil responses that increase their risk of infection and impaired wound healing. We previously demonstrated that Esophageal Cancer Related Gene 4 (ECRG4) regulates early neutrophil recruitment to cutaneous injury through its regulation of neutrophil adhesion receptors and found that loss of ECRG4 results in delayed wound healing and worse infection. Having identified decreased ECRG4 gene expression in diabetic patient leukocytes, we utilized a murine high fat diet (HFD) model of diabetes to evaluate the role of ECRG4 in regulating the inflammatory response to cutaneous injury. Using a full-thickness wound model, we found that HFD mice had delayed wound closure beginning from day 1 post-injury. Evaluation of the early inflammatory response in an aseptic injury model identified impaired neutrophil recruitment in the HFD mice. Neutrophils from HFD mice had decreased surface expression of ECRG4 with increased CD44, similar to ECRG4 KO mice whose neutrophils have increased adhesion receptor expression that impairs early recruitment to injury and infection. Evaluation of neutrophil mobilization from the bone marrow reserves into blood 24 hours after injury demonstrated increased neutrophils in the blood of HFD mice despite decreased recruitment of neutrophils to the site of injury. Ex-vivo functional assessment of HFD mouse neutrophils demonstrated impaired migration to the key end-target chemoattractant, C5a, but increased migration to the intermediate-target chemoattractant CXCL2, suggesting a mechanism for the accumulation of HFD neutrophils in blood but their failure to home to the site of injury. These data indicate that diabetes results in decreased ECRG4 expression, which drives impaired early neutrophil recruitment to the site of injury, with delayed wound healing.

0903

Pressure ulcer development following cardiothoracic surgery: A comparision of surgical closure methods

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Patients recovering from cardiothoracic surgical procedures are at an increased risk of postoperative complications related to immobility. Hospital Acquired Pressure Injuries (HAPIs) are a common complication of hospitalization and can occur during the postoperative period. This study aims to compare the use of sutures with tissue adhesive in patients who underwent surgical procedures in the development of HAPIs following these procedures. Following extensive literature review, the TriNetX database was used to compile de-identified patient information using code G0168 “Wound closure utilizing tissue adhesive only” compared to ICD-10 code Z48.0 “Encounter for attention to dressings, sutures and drains” among patients who underwent surgical procedures on the heart and pericardium using code 1006057. Patients were balanced for age, sex, and ethnicity. Across patients following these surgical procedures (n=721), there was no significant difference in risk of hospital acquired pressure injuries in patients with wounds surgically closed with tissue adhesive compared to suture closure (RR= 0.785, 95% CI= (0.511,1.205). Additionally, patients closed with tissue adhesive compared to those closed with sutures had no significant difference in the according to a Kaplan-Meier Analysis (54.231% compared to 90.038% with a p-value of 0.0878). Across patients with a pressure ulcer following any surgical procedure (n=16,390), there was a statistically significant increased risk of HAPI by 0.373% in patients with sutures compared to tissue adhesive (RR= 1.212, 95% CI= (1.039,1.426). Future studies are needed to evaluate risk factors for HAPIs following cardiothoracic surgical procedures.

0904

Distinct cellular architecture landscape predicts regenerative wound healing outcome

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The ultimate goal of tissue regeneration is re-establish its original structure and function, which requires fostering a morphogenetic competent fields including both molecular and mechanical elements. We previously demonstrated that an optimal range of wound bed stiffness is required for follicular regeneration; however, how mechanical gradient of the wound bed affects cellular behaviour and arrangements leading to different regenerative outcomes (e.g., pattern, repair vs regeneration and cell fate) is still uncertain. Using whole tissue 3D characterization and wound-induced hair neogenesis model, in early regenerative stage, we observed the formations of distinct cellular architectures resembling pre-dermal condensates and early vascular-like structures within the regenerating wound center. These structures later end up as hair primordia, blood vessels, etc., which are distinct from the more mundane cellular arrangements observed in the repairing wound margin that end up as fibrotic scar. Furthermore, these early regenerating structures are also different from their counter parts observed during development. We further showed that perturbation of cell adhesion molecules changed the number, shape and distribution of the overall cellular architecture landscape, and altered the outcome of the wound healing. This study, together with others in the literature, suggests that regenerated skin structures in the wound bed utilize diverse molecular signaling pathways (such as adhesion molecules or cytokines not used in development) to activate collective cell behaviors and achieve similar morphogenetic outcome. The cellular architecture serves as an integrated control layer, offering predictive insights into regenerative outcomes and potential therapeutic applications.

0905

Mechanisms and efficacy of home-based facial rejuvenation devices: An evidence-based review

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Recent years have seen a growing interest in improving skin appearance and reversing age-related changes, driven by an increased awareness of the impact of skin health on overall well-being and self-esteem. As individuals seek more accessible and convenient alternatives for dermatologic care, home-based devices for facial rejuvenation have gained popularity. This review aims to evaluate the safety and efficacy of home-based devices for facial rejuvenation, providing insights into their mechanisms, clinical outcomes, and levels of supporting evidence. The strength of evidence was classified according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system. Level A evidence signifies consistent results from randomized controlled trials, while Level D evidence reflects case studies or observational studies with variable outcomes. We also provided recommendations categorized as Grade I, indicating that benefits outweigh risks, and Grade II, indicating that risks outweigh benefits. Fractional laser, using the PaloVia device, earned Level A evidence and a Grade I recommendation due to its effectiveness in promoting collagen synthesis and enhancing wound healing. LED and radiofrequency home devices obtained Level B evidence and a Grade I recommendation for their ability to stimulate collagen and elastin synthesis, as well as promoting fibroblast proliferation. In contrast, microneedling home devices, which promote collagen induction and growth factor release, are not recommended for home use (Grade II) and obtained Level D evidence due to numerous reported adverse events. By understanding the strengths and limitations of these technologies, healthcare providers can provide informed guidance on the safety, efficacy, and the levels of evidence associated with these home-based devices for facial rejuvenation.

0906

Spatiotemporal molecular changes of the cutaneous wound after endothelial Sox9 inactivation

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Cutaneous expression of SRY-Box transcription factor 9 (Sox9) is tightly regulated during skin homeostasis and is re-activated in fibroblasts and endothelial cells (ECs) upon injury. Notably, EC Sox9 expression has emerged as one of the contributing factors to cutaneous and cardiac fibrosis via the endothelial to mesenchymal transition (EndMT). Abrogating Sox9 activity in ECs using the endothelial-specific Cdh5Cre^{ERT}/Sox9$^{fl/fl}$/Rosa-YFP (Sox9EKO) mouse model reduced wound scaring and improved closure rate. However, the underlying molecular mechanism remains unknown. In this study, using spatial transcriptomic profiling (10X Visium), we investigated the immune landscape and spatial molecular changes of the day 7 wildtype (Cdh5Cre^{ERT}/Rosa-YFP) and Sox9^{EKO} skin wounds. Spatial deconvolution using public wound sc-RNA sequencing datasets identified 20 major cell populations. We observed fewer C1q^{Hi} macrophages and more T cells within the EC niche in the Sox9^{EKO} wounds. In concordance, gene set enrichment analysis showed signatures of increased T cell activation/differentiation, hypoxia, angiogenesis, and apical junction. Reduced expression of inflammation signalling (e.g., type II interferon) within the EC niche has suggested a less inflammatory EC phenotype, probably due to reduced apoptosis and autophagy, contributing to reduced EndMT, evident by lower TGFβ and PDGFR signalling. Ligand-receptor analysis showed reduced Caveolin 1 (Cav1) interaction in EC spots. Cav1 is required for oxLDL uptake and was shown to induce EC stiffening upon exposure, one factor that triggers EndMT. Overall, our data indicate that changes in the immune milieu might favour a less inflammatory EC phenotype or vice versa in the Sox9^{EKO} wounds and potentially contribute to less EndMT and rapid wound closure. In conclusion, loss of Sox9 in the endothelium accelerates wounds and reduces fibrosis through the modulation of inflammation and a reduction of endothelial to mesenchymal transition.

0907

Transcription elongation factor SPT6 maintains epidermal homeostasis and suppresses skin inflammation in mice

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The development of epidermal stem and progenitor cells (EPSCs) is vital for maintaining skin homeostasis, including protection against bacterial and viral infections and prevention of water loss. Abnormal epidermal development can disrupt skin homeostasis, potentially leading to various severe skin diseases. Our previous work identified the histone chaperone SPT6, a key regulator of genomic stability, playing a crucial role in promoting epidermal differentiation and stratification by facilitating transcriptional elongation of key differentiation-inducing genes in human EPSCs. Notably, SPT6 deficiency leads to spontaneous transdifferentiation of EPSCs into intestinal-like cells due to stalled transcription of the epidermal fate master regulator P63. However, the specific role of SPT6 in epidermis *in vivo* remains poorly understood. To investigate this, we developed an inducible, epidermis specific SPT6 knockout mouse model. Five days after the final tamoxifen injection, SPT6 knockout mice exhibited severe skin abnormalities, including extensive scaly crusting, prominent neutrophilic microabscesses, delayed hair follicle development, and impaired wound healing. Transmission electron microscopy revealed partial disruption of the basement membrane, further indicating compromised skin integrity. RNA sequencing of lesional skin highlighted significant correlations between SPT6 knockout profiles and gene expression signatures associated with psoriasis and atopic dermatitis. By integrating single-cell RNA sequencing and ChIP-seq, we delineated the molecular mechanisms by which SPT6 sustains skin homeostasis. In conclusion, this study is the first to reveal that the transcription elongation factor SPT6 plays a critical role in regulating inflammation, hair follicle development, and wound healing *in vivo*. These findings provide valuable insights into the biological functions of SPT6 in skin homeostasis and open new avenues for developing therapeutic strategies to treat skin disorders, including psoriasis.

0908

Unveiling the inflammatory and cardiovascular signatures in keloid pathogenesis through multiomic analysis

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Keloids are disfiguring scars resulting from an abnormal wound-healing response, with a higher prevalence among Asian and Black populations. Despite their impact, no targeted treatments exist, likely due to a limited understanding of their pathogenesis. This study aimed to identify disease-specific molecular mechanisms through multiomic profiling of keloid serum and skin samples. Serum and lesional skin from 34 individuals with keloids and 18 healthy controls were analyzed using the Olink Proteomics assay (552 markers). Skin samples were further assessed by RNA sequencing and PCR and correlated with clinical severity metrics. Results revealed significantly (fold-change>1.3; $p<0.05$) elevated proinflammatory serum proteins, including TNF, Urokinase receptor, and LPL, immune-regulatory markers such as IL10, extracellular matrix development as MATN2, and TGF-β signaling related proteins such as BMP6. Skin biomarkers showed polar immune dysregulation with increased expression of innate (IL6), Th1 (CXCL10, CXCL11), Th2 (CCL17), and Th17 (CCL20) proteins. Additional findings included heightened Wnt activation (RSPO3 upregulated, WIF1 downregulated) and profibrotic markers (MMP2, SPARC, SERPINE1). RNASeq and PCR analysis corroborated proteomic results, and skin proteomics strongly correlated with RNA transcriptomics ($ρ=0.58$, $p<0.01$). Moreover, protein expression in skin and/or serum showed significant correlations with clinical severity metrics (e.g., keloid size was correlated with CCL20; $ρ=0.4$, $p<0.05$). This study highlights inflammatory and cardiovascular signatures in keloid skin and serum, revealing novel molecular mechanisms that could potentially inform therapeutic development.

0909

Exploring strategies to mitigate sebaceous gland cell aging

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Objective: Sebaceous glands (SGs) are essential for skin health, producing sebum that forms a protective lipid barrier to maintain hydration and defend against environmental damage. However, aging and stressors such as UV radiation compromise SG function, leading to dryness, oxidative stress, and reduced barrier integrity. This study investigates the protective effects of pterostilbene on UV-damaged SG cells and its potential for mitigating skin aging. Methods: An *in vitro* model of UV-damaged sebaceous gland cells (SG cells) was established to evaluate the effects of pterostilbene on lipid synthesis, oxidative stress reduction, and the regulation of senescence- and inflammation-related genes. Results: UV irradiation accelerated SG aging in a dose-dependent manner, reducing lipid synthesis by 10.71% and 17.50% at doses of 10 J and 20 J, respectively, while ROS levels increased to 401% and 555%. Gene expression analysis showed elevated senescence markers (p53, p16) and decreased expression of differentiation- and lipid-regulating genes (Blimp1, c-Myc, PPARγ). Pterostilbene effectively counteracted these effects, reducing ROS levels, enhancing lipid synthesis, and modulating key senescence and differentiation-related gene pathways. Conclusion: This study provides initial evidence that pterostilbene effectively mitigates UV-induced aging in sebaceous gland cells by enhancing lipid production, reducing oxidative stress, and modulating key molecular pathways, including senescence- and differentiation-related genes. These findings lay a foundation for developing targeted skincare solutions to promote sebaceous gland health and address age-related skin conditions, offering a promising avenue for anti-aging interventions.

0910

High-dimensional cutaneous and systemic immunophenotyping of prurigo nodularis reveals dysregulation of IL-6 family cytokine signaling

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Prurigo Nodularis (PN) is a chronic inflammatory skin disease characterized by severe pruritus and hyperkeratotic nodules. The role of IL-4, IL-13, and IL-31 emerged in PN, but the involvement of other cytokines in its pathogenesis is unclear. Furthermore, disease endotypes and heterogeneous therapeutic responses highlight the need to investigate immune dysregulation in PN. This study compared the circulating blood immune cells and cytokine profiles between PN patients (n=66; 44% female, 32% African American, severe itch (mean NRS >8/10), mean age 53) and healthy controls (HC) (n=21; 27% female, 14% African American, mean age 49). Immune infiltration and cytokine production were analyzed using flow cytometry (20 markers), plasma cytokine assays, and cutaneous lesional skin analysis via immunohistochemistry and imaging mass cytometry. Monocytes producing IL-6+TNF+ ($p<0.0001$) and TNF+ ($p<0.0001$) were elevated in PN vs. HC. M1 macrophages in PN exhibited increased IL-6 ($p<0.0001$) and IL-6+TNF+ ($p<0.001$), and plasma IL-6 ($p<0.01$) and TNF-α ($p<0.008$) were also higher. Skin biopsies from PN patients showed greater monocyte and M1 macrophage infiltration compared to HC. CD4+ T cells in PN expressed higher IL-31 ($p<0.01$), OSM ($p<0.001$), IFN-γ ($p<0.05$), TNF ($p<0.05$), and IL-17 ($p<0.01$). African American patients had higher CD4+ T cells producing IL-31 ($p<0.01$), TNF ($p<0.05$), and IL-17 ($p<0.01$) than Caucasians, contributing to worse outcomes. Dupilumab non-responders showed significantly higher CD4+IL-31+ expression ($p<0.01$) than responders. These findings highlight the roles of monocytes, M1 macrophages, and IL-6 family cytokines in PN pathogenesis. Targeting these components may improve treatment for various disease endotypes utilizing a precision medicine approach.

0911

A novel antagonist of transient receptor potential vanilloid 3 (TRPV3): hydroxychloroquine alleviates TRPV3-dependent atopic dermatitis

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The transient receptor potential vanilloid 3 (TRPV3) channel is closely linked to skin inflammation, yet specific and effective antagonists for clinical use are scarce. In this study, we identified the antimalarial drug hydroxychloroquine (HCQ) as a selective antagonist of TRPV3 through network pharmacology analysis. Whole-cell patch-clamp recordings demonstrated that HCQ inhibited TRPV3 channel currents with an IC50 of 51.69±4.78 mM. At the single-channel level, HCQ decreased the open probability and conductance of TRPV3. Molecular docking and site-directed mutagenesis revealed that pore domain residues are crucial for HCQ's inhibitory effect. In a mouse model, HCQ reduced carvacrol-induced epidermal thickening, erythema, and desquamation. Additionally, serum immunoglobulin E levels and inflammatory cytokines, such as tumor necrosis factor alpha and interleukin-6, were significantly lower in the dorsal skin tissues of the HCQ-treated group compared to the model group. These results suggest that HCQ may serve as a potential therapeutic agent for alleviating skin inflammation by targeting TRPV3 channel.

0912

Dupilumab unmasking cutaneous γδ T cell lymphoma through promoting tumorous T cell aggressiveness and microenvironment reprogramming

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Recent case reports suggest that dupilumab, a monoclonal antibody blocking interleukin-4 and interleukin-13, indicated for allergic disease, may unmask or promote cutaneous T-cell lymphoma (CTCL), though the mechanism remains unknown. Here, we report a rare case of a patient with a 3-year history of eczema who developed CD4+ γδ T cell lymphoma with severe peripheral blood involvement after 3 months of dupilumab. To explore the underlying mechanisms, we performed single-cell sequencing on the patient's PBMCs and treated PBMCs *ex vivo* with IL-4, IL-13, with and without dupilumab. We identified a CD4+ Vγ2/5+ Vδ1+ non-cytotoxic skin-resident T cell lymphoma involving both skin and peripheral blood. IL4R was widely expressed across all cell types, while IL13RA1 was restricted to monocytes. Dupilumab reduced IL4R expression and increased IL13RA1 expression in corresponding cell types. Notably, dupilumab significantly increased the proliferation of tumorous T cells, which exhibited a markedly higher γδ T-cell aggressive score and upregulated exhaustion markers. The interferon response pathway was enriched after dupilumab, a pathway known to be linked to aggressiveness and poor prognosis in γδ T-cell lymphoma. Further analysis of the immune microenvironment revealed that in the IL-4-treated group, CD8+ T cells under dupilumab treatment showed reduced cytotoxicity (marked by decreased GZMA, GZMB and GZMK) and increased exhaustion. Meanwhile, in the IL-13-treated group, the phenotype of CD8+ T cells remained unchanged under dupilumab treatment, consistent with the monocyte-restricted expression of IL13RA1. Additionally, dupilumab upregulated genes (S100A8, S100A9, IL15, IL1B, CD274, IDO1) in monocytes that are known to promote tumor progression. This case provides the first evidence that dupilumab promotes tumor progression in T cell lymphoma. However, whether its effects are confined to γδ T-cell lymphoma remains unknown. These findings offer novel insights into dupilumab-associated CTCL and may guide future clinical monitoring strategies.

0913

Developing an *in vitro* 3D model replicating psychologically stressed skin

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Psychological stress (PS) affects both physical and emotional homeostasis. Stress can exert multiple and deleterious wide-ranging physiologic and clinical impacts on peripheral tissues, including skin. Moreover, stress exacerbates existing skin conditions such as acne and atopic dermatitis and can accelerate the appearance of aging. One mechanism by which stress affects the skin is by weakening the skin barrier through inhibition of keratinocyte proliferation and differentiation and decreased secretion of lamellar bodies and density of corneodesmosomes. PS triggers the activation of the hypothalamic-pituitary-adrenal (HPA) axis which induces the release of stress-related neurotransmitters and hormones (e.g., the glucocorticoids cortisol/cortisone). Skin barrier dysfunction is, in part, a result of the excessive release of glucocorticoids. While much research has been conducted on individual neurotransmitters and hormones in mouse models or 2D culture systems of skin cell subtypes, less is known about changes in 3D skin-equivalent tissues or molecular changes of keratinocytes in chronically stressed human skin. Understanding the effects of PS on the skin is crucial for developing effective strategies to mitigate its impact. In this study we aim to 1) develop an *in vitro* 3D skin model to assess the effects of PS and 2) test whether topically applied actives can reduce the effects of stress on the PS skin model. The PS skin model was developed by topically applying actives targeting the cortisol pathway in formulation, followed by addition of cortisol or cortisone, the inactive form of cortisol, to the media of 3D skin-equivalent tissues (MatTek EpiDerm-FT). Consequently, we created a model to replicate some of the effects of PS through applying key stress hormones (cortisol/cortisone) to a skin equivalent 3D tissue model and identified actives that can reduce excessive cortisol release. These ingredients provide options for future skincare product development aimed at reducing the effects of PS on skin.

0914

Glucose binds and modulates the function of RNA helicases in epidermal differentiation

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RNA helicases are pivotal enzymes that regulate RNA structure and function, contributing to processes such as transcription, splicing, and translation. In this study, we uncover a novel role for glucose as a direct modulator of RNA helicase activity in epidermal differentiation. Using biochemical and biophysical approaches, we show that glucose binds to specific DEAD-box RNA helicases, altering their ATPase activity and regulating their functions. Functional studies in epidermal keratinocytes demonstrate that glucose-regulated RNA helicases is essential for proper splicing and stability of differentiation-specific genes. Our findings establish glucose as a critical metabolic regulator of RNA helicases, linking cellular energy status to RNA processing and epidermal differentiation. This study provides new insights into the interplay between metabolism and gene regulation in tissue development and homeostasis.

0915

Impact of spaceflight on cutaneous carcinogenesis: Microgravity, hypergravity, and radiation

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Space missions expose astronauts to unique stressors, including microgravity, hypergravity, and radiation. While studies have reported no significant differences in cancer-related mortality between astronauts and control populations, prolonged exposure to these conditions poses risks of genetic alterations and carcinogenesis, particularly in skin cells. This study systematically reviews the effects of spaceflight on skin cancer development, focusing on microgravity's influence on cellular behavior and molecular pathways. Our systematic review, conducted following the PRISMA-SR checklist, included searches of PubMed, Scopus, Embase, Cochrane, and Web of Science. The final analysis included 11 studies directly addressing the effects of spaceflight or simulated microgravity on dermatologic cancers. Microgravity downregulated cancer-related gene expression, such as EGF and c-fos, and disrupted cytoskeletal organization, reducing cell motility and adhesion. Studies in melanoma cells highlighted suppression of pathways like NOS-sGCMRP4/MRP5 and FAK/RhoA-regulated mTORC1, leading to reduced proliferation, motility, and metastasis. Simulated microgravity increased apoptosis via pathways involving NF-κB and DNA-damage response regulation. Lab-on-a-chip technologies demonstrated that melanoma cells under simulated microgravity exhibited reduced proliferation and increased caspase activity, underscoring their value for future research. Emerging models, including tumor spheroids and bioreactors, provide novel insights into tumorigenesis under altered gravity conditions. These findings underscore the need for further research in real microgravity settings to validate current evidence.

0916

Metabolomic and lipidomic profiling of granuloma annulare lesional skin

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Granuloma annulare (GA) is an idiopathic, inflammatory skin condition characterized by granulomatous inflammation. GA is associated with systemic metabolic dysfunction including diabetes and dyslipidemia. Moreover, immune cell metabolic rewiring within granulomatous inflammation has been shown to support granuloma formation and propagation. Despite this, there has been little investigation into immunometabolic mechanisms in GA pathology. Here, we perform metabolomics and lipidomics on skin biopsies from GA lesional skin and contralateral non-lesional biopsies from 20 subjects. We combine these data with subjects' clinical data and previously generated spatial transcriptomics data to profile metabolism in GA lesional skin. We discovered that GA lesional skin had a unique metabolic profile with significant modulation of 32/103 identified polar metabolites and 85/314 identified lipids. We discovered significant accumulation of kynurenine and loss of its receptor in GA lesional skin. Pentose phosphate pathway and purine metabolism intermediates accumulate in GA lesional skin, consistent with activation of pro-inflammatory macrophages. Lastly, there is accumulation of polyunsaturated phospholipids suggesting increased synthesis of inflammatory signaling mediators. Using this data, we aim to build a foundation for future studies on the mechanisms of metabolic regulation driving GA pathology and identify new therapeutic targets for GA and other granulomatous diseases.

0917

GABA-responsive neuronal regulation of TRPV1-mediated neuroinflammation in neurogenic rosacea

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Neurogenic rosacea is marked by vasodilation, telangiectasia, and flushing, with neurogenic inflammation central to its pathophysiology. Our previous study identified TRPV1 activation in DRG as a key driver of cutaneous neuroinflammation. While gabapentin (GBP) effectively alleviates neurogenic rosacea symptoms, its precise mechanism remains unclear. Hence, we investigated the neuroinflammatory pathways underlying rosacea using bulk RNA sequencing of skin and DRG from a rosacea mouse model. The data were analyzed through IPA and R programming, while protein analysis was conducted to validate the identified signaling pathways and GBP's therapeutic role in alleviating vasodilation. RNA sequencing revealed upregulation of Th2 pathway in skin tissues and then TLR and Th2 pathways in DRG tissues, alongside activation of a vasodilation pathway associated with GABA signaling. Notably, the IGF pathway, related to neurogenic pain, was upregulated in DRG. In induced mice, CGRP levels were elevated in the skin compared to the control group, with increased expression near CD31-positive areas correlating with vasodilation, which was reduced following GBP administration. GBP reduced CGRP expression in the skin and CGRP/NF200 in DRG, demonstrating inhibition of peripheral vasodilation. This inhibitory mechanism was linked to GBP-induced downregulation of the NF-κB-eNOS/iNOS-VIP pathway in the skin. This study reveals novel signaling pathways in rosacea and demonstrates GBP's efficacy in modulating TRPV1-mediated neuroinflammation and vasodilation, highlighting its therapeutic potential in neurogenic rosacea and related conditions.

0918

Resistance to biologics therapy in psoriasis is associated with obesity and markers of innate immunity

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Currently available biologics specifically target dermal adaptive immune molecules, such as IL-17 and IL-23, which are crucial in the pathogenesis of psoriasis. Despite their remarkably enhanced therapeutic effects compared to those of traditional anti-inflammatory systemic medications, 25-50% of patients are still resistant biologic therapy. We analyzed clinical and inflammatory factors associated with sustained response to biologics therapy. Patients with severe plaque type severe psoriasis (Psoriasis Area and Severity Index > 10 and body surface area > 10) despite conventional treatment with cyclosporine, methotrexate, acitretin, and phototherapy for longer than 3 months, and treatment with biologics for at least 24 months were included. Spatial transcriptomic analysis was performed in 6 biologic-naïve lesional skin. Among the total 87 patients included in the study, 18.4% had to switch to other biologics because of an early loss of therapeutic efficacy. Being overweight (body mass index > 25 kg/m^2) was the only clinically relevant factor. Spatial transcriptomics pathway analyses revealed enriched innate immune signaling and Th17/IL-17 signaling pathways, with significantly upregulated expression of innate immune- or neutrophil-related genes, such as TNFSF10, CXCL8, LCN2, S100A8, and S100A9, mainly in the epidermis. Enriched ligand-receptor interactions were observed in the IL-36 family of cytokines, antimicrobial peptides, and TNF signaling. Immunofluorescence analysis showed significantly enhanced protein expression of lipocalin 2, S100A8/A9, IL-36α, IL-36γ, IL-1RA, and TRAIL in the epidermis. Dysregulated innate immune responses in the epidermis and heightened neutrophil activity may be responsible for decreased sustainability of therapeutic responses to biologics.

0919

Clearance of neutrophil extracellular traps is a promising therapeutic strategy for severe cutaneous drug reactions

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We have recently reported that neutrophil extracellular traps (NETs) drive keratinocytes to undergo necroptosis, a programmed cell death, in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Considering that NETs can potentially trigger extensive epidermal death, their prompt degradation is critical for maintaining homeostasis. PMA-induced NETs were effectively degraded in the presence of sera from healthy individuals or patients with maculopapular exanthema (MPE). However, sera from SJS/TEN exhibited minimal impacts on NET clearance, suggesting impaired intrinsic NETs-degrading mechanisms in SJS/TEN. To explore the regulatory mechanism of NETs, sera were collected from acute SJS/TEN patients (n=29), MPE (n=32), DRESS/DIHS (n=19), systemic lupus erythematosus (SLE, n=5), and psoriasis (n=6) across seven institutions in Japan. The level and activity of DNase1 and DNase1-like 3 (DNase1L3), essential enzymes for NETs degradation, were significantly lower in SJS/TEN sera compared to healthy controls and other diseases. To investigate the dysregulated clearance of NETs *in vivo*, LPS was administered to wild-type mice to induce systemic NET formation. While the production and activity of DNases from their major sources (e.g., kidney, thymus, pancreas, spleen, liver, skin) remained unaffected, circulating DNase levels and activity were decreased following NET formation, which was restored by neutrophil depletion. These results imply that DNases were consumed and metabolized by NETs from the circulation. Collectively, intrinsic DNase1 and DNase1L3 physiologically regulated NETs under steady-state conditions, but they were consumed by NETs in SJS/TEN, promoting further NET formation. Current therapeutic strategies for SJS/TEN, including corticosteroids, immunosuppressants, and anti TNF-α antibodies, had less impacts on NETs. In contrast, exogenous DNase1 effectively degrades SJS/TEN sera-induced NETs, implying DNases is a promising and feasible treatment strategy for SJS/TEN.

0920

Stromal NNMT links metabolic and epigenetic drivers of fibrosis in systemic sclerosis

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Background: Fibroblasts in systemic sclerosis (SSc) show striking cellular metabolic and epigenetic changes. Enzymes mediating fibroblast activation and senescence require NAD. NAD bioavailability is regulated by nicotinamide N-methyl transferase (NNMT), which converts nicotinamide (NAM) to 1-MNAM, thereby disrupting the NAD salvage pathway and methylation donors. Since NNMT is a hub gene in SSc, and its product 1-MNAM is elevated in SSc patients, here we sought to characterize the pathogenic role of NNMT. Methods: Expression and regulation of NNMT was measured in SSc skin biopsies and explanted fibroblasts. Its pathogenic role was examined using genetic and pharmacological loss -of-function experiments in isolated human fibroblasts, 3D systems and in animal models. Results: NNMT was significantly elevated in SSc skin biopsies and localized to COL8A1^{+} fibroblasts. *In vitro*, NNMT expression and activity were stimulated by TGF-ß, and constitutively up-regulated in SSc fibroblasts. Inhibiting NNMT with a novel small molecule mitigated cellular senescence, oxidative stress and fibrotic phenotypes in healthy and SSc fibroblasts, while boosting NAD levels and H3K4 methylation. Treatment with NNMT inhibitor prevented and reversed bleomycin-induced skin fibrosis in C57/BL6 mice. NNMT-null mice showed elevated NAD and altered fibrosis. Conclusions: Upregulation of the inducible metabolic enzyme NNMT in stromal cells has a previously unrecognized role in pathological fibrosis. Thus, targeting NNMT with selective inhibitors represents an entirely novel therapeutic approach for SSc and other fibrotic diseases.

0921

Sphingosine 1-phosphate receptor 1 and 5 paradoxically regulate IL-9 and IL-13 production in atopic dermatitis

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Atopic dermatitis (AD) is a common inflammatory skin disease associated with T_H2, T_H9, and T_H22 skewing. Recent studies have identified that various lipid mediators are associated with T_H skewing. However, the relationship between the T_H skewing in AD and those lipid mediators is not fully understood. In this study, we sought to determine the lipid mediator that impacts cytokine production in AD-related T_H skewing. RNA-sequencing carried out in CD3$^{+/-}$ T cells from AD patients showed significant changes of several lipid mediator-related genes including sphingosine 1-phosphate receptor (S1PR) 5, which is one of the receptor subtypes in S1PRs. Indeed, serum S1P levels were increased in AD patients and intracellular staining using PBMCs showed that S1P treatment enhanced IL-13 and IL-9 production from CD4^{+} T cells. Our further results indicate that the S1P signal paradoxically regulates IL-13 and IL-9 production through S1PR5 and S1PR1. This is the most comprehensive profiling of bioactive lipid mediators, which impact T_H skewing, as well as the first study to evaluate the role of S1P-S1PR1/S1PR5 signaling in AD. Our results suggest that S1PR5 and S1PR1 may be therapeutic targets for controlling IL-13/IL-9-associated immunoinflammatory responses in AD.

0922

Assessing the therapeutic potential and selectivity of novel JAK PROTACs in CTCL

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Cutaneous T-cell lymphoma (CTCL) is a group of rare non-Hodgkin lymphomas driven by the proliferation of malignant, skin-homing T-cells. In advanced stages, CTCL often progresses to systemic disease, becoming fatal with no curative treatments. This highlights an unmet need for more effective, targeted therapies. The JAK/STAT signaling pathway plays a critical role in CTCL progression, making it a compelling therapeutic target. PROTACs (proteolysis-targeting chimeras) are bifunctional molecules that selectively degrade target proteins, offering a novel approach to overcoming resistance associated with small-molecule inhibitors. We conducted preclinical, *in vitro* screening of 10 newly designed JAK PROTACs by assessing cell death induction (Cell Titer Glo) in CTCL cell lines and patient-derived malignant T-cells. Cell lines MyLa, HH and HUT78 gave highly variable responses to JAK degradation, with HUT78 showing the greatest sensitivity: IC50: 67.06±33.97 nM across all 10 PROTACs. These compounds also exerted potent anti-tumor effects against patient-derived malignant T-cells, exemplified by top performers YW-JK-25 (IC50: 38.25±30.71 nM, N=4), and YW-JK-28 (IC50: 31.47±23.78 nM, N=3). To evaluate potential selectivity of action in malignant vs normal T cells (that may vary in JAK activity dependence), assays were also performed on non-malignant CD4^{+} control cells and specificity indices (SI: mean IC50 control/IC50 malignant) were calculated, with JAK inhibitor, fedratinib, used for comparison. Several JAK PROTACs demonstrated higher SI than fedratinib, with YW-JK-28 achieving SI = 30.62 vs 0.6880 for fedratinib. These findings highlight the potential of JAK PROTACs to selectively target malignant CTCL cells, providing a foundation for further investigation into their role as promising therapeutic candidates.

0923

A novel c-Rel bioassay for drug repurposing in head and neck squamous cell carcinomas

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The p63 isoform, ΔNp63α, is commonly overexpressed in human squamous cell carcinomas, including those arising in the head and neck (HNSCC). Our lab has reported that elevated levels of ΔNp63α activate and interact with NF-κB/c-Rel in primary murine epidermal keratinocytes. Furthermore, c-Rel is required for the continued proliferation seen in ΔNp63α-overexpressing primary keratinocytes under high Ca^{+2} conditions, and for orthotopic growth of lenti-ΔNp63α/v-Ras^{Ha} carcinomas. Nuclear ΔNp63α and c-Rel co-localize in the proliferating compartment of primary HNSCC. Stimulation of HNSCC cells with TNFα results in the activation and nuclear localization of c-Rel, which binds to ΔNp63α, displacing and inactivating the tumor suppressor TAp73 from ΔNp63:TAp73 complexes. Consistent with a role in growth promotion, ΔNp63α:c-Rel complexes bind a promoter motif in both human HNSCC cell lines and lenti-ΔNp63α-expressing murine keratinocytes, repressing the expression of cyclin-dependent kinase inhibitor p21WAF1. By western blot, we confirmed that TNFα stimulation enhances nuclear c-Rel localization in human HNSCC cell lines. We then designed and optimized a high-throughput screening bioassay to measure c-Rel activation under TNFα stimulation. The specificity of the c-Rel antibody was validated using CRISPR/Cas9-generated c-Rel knockout cell lines. Both 1536-well and 384-well immunofluorescence assays were developed using high-content image analysis to quantify c-Rel nuclear localization and used to evaluate compounds from the NCATS pharmaceutical collection of FDA-approved drugs. Of 2,678 compounds screened, we identified 70 inhibitors (3% hit rate). Of these "hits" 27 compounds were confirmed as inhibitors in dose-response in 384 and 1536 well assays. Other NCATS compound libraries will be screened to discover new candidate inhibitor compounds. Top candidates will undergo further investigation for drug synergy with current standard-of-care therapeutics *in vitro*, *ex vivo*, and *in vivo* to explore the possibility of repurposing drugs for HNSCC therapeutics.

0924

Biomarkers of disease severity in morbilliform drug eruption identified by skin tape strip proteomics

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Morbilliform drug eruptions (MDE) account for ~90% of cutaneous drug reactions and up to 2% of all systemic drug exposures. While most MDE cases are mild and largely skin-limited, others quickly progress to erythroderma or portend underlying systemic involvement, such as with drug reaction with eosinophilia and systemic symptoms (DRESS). Identifying reproducible MDE-associated biomarkers and differentiating severe, higher-risk cases are of critical importance. Skin tape stripping is gaining recognition as a simple non-invasive method for identifying and tracking disease biomarkers. Tape strips from lesional skin of 12 MDE cases, including 6 with DRESS and 5 with erythroderma, and matched sites of 13 healthy controls (HC) were analyzed with a multiplex proximity extension immunoassay of 368 proteins relevant to inflammation. Differentially expressed proteins (DEPs) were assessed comparing all MDE vs HC, DRESS vs HC, DRESS vs non-DRESS, and erythrodermic vs non-erythrodermic cases. A total of 126 DEPs were upregulated in MDE skin compared with HC ($p<0.05$, FDR<0.05) including those involved in Th2 responses and IL-10 and MAPK signaling. Many DEPs have been previously validated in hypersensitivity drug reactions. When comparing DRESS vs HC, 203 DEPs were upregulated in DRESS ($p<0.05$, FDR<0.05) including strong IL-4 and IL-18 signaling and cell death receptor signaling (e.g. FAS). When comparing DRESS vs non-DRESS, 121 proteins trended higher ($p<0.05$, FDR>0.05) in DRESS, including those involved in IL-4, IL-5 and IL-12 signaling, NFkB signaling, and response to wounding. When comparing erythrodermic vs non-erythrodermic skin, 168 proteins were upregulated in erythrodermic skin ($p<0.05$, FDR<0.05). DEPs spanned pathways of IL-17 signaling, NFkB signaling, programmed cell death, and VEGF signaling. In conclusion, skin tape strips were able to identify biomarkers that may prove useful in diagnosing and predicting disease severity in MDE and guiding management for these patients.

0925

REDD1/DDIT4 knockout prevents skin atrophy in aged mice

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Glucocorticoids (GCs) are the drugs of choice for treating inflammatory skin diseases in the elderly, and their use is expected to increase, despite their well-known side effects, including skin atrophy. In previous studies, we identified that mTOR inhibitor REDD1/DDIT4 plays a causative role in steroid-induced atrophy in young mice and showed that REDD1 knockout (KO) and pharmacological inhibition of REDD1 protected young mice against GC-induced skin thinning. However, the role of REDD1 in GCs-induced atrophy in aged skin is not known. We observed that chronic fluocinolone acetonide (FA) treatment in 20-month-old REDD1 KO mice induced epidermal hyperplasia, in contrast to significant epidermal thinning in WT isogenic controls. Transcriptomic analysis of FA-induced changes (2 µg, 24 h) revealed a much lower number of differentially expressed genes (DEGs; fold change > 2, $p < 0.01$) in 2-month-old REDD1 KO compared to WT males (550 vs. 1178), but in aged WT and REGG1 KO males the total number of DEGs was similar. Glucocorticoid receptor (GR) target genes involved in metabolic GC effects were induced, and genes related to proliferation and cell cycle regulation were downregulated regardless of age/genotype. Interestingly, in aged REDD1 KO mice the changes in transcriptome were shifted towards transrepression: 76% of GEGs were downregulated and the magnitude of downregulation was significantly higher than in WT animals. Gene set enrichment analysis (GSEA) identified a significant number of histone genes, including targets of Polycomb Repressive Complex 2 (PRC2) methylation, only in aged REDD1 KO mice. These findings suggest that the absence of REDD1 gene may reverse the phenotypic skin changes associated with GC-induced atrophy in aged mice, possibly through modulation of epigenetic pathways altered during intrinsic aging.

0926

Retinoids anti-ferroptosis in human epidermal keratinocytes

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Dermatology, The Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou, China Retinoids, a group of substances exhibiting retinol-like biological activity, primarily include retinol, retinal, and retinoic acid. It has been indicated that retinol and its metabolites, all-trans retinal (atRAL) and all-trans retinoic acid (ATRA), possess anti-ferroptotic effects in both neuronal and non-neuronal cell lines. Increasing evidence suggests that the progression of various skin diseases, such as psoriasis, photosensitive dermatitis, and melanoma, is associated with ferroptosis. Herein, we aimed to investigate whether Retinoids can rescue human keratinocytes from ferroptosis. We established a ferroptosis model in immortalized human keratinocyte HaCaT cells using RSL3 and assessed the anti-ferroptotic effects of seven Retinoids, including all-trans retinal (atRAL), 9-cis retinal (9-cis RAL), 11-cis retinol (11-cis ROL), retinyl palmitate (RP), retinyl acetate (RA), all-trans retinoic acid (ATRA), and all-trans retinol (Vit A). After 24 hours of co-culture, the compounds that exhibited significant anti-ferroptotic effects were further evaluated for their ability to reverse RSL3-induced lipid peroxidation and increased iron levels in HaCaT cells. Lipid peroxidation and iron levels were detected using the Liperfluo probe and FerroOrange probe by flow cytometry. The results showed that the metabolites of retinol, atRAL and ATRA demonstrated a pronounced rescue effect on ferroptosis in immortalized human keratinocyte HaCaT cells. They exerted their anti-ferroptotic effects by reducing lipid peroxidation and lowering intracellular iron concentrations induced by RSL3 in HaCaT cells. Taken together, these findings suggest that atRAL and ATRA may have potential therapeutic implications for skin diseases related to ferroptosis.

0927

Fibulin-5 enhances extracellular matrix proteins production through integrin signaling pathway in human dermal fibroblasts: A potential application of four-leaf clover extract for well-aging

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Fibulin-5 is generally known as a structural protein involved in the formation of elastic fibers in various tissues including skin. Additionally, fibulin-5 is considered as a signaling molecule regulating cell proliferation, angiogenesis, and tumorigenesis in endothelial cells. However, little is known about its signaling potential in skin, particularly in human dermal fibroblasts. We investigated the effects of recombinant fibulin-5 on the production of the three major extracellular matrix (ECM) proteins namely elastin, collagen I, and collagen IV in normal human dermal fibroblasts under normal physiological conditions. Since fibulin-5 mediates integrin signaling, we also investigated the impact of a potent integrin inhibitor, Cilengitide, on fibulin-5-induced collagen I production. The protein levels of elastin, collagen I, and collagen IV were measured by ELISA techniques following the manufacturer instructions. Fibulin-5 was found to stimulate the synthesis and release of elastin, collagen I and collagen IV in the medium of cultured fibroblasts in a concentration-dependent manner. To further elucidate the mechanism, we incubated the fibroblasts with fibulin-5 in the presence or absence of different concentrations of Cilengitide for various time intervals (24, 48, 72 hrs), followed by the measurement of collagen I. Cilengitide dose- and time-dependently inhibited the fibulin-5-induced production of collagen I. The overall data suggests that fibulin-5-integrin signaling pathway is necessary for ECM components production. Interestingly, a natural extract derived from the leaves of the four-leaf clover (Trifolium repens) was identified as a potent stimulator of fibulin-5 production in human dermal fibroblasts. Therefore, by increasing the production of collagen I & IV, and elastin via fibulin-5, the four-leaf clover extract could hold a great potential as a cosmeceutical ingredient for well-aging applications.

0928

Arsenic trioxide inhibits refractory lymphoma by targeting BCL6 and triggering degradation

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Arsenic trioxide (As_2O_3, ATO), one of the first-line anticancer drugs in clinical practice, is characterized by multi-target properties and involved in varieties of biological responses. BCL6 (B-cell lymphoma 6 protein), a transcriptional repressor and proto-oncogene, is a potential target for refractory lymphoma and IVLBCL with a typical cutaneous phenotype. It is reported that ATO downregulate the expression level of BCL6 and inhibit lymphoma. However, the mechanism is not clear. In this study, we demonstrated the effectiveness of ATO in inhibiting the proliferation of lymphoma cell lines and identified arsenic-binding proteins in two lymphoma cell lines by proteomics, in which BCL6 was identified as a key target protein. In addition, we confirmed that As^{III} directly bind to the zinc finger domain of BCL6. We further verified that ATO exerts its therapeutic effect by promoting BCL6 ubiquitination to induce its proteasomal degradation. In addition, the effectiveness of ATO for the treatment of lymphoma *in vivo* has proved through animal models. This work reveals the mode of action of the ATO in molecular level and its specificity for refractory lymphoma, and is expected to be a potential therapeutical strategy for refractory lymphoma and IVLBCL with a typical skin phenotype.

0929

Repulsive guidance molecule a expression in normal human skin cells

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Background: Repulsive guidance molecules (RGMs) gene family consists of four members, RGMa, RGMb, RGMc and RGMd. Previous studies have found that RGMs expression is limited to a few tissues and their biological functions are not well understood. RGMs are now known as key players in many fundamental processes, such as cell migration, differentiation, iron homeostasis and apoptosis, etc. However, the expression and function of RGMs in normal human skin cells has not been reported. Objective: The aim of the present study was to evaluate RGMs expression in human skin. Method: Human skin cell was derived from prepuce tissue discarded after surgery in children. Suspended melanocyte were obtained from children foreskin with two-step enzyme-digestion method and then cultured in M254 medium supplied with human melanocyte growth supplement for three passages. The keratinocyte was grown in EpiLife® medium with human keratinocyte growth supplement for three passages. The fibroblasts were harvested from human dermis tissues with the tissue explants adherent method and was cultured in DMEM supplemented with 10% fetal bovine serum supplement for three passages. The mRNA and protein levels of RGMs in melanocytes, keratinocytes and fibroblasts were detected by RT-qPCR and western blot analysis, respectively. The expression and localization of RGMs in these cells were detected with immunofluorescent staining under laser scanning confocal microscopy. Results: The results of RT-qPCR and western blot demonstrated that the expression of RGMa mRNA and protein were detected in melanocytes, keratinocytes and fibroblasts. Remarkably, the RGMb and RGMc mRNA and protein were not detected. RGMa was expressed and localized to the nucleus and membrane of melanocytes, keratinocytes and fibroblasts under laser scanning confocal microscopy. Conclusion: RGMa expression in normal human skin melanocytes, keratinocytes and fibroblasts and may play an important role in human skin physiological functions.

0930

Opsin 5 photoreceptor in human skin sensory neurons: Putative regulators of their functionality

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Background: Opsins (OPNs) are the universal photosensitive proteins responsible for visual and nonvisual photoreception in animals and are G protein-coupled receptors having a seven-transmembrane a-helical structure. OPN5 is the most recently identified opsin in the human and mouse genomes, as a UV photoreceptor, and functions for various non-visual photoreceptions. OPN5 are now known as key players in many fundamental processes, such as local light-dependent circadian clock entrainment, melanogenesis, corneal wound healing and thermogenesis response. However, the expression and function of OPN5 in in human skin sensory neurons has not been reported. Objective: The aim of the present study was to evaluate OPN5 expression in human skin sensory neurons. Method: Differentiate sensory neurons according to the previously described scheme. human induced pluripotent stem cell (iPSC)-derived nociceptive sensory neurons (hSN) in Sensory Neuron Medium. Sensory neuron differentiation was assessed using RT-PCR. The mRNA and protein levels of OPN5 in human hSNs were detected by RT-PCR and western blot analysis, respectively. The expression and localization of OPN5 in hSNs were detected with the immunofluorescent staining under laser scanning confocal microscopy. Additionally, the skin transparent method to observe the expression of OPN5 in sensory neurons in human skin tissue. Results: The results of RT-PCR and western blot demonstrated that the expression of OPN5 mRNA and protein were detected in hSNs. OPN5 was expressed and localized to the cell membrane of hSNs under fluorescence microscopy and laser scanning confocal microscopy. 3D images of intracutaneous nerve fibers (ICNFs) of entire cleared skin sample were acquired by confocal microscopy, and the images were rendered to obtain 3D structures of the nerves. The nerve branches extend more toward superficial layers in skin and OPN5 protein expression in skin sensory neurons. Conclusion: OPN5 expression in normal skin sensory neurons and may sheds new light on the skin physiology.

0931

Virtual screening of molecular compounds targeting human OPN5 protein

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Neuropsin (OPN5) is an opsin family member known to function as a photopigment responsive to wavelengths in the near UV (λmax = 380 nm). OPN5 studies started with the initial cloning of human OPN5 and mouse OPN5, regulates seasonal breeding behaviour in birds and the activity cycle, mediates photoentrainment of the retinal circadian clock and regulates vascular regression timing in mice. but also mediate light dependent melanin synthesis in humn skin melanocytes. In summary, the function of OPN5 in organ tissues has been well characterized. However, the molecular compound inhibitors of human OPN5 protein are not yet clear. This study aims to explore molecular inhibitors targeting Human OPN5 protein. To explore molecular compounds targeting Human OPN5 protein, the software used for virtual screening in this project is Schrödinger Maestro 12.8 and the 3D drawing software is PyMol. The flowchart is as follows: Download the 3D structure of Human OPN5 from the AlphaFold database (AlphaFold ID:AF-Q6U736-F1). Use Protein Preparation Wizard modules to hydrogenate, followed by energy optimization Transform. Set the box size to 20 Å x 20 Å x 20 Å with LYS296 as the center. Using Schrödinger software to perform hydrogenation, energy optimization, and other treatments on small molecule compounds, followed by virtual screening using 3D structures. Finally, we will import the prepared small molecule compounds and use the Glide module for molecular docking, where the receptor and ligand molecules dock with each other through geometric and energy matching. Our studies showed that the top five compounds(HY-W013093, Docking score: 15.547; HY-N4310, Docking score:14.329; HY-Q29623, Docking score: 2.995; HY-Q43805,Docking score:12.403; HY-Q36970,Docking score:12.327) for further research based on their docking score values. This study laid the experimental foundation for the development of OPN5 inhibitors.

0932

Thrombin-activated osteopontin is essential for granuloma formation

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Background: Non-infectious granulomatous diseases, including sarcoidosis and granuloma annulare, cause abnormal collections of inflamed immune cells or granulomas. The factors responsible for inducing granuloma formation remain to be elucidated and clinicians lack rational targeted treatments to block granuloma formation. Methods: We perform single-cell RNA sequencing and spatial transcriptomics on skin biopsies from 28 patients with granulomatous skin diseases. We use genetically engineered mice in a well-characterized *in vivo* mouse model of pulmonary granuloma formation. We delete osteopontin receptors by CRISPR in macrophage cell lines. We perform *in vitro* assays to assess macrophage function. Student's t test and ANOVA are used for statistical analysis. Results: Osteopontin is one of the highest specifically induced genes within macrophages in human skin granulomas. Mice deficient in osteopontin (n=9) exhibited reduced granuloma formation compared to wild-type mice (n=12, p=.0001). Notably, mice carrying a knock-in mutation that renders full-length osteopontin resistant to thrombin cleavage (n=12) also demonstrated reduced granuloma formation compared to littermate control mice (n=10, p<0.0001). We show that macrophages secrete full length osteopontin, which is locally cleaved by thrombin and exerts autocrine signaling specifically through the a4 integrin receptor to induce macrophage aggregation. Excitingly, two custom antibodies targeting thrombin-cleaved osteopontin reduced granuloma formation in wild-type mice (n=10 per group, p<0.001). Conclusions: Thrombin cleavage of osteopontin is necessary for granuloma formation. Thrombin-cleaved osteopontin fragments induce macrophage aggregation through a4 integrin receptor. This study highlights the underlying mechanisms of granuloma formation and may identify novel therapeutic targets against granulomatous diseases.

0933

Reprogramming of fatty acid metabolism via PPARα-orchestrated FADS2 in keratinocytes modulates skin inflammation in psoriasis

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Psoriasis is a chronic inflammatory skin disease characterized by excessive keratinocyte proliferation and disrupted immune homeostasis. The precise relationship between metabolic disturbances and inflammatory responses in psoriasis remains poorly understood. This study investigates the role of FADS2- the first and rate-limiting enzyme in PUFA biosynthesis in psoriasis and explored its underlying mechanisms. Our study revealed a marked decrease in FADS2 expression in the keratinocytes of the skin lesions from psoriasis patients and imiquimod (IMQ)-induced psoriasis mouse model. Silencing FADS2 by topical application of small interfering RNA (siRNA) in mice exacerbated IMQ-induced psoriasis-like dermatitis, accompanied by increasing the expression of neutrophil chemotaxis-related genes and neutrophil infiltration in skin lesions. In cultured human keratinocytes, silencing FADS2 elevated the expression of multiple chemokines and antimicrobial peptides. Mechanically, FADS2 suppression disrupted PUFA metabolism with an inhibition of docosahexaenoic acid (DHA) biosynthesis, thereby amplifying inflammation through the NF-κB pathway. Furthermore, we found that FADS2 expression in keratinocytes was regulated by peroxisome proliferator-activated receptor alpha (PPARα), a transcription factor involved in lipid metabolism. A reduction in the PPARα-FADS2 axis was also observed in the lesional skin of both psoriasis patients and IMQ-induced psoriasis mouse model. Enhancing FADS2 expression through PPARα activation using its agonist, WY14643, significantly alleviated psoriatic inflammation in IMQ-induced psoriasis mouse model, and inhibited pro-inflammatory mediator production in cultured human keratinocytes. These findings identify the PPARα-FADS2 axis as a key regulatory pathway in fatty acid metabolism and inflammatory responses in psoriasis. Therefore, targeting the PPARα-FADS2 axis presents a promising therapeutic approach for psoriasis management by restoring PUFA homeostasis and reducing keratinocyte-driven inflammation.

0934

Serum lactate dehydrogenase stratification allows identifying atopic dermatitis patients with predominant IL-13, IL-5 and IL-9 secretion in response to house dust mite allergen and higher prevalence of allergic comorbidities

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Lactate Dehydrogenase (LDH) is a serum biomarker that correlates with disease severity in atopic dermatitis (AD), but immune-mediated mechanisms depending on the LDH levels are poorly characterized. Circulating CLA^+ T cells constitute a memory subset involved in cutaneous immune responses that reflect skin abnormalities in AD, and they are linked to several biomarkers and targeted therapies. Here, we studied the effector function of memory CLA^+ T cells in AD patients in relation to high or low serum LDH levels. To this end, 56 non-treated moderate-to-severe adult AD patients were stratified into LDH^H (LDH>206 kU/L) or LDH^L (LDH>206 kU/L) according to the median levels of LDH detected in blood. Memory $CLA^{+/-}$ T-cell response, in the presence of autologous lesional epidermal cells activated with house dust mite (HDM), was compared between groups. CLA^+ memory T cells, rather than CLA^-, showed significantly higher levels of IL-13, IL-5 and IL-9, but not IL-4, IL-17A, IL-22, IL-31 nor IFN-γ, in LDH^H than LDH^L patients and controls. Interestingly, no differences were found using staphylococcal enterotoxin B (SEB) as stimulator in the same cohort. LDH^H patients were younger, exhibited higher disease severity and eosinophilia, and total, HDM- and SEB-specific IgE plasma levels compared to LDH^L. Of note, the number of AD patients with allergic rhinitis and conjunctivitis was significantly higher in LDH^H. Our results highlight that serum levels of LDH distinguish AD patients with distinct immunological and clinical features, which may be of help to stratify patients for directed therapies.

0935

Unravelling the role of JAK3/TEC kinase signalling with ritlecitinib in alopecia areata lesional skin and alopecia areata-induced human hair follicles *ex vivo*

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JAK3/TEC signalling is clinically relevant in alopecia areata (AA). Ritlecitinib is an FDA-approved inhibitor of JAK3/TEC signalling. JAK3/ TEC family kinases regulate T-cell activity by acting downstream of cytokines such as IL-2 and T-cell receptors (TCR), respectively. Here we aim to further dissect their role in AA pathogenesis. TCR activation in healthy hair follicles (HFs) with αCD3/αCD28+IL-2 significantly up-regulated intra- and peri-follicular T-cell numbers, and proliferation, and enhanced secretion of cytokines, including the key AA pathogenic factor IFNγ, and the cytolytic molecules perforin, granzyme A and B, granulysin, and FasL. Furthermore, it significantly increased bulbar MHC class I and ectopic MHC class II expression in the outer root sheath. All these effects were prevented by ritlecitinib 2μM treatment. Qualitative analysis of chronic lesional AA compared to healthy scalp skin showed increased intra- and peri-bulbar pSTAT5+CD3+, pSTAT3+, and pSTAT6+ cell numbers (JAK3 signalling) along with more CD8+GranzymeB+ T-cells. IRF4 expression, a downstream target of TCR-TEC, was also increased in the HF epithelium and in infiltrates around AA HFs. In lesional AA skin, under re-stimulation with αCD3/αCD28+IL-2, ritlecitinib decreased follicular and perifollicular pSTAT3+ cell numbers and IRF4+CD3+ cell numbers as well as percentages amongst CD3 cells. Thus, JAK3/TEC signalling is active in lesional AA skin and can be inhibited by ritlecitinib treatment. This, together with the ability of ritlecitinib to interfere with αCD3/αCD28+IL-2-induced peri-follicular T-cell expansion and HF immune privilege collapse in HFs *ex vivo*, highlights the clinical mechanism by which JAK3/TEC inhibition reduces symptoms of AA.

0936

Flavin-containing monooxygenase 3 (FMO3) is the achilles heel in the TMA-TMAO metaorganismal pathway linking the gut and skin fibrosis

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Intestinal bacteria generate aliphatic amine trimethylamine (TMA), which in the host is converted to trimethylamine N-oxide (TMAO), an enzymatic reaction catalyzed by FMO3 primarily in the liver. This metaorganismal axis linking dietary precursors, microbial metabolism and bioactive TMAO, is implicated in metabolic and cardiovascular diseases. Because we showed that TMAO is elevated in patients with systemic sclerosis (SSc), the present study sought to explore pathogenic role of FMO3 and TMAO. The effect of FMO3-derived TMAO, and of FMO3 silencing, on fibrotic responses was examined in fibroblasts and endothelial cells. FMO3 was quantified in SSc skin biopsies and explanted skin fibroblasts. Fibrosis and inflammation were examined in FMO3-deficient mice. TMAO induced fibroblast activation via ER stress-mediated PERK/ eIF2α/ATF4 signaling, and endothelial-mesenchymal transition. Silencing FMO3 attenuated fibro-inflammatory responses in human fibroblasts and activated PERK. SSc skin biopsies and explanted skin fibroblasts showed elevated FMO3 protein and mRNA expression, which colocalized with markers of ER stress and elevated collagen gene expression. FMO3 deletion in mice led to a decrease in circulating TMAO levels but no spontaneous phenotype. However, FMO3-null mice showed significantly reduced fibro-inflammatory responses and ER stress in a bleomycin-induced multi-organ disease model. FMO3, which catalyzes production of profibrotic TMAO from intestinal microbiome-derived precursor TMA, showed aberrant expression in dermal stromal cells in SSc. Loss of FMO3 markedly attenuated fibrosis *in vitro* and *in vivo*. These results for the first time implicate FMO3 as a novel vulnerability in pathological skin fibrosis and a potential target for treatment of SSc.

0937

Epithelial-mesenchymal transition and immune exclusion underpin the natural history of primary cutaneous melanoma

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Although outcomes in primary melanoma are chiefly dictated by Breslow depth, the pathways through which thicker tumors predispose to metastasis and recurrence are poorly described. This translational study leveraged complementary omics modalities (Visium spatial RNAseq, Chromium single-cell RNAseq, and CODEX spatial protein profiling) on multiple primary melanoma cohorts to characterize the natural history of thin versus thick melanoma. We first generated a single-cell dataset for primary cutaneous melanoma from Cohort A (Chromium, n = 50) - currently the largest single-cell reference for primary melanoma in the literature. This was employed for cell type deconvolution in our transcriptomics cohort. On pseudobulked GSVA of Cohort B (Visium, n = 101), thick primary tumors (>1mm Breslow depth) demonstrated enrichment of EMT- (BH-adj p: 0.019) and E2F-associated gene sets(adj p: 0.008) in melanoma spots as compared to thin tumors. Thick tumors exhibited an immune-excluded phenotype relative to thin tumors, with a lower ratio of intra-tumoral:peri-tumoral lymphocytes (adj p: 0.017) and a higher median NN distance between tumor cell-T cell pairs (adj p: 0.037). Ligand-receptor analyses indicated greater spatial interaction between immunosuppressive gene pairs in thick versus thin melanomas (CD163-TWEAK, adj p: 0.001; CD160-HVEM, adj p: 0.042). These features persisted in T1b vs T1a melanoma in Cohorts C (Visium, n = 54) and D (CODEX, n = 6), suggesting that phenotypic delineation by tumor thickness is present from the earliest stages of the disease. On Cox regression. EMT enrichment (aHR: 2.83; p: 0.007), E2F enrichment (aHR: 2.19; p: 0.032), and T cell exclusion (aHR: 2.56; p: 0.025) were each correlated with lower recurrence-free survival in Cohort B (min. 7y follow-up). These spatially derived metrics capture biologically relevant tumor features that may partially mediate the association between tumor stage and recurrence in primary melanoma.

0938

Casearia sylvestris extract and hymenaea courbaril extract (Jatobá) suppresses UVB inducted premature cellular senescence in human dermal fibroblasts

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The skin is the organ constantly exposed to various stimuli that influences its morphology and function. Skin aging can be categorized as intrinsic, a natural process driven by chronological time, and extrinsic, influenced by environmental factors such as sun exposure. UV radiation is the primary accelerator of premature aging, causing oxidative damage and DNA harm, which induces cellular senescence. Senescent cells are characterized by reduced proliferation, resistance to apoptosis, and the secretion of factors that promote inflammation and tissue deterioration, known as senescence-associated secretory phenotype (SASP). These cells accumulate with age, contributing to the changes in the skin associated with aging. The SASP plays a pivotal role in chronic skin inflammation, as it exhibits a modified secretome that includes pro-inflammatory cytokines, chemokines, proteinases, and growth factors, which significantly alter the skin microenvironment. In the present study, 44 molecular targets were evaluated for their capacity to identify the senescent state in prematurely aged cells. Primary human dermal fibroblasts were irradiated for 4 consecutive days with UVB radiation, totaling 1J/cm2. A real-time RT-PCR assay, followed by protein quantification, was conducted to assess the potential of the ingredients in preventing premature senescence within this *in vitro* model. Gene expression analysis was performed using IPA (Ingenuity Pathway Analysis) software, and the activation of biological pathways was evaluated. The results demonstrated that the Casearia and Jatobá extracts effectively inhibited the activation of the Senescence pathway, as well as the signaling pathways of IL6, IL8, and STAT3, by suppressing the gene expression of their key markers: CDKN1A, CDKN2A, IL1α, IL1β, IL6, and IL8. This effect was corroborated by protein expression analysis, revealing a gene expression profile similar to those non-senescent cells when compared to UVB-induced senescent cells.

0939

Discovery and validation of nanobody antagonists to the itch receptor MRGPRX2 using AlphaFold-Multimer

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The purpose of this study was to investigate if in silico antibody screening methods could identify high-affinity antibodies to a cellular surface receptor. VHH antibodies, also known as nanobodies, are single-domain antibodies naturally derived from camelids but which can be humanized and have recently received FDA approval. The smaller size and biochemical stability of nanobodies offer certain advantages, such as increased tissue penetration, relative to conventional antibody biologics. We computationally screened 10,000 nanobodies against the G protein-coupled receptor (GPCR) MRGPRX2, a promising target for the treatment of itch and chronic spontaneous urticaria. Based on our in silico confidence metrics, we selected ten nanobody candidates to purify and biochemically evaluate. Our results show that 3/10 nanobodies exhibited nanomolar affinity for MRGPRX2. Binding affinity was tested on both ROSA mast cells at endogenous receptor levels and on HEK293T cells overexpressing MRGRPX2 relative to cells lacking receptor. We validated that these nanobodies are apparent physiological antagonists through various approaches. Pretreating mast cells with the three nanobodies resulted in a significant reduction in agonist-induced mast cell degranulation ($p<0.05$, one-way ANOVA) as well as a rightward shift in EC50 and reduced Emax in G protein activation relative to control non-binding nanobodies ($p<0.05$, two-way ANOVA). Structural predictions suggest that the three nanobodies block the MRGPRX2 orthosteric binding pocket, which was supported by mutagenesis studies. Our results demonstrate a computational antibody discovery pipeline for a GPCR that can effectively bypass certain laboratory experiments.

0940

Assessing the preclinical potential of the selective p38δ silencing in human skin organoids (HSO) and *ex vivo* human skin explant model of atopic dermatitis.

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p38δ genetic deletion caused an inflammatory skin phenotype in an irritant contact dermatitis mouse model. However, the p38δ role in atopic dermatitis (AD) pathophysiology remains unexplored. To circumvent the lack of selective p38δ inhibitors, we employed a rationally designed hydrophobic conjugate docosanoic acid (DCA)-linked fully chemically stabilized small interfering RNA (siRNA) approach to silence p38δ in HSO and *ex vivo* human skin explant model of AD. *In vitro* screening identified two lead siRNAs, si-p38δ-1 and si-p38δ-2, that yielded the highest p38δ knockdown (KD) efficacy and potency versus the non-targeting control. DCA-si-p38δ-1- and -2-mediated p38δ KD in HSO disrupted epidermal morphogenesis and caused marked epidermal hyperplasia during the early stages of the organotypic epidermal development and hyperkeratosis at later stages, as well as gross tissue disturbances and aberrant filaggrin and desmoglein 1 expression patterns. Next, we efficiently silenced p38δ in *ex vivo* human skin explants using intradermal injections of DCA-si-p38δ-1 and -2 in the absence and presence of T_H2 (IL4+IL13) cytokine stimulation. Remarkably, p38δ expression was significantly upregulated by the T_H2 cytokine treatment. Multiplex chemokine/ cytokine array and bulk RNA sequencing data showed dysregulation of expression of genes related to epidermal inflammation, differentiation, lipid storage and transport, iron homeostasis and transport, and glycoprotein biosynthesis and metabolism upon p38δ KD in unstimulated and T_H2 cytokine-stimulated *ex vivo* skin. These data support the p38δ role in epidermal morphogenesis and differentiation and in regulating AD-like inflammatory responses in human skin. Furthermore, the siRNA drug approach outlined in this work provides novel opportunities to modulate other disease targets in the skin.

0941

Disulfiram induces immunogenic cell death in merkel cell carcinoma

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Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine skin cancer. Although immune checkpoint inhibitors are approved for the treatment of advanced MCC, less than half of patients achieve durable benefit. Therefore, new treatments are needed for MCC. Accordingly, we conducted a high-throughput drug screen of approximately 4,000 small molecules and identified disulfiram, an aldehyde dehydrogenase inhibitor approved for alcohol use disorder, as an agent that selectively reduced MCC cell viability. We found that complexing disulfiram with copper increased its potency, and treatment with disulfiram plus copper caused induced non-apoptotic cell death. Interestingly, this drug combination led to the expression of the ER marker calreticulin on the surface of MCC cells and the release of the nuclear protein high mobility group box 1 (HMGB1) and ATP from cells, suggesting that disulfiram plus copper induces immunogenic cell death in MCC. Taken together, our data supports the repurposing of disulfiram plus copper for the treatment of MCC as a way to enhance responses to immunotherapies with the potential to generate anti-tumor immunity.

0942

Beyond the binary: NOA-104 as a novel modulator of the aryl hydrocarbon receptor for the treatment of inflammatory skin diseases

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Immune diseases involving barrier dysfunction, such as atopic dermatitis, psoriasis, or inflammatory bowel disease are characterized by a high degree of heterogeneity with chronic and sustained inflammation driving dysfunction of protective epithelial barriers. The aryl hydrocarbon receptor (AhR), a regulator of tissue homeostasis, has been demonstrated to induce differential transcriptional profiles and therapeutic pathways by different ligands to coordinate inflammatory signalling and repair barrier function. Herein, we describe a novel AhR modulating small molecule, NOA-104 for the treatment of inflammatory dermatological barrier diseases. Designed to more comprehensively modulate AhR to initiate a tailored signalling response, NOA-104 restores barrier function and resolves inflammation in pre-clinical models of atopic dermatitis. Through RNAseq, the NRF-2 pathway was demonstrated to be modulated alongside AhR in human keratinocytes. When challenged with menadione, NOA-104 treatment was demonstrated to reduce ROS induction in human keratinocytes. NOA-104 treatment on human keratinocytes induced with IL4/IL13 increased the genetic expression of filaggrin equivalent to a mechanistic competitor, while simultaneously reducing the gene expression of stat6 more effectively. In an MC903 murine model, NOA-104 treatment rapidly resolved scratching time ($p < 0.01$) and occurrence ($p< 0.001$) within 3 days of initiating treatment, while increasing gene expression of the barrier function protein filaggrin ($p <0.05$). Further, NOA-104 treatment significantly reduced gene expression of TH2-driven biomarkers, including IL-4 ($p<0.01$), IL-13 ($p<0.05$), and stat6 ($p<0.001$), more effectively when compared to a leading mechanistic competitor. These studies demonstrate the translation of *in vitro* to *in vivo* efficacy of NOA-104, supporting potential advancement towards the clinic; further work to follow.

0943

WITHDRAWN

0944

WITHDRAWN

0945

Single cell rna sequencing reveals differential dendritic cell subtypes in early vs. late-stage mycosis fungoides disease

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In the tumor microenvironment of mycosis fungoides (MF), dendritic cells (DC) play a dual role in promoting and restraining disease progression; however, DC subtypes in MF disease are not well-defined. Immature DCs expressing DC-SIGN/CD209 have been shown to be highly expressed in late-stage MF and are associated with T-cell tolerance. To identify DC subtypes, single-cell RNA sequencing techniques were applied to dissociated skin tissue from one unaffected patient, two early-stage, and two late-stage MF patients. 1138 dendritic cells were identified using canonical gene markers. Analysis of the top 3000 most highly variable expressed genes revealed four DC subclusters. The top 5 DEGS per subcluster and gene ontology analysis identified clusters 0, 1, and 3 as conventional DCs (cDC) and cluster 2 as plasmacytoid DCs. Cluster 0 was identified as a mature, partially activated cDC population ($CD14^{+}/CD83^{mid}$) and was decreased in all MF patients compared to the control sample. Cluster 1 was identified as an immature, inactivated cDC population ($CD14^{+}/CD83^{low}$) and was increased in early-stage MF patients. Cluster 3 was identified as mature/fully activated cDCs ($CD14^{+}/CD83^{high}$) and was more prominent in MF patients than in the control group, with an increased number in early-stage MF. Interestingly, Cluster 3 had significant gene expression of DC-SIGN/CD209 ($log2FC = 2.1$, $p = 2.16E^{-18}$), suggesting this mature DC cluster may be responsible for MF disease progression. Further defining DC subtypes by MF stage will provide new insights into disease progression.

0946

Metformin as an early intervention for melanocyte senescence via autophagy-redox balance

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Melanocyte senescence predominantly occurs in aging skin and represents a critical target for addressing skin aging and pigmentary disorders. Single-cell transcriptomics and time-course analyses revealed dynamic changes of autophagy regulation during early and late stages of UV-induced melanocyte senescence. A reduction in ATG7 was a key event preceding full melanocyte senescence. The ATG7 knockdown induced premature senescence, characterized by elevated reactive oxygen species (ROS) levels. In contrast, glycolysis pathways were significantly upregulated only in fully senescent cells. Metformin treatment restored autophagic activity, including ATG7 expression, and mitigated oxidative stress, thereby delaying senescence. These findings suggest that targeting the interplay between autophagy and oxidative stress could provide a novel early intervention strategy for melanocyte aging.

0947

Generation of hidradenitis suppurativa keratinocyte models using a novel CRISPR editing approach

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Hidradenitis suppurativa (HS) is a chronic inflammatory condition with recurrent flaring of painful, draining abscesses, nodules, and sinus tracts. HS is an underdiagnosed disease with the lowest quality of life measurements among common dermatologic conditions. Therefore, new methods of diagnosis and treatment must be developed to improve early identification and treatment stratification for HS patients before the progressively heavy disease burden can exact its toll. There is a lack of disease models for HS, resulting in gaps in our understanding of the pathogenesis of the disease. Previous genome-wide linkage analyses have demonstrated connections between the genes that code for the γ-secretase complex (GSC) and HS. As a result, our research focused on producing, to our knowledge, the first isogenic keratinocyte cell line models with wild-type and HS patient-specific GSC mutations. Our methodology employed a recently reported minimal promoter-fluorescent protein cassette, which can be embedded within an adjacent intron of a target gene, producing log-fold improvements in the enrichment of CRISPR-edited cells. We report further refinements to this approach, including implementing site-specific recombinase technology to allow near-scarless editing. Here, we demonstrate the successful incorporation of the fluorescent protein cassette into the introns of GSC genes and the identification of edited clones via fluorescence-activated cell sorting (FACS). Through sequential targeting of alleles, cell lines with homo- or heterozygous HS-associated missense mutations in keratinocytes can be achieved. Our project aims to facilitate HS pathogenetic research by providing novel *in vitro* disease models and demonstrating a streamlined approach for the rapid generation of *in vitro* disease models for other dermatologic conditions.

0948

Investigating cell of origin of merkel cell carcinoma, a historic misnomer

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Merkel cell carcinoma (MCC) is a highly aggressive skin cancer with the poorest prognosis, posited to be derived from Merkel cells. Emerging evidence, however, suggests other potential origins for MCC, including hematological lineages. Given the high fatality of MCCs and their prevalence in immunosuppressed populations, it is important to determine the cell of origin for these cancers to elucidate targetable pathways and enable novel treatment strategies. We utilized targeted and multi-omics approaches to explore expression patterns at both the protein and RNA level of MCCs. Western blotting, immunofluorescence and immunohistochemistry were performed for two patient-biopsied MCC samples, one MCC cell line (MS-1), and 92 FFPE MCC samples, respectively, for several B-cell markers. RNA sequencing of 17 FFPE MCC samples was conducted to determine differentially expressed genes based on patient factors, identify gene co-expression networks and evaluate tumor cell enrichment. We observed heterogeneous interindividual expression of B-cell and neuroendocrine markers, including PAX5, TdT, IgA, CD19, CK20 and chromogranin A. Transcriptome analysis demonstrated differentially expressed genes based on sex and Merkel cell polyomavirus (MCPyV) status, with MCPyV+ tumors having upregulation of pathways involved in immune cell function and downregulation of those related to neuronal activity. Co-expressed gene networks highlighted enrichment of pathways involved in immune function, including B-cell differentiation, while cell type analysis highlighted enrichment for multipotent stem cells, several immune cell types, and keratinocytes. Our findings indicate that MCCs are not derived from Merkel cells and instead from multiple or divergent cell types, including those of B-cell lineage. Further, MCC cell of origin may depend on patient and tumour specific characteristics, including sex and cell type/differentiation state of MCPyV+ tumors. Our work highlights significant variability in the molecular landscape of MCCs and merits a precision medicine approach to their characterization and treatment.

0949

Biologics targeting OX40 and OX40L for treatment of atopic dermatitis have distinct inhibitory binding mechanisms

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Atopic dermatitis (AD) is a chronic inflammatory skin disorder affecting ~200 million individuals worldwide, with children and adolescents commonly affected. Although AD pathogenesis is multi-faceted, the heterotrimeric immune checkpoint molecules OX40 and OX40L play a critical role. Recent clinical trials demonstrated the OX40-targeting antibodies rocatinlimab (KHK4083/AMG-451) and telazorlimab (GBR-830/ISB-830), as well as the OX40L-targeting antibody amlitelimab (KY1005), significantly improve AD signs and symptoms. However, the structural mechanisms of how these antibodies disrupt downstream OX40-OX40L signaling, such as antibody epitope properties, remain unknown. Thus, we computationally modeled the antibody-protein complexes and biochemically characterized their binding interfaces. We performed molecular dynamics simulations to evaluate antibody-target complex stability. The cognate OX40-OX40L heterotrimeric complex has two distinct OX40-OX40L interaction interfaces, as well as a symmetric OX40L-OX40L interface. Rocatinlimab is predicted to have 37% overlap with the two OX40L binding sites, binding the highly conserved OX40 residue T85. Contrarily, telazorlimab showed minimal overlap with the OX40L binding sites but disrupted the critical salt bridge between R65 of OX40 and E82 of OX40L. Amlitelimab demonstrated 75% overlap with one of the OX40 binding sites, where it binds the highly conserved OX40L residue N166, as well as 16% overlap with the physiologic OX40L trimer interface. Our results provide initial prediction and analysis of the epitopes of OX40 and OX40L targeted biologics emerging for AD treatment. Rocatinlimab and amlitelimab appear to directly inhibit OX40-OX40L interactions via steric occlusion, with amlitelimab also possibly inhibiting OX40L trimer formation, whereas telazorlimab more specifically disrupts a critical intermolecular interaction.

0950

Exploring hair aging through *ex vivo* induction of DNA damage and senescence

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In hair follicle (HF) aging hair density and thinning occur, caused by prolonged telogen and/or catagen phases and HF miniaturization. While models for extrinsic aging exist, there is a lack of models for intrinsic cell aging mechanisms such as DNA damage, repair defects, and cellular senescence. Here, we investigated whether the DNA-intercalating nucleotide BrdU, known to induce intrinsic skin aging *ex vivo*, could similarly affect aging and senescence in human HFs *ex vivo*. Microdissected HFs from 3 healthy donors were treated with different BrdU concentrations (10µM-1mM) and analyzed by quantitative (immuno-) histomorphometry. None of the tested concentrations increased LDH release or melanin clumping. Instead, BrdU increased the number of cells expressing the DNA damage marker γH2AX or the cell cycle inhibitor p21. Furthermore, BrdU tendentially enhanced expression of the senescence-associated secretory phenotype indicator CXCL10. Most of these effects occurred in a dose-dependent manner in the HF epithelium. Next we assessed how these changes would translate into HF function. BrdU inhibited hair shaft production and reduced hair shaft quality, demonstrated by a significantly and tendentially decreased pre-cortical hair matrix (HM) expression of Keratin 85 (K85) and K86, respectively, and significantly lower levels of keratin associated protein 3.3 (KRTAP3.3) in the inner root sheath. Furthermore, BrdU induced premature catagen development accompanied by a significant reduction in the hair cycle score and HM keratinocyte proliferation (Ki-67$^+$ cells). Our findings show that BrdU accelerates intrinsic aging and senescence in human HFs *ex vivo* without causing cytotoxicity. Additionally, our assay serves as a tool to study chronological aging mechanisms and test potential senolytic compounds, potentially reducing HF aging also *in vivo*.

0951

Breezula, a clinical stage topical anti-androgen, promotes dermal papilla inductivity and reduces IL-6 secretion in balding skin samples *ex vivo*

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Male pattern hair loss (MPHL), the most prevalent form of hair loss in men, is marked by decreased anagen/catagen-telogen ratio and hair follicle (HF) miniaturization in the frontal/vertex scalp. It is primarily driven by increased androgen receptor (AR) activity in the dermal papilla (DP), impairing DP inductivity and consequently hair matrix (HM) keratinocyte proliferation. The AR antagonist Breezula® (clascoterone 5% solution) is currently being clinically tested for MPHL management. Here, we compared its efficacy *ex vivo* with the FDA-approved drug Minoxidil (5%). Biopsies from balding scalp of 5 MPHL patients (Hamilton-Norwood scale III-VI) were subjected to a clinically relevant testosterone concentration *ex vivo*. Following a 24-hour resting period, Breezula® or Minoxidil were topically applied every other day for 5 days. Microscopic hair cycle analysis confirmed the clinical MPHL diagnosis, revealing high percentages of telogen/catagen HFs and the presence of intermediate HFs. Analysing DP inductivity, versican expression remained relatively unaffected by Breezula® or Minoxidil treatment, whilst both enhanced AP activity, particularly in terminal anagen HFs. AP activity is positively correlated with Wnt pathway activation, promoting HM keratinocyte proliferation and hair growth. Consistently, we observed a significant increase in HM keratinocyte proliferation in anagen HFs from at least 2 patients following treatment with both Breezula® and Minoxidil. Additionally, Breezula® reduced the secretion of the hair growth inhibitor IL-6, reported to be up-regulated in balding DP cells, after 5 days of culture, whereas Minoxidil did not exert a clear effect. Our data suggest that Breezula® restores DP inductivity and promotes HM keratinocyte proliferation to a similar extent as Minoxidil while its effect in reducing IL-6 secretion may indicate a greater potency for promoting hair growth, warranting further investigation.

0952

Spatial transcriptomics reveal compartmentalized dysregulation of lipid metabolism in acne vulgaris

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Multiple observations suggest that increased sebaceous lipid synthesis and altered sebum composition contribute to lesional formation in acne vulgaris. However, the signaling pathways by which keratinocytes sense and respond to sebaceous lipids, as well as the epithelial compartments that become perturbed during disease, remain incompletely defined. To study the role of sebaceous-keratinocyte crosstalk in acne vulgaris, we performed Xenium in situ transcriptomics on punch biopsies from patients (comedonal, pustular, and non-lesional) and healthy controls. We find that sebocytes in acne comedonal skin show a transcriptional signature associated with increased sebaceous lipid production ($FASN^{high}AWAT2^{high}$), decreased synthesis of glycosphingolipids ($FA2H^{low}$), and upregulated growth factors and inflammatory mediators ($CXCL8^{high}TNF^{high}$). By contrast, in acne pustular lesions, sebaceous lipogenesis is suppressed, suggesting the inflammatory milieu of the acne pustule leads to a localized, temporary shutdown of sebum production. We also demonstrate that epidermal and upper hair follicle keratinocytes in acne lesions have a hyper-keratinizing phenotype ($KRT10^{high}$) and demonstrate resistance to retinoid signaling as manifested by decreased retinoid receptor expression ($RARG^{low}RXRA^{low}$) and increased expression of fatty acid binding protein 5 (FABP5), which shuttles fatty acid ligands away from retinoid receptors and toward peroxisome proliferator-activated receptors (PPARs). In human N/TERT keratinocytes, we probe the effects of specific sebaceous lipids on FABP5 expression and signaling. Overall, our results suggest a model in which sebum dysregulation promotes retinoid resistance and hyper-keratinization in acne lesional skin.

0953

Double knockdown of DKK1 and SFRP1, two key players in androgenetic alopecia, does not accelerate the hair-growth promoting effect of individual SFRP1 knockdown in healthy human hair follicles *ex vivo*

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Androgen receptor (AR) signaling plays a key role in male pattern baldness. Here, we investigates the potential of targeting multiple AR-regulated genes as a therapeutic approach for hair loss management. AR mRNA and protein were identified in the dermal papilla (DP), dermal cup (DC), and proximal outer root sheath (ORS) of human hair follicles (HFs) *ex vivo*. AR knockdown (KD) reduced AR mRNA (qPCR) and protein (IF) levels; however, it did not sustain the anagen phase. Notably, AR KD decreased the mRNA levels of Wnt modulators SFRP1 and DKK1. SFRP1 mRNA was detected in the DP and ORS, with its protein expressed in the DP and hair matrix (HM). Meanwhile, DKK1 mRNA was found in the distal ORS and connective tissue sheath, with protein present in the DC. This distinct localization suggests that simultaneous targeting of these AR-regulated genes may yield additive or synergistic effects on HF function. Supporting this, siRNA-mediated DKK1 KD resulted in a compensatory upregulation of SFRP1 mRNA in HEK239 cells, and SFRP1 KD triggered an increase in DKK1 mRNA in DP cells *in vitro*. To further explore this interaction, combined and single siRNA KD of DKK1 and SFRP1 was performed in human HFs *ex vivo*. While KD was confirmed at both mRNA (qPCR) and protein (ELISA) levels, only SFRP1 KD prolonged the anagen phase, significantly increased HM keratinocyte proliferation, and reduced apoptosis. The combination of SFRP1 and DKK1 KD did not enhance the effetcs observed with SFRP1 KD alone. Interestingly, SFRP1 KD induced a compensatory upregulation of DKK1 expression at both mRNA and protein levels, an effect not observed with DKK1 KD. These findings reveal a culture system-dependent regulatory interaction between DKK1 and SFRP1, emphasize the complexity of modulating Wnt signaling for anagen phase maintenance, and underline the therapeutic potential of SFRP1 as a target for addressing hair loss.

0954

MPZL3 is a novel, therapeutically targetable mitochondrial regulator of human sebaceous gland homeostasis and function

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Both, PPARg and the mitochondrial protein, Myelin Protein Zero-like 3 (MPZL3), are known regulators of murine sebaceous gland (SG) homeostasis, while MPZL3 GKO and PPARg KO mice show a similar SG phenotype. Yet, the function of MPZL3 in human SG physiology and if PPARg signaling is upstream or downstream of MPZL3 remain unknown. To clarify this, we have co-administered the PPARg agonist, AGED, with MPZL3 siRNA or non-targeting oligos (NTO) in human SG organ culture. MPZL3 knockdown (KD) *ex vivo* significantly increased the % of $PPARg^+$ sebocytes, the differentiation of $Blimp1^+$ sebocyte progenitors, and stimulated the production of neutral lipids. Co-administration of AGED with NTO significantly reduced the expression of MPZL3 within SGs, which was further reduced when siMPZL3 was co-administered with AGED, suggesting that PPARg is upstream of MPZL3 and negatively regulates its expression. The % of PPARg+ cells in the central and peripheral zone of SGs was increased in SGs treated with siMPZL3+AGED compared to NTO+AGED. Thus, MPZL3 signaling may also be part of a negative feedback loop that downregulates PPARg expression. Moreover, the % of proliferative sebocytes in the SG's peripheral zone is significantly reduced in siMPZL3+AGED compared to NTO+AGED-treated SGs, indicating that sebocyte differentiation is more prominent in when MPZL3 is silenced. Lipid/sebum production *ex vivo* was also significantly enhanced after MPZL3 silencing in the presence of PPARg stimulation, as shown by increased SG protein expression of perilipin-2 and fatty acid synthase expression. Our study identifies MPZL3 as a novel mitochondrial regulator downstream of PPARg that negatively controls human SG function and lipid production. Therefore, MPZL3 agonists deserve to be explored as therapeutics for disorders characterized by seborrhea and/or SG hyperplasia.

0955

Selective BET inhibition as potential hidradenitis suppurativa treatment

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Bromodomain and extraterminal (BET) proteins regulate immune-related gene expression. Here we assessed the effects of a 3rd generation BET inhibitor (DC-9476, DC) on the Hidradenitis suppurativa (HS) phenotype *in vitro* and *ex vivo*. Treatment of PBMCs from 3 healthy donors (HD) and 3 HS patients with DC (0.03-3µM) for 24h decreased CCL2, GM-CSF and TNF-α secretion in all groups. DC also lowered $CD8^+$ T-cell numbers in HS PBMCs but did not affect $CD4^+$ T-cells, monocytes and B-cells. *Ex vivo* analysis of nodule- or fistula-containing lesional skin vs peri-lesional skin from 3 HS patients showed increased MKI67 expression in nodule-lesional skin (qRT-PCR), enhanced cytokine expression (IL1B, CXCL8) and/or secretion (CXCL8, IL-17A, IL-6) in both lesion types, and higher CCL20 expression in nodules, confirming abnormal keratinocyte proliferation and a complex HS cytokine profile. DC treatment (300nM, 1µM) robustly lowered MIK67 expression in all skin types, while it reduced IL-17A secretion in fistula-containing skin, downregulated CCL20 expression in peri-lesional and nodule-containing skin, and decreased CXCL8 expression and CXCL8 secretion in nodule-containing skin in 2 out of 3 donors. To assess T cell activation and recruitment, hair follicles (HFs) from 1 HD were stimulated with a HS-relevant cytokine cocktail (TNF-α, IL-17A, IL-1β) and co-cultured with autologous PBMCs. HFs and/or PBMCs were treated with vehicle or DC (300nM, 1µM). Cytokine stimulation caused intrafollicular PBMC infiltration, which was reduced by HF treatment with 300nM DC, while PBMC treatment with 1µM DC reduced CXCL8 secretion from HFs. In summary, these *in vitro* and *ex vivo* data demonstrate the potential of DC to ameliorate early HS responses but further pre-clinical studies are needed to refine treatment strategies and identify responsive patients.

0956

Impact of skin blemishing on self-confidence counteracted by an innovative chamomilla recutita extract

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GenZ & Millenials beauty are driven by social media (Tiktok, Instagram), the skin must be perfect uniform, pores refined, without any imperfections. This quest for perfection decreasing their self-confidence and therefore, increase resort to invasive solution as micro-Botox injections to tighten pores, control sweat production and avoid skin imperfections. To prevent from such treatment, high-tech Chamomilla recutita leaf and flower extract (CE), with effects on skin relaxing and hyperpigmentation, has been developed and designed using Ashland's Zeta Fraction™ technology. Preliminary studies showed that CE counteract the overexpression of lipids in sebocytes of different ethnicities induced by different exposomes factors and help to reduce sebum secretion, *in vivo*. Here, the aim of this study was to demonstrate the effect of CE on smoothen skin flaws (uneven skin tone, dilated pores, hyperpigmentation) impacted self-confidence. First, the lipase activity on c.acnes was tested with CE which reduces the activity of the lipase thus to control the virulence of c.acnes. Then, the inflammation and appearance of pigment spots induced by c.acnes were evaluated after application or not of CE. The application of c.acnes on ex-vivo skin induces a cutaneous inflammation which has as consequence hyperpigmentation from different ethnicities countered by CE. Finally, to demonstrate *in vivo*, the efficacy of the extract on skin blemishing, two clinical studies were performed on different ethnicities (Caucasian and Asian skins). After 1 month of application with cream containing the extract at 1%, pores were significantly less dilated with an improvement in skin evenness compared to placebo. Likewise, hyperpigmentation was reduced for the side treated with 1% CE containing cream compared to placebo side. Skin blemishing has a real negative impact on self-confidence accentuated by social media. Applications of Chamomilla recutita extract help to improve self-confidence by limiting skin flaws as skin hyperpigmentation and obvious pores.

0957

When AI helps developing an innovative anti-aging biofunctional

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Skin aging is one the most preoccupation of consumer. It is characterized by appearance of wrinkles, loss of elasticity, dryness due to loss of collagen, enhanced by extrinsic factors. For this reason, a new kind of biofunctional was designed by artificial intelligence (AI). This ingredient contains, a molecular complex composed of hydrolyzed sodium hyaluronate (HA) and two peptides, known for their anti-aging efficiency. These interactions were strengthened thank to a unique patented technology named 2HP™ technology and was embedded in cellulose gum matrix bringing a dual action: texturing and bioactive. *In vitro* studies showed a beneficial effect on the expression of 20 collagen-chains distributed in the 8 collagen families by immunohistostaining of collagen-chains as well as by immunocytostaining and qPCR in skin's cells. These results were supported by two double-blind clinical studies. The first one, was a short-term study conducted on 30 Asian volunteers. They applied during 30 min a mask embedded with 5% biofunctional on one side or with placebo on the other side. 30 min after mask removal, the skin was significantly more hydrated with a better elasticity. After 4h, fine lines were smoothness with better skin glower compared to placebo keeping the effect on hydration and elasticity. The second study was a long-term study carried out on 34 volunteers divided in two homogeneous groups. Both groups applied a cream containing 5% biofunctional or its placebo for 1 month. Since D14, the skin was more hydrated with a smoother and softer skin. After one month of applications, with the biofunctional containing cream, the main wrinkles significantly decreased in circumference and depth. Likewise, the skin elasticity was improved while still having better hydration compared to placebo. In this study, we investigated the *in vivo* effect of this new ingredient from 2HP™ technology and having a dual action. These results highlighted short and long-term effects on skin hydration and aging.

0958

Nuclear epidermal growth factor receptor modulates skin laxity and fibrosis.

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Systemic sclerosis (SSc) is an autoimmune disease that causes high morbidity and mortality due to fibrosis of the skin and internal organs but lacks safe and effective therapies. Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that is highly associated with fibrosis of multiple organs including the skin. In response to activation, EGFR is internalized and traffics to multiple cellular compartments, including the nucleus. The function of EGFR in the nucleus during fibrosis remains unexplored. We validate nuclear trafficking of EGFR occurs in fibroblasts in response to the high affinity EGFR ligand TGFA by cellular fractionation, immunofluorescence and electron microscopy. To assess the function of nuclear EGFR *in vitro* and *in vivo*, we generated mice lacking the EGFR nuclear localization sequence ($Egfr^{\Delta NLS}$). Biophysical characterization of these mice showed a phenotype consistent with altered EGFR signaling, including wavy hair and whiskers. Assessment of $Egfr^{\Delta NLS}$ skin demonstrated increased skin laxity ($p < 0.05$) and reduced scarring due to full thickness skin wounds ($p < 0.01$) compared to wild type controls, suggesting nuclear EGFR can regulate pathways that drive wound repair associated fibrosis. To understand the mechanism, we isolated neonatal dermal fibroblasts from $Egfr^{\Delta NLS}$ mice and wild type controls. $Egfr^{\Delta NLS}$ fibroblasts showed decreased expression of interferon stimulated genes and EGR1 regulated genes in response to TGFA ($p < 0.01$). TGFA induced EGR1 expression in fibroblasts could also be abrogated by inhibition of importin b-dependent nuclear transport, supporting this as a profibrotic process. In all, our investigation of the role of nuclear EGFR in fibrosis has elucidated a new regulatory function of fibrotic transcriptional profile by this growth factor receptor in the nucleus.

0959

Effects of M1 homeopathic complex on human melanoma cells

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The treatment of melanoma has advanced consistently in the past 15 years with targeted and immunotherapy. The great improvement in survival rate comes with the cost of moderate to severe side effects in up to 40% of patients treated with combined therapy. Our group is testing homeopathic complex medication to search for less toxic treatments for melanoma. Homeopathy consist of natural substances (plant extracts and minerals) that have little to no side effects. M1 is a combination of Calcarea carbonica plus 18 homeopathic compounds that has previously showed inhibition activity against B16F10 murine melanoma. Previous *in vitro* research showed reduced tumor cell migration and invasion compared to control, and reduced tumor burden in subcutaneous and lung metastasis mice model. We are performing functional analysis with SK Mel28 cells to check if M1 is also effective against human melanoma cells. We were able to see a decrease in cell number in a 3 day dosage curve test. We used 3 different concentrations of the M1 solution: 2%, 10% and 20%. When cells were cultured in the medium with 5% FBS and treated with 2%, 10% and 20% M1 solution the tumor cells reduced 16%, 27% and 27% respectively. When cells were cultured in the medium with 1% FBS and treated with 2%,10% and 20% M1 solution the tumor cells reduced 53%, 61% and 61% respectively. When analyzing cell viability there was not increased number of dead cells in the M1 cultured cells, which led us to the conclusion that the effect was due to inhibition in cell proliferation and not due to cell death (cytotoxicity). Our next steps will be migration and invasion *in vitro* assays and tumor growth and metastasis model *in vivo* studies. With these promising preliminary results we anticipate that M1 might be a candidate treatment for melanoma.

0960

Evidence for resident memory T cells and necroptosis as drivers of fibrosis in eosinophilic fasciitis and morphea

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The pathogenesis of eosinophilic fasciitis (EF) and morphea is poorly understood. There are currently no FDA-approved treatments for either condition, and no cure exists to reverse established fibrosis. We analyzed skin biopsies from EF and morphea patients with established fibrosis compared to adult healthy skin (HS) using gene expression profiling, Ingenuity Pathway Analysis (IPA), and immunostaining. We used digital spatial profiling (DSP) to evaluate early inflammatory lesions from both conditions and HS. In established fibrosis, morphea and EF shared 51/61 differentially expressed genes, 80/99 canonical pathways, and 40/51 upstream regulators. There was significant upregulation of cytotoxic injury signatures, antigen-specific T cell activation genes (ZAP70, LAT, ITK) and activation of T cell receptor signaling, despite their pauci-inflammatory histological appearance. The number of T cells in morphea and EF did not differ from HS, suggesting a potential role for skin resident memory T cells (TRM) in chronic fibrosis. IPA predicted activation of necroptosis, an immunogenic form of cell death, in morphea ($z = 3.9$) and EF ($z = 2.668$). Compared to HS, morphea and EF showed significantly increased expression of necroptosis effector RIPK3. Immunostaining revealed increased numbers of T cell-associated apoptotic and necroptotic endothelial cells in EF and morphea compared to HS, implicating T cell-driven vascular injury in both conditions. Immunostaining showed TRM-associated necroptotic endothelial cells. DSP of early inflammatory EF and morphea skin demonstrated that the fibrotic niche includes macrophages expressing TREM2, a lipid sensor that recognizes DAMPs released from necroptotic cells. CXCR3-secreting macrophages and fibroblasts in early disease co-localized with $CD8^+$ T cells, which we hypothesize become TRM and maintain chronic fibrotic injury through immunogenic cell death. Our findings suggest that targeting TRM or necroptosis may be a novel therapeutic approach in treating cutaneous fibrosis.

0961

Exploring mitochondrial dysfunction in miniaturized hair follicles: Insights into androgenetic alopecia

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Androgenetic alopecia (AGA) is the most common type of alopecia. The pathological hallmark of AGA is miniaturization, where terminal hairs transform into vellus hairs and eventually disappear. AGA exhibits a distinct patterned distribution, with follicles in androgen- sensitive areas like vertex undergoing miniaturization, while occipital follicles remain unaffected. The metabolic processes of hair follicles, particularly mitochondrial metabolism, remain poorly understood. Current studies suggest that hair follicle respiration primarily relies on aerobic glycolysis. In AGA, only one study showed that dermal papilla cells(DPC) in balding areas exhibit mitochondrial dysfunction to non-balding areas, yet mechanistic insights remain limited. To explore these changes, we analyzed miniaturized follicles from the vertex and normal follicles from the occipital region both in anagen, of AGA patients using bulk RNA sequencing and single-cell transcriptomics. Data revealed elevated mitochondrial activity in miniaturized follicles, especially in DPCs, including transcriptional upregulation of mitochondrial synthesis, degradation, mitophagy, and ROS production. IF staining demonstrated the characteristic expression of mitophagy-related proteins in DPCs of miniaturized follicles. Structural analysis using TEM showed mitochondrial abnormalities, including disrupted membrane structures, endoplasmic reticulum stress, and mitophagy in DP cells in vertex . Functional assays using mitochondrial probes revealed decreased membrane potential, elevated ROS production etc. in vertex follicles. IF staining of related proteins confirmed these results. Furthermore, we also obeserved impaired aerobic glycolysis in miniaturized follicles. This study is the first to combine high-throughput transcriptomics with mitochondrial staining to identify distinct mitochondrial phenotypes in miniaturized follicles. Based on observations, we hypothesize that reduced aerobic glycolysis leads to compensatory mitochondrial respiration, which results in structural and functional mitochondrial damage in AGA.

0962

Cyclin-dependent kinase 1 (CDK1)-loaded extracellular vesicles promote wound healing in diabetic obese mice

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Small extracellular vesicles (sEVs) mediate intercellular signaling to coordinate proliferation of cell types that promote re-epithelialization of skin following injury. Cyclin-dependent kinase 1 (CDK1) drives cell division and is a key regulator of cell cycle. To understand the potential of sEV-mediated delivery of CDK1 to reverse impaired wound healing, we generated CDK1-loaded sEVs (CDK1-sEVs) and evaluated their ability to mediate cell proliferation, re-epithelialization and downstream signaling responses in the wound bed. We found that treatment of human keratinocytes with CDK1-sEVs increased phosphorylation of the CDK1 target, eukaryotic translation inhibition factor 4E-binding protein 1 (4E-BP1), and histone H3 within 24 hours via AKT and ERK phosphorylation, driving increased proliferation and cell migration. Treatment of the wound bed of diabetic obese mice, a model of delayed wound healing, with a single (or repeated) dose of CDK1-sEVs accelerated wound closure, increased re-epithelialization, and promoted keratinocytes proliferation. These studies show that delivery of CDK1 by sEVs can stimulate selective and transient proliferation of keratinocytes to increase re-epithelialization and accelerate wound healing.

0963

Cellular senescence burden across chronic skin conditions

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Cellular senescence is a physiologic anti-proliferative defense mechanism in response to cellular damage and stress. Chronic accumulation of senescent cells is implicated in the pathogenesis of various skin diseases, such as psoriasis and skin cancer. The detrimental role of senescent cells can be largely attributed to the paracrine effect of secreted proinflammatory cytokines, growth factors, and proteases. In skin, this can cause chronic low grade inflammation, barrier dysfunction and immunosenescence. The distribution and the level of cellular senescence across skin conditions is poorly understood. We evaluated human skin biopsies from patients with psoriasis, dermatitis, radiation-induced dermatitis, bullous pemphigoid, prurigo nodularis, rosacea, alopecia areata, scleroderma, vitiligo, hidradenitis suppurativa, lichen planus, urticaria, actinic keratosis, seborrheic keratosis, and keloids. The skin samples were profiled by multiplexed immunostaining for markers of cellular senescence. In parallel we analyzed published single cell RNA sequencing data from the same diseases to identify cell populations enriched in senescence markers. Our findings indicated that a subset of chronic skin conditions present an elevated burden of senescent cells suggesting a therapeutic use of novel senolytics drugs to target senescent cells and trigger regulated cell death mechanisms.

0964

Gut short-chain fatty acids are decreased in cutaneous T-cell lymphoma patients

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Short-chain fatty acids (SCFAs) are critical metabolites produced by gut microbiota that play a key role in modulating inflammation and regulating systemic immunity, including against cancer. Decreases in SCFAs can foster a permissive tumor immune environment. Recent studies have shown that cutaneous T-cell lymphoma (CTCL) patients exhibit increasing gut dysbiosis and loss of bacteria predicted to produce SCFAs with increasing disease severity. To investigate this functional connection, we collected stool swab samples from 8 mycosis fungoides (MF) patients and 7 closely-matched healthy controls (HC) and quantified concentrations of four SCFAs (acetate, propionate, isovalerate, butyrate) via liquid chromatography-mass spectrometry. Only MF patients not yet on systemic CTCL medications were selected to prevent confounding. Diet and other concurrent systemic medications did not differ between cohorts. Our results demonstrated significantly reduced total measured SCFA concentrations (1226 µg/g in the MF group versus 2759 µg/g in HC; p=0.048), including significantly reduced acetate (671.3 µg/g in the MF group versus 1807.2 µg/g in HC; p=0.024) and propionate (156.3 µg/g in the MF group versus 544.4 µg/g in HC; p=0.030) concentrations in MF patients when compared to HC. Both propionate and acetate have been previously demonstrated to promote tumor apoptosis, inhibit tumor proliferation, and enhance antitumor immunity. These also align with our prior CTCL gut microbiome studies showing reductions in Lactobacillaceae, Ruminococcaceae, and Lachnospiracae, which are linked to these SCFA levels. Thus, optimizing SCFA levels may enhance concurrent CTCL therapy by creating a less permissive tumor environment. Our pilot findings add to the growing body of knowledge implicating the gut microbiota-SCFA axis in CTCL pathogenesis and offer potential new avenues for therapeutic intervention.

0965

Screening for novel senolytic compounds for skin care treatments using machine learning approach.

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Aging skin accumulates senescent cells that compromise its function and health. Our aim was to discover novel compounds for skin care to improve skin health and delay skin aging by selectively removing senescent cells. Senescent cells are in delicate balance between survival and self-sacrifice. While the cells have a pro-apoptotic microenvironment, they also have so-called senescent cell anti-apoptotic pathways (SCAPs) engaged. Senolytics are compounds that inhibit these SCAPs, inducing apoptosis of the cells. Notably, normal cells remain unaffected as they are not pro-apoptotic. Previous studies have demonstrated the efficacy of the BCL-2 inhibitor Navitoclax leading to selective senescent cell elimination. In our search for novel senolytic compounds we identified BCL-2 inhibitors using machine learning and structure-based molecular screening. After in silico screening of 29299 structures from commercially available natural products, 14 candidates were triaged and tested in an *in vitro* senolytic assay. Senescent cells were obtained by H_2O_2 treatment over several days and used to obtain mixtures of normal (70%) and senescent cells (30%). Senescence was quantified by beta-Gal staining combined with flow cytometry. Here we report on the discovery of 6 novel natural compounds* with confirmed senolytic activity on senescent dermal fibroblasts. The candidates significantly ($p<0.001$) reduced senescent cells by 35% to 80% at 10 µM and were not cytotoxic at this level to normal fibroblasts. We further confirmed the mode of action of our new candidates in an assay using time resolved fluorescence resonance energy transfer (TR-FRET) to quantify inhibition of BCL-2 ligand binding. Finally, we selected one candidate to test on *ex vivo* human skin explants with 21 days treatment time to evaluate abundance of senescent cells before and after treatment using immunofluorescent staining methods and gene expression analysis. For the *ex vivo* model we used Navitoclax and quercetin as reference compounds. *identity of the compounds to be disclosed at poster presentation after IP filing

0966

Peripheral blood high-dimension flow cytometry of chronic pruritus of unknown origin reveals il-31 and oncostatin m+ producing circulating blood cd4+ tcells

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Chronic pruritus of unknown origin (CPUO) is a prevalent yet underrecognized condition that severely impairs quality of life, with no FDA-approved treatments or established clinical guidelines. Characterized by intense, disabling itch without primary skin lesions, CPUO's pathophysiology remains poorly understood. This study aimed to define circulating blood inflammation in CPUO patients using high-dimensional 17-color flow cytometry of peripheral blood mononuclear cells (PBMCs). PBMCs were analyzed from CPUO patients (n=56; mean age 70 years; 80% Caucasian, 11% African American) and healthy controls (HC, n=21; mean age 51 years; 52% Caucasian, 38% African American). CPUO patients reported a mean Worst-Itch Numeric Rating >8/10. Significantly increased immune cell populations in CPUO patients included CD4+IL31+ T cells ($p<0.0125$), CD4+OSM+ T cells ($p<0.0010$), CD8+TNF+ T cells ($p<0.0042$), γδT+TNF+ cells ($p<0.0293$), IL6+TNF+ monocytes ($p<0.0032$), and TNF+ monocytes ($p<0.0078$). These findings reveal a complex interplay of immune cells and cytokines in CPUO, involving Th1 and Th2 inflammation. Elevated IL-31-producing CD4+ T cells align with Th2-mediated pathways, while increased OSM+ CD4+ T cells suggest a role in neuronal sensitization. TNF-producing cells across multiple lineages emphasize TNF-α's importance in CPUO pathophysiology. This study provides novel insights into CPUO's immunological landscape, identifying potential therapeutic targets and biomarkers across T helper cell subsets. These findings may inform future research on targeted therapies to address the unmet need for effective CPUO treatments.

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Injection of cross-linked hyaluronic acid dermal filler into sun-exposed forearm skin of early middle-aged persons stimulates collagen expression in dermal fibroblast

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Mechanical support and function of the dermis depend on the integrity of the extracellular matrix (ECM), which is primarily composed of type I collagen fibrils in association with other structural proteins, including several types of collagens, proteoglycans, and glycoproteins. Dermal fibroblasts reside within the ECM and coordinately regulate its production, turnover, and maintenance. With the passage of time and chronic exposure to the environment, including ultraviolet irradiation, the dermal ECM becomes fragmented. This loss of structural integrity disrupts interactions between fibroblasts and the ECM. It has been demonstrated that injection of cross-linked hyaluronic acid dermal filler (CL-HA) into sun-protected or sun-exposed skin of elderly individuals (>70 years of age) activates fibroblasts, leading to deposition of new ECM, thereby improving dermal structural integrity. The aim of this study is to investigate the impact of CL-HA injection on dermal fibroblast collagen expression in sun-exposed forearm skin of early middle-aged persons (30-50 years, N=16). Each study participant received injections of CL-HA and its vehicle (saline) in adjacent sites of forearm skin. Skin samples (4 mm punch biopsies) were obtained at one- and three-months post-injection and analyzed using histochemistry, immunohistochemistry, in situ mRNA hybridization, and multiphoton confocal laser scanning second harmonic generation microscopy. Substantial activation of dermal fibroblasts surrounding pockets of injected CL-HA was observed at one-month post-injection and continued for at least three-months. In particular, the expression of type I collagen mRNA and protein significantly increased 44% and 92%, respectively, compared with vehicle injection. Thus, our results show that injection of CL-HA activates dermal fibroblasts and enhances dermal ECM integrity in sun-exposed skin of early middle-aged individuals, similar to that observed in persons of advanced age.

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Shared gene signatures in keloid pathogenesis across ethnically diverse populations: Insights from scRNA-seq

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Keloids, pathological scars characterized by aberrant wound healing and excessive collagen deposition, are more prevalent in individuals with skin of color (SoC) and pose significant cosmetic and therapeutic challenges. This cross-sectional study aimed to uncover the molecular mechanisms underlying keloid formation using single-cell RNA sequencing (scRNA-seq). Keloid tissues from ten SoC patients, representing Asian, African American, Caucasian, and Hispanic populations, were analyzed alongside six normal skin controls. Analysis revealed 98 differentially expressed genes (DEGs) conserved across all ethnic groups, implicating critical biological processes in keloid pathogenesis. These include extracellular matrix organization (COL1A1,), inflammation (F2RL1), lipid metabolism (PLPP4), small leucine-rich proteoglycans (ASPN), the renin-angiotensin system (ACE), enzymatic activity (MMP11), and intracellular signaling pathways (MAPK11-12). The shared genetic signatures underscore the complex molecular interactions contributing to keloid development across ethnically diverse populations. Our findings underscore the importance of inclusive research to identify conserved molecular pathways in keloid pathogenesis and provide a robust foundation for developing targeted, effective therapies to improve clinical outcomes across diverse populations.

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Exploring BMI-associated gene expression patterns in hidradenitis suppurativa lesions through transcriptional profiling

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Hidradenitis Suppurativa (HS) is a multifactorial skin disease characterized by local and systemic inflammation; the latter is often linked to higher BMI. However, the precise relationship between elevated BMI and HS remains unclear. This study investigated transcriptional changes associated with BMI in HS lesions using bulk RNA-sequencing datasets. We analyzed an IRB-approved dataset generated at Henry Ford Health (n=19) and a publicly available dataset (GSE151243, n=20). Samples were stratified into BMI-Low (≤35) and BMI-High (≥35, Class 1 Obesity) groups. Differential expression (DE) analysis identified 28 differentially expressed genes (DEGs): 5 DEGs in the BMI-High cohort and 23 DEGs in the BMI-Low cohort. These genes included inflammatory markers, obesity-associated genes, and genes involved in keratin filament formation and hair follicle development. Our findings, supported by published datasets, highlight novel genes associated with high BMI and suggest potential pathways linking obesity to HS development. Future research should further explore the role of BMI in HS pathogenesis and evaluate weight loss interventions or targeted therapies addressing these pathways.

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Autophagy induction as a new therapeutic target for pachyonychia congenita

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Introduction: Pachyonychia Congenita (PC) is an ultrarare dermatologic disorder affecting an estimated 10,000 people worldwide. PC is caused by an autosomal dominant mutation in a series of keratin genes (KRT6A/B/C, KRT16, & KRT17). PC manifests with blisters, ichthyosis, deformed, thickened, or discolored nails and constant plantar pain. Plantar pain has the greatest impact on quality of life. PC is an unmet need with no approved therapies. PC and epidermolysis bullosa simplex (EBS) are caused by mutated keratins that form structurally weakened keratin intermediate filaments (KIFs). Stress collapses the KIFs into aggregates weakening the suprabasal keratinocytes causing premature cell death which contributes to ichthyosis. Clinical trials for oral rapamycin were not well-tolerated. Topical rapamycin trials did not reach significance. Our research suggests a potential benefit of autophagy induction by mTOR inhibitors to treat EBS. The purpose of this research was to evaluate mTOR inhibitors including BM-3103 (4-Hydroxy 4'-methyoxytolan) and rapamycin *in vitro* in PC keratinocytes. Specific aims: 1) autophagy induction, 2) KIF stability, 3) uptake of keratin by the autophagosome. Methods: *In vitro* analysis was performed using immortalized cell lines (K6a N171K, K16, N125D) derived from PC patients. Autophagy signaling was evaluated using western blotting and immunocytochemistry. A heat stress assay was used to assess KIF aggregation. Colocalization using immunofluorescence of keratin (K6a/K16) uptake by the autophagosome (LC3-II) was done. Results: At 25uM BM-3103 was significantly better than rapamycin at inducing autophagy(p=0.03). BM3103 increased LC3-II levels 5-12-fold vs 0.5-1.6-fold for rapamycin (0.4μM). BM-3103 treated cells resisted KIF collapse after heat stress. Keratin was colocalized with LC3-II staining of autophagosomes. Conclusions: Induction of autophagy in PC cells increasing KIF network stability through the degradation of mutant and damaged keratins. mTOR inhibitors like BM-3103 need to be clinically tested to assess impact on blistering and ichthyosis.

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A multi-action inhibitory mechanism of allosteric TYK2-specific inhibitors

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Deucravacitinib is a highly selective allosteric inhibitor of protein tyrosine kinase 2 (TYK2). It targets the Janus kinase (JAK) signal transducer and activator of transcription (STAT) pathway. Despite its selectivity, the structural basis for its inhibition mechanism remains poorly understood. Here, we analyzed available atomic resolution structures relevant to the JAK-STAT pathway to investigate the TYK2 inhibition mechanism. TYK2 mediates a relatively rapid interferon-induced gene expression compared to other cytokine pathways; our computational analysis revealed a mechanistic hypothesis for this TYK2 activity. We find that deucravacitinib and other TYK2-specific allosteric drugs inhibit TYK2 kinase in three distinct states: an autoinhibited state and two activated states. The activated states are involved in autophosphorylation and the phosphorylation of downstream proteins. In the autoinhibited state, deucravacitinib binds to the TYK2 pseudokinase domain. This binding restricts essential dynamics of the TYK2 kinase domain needed for kinase activity. Additionally, deucravacitinib competes with ATP binding in the pseudokinase domain. This competitive binding directly prevents the formation of the active TYK2 state through steric clashes. Furthermore, we propose a structural mechanism that explains how phosphorylated STAT homo- and hetero-dimers are produced after activation during JAK-STAT signaling.

0972

Identification of biomarkers in cutaneous T cell lymphoma tumors associated with radiotherapy response and durability

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Radiotherapy (RT) is a common, established treatment for cutaneous T-cell lymphoma (CTCL) but typically only given with palliative intent. Duration of response is often unpredictable and many patients encounter disease progression over time. Identifying biomarkers that may be predictive of tumors that are more likely to progress versus remain in remission is critically important. Herein, we performed spatial transcriptomics and/or multiplex proximity extension immunoassay on punch biopsy and skin tape strip samples, respectively, and 16S rRNA sequencing on lesional swabs on 11 CTCL patients who underwent RT. Patient samples were categorized into progression or remission categories based on clinical follow-up data after ~1 year. Within the post-RT tumor microenvironment (TME) of patients who progressed, we observed an increase in CTCL and tumor-associated markers (JAK3, CCL17, CCL18, CXCL9) and markers related to radiation resistance (SOD2, XBP1, DUX4). Patients who experienced disease remission possessed an increase in Type 1 interferons (IFI6, IFI27, IFI44) and connective tissue markers (COL1A1, FBN1, MMP2, ADAMTS2). Skin tape strip analysis of 368 proteins relevant to inflammation revealed higher levels of VEGFD and IL-13 in cases that progressed. In general, there was a decrease in CTCL-associated biomarkers from pre to post-RT including JAK3, TRBC1, IL32, CD52, and IL2RG in CD3+CD8- T-cells, IL32 and ITK in CD3+CD8+ T-cells, and HMOX1 and TGFB1 in CD68+ macrophages. 16S data showed distinct microbial communities in progression versus remission groups but similar Shannon diversity scores. Staphylococcus capitis was higher in non-lesional samples from remission patients. In summary, RT response is associated with greater durability when there is higher activation of Type 1 interferons, fewer markers of tumor activity and radiation resistance, and a less favorable TME.

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Crystal structure of rademikibart Fab-IL-4Rα complex reveals molecular basis for next-generation potent IL-4Rα inhibition

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Rademikibart (CBP-201) is a human monoclonal antibody with higher binding affinity to IL-4Rα compared to dupilumab. Dupilumab was the initial first-generation interleukin-4 receptor alpha (IL-4Rα) inhibitor for treating both type I and type II IL-4Rα-dependent inflammatory disorders, like atopic dermatitis and asthma. Rademikibart, however, demonstrated better inhibition of STAT6 intracellular signaling *in vitro* and provided similar potency inhibiting both IL-4 induced TARC release and IL-4 induced B cell activation. We determined the crystal structure of rademikibart fragment antigen binding (Fab) bound to IL-4Rα at 2.71 Å. This structure was analyzed and compared to the 2.82 Å resolution structure of dupilumab Fab bound to IL-4Rα. The rotation angle between dupilumab and rademikibart bound to IL-4Rα is 59.17°. This rotation enables the epitope of rademikibart, but not dupilumab, on IL-4Rα to overlap more closely with the conserved binding interface utilized by IL-4 and IL-13 cytokines. Molecular dynamics (MD) studies on rademikibart and dupilumab bound to IL-4Rα examined the stability of the complexes and effects of amino acid mutations on complex formation. MD simulations showed the third interface loop (residues 148 to 152 in domain 2) of IL-4Rα interacts directly with rademikibart, which is absent in dupilumab/IL-4Rα complex. This finding is confirmed by hydrogen bond interactions at the interface between the antibodies and IL-4Rα, demonstrating superior binding energy for rademikibart. Through single amino acid mutation analysis on rademikibart, we identified residue Y50 on rademikibart as the key residue interacting with IL-4Rα's third interface loop. Our data provide a molecular and structural rationale for the enhanced IL-4Rα inhibition by rademikibart over dupilumab, confirming rademikibart as an optimized second-generation IL-4Rα inhibitor.

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Single-cell profiling of scleroderma-like syndromes: Identifying key molecular pathways in skin fibrosis

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Scleroderma-like syndromes (SLS) are a group of disorders characterized by skin hardening due pathological fibrosis. However, their pathogenesis and mechanism of fibrosis remain unclear. Here, we performed single-cell, bulk and spatial profiling of 3 cases of Stiff Skin Syndrome, a disease caused by a mutation in the fibrillin 1 (FBN1) gene and characterized by progressive fibrosis, contractures and hypertrichosis. We contrasted the data against single-cell data from 4 systemic sclerosis (SSc) and 4 healthy controls (HC). We identified 52,420 cells across seventeen major cell type across all skin samples capturing all major stromal, epithelial and immune cell types. Patients with Stiff Skin Syndrome had increased hair follicle but lower immune cell proportions, particularly myeloid cells, compared to SSc. COL1A1 mRNA expression was markedly increased in both Stiff Skin Syndrome and Systemic Sclerosis (9.7-fold, $p=8.8x10^{-11}$, and 13.5-fold, $p-1.6x10^{-8}$, respectively) and shared enriched Biological Processes including Extracellular Matrix Organization, Integrin Cell Surface Interactions, and Smooth Muscle Contraction. Myofibroblasts (COL8A1+) were enriched in both Stiff Skin Syndrome and SSc but had strikingly different distribution on spatial sequencing with myofibroblasts in Stiff Skin Syndrome being prominent in the upper dermis and around adnexal structures including hair follicles and eccrine glands, whereas myofibroblasts in SSc were denser in the deeper dermis. Notably, prominent receptor-ligand interactions specific to Stiff Skin Syndrome were seen, with hair follicle cells being a major sender and receiver of cell communication. These data outline distinct compartmentalization of fibrotic processes in different fibrotic diseases and provide a deeper understanding of the molecular and cellular mechanisms involved.

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Effect of whole blood platelet concentration on platelet-rich plasma platelet concentration

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Platelet-rich plasma (PRP) is an autologous blood product consisting of mostly platelets created from the centrifugation of whole blood (WB). One may intuitively assume that the concentration of platelets in PRP would vary based on the concentration of platelets WB drawn at the time of preparation, but validating this assumption is important for conducting research on PRP. The aim of this study is to compare the WB platelet concentration (WBP) to the corresponding PRP platelet concentration (PRPp). This single academic center retrospective study used data from an alopecia specialty clinic. WB volume pre-centrifugation, WBp, PRP volume post-preparation, and PRPp were assessed from quality control blood specimens. As some patients had multiple PRP treatments, a linear mixed-effects model was used to compare WBp to PRPp at each visit. Two PRP preparation devices (A and B) were modeled independently to evaluate the association between WBp and PRPp while controlling for repeated measures and the ratio of WB to PRP volume collected for α=.05. Box-Cox transformation was applied to both models due to violation of normality. Forty-three treatments were excluded due to missing data, leaving 124 treatments using device A and 131 using device B in 67 patients for analysis. An average of 20.3 ml of WB and 8.5 ml of PRP was collected each visit. There was a statistically significant correlation between WBp and PRPp for both device A (β'=0.018,P= .005) and device B (β'=0.007,P= .013). The results of this study support an association between the WBp and PRPp, although the impact of WBp varied between devices. Most patients in the dataset used had WBp between 150,000 to 400,000 platelets/ml, it is unclear how well the model extrapolates to values outside this range. These results may assist providers in making clinical decisions for using PRP in patients with low-normal WB platelet concentrations. Future studies are planned to assess the effect PRPp on PRP efficacy.

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Palisaded neutrophilic and granulomatous dermatitis presenting in a patient with hidradenitis suppurativa on infliximab

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To describe a case of PNGD associated with infliximab therapy in a patient with HS and present relevant clinical and histopathological findings. Hidradenitis suppurativa (HS) is a chronic, debilitating skin disorder involving follicular biology, often treated with a combination of antibiotics, anti-androgen, and anti-inflammatory therapy. Tumor necrosis factor-alpha (TNF-α) inhibitors, such as infliximab, are well-tolerated options for patients with inflammatory lesions, tunnels, and scarring who fail to achieve disease control with conventional therapies[1]. However, TNF-α inhibitors can paradoxically trigger adverse cutaneous reactions, including palisaded neutrophilic and granulomatous dermatitis (PNGD)[2]. A 26-year-old African American female with a 13-year history of HS presented to our dermatology center for management. Shortly after initiating infliximab therapy, the patient developed eruptive, monomorphic flesh-colored papules involving the face, anterior trunk, and proximal upper extremities. After 3 months, a 4.0-mm punch biopsy of a representative lesion on the on the shoulder revealed ischemic-driven necrobiosis with palisading histiocytes, consistent with a rheumatoid nodule. Ischemic-driven necrobiosis with palisading granulomatous inflammation, resembling rheumatoid nodules, is a recognized, paradoxical complication of TNF-α inhibitor therapy.[2,4,5] This auto-inflammatory reaction may result from downregulation of T-regulatory cell activity, contributing to neutrophilic and granulomatous inflammation. While PNGD is well-documented in patients with rheumatoid arthritis receiving TNF-α blockade,[3] this case highlights its occurrence in the setting of HS treated with infliximab. This case underscores the importance of identifying paradoxical cutaneous reactions, such as PNGD, in HS patients undergoing TNF-α inhibitor therapy. Further studies are needed to elucidate the underlying immunopathogenesis and guide management in such cases.

0977

Pathogenic hallmarks of primary lymphocyte-mediated scarring alopecia revealed by single nuclear and spatial multiomics

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Primary lymphocyte-mediated scarring alopecias (PLSA) are characterized by autoimmune attack and loss of hair follicle stem cells and perifollicular scarring. To better understand the pathogenesis of PLSA, paired single nuclear RNA sequencing (snFFPEseq) and Visium spatial transcriptomics were performed on archived patient samples from two healthy scalp skin specimens and six PLSA specimens. snFFPEseq demonstrated increased percentages CD4+ T effector cells, CD8+ T cells, and B cells in PLSA biopsies. Furthermore, analysis of keratinocyte and fibroblast clusters demonstrated increased numbers of cells with an epithelial-to-mesenchymal (EMT) signature in the scarring alopecia specimens. Visium spatial transcriptomics confirmed that the EMT signature was restricted to the interface of damaged hair follicle keratinocytes and perifollicular concentric fibrosis. Additionally, Xenium spatial transcriptomics performed on non-paired patient samples showed expression of EMT genes, such as POSTN, GREM1, and INHBA in KRT15+ hair follicle keratinocytes undergoing autoimmune attack and in adjacent sclerosing fibroblasts. CD8+ T cells expressing IFNG and GZMB were also major immune constituents at pathogenic interface zones. Overall, there is emerging evidence that effector T cells and B cells are associated with and EMT gene signature in pathogenic regions of PLSA.

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Using oncogenic stress to sensitize RAS-mutant cancers to immunotherapy

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Oncogenic pathways are key targets for inhibition but the emergence of resistance and the unclear ability to safely combine these approaches with immunotherapies remain major challenges. While immunotherapy is effective for NRAS-mutant melanoma, no clear options exist for resistant disease. We explored the concept of oncogenic pathway agonism. BRAF-mutant melanomas respond to BRAFi due to decreased ERK signaling. They can recover signaling by acquiring activating RAS/MEK mutations, but exhibit decreased proliferation upon withdrawal of inhibitor, suggesting that supraphysiologic ERK signaling also compromises fitness. Therefore, we wondered whether increasing ERK hyperactivation in RAS-mutant cancers might elevate ERK signaling to a degree to induce senescence and also create an inflammatory tumor microenvironment. We tested this in RAS-mutant tumors because BRAFi induces paradoxical ERK activation in RAS-mutant cells. 15/21 RAS-mutant cancer cell lines hyperactivate ERK and undergo senescence-like arrest following exposure to all FDA-approved BRAF inhibitors at clinically relevant doses, with IC50s in the nanomolar range. Biochemically, ERK hyperactivation is the key driver. We then asked whether these changes could enhance responses to immunotherapy in two novel, genomically characterized immunocompetent mouse models of Nras-mutant melanoma and Kras-mutant pancreatic adenocarcinoma. Surprisingly, both Ras-mutant models showed sustained tumor regression and suppression of metastasis only when mice were treated with combined anti-PD1 and dabrafenib. Profiling of the tumor microenvironment showed increased cytokines related to senescence including IL6 and infiltration of activated CD8+ T-cells. We linked ERK pathway hyperactivation to a IFNg-driven stress response. Oncogenic pathway agonism is a novel and potentially useful strategy to induce proliferation arrest, induce a IFNg signature, and sensitizes cancers to immunotherapy.

0979

Mechanism of oligofructans from Ophiopogon japonicus root extract on cutaneous inflammation, barrier function, and microbial defenses in an *in vitro* atopic dermatitis model

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Background: Prescription therapies for Atopic Dermatitis(AD) predominantly target the dysregulated inflammatory burden, while over the counter(OTC) products repair the barrier dysfunction and aid the implicated cutaneous dysbiosis. Mechanistic data supporting clinical findings is often lacking for OTC ingredients. To address this gap, oligofructan extract(OFE) from the Ophiopogon japonicus plant, which has shown improvement of clinical symptoms in patients with AD, was investigated *in vitro*. Methods: Reconstructed epidermis(RE) from normal human keratinocytes and RE with altered barrier function (RE-ABF, treated with sodium lauryl sulfate) were prepared. Experimental RE-ABF samples were exposed to OFE, Poly I:C, TNFα, IL-4/IL-13; select samples were exposed to Staphylococcus aureus. ELISA, flow cytometry, PCR, microscopy, and immunohistochemistry assessed inflammatory byproduct and barrier protein levels. H&E staining, lucifer yellow penetration, and transepithelial resistance assessed barrier integrity/resistance. Mann-Whitney-Wilcoxon and Student's t test were performed. Results: Systemic 0.04% OFE reduced synthesis of TSLP (-31%) and IL-8 (-20%). Treatment with 0.15% OFE inhibited production of IL-4, IL-13, and IL-31, increased expression of TLR2 (+80%), TLR6 (+69%), HBD2 (+117%), HBD3 (+52%), and RNase7 (+74%), and limited S. aureus adhesion/biofilm formation (-63%). 0.15% OFE application increased claudin-1 (+59%), loricrin (+21%), and filaggrin (+250%) while reducing epidermal permeability (-60%) and improving skin barrier electric resistance (all results reported as change from baseline and at $p<0.05$). Conclusion: These findings provide mechanistic insights into OFE's clinical activity. Specifically, OFE treatment reduced keratinocyte-mediated and Th2 inflammation, limited S. aureus adhesion/biofilm formation, and improved skin barrier function, integrity, and resistance.

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Preclinical development of ABCL575, a half-life extended anti-OX40L monoclonal antibody for the treatment of autoimmune conditions

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The OX40/OX40L pathway is a key regulator of inflammation underlying T cell-mediated autoimmune conditions of high unmet need, such as atopic dermatitis. Antibody-mediated blockade of the OX40/OX40L axis has shown promise in the clinic as a targeted, non-depleting mechanism to modulate inflammation. Here, we present preclinical data on ABCL575, a novel anti-OX40L antibody that potently inhibits OX40/OX40L binding. ABCL575 is a fully human IgG1 monoclonal antibody with high affinity to human and cynomolgus monkey(cyno) OX40L and a modified Fc domain(LALA-YTE) to support Fc-silencing and half-life extension. Variable region sequences were generated by deep screening of ~1.3 million B cells obtained from human immunoglobulin mice immunized with OX40L protein. Antibodies were screened in high-throughput functional and developability assays to identify potent molecules with favorable properties. Function was measured in reporter and primary cell assays. *In vivo* pharmacokinetics(PK), tolerability, and safety were assessed in Tg32 (FcRn transgenic) mice and cyno. ABCL575 shows potent *in vitro* activity comparable to the most advanced clinical benchmark, with inhibition of OX40L-induced signaling (IC_{50} 2.7 nM), T-cell activation (IC_{50} 10.9-14.1 nM), and Th2 cytokine release (single-digit to sub-nM IC_{50}). *In vivo* PK and safety studies support potential best-in-class dosing frequency and show that ABCL575 is well-tolerated. Non-clinical safety studies, including tissue cross-reactivity and non-GLP toxicology, indicate early signals of safety. Further, *in vitro* antibody-dependent cellular cytotoxicity assessment shows abrogation of Fc-mediated effector function. ABCL575 is formatted as a high-concentration formulation to support subcutaneous administration and exhibits low viscosity and favorable stability/product quality attributes. Together, these data show that ABCL575 is a potential best-in-class antibody for the treatment of T cell-mediated autoimmune conditions and support further clinical evaluation.

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Benzo[a]pyrene exacerbates psoriasis-like dermatitis through aryl hydrocarbon receptor modulation and exosomal miRNA regulation in imiquimod-induced psoriatic mouse

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This study explored the role of benzo[a]pyrene (BaP), a xenobiotic pollutant, in immune responses through exosomes in imiquimod (IMQ)-induced psoriatic mice. We assessed clinical and histopathologic changes after topical BaP treatment in IMQ-treated mice. Psoriasis-related proinflammatory cytokines and the aryl hydrocarbon receptor (AHR) were measured using western blotting and qRT-PCR, while oxidative stress factors were evaluated by immunofluorescence staining. We also examined how serum exosomes from BaP-treated psoriatic mice influence cytokine expression in mouse keratinocytes. Next-generation sequencing (NGS) of small RNAs in serum exosomes was performed. BaP worsened skin inflammation in IMQ-induced psoriatic mice by increasing AHR, CYP1A1, proinflammatory cytokines (TNF-α, IL-6, IL-17a, IL-17F, IL-22, IL-23), and oxidative stress markers (NOX2, NOX4) in lesional skin. Serum exosomes from BaP-treated psoriatic mice significantly upregulated TNF-α, IL-6, and IL-23 in primary mouse keratinocytes compared to those from IMQ-only treated mice. NGS analysis revealed 88 differentially expressed exosomal miRNAs in BaP + IMQ-treated mice, with mmu-miR-423-3p notably upregulated. Its 44 predicted target genes were associated with oxidative phosphorylation, neurodegeneration, and chemical carcinogenesis according to KEGG pathway analysis. In conclusion, BaP aggravated psoriasis-like dermatitis by modulating AHR and promoting inflammation and oxidative stress. Circulating exosomal miRNAs, particularly mmu-miR-423-3p, may serve as potential biomarkers for BaP-induced psoriasis exacerbation.

0982

Formulation and activity of a topical product with hyperfermented extract of kazanlink rose petals encapsulated in liposomes

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This work was aimed to study the stability, and the activity of topical products formulated with hyperfermented extract of Kazanlink Rose petals encapsulated in liposomes, produced in Chianti (Tuscany-Italy). Recent studies have suggested a possible moisturizing and elasticizing activity of extract of Kazanlink Rose. For such characteristics hyperfermented extract of Kazanlink Rose petals encapsulated in liposomes appears an appropriate ingredient to be used in topical preparations for the treatment of skin hydration. On these bases we evaluated the activity of 4 gel preparations, respectively, containing: (a) gel without active ingredients as control, (b) gel containing liposomes without active ingredients, (c) gel with 3% of hyperfermented extract of Kazanlink Rose petals encapsulated in liposomes, (d) gel with 3% of hyperfermented extract of Kazanlink Rose petals. The investigation was carried out on 10 healthy male and female volunteers, between the ages of 32 and 66, with normal or dry skin. Each product was applied to the volar surface of the forearm at a dose of 3 mg/cm^2. As control, the same cream without active ingredient was applied to the other forearm. To evaluate TEWL was used the device Moisture Meter Epid Delfintech®, and skin elasticity was evaluated with Elasti Meter Delfintech®. The skin hydration action of the formulations was evaluated in relation to basal value, and the formulations without active ingredient, respectively after 15 minutes and 15 days. The skin elasticity was evaluated after 15 minutes and 15 days. The results showed that the gel with hyperfermented extract of Kazanlink Rose petals encapsulated in liposomes, compared to the gel formulation without active ingredients, significantly increase the degree of hydration and elasticity of the skin, both short and long term.

0983

Real time virtual histology video of squamous and basaloid neoplasms using a portable confocal microscope

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The time from biopsy to histological diagnosis can take days to weeks due to traditional histology preparation times. Reflectance Confocal Microscopy (RCM) can offer real time cellular-level resolution of skin lesions, but output images do not resemble traditional histologically stained slides as images are in grayscale. Herein, we applied our machine learning-based "virtual histology" algorithm to RCM images of the skin to determine if transformations can occur in near-real time for rapid assistance of diagnosis. We hypothesize that combining portable RCM with near instant videos of VH could aid in rapid, accurate skin diagnosis. The study was conducted as a prospective, consecutive trial at a VA Medical Center. In-vivo confocal RCM videos were taken with the portable RCM from the epidermis to dermis and run through the generative adversarial network-based algorithm to create real time H&E pseudo-stained VH videos. Whether VH combined with standard or portable RCM, we were able to use virtual histology to convert captured RCM images to virtually stained H&E-like images with a few second delay. The near instant VH videos directly correlated with pathology seen in conventional histology slides. The combination of portable RCM with real time VH video represents a promising clinical tool to consolidate visits, improve workflow, decrease time to management, and improve access to care.

0984

Leveraging urinary microRNAs as systemic biomarkers for dermatologic diseases: Non-invasive prediction of diabetic foot ulcer healing

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Skin inflammation releases short, stable non-coding microRNAs (miRNAs) into circulation, and miRNAs from extra-cutaneous tissues can target the skin. As such, systemic miRNAs are attractive prognostic and therapeutic biomarkers for dermatologic disease, particularly when captured non-invasively in patient urine. To this end, a robust amplification-free method was developed to profile urinary miRNAs in diabetic foot ulcer (DFU) individuals, aiming to identify early miRNA predictors of DFU healing outcomes (healed or not healed) 12 weeks after initial clinical presentation. MiRNAs were successfully profiled in a pilot cohort of 55 DFU individuals at enrollment in the NIDDK Diabetic Foot Consortium, normalized to urine quantity and concentration, and subjected to combined data reduction and prognostic modeling. Using this approach, a multi-miRNA biomarker was successfully identified that predicted DFU healing outcome 12 weeks after study enrollment with a sensitivity of 86%, specificity of 79%, and an aROC of 0.8. In this pilot cohort, the miRNA biomarker outperformed clinical risk factors known to be linked to non-healing DFUs, including wound area, race, and renal function, and is undergoing further validation in an expanded cohort. The methods and modeling approaches utilized in this study can profile urinary miRNAs from a spectrum of skin diseases, with the goal of developing non-invasive prognostic and therapeutic biomarkers for clinical outcomes to improve the lives of people with dermatologic disease.

0985

Attenuation of inflammatory cytokines with invasive vagus nerve stimulation in the skin of mouse models of psoriasis and eczema

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The cholinergic anti-inflammatory pathway, activated through vagus nerve stimulation (VNS), plays a crucial role in immune response regulation. Although the skin lacks direct vagal innervation, we hypothesized that vagal modulation of systemic inflammation might influence cutaneous inflammatory disorders. We investigated this possibility using two mouse models: C57/BL6 mouse with imiquimod-induced psoriasis-like lesions and NC/Nga mouse with dinitrochlorobenzene (DNCB)-induced eczematous dermatitis. Left vagus nerve stimulation (5V/5mA/5Hz/5ms/5min) was applied at 6 and 24 hours pre-sacrifice in the imiquimod model, and 24 hours pre-sacrifice in the DNCB model. In both models, VNS significantly reduced epidermal thickening, pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), and CD11b-positive macrophage infiltration in the skin. Immunofluorescence staining revealed decreased TNF-α response in the epidermis after VNS. In DNCB-treated mice, a single VNS application reduced plasma TNF-α levels by 32% ($p<0.01$). Notably, protein levels of TNF-α and IL-1β in the spleen were elevated in both models and downregulated by VNS, suggesting that local dermatitis may be linked to systemic inflammation. VNS treatment reduced inflammatory markers in both splenic tissue and plasma, indicating its therapeutic effects may be mediated through modulation of systemic inflammation. These findings establish VNS as a potential therapeutic approach for inflammatory skin diseases and provide mechanistic insights into its anti-inflammatory effects in cutaneous tissue.

0986

Antimicrobial activity of commonly used topical moisturizers on the survival of methicillin-resistant Staphylococcus aureus USA300

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Patients with atopic dermatitis (AD), who are frequently colonized with Staphylococcus aureus (S. aureus), are often advised to use moisturizers to protect their skin barrier, though the effects of these products on the skin microbiome remains under exploration. This cell culture study investigates the impact of commonly used topical moisturizers on the survival of community-associated Staphylococcus aureus USA300, one of the dominant community-associated methicillin-resistant strains known to produce superantigens that impact barrier function. Commercially available products were inoculated with USA300, incubated at 30°C, and sampled in triplicate at 0, 1, 3, 5, 12 and 24 hours before agar plate analysis for colony-forming units (CFU). Results demonstrated differential effects among the moisturizers on USA300 survival. Cetaphil Eczema Restoraderm and Curel inhibited USA300 by the 5-hour timepoint, whereas Cerave Moisturizing Cream and Cerave Daily Moisturizing Lotion inhibited it at the 12-hour timepoint. In contrast, other tested moisturizers did not significantly inhibit and instead sustained methicillin-resistant S. aureus USA 300 survival to the 24-hour timepoint. These differences may contribute to the variable efficacy of these moisturizers in alleviating AD. Further studies will need to be performed to identify the factors influencing the survival of USA300 and other key bacteria involved in AD dysbiosis. This study highlights notable differences in the ability of common moisturizers to influence pathogenic S. aureus USA300 survival, highlighting the need for studies investigating the therapeutic potential of moisturizers in modulating the skin microbiome in atopic dermatitis.

0987

Bruton's tyrosine kinase (BTK) is indispensable in neutrophils to initiate and maintain skin inflammation in a model of pemphigoid diseases

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The Tec kinase Bruton's tyrosine kinase (BTK) is essential for B cell functions rendering it a potential therapeutic taget for antibody-induced autoimmune diseases. The role of BTK in myeloid cells is less understood. More insights into the significance of BTK in myeloid cells is required to evaluate the potential of BTK as therapeutic target in the effector phase of antibody-induced autoimmune diseases when inhibiting the production of autoantibodies usually cannot suppress tissue inflammation swiftly. Such a situation can be found, e.g., in acute flares of pemphigoid diseases, a group of autoimmune diseases. We examined the effect of neutrophil-specific Btk gene knockout and of the BTK inhibitor ibrutinib on skin inflammation in the antibody transfer model of bullous pemphigoid (BP)-like epidermolysis bullosa acquisita (EBA). The model solely reflects the effector phase of antibody-driven autoimmune diseases. Furthermore, we investigated the effect of BTK inhibitors on responses of neutrophils relevant for antibody-induced autoimmune diseases *in vitro*. Both neutrophil-specific genetic deficiency of BTK and ibrutinib vastly protected from skin inflammation. Stimulation of murine neutrophils with immune complexes activated BTK and induced the release of leukotriene B_4 (LTB_4) and reactive oxygen species (ROS). Genetic deficiency in BTK nullified LTB_4 but not ROS release. *In vitro*, ibrutinib and other inhibitors of BTK, including rilzabrutinib and CGI-1746, inhibited neutrophil responses to immune complexes. Our results indicate that BTK in neutrophils is essential to initiate and maintain neutrophil recruitment thus precipitating tissue inflammation in EBA. The marked responsiveness of EBA to BTK inhibition results from a nonredundant role of BTK in relaying Fcγ receptor signaling in neutrophils to induce the release of LTB_4. This highlights BTK as promising drug target to treat EBA and potentially other antibody-induced autoimmune disease.

0988

A patent analysis of laser innovations in dermatologic applications

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Laser technology has become pivotal in dermatology, with widespread applications in both medical and cosmetic treatments. However, the distribution of innovations and advancements across these areas remains insufficiently explored. This retrospective aims to offering insight into the technological trends shaping the field. Utilizing the Lens platform, granted medical-use patents that included terms "laser" and "derm*" in their titles, abstracts, or claims were identified. The top 100 most cited patents were identified and ranked by citation number then categorized into: "Cosmetic Applications," "Laser Components and Materials," "Laser System Architecture," and "Treatment of Dermatological Conditions." The top 100 cited laser dermatology patents ranged from 1983 to 2012 with 17% average growth in granted patents over five-year intervals. "Laser System Design" emerged as the largest category (n=33) followed by "Cosmetic Applications" (n=26), "Laser Components and Material" (n=24), and "Treatment of Dermatological Conditions" (n=17). When stratified by quintiles based on citation rank, "Laser Components and Materials" were the most prevalent among the top quintile (n=7). Although the smallest category overall, "Treatment of Dermatological Conditions" ranked second in the top quintile (n=6). Among the bottom quintile, "Cosmetic Applications" were the most prevalent (n=9). "Laser System Architecture" patents are the most prevalent, serving as a foundation for innovation in areas like "Treatment of Dermatological Conditions" and "Cosmetic Applications." While patents for "Treatment of Dermatological Conditions" are the most frequently cited, highlighting their significant clinical impact, "Cosmetic Applications," despite their larger volume, exhibit fewer citations, suggesting a comparatively lower influence in the field.

0989

An immunohistochemical classification panel for predicting molecular subtypes of mycosis fungoides with therapeutic implications

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Mycosis fungoides (MF) is the most common cutaneous T-cell lymphoma, with wide variability in patient outcomes. This study aimed to develop an immunohistochemical (IHC) panel to predict molecular subtypes of MF and evaluate its therapeutic implications. Using single-cell RNA sequencing, we previously identified two molecular subtypes of MF, the central memory T cell (T_{CM}) group and the cytotoxic effector memory T cell (T_{CyEM}) group, which show distinct tumor microenvironment profiles and prognoses (Liu et al., Nature Communications, 2022). In this study, we developed an immunohistochemical (IHC) panel to identify these subtypes in paraffin tissue using antibodies targeting key differentially expressed genes: CD27 and TOX for T_{CM} group, and GZMA and HOPX for T_{CyEM} group. A total of 126 MF cases were included, with 69 having RNA-seq data to determine the molecular subtype and establish cut-off values for each IHC marker. The cut-off values (CD27 ≥ 0.5, TOX ≥ 0.5, GZMA ≥ 0.2, HOPX ≥ 0.1) were used to classify patients into three groups: T_{CM} (n=35), T_{CyEM} (n=70), and undetermined (n=21). The IHC panel identified T_{CM} and T_{CyEM} groups with high sensitivity (85%), and these subtypes showed a significant difference in progression-free survival (PFS) (P<0.001). In multivariate analysis, folliculotropism subtype and the T_{CM} subtype, as determined by IHC, were independent adverse predictors of PFS (P=0.001), regardless of age, sex, stage, and large cell transformation. Additionally, retrospective analysis of clinical treatment regimens revealed that for the T_{CM} group, treatment primarily with retinoids resulted in a longer time to next treatment (TTNT) (P=0.006). For the T_{CyEM} group, interferon-based therapy maintained TTNT and offered better safety. Thus, the IHC classification panel will aid in identifying the 2 subtypes in clinical practice, which will aid the future clinical management of patients and facilitate risk stratification in clinical trials.

0990

Dermal fibroblasts subsets activate Ccr3 to promote allergic inflammation

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Dermal fibroblasts are involved in various inflammatory diseases, including acne, psoriasis, and S. aureus infections. However, the role of fibroblasts in atopic dermatitis (AD) remains unclear. To investigate this, we analyzed scRNA-seq data from patients with AD (n=5 non-lesional skin, n=4 lesional skin) compared to controls (n=8). Unbiased CellChat analysis revealed that PDGFRa+ fibroblasts exhibit increased communication with T cells and myeloid cells in AD, along with higher expression of CCL5, CCL8, CCL11, CCL13, and CCL26 relative to normal skin. Analysis of scRNA-seq data in a mouse AD model (MC903 +S. aureus) demonstrated a similar response, with certain dermal fibroblast clusters showing elevated levels of several chemokines that interact with the Ccr3 receptor. Furthermore, this response was absent in IL4ra-/- mice, indicating a specific role for IL4/IL13. To test this, cultured 3T3 fibroblasts were treated with and without IL4/IL13 after administration of an inflammatory cocktail (IL1b, IL17A, and TNFa). RNA sequencing and subsequent qPCR validation confirmed that IL4 and IL13 induce fibroblast expression of CCR3 ligands (Ccl2, Ccl7, Ccl8, and Ccl11). This was functionally relevant, as conditioned media from fibroblasts showed increased protein levels of Ccl8 and Ccl11 following the addition of IL4/IL13, and this conditioned media promoted T cell migration, which was inhibited by a Ccr3 antagonist ($P<0.05$). Targeted siRNA against Ccl8 in fibroblasts also reduced the ability of IL4 and IL13 to stimulate fibroblasts to enhance T-cell migration ($P<0.01$). Finally, administering a Ccr3 antagonist in the AD mouse model via intraperitoneal injection reduced inflammation and T-cell migration into the skin. These findings demonstrate that fibroblasts are key responders to Th2 cytokines and that Ccr3 ligands, particularly Ccl8 from fibroblasts, may play a role in leukocyte recruitment during allergic inflammation.

0991

Validation of safety and efficacy of the antimicrobial hydrogel for rapid elimination of bacterial infection in murine and porcine infected wounds

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Our study focused on development of a targeted antibacterial pH/temperature responsive silver nanoparticle (AgNP) hydrogel allowing triggered release of silver ions in response to changes in wound microenvironment. Optimization and characterization of the hydrogel delivery system was achieved using cross-linking of N-isopropylacrylamide with acrylic acid and loading with ultrasmall AgNPs. Material characterization, biocompatibility and release studies were undertaken to demonstrate temperature and pH responsive properties and in-vitro efficacy against common wound pathogens. Demonstration of in-vivo antimicrobial safety and efficacy against industry standard of care (silver sulfadiazine) was achieved using a preclinical murine and porcine wound infection models. We demonstrate that the dual-responsive hydrogel is highly sensitive to a typical pH and temperature changes during infection development, with restricted release of silver ions at acidic pH (<pH 5.5) and significant release in alkaline conditions (>pH 7.4) (>90% release). The pH dependent release and antimicrobial effect resulted in elimination of 95% of pathogens in-vitro at alkaline pH which was confirmed by potent clearing of S. aureus infection and significant improved healing using preclinical models including faster reepithelization and improved early collagen deposition. Treatment safety were further validated in porcine model of wound infection, with developed hydrogel showing no toxicity and equivalent antimicrobial effects to industry standard of care. This multifunctional hydrogel presents a promising bacteria responsive delivery platform that serves as an on-demand carrier to not only reduce side effects but also boost the antibacterial efficiency based on physiological needs. It offers great potential to improve the way we manage wound infections, providing a single platform for a long-lasting application in wound management.

0992

Advancing skin health and longevity through targeted metabolic activity optimization

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Background: The progression of skin aging is marked by a distinct metabolic shift. In youth, skin cells exhibit robust production of structural proteins like collagen and elastin. However, as we age, cellular metabolism pivots towards heightened inflammation and increased generation of reactive oxygen species. This metabolic alteration leads to cellular dysfunction, particularly affecting mitochondrial health, and ultimately propels cells towards senescence. This transition from a constructive to a potentially destructive cellular environment is a hallmark of the skin aging process. Objective: Our research explored the age-dependent metabolic alterations and their cascading effects on various aspects of cellular health. We examined the correlation between these metabolic shifts and key biofunctional markers in skin, with a particular focus on indicators of cellular senescence and extracellular matrix (ECM) composition. Results & Conclusion: Age-related changes in fibroblasts are characterized by various phenotypic attributes at the cellular level. We found that fibroblasts undergo age-associated metabolic reprogramming, characterized by heightened metabolic activity. This metabolic shift demonstrates a strong correlation with diverse biofunctional indicators in the skin. Strategic modulation of these metabolic alterations may potentially preserve and promote the maintenance of a youthful skin appearance.

0993

IL-17 elicits skin inflammation by acting on different cell types depending on disease context

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Therapeutic blockade of IL-17 is highly effective in treating inflammatory skin conditions, but the mechanisms responsible for efficacy are incompletely understood. IL-17 synergizes with PAMPs, DAMPs, and cytokines—especially TNFα—to induce neutrophil chemokine expression and drive tissue inflammation. While keratinocytes have been considered the primary targets of IL-17, we recently showed that subsets of immune-acting fibroblasts in the dermis are also key targets. Here, we evaluated the relative importance of fibroblasts versus keratinocytes in driving type 17 inflammation in skin. Single-cell transcriptomics of healthy human and mouse skin show that keratinocytes and fibroblasts express similarly high levels of IL-17 and TNFα receptors. Functional experiments with primary cultured cells demonstrate that both cell types recognize IL-17 and TNFα but that fibroblasts are induced to express 5-fold more neutrophil chemokine Cxcl1 than keratinocytes ($P<0.0001$). To evaluate the relative role of each cell type, we developed conditional knockout mice lacking the IL-17 receptor specifically in fibroblasts ($Pdgfra^{\Delta Il17ra}$) or keratinocytes ($Krt14^{\Delta Il17ra}$) and exposed these mice to topical or intradermal stimuli. Skin neutrophilia induced by intradermal injection of IL-17 and TNFα was reduced by 80% in $Pdgfra^{\Delta Il17ra}$ mice ($P<0.01$) but was unchanged in $Krt14^{\Delta Il17ra}$ mice. Conversely, skin neutrophilia after topical imiquimod was reduced by 50% in $Pdgfra^{\Delta Il17ra}$ mice ($P<0.01$) and by 50% in $Krt14^{\Delta Il17ra}$ mice ($P=0.06$). Immunostaining showed CXCL1 protein expression by keratinocytes was more abundant in response to topical stimuli (imiquimod, C. albicans) compared to intradermal ones (IL-17/TNFα, S. aureus, C. acnes). Additionally, neutrophil migration to the epidermis was more pronounced with topical stimuli than intradermal ones. Collectively, these findings demonstrate that IL-17 drives skin inflammation through context-dependent cellular targets, with fibroblasts and keratinocytes playing distinct roles based on the depth of inflammatory stimulus.

0994

Single-cell RNA sequencing reveals oncogenic drivers and markers of blood involvement in patients with cutaneous T-cell lymphoma

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Cutaneous T-cell lymphoma (CTCL) is a rare form of non-Hodgkin's lymphoma that affects the skin and can progress to involve the blood, lymph nodes, and visceral organs. This study aimed to identify genetic oncogenic drivers and markers of blood involvement in patients with CTCL using single-cell RNA sequencing and T-cell receptor (TCR) mRNA sequencing. Skin biopsy samples from five CTCL patients (ages 32-78, stages IB-IVA1, 3 white, 1 female, 2 blood involvement) were analyzed. Malignant T-cells were identified based on CD3+CD4+ expression and clonal TCR. Data were adjusted for batch effects, and differential gene expression analysis was performed using |Log2FC| > 0.15 and FDR-adjusted p-value < 0.05 as thresholds for significance. We identified genes distinguishing malignant from non-malignant T-cells, including GATA3 (Log2FC = -0.34, p=0.006), HDAC9 (Log2FC = -0.87, p=0.01), S100A6 (Log2FC = -1.05, p=0.04), and CD99 (Log2FC = -0.57, p=0.02), which are associated with T-cell differentiation, epigenetic regulation, cell cycle regulation, and cell adhesion/migration, respectively. Markers associated with blood involvement included CTLA4 (Log2FC = 1.69, p<1e-4), IKZF2 (Log2FC = 1.77, p<1e-4), TOX (Log2FC = 1.69, p=0.02), TIGIT (Log2FC = 1.30, p<1e-4), TCF7 (Log2FC = 1.51, p=0.01), SELL (Log2FC = 1.49, p<1e-4), and PTPRC (Log2FC = 1.28, p<1e-4), which contribute to immune evasion by malignant T-cells and T-cell migration and activation. Markers associated with no blood involvement included CXCR3 (Log2FC = -0.92, p<1e-4), CD96 (Log2FC = -1.36, p<1e-4), and CD63 (Log2FC = -1.06, p<1e-4), which may facilitate localized migration of T-cells and immune evasion within the tumor microenvironment of the skin. Our findings provide novel insights into the molecular pathogenesis of CTCL and identify candidate markers for improved prognostic stratification based on likelihood of developing blood involvement. Future work will focus on validating markers of blood involvement through immunohistochemistry staining in a cohort of 50-100 patients.

0995

Suppressed pain signaling in recessive dystrophic epidermolysis bullosa with a MNK1/2 inhibitor

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Recessive Dystrophic Epidermolysis Bullosa (RDEB) is a rare autosomal recessive disease caused by biallelic variants in COL7A1 and characterized by blistering, inflammation, and scarring. RDEB patients experience neuropathic pain, exacerbated during dressing changes and treated largely with morphine and gabapentin. The MAP interacting protein kinase (MNK) signaling pathway modulates the neuronal sensitivity of neuropathic pain. We hypothesized that the MNK pathway is activated in and contributes to chronic pain in RDEB. C7 hypomorphic mice with biallelic Col7a1 variants exhibit similar blistering and acral scarring deformities, as well as pain behaviors and poor life quality, of RDEB patients. mRNA expression of MNK pathway components (Mknk, Eif4e, Bdnf, Par2, Il6ra) was upregulated in the dorsal root ganglia (DRGs) of RDEB mice by 2-4-fold compared to wildtype littermates (all p<0.05). Similarly, phosphorylated eIF4E, a downstream target of MNK1/2, was increased in RDEB DRGs, suggesting hyperactivated MNK signaling in RDEB nerves. Daily intraperitoneal injections of the MNK inhibitor, tomivosertib, reduced expression of Bdnf, Mknk, and Eif4e compared to vehicle in RDEB mice (all p<0.05). However, expression of Tac1, a downstream effector of IL4R/IL13RA1 signaling, which augments itch, was unchanged. Mouse pain behaviors (excessive grooming, paw nibbling, and facial grimacing) were observed, and duration of pain behavior was significantly decreased (50%; p<0.05) in RDEB mice treated with the MNK inhibitor versus vehicle control. Our preliminary findings identify a basis for pain in RDEB and implicate targeting the MNK pathway with tomivosertib as a new therapeutic direction in RDEB management.

0996

Immunomodulatory potential of human dermal fibroblast spheroids in psoriasis therapy

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Psoriasis is a chronic, immune-mediated skin disease with limited options for achieving sustained remission. This study investigates the therapeutic potential of human dermal fibroblast (HDF) spheroids as a cell-based therapy. HDFs were cultured into three-dimensional spheroids ($1x10^6$ cells/mouse, 1,733 cells in each spheroid with an average diameter of 150 mm) and assessed in mouse models of imiquimod (IMQ)-induced psoriasis. A single dose of HDF spheroids significantly reduced skin lesion severity in mild psoriasis, normalized blood cell counts, alleviated spleen enlargement, and improved cytokine dysregulation. In moderate-to-severe cases, repeated doses were required to achieve similar efficacy. Moreover, HDF spheroids demonstrated therapeutic efficacy comparable to multiple doses of an anti-IL-23 monoclonal antibody, a standard psoriasis treatment. Importantly, HDF spheroids inhibited monocyte production and infiltration in the spleen and skin—an immunomodulatory mechanism not observed with anti-IL-23 therapy. In the SKH-1 hairless mouse model with a cyclic IMQ regimen mimicking the chronic and relapsing nature of human psoriasis, HDF spheroids administered during the initial disease cycle alleviated severity and reduced relapse likelihood in subsequent cycles. These findings suggest HDF spheroids' immunomodulatory and translational potential as a practical, durable therapy for psoriasis. Their distinct mechanism of action and scalability make them a promising cell-based approach for managing psoriasis and other chronic skin inflammatory diseases.

0997

TLR7 is a critical mediator of skin inflammation

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Multiple toll-like receptors (TLRs), including TLR3, TLR7, and TLR9, regulate proinflammatory signaling in dermatopathology. Controlled agonist-based activation of TLR7 is used as a clinical approach to induce beneficial skin inflammation, but it also results in adverse chronic inflammation resembling psoriasis. However, the pathophysiological role of TLR7 in psoriasis and the discrete downstream effectors mediating TLR7 signaling in the skin are poorly defined. We found that TLR7 is expressed in both immune and non-immune cells in the skin. However, its primary function in myeloid cells, rather than in keratinocytes, is critical for regulating both cytokine expression and T cell function involved in skin inflammation. TLR7 regulates activation of a NF-κB pathway, distinct from that regulated by TLR3 and TLR9, which controls inflammatory gene output associated with skin pathology, and its disruption protects mice from experimental skin inflammation. We also found that the proinflammatory effects of the clinically used Aldara cream, which contains the TLR7 agonist imiquimod, specifically depend on the TLR7-NF-κB signaling axis, independent of the fatty acid components in the topical formulation. NF-κB is a psoriasis susceptibility locus that is highly expressed in the lesional skin of patients and experimental mice. Our findings reveal novel TLR7-mediated mechanisms activating NF-κB with potential therapeutic implications for controlling chronic skin inflammation.

0998

Serum proteomic profiling of patients with immune checkpoint inhibitor-associated eczematous dermatitis highlights therapeutic targets and immunologic distinctions from atopic dermatitis

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The use of immune checkpoint inhibitors (ICIs) to treat cancer leads to dermatologic side effects known as cutaneous immune-related adverse events (cirAEs) in up to 60% of patients. Despite their substantial impact on quality of life, no standardized treatment protocol exists for the various cirAE phenotypes, and, to our knowledge, the proteomic profiles of cirAEs have not yet been characterized. To better understand the pathophysiology underlying cirAEs, serum samples were collected from 4 patients with ICI-induced eczematous reactions (ICI-Ecz) and 11 patients with atopic dermatitis (AD), the hallmark eczematous dermatitis, matched on age, race, and sex. Proteomic data for 393 proteins were extracted using the OLINK Proximity Extension Assay and analyzed using R software and Bioconductor packages. Differential expression was defined as |fold change|>1.4 and false discovery rate<0.1. Compared to AD patients, ICI-Ecz patients displayed positive Th1-skewing, with increased expression of IL2-RA, TNF-R1, TNF-R2, IL-1RT1, and IL-1RT2. Many proteins in the Th17 immune pathway (IL-17RA, IL-6RA, PI3/elafin) were also upregulated in ICI-Ecz serum. Moreover, pathway analysis performed by Gene Set Variation Analysis (GSVA) exhibited significant upregulation of Th1 and Th17 pathways ($p<0.05$), the former of which is known to play a key role in anti-tumor immunity. There were no significant differences in GSVA scores for the Th2 and JAK/STAT pathways, indicating similar overall expressions of these common therapeutic targets in ICI-Ecz and AD. These preliminary results demonstrate immunologic distinctions between eczematous cirAEs and AD, as well as offer insight into the insufficiently studied pathophysiology of cirAEs. This understanding is critical to clinicians' ability to successfully treat cirAEs while maintaining the anti-tumor efficacy of ICIs.

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Tape strip transcriptomic analysis of Thai patients with atopic dermatitis shows greater immune and barrier abnormalities in the setting of comorbid food allergy

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Atopic dermatitis(AD) and food allergy(FA), both in the atopic march, commonly co-occur, and may share immune and barrier abnormalities. Studies show that FA may exacerbate AD and induce changes in the skin barrier and microbiome. Using tape strip transcriptomics, we aim to compare the molecular features of a pediatric Thai moderate AD cohort with and without comorbid food allergy. Tape strips were collected and analyzed via RNAseq from the lesional(LS) and nonlesional (NL) skin in a Thai cohort of children with AD+FA (n=17), AD only (n=12), and from healthy controls (HC) (n=8). Differentially expressed genes (DEGs) were defined by fold change>1.5 and false discovery rate<0.05. While all AD patients showed immune and barrier alterations compared to HC in both LS and NL skin, FA exacerbated the inflammatory tone in LS skin, with 1,260 DEGs (638up/622down) in the AD+FA group vs 600 DEGs (277up/323down) in AD only. Markers of innate immunity (IL1B/IL6), Th2 (CCL13/CCL24/IL10), and Th1 (CXCL10/MX1) showed stronger upregulation in AD+FA. Th17 skewing, associated with Asian and pediatric AD, was universal, but especially pronounced in AD+FA (IL17A/IL-17F/CXCL1), while Th22 (IL22/S100A8/9) was higher in AD only. Barrier dysfunction was higher in AD+FA, with greater attenuation in genes associated with terminal differentiation (FLG/LCE1B/2A) and tight junctions (CLDN8). Significant increases in key markers of pruritus (IL-31), interferon (IFIT1/44), histamines (HRH4/HDC), mast cells (CPA3), and eosinophils (RNASE2) were also uniquely seen in AD+FA, but not AD only. We demonstrate that the immune and barrier dysregulation in AD worsen in the setting of concomitant FAs, which may drive more severe and persistent AD disease. The presence of FA may define a distinct AD endotype, warranting more aggressive immune targeting approaches to control higher inflammation.

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Effects of JAK/STAT inhibitors in cutaneous T-cell lymphoma cells

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Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common types of cutaneous T-cell lymphoma (CTCL), characterized by defective apoptosis and uncontrolled proliferation of malignant T-cells. Current treatments alleviate symptoms but lack a definitive cure. Dysregulation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is a key driver of CTCL pathogenesis, making it a promising yet understudied therapeutic target. This study evaluates the effects of JAK/STAT inhibitors on MF-derived MJ cells and SS-derived HuT 78 cells *in vitro*. Four JAK inhibitors were tested: Abrocitinib (JAK1), Tofacitinib (pan-JAK, potent JAK3 inhibition), Ritlecitinib (JAK3), and Brepocitinib (pan-JAK, potent TYK2/JAK1 inhibition). Two STAT inhibitors targeted STAT3 (TTI-101) and STAT6 (AS1517499). Cell proliferation was assessed using the MTS assay, and apoptosis was analyzed by flow cytometry. For proliferation inhibition, all inhibitors demonstrated inhibitory effects in both cell lines. Among JAK inhibitors, HuT 78 cells were most sensitive to Abrocitinib (IC_{50}: 1.71 μM), followed by Brepocitinib (2.30 μM), Tofacitinib (7.42 μM), and Ritlecitinib (14.30 μM) at 48 hours. MJ cells were most sensitive to Tofacitinib (IC_{50}: 4.35 μM), followed by Brepocitinib (6.97 μM), Ritlecitinib (13.77 μM), and least sensitive to Abrocitinib (24.83 μM). STAT inhibitors showed strong effects, with HuT 78 cells sensitive to both AS1517499 (2.19 μM) and TTI-101 (1.23 μM). MJ cells were more sensitive to AS1517499 (1.23 μM) than TTI-101 (5.75 μM). For apoptosis induction, STAT inhibitors exhibited stronger effects than JAK inhibitors in both cell lines. AS1517499 induced greater apoptosis than TTI-101. Notably, Tofacitinib combined with AS1517499 or TTI-101 showed synergistic apoptotic effects, as did the combination of the two STAT inhibitors. These findings underscore the efficacy of JAK/STAT inhibitors in MJ and HuT 78 cells, highlight differential sensitivities between the cell lines, and support ongoing investigations into the underlying mechanisms.

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Development of GE8820 for selective and rapid removal of pathogenic autoantibodies in pemphigus vulgaris

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Pemphigus vulgaris (PV) is an autoimmune skin blistering disease characterized by autoantibodies (AutoAb) directed against desmoglein proteins, primarily DSG3. Pathogenicity is caused by AutoAb disruption of desmosome assembly via direct inhibition and alteration in keratinocytes signaling pathways. AutoAb targeting DSG3 are predominantly of the IgG4 isotype, pathogenicity is contained in the IgG4 fraction, and their titer correlates with disease activity. GE8820 is a recombinantly expressed bifunctional glycoprotein that selectively binds to human IgG4 and, through a glycan mediated engagement of ASGPR on hepatocytes, targets it for lysosomal degradation in the liver. GE8820 was designed, cloned and expressed using the proprietary BiND™ platform, which allows for 1-step recombinant expression of bifunctional glycoprotein degrader molecules. Recombinantly expressed DSG AutoAb that were identified from PV patient serum have been extensively used to investigate the role of DSG3 AutoAb in PV pathogenesis using *in vitro* and *in vivo* models. Here we show that GE8820 completely removed patient derived recombinantly expressed DSG3 AutoAb spiked in cell culture medium using an immuno-depletion assay. Experiments to test AutoAb pathogenicity using a keratinocytes fragmentation assay confirmed that treatment of samples with GE8820 completely removed their pathogenicity and blocked fragmentation. Finally, in a rodent model, GE8820 resulted in rapid (≤ 2hrs) and near complete (≥95%) depletion of exogenous administered patient derived DSG3 AutoAb in a dose dependent manner. Taken together, we present data that demonstrate that GE8820 is a promising rapidly acting, durable, steroid-sparing and non-immunosuppressive therapy for the treatment of PV and other IgG4 autoantibodies driven diseases such as primary membranous nephropathy and muscle specific kinase driven myasthenia gravis.

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A novel RXR agonist suppresses tumor formation accompanied by increased CD8⁺ T cells in a murine model of cutaneous T cell lymphoma (CTCL)

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Nuclear retinoid X receptors (RXRs) play critical roles in developmental, metabolic, biochemical, and immunomodulatory processes via dimerization and ligand activation. Bexarotene (Bex), the first and only FDA-approved RXR-targeted agonist for cutaneous T-cell lymphoma (CTCL), promotes tumor cell differentiation and apoptosis. With limited patient response to bexarotene and adverse effects such as hepatotoxicity and hypertriglyceridemia, more effective and safer RXR agonists for cancer therapy are needed. Using our published method, murine MBL2 T cell lymphoma cells were subcutaneously injected in the ear skin of mice, followed by a single topical application of dinitrofluorobenzene (DNFB), inducing tumor formation as early as day 7 in an inflammatory tumor microenvironment (TME). To test RXR drugs, mice were fed a powdered chow mixed with either Bex or a novel RXR agonist, ASU052317 (ASU), starting on day 3 after tumor inoculation. After one week of treatment, ASU significantly inhibited tumor growth compared to the control diet, while Bex showed no inhibitory effect (Turkey's multiple comparisons: p=0.0043 for Bex vs. ASU; n=6). Flow cytometry and microscopy analyses revealed that ASU, but not Bex, markedly altered immune profiles relative to normal and vehicle-treated groups, particularly by increasing CD8+ lymphocyte numbers in both the spleen ($p<0.01$) and the TME, where these cells densely accumulated at the invasive edges of tumors ($p<0.01$). Importantly, these CD8+ lymphocytes lacked PD-1 expression, suggesting they retained cytotoxic functionality. As expected, Bex treatment elevated serum triglycerides and cholesterol levels, while ASU-treated mice showed no such abnormalities. Thus, ASU052317 reduced tumor formation (accompanied by an anti-tumor response) in a murine CTCL model without affecting the lipid profile in treated mice, prompting further exploration of unique RXR agonists for CTCL.

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Skin vaccination unravels novel intravascular CD8 memory T cell population which protects against influenza

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Respiratory viral pathogens like influenza A and SARS-CoV-2 pose significant global challenges, with vaccination efforts hindered by rapid viral evolution and a focus on antibody generation. We explored epidermal disruption (e.d.) as an alternative vaccination method, which generates protective CD8⁺ T memory cells in the lung vasculature. Unlike intramuscular (i.m.), e.d. vaccination generates CD8⁺ T cells that home to both the skin and lungs. Using a non-replicating poxvirus (MVA_{NP}) delivered via e.d., we tested its ability to protect against a lethal dose of PR8 (H1N1) influenza A. A single e.d. dose demonstrated superior protection, with 100% survival, compared to 40% survival of i.m animals. E.d. vaccinated mice showed lower viral loads in the lung and robust protection independent of antibodies, B cells, and CD4⁺ T cells, however this protection was abrogated upon CD8⁺ T cell depletion. Longitudinal analysis revealed these protective cells are not lung parenchyma resident but are lung-vasculature-residing memory cells, and they extravasate into parenchyma upon infection, initially involving CD8⁺ T cells already present in the vasculature (0-3 days). Depletion of CD8⁺ T cells before infection (day -1) abolished protection, while depletion at day 3 had a much less effect, highlighting the importance of the first wave, rapid acting, lung-vasculature-residing, CD8⁺ T cells. This population has a transcriptional profile distinct from central and effector memory cells and exhibits durable immune memory (up to 80 days post-immunization) and a robust protection against immune challenge up to 120 days post-immunization, compared to waning natural sublethal immunization. Our approach to immunization may offer lasting protection against respiratory pathogens and inform future vaccine strategies.

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Use of 2,6-diaminopurine as a highly potent corrector of UGA nonsense mutations in recessive dystrophic epidermolysis bullosa.

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Recessive Dystrophic Epidermolysis Bullosa (RDEB) is a debilitating blistering skin disease caused by mutations in the gene encoding type VII collagen (C7), a crucial component of the dermal-epidermal junction. Among patients with RDEB, approximately 25% possess nonsense mutations that introduce premature termination codons (PTCs), leading to impaired protein production. Our prior research demonstrated that gentamicin, administered topically or intravenously, could facilitate PTC readthrough and promote the production of functional C7 in patients with RDEB. However, the extended use of gentamicin is restricted by its toxicity, including nephrotoxicity and ototoxicity, necessitating the exploration of safer and more effective alternatives. Recent efforts have centered on identifying compounds with enhanced PTC readthrough efficiency and reduced toxicity. Among these, 2,6-diaminopurine (DAP) has emerged as a promising candidate, exhibiting the ability to promote efficient readthrough of UGA premature stop codons in various *in vitro* and *in vivo* disease models. In the current study, we sought to evaluate whether DAP could induce PTC readthrough and restore C7 expression in primary fibroblasts and keratinocytes derived from RDEB patients harboring different nonsense mutations. Our findings revealed that DAP significantly increased the synthesis of C7 in RDEB cells in a dose-dependent manner, achieving superior efficacy compared to high-dose gentamicin. Mechanistically, DAP-induced PTC readthrough and C7 production in RDEB cells are mediated by increasing mRNA stability. Additionally, the restored C7 reversed the abnormal hypermotility characteristic of RDEB cells, indicating functional recovery. Importantly, in RDEB skin equivalents, DAP-induced C7 localized accurately to the dermal-epidermal junction. These results suggest that DAP holds significant potential as a novel, safe, and effective treatment for RDEB and other genetic disorders caused by nonsense mutations.

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MDI1228, a novel topical small molecule JAK inhibitor, alleviates autoimmune skin diseases by inhibiting dermal fibroblast-T cell interactions

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The JAK-STAT signaling pathway plays a crucial role in the pathogenesis of various allergic and inflammatory diseases, making it a promising target for the treatment of autoimmune skin diseases. Dermal fibroblasts (dFBs) are pivotal in the skin's innate immune defense and inflammation regulation. However, the distinct activation states of dFBs and their interactions with T cells in different inflammatory contexts are not well understood. In this study, we developed a novel small-molecule JAK inhibitor, MDI1228, and investigated its anti-inflammatory efficacy and mechanism of action in targeting dFBs and T-cell interactions in allergic contact dermatitis (ACD) and atopic dermatitis (AD) mouse models, which are dominated by type I and type II inflammation, respectively. MDI1228 exerted a JAK protein binding activity over 650-fold higher than that of the classical JAK1 inhibitor filgotinib, and it inhibited STAT phosphorylation more than 3-fold higher than that of the classical JAK1/3 inhibitor tofacitinib. Topical application of MDI1228 hydrogel effectively suppressed IFNγ and IL-4/IL-13-induced dermatitis phenotypes and dFB chemotaxis on T cells in ACD and AD mouse models, respectively. In addition, MDI1228 significantly attenuated IFNγ and IL-4/IL-13-mediated activation of mouse or human dFBs *in vitro* and inhibited the activated dFB-mediated naïve T cell polarization by blocking the IFNγ-CXCL9/10 or IL4/IL13-CCL11 signaling axes. Moreover, long-term application of hydrocortisone, but not MDI1228, resulted in atrophy of the dermal white adipose tissue and immune organs, as well as osteoporosis in mice. In conclusion, the novel pan-JAK inhibitor MDI1228 developed in this study effectively alleviates the development of type I and II autoimmune skin inflammation in mice. Mechanically MDI1228 interferes with the cellular crosstalk between dFBs and T cells. These preclinical results indicate that MDI1228 is a promising candidate for treating type I and/or type II autoimmune skin diseases.

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Reduction of type I interferon biomarkers by cGAS inhibition in scleroderma and GvHD skin

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Systemic sclerosis/scleroderma (SSc) and the sclerotic form of chronic graft-versus-host-disease (SclGvHD) both feature elevated type I interferon gene expression and skin fibrosis. However, direct evidence of cGAS-STING activation as source of type I interferon in SSc and SclGvHD has remained unclear. To assess interferon stimulated gene (ISG) expression in each disease, we generated an integrated scRNA-Seq atlas of skin from patients with SSc (n=17), SclGvHD (n=3) and healthy controls (n=16). ISG were highly expressed in both SSc and SclGvHD, including myeloid APCs and pericytes in both diseases, fibroblasts in SSc, and endothelial cells in SclGvHD. High ISG RNA levels corresponded with high STING protein staining by immunohistochemistry. Compared to lupus as a positive control, STING was elevated in diffuse SSc, morphea and SclGvHD, but unchanged in limited SSc like healthy controls. To validate cGAS inhibition as a potential therapeutic strategy in fibrotic skin, we used two skin explants assays. The first was an inducible model of cGAS activation via mitochondrial DNA leakage. In the second, we tested cGAS inhibition on active SclGvHD (n=3) and SSc (n=1) patient skin explants. We observed in both models reduction in biomarkers associated with type I interferon. In the inducible model of cGAS activation, cGAS inhibition decreased MX1(p=0.0008) and IFI27(p=0.0004) RNA levels and CXCL10(p=0.048) protein secretion. In the patient skin explants, cGAS inhibition decreased secreted fibrotic and inflammatory proteins IL6(p=0.042), pro-collagen1 N-terminal peptide (PINP) (p=0.037), and TNC(p=0.0046). In sum, our results indicate differential cGAS-STING activity among SSc disease subsets and SclGvHD and that cGAS inhibition can reduce interferon associated disease biomarkers in skin.

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Phloretin microneedle patches applied on human psoriatic reconstructed skin

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Problem: Plaque psoriasis causes scaly inflamed lesions and epidermal thickening. Patients frequently require lifelong medication, increasing the risk of toxicity from systemic and biological therapies. Topical treatments are therefore prioritized, but their daily prescriptions can limit therapeutic adherence. Detachable and biodegradable microneedle (MN) skin patches could be the key. Phloretin, an antiproliferative and anti-inflammatory polyphenol, was incorporated into the MNs to assess their effect in human psoriatic reconstructed skin. Objectives: 1) Evaluate methods of applying MN patches on human reconstructed skin to maximize MN implantation. 2) Analyze the cutaneous diffusion of a fluorophore incorporated into MNs over two weeks of implantation in the skin. 3) Study the anti-psoriatic effect of these MN patches loaded with phloretin and applied on human psoriatic reconstructed skin, by measuring the epidermal thickness. Methodology: 1) MN patches loaded with a fluorophore, Cy5-COOH, were applied on reconstructed skin, then detached, leaving the MNs in the skin. The percentage of implanted MNs was determined by fluorescence imaging. 2) The diffusion of Cy5-COOH in the skin and culture supernatants were analyzed over 2 weeks. 3) Phloretin or methotrexate (psoriasis reference treatment) patches were applied to psoriatic substitutes for one week and compared with the molecules added to the culture medium. The epidermal thickness was compared. Results: 1) 91.5% of the microneedles remained implanted in the reconstructed skin. 2) Up to 105 pg/mL of Cy5-COOH were quantified in the culture supernatants after 5 days, indicating diffusion to the dermis. 3) Epidermal thickness of the skin near the patches was reduced by 37.33% with phloretin patches. Conclusion: Microneedle patches loaded with phloretin are promising for psoriasis.

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Small samples, big data: Microcoring for advanced skin -omics profiling

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This study introduces microcoring, a minimally invasive biopsy technique, as an innovative tool for -omics research and clinical applications.It offers significant advantages over traditional biopsy methods, which are often associated with discomfort, scarring, and prolonged sequencing times. Combined with STARmap (Spatially Resolved Transcript Amplicon Readout Mapping), a cutting-edge spatial transcriptomics technology, microcoring enables high-resolution gene expression mapping while preserving skin structure organization. Its small sample size supports scalable workflows, and optimized protocols integrating STARmap with H&E staining provide dual-layered gene expression and histology analysis. Microcoring uses a modified hypodermic needle to extract minimally invasive, full-thickness skin samples optimized for -omics workflows. The technique was evaluated for biomolecular preservation, spatial resolution, and feasibility in high-throughput applications like STARmap, which enables spatial mapping of gene expression within intact tissues. Metrics for RNA integrity, protein quantification, and metabolite stability were assessed. Microcoring produced high-quality skin samples with intact biomolecular profiles suitable for -omics analysis. STARmap imaging validated spatially resolved transcriptomic integrity, demonstrating its effectiveness for high-resolution molecular mapping. The minimally invasive approach reduced tissue disruption and variability. Smaller wound size and enhanced patient tolerability support repeated sampling for longitudinal studies and personalized monitoring. Microcoring is a minimally invasive, transformative tool for dermatologic research, enabling scarless sampling while preserving molecular quality. Combining high-resolution -omics capabilities with patient-centered benefits advances understanding of genetic skin conditions, improving diagnostics, therapeutic development, and pathology research.

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Early markers and drivers of cutaneous T-cell lymphoma in atopic dermatitis patients via transcriptomic/genomic profiling

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Cutaneous T-cell lymphoma (CTCL) is a rare form of non-Hodgkin's lymphoma predominantly affecting the skin. Atopic dermatitis (AD) and CTCL share clinicopathologic features, complicating early CTCL detection. A history of AD is further linked to higher CTCL prevalence and worse outcomes. This study identified early diagnostic markers and drivers of CTCL in patients with a history of AD using spatial transcriptomic and genomic profiling. Skin biopsies were collected from three male patients with AD diagnosed >2 years prior to CTCL (ages 64.3±0.9 yrs; stages IB-IVA; AD-to-CTCL time: 6±3 yrs; all used biologics for AD). For each patient, one biopsy diagnostic of AD and another of CTCL were analyzed using Xenium In Situ. We identified seven differentially expressed genes only in AD biopsies, 102 shared by AD/CTCL biopsies, and 21 genes unique to CTCL biopsies ($p < 0.05$, $|Log2FC| > 1.5$). AD biopsies exhibited Th2 skewing/chronic inflammation, while CTCL biopsies demonstrated immune evasion and T-cell survival/proliferation. Notably, both the AD and CTCL biopsies expressed CTCL-associated genes typically absent in AD that may represent early markers of CTCL—GIMAP7 (supports T-cell survival through PI3K/AKT signaling), RHOV (facilitates immune cell infiltration by modulating cell adhesion), MAL2 (contributes to immune evasion by downregulating MHC-I), and NOTCH3 (promotes angiogenesis/tumor cell migration). Additionally, two genes with increased expression in CTCL biopsies and not AD biopsies may represent oncogenic drivers of CTCL progression—CCL22 (drives recruitment of immune-suppressive cells) and PTPRCAP (enhances TCR signaling to promote T-cell survival and proliferation). These findings elucidate the molecular differences between AD and CTCL and identify potential biomarkers to improve CTCL detection and treatment in AD patients. Currently, we are integrating spatial data through pathway enrichment analysis and ligand-receptor interaction mapping within tissue niches to further clarify disease mechanisms.

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The oxazolone challenge model captures key features of human atopic dermatitis

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Atopic dermatitis (AD) is a complex chronic skin disease characterized by relapsing-remitting inflammatory skin lesions and chronic itch. Treatment with dupilumab, an IL-4Ra-specific antibody that simultaneously blocks IL-4 and IL-13 signaling, has shown clinical benefit in AD and validated type 2 inflammation as a central driver of disease pathology. To model AD preclinically and characterize mechanisms of action of IL-4Ra signaling in disease, we used a model of topical challenge with the hapten, oxazolone, which mimics a classical pruritic dermatitis driven by mixed inflammation. We characterized canonical features associated with human disease (such as itch, epidermal hyperplasia and skin inflammation) in the model and showed that these endpoints were significantly reduced with anti-IL-4Ra treatment, recapitulating key aspects of human disease. In addition, using next generation sequencing we compared bulk transcriptome of oxazolone-challenged lesional skin to that of human AD patients. Transcriptomic data highlighted similarities in key pathways induced in disease between our mouse model and AD patients, including genes involved in immune responses, epidermal hyperplasia, barrier dysfunction and tissue remodeling. Furthermore, we also observed a parallel overlap in transcriptional changes in response to anti-IL-4Ra treatment. In summary, our data support the translational relevance of the oxazolone challenge model as a preclinical model of AD.

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House dust mite-derived IL-22 secretion by circulating CLA$^+$ memory T cells identify atopic dermatitis patients with a distinct molecular signature in lesional skin

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IL-22-producing cells express the skin-homing markers CCR4, CCR6, CCR10 and the cutaneous lymphocyte-associated antigen (CLA), and are known to be the main source of this cytokine in atopic dermatitis (AD). Although the clinical relevance of IL-22 has been demonstrated by directed therapies, no studies have functionally explored the secretion of IL-22 by CLA$^+$ memory T cells, in a physiological setting and in relationship with patients' clinical features. To address this, we used a coculture of circulating memory CLA$^{+/-}$ T cells with autologous lesional epidermal cells activated with house dust mite (HDM) and quantified IL-22 levels in the supernatants. Production levels of IL-22 positively correlated with patients' epidermal thickness of lesional areas as well as HDM- and staphylococcal enterotoxin B (SEB)-specific IgE plasma levels. IL-22 *in vitro* response by CLA$^+$, but not CLA$^-$, memory T cells enabled AD patient (n=60) stratification into IL-22 producers (IL22P) and non-producers (IL22NP). Lesional skin of IL22P showed increased epidermal hyperplasia, upregulation of IL22 mRNA expression and reduced expression of epidermal structural proteins (FLG, LOR). Because of a compromised skin barrier, they also exhibited increased IgE sensitization to HDM and SEB. Interestingly, the activation of cocultures with SEB elicited a distinct IL-22 response that was not associated with the clinical, histological and molecular features of the patients. Our results indicate that the IL-22 response induced by HDM allergen, but not SEB, identify a subgroup of patients that may benefit from anti-IL-22 targeted therapies.

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Impact of formulation differences on performance of topical gels

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Changes in the components and composition of a topical formulation may influence its performance by impacting the physicochemical and structural (Q3) properties of the product and the thermodynamic activity (TA) of the active pharmaceutical ingredient (API). The objectives of this research were to evaluate the impact of 1) quantitative (Q2) variations of solubility modifiers on API's bioavailability (BA) in the skin and 2) Q2 changes in several excipients on sensorial properties of the topical gels. For the first aim, diclofenac sodium gels were made with varying amounts of either propylene glycol (PG) or polyethylene glycol (PEG) 400. In an in situ drying study, the contents of water, PG, and API remaining on the human skin were assayed (n=3). Fractional solubility (FS) or TA was calculated as the ratio of API concentration to its saturation solubility (SS) in the formulation. An *in vitro* permeation test (IVPT) was performed (3 skin donors, 6 replicates) with a dose of 300 mg/cm^2. For the second objective, several gels were prepared with various amounts of PG and ethanol and their relevant Q3 properties were measured. The sensorial perceptions of selected gels were evaluated in a human subject sensory panel test. The SS of diclofenac increased with increasing level of the solubilizing agents (0-80%) in the binary solutions. The drying studies revealed that ±25% variations in PG/PEG 400, as opposed to ±10%, resulted in discriminated TA profiles and greater differences in permeation for diclofenac, compared to the reference gel. The assessment of Q3 and *in vivo* sensory properties of vehicle gels, suggests that overall, higher ethanol content in the gels resulted in increased drying rate and reduced slipperiness of these formulations. Moreover, assessing the relevant Q3 data such as zero sheer viscosity may be valuable to predict changes in human sensorial perception of the gels. Further research is underway to develop and generalize such methods for multiple excipients and topical dosage forms.

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Sclerotic graft-vs-host disease shares dysregulated gene expression with scleroderma that can be targeted with epiregulin inhibition

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Chronic graft-versus-host-disease (cGvHD) causes skin fibrosis in more than half of affected patients that is similar to systemic sclerosis (SSc), suggesting similar pathologic processes. To understand common signaling mechanisms, we compared differentially expressed genes (DEGs) in skin biopsies of patients with sclerotic GvHD to SSc and healthy controls by scRNA-Seq. Among most cell types, sclerotic GvHD and SSc shared similar proportions of overlapping and unique DEGs. SSc showed elevated number of unique DEGs by endothelial cells, consistent with its well-established vasculopathy. Remarkably, sclerotic GvHD showed strong upregulation of gene ontology terms associated with DC3 dendritic cells including TNFA, type I interferon, and IL-1 signaling ($p<10^{-7}$-10^{-11}), and enrichment by ligand-receptor analysis of the DC3 derived EGFR ligand epiregulin (EREG, p=0.014) which we previously demonstrated to be pathogenic in SSc. To understand EREG inhibition as a therapeutic strategy in sclerotic GvHD, we generated a high affinity fully human EREG neutralizing antibody (NAb, K_D 5x10^{-11}, IC50 2.5 nM). Our fully human EREG NAb was not cross reactive with mouse EREG or other EGFR ligands. We therefore developed a human skin explant system in which viable human skin biopsies could be maintained in culture. Skin explants retained a full repertoire of immune cells, including CD4 and CD8 T cells, macrophages, and dendritic cells. Using the skin explant model with sclerotic GvHD skin biopsies, we found that the human EREG NAb reduced production of key fibrotic and inflammatory disease biomarkers MCP1 ($p<0.0001$), TNC ($p<0.001$), TIMP1 ($p<0.01$), and FN1 (p=0.06) by patient skin. Thus, sclerotic GvHD and SSc share pathways activated by DC3 dendritic cells that can be targeted therapeutically with an EREG neutralizing antibody.

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Agonism of VISTA immune checkpoint as a potential treatment therapy for hidradenitis suppurativa

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Hidradenitis Suppurativa (HS) is a chronic follicular occlusion disease marked by persistent inflammation, scarring, and tunnel formation. New evidence implicates immune checkpoints, notably the V-domain Ig-containing suppressor of T cell activation (VISTA), in HS etiology. Nanostring DSP GeoMx transcriptomic analysis shows elevated VISTA in CD8 region of HS tissues when compared to ruptured follicular cysts (RFC), a histologic mimicker that spontaneously resolves. The GeoMx proteomic panels confirm heightened VISTA and T cell activation markers (LAG3, GITR, ICOS) in CD8+ regions of HS, while multiplex immunofluorescence reveals a threefold increase in VISTA+ cells. Notably, VISTA-positivity correlates negatively with its inhibitory ligand IGSF11 across HS samples, suggesting that decreased agonistic signaling to VISTA may contribute to unchecked, chronic inflammation in HS. We developed a novel *in vitro* explant system to evaluate VISTA agonists as potential therapeutics, using interleukin-6 (IL6) as a readout because it strongly correlates with HS severity in clinical setting. Triamcinolone served as a positive control by reducing IL6 levels in all samples. Notably, in a patient sample where the patient had been injected with triamcinolone one week prior to excision, IL6 levels were similarly reduced but returned to baseline when the sample was placed in our control medium. Baloxavir, recently identified as a VISTA agonist, also significantly decreased IL6 in our explant system, suggesting a role for VISTA-mediated inflammation control. Given the absence of established HS mouse models, this *ex vivo* platform is an essential tool for screening targeted therapies and lays the groundwork for future VISTA-based treatments for HS.

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ORKA-002, a novel extended half-life monoclonal antibody targeting IL-17A/F for the treatment of psoriatic disease

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ORKA-002 is a novel, extended half-life, humanized, monoclonal antibody that binds to IL-17A/F with high affinity. ORKA-002 has been engineered to have optimized properties and deliver enhanced clinical profile. ORKA-002 was evaluated in multiple *in vitro* and *ex vivo* assays in comparison to BIME. Binding affinity to IL-17A and IL-17F was determined by surface plasmon resonance (SPR). Antagonism of IL-17A and IL-17F signaling was evaluated via assays measuring NFκB activation in reporter cell lines. Inhibition of IL-17A-induced or IL-17F-induced IL-6 secretion was assessed using *in vitro* cellular assays using normal human dermal fibroblasts. Half-life extension was measured via pharmacokinetic (PK) analysis in cynomolgus monkeys dosed with a single bolus of ORKA-002. ORKA-002 bound specifically to human IL-17A and IL-17F with high affinity. IL-17A/F binding affinity and functional potencies for IL-17A/F antagonism were comparable to BIME. The half-life of ORKA-002 was significantly extended in cynomolgus monkeys compared to BIME. Based on allometric scaling of the clearance of ORKA-002 observed in this study, predictive simulations of ORKA-002 PK in humans suggest that subcutaneous maintenance dosing every four to six months could be achieved while maintaining high antibody exposures. ORKA-002 exhibits high selectivity and affinity for IL-17A and IL-17F *in vitro*, potent inhibition of downstream cellular signaling *ex vivo*, and an extended half-life in non-human primates compared to BIME, providing the potential for comparable or increased efficacy compared with BIME combined with dosing every four to six months. Pre-clinical evidence for ORKA-002 reported here may lead to therapeutic improvements for psoriatic disease and other inflammatory conditions amenable to IL-17 inhibition. Clinical studies are planned to explore this potential.

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Biophysical prevention of chemotherapy-induced alopecia: Low-intensity ultrasound significantly reduces taxane-induced human hair follicle damage *in vivo*

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Chemotherapy-induced alopecia (CIA) remains one of the most distressing adverse effects of cancer therapy. Since there are no pharmacological treatments that reliably protect human hair follicles (HFs) and their epithelial stem cells (eHFSCs) from acute and permanent CIA, we have explored the impact of biophysical disruption of taxane-induced microtubule cross-linking by low-intensity ultrasound (LIUS). While LIUS is known to limittaxane-induced HF and eHFSCs damage *ex vivo*, it is unknown if this also works *in vivo*. To probe this, a single dose of paclitaxel (PTX, 20mg/kg) was injected i.p. into SCID/beige mice xenotransplanted with healthy human scalp skin in the presence/absence of LIUS (5min at 45KHz applied 2x in a water bath 6 and 24hr after PTX injection). 30 hours after PTX injection, xenotransplants were cryoembedded for quantitative immunohistomorphometry. This showed that LIUS reduced melanin clumping and ectopic melanin in the anagen hair bulb human scalp HFs, indicating reduced HF toxicity and the % of apoptotic cells was also reduced. Moreover, LIUS significantly reduced DNA damage of eHFSC, i.e., the % of gH2A.x+/K15+ cells, and taxane-induced micronucleation in both the bulge and bulb epithelium. Interestingly, LIUS also significantly increased the protein expression of RARa and RXRg in the bulge and bulb, i.e. key signaling pathways that promote clearance of apoptotic eHFSCs in the bulge of mice. These preclinical data from a novel "humanized" mouse model if CIA provide the first evidence that a simple, widely available biophysical intervention (LIUS) can greatly reduce PTX-induced HF damage in both, highly proliferative hair matrix epithelium and quiescent human eHFSCs *in vivo*, and strongly support that LIUS promises to limit both acute and permanent taxane-induced CIA.

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Skin-targeted polyphosphazene adjuvanted vaccines

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Driven by their affordability, ease of manufacture, and safety, subunit antigens have been a cornerstone of modern vaccinology. However, their poor immunogenicity necessitates the development of strategies to enhance their effectiveness. Here, we present polyphosphazene (PPZ)-adjuvanted microneedle patches (MNPs) as a strategically developed skin vaccination platform to increase the immunogenicity of subunit antigens. This platform employs two strategies: (1) co-delivery of the clinically viable PPZ adjuvant with antigen and (2) targeting vaccine components (antigen and adjuvant) to the skin, a highly potent site for immunization compared to traditional sites such as muscle. In murine studies, we evaluated two common PPZ macromolecules, PCEP and PCPP, delivered via a dissolvable MNP format to compare their potency as skin adjuvants. While both PCEP and PCPP enhanced the immunogenicity of subunit antigens, PCEP exhibited superior skin adjuvanticity to PCPP. Mice vaccinated with PCEP MNP loaded with the subunit antigen (PCEP MNP-VAX) exhibited significantly higher levels of antigen-specific IgG antibodies compared to those immunized with PCPP MNP integrating the same antigen (PCPP MNP-VAX). Moreover, PCEP MNP-VAX elicited stronger cellular immune responses, with immune signatures skewed towards Th1-associated responses, in contrast to the responses observed with PCPP MNP-VAX. In translationally relevant studies, PCEP MNP-VAX also induced immunostimulatory migratory antigen-presenting cells in human skin. Collectively these results support the clinical development of PCEP MNPs as a safe and effective subunit vaccine platform for combating emerging and re-emerging pathogens.

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Cutaneous STING pathway agonism enhances the immunogenicity of a SARS-CoV-2 ferritin nanoparticle vaccine in both young and aged mice

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Low thermotolerance, waning immunity, limited breadth, and age-dependent immunogenicity of existing SARS-CoV-2 vaccines justify the development of new thermostable vaccines capable of inducing durable protection against existing and future coronaviruses across the lifespan. Here, we report a thermotolerant coronavirus vaccine candidate combining SARS-CoV-2 Spike protein Ferritin Nanoparticle (SpFN) and the rationally selected STING pathway agonist ADU-S100 in a microneedle patch (MNP). We demonstrate that skin delivery of SpFN+ADU-S100 MNP elicits improved humoral responses in young and aged mice without any systemic reactogenicity, compared to either intramuscular injection of SpFN or MNP administration of monomeric SARS-CoV-2 Spike protein. Co-delivery of ADU-S100 with SpFN in the same MNP improves antigen-specific adaptive immune responses by inducing Th1-predominant pro-inflammatory cytokines and chemokines (IFNβ1, CCL2, CXCL10) in the vaccine-targeted skin microenvironment. Skin vaccination with SpFN+ADU-S100 MNP generates robust, durable, and broadly neutralizing antibodies, as well as potent systemic and pulmonary cellular responses against coronaviruses. Notably, the key immunopotentiating benefits of ADU-S100 as a skin adjuvant is evident in both young and aged mice, as well as in translational studies using human skin models. Together, SpFN+ADU-S100 MNP supports the utility of emerging bioengineering platforms and adjuvants for the development of a next-generation coronavirus vaccine focused on addressing the limitations of authorized SARS-CoV-2 vaccines.

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Subclinical extramedullary leukemia in the skin is a source of relapsed leukemia

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Acute Myeloid Leukemia (AML) is the most common adult leukemia with a 5-year survival rate of 32% and a relapse rate of greater than 50%. Extramedullary leukemia, where leukemic cells seed organs outside the blood and bone marrow, occurs in ~10% of AML patients. Leukemia cutis, or clinically apparent leukemic cell skin infiltrates, is the most common extramedullary site. We observed the pervasive presence of AML-associated mutations in clinically normal patient skin. Event-free survival was 14.3 months versus 8.1 months (p=0.002) for those who had below median variant allele frequency (<2.5% VAF) of AML mutations in the skin (N=94) compared to those who had >2.5% VAF (N=96). A multivariate Cox proportional hazards analysis including the percentage of blasts in marrow and blood, and WBC count revealed that >2.5% AML VAF in the skin was an independent predictor of worse event-free survival (HR=1.49, p=0.051). Some patients retain AML variants in the skin despite clearing marrow after chemotherapy, suggesting that subclinical skin disease may be a source of relapse. Indeed, we observed sporadic leukemic cell infiltration of normal skin at the dermal subcutaneous junction in two murine AML models, one driven by FLT3-ITD and DNMT3A deficiency and another by MYC overexpression. We demonstrate that subclinical skin resident AML is sufficient to cause medullary relapse using a skin transplant model. Single-cell RNA sequencing of marrow, blood, lung, and skin tissue revealed heterogeneity in AML cells across the tissues, including distinct clusters in extramedullary tissues which exhibited downregulation of Il2ra, a T-cell activating gene, and upregulation of the cellular motility and invasion genes S100a4 and Ahnak. We demonstrate that subclinical leukemia is common, and high levels are associated with poor outcomes. In an experimental model, we demonstrate that normal skin can adoptively transfer AML, suggesting that skin-directed therapy and surveillance may be important in AML patients.

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EVO756: An emerging oral MRGPRX2 inhibitor with compelling data from early studies

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Chronic inflammatory diseases often involve complex neurogenic and mast cell-related pathways, with the Mas-Related G-Protein Coupled Receptor X2 (MRGPRX2) playing a pivotal role. This receptor, highly expressed on mast cells and peripheral neurons, has drawn attention for its involvement in non-IgE-driven mast cell degranulation and neurogenic inflammation, contributing to symptoms like itching, coughing, and pain. Because MRGPRX2 responds to a wide range of ligands in inflamed tissues, it is a promising target for therapeutics addressing conditions like chronic urticaria, atopic dermatitis, and severe asthma. EVO756, a novel small molecule, has emerged as a promising oral inhibitor of MRGPRX2. Preclinical data demonstrate robust inhibition of MRGPRX2-mediated responses across experimental models, such as LAD2 cells, human skin-derived mast cells, and skin explants. These findings highlight its broad activity in targeting this receptor. Initial human trials support EVO756's potential. A Phase 1 randomized, double-blind study showed it to be well-tolerated with a dose-proportional pharmacokinetic profile. Its mechanism of action was confirmed through a skin wheal challenge with icatibant, where significant reductions in wheal size affirmed effective receptor blockade. EVO756 stands out as an innovative therapy with the potential to regulate MRGPRX2-mediated processes. Its favorable early-stage results pave the way for further investigations into its clinical utility for managing mast cell-driven and neuro-inflammatory diseases.

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Advanced human skin platform for accelerated bioactive discovery

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Natural product (NP) libraries are a critical source for discovering bioactives in cosmetic, dermatological, and medicinal applications. However, identifying and characterizing novel bioactives from crude materials remains challenging, necessitating biologically complex, and long-lasting skin models capable of capturing subtle molecular and cellular changes. To address these gaps, we developed an advanced human skin platform with the longevity, complexity, and sensitivity required for comprehensive bioactive discovery for skin health. This platform maintains the cellular and structural integrity of human skin within bioengineered culture inserts, supporting extended viability up to one month. Histological and immunohistochemical analyses (e.g., H&E, keratin 5, keratin 10, and filaggrin staining) confirmed sustained tissue integrity and healthy morphology throughout the culture period. This platform has been applied to various applications, including anti-aging, inflammation, and cellular senescence studies, utilizing diverse human skin donors and experimental conditions. For instance, inflammatory models were induced using lipopolysaccharides (LPS), tumor necrosis factor alpha (TNF-alpha), or cytokine cocktails (e.g., IL-17/IL-22) and tested with compounds like clobetasol propionate, epigallocatechin gallate, and fisetin, which showed dose-dependent reductions in pro-inflammatory cytokines and associated gene expression changes. Additionally, extracts from plant-, endophyte-, and marine-derived NP libraries were screened and compared against known tool compounds. Each skin sample generated over 30,000 multi-modal data points, integrating biochemical, transcriptomic, histological, and functional analyses. This data-rich platform provides deep mechanistic insights, enhances clinically relevant efficacy assessments, and bridges critical gaps in longevity, complexity, and scalability. It represents a transformative tool for advancing bioactive discovery and accelerating the development of safer, more effective solutions for skin health.

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Oral and topical formulated fisetin ameliorates psoriasis-like responses in vivo in imiquimod-induced dermatitis in mice

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Conventional psoriasis treatments are effective but often have severe side effects and reduced efficacy, highlighting the need for safer, cost-effective alternatives. We previously demonstrated that fisetin, a dietary flavonol, has mTOR-inhibitory and anti-inflammatory properties, promotes keratinocyte differentiation, and suppresses psoriasis-like responses *in vitro*. However, its *in vivo* efficacy and mechanisms remain unclear. In this study, we evaluated fisetin's effects, delivered topically and orally, on cytokine expression (TNF-α, IL-17), T-lymphocyte activation, and psoriasis features in imiquimod-induced mouse model, compared to rapamycin, a known mTOR inhibitor. Both fisetin formulations significantly reduced psoriasis hallmarks – epidermal hyperplasia, erythema, scaling, and splenomegaly – while inhibiting mTOR activity ($p<0.001$), decreasing cytokine expression, and reducing T-lymphocyte activation. RNA-seq revealed 557 differentially expressed genes (DEGs) in fisetin-treated groups (245 upregulated, 312 downregulated) $p<0.05$, compared to 1,312 DEGs in rapamycin-treated groups, with notable effects on IL-17 signaling, keratinocyte cornification (Loricrin, LCE3C), and cytokine-mediated mTOR activation (CXCL13, HLA-B). Topical fisetin showed superior efficacy, enhancing keratinocyte autophagy via LC3A/B nuclear translocation, absent with systemic (oral) delivery. It also normalized keratin-14 and CD11c+ dendritic cells, suppressed TNF-α production, and inhibited T-lymphocyte activation and STAT3 signaling. Transcriptomic analysis highlighted fisetin's affinity for IL-17A, Calmodulin-4 and mTOR pathway components, supporting its multitargeted therapeutic potential. Our findings suggest fisetin as a potent nutraceutical capable of alleviating psoriasis by inhibiting mTOR signaling, reducing inflammation, and promoting autophagy. Fisetin shows promise as a standalone or adjunctive therapy for psoriasis.

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Inhibiting myeloid-lineage mTOR alleviates psoriasis-like reponse in vivo in imiquimod-induced dermatitis in mice

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While therapeutic advancements have improved disease management, psoriasis' pathogenesis remain underexplored. We recently demonstrated that inhibition of mTOR signaling by phytochemicals, like fisetin mitigate inflammation and psoriasis development in a 3D human skin model of psoriasis. But the significance of mTOR signaling inhibition in inflammation-related cells, particularly myeloid-lineage cells, and their contribution to psoriasis development, remains poorly understood. In this study, we investigated the impact of deleting mTOR signaling in myeloid cells using a novel genetic model of myeloid-specific mTOR knockout (mTORmyeKO) mice subjected to an imiquimod (IMQ)-induced psoriasis-like model. mTORmyeKO mice demonstrated significantly reduced psoriasiform skin lesions, marked by lower Psoriasis Area and Severity Index (PASI) scores, decreased epidermal thickness, and attenuation of hyperplasia and parakeratosis compared to wild-type controls ($p<0.05$). Histological and immunostaining analyses revealed reduced activation and infiltration of CD11c+ dendritic cells and CD3+ T cells, along with diminished keratin 14 expression, a hallmark of hyperproliferative keratinocytes. Dermal inflammatory infiltrates, including helper T cells and macrophages, were markedly suppressed in mTORmyeKO mice ($p<0.05$), underscoring the pivotal role of myeloid-derived mTOR signaling in psoriasis pathogenesis. Mechanistic insights identified a significant reduction in pro-inflammatory lipid kinases, such as PIP5K1 ($p<0.05$), linking mTOR activity to lipid signaling pathways critical for keratinocyte and immune cell crosstalk. These findings establish myeloid-specific mTOR signaling as a central regulator of the inflammatory and proliferative cascades underpinning psoriasis. Our findings highlight a novel therapeutic avenue by targeting myeloid-derived mTOR signaling, providing a foundation for precision therapies to mitigate systemic inflammation and hyperproliferation in psoriasis and related inflammatory disorders.

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Late-Breaking Abstracts

Society for Investigative Dermatology **May 7-10, 2025**

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LB1024

Acquired epidermodysplasia verruciformis (EDV) in a pediatric post-heart transplant patient

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A 13-year-old male with a history of orthotopic heart transplantation at 8 months, stable on tacrolimus and mycophenolate mofetil (MMF), presents with flat warts on the hairline that progressively spread into his scalp. The lesions had been present for 4 years and became more noticeable with sun exposure. Previous treatment with a compound wart gel was ineffective. Physical examination revealed coalescent, hypopigmented papules extending into the frontal hairline. A diagnosis of flat warts (verruca vulgaris) was made in the context of the patient's immunocompromised status. Treatment started with Tretinoin 0.025% cream every other night, along with a single intralesional (IL) candidal antigen injection (0.1 cc). After one month, Tretinoin was increased to 0.1%, a second IL candidal antigen injection was administered, and cidofovir 3% cream was applied twice daily. Over two months, the warts flattened, but the affected skin remained hypopigmented, and PIH was more pronounced due to the patient's skin type. Tacrolimus 0.03% ointment was started for facial hypopigmentation (pityriasis alba). Clindamycin solution was prescribed for scalp folliculitis, and imiquimod 5% cream was started for the warts. At follow-up, no new lesions appeared, but improvement of existing lesions was minimal. HPV vaccination was recommended. Cimetidine was avoided due to potential interactions with MMF. Punch biopsy of the posterior neck confirmed EDV, showing basket-weave keratin overlying mildly acanthotic epidermis with enlarged keratinocytes in the mid and upper epidermis. These cells exhibited blue-gray cytoplasm, vesicular chromatin, and keratohyaline granules. In conclusion, acquired EDV in pediatric heart transplant recipients with skin of color presents unique challenges, particularly with the increased prominence of PIH. A multi-faceted treatment approach and careful monitoring are essential for optimal management

LB1025

Robustness of ex vivo, human skin as a model of general inflammation

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For skin-associated, inflammatory diseases such as psoriasis and atopic dermatitis, explant skin has been used to better understand disease pathogenesis and to investigate the capabilities of experimental treatments to alter disease-specific inflammatory pathways. However, the inflammatory pathways which govern these diseases are not limited to only those of the skin. These pathways have been shown to play significant roles in several cancers and connective tissue diseases such as rheumatoid arthritis and systemic sclerosis. Given this, we investigated the potential of our ex vivo skin models of Th1, Th2, Th17, and LPS-mediated inflammation to be used for studies involving general inflammation in non-skin associated diseases. Here we describe the effects of various small molecule inhibitors on molecular targets which have been shown to be associated with general inflammatory response pathways. Healthy, human explants (n = 1 donor per stimulation) were treated overnight with a range of concentrations for each inhibitor (three concentrations at n = 4 replicates per concentration), followed by stimulation with our inflammatory cocktails and fresh inhibitor for 24 hours. At the conclusion, skin biopsies were collected for total RNA isolation and subsequent RT-qPCR analysis. The results for many of the inhibitors showed a robust dose response for several genes in each of the stimulation pathways, with some showing more than 50% inhibition when compared to stimulated explants only. From the data, we were able to determine the best match between each pathway target and at least one of the stimulation models. This lends evidence to the idea that our ex vivo skin models of Th1, Th2, Th17, and LPS-mediated inflammation can be a vital tool for investigating general inflammation outside of skin alone.

LB1026

Evaluating guselkumab in psoriatic arthritis

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Psoriatic arthritis (PsA) is a chronic inflammatory disease affecting approximately 30% of individuals with psoriasis. The IL-23/Th17 pathway plays a central role in PsA pathogenesis, driving inflammation and joint damage. Guselkumab, a human monoclonal antibody targeting the IL-23 p19 subunit, offers a novel therapeutic approach by selectively inhibiting IL-23 signaling, thereby reducing Th17-driven cytokine production. This review aims to evaluate the therapeutic potential of guselkumab based on recent clinical trial data. A comprehensive literature search was conducted using PubMed, focusing on clinical trials that examined the use of guselkumab in PsA up to September 1, 2024. After applying exclusion criteria, nine randomized controlled trials (RCTs) were included in the review. These trials assessed key efficacy endpoints, including ACR20, ACR50, and ACR70 responses, as well as secondary outcomes such as patient-reported quality of life measures and work productivity indices. ACR20 response rates ranged from 44% to 76% in patients receiving guselkumab, compared to 20% to 33% in placebo groups. Similarly, ACR50 and ACR70 response rates showed consistent improvements over time, reflecting its ability to control disease activity effectively. In addition to its impact on clinical symptoms, guselkumab was associated with enhanced work productivity, reduced presenteeism, and improved overall quality of life scores, reinforcing its broader benefits beyond disease control. The most commonly reported side effects included nasopharyngitis, upper respiratory infections, and headaches, while serious adverse events were infrequent. Overall, guselkumab's selective IL-23 inhibition offers distinct advantages over existing biologics, supporting its role as an effective and well-tolerated treatment option. Future research should explore long-term outcomes, comparative efficacy with other biologics, and biomarker-driven treatment personalization.

LB1027

Spatial transcriptomic profiling reveals fibroblast activation and inflammatory signatures in calcinosis cutis of autoimmune connective tissue diseases

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Calcinosis cutis (CC) is a debilitating condition characterized by calcium deposition in the skin of patients with rheumatic skin diseases; however, its pathogenesis remains poorly understood. We employed spatial transcriptomics to define the molecular signatures of CC in dermatomyositis (DM) and chronic cutaneous lupus erythematosus (CCLE). Skin biopsies from patients with DM (n=3; 1 with CC, 2 without) and CCLE (n=4; 2 with CC, 2 without) were analyzed using the Xenium platform with a human skin gene panel plus 100 custom inflammatory markers. After filtering, the data were normalized, followed by unsupervised clustering and cell type annotation via the SingleR algorithm. CC samples revealed a global upregulation of pro-inflammatory genes (NLRP10, IL1R2, GSDMA) in both DM and CCLE ($q<0.05$), with gene set enrichment analysis demonstrating significant enrichment of calcium ion binding and ECM structural pathways in CCLE samples. In both diseases, histologically-identified CC areas showed differential expression of inflammasome components (AIM2, ZBP1) and immune cell markers (CD68, TYROBP, CXCR4) compared to adjacent non-calcified tissue. Across DM and CCLE, global comparison of fibroblasts demonstrated significant increases in markers of myofibroblast-transition (POSTN, ACTA2) and ECM regulation (ADAM12, MMP2) ($q<0.05$) in CC samples, with enriched pathways involved in mesenchyme development, Wnt-signaling, and Notch pathway regulation ($q<0.05$). Notably, SFRP2+ fibroblasts, a phenotype previously hypothesized to promote fibrosis in CCLE, were not only globally enriched in CC samples of both CCLE and DM but also spatially localized in areas of CC. Our findings suggest that various sources of persistent inflammation drive fibroblast-to-myofibroblast transition, promoting a pro-fibrotic and potentially pro-calcific microenvironment. This spatial transcriptomic approach provides novel mechanistic insights into CC pathogenesis and identifies potential therapeutic targets for this treatment-resistant condition.

LB1028

Association between congenital melanocytic nevi and vitiligo

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Congenital melanocytic nevus (CMN) is a neural crest derived hamartoma that are usually present at birth. Spontaneous involution of CMN with vitiligo can occur in rare cases. Herein, we present a case report about a unique case of onset of vitiligo following changes in a medium sized CMN in a pediatric patient. A 5-year-old female with significant history of a medium size congenital melanocytic nevus present at birth, located on right posterior leg, presented to the dermatology clinic with white macules localized around the mouth, nose, and left knee that have been present for 6-9 months. Upon further questioning, parents reported that the mentioned birthmark had also changed in size and color, developing also, a depigmented macule around it. Per patient's mother, the affected areas were asymptomatic, with no pain, itching, or bleeding. On physical exam, well defined depigmented patches on face and lower extremities were noted, as well as 7.5 x 5 cm brown plaque with hypertrichosis and an adjacent 3.5 x 2.4 cm depigmented patch on the posterior right leg. Patient was started on hydrocortisone 2.5% cream for these depigmented areas. The patient presented a month later for a follow-up. At this time, the mother stated that she has been applying the cream, but lesions appear to be the same. Patient was then started on fluticasone propionate 0.05% cream. This case brings clinical evidence of an association of congenital melanocytic nevus and early vitiligo, especially to understand the prognosis of this autoimmune disorder. Although a benign condition, it is vital that dermatologist monitor the CMN due to its association with melanoma. Knowing the potential association can guide dermatologist to recognize the cause of early vitiligo in young children with CMN.

LB1029

Impact of the autoantibody reactome on disease outcomes in Merkel cell carcinoma

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Merkel cell carcinoma (MCC) is a rare and aggressive skin cancer with a mortality of ~30%. In 80% of cases, MCC arises from integration of the Merkel cell polyomavirus (MCPyV) and expression of viral oncoproteins. Immune checkpoint inhibitors benefit ~50% of patients with advanced disease, but new therapeutic approaches are still needed to address recurrent and resistant disease. To gain insight into potential novel targets for MCC therapy, we sought to understand the potential impacts that natural patient autoantibodies may exert on disease outcomes. While prior studies have identified a protective role of MCPyV-specific B cells, the role of autoantibodies in MCC anti-tumor immunity has not been characterized. Rapid Extracellular Antigen Profiling (REAP), a high-throughput yeast surface protein display-based assay, allows for the identification of autoantibodies targeting ~6,500 different extracellular and secreted proteins. Using REAP, we screened antibodies isolated from 444 MCC patient serum/plasma samples collected within 3 months of diagnosis (avg. 36 days) to identify trends in the autoantibody reactome that associate with disease extent and patient outcomes. By performing Cox proportional hazard ratio analyses, we identified autoantibody responses that were associated with both enhanced (HR < 0.5) and diminished (HR > 2) survival outcomes. These autoantibodies target a diverse set of protein antigens including immunoregulatory cytokines and serine protease pathways that potentially modulate the tumor microenvironment. Ongoing studies aim to biochemically validate the functional effects of autoantibodies on their antigen targets and to isolate and phenotype circulating B cells that recognize autoantigens.

LB1030

The impact of air pollution on the progression of cutaneous lupus erythematosus from a cellular and molecular perspective

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Air pollution accelerates cutaneous lupus erythematosus (CLE) progression through oxidative stress, immune dysregulation, and epigenetic alterations. Fine particulate matter (PM2.5), nitrogen dioxide (NO2), and polycyclic aromatic hydrocarbons (PAHs) penetrate the skin barrier, inducing reactive oxygen species (ROS), mitochondrial dysfunction, and DNA damage in keratinocytes and fibroblasts. Oxidative stress disrupts autophagy, promotes apoptosis, and enhances immune activation via damage-associated molecular patterns (DAMPs). The aryl hydrocarbon receptor (AhR) becomes activated, driving the transcription of pro-inflammatory mediators which perpetuate cell infiltration and further tissue inflammation. Epigenetic modifications, including DNA methylation and histone acetylation shifts, further prime autoreactive responses. A PubMed-based literature review synthesizes molecular, epidemiological, and clinical data to elucidate the mechanistic link between air pollution and CLE disease progression. Clinical studies suggest that patients residing in urban environments with high pollution indices exhibit increased CLE disease severity and heightened photosensitivity, potentially linked to pollutant-driven alterations in UV-induced skin damage responses. Environmental toxins may alter immunosuppressive drug metabolism, affecting treatment efficacy. Findings highlight air pollution as a modifiable disease driver, warranting targeted interventions and public health strategies.

LB1031

Keratinocytes initiate fibroblast reprogramming in autoimmune skin fibrosis

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Fibrosis is a hallmark of select autoimmune skin diseases such as discoid lupus erythematosus. Few animal models of autoimmune disease recapitulate fibrosis, limiting mechanistic and therapeutic discovery. Here, we integrate data from our previously described K5-Vgll3 murine lupus model and human lupus patients to establish a role for keratinocytes in initiating autoimmune skin fibrosis through altering fibroblast transcriptional states. Single-cell RNA-sequencing of pre-lesional transgenic mouse skin suggests that epidermal VGLL3 overexpression initiates inflammation through keratinocyte hypersecretion of cytokines such as TNF and CCL20 and generation of an interferon-rich environment. Pre-lesional fibroblasts respond with induction of a profibrotic, proinflammatory transcriptional program characterized by enhanced expression of extracellular matrix genes and upregulation of chemokines like CCL2, implicated in multiple fibrotic diseases. Primary human fibroblasts cultured in conditioned media from VGLL3-overexpressing keratinocytes show CCL2 induction, confirming a direct effect. Subclustering of murine fibroblasts reveals expansion of a profibrotic fibroblast subset in both pre-lesional and lesional skin. Ligand-receptor analysis identifies this subset as one of the most differentially activated cellular communicators in both pre-lesional and lesional versus control skin. In lesional skin, fibroblasts show induction of classic fibrotic transcripts including targets of TGFB and YAP-TEAD. Comparison of our murine and human single-cell data corroborated many of these findings in human lupus. These results suggest that keratinocytes play a dual role in early autoimmune skin fibrosis through both fibroblast reprogramming and immune cell recruitment and support the use of the K5-Vgll3 model of sex-biased autoimmune disease for investigation of autoimmune skin fibrosis.

LB1032

Leveraging TREM2 agonism to enhance efferocytosis in lupus

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Efficient clearance of apoptotic cells, known as efferocytosis, is crucial for maintaining self-tolerance. Impaired efferocytosis is linked to the progression of inflammatory disorders such as systemic lupus erythematosus (SLE) and cutaneous lupus erythematosus (CLE). Uncleared apoptotic cells accumulate in peripheral tissues as a contributing source of inflammatory stimuli to enhances type-I interferon production, further promoting disease progression. Lipid metabolism plays a significant regulatory role in macrophage efferocytosis and leads to macrophage reprogramming to promote resolution of inflammation. Even so, the mechanisms that control macrophage metabolism during efferocytosis in lupus-like inflammatory conditions are not yet fully understood. Given the potent immune-regulatory function of lipid metabolism on macrophages induced by efferocytosis, we aimed to augment efferocytosis to reprogram macrophages to ultimately support anti-inflammatory responses. We identified TREM2-expressing macrophages as a candidate cell population to control inflammation and thus developed a therapeutically relevant TREM2 agonist to interrogate the effects of TREM2 signaling under inflammatory conditions. Here, we demonstrate that macrophages treated with a TREM2 agonist show enhanced efferocytosis in vitro and ex vivo using macrophages derived from peripheral blood monocytes or isolated from human skin, respectively. We found that this agonist rescued defective efferocytosis by macrophages cultured in the presence of serum from patients with SLE or in the presence of IFN-β without altering phagocytosis of live cells. Mechanistically, TREM2 agonism created a heightened dependency on lipid metabolism leading to enhanced efferocytosis, a process itself known to support pro-resolution phenotypes in macrophages. The insights gained from our investigation present promising avenues for therapeutic intervention in SLE and CLE, emphasizing the manipulation of macrophage metabolism and subsequent effector functions.

LB1033

Demographics, latency, and mortality of severe cutaneous adverse reactions in an FDA pharmacovigilance database

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Adverse drug reactions (ADR) are a significant concern in medicine due to their potential to cause substantial morbidity and mortality. Among the most serious of ADRs are severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and generalized bullous fixed drug eruption (GBFDE). These conditions differ in phenotype, causative drugs, demographics, and latency (time between administration and reaction). We used the FDA Adverse Event Reporting System (FAERS), a comprehensive database with millions of reports submitted by providers, patients, and manufacturers, applying disproportionality measures and machine learning to analyze these rare reactions at scale. After sanitization and deduplication, FAERS was queried from 2004 to 2003 for SCAR cases. A total of 56,683 cases were reported, with median age 53 years (interquartile range [IQR] 32-68), with significant differences in age between phenotypes. Over 200 drugs had positive disproportionality signals. SCAR reporting has increased over time, particularly to biologics and checkpoint inhibitors. Using random forest classifiers, we showed causative drug is the most influential variable on latency, followed by number of concomitant drugs, and mortality is most strongly tied to age and number of concomitant drugs, regardless of SCAR phenotype. This largest retrospective study of SCAR to date shows the variety of phenotypes, causative agents, demographic variables, latencies, and mortality in SCAR patients. Continued mining of these databases, retrospective analyses of electronic health records, and prospective data can expand upon these results, better characterize variations, and improve recognition and care for patients with SCAR.

LB1034

Treatment options for refractory chilblain lupus

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Chilblain lupus (CHLE), also called chilblain lupus erythematosus, is a rare subtype of cutaneous lupus erythematosus (CLE) that mainly affects the extremities in the cold. However, unlike Raynaud's, these lesions do not completely resolve after the cold exposure. Current treatments for CHLE rely on avoidance and off-label medications. Oral steroids, calcium channel blockers, and topical steroids have been used to relieve vasoconstriction. However, many patients find these therapies ineffective or coupled with adverse side effects, emphasizing the demand for alternative therapies. Therefore, we conducted a systematic review to assess the safety and efficacy of alternative treatment options for CHLE. Of the treatments found, patients most often showed significant or complete responses to antimalarials (82%). Antimalarials were also the most common treatment used in the included studies (n=17/40). JAK inhibitors were the next most used treatment in this group (n=9) and also the next most effective (78%). For antimalarials, the most common side effect reported was persistent skin discoloration. For JAK inhibitors, 1 patient experienced transient thrombocytopenia that resolved with ruxolitinib holiday and did not recur upon reinitiation. The most promising treatments in this review were JAK inhibitors, given their similar efficacy and a more favorable safety profile than antimalarials.

LB1035

Development of a skin explant system for testing pharmacologic inhibitors of VGLL3-TEAD in murine lupus

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Systemic lupus erythematosus is a strongly sex-biased disease that affects women at a 9:1 female-to-male ratio. We previously established that VGLL3, a transcription coregulator enriched in skin of women, drives expression of proinflammatory genes in keratinocytes. Murine models with epidermal overexpression of Vgll3 develop cutaneous and systemic lupus-like autoimmune disease that can be ameliorated with normalization of epidermal VGLL3 activity. VGLL proteins bind transcription factors including TEAD proteins. Here, we show that epidermal deletion of TEAD1 dramatically improves survival of mice with epidermal Vgll3-driven murine lupus, suggesting potential therapeutic benefit to VGLL3-TEAD targeting in lupus. However, VGLL3 competes for TEAD binding with the Hippo pathway effector YAP, whose activity is affected by cell density and matrix stiffness. This complicates study of pharmacologic inhibition in cell culture. We have thus developed a skin explant system to test candidate inhibitors of VGLL3-TEAD and YAP-TEAD in murine lupus-like disease. This system uses skin from mice with transgenic epidermal Vgll3 overexpression that is suppressible with doxycycline (K5-tTA;TRE3G-Vgll3-eGFP). We have identified conditions wherein doxycycline treatment reliably downregulates Vgll3 and linked reporter eGFP, as well as proinflammatory and profibrotic target genes that are robust across our systems such as Tnfsf18, Irf1, and Ctgf. Efforts to test predicted VGLL3-TEAD inhibitors and emerging YAP-TEAD inhibitors in clinical trials for oncologic applications are currently ongoing. The results of this work are anticipated to provide vital preclinical data supporting the further exploration of targeting VGLL3-TEAD inhibition in lupus patients with cutaneous involvement.

LB1036

Spatial proteomics of immune checkpoints in discoid lupus and lichen planus

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Interface dermatoses a histopathological pattern observed in several autoimmune connective tissue diseases, including discoid lupus erythematosus (DLE) and lichen planus (LP). Despite distinct clinical presentations, both diseases share histologic features suggestive of common underlying pathogenic mechanisms. However, their immunoregulatory landscapes remain unclear. This study employs spatial proteomics to characterize immune inhibitory receptor expression in DLE and LP, revealing disease-specific and overlapping immune checkpoint pathways. We analyzed archival DLE and LP skin biopsies using the NanoString GeoMx Immuno-Oncology protein panel. Heatmap and UMAP clustering demonstrated distinct protein expression profiles between DLE and LP. Cross-segmentation analysis of keratinocytes (PanCK+), CD4+, and CD8+ T cells identified differential immune checkpoint and T cell activation expression. In DLE, immune modulation was compartmentalized, with keratinocytes expressing PD-L2, CD44, and CD127 compared to CD4+ and CD8 T cells. Additionally, CD4+T cells in DLE expressed greater ICOS, CTLA4, OX40L, CD40, 4-1BB, and PD-1 compared to CD8+ T cells. In contrast to DLE, CD4+ and CD8+ T cells within LP tissues expressed VISTA, PD-L1, and STING, whereas keratinocytes express OX40L, CD127, CD44 and ARG1. These findings underscore key immunoregulatory differences in interface dermatoses and suggest potential therapeutic strategies, including immune checkpoint agonists, for targeted intervention in autoimmune dermatoses

LB1037

Single-cell and spatial transcriptomics reveal elevated pro-inflammatory fibroblasts and hormonal activity in hidradenitis suppurativa

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Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition characterized by painful nodules, abscesses, and draining tunnels. While immune dysfunction and follicular occlusion are central to HS pathogenesis, dysregulated fibroblast activity may contribute to fibrosis and tunnel formation. Fibroblasts play a key role in tissue repair and exhibit heterogeneity in multiple fibrotic skin diseases, which are often characterized by fibroblast hyperproliferation and excessive extracellular matrix accumulation. However, fibroblast heterogeneity in HS is not fully characterized and the role of fibroblasts in disease progression remains of interest. In this study, we explored fibroblast heterogeneity in HS by performing single-cell RNA seq and spatial transcriptomics on skin samples from HS nodules, perilesional skin and normal skin. Our results identify five HS fibroblast subpopulations: secretory-papillary, secretory-reticular, mesenchymal, pro-inflammatory and myofibroblasts. A population of pro-inflammatory fibroblasts expressing inflammatory cytokines and other markers of immune activity was uniquely present in HS nodules but absent in perilesional and normal skin. Importantly, genes encoding hormone receptors, including those for androgen, glucocorticoid, estrogen, progesterone, thyroid, and growth hormone, were more highly expressed in HS nodule fibroblasts, as compared to fibroblasts from normal skin. While the involvement of hormones in HS pathogenesis is undefined, the disease's onset after puberty, flare-ups during menstruation and pregnancy, and the effectiveness of hormonal therapies in treating some HS patients strongly suggest a link between sex hormones and immune activity in HS. Our findings offer new insight into the inflammatory and hormonal activity of HS fibroblasts and their potential role in disease progression. Targeting fibroblast-driven inflammation and hormonal signaling may offer new therapeutic approaches for HS treatment.

LB1038

Characterizing antigen specificities of skin-infiltrating B and plasma cells in cutaneous lupus reveals anti-nuclear and hemidesmosome-specific targets

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that causes tissue damage across multiple organ systems, including the skin. Cutaneous lupus erythematosus (CLE) can occur in the presence or absence of SLE, and patients with isolated CLE can progress to SLE. B cells are known to contribute to SLE disease initiation and progression via multiple mechanisms, yet the role of skin-infiltrating B and plasma cells in CLE pathogenesis and progression is not clear. Prior studies demonstrate CLE lesional B cells forming diffuse infiltrates or pseudofollicular structures, suggesting a role in antigen-presentation and T cell activation. Here, we interrogate the antigen specificities of B and plasma cells in CLE skin lesions to investigate the potential roles of CLE lesional B and plasma cells in disease pathogenesis. We expressed and purified recombinant IgG (rIgG) using B cell receptor (BCR) heavy and light chain sequences obtained from single-cell RNA sequencing of skin-infiltrating B and plasma cells in CLE skin lesions from 2 patients with CLE and concurrent SLE. This panel of 29 rIgG was purified and rIgG specificities were evaluated using reactivity assays including antinuclear antibody (ANA) ELISA, extractable nuclear antigen ELISA, autoantibody microarray, skin immunofluorescence, and phage immunoprecipitation-sequencing (PhIP-Seq) to identify putative antigen specificities of the B and plasma cells from CLE skin lesions. rIgG that specifically bound skin hemidesmosome proteins as well as ANA targets were identified, suggesting a potential role for skin-lesional B and plasma cells in promoting tissue damage in CLE.

LB1039

From depth to distribution: Multimodal PRAME analysis improves prognostication and surgical planning in acral melanoma

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The purpose of this study was to develop and validate a combined 2D/3D approach integrating tumor depth assessment with quantitative PRAME expression for improved pre-operative acral melanoma evaluation. We employed complementary approaches using 3D pathological analysis with tissue clearing, immunofluorescent staining, and volumetric imaging to characterize PRAME spatial distribution, along with clinicopathological analysis on 88 acral melanoma specimens. Using QuantCenter® software, we developed a depth-PRAME combined (D-PRAMEC) scoring system. Our 3D visualization revealed that PRAME-positive cells predominantly localize to invasive borders. Quantitative 2D analysis demonstrated that PRAME expression positively correlates with aggressive histological features (necrosis, increased mitoses, ulceration). The D-PRAMEC scoring system effectively stratified patients into prognostic groups. In multivariate analysis, high D-PRAMEC levels independently predicted progression-free survival (aHR 5.78, 95% CI 1.97-16.98, p=0.001). Notably, patients with medium/high D-PRAMEC scores showed significantly higher progression risk than those with low scores. Our approach combines 3D PRAME distribution mapping with quantitative 2D analysis to better characterize tumor architecture and prognostic information compared to conventional assessment. This integrated methodology enhances pre-operative decision-making for acral melanoma surgery, particularly in planning margins and predicting aggressive disease behavior.

LB1040

Large language models display skin tone biases in the evaluation of common dermatological conditions

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SkinGPT-4, a large vision-language model, leverages datasets of annotated skin disease images to augment clinical workflows and treatments in underserved communities. However, its existing training dataset predominantly represents lighter skin tones, and hence may limit diagnostic accuracy for darker skin tones. Here, we evaluated performance biases in SkinGPT-4 across skin tones on common skin diseases, including eczema, allergic-contact dermatitis, and psoriasis on the open-sourced SCIN dataset. A clinical evaluation of SkinGPT-4 was conducted by a board-certified dermatologist on six clinically-relevant skin diseases, including eczema and allergic contact dermatitis, from 300 cases in the open-sourced SCIN dataset. Images were assessed based on diagnostic accuracy, informativity, physician utility, and patient utility. Model fairness metrics, including democratic parity and equalized odds, were calculated over skin tones for each evaluated condition. SkinGPT-4 achieved an average demographic parity of 0.10 across all skin tones on the Fitzpatrick scale. Notable differences of 0.10, 0.10, 0.11, and 0.15 in demographic parity were observed between the lightest and darkest skin tones relative to diagnostic accuracy, informativity, physician utility, and patient utility respectively. Model hallucinations in physical artifacts and body anatomy occurred at a rate of 17.8%. SkinGPT-4 demonstrates weaker performances on darker skin tones compared to lighter skin tones among prevalent skin conditions. Model biases exist across diverse evaluation criteria, and model hallucinations may affect diagnostic efficacy. Further research is needed to better understand and mitigate biases in large vision-language models to promote equitable deployment in dermatological workflows.

LB1041

SkinGPT-4 provides a generalizable foundation for fair and customizable skin disease classification models

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SkinGPT-4 is a large vision-language model used to interpret skin disease images. Preliminary evaluations on the open-sourced SCIN dataset have observed skin tone biases in SkinGPT-4 performance. Here, we leveraged the SkinGPT-4 backbone to develop finetuned models for custom skin disease classification tasks and explored bias mitigation strategies. Six-hundred cases with uniform skin tone representation were queried from the SCIN dataset containing common skin diseases, such as Tinea and Urticaria, for model training. Customized image classification models were designed by attaching a learnable multilayer perceptron (MLP) head to the SkinGPT-4 vision encoder. Hyperparameters such as learning rate, batch size, and MLP-depth were tuned, and model performance was evaluated across skin condition pairs with similar presentations. Performance metrics, such as AUROC and demographic parity, were measured. Across skin disease pairs with similar appearances, our models achieved an average F1, precision, and AUROC of 0.75, 0.78, and 0.78, respectively. The average demographic parity and the largest difference between distinct skin tones were observed as 0.75 and 0.21, respectively. In our best model, group-stratified demographic parity scores of 0.83, 0.83, 0.76, 0.89, 0.90, and 0.90 were achieved across skin tone categories in the Fitzpatrick scale from 1-6, respectively, indicating robust fairness. Similar performances were observed when adapting our base model to disease triplets, providing evidence of generalizability. This study demonstrated the efficacy of training accurate and fair machine learning models using SkinGPT-4 for custom skin disease classification tasks. Our study hopes to improve the clinical application of AI in dermatology, particularly regarding demographic biases.

LB1042

The binding of phenobarbital, phenytoin, and dapsone to HLA-B*13:01 differs from that of allopurinol to HLA-B*13:02

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Background: The relationship of drugs that cause severe cutaneous adverse reactions (SCARs) with human leukocyte antigen (HLA) type has been investigated extensively. Carriers of HLA-B*13:01 have been reported to be prone to drug eruptions of phenobarbital, phenitoin, and dapsone. Also, SCARs due to allopurinol reportedly occur in carriers of HLA-B*13:02. Objectives: To assess the associations of drugs with HLA-B*13:01, which is related to SCARS, by comparing their chemical structures. Also, to examine the binding structure of allopurinol to HLA-B*13:02 and that of phenobarbital, phenitoin, and dapsone to HLA-B*13:01. Methods: A BLAST search of the Protein Data Bank was performed based on the α-domain sequences of HLA-B*13:01 and HLA-B*13:02 and the 10 most homologous structures were selected as templates for homology modeling. Three-dimensional models of HLA-B*13:01 and HLA-B*13:02 were generated using Modeller 9.13. Next, docking experiments were carried out between the modelled 3D structure of HLA-B*13:01 and HLA-B*13:02 with phenobarbital, phenitoin, dapsone, and allopurinol using Autodock vina, and the binding modes were compared. Results: HLA-B*13:01 has a sub-pocket because amino-acid residue 95 is isoleucine (I95), which has a small side chain and binds to that site, causing severe eruption. The docking of phenobarbital, phenitoin, and dapsone to HLA-B*13:01 involved the sub-pocket, indicating an association with SCARs. A comparison of the binding modes of HLA*13:01 to phenobarbital, phenitoin, and dapsone revealed structural commonalities. Conclusion: The common binding modes of HLA*13:01 and phenobarbital, phenitoin, and dapsone suggest the hot spots of their interaction with, and the key residues for their binding selectivity to, HLA-B*13:01.

LB1043

Effect of oral baricitinib on experimental cutaneous allergic and irritant reactions

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Janus kinase inhibitors (JAKi) are becoming more commonly utilized in the treatment of dermatologic inflammatory and autoimmune diseases. Yet, the effect of JAKi on allergic and irritant skin reactions is an underdeveloped area of investigation. The goal of the present double-blinded placebo-controlled pilot study was to assess the ability of oral baricitinib (2mg/daily x 14 days) to treat experimental delayed-type hypersensitivity reactions (DTH) from Candida albicans antigen and irritant reactions from sodium laurel sulfate (SLS). Twenty-one healthy male subjects were recruited and were subjected to DTH testing with Candida antigen and SLS treatment. Measurement of DTH reactions by erythema and area of reaction by calipers along with pruritus and tissue RNA-seq by minimally invasive dermal biomarker patches were tested before and on repeat challenges following treatment with baricitinib or placebo. Oral baricinitib decreased the erythema responses and pruritus but not the area of induration by the second DTH challenge in comparison to placebo. The results of the tissue-seq indicated decreased inflammatory responses in both DTH and irritant skin reactions in response to JAKi. These pilot studies suggest that oral baricitinib could have efficacy in the management of both irritant and allergic contact dermatitis.

LB1044

Effects of IL-31 inhibition on Th2 clonality in prurigo nodularis

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Previous studies have indicated the increased expression of Th2-released IL-31 in Prurigo Nodularis (PN), with associated increase in keratinocyte proliferation and fibrosis. We utilized data from a cohort of n=16 patients with PN treated with the IL-31R inhibitor nemolizumab (total of 81 bulk RNAseq datasets from lesional and non-lesional PN) to identify T cell clonotypes. We further integrated the results with three independent PN scRNA-seq cohorts, totaling 246k cells from 34 samples. TCR sequences from the bulk and scRNA-seq data were identified by mapping reads to the TCR regions by TRUST4 using the IMGT reference. We identified 409 and 103 unique clonotypes from the scRNA-seq and bulk RNA-seq cohorts, respectively, with 68 of the TCRs overlapping between the two sample types. Notably, 45.8% of the overlapping sequences were from Th2 cells (IL4RA+, IL13+, and IL10+). Five TCR clones from the PN lesions at baseline became absent in the nemolizumab treated cohort by week 12, while remaining stable in the placebo group at the same time point. Notably, from the bulk lesional skin, nearly twice as many TCR clones were detected in the placebo group when compared to the nemolizumab treated group after 12 weeks of treatment (25 vs. 14 unique clonotypes; compared to lesional baseline with 46 and 33). We found expression of the TCRs TRBV9*01_TRBJ2-1*01 and TRGV10*02_TRGJ1*02 in bulk RNA-seq data and lesional scRNAseq data from PN lesions at baseline. From the bulk RNAseq, we found that TRGV10*02_TRGJ1*02 positively correlated with IL-13/IL-4 signaling ($p= 1.28x10^{-9}$, R > 0.7; including IL13RA2 and IL4R), keratinocytes differentiation (including DEFB4B R=0.85, $p=1.43x10^{-18}$ and KLF7 R=0.66, p=7.97x10-9), and IL-31 signaling (including OSMR R=0.34, $P=7.47x10^{-3}$), providing evidence for clonal specific Th2-keratinocyte interactions. Our findings demonstrate that IL-31 inhibition with nemolizumab suppresses Th2 clonality and associated type 2 signaling, providing evidence for the role of IL-31 in driving Th2-keratinocyte cross-talk in PN skin.

LB1045

Modeling keloid expansion: Integrating single-cell and spatial transcriptomics with mathematical approaches

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Keloid is a tumor-like scarring disorder of human skin that arises in genetically predisposed individuals following injury. Unlike other pathological scars, keloids exhibit a distinctive horizontal propagation pattern. Here, we integrated single-cell RNA sequencing (scRNA-seq), spatial transcriptomics (ST), and agent-based mathematical modeling (ABM) to investigate the mechanisms driving keloid progression. Our integrated analysis on scRNA-seq and ST data revealed that heterogeneous fibroblast populations are uniquely enriched at the keloid periphery, forming a distinct spatial distribution pattern. To explore the signaling mechanisms underlying keloid propagation, we developed an ABM incorporating fibroblasts and extracellular collagen fibers. We evaluated multiple interaction models for fibroblast subtypes, and simulations demonstrated that keloid propagation was consistently recapitulated under specific models with defined activation and inhibition dynamics. These findings suggest that fibroblast-mediated signaling networks are key drivers of keloid expansion. Targeting these interactions may provide promising therapeutic strategies for next-generation keloid treatments.

LB1046

Functionality of novel handheld 3D imaging system for the measurement of pigmented lesions

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Diagnosing melanoma requires accurate evaluation and monitoring of pigmented lesions. Digital imaging has become increasingly important, including 3D imaging. However, most 3D imaging requires whole-body instruments, which oftentimes requires large funds, specialists and cannot be used in rural settings. Here we examine the use of a novel handheld 3D imaging system to evaluate pigmented lesions. This clinical trial evaluated 161 pigmented lesions using the 3D Derma Monitor and iPad, then compared to dermatoscope, the gold standard. Variables investigated included primary diameter (mm), secondary diameter (mm), area (mm^2), shape border irregularity (%), and primary and secondary shape asymmetry (%). Absolute differences in measurements from the Derma Monitor and iPad compared to the dermatoscope were calculated. A Wilcoxon's signed-rank test found statistically significant differences between the Derma Monitor and the iPad, with consistently more accurate measurements for the Derma Monitor (p-value <0.05 for all variables, including primary and secondary diameter, area, primary and secondary asymmetry, and border irregularity). The Derma Monitor demonstrated significantly improved measurement accuracy compared to iPad imaging. The handheld device also allowed for image capturing of larger surfaces, such as entire backs with up to 0.1mm resolution. This presents a unique opportunity for improved monitoring of lesions, while also being used for a diverse set of conditions, including rashes, wounds and pre-/post-operative follow up. Reliable and reproducible imaging is crucial for telemedicine and computer-aided follow-up of skin lesions to increase high quality coverage of underserved areas

LB1047

Multi-target drug repurposing through exploration of melanoma omics data

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Backgrounds: Melanoma is an aggressive skin cancer driven by complex molecular alterations. Integrating multi-omics data can uncover potential drug targets for improved treatment strategies. Methods: Genomic and copy number altered genes were obtained from the GDC Data Portal and cBioPortal, melanoma drug-associated mutated genes from CIViCdb, differentially expressed genes(DEGs) from GEPIA2 and survival-related genes using GEPIA2, SurvNet, and HPA. Proteomic candidates are linked with melanoma staging and survival or are central in the co-expression network of TCPA, and high-abundance blood proteins are gathered from the HPA. The intersection between different omics candidates searched and those presented in at least three datasets was prioritized. Functional validation was conducted via Enrich-KG for pathway analysis, VarElect for genetic associations with melanoma, and CancerHallmarks for hallmark relevance. Drug repurposing targeted multi-gene FDA-approved drugs by enriching candidates across IDG Drug Targets, MAGMA Drugs, DGIdb, and DSigDB using Enrichr. Results: A total of 620 genomic and 789 copy number altered genes(≥10% in melanoma patients), 725 survival-associated genes, 2,148 DEGs, and 118 proteomic candidates were identified. EGFR appeared across all omics datasets, CTNNB1 and MYH11 in four, and 39 candidates in three. Pathway enrichment analysis highlighted PI3K-AKT signaling, cell proliferation and multiple cancer-related pathways. VarElect confirmed strong melanoma associations, particularly for CTNNB1 and AKT1, with CancerHallmarks enrichment linking candidates to all cancer hallmarks. Drug repurposing identified Paclitaxel, Imatinib, Sorafenib and Everolimus as the most promising FDA-approved therapies targeting multiple candidates. Conclusion: Our multi-omics approach identified key melanoma-associated genes and repurposable FDA-approved drugs. Further validations translation are needed to improve melanoma treatment.

LB1048

Assessment of cutaneous tissue using light-sheet microscopy: Evaluating feasibility of 3D-microscopy for mohs micrographic surgery

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Mohs micrographic surgery(MMS) offers high cure rates for high-risk skin cancers but is time-consuming. Hybrid open-top light sheet microscopy(OTLSM) enables fast 3D imaging and holds promise for MMS with rapid staining protocols. The aims of this research were to 1) develop a fast-staining protocol for imaging of debulk MMS tissue using OTLSM, and 2) determine feasibility, challenges, strengths, and future applications of the use of the OTLSM for MMS. Patients undergoing MMS for squamous cell(SCC) or basal cell carcinoma(BCC) were eligible to participate. For each tumor, a shave debulk was taken as part of MMS. Two novel ultra-fast protocols, using either DRAQ5 or SYBR Gold with NHS ester, were developed for staining the tissue in pseudo-H&E, followed by clearing in 2,2'-Thiodiethanol. The surface of the tissue was then imaged using OTLS with a custom sample holder with an adjustable-pressure lid. The total imaging and processing time was less than 5 minutes. The study included 32 MMS debulks from 27 patients, mostly from head or neck tumors (n=31). Diagnoses included BCC (65.6%, n=5), SCC (18.8%, n=6), and SCC in-situ (15.6%, n=5). The ultra-fast staining protocol enabled quicker visualization than traditional methods, but interpreting live images was challenging due to the OTLSM 45-degree geometry. Additional challenges included ensuring tissue flatness, balancing stain penetration with timing, and maintaining proper tissue orientation during imaging. Additional optimization of our OTLSM imaging protocol has the potential to reduce tissue processing and imaging times as compared to frozen pathology. Furthermore, if challenges are overcome, the 3D-nature of the OTLSM technology will allow for a more complete analysis of surgical margins compared to traditional pathology. Jorge A. Rios-Duarte and Shikhar Dhingra contributed equally. Shikhar Dhingra works for Alpenglow Biosciences.

LB1049

Machine learning-driven screening of cosmetic allergens: Integrating consumer reviews of cosmetics

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Introduction: As cosmetic use increases, adverse reactions pose growing clinical and public health concerns. This study leverages machine learning to predict risky cosmetics and ingredients by integrating data on ingredients and online-cosmetic consumer reviews describing adverse reactions. Method: The method involves collecting ingredient and review data, preprocessing to recognize fake reviews and extract aspects, and training models to identify risky cosmetics and ingredients associated with adverse reactions. Finally, suspect ingredients were primarily verified by patch test. Results: Among the machine learning models we used, the CatBoost model demonstrated the best predictive performance in suspected allergen screening, achieving an area under the curve (AUC) of 0.74. It identified 13 suspected allergens, among which 11 (84.6%) demonstrated positive reactions in a clinical cohort of 22 participants. Sorbitan sesquioleate exhibited the highest positive rate among participants at 31.8%, followed by xanthan gum, Pigment Red (CI16035) and propylene glycol, each with a positive rate of 22.7%. Conclusion: This study establishes a machine learning-driven framework for time-efficient and cost-effective identification of cosmetic allergens through large-scale analysis of real-world consumer reviews. Our approach leverages publicly accessible online consumer data of cosmetics, and represents the first instance of cosmetic adverse reaction risk assessments solely based on consumer reviews. Besides, primary verification confirms that the method effectively screened potential allergens in cosmetics.

LB1050

Identification of biomarkers of mastocytosis: Insights from whole transcriptome analysis with single cell resolution and immunohistochemical analysis

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Systemic mastocytosis (SM) is a rare disorder characterized by an excessive accumulation of mast cells in various tissues, presenting significant challenges in both diagnosis and treatment. In this study, we aimed to identify pathway expression profiles and potential biomarkers in the skin of SM patients. We performed whole transcriptome analysis with single-cell resolution using Visium HD (10x Genomics) on skin samples from two SM patients. This was followed by in-silico analysis of mast cell-specific genes (TPSG1, CMA1, CPA3), which encode mast cell tryptase, chymase, and carboxypeptidase, respectively, as well as activation markers for FcεRI-mediated Ca2+ mobilization and NF-kB pathways, to definitively characterize the mast cell population. Further analysis revealed that members of the galectin family—particularly galectin-3 and galectin-8, glycan-binding proteins involved in immune modulation and inflammation—are expressed by mast cells. Immunohistochemistry (IHC) confirmed the expression of these galectins in mast cells within mastocytoma and cutaneous mastocytosis. In addition, Visium HD and IHC data both showed prominent galectin-3 expression in keratinocytes and galectin-8 expression in endothelial cells. These findings suggest that targeting galectin-3 and galectin-8, which may play a role in disease pathology, could offer a promising approach for developing precision therapies for mastocytosis.

LB1052

The skin-brain connection: How mental health impacts dermatological conditions

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Recent dermatological research is uncovering new insights into the intricate connection between the skin and the brain, emphasizing the brain's profound impact on skin health and dermatological symptoms. Studies have shown that psychological stress, anxiety, and depression can significantly exacerbate various skin conditions, such as acne, eczema, and psoriasis. Neurotransmitters and hormones released by the brain, such as cortisol and substance P, can influence inflammatory pathways in the skin, leading to increased sensitivity, irritation, and flare-ups of existing dermatologic issues. Furthermore, the brain's regulation of immune function plays a pivotal role in developing and progressing conditions like atopic dermatitis and psoriasis. Integrating neurodermatology into dermatological practice offers a more comprehensive approach to patient care, where mental health and stress management are considered key components in managing chronic skin conditions. This review examines how the brain influences skin health and leverages this connection to improve treatment outcomes, emphasizing the importance of a multidisciplinary approach that combines dermatology, mental health interventions, and the skin-brain axis. Ongoing research focuses on developing therapies that target both the brain and skin, offering the potential for more effective treatments that address the root causes of dermatological symptoms. Future directions will look into integrating mental health care into dermatology for holistic, personalized skin care and healing approaches.

LB1052

The skin-brain connection: How mental health impacts dermatological conditions

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Recent dermatological research is uncovering new insights into the intricate connection between the skin and the brain, emphasizing the brain's profound impact on skin health and dermatological symptoms. Studies have shown that psychological stress, anxiety, and depression can significantly exacerbate various skin conditions, such as acne, eczema, and psoriasis. Neurotransmitters and hormones released by the brain, such as cortisol and substance P, can influence inflammatory pathways in the skin, leading to increased sensitivity, irritation, and flare-ups of existing dermatologic issues. Furthermore, the brain's regulation of immune function plays a pivotal role in developing and progressing conditions like atopic dermatitis and psoriasis. Integrating neurodermatology into dermatological practice offers a more comprehensive approach to patient care, where mental health and stress management are considered key components in managing chronic skin conditions. This review examines how the brain influences skin health and leverages this connection to improve treatment outcomes, emphasizing the importance of a multidisciplinary approach that combines dermatology, mental health interventions, and the skin-brain axis. Ongoing research focuses on developing therapies that target both the brain and skin, offering the potential for more effective treatments that address the root causes of dermatological symptoms. Future directions will look into integrating mental health care into dermatology for holistic, personalized skin care and healing approaches.

LB1053

Exploring the pathogenesis of bullous pemphigoid and stroma–immune cell interactions using single-cell sequencing and spatial transcriptomics

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Background: Bullous pemphigoid (BP) is an autoimmune skin disorder characterized by the formation of blisters on the skin and mucous membranes. Although the immune mechanisms underlying pemphigoid have been partially elucidated, traditional research methods struggle to fully uncover the immune cell subpopulations, their interactions, and spatial distribution within the lesions. Objective: This study utilized single-cell RNA sequencing and spatial transcriptomics to construct a comprehensive single-cell atlas of the epidermis, dermis, and full skin from BP patients, systematically analyzing the immune microenvironment characteristics of BP skin lesions. Methods: We collected 4 epidermal and 9 dermal skins from BP patients, and full skin from 3 BP patients, in addition to 6 full skin samples from healthy controls. Additionally, single-cell transcriptomic data from 2 normal epidermal and 4 normal dermal were obtained from public databases. FFPE samples from 6 BP patients and 2 healthy controls were also collected, and spatial transcriptomic analysis was performed using the 10 × Genomics CytAssist Visium platform. Results: TNC+ fibroblasts were notably enriched in the BP dermis, particularly in the upper dermis beneath the blister. These TNC+ fibroblasts responded to IL-1β signaling and contributed to the inflammatory response in BP lesions. INHBA+ macrophages, which were enriched in BP lesions, exhibited high IL-1β characteristics, suggesting that they may regulate IL-1β production through endoplasmic reticulum stress. Cell-cell communication analysis revealed frequent interactions between TNC+ fibroblasts and INHBA+ macrophages as well as classical dendritic cell type 1 (cDC1) subpopulations, indicating their critical roles in the immune response of BP. Conclusion: The results suggest that the IL-1β signaling pathway plays a pivotal role in the immune pathogenesis of BP. Moreover, the interaction between TNC+ fibroblasts and INHBA+ macrophages may be a key mechanism in BP pathogenesis. These findings provide new insights for future research on the immune mechanisms of BP.

LB1054

Cell atlas of palmoplantar pustulosis reveals inflammation-associated fibroblast populations

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Palmoplantar pustulosis (PPP) is a chronic inflammatory skin disease characterized by recurrent sterile pustules on the palms and soles. However, the role of fibroblasts in the disease pathogenesis remains unclear. To investigate the cellular heterogeneity and microenvironmental alterations in PPP, we performed single-cell RNA sequencing on paired lesional and non-lesional skin samples from a PPP patient. Through unbiased clustering analysis, we identified eight major cell populations, including keratinocytes, T cells, antigen-presenting cells, endothelial cells and fibroblasts, among others. Our study revealed novel fibroblast subpopulations with distinct inflammatory signatures. Specifically, we identified six FIB subsets characterized by the expression of unique marker genes, including CCL19, CCL26, COMP, CXCL12, IGFBP7, and TIMP3. Comparative analysis between lesional and non-lesional areas revealed a significant expansion of five FIB subsets in the lesional skin, suggesting their potential role in PPP pathogenesis. Notably, the COMP fibroblast subset was the only group that showed a marked decrease in lesional areas, whereas all other subsets were significantly upregulated in inflamed regions. This pattern highlights a dynamic shift in fibroblast composition, indicating that different FIB subsets may contribute to disease progression through distinct mechanisms. The enrichment of inflammatory-associated fibroblasts in PPP lesions suggests their involvement in immune cell recruitment, extracellular matrix remodeling, and tissue inflammation. Our findings provide novel insights into fibroblast heterogeneity in PPP and suggest that fibroblast subsets actively participate in shaping the inflammatory microenvironment. Targeting specific fibroblast populations may offer new therapeutic opportunities for treating PPP. Further research is needed to explore the molecular pathways regulating these fibroblast subsets and their crosstalk with immune cells.

LB1055

A mast cell-derived neuropeptide recruits eosinophils to promote skin inflammation

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The skin functions as a crucial barrier organ, capable of detecting and reacting to environmental stimuli. As a highly dynamic tissue, the skin is densely populated with a variety of immune cells and extensively innervated by the peripheral sensory nervous system, creating a unique interface for neuroimmune interactions. Neuropeptides are vital chemical messengers released by the nervous system to convey neural signals. Emerging evidence underscores their significance in regulating immune responses in barrier tissues. Neuromedin B (NMB), a recently discovered neuropeptide expressed by sensory neurons, is known to mediate itch sensations and sneezing reflexes. However, its role in inflammatory responses has remained largely unclear. Using a murine model of atopic dermatitis (AD)-like disease, we discovered that NMB is indispensable for both skin inflammation and itch-related scratching behavior. Intriguingly, specifically depleting NMB in sensory neurons reduced scratching without affecting inflammation, indicating that a non-neuronal source of NMB contributes to inflammation. Whole-mount staining of the skin revealed that NMB is rarely expressed in sensory fibers but is mainly produced by cellular components. Utilizing an NMB-EGFP reporter mouse line, we identified skin mast cells as the primary source of skin NMB, a characteristic that differentiates them from mast cells in other tissues. Furthermore, the NMB receptor (NMBR) was found to be highly expressed on eosinophils and elevated in AD-like conditions. Through loss-of-function and gain-of-function experiments, we demonstrated that mast cell-derived NMB recruits eosinophils to the skin, exacerbating AD-like inflammation. Our findings position mast cells at the center of neuroimmune interactions through their release of neuropeptides like NMB, establishing mast cell-derived NMB as a potential therapeutic target for type 2 immune-driven skin diseases.

LB1056

Single-cell RNA sequencing reveals an exhausted immune landscape in human sclerotic chronic graft-versus-host disease

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We aimed to investigate the cell types and signals that produce human cutaneous sclerotic chronic graft-versus-host disease (cGVHD), a highly morbid complication of allogeneic hematopoietic stem cell transplantation. Using single-cell RNA sequencing, we compared the predominant skin cell populations of sclerotic cGVHD patients (n=8) and normal skin controls (n=8). An increased proportion of CD8+ T cells were identified in affected skin from sclerotic cGVHD patients compared to normal skin controls that were characterized by an exhausted phenotype, expressing PDCD1, LAG3, and TNFRSF9, with unaffected skin showing an intermediate phenotype. Additionally, a population of CXCL13+ T follicular helper cells was identified most prominently in sclerotic cGVHD skin, expressing PDCD1, LAG3, and TIGIT. These exhausted T cell populations are likely induced by chronic alloantigen stimulation in the setting of cGVHD, and published murine data suggest that exhausted progenitor CD8+ T cells maintain GVHD. Distinct profibrotic myeloid cell populations were also identified in affected skin, along with SFRP4+/ADAM12+ myofibroblasts, which have been identified in skin in systemic sclerosis. While sclerotic cGVHD pathogenesis is believed to be initiated by tissue damage, promoting innate immune activation, recruitment of alloreactive lymphocytes, macrophage activation and fibroblast extracellular matrix deposition, the specific mediators and cell types required for disease have not been defined, and this study identifies key subsets of cells in affected skin. Additionally, as cellular therapy is being investigated as a means to treat fibrosis, identifying distinct markers in fibrotic skin will provide potential drug targets in the future.

LB1057

STING-mediated neutrophil recruitment in DRG: A potential driver of alloknesis in atopic dermatitis

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Alloknesis, an abnormal itch response to non-pruritic stimuli, is a common symptom of atopic dermatitis (AD). Recent research suggests that neutrophil accumulation in the dorsal root ganglion (DRG) contributes to sensory hypersensitivity, including mechanical allodynia. However, the precise mechanisms underlying alloknesis in AD remain unclear. Our previous findings demonstrated a significant increase in STING expression in DRG neurons, along with increased neutrophil infiltration of the DRG in AD mice. In this study, we investigated whether STING activation in DRG neurons induces neutrophil activation and recruitment, contributing to alloknesis. In AD mice, STING mRNA levels in the DRG were positively correlated with clinical severity, neutrophil infiltration, and neutrophil extracellular trap (NET)-related gene expression. Among these, cathepsin G (Ctsg) mRNA expression showed a strong correlation with pruritic behavior, suggesting its role in itch modulation. Moreover, intrathecal administration of the STING agonist ADU-S100 induced alloknesis and significantly increased neutrophil infiltration in the DRG, along with upregulation of NET-associated genes. Notably, alloknesis scores were positively correlated with neutrophil infiltration and the mRNA levels of Il6 and Ctsg in the DRG. Furthermore, neutrophil migration assays demonstrated that supernatants from cultured DRG neurons treated with ADU-S100 induced neutrophil chemotaxis in a concentration-dependent manner. These findings suggest that STING activation in DRG neurons drives neutrophil recruitment and activation, contributing to alloknesis in AD. Further research into neuro-neutrophil interactions in the DRG may provide new insights into itch sensitization in AD and serve as a potential therapeutic target for chronic itch.

LB1058

The molecular basis of scabies itch

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Scabies, a parasitic skin infestation, affects over 200 million people worldwide with intense itch responses in afflicted individuals and poses significant morbidity, discomfort, and economic burden. Despite its prevalence, current treatments, such as topical (permethrin) and oral (ivermectin), have limitations, including resistance, side effects, and incomplete efficacy. Moreover, these treatments often fail to alleviate the itch, which can persist for weeks after mite eradication. To address this knowledge gap, we employed a multidisciplinary approach, combining protein identification and recombinant production, pharmacology, mouse behavior, and genetics to elucidate the signaling pathways involved in scabies-induced itch. We identified scabies mite cysteine protease (Sar s 1c) as a key itch trigger in a mouse model. We demonstrated that Sar s 1c induces dose-dependent itch in mice, which is mediated by the PAR1 (protease-activated receptor) but not PAR2. Furthermore, our data suggest that PAR1 is linked downstream to TRPV1, as evidenced by global knockout mice studies. Our findings reveal a novel signaling pathway (Sar s 1c/PAR1/TRPV1) associated with scabies itch, providing a potential therapeutic target for the development of more effective treatments.

LB1059

A single-cell atlas of healthy human skin reveals body site-specific cellular diversity, pathway enrichment and disease-associated gene expression.

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Skin diseases affect nearly one in four Americans and are vastly heterogeneous. One striking aspect of many skin diseases is their predilection for specific anatomic sites, but the underlying mechanisms and nature of this site predilection has remained unknown. Better understanding of the physiological processes that regulate skin homeostasis across different body sites may offer valuable insights into disease susceptibility and risk. Thus, we developed a reference single-cell RNA sequencing (scRNAseq) atlas of healthy human skin from 96 subjects across diverse body sites, including the acral regions (palm/plantar), face, arm, axilla, back, leg, and scalp, to provide a valuable resource for comparing healthy and diseased skin. We highlight significant body site-specific variations in cellular composition, pathway enrichment, and immune cell interactions at distinct anatomic skin sites. Pathway analyses revealed enrichment of processes such as hypoxia, and glycolysis in scalp skin, and UV response and epithelial-mesenchymal transition pathways in facial skin, reflecting site-specific adaptations. Immune profiling further demonstrated differences in the proportions and interaction strengths of myeloid and T cell subsets across body sites, emphasizing localized immune regulation. Notably, expression of disease-associated genes, including RASGRP3 (linked to lupus) in myeloid cells of facial skin and PDE4D (associated with psoriasis) in T cells of scalp and acral skin, were found even in healthy conditions. These findings establish a detailed baseline of skin homeostasis, providing a critical framework for studying the transition from health to disease and advancing the field of precision dermatology by identifying potential therapeutic targets and susceptibility markers.

LB1060

Trends in radiation therapy and other procedural treatments for keratinocyte carcinomas among dermatologists: A cohort study

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Background: Prior findings from aggregated national Medicare claims data indicate that dermatologist use of radiation therapy (RT) has increased over time, but RT has not been investigated at an individual tumor level. Our objective was to report the proportion of procedures used to treat keratinocyte carcinomas (KC), including RT, among general dermatologists and Mohs surgeons, and assess trends over time within a Medicare cohort. Methods: We conducted a retrospective cohort study using a de-identified random sample of 5,560,291 Medicare beneficiaries from 2009-2021. We included all KCs procedurally treated by dermatologists, defined by at least 1 CPT code for KC treatment (ED&C, excision, Mohs surgery, photodynamic therapy (PDT), or RT) and at least 1 ICD code for a KC diagnosis on the same date. We assessed trends over time of the proportions of KCs treated by each procedure type with Kendall Tau-b tests. Results: We identified 818,685 patients with 2,684,775 procedurally treated KCs (42.9% by general dermatologists and 57.1% by Mohs surgeons). There were 10,906 KCs treated with RT (0.004%; with 45% basal cell carcinoma, 47.2% squamous cell carcinoma, 7.8% unspecified in a 2011-2021 subset). Most RT overall was performed by Mohs surgeons (58.7%); Mohs surgeons used RT on a 0.42% of treated KCs, general dermatologists used RT on 0.39% of treated KCs. The proportion of KCs treated with RT increased over time, as did the proportion treated with Mohs surgery, while the proportion of KCs treated with ED&C decreased over time (all p for trend <.05). Conclusions: Our findings indicate that although RT makes up a small proportion of KC treatments, the proportion is increasing over time.

LB1061

Thermal imaging analysis of HS patients using forward-looking infrared technology

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Hidradenitis suppurativa (HS) is a chronic inflammatory skin disorder that affects the folliculopilosebacous unit. HS is associated with upregulation of inflammatory cytokines, suggesting that the cycle of inflammation begins before visible manifestations. Forward-looking infrared (FLIR) imaging offers a non-invasive method to refine surgical resection boundaries by using temperature analysis. This pilot study evaluates the utility of FLIR imaging in mapping affected skin in HS patients to improve surgical outcomes. HS patients undergoing surgical excision were imaged pre- and post-operatively using standard photographs and FLIR imaging after acclimating to operating room temperature. FLIR data identified areas of highest temperature readings, comparing adjacent normal and affected skin to evaluate the accuracy of preoperative surgical markings in resecting diseased tissue while preserving healthy skin. No changes to surgical markings were made based on FLIR analysis. Patients were monitored postoperatively for persistent disease and complications. FLIR imaging of the HS lesion on the left thigh in patient 1 revealed high-temperature areas both within and extending beyond preoperative markings. Post-operative complications included mild wound dehiscence, cellulitis, and an abscess. For patient 2, FLIR imaging of the HS lesions on the right labia revealed high-temperature regions outside surgical borders. Healing was uneventful with no complications or flares observed. This pilot study highlights the potential role of FLIR imaging in enhancing surgical planning for HS patients. The methods used to analyze infrared images provide a framework for future research into thermal mapping to optimize surgical interventions for HS.

LB1062

The impact of GLP-1 receptor agonists on major adverse cardiovascular events among hidradenitis suppurativa, psoriasis, and atopic dermatitis patients: A population-based cohort study

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The cardioprotective potential of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in hidradenitis suppurativa (HS), psoriasis (PsO), and atopic dermatitis (AD) remains understudied. Patients with these inflammatory skin diseases are at a higher risk of adverse cardiovascular events. Among HS, PsO, and AD patients, we aim to compare cardiovascular outcomes in patients who use GLP-1RAs versus those who do not. Using the TriNetX Research Network (2005-2024), we conducted a population-based cohort study. We identified patients aged ≥12 years with HS, PsO, or AD who were prescribed GLP-1RAs, along with propensity-matched controls with the same skin diseases who were not on GLP-1RAs. GLP-1RA users with HS (N=19,920), PsO (N=41,873), or AD (N=24,761) had a significantly reduced risk for cerebrovascular disease (CVD), ischemic heart disease (IHD), heart failure (HF), and atherosclerosis versus non-users (p<0.05). For HS, adjusted odds ratios (aOR) were: CVD, aOR=0.73 (95% CI, 0.66-0.80); IHD, aOR=0.77 (95% CI, 0.72-0.81); HF, aOR=0.71 (95% CI, 0.66-0.75); atherosclerosis, aOR=0.75 (95% CI, 0.68-0.81). For PsO, aORs were: CVD, aOR=0.74 (95% CI, 0.68-0.80); IHD, aOR=0.90 (95% CI, 0.86-0.95); HF, aOR=0.79 (95% CI, 0.74-0.83); atherosclerosis, aOR=0.77 (95% CI, 0.73-0.82). For AD, aORs were: CVD, aOR=0.74 (95% CI, 0.67-0.83); IHD, aOR=0.89 (95% CI, 0.83-0.95), HF, aOR=0.78 (95% CI, 0.72-0.84); atherosclerosis, aOR=0.78 (95% CI, 0.73-0.84). Our findings suggest that GLP-1RA use is associated with a significantly reduced risk of CVD, IHD, HF, and atherosclerosis in patients with HS, PsO, and AD. Given the increased cardiovascular risk in individuals with these inflammatory skin diseases, GLP-1RAs may offer a cardioprotective benefit beyond their established metabolic effects.

LB1063

Cardiovascular risk remains significant in psoriasis patients despite management of cardiometabolic comorbidities

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Patients with psoriasis are known to have an increased prevalence of cardiovascular (CV) risk factors and be at increased risk for major adverse cardiovascular events (MACE). We designed a retrospective cohort study using a multicenter research network (TriNetX) to investigate whether disease-specific therapy of CV risk factors is associated with the incidence and risk of MACE in biologic-treated psoriasis patients aged 18 to 70, compared to patients in the general population. A series of analyses were conducted based on the presence of CV risk factors (dyslipidemia, hypertension, diabetes) and their treatment (statins, antihypertensives, antidiabetics). Patients were matched 1:1 by demographics, ASCVD score, and other potential confounders (SMD <0.2). Compared to the general population, psoriasis patients demonstrated an increased incidence and risk for MACE (116 vs 64, HR 3.4 95% CI 2.5-4.7), independent of traditional risk factors. Stratification by comorbidity revealed increased incidence and risk for MACE among psoriasis patients with dyslipidemia (1,407 vs 293, HR 5.6 95% CI 4.9-6.4), hypertension (1,387 vs 200, HR 8.00 95% CI 6.9-9.3), and diabetes (676 vs 106, HR 7.4 95% CI 6.0-9.1), compared to controls in the general population. Comparing biologic-treated psoriasis patients stratified by comorbidity and pharmacologic management, those with dyslipidemia had a higher incidence and risk for MACE despite receiving a statin (153 vs 49, HR 3.1 95% CI 2.2-4.3); similarly, those with hypertension had a higher incidence and risk for MACE despite receiving antihypertensives (85 vs 31, HR 2.6 95% CI 1.7-3.9), while psoriasis patients receiving management for diabetes did not have significant differences in the incidence or risk for MACE compared to those not receiving antidiabetics (60 vs 57, HR 0.9 95% CI 0.7-1.4). Despite pharmacologic management of both psoriasis and CV risk factors, significant residual cardiovascular risk remains in patients with psoriasis.

LB1064

Advancing laser therapies for pediatric dermatology: Enhancing safety and efficacy in skin of color

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Skin conditions in pediatric patients, particularly those with skin of color, often present unique challenges in treatment. Laser therapies, despite their potential, have been underutilized in this population due to potential adverse effects such as burns and post-inflammatory hyper- or hypopigmentation. However, advancements in understanding of laser technology and its use in pigmented skin have prompted a reevaluation of their use in pediatric patients across different skin types. This study aims to address this gap, as successful laser treatments can significantly improve dermatologic outcomes for children, promoting both physical and psychosocial well-being. We examined laser treatment outcomes across a spectrum of dermatological conditions prevalent in pediatric patients with skin of color in the setting of a city hospital that serves a predominantly non-white population. Our retrospective analysis of patient records at our center illustrates the safety profile and efficacy of lasers in achieving optimal therapeutic outcomes in this specific population using images and laser parameters. Our findings suggest that laser treatments, when performed using conservative parameters, appropriate wavelengths, and in consideration of patient-specific factors can be a viable and effective option for pediatric patients with skin of color. We found negligible adverse effects with three (0.07%) adverse outcomes prompting a pause to treatment. However, a major factor in not completing treatment was losing patients to follow up. 27% of pediatric patients with skin of color did not show up for their next treatment session, compared to 15% of white pediatric patients. This is valuable information that needs to be further investigated to adequately treat this population. Ultimately, this research seeks to bridge existing knowledge gaps, providing evidence-based guidance for dermatologists and healthcare practitioners in delivering safe and efficacious laser treatments for pediatric patients with skin of color.

LB1065

Comparative effects of dupilumab versus disease-modifying anti-rheumatic drugs on future sequelae and comorbidities in patients with atopic dermatitis

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Purpose: Atopic dermatitis (AD) is a chronic inflammatory skin disease associated with an increased risk of cardiovascular disease, lymphoma, osteoporosis, and infections. However, data remain limited on how treatment with dupilumab influences the risk of these comorbidities compared to traditional systemic therapies. Methods: For this retrospective cohort study, the TriNetX database was used to identify patients with AD from 98 healthcare organizations across the United States. Patients were classified into those who had received dupilumab and those who had received systemic therapies including cyclosporine, mycophenolate mofetil, methotrexate, or azathioprine. Propensity score matching was used to balance baseline differences. Results: After matching, 5,434 pairs of AD patients treated with dupilumab and matched controls treated with traditional systemic therapy were included. Dupilumab initiators had a lower risk of death (HR 0.76; 95%CI 0.61-0.96; P=0.021), major adverse cardiovascular events (HR 0.68; 95%CI 0.54-0.85; P=0.001), ischemic heart disease (HR 0.8, 95%CI 0.65-0.95, P= 0.013), respiratory infections (HR 0.74; 95%CI 0.64-0.87; P=0.0001), sepsis (HR 0.47; 95%CI 0.34-0.63; P=0.0001), and osteoporosis (HR 0.66; 95%CI 0.53-0.83; P=0.0001). There was no difference in the risk of lymphoma (HR 1.13; 95%CI 0.77-1.66; P=0.53). The dupilumab group had a higher risk of conjunctivitis (HR 1.30; 95%CI 1.11-1.51; P=0.001). Conclusion: This study supports the effectiveness of dupilumab in reducing AD-related comorbidities and suggests that dupilumab may be a preferred systemic treatment option for patients with AD. Further research is needed to understand the mechanisms underlying the differential comorbidity risks associated with dupilumab compared to other systemic treatments.

LB1066

Medicare trends in auricular cartilage and composite graft utilization amongst Mohs surgeons and other specialists from 2013 to 2022

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Purpose: Cartilage and composite grafts are technically challenging yet remain valuable reconstruction methods in Mohs surgery. The frequency of utilization by Mohs surgeons compared to other specialists is currently unknown. Herein, we determine the frequency of auricular cartilage and composite graft utilization by Mohs surgeons compared to other specialists treating the Medicare population over the last decade. Methods: A cross-sectional analysis was performed using the Medicare Public Use Files from 2013 through 2022. Results: Of all Mohs surgeons billing Medicare from 2013 through 2022, a total of 7.95% (278/3498) utilized auricular cartilage grafts and 0.09% (3/3498) utilized composite grafts. Mohs surgeons performed their highest number of auricular cartilage grafts in 2015 (419/1563, 26.8%) and their lowest in 2020 (249/1160, 21.5%). Mohs surgeons performed 100% of all Medicare composite grafts in 2018 (17/17) and 2022 (19/19) and none in 2017, 2019, or 2021. Mohs surgeons performed the most composite grafts (125/343, 36.4%) across all specialties. The only specialty surpassing Mohs surgery (3345/14303, 23.4%) in auricular cartilage graft usage was otolaryngology (6371/14303, 44.5%). Conclusion: Auricular cartilage grafts are utilized more often than composite grafts across all specialties. Mohs surgeons comprise a large subset of specialists employing both auricular cartilage and composite grafts, underscoring the utility of both in Mohs reconstruction. Analyzing these demographics within the Medicare-eligible population enables healthcare providers to strategically adapt surgical protocols, enhance physician training, and optimize resource allocation to better serve the evolving needs of older adults.

LB1067

Understanding the impact of social determinants of health on wait time for Mohs surgery

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Mohs surgery is considered the best treatment for high-risk skin cancers including basal cell (BCC) and squamous cell (SCC) carcinomas. Considering the aggressive nature of BCC and SCC, Mohs surgery should be performed as early as possible to achieve optimal results. This correlational research study sought to determine whether there is any correlation between wait time for Mohs surgery and Area Deprivation Index (ADI), a measurement for social determinants of health. The 2021 Medicare Provider Utilization and Payment Data dataset was used to identify and contact Mohs surgeon offices to collect Mohs surgery wait time data. The Neighborhood Atlas was used to collect ADI associated with each Mohs surgeon's office zip code. The mean Mohs surgery wait time was 4.9 and 4.4 weeks for BCC and SCC, respectively. The Spearman rank correlations between Mohs surgery wait time for BCC and ADI as well as SCC and ADI were 0.09 ($p<0.001$) and 0.06 ($p=0.003$), respectively. Geographic analysis was performed with heat maps showing the distribution of Mohs surgeons across the US. There is a statistically significant positive correlation between Mohs surgery wait time and ADI for both BCC and SCC. Additionally, there is a geographic maldistribution of Mohs surgeons with rural areas having less access to Mohs surgery. These discrepancies impact patient outcomes and exacerbate existing health disparities. Moving forward, it is essential to address these discrepancies, so we can work to ensure equitable access to Mohs surgery for those in underserved and under-resourced areas.

LB1068

Increasing concern over the cost of facial cosmetic dermatological procedures since the onset of COVID-19

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Cosmetic procedures have increased since the onset of the COVID-19 pandemic in March of 2020. The ASDS reports a nearly 63% increase in facial cosmetic surgeries between 2020 and 2021 with a steady increase in the following years. Thus, this study aimed to evaluate interest in the cost of common cosmetic dermatology procedures since March of 2020. Google Trends was used to explore interest in the cost of common cosmetic dermatological procedures. This platform normalizes search terms to a scale from 0 to 100 which represents the range of interest on a given topic. Data were collected from March 1st, 2020 to March 1st, 2025. The term "cost" followed by various cosmetic dermatological procedures were queried. Search terms for the cost of PRP injections (243%) and microneedling (162%) had significant increases since March 2020. Interest in the cost of filler (136%) also increased drastically over this time period with lip (189%) and cheek (115%) being the most common search terms. The drastic increase in search terms for PRP injections, microneedling, and facial filler suggest that concerns over the cost of facial cosmetic procedures have drastically increased since the onset of COVID-19. As more individuals transitioned to online virtual workspaces such as Zoom during the pandemic, interest in enhancing facial aesthetics began to increase. The transition away from wearing masks in public spaces may have contributed to increased interest in pursuing facial augmentation such as lip and cheek filler. The increasing number of searches associated with cost may therefore be correlated with an overall increase in the pursuit of facial cosmetic procedures. Given the financial hardships that many individuals experienced in recent years, it is important for providers to consider how these rising prices have impacted peoples' decision-making process in their pursuit of cosmetic care.

LB1069

Associations of exposure to acrylamide and glycidamide with psoriasis among adults: Findings from a population-based study

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Acrylamide (AA), a hazardous chemical prevalent in the environment and human diet, and its metabolite glycidamide (GA) are suspected contributors to psoriasis. However, the relationship between AA, GA exposure and psoriasis incidence remains unclear. Using data from the National Health and Nutrition Examination Survey (NHANES) cycles 2003-2004, 2005-2006, and 2013-2014, we conducted a cross-sectional study involving 6,999 participants. While no overall association was observed between AA-hemoglobin adduct (HbAA), HbGA levels, and psoriasis risk, subgroup analyses revealed positive relationships among individuals aged 20-40 years and those with serum cotinine levels between 0.011 and 10 ng/mL. We also assessed the relationship between HbAA, HbGA exposure and various laboratory biomarkers. HbAA exposure was positively associated with high-density lipoprotein (HDL) and white blood cell counts, but negatively associated with folate. HbGA exposure was negatively associated with HDL and vitamin B12. Interaction analyses indicated that higher levels of serum HDL, folate, vitamin B12, and peripheral white blood cell and monocyte counts attenuated the detrimental effects of HbGA exposure on psoriasis risk. Sensitivity analysis based on dietary AA intake from NHANES 24-hour dietary recall data (2003-2004, 2005-2006 cycles, N = 4,932) yielded results consistent with those observed for HbAA and HbGA exposure. These findings suggest that AA and GA exposure may contribute to psoriasis incidence, particularly among younger adults and smokers, and that improving nutritional intake and lifestyle factors could help mitigate this risk. Further research is needed to confirm these associations in diverse populations and elucidate the underlying mechanisms of AA/GA-related psoriasis pathogenesis.

LB1070

Cardiovascular and thrombosis risks of prolonged vs. short-term use of oral corticosteroids among atopic dermatitis patients in the United States.

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Background: Despite guidelines discouraging their use, oral corticosteroids (CS) remain commonly prescribed for managing moderate-to-severe atopic dermatitis (AD). Given limited safety data on oral CS in AD, we evaluated the risks of major adverse cardiovascular events (MACE), and venous thromboembolism (VTE) associated with prolonged vs short-term use, within a cohort from a commercially insured U.S. population. Type of Study: Population-based cohort study: Methods: Using the U.S. Optum CDM database (03/2017–03/2024), we included AD patients aged ≥12 years who initiated oral CS. We emulated a hypothetical "per-protocol" target trial using a clone-censor-weight approach to compare the risks of VTE (deep vein thrombosis, pulmonary embolism) and MACE (non-fatal MI, non-fatal stroke, and all-cause death) with prolonged (>30 days) vs short-term (≤30 days) oral CS use at 2 years. Results: Among 52,688 AD patients who initiated oral CS (average age 53; 62% female), crude incidence rates (IR) were higher for prolonged users, with IRs of 2.62 (95% CI, 2.40–2.84) per 100 person-years for MACE and 0.43 (95% CI, 0.35–0.53) per 100 person-years for VTE, compared to short-term users, with IRs of 1.61 (95% CI, 1.50–1.74) per 100 person-years for MACE and 0.16 (95% CI, 0.12–0.20) per 100 person-years for VTE. Adjusted analyses showed a 2-year risk increase for prolonged vs short-term use of 1.24 (95% CI, 1.1–1.4) for MACE and 1.81 (95% CI, 1.3–2.5) for VTE. Conclusion: In patients with AD, prolonged oral CS use >30 days showed an increased risk of MACE and VTE compared to short-term use ≤30 days.

LB1071

Differentiation and proteomic insights into psoriasis and TNFi-induced psoriatic dermatitis in pediatric patients

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Psoriasiform dermatitis (PsoD) is a potential adverse effect of tumor necrosis factor inhibitor (TNFi) treatment. Differentiating TNFi-induced PsoD from plaque psoriasis (PsO) can be challenging in children. Tape strips were collected from lesional skin of pediatric patients with PsO (n=13) and TNFi-PsoD (n=11) (mean age 12.7 years; mean Physician Global Assessment scores 2.9 vs 2.7, respectively, p>0.05) and from age/sex-matched healthy control (hc) skin (n=20). Affected body surface area was greater in PsO (15%) vs. TNFi-PsoD (2%) and non-scalp body sites (TNFi-PsoD especially on retroauricular, face, and palm) and morphology (TNFi-PsoD less well circumscribed and crustier) differed. Olink proteomic analysis was performed on proteins extracted from tape strips and identified 362 distinct proteins. Principal Component Analysis (PCA) showed distinct separation between all three groups based on disease identities, unaffected by age, sex or race. Differential protein expression based on ANOVA testing showed enriched Th1 (CXCL9/10), Th17 (IL17A) and Th2 (IL4R) pathways, as well as chemokines supporting immune cell infiltration (CXCL8, CCL4) and VEGFA between PsO and TNFi-PsoD groups. Most interesting among 19 proteins differentially expressed in PsO vs. TNFi-PsoD were IL-17C (higher in PsO; adj p<0.001; major IL-17 produced by keratinocytes), and LSP1 (adj p=0.006; neutrophil infiltration), HCLS1 (adj p=0.016; involved in immune responses), and CD200R1 (adj p=0.03; regulates skin cell interactions with CD4+ T cells and expression of TNFa, interferons, and inducible nitric oxide) (TNFi-PsoD>PsO). These data suggest that a small panel of tape-stripped proteins can distinguish pediatric PsO vs TNFi PsoD and provide insight into these pediatric disorders.

LB1072

Development of an ELISA for the efficient detection of autoantibodies against nuclear valosin-containing protein-like protein (NVL) 2 using its manipulated cDNA: Anti-NVL2 antibodies in various diseases beyond systemic sclerosis

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Purpose: Anti-nuclear valosin-containing protein-like protein (NVL) antibodies have been detected only in systemic sclerosis (SSc) patients, and diverse comorbidities have been reported in anti-NVL antibody-positive SSc patients. To clarify the clinical features of anti-NVL antibody-positive patients, we developed an ELISA for measuring antibodies against NVL2, a major target of autoantibodies against NVL. Methods: Sera from 1,676 patients with various conditions were included. 167 anti-nucleolar antibody (ANoA)-positive sera, 120 ANoA-negative sera, and 17 healthy control sera were examined by an ELISA that uses the recombinant protein of NVL2 derived from its gene-manipulated cDNA clone (modified NVL2; mNVL2). Results: Eighteen ANoA-positive sera subjected to indirect immunofluorescence analysis were positive for anti-mNVL2 ELISA. Although one ANoA-negative serum was judged false positive in our anti-mNVL2 ELISA, the above 18 anti-mNVL2 ELISA-positive sera were confirmed to be positive for anti-NVL2 antibodies by immunoprecipitation-Western blotting. Six SSc patients had anti-NVL2 antibodies, whereas five with idiopathic interstitial pneumonia and seven with other diseases had anti-NVL2 antibodies. Anti-mNVL2 ELISA titers were significantly higher in the anti-NVL2 antibody-positive SSc patients than in the anti-NVL2 antibody-positive non-SSc patients ($P<0.042$). Conclusions: This is the first report on non-SSc patients positive for anti-NVL2 antibodies. We found more anti-NVL2 antibody-positive cases than any previous study, to the best of our knowledge. Our ELISA, which showed an association between titers of these antibodies and SSc diagnosis, promises to expand knowledge about anti-NVL2 antibodies.

LB1073

Atopic dermatitis is negatively associated with thyroid disorders among adults in Korean NHANES 2010-2023

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A previous study using data from the US National Health and Nutrition Examination Survey (NHANES) reported a positive association between atopic dermatitis (AD) and thyroid disease. The purpose of this study was to replicate those findings using analogous data from the Korean NHANES (K-NHANES). We analyzed data from 45,831 adults aged 20-59 from the nationally representative K-NHANES dataset from 2010-2023. The exposure of interest was self-report of ever having AD, and the outcome of interest was selfreport of ever having thyroid disease. We used logistic regression to calculate odds ratios (OR), accounted for survey weights, and adjusted for age, sex, educational attainment, income, smoking status, diabetes, and body mass index. Contrary to previous literature, atopic dermatitis was overall found to be inversely associated with thyroid disease (adjusted OR: 0.46, 95%CI: 0.27-0.79). Stratified analysis by age showed a consistent inverse association among adults aged 20-39 (adjusted OR: 0.30, 95%CI: 0.14-0.68), but not among adults aged 40-59 (adjusted OR: 0.85, 95%CI: 0.41-1.77). There was also a consistent inverse association among females (adjusted OR: 0.46, 95%CI: 0.25-0.82), but not among males (adjusted OR: 0.52, 95%CI: 0.15-1.81). A closer review of NHANES survey wording revealed that while the Korean version specifically addresses AD, certain waves of the US version are not as specific, potentially impacting conclusions drawn about AD from the US data. Our findings highlight the importance of replication in different populations to assess the generalizability of conclusions from national cross-sectional surveys. Furthermore, using objective data on thyroid hormone levels and thyroid peroxidase autoantibody titers from the survey respondents, our future research will examine whether variations in screening and treatment practices or whether differences in Th1/Th17- vs Th2-predominant disease processes may explain these inverse associations.

LB1074

Who still indoor tans in the U.S.? An analysis of the 2019 behavioral risk factor surveillance system

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Despite significant declines in indoor tanning prevalence over the past two decades, it remains a public health concern due to its association with photoaging and melanoma risk. Using data from the 2019 Behavioral Risk Factor Surveillance System (BRFSS), we analyzed national prevalence and factors associated with indoor tanning among U.S. adults, stratified by sex. We analyzed responses from 11,228 adults (6,116 females, 5,112 males). Participants reported indoor tanning use in the past year, dichotomized as "ever" versus "never." Logistic regression models adjusted for sampling probabilities assessed associations with race/ethnicity, age, income, education, health status, smoking, binge drinking, obesity, urban/rural residence, skin cancer history, marital status, and sexuality. The prevalence of indoor tanning in the past year was 1.96% among females and 0.87% among males. Among those who tanned, 59.5% reported ≥10 sessions in the past year. Tanning was most common among White, non-Hispanic females (3.10%) and those aged 18-24 years (2.74%). In females, risk factors included smoking (AOR 2.57, 95% CI 1.04-6.32), binge drinking (AOR 2.16, 95% CI 1.25-3.73), rural residence (AOR 2.35, 95% CI 1.07-5.17), and never-married status (AOR 2.22, 95% CI 1.05-4.68). Obesity was associated with decreased odds of tanning in females (AOR 0.33, 95% CI 0.18-0.61). In males, predictors included Hispanic ethnicity (AOR 2.88, 95% CI 1.00-8.33), smoking (AOR 6.85, 95% CI 2.14-21.92), higher education, and sexual minority status (AOR 8.18, 95% CI 3.51-19.05). Neither skin cancer history nor general health influenced tanning in either sex. While indoor tanning prevalence has declined, high-frequency tanning persists among a small subset, posing a public health challenge. Behavioral risk factors and demographic disparities such as rural residence in females and sexual minority status in males highlight the need for targeted interventions. Addressing high-frequency tanning is essential to reduce melanoma and non-melanoma skin cancer risks and advance public health goals.

LB1075

Impact of the war on melanoma educational campaign on melanoma literacy in Oregon

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The War on Melanoma™ (WoM) literacy surveys assessed the impact of a health promotion campaign in Oregon aimed at improving early melanoma detection through community education. A baseline survey conducted in 2019 assessed the public's existing melanoma knowledge, attitudes, and behaviors. These served as indicators of melanoma literacy and performance of self-skin exams (SSEs). Between 2019 and 2022, the WoM intervention (an early detection education campaign) was carried out through multiple health advertising campaigns and educational efforts across a variety of media platforms. After the intervention, a follow-up survey was conducted, including the original baseline questions and additional items designed to measure the campaign's reach and its effect on melanoma literacy. The surveys targeted 3 groups: the intervention group, consisting of Oregon (OR) and Southwest Washington (SW WA) (where the campaign took place), and 2 control groups comprising the rest of Washington (WA) and Utah (UT). Sampling weights were used to ensure that the final sample was representative of the population of the included states. Regression models were used to examine the association between self-reported messaging exposure and melanoma literacy outcomes. Demographic characteristics of survey respondents were similar across both surveys and similar across all regions. On a population level, OR+SW WA overall literacy levels remained unchanged after the campaign, but 73% of those who reported seeing messaging also reported SSE behavior, compared with 56% who did not report seeing messaging. In all states, significantly more individuals exposed to melanoma-related messages reported engaging in SSEs, suggesting that targeted awareness campaigns may influence SSE behavior.

LB1076

Safety and effectiveness of concurrent intravenous immunoglobulin and biologics

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This study analyzes treatment discontinuation rates and adverse events in patients receiving concurrent intravenous immunoglobulin (IVIG) and biologics to evaluate the real-world impact of IVIG on biologic effectiveness, as prior studies showed IVIG accelerates clearance of monoclonal antibodies and thus potentially reduce effectiveness of biologics. A retrospective analysis was conducted to identify patients who received both IVIG and biologic treatments for at least 4 overlapping weeks between 2000 and 2024 at Mayo Clinic locations in Minnesota, Arizona, and Florida; patients with autoimmune or autoinflammatory disorders received IVIG and biologics as complementary therapies for the same condition or as distinct treatments for coexisting autoimmune conditions. 19 patients met the inclusion criteria and were treated with concurrent IVIG and biologics: dupilumab (7), ustekinumab (5), infliximab (4), adalimumab (2), and etanercept (1). 7 were treated with high-dose IVIG (2g/kg every 4 weeks). 4 patients received biologics and IVIG for the same indications: pyoderma gangrenosum (2), polyarteritis nodosa (1), and bullous pemphigoid (1). 15 (79%) patients remained on IVIG and biologics for at least 3 months, with a median concurrent treatment duration of 313 days. 17 (89%) patients experienced response with biologic. Biologics were discontinued due to complete remission (3), side effects (2), and treatment ineffectiveness (1). Adverse events related to IVIG included hypertension (1), itching (1), and headaches (1). No thromboembolic events occurred. Side effects in patients receiving biologics included bruising, fatigue, and flaring of CIDP (1; ustekinumab) and diarrhea and transaminitis (1; ustekinumab). Our findings support the safety and effectiveness of concurrent IVIG and biologics, without evidence of significant adverse events, though further studies with larger sample sizes are needed to further evaluate this combined therapeutic approach.

LB1077

Dermatofibrosarcoma protuberans in children: Favorable outcomes with wide local excision and narrower margins

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Dermatofibrosarcoma protuberans (DFSP) is a rare cutaneous sarcoma that is locally aggressive with a high risk of local recurrence if incompletely excised. The National Comprehensive Cancer Network (NCCN) recommends wide local excision (WLE) with 2–4 cm margins or Mohs micrographic surgery (MMS) for adults; however, there are no established pediatric-specific guidelines. As a result, management of DFSP in children is often adapted from adult recommendations. Pediatric patients present unique challenges, because treatment cannot often be performed under local anesthesia, and achieving adequate margins can be difficult due to smaller body size. To address this gap, we conducted a retrospective review of pediatric DFSP patients treated with WLE at a single institution, focusing on surgical margin width and clinical outcomes. Seventeen patients under the age of 20 who were diagnosed with DFSP and treated with WLE between 2004 and 2024 were included. The mean age at diagnosis was 13.2 years; 76.5% were female. The average lesion size was 2.73 cm. 16/17 patients had exact margins recorded. 15/17 (88.2%) were treated with margins ≤2 cm (average 1.76 cm, range 1-3 cm). No patients received adjuvant therapy with imatinib or radiation. At a mean follow-up of 44 months, the cohort demonstrated 0/17 recurrences with 100% disease-specific and overall survival. These findings suggest that the prognosis for children with DFSP is excellent, and that favorable outcomes can be achieved using WLE with margins smaller than adult NCCN guidelines.

LB1078

Characterizing acute skin failure in the critically ill

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Prevention of hospital acquired wounds is of great concern to clinicians and institutions. Unpreventable wounds as a result of acute skin failure (ASF), akin to other types of organ failure, has not been well studied and remains poorly understood. The purpose of this study is to describe the natural history and risk factors associated with the development of ASF and propose a risk prediction model. It is crucial to establish ASF as a distinct clinical syndrome and investigate its underlying mechanisms due to its significant impact on patient care and healthcare policy. 16 patients with multiorgan dysfunction who developed increasing number of wounds despite aggressive preventative strategies and standard of care treatment at the University of Miami Hospital over a four-year period were identified. All patients experienced unfavorable evolution of wounds and an increase in the number of wounds, with an average number of lesions prior to diagnosis being 2.68 and increasing to 7.21 after diagnosis. In addition to this 2.7x increase in number of wounds, some of these wounds developed in non-pressure dependent areas and did not show thermographic infrared findings associated with pressure ulcers. 62.5% (n=10) of patients in this cohort are deceased, with an average number of days between diagnosis and death being 104.8. However, 25% (n=4) were transferred to long term acute care facilities so this reported mortality is likely an underestimation. Upon analysis of risk factors, 100% (n=16) of patients had an albumin <3.5, 93.75% (n=15) had hemodynamic instability requiring vasopressors, 93.75% (n=15) had acute respiratory failure requiring mechanical ventilation, 87.5% (n=14) had a diagnosis of sepsis, and 87.5% (n=14) had acute kidney injury requiring hemodialysis. In conclusion, organ dysfunction, nutritional deficiency, and hemodynamic instability are highly sensitive findings for diagnosis of ASF. A call to action for hospital administration and critical care and wound care providers to distinguish ASF from hospital-acquired pressure injuries is paramount.

LB1079

Observational pilot study investigating skin metrics in acute radiation dermatitis

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Radiation dermatitis (RD) occurs in ~ 95% of those undergoing radiation therapy (RT), with severe reactions observed in 10-30% of individuals. The pathophysiology of RD is complex and multifactorial, with skin barrier disruption thought to play a central role. This single institution observational pilot investigates the effects of RT on skin metrics to uncover any association of skin changes with acute RD severity. We hypothesize that worse acute RD outcomes are associated with greater skin barrier impairment, high S. aureus (Sa) abundance, and pre-existing skin conditions. Outcomes include: skin metrics (trans epidermal water loss/TEWL, stratum corneum hydration/SCH, Sa abundance, pH, and colorimetry), pre-existing dermatological history, itch (ItchyQuant), quality of life (Skindex-mini), and RD severity (CTCAE; RISRAS). Subjects receiving standard of care RT for breast (40-60Gy over 15-30 sessions) or head/neck (H/N, 60-70Gy over 30-35 sessions) cancer complete 3 study visits: baseline (V1), end of RT (V2) and 3-months post-RT (V3). So far, 26 subjects (16 breast, 10 H/N) are actively enrolled; 14 breast and 3 H/N subjects have completed V2. Enrollment goal is 30 fully evaluable subjects. The mean age is 63±10 years, with H/N being 50% female and breast 100% female. Subjects are mainly white (92.3%), with 61.5% Fitzpatrick skin type III/IV. Among all, 21 (80.8%) had history of ≥1 skin condition (e.g. blistering sunburn, hives, contact dermatitis, atopic dermatitis, rosacea). At baseline, TEWL was higher at neck vs breast sites (mean±SD; 11.1±4.8 vs 5.7±2.1; p=0.0006) while SCH was similar across sites (neck: 22.9±10.5 vs breast: 15.7±8.5; p=0.07) and pH was lower at neck than breast (5.9±0.4 vs. 6.3±0.5; p=0.03). Sa was detectable in 34.6% of subjects at baseline (4 breast and 5 H/N), with range 106.0 to 1921.9 rCFU/cm^2. Results will inform future clinical trials by providing critical insight into skin barrier dysfunction and other skin related variables associated to acute RD severity.

LB1080

Pathologic margin negativity is not a guarantee: The risk of merkel cell carcinoma recurrence can be reduced with a single dose of radiation

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Merkel cell carcinoma (MCC) differs from most skin cancers by having a high overall recurrence rate (≈40%) and an aggressive disease course. While surgery with path-negative margins is sufficient for most skin cancers, its effectiveness in early-stage MCC is controversial. We analyzed a prospectively enrolled cohort of 98 patients with early-stage MCC and path-negative margins who did not receive adjuvant radiation therapy (RT). Of these, 10 (10%) developed a local recurrence (LR), typically by one year after surgery (median follow-up: 8.5 years). No significant differences were noted between LR and non-LR groups in demographics, stage, or known LR risk factors (lymphovascular invasion, head/neck site, immunosuppression, >1 cm primary, positive sentinel node). Among patients with LR, 6 of 8 arose on the head/neck and the mean number of risk factors was 1.3±0.7. A 10% local recurrence rate is not extremely high and may not justify the toxicity (nearly all patients experience at least transient side effects) and inconvenience of conventional adjuvant RT typically involving 25 doses. However, path-negative margins are clearly not a guarantee of local control. A well-tolerated alternative approach, one dose of 8 Gray adjuvant RT, has been used in an analogous cohort (mean risk factors: 1.6±0.9) of 43 patients with MCC. None of these 43 experienced LR (median follow-up: 2.7 years) and 82% had no side effects. The risk of recurrence for the single-dose cohort was lower than the no-RT cohort (p=0.032). Adjuvant RT is well known to reduce MCC recurrences, likely by eliminating microscopic discontiguous disease. However, patients with low-risk MCC often forgo a conventional course of RT given inconvenience and significant side effects especially in the head/neck region. This study demonstrates that patients with early-stage MCC and path-negative margins still have an appreciable LR risk and could benefit from a low-toxicity adjuvant RT approach.

LB1081

Curriculum on research self-efficacy, motivations, and barriers for dermatology residents in Ethiopia

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Research is a requirement of many dermatology residency programs in Africa, with global collaborations offering an opportunity to expand research capacity. The partnership between Emory University and faculty leaders at Addis Ababa University (AAU) has identified a need for expanded resident training in study design and research dissemination. This study aimed to evaluate changes in self-reported research self-efficacy among AAU dermatology residents before and after a four-day curriculum led by Emory University faculty. The curriculum included joint discussions on research design, feedback on resident-led projects, and guidance on writing and publishing. Research self-efficacy was evaluated using the validated Comprehensive Research Self-Efficacy Scale (C-RSES) across six domains, with pre- and post-curriculum scores compared using Wilcoxon signed-rank tests. Twenty-eight residents (93.3% response rate) completed both pre- and post-curriculum surveys. Median C-RSES domain scores increased across all domains, including Literature Review and Research Problem (3.9 to 4.5), Conceptual/Theoretical Framework (3.0 to 4.0), Research Plan (3.3 to 4.3), Data Analysis (2.7 to 4.0), Discussion (3.5 to 4.5), and Research Ethics (3.9 to 4.5, each p<0.001). At curriculum completion, the most common motivators for conducting research were contributing to medical knowledge (85.7%) and improving career prospects (85.7%); most common barriers were difficulty obtaining research funding (35.7%) and lacking mentorship (32.1%). Research self-efficacy increased after a structured curriculum for Ethiopian dermatology residents at AAU. This single-center study relied on self-reported outcomes, and further research is needed to evaluate if increased self-efficacy leads to greater research productivity. International collaborations have the potential to expand research self-efficacy among dermatology residents in low- and middle- income countries.

LB1082

Comparative outcomes following treatment with mogamulizumab versus brentuximab vedotin for mycosis fungoides or Sézary syndrome

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Mogamulizumab, an anti-CCR4 monoclonal antibody, and brentuximab vedotin, an antibody-drug conjugate targeting CD30, are targeted immunotherapies for mycosis fungoides (MF) and Sezary syndrome (SS), but evidence for choosing between them is limited. We assessed safety outcomes among patients treated with either drug by conducting a retrospective cohort study with TriNetX, a multicenter database. Patients diagnosed with MF or SS between August 2018 and August 2024 within 6 months of starting either mogamulizumab or brentuximab vedotin were included. We performed propensity score matching (PSM) for demographics, comorbidities, and prior MF/SS-targeted treatments. Hazard ratios (HRs) were calculated using Cox proportional hazards regression. After PSM, 153 patients received mogamulizumab, while 153 were treated with brentuximab vedotin. Mogamulizumab was linked to a lower two-year risk of hospitalization (HR, 0.56; 95% CI, 0.38-0.83; P=.008), neutropenia (HR, 0.53; 95% CI, 0.36-0.77; P=.006), sepsis (HR, 0.44; 95% CI, 0.25-0.79; P=.009), acute lower respiratory infections (HR, 0.39; 95% CI, 0.20-0.77; P=.009), major adverse cardiovascular events (HR, 0.31; 95% CI, 0.15-0.66; P=.006), and drug-induced peripheral neuropathy (HR, 0.26; 95% CI, 0.11-0.61; P=.006). However, there was an increased risk of lymphopenia (HR, 1.50; 95% CI, 1.14-1.97; P=.008) and dermatitis (HR, 1.65; 95% CI 1.09-2.50; P=.03) with mogamulizumab. Our data suggest a reduced risk of hospitalization and serious adverse events in MF/SS patients treated with mogamulizumab compared to brentuximab vedotin, possibly related to off-target effects associated with the cytotoxic agent in brentuximab vedotin.

LB1083

Glow or no? A deep dive into tiktok's acne sunbed "solutions"

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Over the past five years, TikTok has seen a rapid rise in the promotion of tanning beds as an acne treatment. This study evaluated sources, risk acknowledgement, and engagement metrics. To minimize logarithmic bias, a new TikTok account was used to evaluate the content objectively. Videos from 2021-2024 were identified using the search terms "acne tanning beds," "sunbeds acne," and "acne treatment tanning beds," and assessed for their promotion of tanning beds for treatment of acne vulgaris. For each term, all videos discussing tanning beds as an acne treatment under the "top" tab were analyzed. Video creators were categorized, associated tanning bed risks were recorded, and quantitative metrics (view, likes) were collected. Of the 92 analyzed videos, 51 (55%) promoted tanning beds for acne treatment, primarily from non-medical creators (36 individuals, 14 tanning companies). All dermatologists (n=4) opposed tanning beds as a safe acne treatment. Risks were mentioned in 23 videos (25%), with anti-tanning bed videos (16%) more frequently citing them than pro-tanning bed videos (7%). Skin cancer was the most commonly cited risk in both groups (n=10). Pro-tanning bed videos averaged higher views (207,478) compared to anti-tanning bed videos (59,397). Region of video origin influenced viewer engagement (p=0.022). As non-evidence based skincare advice continues to influence consumer decisions, providers have a growing opportunity to engage on social media, dispel misinformation, and promote safe, evidence-based treatments.

LB1084

Safety and efficacy of topical imiquimod use in allogeneic hematopoietic stem cell transplant recipients: A multicenter retrospective analysis

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This study assesses the efficacy of imiquimod in allogeneic hematopoietic stem cell transplant (allo-HSCT) recipients and impact on flares of mucocutaneous graft-versus-host disease (GVHD) at application sites. A retrospective analysis of allo-HSCT recipients treated with imiquimod at Brigham and Women's Hospital, Massachusetts General Hospital, and Dana-Farber Cancer Institute (01/2015–09/2024) was performed. Patients had at least three months of follow-up post-imiquimod. Among 54 allo-HSCT recipients treated with imiquimod, 39/54 (72.2%) had history of GVHD prior to initiation; 21/54 (38.9%) had active GVHD at treatment initiation. Localized GVHD flares occurred in 2 (3.7%) patients: one with oral GVHD following mucosal application for leukoplakia and one with sclerotic GVHD at cutaneous sites in the setting of concurrent immunosuppression taper and sunburn. Complete responses to imiquimod were observed in 0/3 (0.0%) leukoplakia, 6/16 (37.5%) superficial keratinocyte carcinomas, 7/18 (38.9%) warts, 1/9 (11.1%) cutaneous lymphoma, 1/1 (100%) leukemia cutis, 3/3 (100%) actinic keratosis, 0/2 (0.0%) vulvar intraepithelial neoplasia (VIN), and 1/2 (50%) molluscum contagiosum. GVHD exacerbation in areas of imiquimod use in allo-HSCT recipients appears to be infrequent but remains a potential risk. Mucosal application was the highest risk site for flaring mucocutaneous GVHD, with a flaring rate of 1/3 (33%). Clinicians should consider alternative topical therapy for mucosal sites, and if none exist, should be counseled on the risk of flaring mucosal GVHD. For cutaneous application, the majority (97.3%) tolerated imiquimod without flaring GVHD locally at application sites, with factors such as concurrent immunosuppression taper and sunburn contributing to the only case of localized cutaneous GVHD flare. Efficacy of imiquimod in allo-HSCT were lower than documented rates of efficacy reported in the literature for immunocompetent patients across multiple indications including leukoplakia and superficial keratinocyte carcinomas.

LB1085

Biologics reduce adverse cardiovascular outcomes in statin-treated psoriasis patients: A global population study

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Psoriasis (PsO) directly increases cardiovascular (CV) risks, such as hyperlipidemia. Thus many patients require statins. While biologics may improve CV outcomes in PsO, their stain-independent-impact is unclear. Our retrospective cohort study aimed to assess biologics' impact on adverse CV outcomes in statin-treated PsO patients and compare effects across classes. Multivariate analysis of 32,552 statin-treated PsO patients in the TriNetX global database (median follow-up: 2.5 yrs) compared CV outcomes between biologic users and other systemic/phototherapy users, adjusting for age, sex, BMI, smoking, diabetes, CKD, and circulatory disorders. Biologics significantly reduced adverse CV events, such as percutaneous coronary intervention (PCI) (aOR 0.48, CI 0.31–0.75), heart failure (HF) (aOR 0.69, CI 0.63–0.75), vascular disease (VD) (aOR 0.70, CI 0.63–0.79), cerebrovascular events (CVE) (aOR 0.73, CI 0.65–0.81), myocardial infarction (MI) (aOR 0.75, CI 0.68–0.82), and ischemic heart disease (IHD) (aOR 0.80, CI 0.76–0.84). Among classes, IL-23 inhibitors were most effective, reducing CVE (aOR 0.30, CI 0.23–0.39), HF (aOR 0.40, CI 0.33–0.48), VD (aOR 0.45, CI 0.36–0.57), MI (aOR 0.52, CI 0.43–0.62), and IHD (aOR 0.63, CI 0.57–0.69). IL-17 inhibitors ranked second, lowering PCI (aOR 0.43, CI 0.21–0.91), HF (aOR 0.55, CI 0.46–0.66), VD (aOR 0.63, CI 0.51–0.78), CVE (aOR 0.64, CI: 0.52–0.80), IHD (aOR 0.73, CI: 0.67–0.80), and MI (aOR 0.77, CI 0.65–0.92). IL-12/23 inhibitors followed, reducing MI (aOR 0.64, CI 0.50–0.81), HF (aOR 0.71, CI 0.57–0.89), VD (aOR 0.72, CI 0.54–0.95), and IHD (aOR 0.86, CI 0.76–0.98). TNF-α inhibitors also reduced VD (aOR 0.76, CI 0.66–0.88), MI (aOR 0.78, CI 0.69–0.88), CVE (aOR 0.78, CI 0.67–0.90), HF (aOR 0.79, CI 0.70–0.88), and IHD (aOR 0.81, CI 0.76–0.86). While all biologics reduced adverse CV outcomes, IL-23 inhibitors were most impactful (mean aOR: 0.46), followed by IL-17 (0.63), IL-12/23 (0.73), and TNF-α inhibitors (0.78).

LB1086

Does the presence of ulceration in localized Merkel cell carcinoma influence treatment outcome?

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Merkel Cell Carcinoma (MCC) is a rare, aggressive skin cancer with treatment response rates ranging from 31% to 95%. Staging, viral status, immunosuppression, comorbidities, and other factors influence treatment; however, little is known about the role of ulceration. Our study aimed to understand the influence of ulceration on the treatment response of localized MCC. This retrospective cohort study included localized MCC cases from 2005 to 2021. Variables collected included age, sex, location, treatment option, presence of ulceration, and treatment outcome. Categorical variables were reported as counts and percentages. A two-tailed Chi-square test was used to assess the association between categorical variables. Statistical analysis was conducted using GraphPad Statistical Software. P-values < 0.05 were considered significant. A total of 180 MCC cases were identified, of which 17 (9.4%) were localized. All patients were white, with an average age at presentation of 76.2 years and a male predominance (10, 58.8%). The most common location was the head and neck (52.9%), followed by the upper and lower extremities (4, 23.5%). Excision was the most common treatment modality utilized. Ulceration was more common in patients with head/neck MCC than in those with MCC at other locations (44.4% vs 12.5%, p>0.05). The mortality rate within 5 years of starting treatment did not differ between MCC with and without ulceration (50%, p>0.05). MCC with overlying ulceration did not influence the progression to metastasis after treatment completion (16.6% vs 27.2%, p>0.05). Despite the lack of statistical significance, these findings are important to report as they provide valuable preliminary insights into the role of ulceration in localized Merkel cell carcinoma. This study may serve as a foundation for future research with larger cohorts to better elucidate the clinical significance of ulceration and draw more definitive conclusions.

LB1087

Psychosocial impact of skin disease in older adults

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This study examines the unique psychosocial impact of skin disease in older adults, exploring its effects on mental health and social well-being, and identifying potential strategies to mitigate these challenges. A comprehensive search of the PubMed and Cochrane databases was conducted for English-language studies on skin disease in older adults published from 1995 to 2024. A total of 39 articles were included, comprising 22 cross-sectional observational studies, 4 matched cohort studies, 3 literature reviews, 2 retrospective chart reviews, 1 retrospective cohort study, 2 prospective studies, 5 meta-analyses, and 1 systematic review. Older adults with skin conditions experience disproportionately higher rates of depression and anxiety than young adults with skin disease, with prevalence reaching as high as 60%, particularly in individuals over 75. Pruritus is significantly associated with anxiety (odds ratio up to 3.69) and depression (odds ratio up to 4.27) in adults aged 45–47 years. Eczema is associated with anxiety (odds ratio of 1.15) and depression (odds ratio of 1.12) in adults over 60. Psoriasis, while weakly associated with anxiety (odds ratio of 0.4), has a strong correlation with depression (odds ratio of 5.52). Psychological resilience strategies may help mitigate these effects. While the psychosocial burden of skin disease in younger adults is well-documented, there is a lack of research on its impact in older adults. This study highlights the unique vulnerabilities of older adults with skin disease, who experience disproportionately high rates of depression, anxiety, and diminished quality of life. Given these unique challenges, dermatologists must closely monitor older adults for psychosocial distress and integrate multidisciplinary care approaches to improve both dermatologic and mental health outcomes.

LB1088

Implementation and outcomes of an inpatient dermatology e-consult pilot service at an academic satellite hospital

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We developed and piloted a dermatology e-consult service for inpatients at a satellite hospital within our academic health system and assessed the patient volume and outcomes associated with the service. An Epic order set for dermatology e-consultation (DEC) was established at the satellite hospital. The on-site wound care team provided all photography and the general surgery team provided biopsies as directed by the consulting dermatologist. Patient volume and procedural outcomes were prospectively recorded, and demographics and outcomes were retrospectively reviewed. Over 18 weeks, 18 inpatient DEC were provided. Of these, 10 patients (56%) were male. The median age was 66 years (range: 27 – 81) and the median hospital length of stay was 5 days(range: 2 – 23). Six patients (33%) required 11 biopsies and three patients (17%) required tissue culture. The most common presumptive diagnosis by the primary team prior to DEC was rash (n=8, 44%). The most common final diagnosis after DEC was drug reaction (n=4, 22%), including drug-induced hypersensitivity syndrome, exanthematous drug reaction, and methotrexate toxicity. Three patients (17%) had an undetermined diagnosis by discharge. The diagnosis changed in 13 cases (72%) following DEC. The primary team was interested in transfer for dermatologic care for six (33%) patients; ultimately, only one patient was transferred given concern for widespread lymphoma. Upon discharge, dermatology recommended outpatient follow up in 10 cases (56%) and no follow up in five cases (28%). There was one readmission (6%) related to dermatologic illness within 30 days of discharge. Two patients (11%) died during admission of causes unrelated to dermatologic illness. The introduction of a dermatology e-consult service for inpatients at a satellite hospital enabled remote evaluation of patients by a dermatologist, allowing for timely diagnosis and direction of care for inpatients with dermatologic illnesses.

LB1089

Successful treatment of delusional infestation with dupilumab

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Delusional infestation (DI) is a neurocutaneous syndrome characterized by crawling sensations and a fixed belief of infestation without verifying clinical evidence. The pathogenesis is poorly understood, and no universally accepted treatments exist. The current standard of treatment includes antipsychotics; however, a major challenge is patient resistance. Further interventions are essential to address the complexity of DI management. We present a case demonstrating the successful treatment of refractory DI with dupilumab, highlighting its use as a novel intervention for DI. A 71-year-old male with Parkinson's disease treated with ropinirole was referred to dermatology for a five-month history of perceived sensations of worms, bugs, and fibers infiltrating his skin, severely affecting his quality of life. Numerous systemic treatments were trialed, including ropinirole cessation, ivermectin (at the patient's request), diphenhydramine, doxepin, fluconazole, gabapentin, naltrexone, and quetiapine without improvement. Most recently, he started dupilumab, which led to the first significant improvement in four years. Seven months after dupilumab was initiated, he reported considerable relief bordering on a complete cure. Dupilumab, an antagonist of inflammatory cytokines, may provide a promising treatment avenue for DI. Dupilumab binds to the interleukin-4 receptor alpha subunit and blocks interleukins (IL) 4 and 13 which influence pain and itch pathways in the dorsal root ganglia. The cutaneous symptom relief may indirectly mitigate patients' delusional ideation by breaking the cycle of discomfort, scratching, and reinforcement of infestation beliefs. The initiation of dupilumab resulted in a complete response following numerous ineffective treatment modalities, supporting the potential role of dupilumab for refractory DI. Larger studies are needed to establish dupilumab's role in psychodermatologic disorder management.

LB1090

No significant differences in complications in outpatient vs inpatient paramedian forehead flap repairs: A single-center retrospective study

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Differences in complications after paramedian forehead flap (PMFF) repairs performed outpatient vs inpatient were assessed. Patients who underwent PMFF repair for facial defects from 1/1/2021 to 11/26/2024 were included. Extracted data included (among others): demographics, tobacco use, antithrombotic use, immunosuppressant use, defect information, flap details, days to takedown, local fibrinolytic use, bleeding (including phone calls, after-hours clinic or ER visits), flap necrosis, infection, and revision procedures. PMFF technique was utilized in all 126 cases. 32/126 of repairs were completed outpatient by a Mohs micrographic surgeon. 94/126 of repairs were completed inpatient. No significant differences in bleeding complications were observed between outpatient and inpatient repairs, including in patient calls (6/32 vs 8/94) and ER visits (2/32 vs 1/94). No significant differences were observed in the incidence of flap necrosis (2/32 vs 1/94) or infection (3/32 vs 4/94). When revisions were indicated, patients with PMFF repairs performed outpatient tended to undergo dermabrasion (10/32 vs 1/94) and intralesional corticosteroid (8/32 vs 1/94), while patients with PMFF repairs performed inpatient tended to undergo surgical revision (6/32 vs 21/94). 5/94 (5.3%) of patients with inpatient repairs required overnight admission. The mean takedown period significantly differed between outpatient (11.7 days) vs inpatient (32.9 days) procedures (-21.2 days (95% CI, -27.3 to -15.1, p<0.0001)). No significant differences in complications were observed between patients who underwent outpatient vs inpatient PMFF repair. Small sample size is a key limiting factor. Large reconstructions such as PMFF have similar outcomes when performed outpatient vs inpatient.

LB1091

TikTok trends: Assessing the quality of rosacea information

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TikTok is a social media platform that presents opportunities for disseminating educational content. Rosacea is one of the most frequently searched dermatology topics on TikTok. This study aims to evaluate the scope and quality of rosacea-related content on TikTok. TikTok was queried for videos tagged with #rosacea and/or #rosaceatreatment. One-hundred videos meeting inclusion criteria and with the highest level of engagement, defined by ([Likes+Comments+Shares+Bookmarks]/[Views]), were analyzed. Content quality was assessed by three reviewers using the DISCERN questionnaire. A two-tailed t-test was used to compare viewer engagement and DISCERN scores. Among 100 videos, 59 were created by non-healthcare professionals, including 38 individuals with rosacea, 9 estheticians, 5 industry professionals, and 7 entrepreneurs. The remaining 41 videos were published by healthcare workers, including 40 dermatologists and one nurse practitioner. Twenty-nine videos (29/100) presented educational content, with 62% (18/29) published by dermatologists. Of the 40 videos by dermatologists, 55% (22/40) focused on product review, including one paid advertisement. Videos of paid advertisements (median=0.06, IQR =0.04-0.08), patient testimony (median=0.06, IQR =0.03-0.09), and beauty tips (median=0.06, IQR=0.04-0.07) had the highest engagement levels. Of content creators, industry professionals (median=0.06, IQR =0.04-0.06) and individuals with rosacea (median=0.05, IQR=0.04-0.08) had the highest engagement levels. Mean DISCERN scores for healthcare and non-healthcare professionals were 3.05±0.97 and 2.35±1.00, respectively (p<0.001). No significant difference in engagement between healthcare and non-healthcare professionals was observed (p=0.11). The majority of the top 100 most engaging rosacea-focused videos on TikTok were created by non-healthcare professionals and influenced by product review. Board-certified dermatologists can enhance visibility and educational efforts by increasing contributions of evidence-based dermatology content on TikTok and other social media platforms.

LB1092

Reevaluating tumor regression in T1 melanoma: Implications for sentinel lymph node biopsy and nodal positivity

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The prognostic significance of tumor regression in melanoma remains controversial. While regression may indicate a favorable immune-mediated response, it can also obscure tumor depth, potentially concealing micro-metastases and influencing sentinel lymph node biopsy(SLNB) decisions. Current SLNB guidelines do not consider regression, despite its potential clinical relevance. This study examined the relationship between tumor regression, SLNB utilization, and regional lymph node positivity(RNP) in T1 melanoma. We analyzed 27,855 patients with T1 superficial spreading and nodular melanomas(Breslow depth <1.0mm) from the National Cancer Database (NCDB, 2004–2022). Regression was present in 5,924 (21.3%) patients and SLNB was performed in 11,033 (14.4%) cases. Multivariable logistic regression, adjusting for Breslow depth, ulceration, mitotic rate, age, insurance status, and T1 subcategory, assessed the association between regression and SLNB. A separate analysis evaluated regression as an independent predictor of RNP among SLNB patients. Regression was associated with an 11% increased likelihood of SLNB (OR 1.11, 95% CI 1.03–1.20, p=0.008), suggesting it does not deter SLNB utilization. However, regression was not significantly associated with RNP (OR 0.99, 95% CI 0.68–1.45, p=0.976). Ulceration (OR 1.44, p=0.157), higher mitotic rate (OR 2.05 for ≥11 mitoses, p=0.015), and younger age (OR 0.60 for 40–59 years, OR 0.55 for ≥60 years, both p<0.02) were independently associated with RNP. Results were consistent across T1a and T1b subgroups, with no significant interaction between regression and ulceration(p=0.329). These large-scale findings suggest that tumor regression does not deter SLNB but is not independently linked to nodal metastasis. Given its potential influence on biopsy decisions and lack of consideration in current guidelines, further research integrating molecular and immunologic markers is needed to better define its role, particularly in T1a melanomas.

LB1093

The impact of socioeconomic and demographic factors in the utilization of mohs surgery for the treatment of sebaceous carcinoma

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This study aims to evaluate the impact of demographic and socioeconomic factors including metropolitan/nonmetropolitan residential status on the utilization of MOHS surgery for the treatment of sebaceous carcinoma. A retrospective, population-based study was conducted using the Surveillance, Epidemiology, and End Results (SEER) Research Plus 17 Registries database. SEER was queried for all cases of sebaceous carcinoma (ICD-O-3/3 code 8410) diagnosed between 2000 and 2021 with extracted variables of interest including age at diagnosis, sex, race in terms of white versus non-white, cause of death, median household income per county, and metropolitan versus nonmetropolitan residential status. Statistical analysis included chi-square and logistic regression performed using SPSS software with significance set to $p < 0.05$. Chi square analysis revealed no statistically significant difference in the utilization of MOHS surgery for patients in metropolitan and nonmetropolitan counties (p=0.508). There was no statistically significant difference in deaths attributable to sebaceous carcinoma between metropolitan and nonmetropolitan counties (p=0.299). Patients that received MOHS surgery were more likely to be white (odds ratio=1.207, p=0.045), less likely to be 70 years old or older (odds ratio=0.851, p=0.024), and more likely to live in a county with a median income greater than $75,000 (odds ratio=1.218, p=0.010). Those that died from sebaceous carcinoma were less likely to be female (odds ratio=0.674, p=0.014) and more likely to be greater than or equal to 70 years old (odds ratio=1.562, p=0.005). The SEER Research Plus 17 Registries database offers the largest collection of sebaceous carcinoma cases to date. The results of this study provide insight into the impact of socioeconomic and demographic factors for the utilization of MOHS surgery for patients with sebaceous carcinoma.

LB1094

Analyzing antibiotic prescribing practices in the treatment of hidradenitis suppurativa

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The purpose of this study is to assess the duration of oral antibiotic treatment in different stages of Hidradenitis Suppurativa (HS). Antibiotics are a mainstay for the treatment of HS with current guidelines recommending 1-12 months of antibiotics. With higher rates of antibiotic resistance in HS, it is essential to assess antibiotic prescribing practices. A retrospective chart review analyzed patients with HS at a single institution from April 2023 to July 2024. Demographic factors and stages of HS disease were analyzed. The duration of antibiotic treatment was analyzed with a linear regression model to assess for differences in duration with various stages of HS. Additionally, disease severity was compared using a multinomial regression model assessing the impact of race, gender, and age. Among 111 patients with HS, 84% were female and 76% were African American, with a mean age of 47.4 years. Hurley staging was used to stratify disease severity with 27% Stage I disease, 19% Stage II disease, and 28% Stage III disease. While age and race had no impact on disease severity, males were found to have a 7.0 times higher chance of having Stage III disease than Stage I disease (p <.03). Oral antibiotics were prescribed to 77.5% of patients with a mean duration of treatment of 15.0 months (standard deviation: 25.0 months). The most commonly prescribed antibiotic was doxycycline (76%), followed by clindamycin/rifampin (19%). There was no significant difference in antibiotic duration across the three stages of disease. The findings of this study indicate that the duration of oral antibiotic prescriptions in HS needs to be re-assessed. The mean duration of treatment is 3 months over recommended guidelines, with no escalation in the duration of antibiotic treatment as the disease progresses. In the future, providers need to be cognizant of their prescribing practices to reduce the risks of antibiotic resistance and improve antibiotic stewardship in HS.

LB1095

Glucagon-like peptide-1 receptor agonists mitigate the risk of major adverse cardiovascular events in patients with atopic dermatitis and type 2 diabetes

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Purpose: Atopic dermatitis(AD) has been linked to adverse cardiovascular events, with severe AD conferring a higher risk. However, the effect of cardioprotective medications like glucagon-like peptide-1 receptor agonists (GLP-1RA) in patients with AD remains unclear. Methods: For this retrospective cohort study, the TriNetX database was used to identify adults with type 2 diabetes(T2D), including a subgroup who were treated with GLP-1RA. Patients with AD were propensity-score matched to controls without AD. Outcomes included major adverse cardiovascular events(MACE), myocardial infarction(MI), heart failure(HF), and stroke within 10 years. Cox proportional hazard models were used to assess the effect of AD on outcomes over time. Interaction analyses evaluated whether GLP-1RA mitigated the disease burden of AD on the pre-specified outcomes. Results: After matching, 80,183 pairs of patients with T2D and AD and controls without AD were included. Among them, there were 2,840 pairs of GLP-1RA-treated T2D patients with AD and non-AD controls. Patients with both T2D and AD had a significantly higher risk of MI(HR 1.08; 95%CI 1.03-1.13; P=0.001), HF(HR 1.18; 95%CI 1.15-1.22; P=0.0001), and stroke(HR 1.11; 95%CI 1.07-1.15; P=0.0001) than did T2D controls without AD. GLP-1RA-treated patients with AD and T2D had a significantly lower risk of MACE (HR 0.74; 95%CI 0.60-0.90; P=0.0088) compared to non-AD T2D controls. Interaction analyses showed that GLP-1RA effectively mitigated the risk of MACE (P=0.0024), MI (P=0.036), and stroke (P=0.01) that were associated with AD. Conclusions: In patients with T2D and AD, treatment with GLP1-RA significantly mitigated the risk of new-onset MACE, MI, and stroke compared to non-AD T2D controls, suggesting a potential interplay between AD immune mechanisms and the efficacy of GLP-1RA. Prospective studies are needed to confirm whether pre-existing AD serves as a predictive biomarker for GLP-1RA efficacy.

LB1096

Exploring trichotillomania on tiktok: Content trends and limited treatment representation

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Trichotillomania, a body-focused repetitive behavior (BFRB), receives limited public attention, restricting awareness and treatment access. TikTok provides insights into related user engagement, knowledge sharing, and support discussions. We analyzed the top 100 TikTok videos, from 2020 - 2025 under the hashtag #trichotillomania using a new account on a private browser to evaluate video metadata, content type, creator demographics, and resource sharing. Most creators were women (91), predominantly influencers (74) (defined as having more than 20k followers) producing educational content, while non-influencers shared personal struggles (p=0.0018). Scalp (70) and eyelash (16) pulling were most discussed, with fewer mentions of other areas (p<0.001). Beard-pulling appeared solely in a subset of videos referred to as "stimming" videos (9), a term used to describe self-stimulatory behavior (i.e. hair pulling), which showed higher engagement compared to all other video types across measured metrics, including likes (151K vs. 14K), saves (6K vs. 734), comments (742 vs. 171), and views (3.3M vs. 268K). While educational/inspirational videos averaged the highest views (10.4M), although evidence-based treatments or support options were rarely presented. Mentions of treatments primarily came from healthcare professionals (9), including one dermatologist. Increased engagement on social media by healthcare professionals may significantly enhance education and encourage care-seeking behaviors.

LB1097

Elevated infliximab antibodies in hidradenitis suppurativa may be predictive of anaphylaxis risk

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Background: Infliximab (IFX), a TNF-α inhibitor, is considered a standard of care for advanced hidradenitis suppurativa (HS). Containing both human and mouse protein; the latter often induces IFX antibodies, that degrade its efficacy and may lead to anaphylaxis. Previous studies describe antibodies during IFX-induced reactions in rheumatoid arthritis, vasculitis and Crohn's disease (1,2). Objective: To analyze the predictive value of IFX antibodies regarding drug efficacy and anaphylaxis in HS. Methods: In a cohort of 48 HS patients tested for IFX levels, we identified eight patients (16.6%) who experienced anaphylaxis. Serum antibodies to IFX were analyzed in the context of demographic data and disease severity (hidradenitis suppurativa physician global assessment [HSPGA] with HSPGA ≥3 reflecting advanced disease). Results: Of eight HS patients who experienced anaphylaxis, the mean age was 45 years; 6 females; 4 Black, 3 Spanish/Hispanic/Latino, 1; White; and, mean body mass index of 36.6. Hypersensitivity during IFX infusions included throat tightening, increased heart rate, shortness of breath, and hives. Infliximab antibody levels were positive in 7 of 8 (88%) patients. Mean HSPGA score was 3. Discussion: The presence of IFX antibodies, a likely risk factor for hypersensitivity, including anaphylaxis encountered in 16.6% of our cohort, implies the desirability of substituting a fully humanized IFX congener, such as golimumab (Simponi Aria®, Janssen) (3). The high HSPGA in our cohort suggests that antibody formation may contribute to disease severity by neutralizing IFX efficacy. The loss of IFX therapy is devastating for HS patients with high BMI, because self-injectable biologics, such as humira, lose efficacy in this setting (4). There has been no evidence of cross reactivity or immunogenicity between infliximab and its fully humanized counterpart, golimumab (5). While limited by small sample size, our findings support prompt reassessment of treatment options once IFX antibodies are detected.

LB1098

Association of sebaceous carcinoma and Janus kinase inhibitors: Case study and retrospective FAERS analysis

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JAK inhibitors (JAKi) are promising treatments for many autoimmune and inflammatory conditions.1 We report a sebaceous carcinoma (SC) developing in the axilla of a patient on upadacitinib. This atypical location of SC is concerning for hereditary or immunosuppression-induced SC.2 Our patient had no germline mutations related to SC. We conducted an analysis of the FDA adverse event reporting system (FAERS) to determine if there is a statistically significant association between JAKi use and SC. The proportional reporting ratio (PRR) with its confidence interval (CI) was calculated for the detection of a safety signal, defined as ≥3 adverse events of interest, chi-square ($\chi 2$) >4, and PRR >2.3,4 Chi-square results, where applicable, were adjusted by the Yates correction for possible overestimation of statistical significance due to high values in the 2x2 contingency tables.3,4 FAERS data for the adverse reaction SC (52 reports) in March 2024 cited JAKi as the drug exposure in 6 reports (11.5%). The PRR was >2 (PRR = 9.281; 95% CI: 3.964 – 21.731), and $\chi 2$ result with Yates' correction was >4 (32.142), representing an association. Thus, JAKis as a class were determined to be statistically significantly associated with SC. While no safety signals were detected for abrocitinib (n=1; $\chi 2$ with Yates correction 1.836; PRR and 95% CI: 3.929, 0.956 – 16.147) and tofacitinib (n=2; $\chi 2$ with Yates correction 29.819; PRR and 95% CI: 125.623, 17.368 – 908.609), a safety signal was detected for ruxolitinib (n=3; $\chi 2$ with Yates correction 28.424; PRR and 95% CI: 9.281, 3.964 – 21.731). Ruxolitinib, first approved in 2011, has been in use longer than abrocitinib (approved in 2022) or upadacitinib (approved in 2019), which could explain the minimal reports for other JAKi-associated SC. No signal was detected for tofacitinib in our study. While tofacitinib (approved in 2012) and ruxolitinib have been on the market for similar periods of time, ruxolitinib may pose a greater risk for skin cancer than tofacitinib.1

LB1099

Evaluating the association between cicatricial alopecia and autoimmune diseases: A population-level cohort study.

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Cicatricial alopecias (CA), inflammatory hair loss disorders [including lichen planopilaris (LPP), frontal fibrosing alopecia (FFA), and central centrifugal cicatricial alopecia (CCCA)], are characterized by lymphocytic infiltration, fibrosis, and potential permanent hair follicle destruction and scarring. Subtypes of CA have been postulated to overlap in mechanisms with autoimmune disease (AID), but these associations remain unclear. Using the TriNetX US Collaborative Network (68 healthcare organizations), we conducted a retrospective cohort study to assess whether CA is associated with an increased risk for AID. CA patients were identified (ICD-10-CM: L66.8 or L66.9) and 1:1 propensity score matched with controls to account for baseline demographics. We excluded patients with a history of alopecia areata (L63). We used 5-year and 10-year Cox proportional hazard models with 95% confidence intervals (CIs) to evaluate risk of AID development. Compared to controls, CA patients had an increased risk for: discoid lupus erythematosus at 5y (hazard ratio (HR) [95% CI] = 5.70 [4.21, 7.73]) and 10y (3.72 [2.57, 5.38]); Sjogren's syndrome at 5y (2.29 [1.89, 2.78]) and 10y (2.22 [1.82, 2.71]); systemic lupus erythematosus at 5y (2.54 [2.05, 3.15]) and 10y (2.14 [1.66, 2.76]); systemic sclerosis at 5y (2.90 [1.71, 4.94]) and 10y (2.03 [1.19. 3.47]); juvenile arthritis at only 10y (1.37 [1.21, 1.56]); and rheumatoid arthritis at only 10y (1.41 [1.21, 1.65]). No significant differences were observed for ankylosing spondylitis, dermatomyositis, or psoriatic arthritis. While further research on CA subtypes and AID are warranted, our findings demonstrate significant associations and highlight the importance of potential AID screening in CA patients.

LB1100

Hormonal influence on hidradenitis suppurativa: Perspective for clinical trial design

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To explore hormonal influence on hidradenitis suppurativa (HS), a prospective natural history study of 28 women with HS was conducted at Duke University Medical Center. Disease activity at both the early follicular phase and luteal phase of same menstrual cycle was evaluated and subjects also maintained daily diaries that assessed pain, odor, drainage and itching. A statistically significant worsening (median difference [Q1-Q3]) of symptoms was seen during the early follicular phase compared to the luteal phase of the menstrual cycle as evaluated by patient-reported outcomes of Dermatology Life Quality Index (2.0 [1.0-5.5], p=0.011) and Hidradenitis Suppurativa Quality of Life (4.5 [-0.5-9.0], p=0.004). However, physician-reported outcomes (abscess-nodule and draining fistula count, and the International Hidradenitis Suppurativa Severity Score System) did not demonstrate statistically significant changes. Physician measures lack sensitivity to detect changes in lesion size and drainage amount; more objective tools like ultrasound or MRI are needed. Poisson regression (incidence rate ratio, 95% CI) of daily diaries across the menstrual cycle also revealed significant increases in pain (1.26, 1.12-1.44, p<0.001), odor (1.09, 1.02-1.16, p=0.007), itch (1.19, 1.09-1.31, p<0.001), and drainage (1.08, 1.01-1.16, p=0.032) during the early follicular phase compared to the luteal phase. A subgroup analysis of 19 Black women found similar patterns. Our study highlights the importance of incorporating hormonal status at the time of disease assessment in HS clinical trials to ensure accurate analysis for treatment responses given the high placebo response rate in HS clinical trials.

LB1101

Evaluating the cardiovascular safety of low-dose oral minoxidil in patients with non-scarring alopecia: A retrospective cohort study.

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LDOM is an effective treatment for non-scarring alopecia, including androgenic alopecia. Originally used as an antihypertensive, minoxidil has an FDA boxed warning for cardiovascular adverse events (CVAEs), raising concerns about LDOM's safety. While reports have linked LDOM to pericardial effusion, large-scale ongoing safety data remains limited. Using the TriNetX US Collaborative Network (68 healthcare organizations), we conducted a retrospective cohort study comparing non-scarring alopecia patients (ICD-10-CM: L64 or L65) treated with LDOM (2.5 mg) to non-scarring alopecia patient controls without LDOM exposure. Cohorts were 1:1 propensity score-matched for baseline demographics. Patients with prior myocardial infarction or heart failure were excluded. 1-year Cox proportional hazards models with 95% confidence intervals (CIs) were used to evaluate the development of pericardial effusion, cardiac tamponade, and angina. Compared to 9,724 matched controls, 9,724 LDOM-treated patients had no significant differences in the risks of pericardial effusion (hazard ratio (HR) [95% CI] = 1.09 [0.53, 2.26]), cardiac tamponade (no events), or angina (HR [95% CI] = 0.86 [0.43, 1.70]) at 1 year. Among LDOM-treated patients vs hair loss controls, there were 15 vs. 14 pericardial effusions, 0 vs. <10 cardiac tamponades, and 15 vs. 18 cases of angina within 1 year. LDOM treatment in non-scarring alopecia was not associated with increased CVAE risk. While future studies are needed to investigate long-term LDOM exposure and other potential CVAEs, our findings provide real-world evidence of LDOM's safety.

LB1102

Retrospective analysis of hyperhidrosis diagnosis association with antidepressant, antipsychotic, and stimulant medication use

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Hyperhidrosis refers to excessive sweating surpassing that needed to maintain thermoregulation. Antidepressant, antipsychotic, and stimulant medications have all been associated with hyperhidrosis. However, limited literature exists examining this association, particularly which medications have the highest risk; analyses of patient cohorts are also rare. In this study, we used retrospective data from a large academic center to examine the association of hyperhidrosis with each of the aforementioned drug classes and the individual medications most commonly implicated. The proportion of patients with hyperhidrosis taking a medication of interest was significantly higher than patients with hyperhidrosis not on a medication of interest ($p < 2.2e-16$). The median time from medication prescription to hyperhidrosis diagnosis was 58 months (IQR: 21 - 112). Antidepressants were found to be the main culprit, with escitalopram being the most common. It is uncertain whether escitalopram is the most commonly associated medication due to a higher mechanistic effect, or because it is very commonly a first-line antidepressant prescribed. Doolittle et al. found that only 51% of patients suffering from hyperhidrosis discuss their condition with healthcare providers. Given the high percentage of patients who are undiagnosed, we recommend providers screen patients on longer-term antidepressants for this adverse effect. Dermatologists often see patients for the management of hyperhidrosis, and many current treatments are employed. However, it is also imperative that dermatologists evaluate for any drug-induced etiology. For these scenarios, dose reduction, antidepressant discontinuation, or substitution may be viable options prior to starting a hyperhidrosis-targeting medication.

LB1103

Tolerability and exacerbation of pre-existing psoriasis among patients undergoing immune checkpoint inhibitor therapy

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Psoriasiform adverse cutaneous reactions to immune checkpoint inhibitor (ICI) therapy for cancer therapy are potentially treatment-limiting. Only a few studies have investigated long-term outcomes related to exacerbations of pre-existing psoriasis and their potential impact on the efficacy of cancer treatment. Understanding the outcomes among patients with pre-existing autoimmune disease is important: it could provide insight on the proper management of these cutaneous reactions and avoid unnecessarily excluding this patient population from access to ICI therapy. We conducted a retrospective cohort study of patient records present in the University of Kansas Cancer Center database. We identified 20 adult patients with pre-existing psoriasis who were treated with ICIs between 2013 and 2022 and had at least 1 year of follow up information available. 15/20 patients had exacerbation of their psoriasis after starting ICIs. Patients who had exacerbation of psoriasis had a higher median number of total ICI cycles completed compared to those with unaffected psoriasis (16 vs. 9 cycles). The rate of ICI discontinuation due to intolerance of side effects was comparable between the two groups (26% vs. 20%). Patients with psoriasis exacerbation had a lower 1-year mortality (20% vs. 40%) and total mortality (33% vs. 60%) over the retrospective period although the numbers were too small for statistical analysis. Two patients with severe flares required discontinuation of ICIs and the addition of systemic therapy. Overall, the use of ICIs among patients with pre-existing psoriasis appears to be well tolerated with greater total ICI cycles received and comparable rates of discontinuation despite the high risk of exacerbation. This study is limited by the retrospective nature and small numbers, but our observations suggest that those with exacerbation of their psoriasis may have improved outcomes compared to those who did not experience an exacerbation.

LB1104

Cancer surveillance, metastasis, and identification on skin of color: A retrospective cohort analysis

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Cancer surveillance, metastasis, recurrence, and identification on skin of color (SOC) have been underreported. This study aims to reduce this knowledge gap and describe the oncodermatological needs of this population encountered at a National Cancer Institute-designated center. This retrospective cohort analysis utilized data from patients with a history of cancer and SOC, evaluated by Dermatology at Montefiore Einstein Comprehensive Cancer Center between 2018 and 2021. Our cohort comprised 257 patients, predominately female (56.8%), with a mean age of 61.2 years (SD= 15.4), who primarily identified as Hispanic (56.4%) and/or Black (35.8%). Overall, the most common cancers identified on the skin were cutaneous lymphoma (24.3%), squamous cell carcinoma (19.8%), sarcoma (16.9%), melanoma (15.8%), and basal cell carcinoma (12.4%). Out of 264 diagnoses, cancer surveillance accounted for 115/264 (43.5%) of total encounters, with 24.3% being newly diagnosed skin cancers. Out of all cancer identifications on the skin, 14.7 % were metastasis or recurrences of previously identified cancers. These findings will aid providers in the diagnosis and anticipation of cancers in this immunosuppressed population, as individuals with darker complexions have historically faced delays in the accurate identification of cutaneous disease.

LB1105

General dermatological needs in cancer survivors with skin of color: A retrospective cohort study

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The general dermatological needs of cancer survivors with skin of color (SOC) have been underreported. This study aims to reduce the knowledge gap and describe the scope of these needs in this population encountered at a National Cancer Institute-designated center. This retrospective cohort study analyzed data from patients with a history of cancer and SOC, evaluated by Dermatology at Montefiore Einstein Comprehensive Cancer Center between 2018 and 2021.Our cohort comprised 528 patients, predominately female (71%), with a mean age of 61.5 years (SD= 13.2), who primarily identified as Hispanic (52.3%) and/or Black (38.4%). Out of 647 diagnoses, the five most common were benign skin lesions (19.2%), dermatitis (13.6%), eczema (10.5%), dyschromia (6.1%), and cysts (4.9%). Infectious disease was prevalent as fungal, viral, and bacterial infections were causative in 9.9% of total diagnoses. These findings will aid providers in the diagnosis and anticipation of dermatological disorders in this immunosuppressed population, as individuals with darker complexions have historically faced delays in the accurate identification of cutaneous medical conditions.

LB1106

Comparative outcomes of burn-specific vs. medical intensive care in stevens-johnson syndrome/toxic epidermal necrolysis: A single-center retrospective cohort study

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Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are life-threatening, associated with up to 50% mortality rate and survivors often endure chronic morbidities. Despite their severity, data on mortality predictors, and the efficacy of both pharmacological and non-pharmacological protocols. This single-center retrospective study compared outcomes in patients receiving >90% of hospital care in burn-specific care units (BSC) vs. medical intensive care units (MIC).The cohort included 74 patients, diagnosed with SJS/TEN by a dermatologist, 30 in BSC group and 44 in MIC group between January 1, 2009, and December 31, 2018. 42% were female, with mean age of 50.1 years (SD=19.5). Patients were matched for age, sex, HIV, dialysis status, and malignancy. No significant differences were found in direct admissions vs. transferred admissions (83.3% vs. 68.2%, p=0.18), time-to-transfer (2.6 vs. 3.3 days, p=0.27), disease severity (BSA necrosis: 28.3% vs. 32.5%, p=0.47; SCORTEN: 2.09 vs. 2.17, p=0.79). Systemic corticosteroid use was higher in MIC group compared to BSC group (79.5% vs. 50%, p =0.01); no significant differences were observed in the use of IVIg (34.1% vs. 50%, p = 0.23) or cyclosporine (2.3% vs. 10%, p = 0.29). Hospital-acquired infections (50% vs. 43.3%, p=0.64), length of stay (10.9 vs. 15.9 days, p=0.15), and in-hospital mortality (18.2% vs. 20%, p=1.0) were similar. This study underscores the importance of institutional expertise and protocols, established referral systems, and intensive management strategy with multidisciplinary management over care location in optimizing outcomes for patients battling SJS/TEN.

LB1107

Trends in acne vulgaris burden in the United States: National and state-level estimates (2010–2021)

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Background: Acne vulgaris is the most common inflammatory dermatologic condition with significant psychosocial and economic burdens. Though often associated with adolescence, its persistence into adulthood and rising prevalence warrant further study. Objective: To assess national and state-level trends in the age-standardized rates for incidence (ASIR), prevalence (ASPR), and disability-adjusted life years or DALY (ASDR) of acne vulgaris in the United States from 2010 to 2021. Methods: This population-based study utilized Global Burden of Disease 2021 data to estimate ASIR, ASPR, and ASDR (per 100,000), stratified by state, gender, and age. Temporal trends were assessed using percentage changes over time. All estimates were reported with 95% uncertainty intervals (UIs). Results: In 2021, there were 4,440,168 incident cases of acne in the US, a 14.29% increase since 2010. Over this period, nationwide prevalence, incidence, and DALY burden consistently increased. In 2021, ASIR was 1,618.10 per 100,000, ASPR was 3,128.48 per 100,000, and ASDR was 66.08 per 100,000, reflecting increases of 12.26%, 11.3%, and 10.8%, respectively. Both sexes experienced a higher burden, with females exhibiting nearly twice the incidence rate of males. Among age groups, adolescents (10–19 years) had the highest age-specific incidence, while children under 14 years showed the largest increase since 2010. State-level variations were notable, with the highest incidence in the District of Columbia and New York and the lowest in Wyoming and Alaska. Conclusion: Acne incidence and burden have increased in the US, with significant state-level differences and a disproportionate impact on younger populations and females.

LB1108

National and state-level burden of decubitus ulcers in the United States, 2010–2021

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Decubitus ulcers, or pressure injuries (PI), are a major cause of morbidity, prolonged hospitalization, increased mortality, and increased healthcare costs, particularly among older adults and critically ill patients. This study evaluated the national and state-level incidence, prevalence, mortality, and disability-adjusted life years (DALYs) of PIs in the United States from 2010 to 2021. This population-based study utilized established from the Global Burden of Disease 2021 framework to estimate age-standardized incidence rate (ASIR), prevalence (ASPR), mortality (ASMR), and DALY (ASDR) across all U.S. states. Bayesian meta-regression models accounted for underreporting; Monte Carlo simulations calculated 95%. Uncertainty intervals (UIs). In 2021, there were 706,150 incident cases of PI in the US (95% UI: 640,985–774,801), leading to 1,411 deaths (95% UI: 1,182–1,626) and 50,615 DALYs (95% UI: 41,961–59,890). ASIR was 119.18, ASPR was 31.83, ASMR was 0.22, and ASDR was 8.70 per 100,000. The burden was predominantly concentrated in older adults, with mortality, incidence, prevalence, and DALY rates peaking in individuals aged 95+ years, decreasing in younger groups, reinforcing aging as the strongest risk factor. State-level variations were noted, with the highest burden observed in the District of Columbia, Louisiana, and Mississippi, while the lowest rates were recorded in California, Vermont, and North Dakota. Temporal trend analysis suggested the COVID-19 pandemic was associated with an increase in ASIR and ASPR, likely due to prolonged hospitalization. Between 2010 and 2021, the prevalence and incidence rates increased in the US by 3.7% and 3.6%, respectively, while the mortality rate remained stable. The rising burden of PI underscores the need for better prevention and early detection, particularly in high-risk populations.

LB1109

National and state-level incidence and prevalence of melanoma in the United States, 2010–2021

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Melanoma as the deadliest skin cancer has a high survival rate with early detection and treatment. We sought to assess the national and state-level incidence, prevalence, mortality, and disability-adjusted life years (DALYs) of melanoma in the United States from 2010 to 2021. This population-based study utilized established methods from the Global Burden of Disease 2021 study to quantify age-standardized incidence (ASIR), prevalence (ASPR), mortality (ASMR), and DALY rates (ASDR) across the US. Percentage changes were calculated with 95% uncertainty intervals (UIs). Disparities based on sociodemographic index (SDI) and geographic location were evaluated. In 2021, there were 90,445 incident cases of melanoma in the US (95% UI: 84,957–93,999), resulting in 9,996 deaths (9,185–10,436) and 263,506.5 DALYs (95% UI: 247,513.3 – 280,592.9). ASIR was 17.33, ASPR was 139.06, ASMR was 1.75, and ASDR was 51.51 per 100,000. Between 2010 and 2021, melanoma incidence and mortality showed an overall decline, with ASIR decreasing by 27.7%, mortality rates dropping by 25%, and DALYs declined by 29%. Despite these national improvements, notable state-level disparities persisted, highest incidence observed in Utah, Colorado, and New Hampshire, the lowest rates were in the District of Columbia, Mississippi, and Hawaii. The highest melanoma burden was among older adults, particularly those aged 85–89 years. Socioeconomic differences contributed to higher mortality and DALY rates, with the greatest burden observed in low-SDI states. Melanoma rates declined nationwide in the US due to access to advanced therapeutics. However, burden remains uneven, highlighting the need for targeted prevention, improved screening, and enhanced healthcare access.

LB1110

National and state-level epidemiology of seborrheic dermatitis in the U.S., 2010–2021

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Background: Seborrheic dermatitis (SD) is a chronic, relapsing inflammatory skin condition that typically affects sebum-rich areas—such as the scalp, face, neck, and upper trunk—in infants and adults. Despite its recognized clinical presentation, the burden of SD in the United States remains insufficiently characterized. Objective: To estimate the national and state-level incidence, prevalence, and disability-adjusted life years (DALYs) of SD in the United States. Methods: In this population-based study, we used established methods from the Global Burden of Diseases, Injuries, and Risk Factors Study 2021 to quantify age-standardized rates for incidence (ASIR), prevalence (ASPR), and DALY burdens in the US. All estimates were calculated with 95% uncertainty intervals (UIs). Results: In 2021, there were 6,208,935 incident cases of SD in the US, a 4.6% increase since 2010. ASIR was 1,913.1 per 100,000 (95% UI: 1,771.6–2,048.7), ASPR was 319.2 per 100,000 (95% UI: 301.8–338.2), and DALYs were 4.2 per 100,000 (95% UI: 2.5–6.7), remaining largely stable since 2010. ASIR was 23% higher in females than males. Rates were higher in adults than in infants and children, peaking in middle adulthood (ages 30–50 years). State-level variations were noted, with the highest burden in the District of Columbia, Hawaii, and Florida and the lowest in New Mexico, Maine, and Wyoming. Conclusion: In the US, despite an increase in total cases, the incidence rate of seborrheic dermatitis has remained largely stable since 2010. Higher incidence was observed in females and middle-aged adults. State-level variations warrant further research into underlying driving factors.

LB1111

Oral immune-related adverse events associated with PD-1 and PD-L1 inhibitor therapies: A retrospective, single-institution study

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Immune checkpoint inhibitors of key programmed cell death 1 (PD-1) and its ligand (PD-L1) are efficacious cancer treatments through augmentation of T-cell mediated tumor destruction. Despite extensive research published on this drug class, there is a paucity of literature describing oral immune-related adverse events (irAEs), which generally occur in less than 10% of patients. Our study aims to characterize the clinical presentation, treatments, and outcomes of patients with oral irAEs on PD-1/PD-L1 inhibitors. We conducted a retrospective chart review including patients on PD-1 (nivolumab, pembrolizumab, cemiplimab) and PD-L1 (atezolizumab, avelumab, durvalumab) inhibitors who were treated with dexamethasone elixir, viscous lidocaine, or magic mouthwash. Patients with oral irAEs that could be attributed to chemotherapy or radiation therapy, or with a history of head and neck carcinomas were excluded to avoid confounding. Descriptive characteristics were collected for 29 patients. Mean age was 63.5 years, and 62.1% patients were female. Most of our patients were Hispanic/Latino (48.3%) and on pembrolizumab (65.5%). 37.9% of patients were concurrently on chemotherapy, 24.1% on targeted cancer therapy, and 34.5% on PD-1/PDL-1 monotherapy. A majority of their cancers did not respond to immunotherapy (55.2%). The mean number of PD-1/PD-L1 doses before oral irAEs appeared was 6.7; the mean number of days before oral irAEs was 223.9. Clinically, the most common description of the oral irAE was mucositis, stomatitis, or ulceration (n=19), then xerostomia (n=11), then color changes (n=6). The most common oral anatomic sites for the irAE were the mucosa (n=12) and tongue (n=9). Four patients had oral biopsies showing ulcerated mucosa with granulation tissue, amyloidosis, and two results with lichenoid mucositis. The results of this study may help clinicians with early identification and management of oral adverse events from PD-1/PD-L1 inhibitors and raise awareness of this important association.

LB1112

Mental health diagnoses and survival in older patients with melanoma: A SEER-Medicare linked cohort study

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Mental health diagnoses (MHD) affected 1 in 5 adults in the United States in 2024. MHD are associated with decreased survival in some cancers, but little is known about MHD and survival in melanoma. This study aimed to estimate the prevalence and survival impact of pre-existing MHD in a SEER-Medicare linked cohort of patients aged 67+ with melanoma diagnosed in 2003-2016. Pre-existing MHD (depression, anxiety, schizophrenia, bipolar disorder) during up to two years of continuous Medicare enrollment prior to melanoma diagnosis were identified using 1 inpatient or 2 outpatient ICD-9/10 codes. Five-year overall and melanoma-specific survival were estimated and compared by mental health diagnoses using multivariable Cox models. Among 178,848 patients with melanoma, 16,989 (9.5%) had pre-existing MHD: 6.0% depression, 5.4% anxiety, 0.7% schizophrenia, 0.5% bipolar disorder. 5-year overall and melanoma-specific survival were 62.6% (95% CI: 61.8-63.5%) and 90.5% (89.9-91.0%) for patients with MHD and 75.6% (75.3-75.8%) and 91.8% (91.6-91.9%) for patients without, respectively. Adjusting for sociodemographic factors and staging, MHD were associated with higher risk of overall mortality (aHR: 1.44, 95% CI: 1.40-1.49) and melanoma-specific mortality (aHR: 1.11, 95% CI: 1.04-1.19). Pre-existing MHD are associated with lower overall and melanoma-specific survival in older patients with melanoma. This study is limited by the use of ICD codes to identify MHD and results may not be generalizable to non-Medicare populations. Future research should examine tailored multidisciplinary interventions aimed to optimize care and outcomes in patients with MHD and melanoma.

LB1113

Molecular features of leukemia cutis in acute myeloid leukemia

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Leukemia cutis (LC) represents cutaneous infiltration by neoplastic leukemic cells, serving as an important extramedullary manifestation of systemic leukemia. Previous studies have found associations between LC in patients with acute myeloid leukemia (AML) and decreased overall and leukemia-specific survival[1]. However, the pathogenesis and molecular features of LC remain poorly understood. A retrospective matched-cohort study was performed including 47 AML patients with LC diagnosed from November 2006 to December 2021 propensity-matched to 141 AML patients without LC, finding that the most frequent molecular alterations in LC were NPM1 mutations (38%, $p < 0.001$), followed by aberrancies in composite FLT3 (28%, $p < 0.05$), chromosome 8 (23%, $p < 0.05$), and NRAS/KRAS (21%, $p < 0.01$). Two of the LC patients had molecular studies performed on skin biopsy samples, both of which carried NPM1 (frameshifts in W288) and KRAS mutations. A literature review revealed studies demonstrating correlation of NPM1 mutations with cutaneous AML including a report of NPM1 mutations in the C-terminus (such as frameshifts in W288) found in 70% skin samples[2]. LC emergence can precede bone marrow involvement suggesting its utility as a biomarker. These molecular insights provide potential therapeutic targets and prognostic indicators that may enhance clinical management of this condition. [1]Wang CX et al. Association of Leukemia Cutis With Survival in Acute Myeloid Leukemia. JAMA Dermatol. 2019;155(7):826–32. [2]Sadigh S et al. Cutaneous Manifestations of Myeloid Neoplasms Exhibit Broad and Divergent Morphologic and Immunophenotypic Features but Share Ancestral Clonal Mutations With Bone Marrow. Mod. Pathol. 2024;37(1):100352.

LB1114

Survival in patients with rheumatoid arthritis and concomitant melanoma receiving disease-modifying antirheumatic therapy

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This retrospective cohort study investigates the survival of patients with rheumatoid arthritis (RA) diagnosed with melanoma, and receiving disease-modifying antirheumatic drugs (DMARDs) after diagnosis. Utilizing SEER-Medicare Melanoma, we analyzed overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) in RA patients aged ≥66 diagnosed with in situ, localized, or regional melanoma between 2008 and 2017. Patients were categorized by DMARD exposure within one-year post-melanoma diagnosis: no DMARDs (n=183), methotrexate (MTX) alone (n=137), or tumor necrosis factor-alpha inhibitors (TNFi) alone or with MTX (n=99). A 1-year landmark analysis was conducted on 419 patients with RA and melanoma with a mean age of 76 years and a median follow-up of 5 years. After multivariable adjustment including stage and propensity score, there was no statistical difference between TNFi (HR 0.65, 95% CI 0.34-1.25), or MTX (HR 0.94, 95% CI 0.58-1.52) compared to the no DMARDs group in OS, or between TNFi (HR 0.51, 95% CI 0.21-1.22) or MTX (HR 0.98, 95% CI 0.51-1.87) compared to the no DMARDs group in RFS. DSS was 95% (95% CI 91%-97%) overall, with no significant differences between groups. Older age, comorbidities, frailty, and steroid use were associated with decreased OS. Our results suggest that TNFi and MTX do not negatively impact survival in patients with RA and melanoma, but further research is needed to explore other biologic therapies and outcomes in younger patients.

LB1115

Skin stretchability and sagging: The impact of aging, ethnicity, BMI, and skincare interventions

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Skin's mechanical properties, including stretchability, are essential for skin function and change with intrinsic and extrinsic aging. Loss of stretchability due to reduced collagen and elastin contributes to skin sagging. We previously introduced a novel tensile test method that appeared to correlate more strongly with skin aging than cutometers and allows direct measurement of stretchability in the direction of gravity. In this study, we applied this method to a large cohort to further investigate correlations between skin stretchability and aging as well as other factors like BMI and ethnicity. Additionally, we assessed improvements in stretchability and visible sagging following a 12-week application of skin creams. A cohort of 280 women (ages 10–78) was evaluated for skin stretchability using our previously validated skin tensile test. Demographic data, including age, height, weight, and ethnicity, were recorded. In a separate open label clinical study, skin stretchability and sagging were evaluated in 92 women (ages 35–64) over a 12-week period following the application of skin creams with assessments at weeks 0, 4, 8, and 12. The cohort analysis revealed a decline in skin stretchability with age ($r= 0.414$, $p<0.001$), with a more pronounced decrease in Caucasians compared to African Americans ($p<0.001$). BMI also influenced the rate of decline. The clinical study demonstrated improved skin stretchability ($p<0.05$) at different time points following cream application, which was aligned with visual reductions in sagging. Our findings confirm the correlation between skin stretchability and aging with variations across ethnic groups and BMI categories in a large cohort. The observed improvements of skin stretchability after skincare treatment correspond to observed sagging improvement. These results underscore the importance of skin stretchability in aging-related concerns and highlight its potential as a target for sagging interventions

LB1116

Factors influencing patient follow-up after skin cancer removal: A retrospective cohort study

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Follow-up with a dermatologist for total body skin exams after skin cancer removal is important as this may help with earlier detection of new skin cancers and is recommended by the National Comprehensive Cancer Network (NCCN). Limited research studies have highlighted clinical and sociodemographic factors that influence patient adherence to follow-up. This study examines the patients' sociodemographic and clinical factors that may affect follow-up adherence after skin cancer removal procedures at The Emory Dermatology Clinic. Among 200 patients randomized for the pilot, 159 were determined eligible. Patients who passed during the follow-up period, did not have documented skin cancer removal procedures, or received most dermatological care outside the Emory Dermatology Clinic were excluded. The cohort's average age is 64.2 years. Most participants were white (96.9%) and had Medicare (64.2%). Follow-up adherence declined from 85.5% of patients attending at least one follow-up visit in the first year to only 38.4% attending consecutive follow-ups for five years. Univariate and multivariate logistic regression models were used to identify barriers and facilitators of follow-up adherence. Facilitators of follow-up adherence included being married, having higher levels of educational attainment, and having a personal history of multiple skin cancers. Insurance type, skin cancer removal procedure type, site of skin cancer, psychiatric comorbidities, and mobility issues did not significantly affect patient follow-up adherence. Our findings suggest that dermatologists may play an important role in improving follow-up adherence by (1) tailoring patient communication to the appropriate level of comprehension and (2) identifying patients who are more socially isolated and offering them outlets of support.

LB1117

Isotretinoin is a potential trigger for acne conglobata in patients with hidradenitis suppurativa

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Objective: Explore risk of acne conglobata in hidradenitis suppurativa patients treated with isotretinoin. Background: Hidradenitis suppurativa (HS) is a chronic, debilitating skin disorder of follicular biology. Isotretinoin has been associated with flares of HS,[1] as well as paradoxical nodulocystic acne and acne conglobata (AC).[2] Following our previous report,[3] we continue to identify new cases of acne conglobata associated with isotretinoin therapy in the setting of HS. Methods: We reviewed clinical histories of 7 males and 1 female patient with HS who developed AC while receiving isotretinoin. Demographic data, body mass index (BMI), HS severity, isotretinoin dosing, and clinical outcomes were collected from the electronic medical records. Results: Age (mean±SD) of participants was 23±3.6 years; 7 identified as White (88%); 3 identified as having Latino ethnicity (37.5%). Mean body mass index was (31±4.1). Severity of HS ranged from 2 - 4 (2.9±0.99). In all cases, isotretinoin therapy led to AC, manifesting as draining abscesses and numerous interconnected sinus tracts, leading to extensive hypertrophic and keloidal scarring. Isotretinoin was discontinued; oral prednisone, 1 mg/kg was required in four patients to achieve remission of AC. Conclusion: Our findings identify a relatively unrecognized and underreported association between isotretinoin and AC in patients with HS. While our cohort is limited, Caucasian males with elevated BMI and HS appear to be at highest risk for AC. We urge caution before starting isotretinoin in the setting HS.

LB1118

Scabies in the United States: National and state-level epidemiologic trends (2010–2021)

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Background: Scabies is a highly contagious parasitic skin disease caused by the microscopic mite Sarcoptes scabiei, resulting in intensely pruritic eruptions. This study examines national and state-level epidemiologic trends of scabies in the United States from 2010 to 2021. Method: Utilizing established methods from Global Burden of Disease (GBD) 2021 framework. This population-based cross-sectional study quantified age-standardized rates for incidence (ASIR), prevalence (ASPR), and disability-adjusted life years or DALY (ASDR) per 100,000 in the US. This analysis integrates national surveys, medical records, and claims databases using Bayesian meta-regression modeling (DisMod-MR 2.1). All estimates were reported with 95% uncertainty intervals (UIs). Results: In 2021, an estimated 1.213 million new cases of scabies were reported in the U.S., representing a 2.9% decline from 1.249 million cases in 2010. ASIR decreased from 440.4 per 100,000 (95% UI: 407.2-474.7) in 2010 to 397.7 per 100,000 (95% UI: 361.4-438.9), reflecting an overall reduction in disease incidence. Females consistently exhibited higher ASIR, ASPR, and ASDR compared to males. Age-stratified analysis revealed the highest ASIR in adolescents (15–24 years: >600 per 100,000), while the youngest (<5 years) and oldest (≥85 years) age groups had the highest DALY burden. At the state level, Mississippi, Tennessee, and Maryland reported the highest incidence rates, whereas Nevada, Arizona, and Colorado had the lowest. Conclusion: While scabies burden have shown a gradual decline, it remains a significant public health concern, particularly among specific age groups and in high-prevalence states.

LB1119

Validation of the spanish version of the dermatology life quality index and skindex-16 instruments in a U.S. latine population

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The Dermatology Life Quality Index (DLQI) and Skindex-16 are validated tools for assessing quality of life in dermatology patients and are frequently used in routine practice and clinical trials. However, these tools have not been validated for Spanish-preferring populations in the United States (U.S.). This study aims to translate, culturally adapt, and validate the DLQI and Skindex-16 into U.S. Latine Spanish, enabling greater participation of Spanish-preferring individuals in dermatology research. We translated the tools using forward and backward translation methods with a panel of 3 bilingual dermatologists and 4 medical students from five Latin American countries. We then conducted 25 cognitive interviews between August 2024 to November 2024 with Spanish-preferring Latine adults at Zuckerberg San Francisco General Hospital to assess comprehension. The participants' mean age was 43.6 (SD=13.3); 56% were women, 47% men, and most had origins from Mexico (44%). The interviews revealed that 14 participants (56%) expressed confusion of at least one term. Commonly misunderstood terms included recurrencia (recurrence) [32%], influido (influence) [20%], and persistencia (persistence) [16%]. Based on feedback, we revised the tools and administered the updated versions to 200 Spanish-preferring Latine adults between December 2024 to March 2025. We analyzed the data using psychometrically robust methods, including factor analysis and convergent validity, to validate both instruments. The translated and culturally adapted DLQI and Skindex-16 will facilitate more inclusive dermatology studies, ensuring better representation of Spanish-speaking Latine populations in the U.S.

LB1120

Psoriasis in the United States: National and state-level trends in disease burden

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Background: Psoriasis is a chronic immune-mediated skin disease that significantly impacts physical and psychological well-being. We assessed national and state-level epidemiological trends of psoriasis across demographic groups in the US. Methods: Using the Global Burden of Disease (GBD) 2021 framework, we quantified age-standardized rates for incidence (ASIR), prevalence (ASPR), and disability-adjusted life years or DALY (ASDR) per 100,000. This analysis integrated national surveys, medical records, and claims databases using Bayesian meta-regression modeling (DisMod-MR 2.1). All estimates were reported with 95% uncertainty intervals (UIs). Results: In 2021, an estimated 3.91 million individuals in the U.S. had psoriasis (95% UI: 3.83–3.98 million), a 15.7% increase since 2010. Incidence reached 380,893 cases (95% UI: 370,220–391,421), reflecting an 11.7% rise over the same period. DALYs increased by 13.9%. ASIR, ASPR, and ASDR increased from 2010, with a slightly higher burden in females than males. Temporal trends varied by age, with a slight decline in incidence among children under 5 years, remaining stable in adolescents, and a gradual increase in adults aged 25–49 years. The most significant rise occurred in older adults (60+ years). The highest incidence rates were reported in Massachusetts, Connecticut, and New York, while the lowest was in New Mexico, Utah, and Colorado. ASPR and ASDR followed the same pattern. Conclusion: The burden of psoriasis has steadily increased in the US, with notable variations by sex, age, and state. Further research is needed to identify the factors contributing to these differences across states and demographic groups.

LB1121

Disparities and determinants of dermatology consultation duration: The influence of sex, age, race, and insurance in a multivariate analysis of NAMCS (2011–2019)

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Health disparities impact access to care, patient-physician interactions, and satisfaction, with race, socioeconomic status, and insurance being key determinants. Visit length serves as an objective marker of communication quality, where shorter visits correlate with reduced preventive care utilization. We evaluated factors influencing disparities in dermatology consultation times using National Ambulatory Medical Care Survey (NAMCS) data (2011–2019). Visits were categorized based on dermatologic conditions without coexisting diagnoses. Gender: Males had significantly longer consultations for common skin infections (p=0.03) and across all dermatologic conditions (+1.34 minutes, p<0.01). Race: No significant differences were found in condition-specific comparisons between the races. However, across all dermatologic conditions, Black patients had shorter visits (-1.85 minutes, p=0.02). Insurance: When aggregated, patients with public insurance had longer visits than those with private insurance (+1.63 minutes, p<0.01). Age: Younger patients (15–24 years) had longer visits for common infections (p=0.047), while adults ≥75 years experienced extended consultations across all dermatologic conditions (+3.83 minutes, p<0.01). Temporal trends: Overall visit durations remained stable. However, consultations for dermatitis/rash declined by 3.13 minutes in 2018–2019 (p < 0.01), and for malignant neoplasms, decreased by 6.51 minutes in 2013–2014 (p<0.01) and 6.45 minutes in 2018–2019(p=0.011). Race- time interactions: Black patients in 2015–2016 had significantly shorter visits for common skin infections (-8.88 minutes, p<0.001) and in 2018–2019 (-9.92 minutes, p<0.001), highlighting potential worsening disparities over time. Similar trend was observed for non-malignant skin neoplasms, but not across aggregated conditions. Our findings suggest that longer consultation durations were observed among males, White patients, publicly insured individuals, and older adults, while racial disparities in visit lengths fluctuated over time.

LB1122

Burden of atopic dermatitis in the United States: National and state-level trends (2010–2021)

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Background: Atopic dermatitis (AD) is a chronic inflammatory skin condition affecting all age groups. While most common in children, its burden in adults is increasing, prompting an updated assessment in the United States from 2010 to 2021. Methods: We used Global Burden of Disease (GBD) 2021 data to estimate age-standardized rates for incidence (ASIR), prevalence (ASPR), and disability-adjusted life years (ASDR) at national and state levels and across demographic groups. Our analysis integrated national surveys, hospital records, and claims databases using Bayesian meta-regression modeling (DisMod-MR 2.1). Estimates were reported with 95% uncertainty intervals (UIs). Results: In 2021, an estimated 9.18 million individuals in the U.S. had atopic dermatitis (95% UI: 8.91–9.48 million), a 2.75% increase since 2010. Incidence reached 922,005 cases (95% UI: 886,551–959,007), reflecting a 1.49% rise over the same period. DALYs increased by 1.7%. In 2021, ASPR for AD was 3,161.5, ASIR was 336.57, and ASDR was 136.56 per 100,000. Females had a 20% higher incidence rate and a 32% higher DALY rate than males, indicating both a higher occurrence of new cases and a greater overall disease burden. Children and adolescents under 20 years had a higher incidence rate than adults. However, compared to 2010, incidence declined in children under 10 years, while prevalence increased in adults, particularly in those aged 25–29 and 65–69 years, highlighting a shifting disease impact across age groups. State-level differences were evident, with Pennsylvania and the District of Columbia reporting the highest rates, while North Dakota had the lowest. Most states saw a slight decline in age-standardized rates, though variations persisted. Conclusion: In the U.S., despite rising total cases, age-standardized AD rates slightly declined, suggesting population growth rather than increased disease risk. The burden remains significant, particularly among adults, and females, with notable state-level variations.

LB1123

Incidence, prevalence, and care for patients with lymphatic malformations (LMs) in the U.S.: A claims-based analysis

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Introduction & Objectives: Lymphatic malformations are a type of vascular anomaly. LMs have a wide spectrum of presentation, from focal and simple to complex and life-threatening. Cutaneous involvement is characteristic of microcystic and mixed types of LM; such patients are often treated by dermatologists who can be part of multidisciplinary teams. There are no approved pharmaceutical treatments specifically for cutaneous LM, but off-label therapies, sclerotherapy, and ongoing clinical trials in patients with LM have increased interest in understanding the epidemiology of LM. No large dataset has been analyzed to determine the number of U.S. LM cases. We used insurance claims to understand epidemiology, diagnosis, physician specialties, and centers of care. Materials & Methods: Medical and pharmaceutical claims data from January 1, 2015 through September 30, 2024 was licensed from Komodo Health. Records from approximately 375,000 patients with potentially relevant claims were included in this analysis. Criteria to guide diagnostic coding for LMs were developed by a professional organization and were utilized in this project. Results: 84,062 high-probability patients with LM diagnosis were identified. An additional 91,349 potential patients were also found, for a total potential pool of 175,410 patients. Using an estimate of cutaneous involvement from the literature, a range of 44,553- 92,967 patients are likely to have skin-involvement. Diagnosis rates differ by age, with young children having a higher probability of diagnosis than adults. Conclusion: This study is the first to quantify the U.S. LM population based on claims data. This may assist vascular anomaly centers, dermatologists and other providers to design clinical trials and meet the needs of LM patients as new therapeutic options arise.

LB1124

Alopecia areata in the United States: National and state-level epidemiologic trends (2010–2021)

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Background: Alopecia areata (AA) is a chronic autoimmune disorder that causes non-scarring hair loss, significantly impacting psychosocial well-being. We assessed national and state-level epidemiology of AA in the US from 2010 to 2021, stratified by age and sex. Methods: In this population-based study, we used established methods from the Global Burden of Diseases (2021) to quantify age-standardized rates for incidence (ASIR), prevalence (ASPR), and disability-adjusted life years or DALY (ASDR) per 100,000 in the US. This analysis integrates national surveys, medical records, and claims databases using Bayesian meta-regression modeling (DisMod-MR 2.1). All estimates were reported with 95% uncertainty intervals (UIs). Results: In 2021, an estimated 1.145 million individuals in the U.S. had AA (95% UI: 1.113–1.178 million), reflecting an 8% increase since 2010. Incidence reached 2.01 million cases (95% UI: 1.95–2.06 million), showing a similar 8% rise over the same period. The point prevalence of AA was 0.34%. The incidence rate in females was 2.53 times higher than in males. Incidence rates increase from adolescence, peak at 30–34 years, and then decline progressively in older adults. The ASIR, ASPR, and ASDR of AA in the U.S. declined slightly over the study period but remained significantly higher than global rates. The District of Columbia and New York had the highest rates, while Wyoming, Mississippi, and Alaska had the lowest. Conclusion: AA continues to affect a substantial portion of the US population, with distinct patterns by age, sex, and state.

LB1125

Real-world evaluation of efficacy and safety of abrocitinib in moderate-to-severe atopic dermatitis across a multi-site hospital system

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Abrocitinib, a selective JAK-1 inhibitor, is approved to treat moderate-severe atopic dermatitis (AD) in adults and adolescents. Although clinical trials have demonstrated the efficacy and safety of abrocitinib in AD, there remains a lack of comprehensive, long-term real-world studies to further evaluate its effectiveness and safety in diverse patient populations. The objective of the study was to characterize long-term treatment responses and adverse events in patients with moderate to severe AD in real-world practice. In this retrospective observational study, electronic medical records of adolescents and adult AD patients treated with abrocitinib across a multi-site hospital system were reviewed from January 1, 2021, and March 2024. 50 patients were included (mean age 40 ± 14 years), with 56% female. The racial distribution was 36% White, 24% Asian, 24% Black, and 16% other. 96% of patients had prior exposure to systemic therapy, which they had discontinued due to inadequate response or intolerance before initiating abrocitinib, including prior treatment with dupilumab (80%), prednisone (34%), and upadacitinib (10%). Mean ± SD treatment duration of abrocitinib was 57 ± 40 weeks. Mean ± SD improvements in BSA, EASI, and IGA were 60.3% ± 44.3%, 58.6% ± 30.4%, and 48.5% ± 35.1%, respectively ($p < 0.0001$). Of the patients (n = 29) treated with abrocitinib for over 1 year, 49% achieved 75% improvement in EASI and 57% achieved IGA 0/1. No significant changes in AST, ALT, cholesterol, triglycerides, or LDL were observed throughout treatment. 15 patients had adverse events (30%), of which acne (16%) and abdominal pain (6%) were the most common. Of 10 patients discontinuing abrocitinib, 5 due to inefficacy, 1 to infection, and 4 lost to follow-up. No serious adverse events occurred. Abrocitinib was well-tolerated and effective across various age, sex, race, or ethnicity and demonstrated strong therapeutic potential in refractory cases where other systemic therapies failed.

LB1126

A decade-long comparative analysis of skin disease trends in the United States and globally using the global burden of disease database

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Skin diseases impact the quality of life and strain healthcare systems. Studying long-term trends helps guide prevention and treatment options. Our study aims to analyze 2011–2021 US and global skin disease trends using the Global Burden of Disease Database, showing heightened disparities and potential causes. We extracted prevalence and incidence data for 15 conditions, including acne vulgaris, atopic dermatitis (AD), bacterial skin infections (BSI), decubitus ulcers (DU), scabies, viral skin diseases (VSD), and pyoderma. Changes were compared between US and global populations, with confidence intervals (95% CI) used to assess significance. Several conditions showed a greater burden in the US. BSIs rose to 0.1511 (95% CI: 0.13-0.17), nearly double the global rate (0.0806, 95% CI: 0.0773-0.0839). Cellulitis also increased (0.1022, 95% CI: 0.08-0.12) compared to global levels (0.0855, 95% CI: 0.0773-0.0943). DUs (0.2242, 95% CI: 0.16-0.27) and pyoderma (0.2440, 95% CI: 0.23-0.26) were significantly higher than global rates (0.1121, 95% CI: 0.0891-0.1330 and 0.0803, 95% CI: 0.0768-0.0838), reflecting greater challenges in wound care. Some conditions declined in the US. Scabies fell to −0.0966 (95% CI: −0.0293 to −0.0415), a sharper drop than globally (−0.0293, 95% CI: −0.0415 to −0.0174), likely due to improved hygiene. VSD followed a similar trend (−0.0246, 95% CI: −0.0289 to −0.0239 in the US vs. −0.0263, 95% CI: −0.0289 to −0.0239 globally). AD declined in both (−0.0563, 95% CI: −0.07 to −0.04 in the US, −0.0680, 95% CI: −0.0756 to −0.0610 globally). Acne vulgaris remained stable (−0.00046, 95% CI: −0.01146 to 0.01048). Our analysis shows differing US and global skin disease trends, with rising infections and chronic wounds in the US and a decline in scabies and AD. Our results underscore the need for better infection control and further research into healthcare disparities and environmental factors.

LB1127

Epidemiologic trends of cellulitis in the US: National and state-level insights (2010–2021)

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Background: Cellulitis is a common bacterial skin infection affecting the dermis and subcutaneous tissues, characterized by erythema, edema, and tenderness. This study evaluates the epidemiologic trends and burden of cellulitis in the United States across demographic groups and states from 2010 to 2021. Methods: In this population-based study, we utilized established methods from the Global Burden of Diseases (2021) framework to quantify age-standardized rates for incidence (ASIR), prevalence (ASPR), and disability-adjusted life years or DALY (ASDR) per 100,000 in the US. This analysis integrates national surveys, medical records, and claims databases using Bayesian meta-regression modeling (DisMod-MR 2.1). All estimates were reported with 95% uncertainty intervals (UIs). Results: In 2021, there were 10.75 incident cases of cellulitis (95% UI: 10.15–11.37), reflecting an 18.53% increase from 2010. The ASIR increased from 2,664.7 per 100,000 (95% UI:2,524.2–2,815.7) in 2010 to 2,800.3 per 100,000 (95% UI: 2,648.9–2,964.4) in 2021. Males had a slightly higher incidence than females, and incidence rates increased progressively with age. The highest ASIR was observed in adults aged 80–84 years (7,547.5 per 100,000; 95% UI: 6,372.5–8,732.6). The highest incidence rates were reported in Louisiana, New York, Alabama, and Mississippi, while the lowest were observed in Minnesota, Colorado, and North Dakota. Conclusion: The burden of cellulitis in the U.S. significantly increased from 2010 to 2021, with a higher incidence in older adults, males, and specific states.

LB1128

Evaluation of imaging-based methods for facial aging detection

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Introduction: Quantifying facial aging is essential in dermatology for studying age-related changes and assessing the effectiveness of skincare products. However, facial aging detection remains challenging due to the absence of standardized benchmarks and unified testing protocols, making it difficult to compare different methods fairly. In this study, we evaluate the performance of commonly used imaging-based facial aging detection methods, focusing on accuracy, stability, and sensitivity. By highlighting their strengths and limitations, this research aims to provide a comprehensive review of facial aging detection approaches to help researchers select the most suitable method for their studies. Methods: A dataset of 2,000 individuals was analyzed under standardized conditions using imaging systems (Visia CR 5.0, Antera 3D, EVE V). To compare the performance of the methods, we calculated correlations with age, consistency across repeated measurements, and detection of subtle changes post-intervention. Human assessments were used as the gold standard for measuring accuracy. Results: EVE V demonstrated the highest correlation with age, with results exceeding 0.82, outperforming Visia CR 5.0 (average 0.73) and Antera 3D (average 0.77). Compared to human assessments as the gold standard, the accuracy adjustment for EVE V averaged 0.75, while Visia CR 5.0 was 0.68, and Antera 3D was 0.63. Antera 3D showed superior sensitivity, detecting over 20% changes in localized skin features. In terms of stability, EVE V achieved the highest score at 0.93, followed by Visia CR 5.0 at 0.88, and Antera 3D at 0.80. Discussion and Conclusion: Antera 3D's high sensitivity makes it ideal for analyzing localized skin features, while EVE V and Visia CR 5.0 excels in accuracy and stability, making it well-suited for research on age-related skin changes. These findings offer valuable insights for selecting the most appropriate imaging systems for clinical dermatology and efficacy testing.

LB1129

Bridging the gap in dermatologic care for afro-textured hair: Addressing disparities through collaboration and education

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Hair and scalp health are vital components of dermatologic care, yet patients with Afro-textured hair face persistent disparities in diagnosis and treatment. These inequities stem from limited representation of dermatologists and insufficient training on Afro-textured hair in medical education. Patients often experience inadequate care and report discomfort addressing hair and scalp concerns with racially incongruent providers, further burdened by the need to explain cultural hair practices. Meanwhile, dermatologists cite a lack of confidence and minimal training on Afro-textured hair as barriers to providing equitable care. Hairstylists, often serve as primary assessors of hair and scalp health but rarely collaborate with dermatologists. Initiatives like The Black Hair Curriculum and The S.T.R.A.N.D. Network highlight the potential of integrating culturally relevant education into medical training and fostering partnerships between hairstylists and healthcare professionals. These efforts aim to improve diagnostic accuracy, patient-provider relationships, and health outcomes for patients. This paper explores the root causes of disparities in dermatologic care for Afro-textured hair, evaluates current solutions, and proposes systemic changes to center Afro-textured hair in medical education. By addressing knowledge gaps and leveraging community partnerships, we can dismantle hair care inequities and create a healthcare system that prioritizes inclusivity and cultural competence.

LB1130

The effect of tissue glue on the healing of second intention wounds after dermatologic surgery

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Tissue glue (TG; n-butyl-2-cyanoacrylate) is commonly used in dermatologic surgery for its ease of application and simplified wound care. This randomized controlled trial compares TG to standard of care (SOC; petrolatum, non-adherent dressing, and tape) for managing second-intention wounds on high-mobility areas, including the hands, feet, and genitalia. Patients were randomized into three groups: TG applied with reapplication at two weeks (TG+TG), TG applied then transitioned to SOC at two weeks (TG+SOC), or SOC alone. Wounds were evaluated at two weeks, one month, and three months for complications (infection, erythema, edema), patient-reported outcomes (drainage, bleeding, time commitment, functionality), and overall satisfaction with ease of wound care using a 10-point Likert scale. Among 22 patients (SOC=11, TG+SOC=5, TG+TG=6), satisfaction with ease of wound care was significantly higher in TG groups compared to SOC at two weeks (p=0.04), though questionnaire scores (assessing drainage, bleeding, time commitment, and functionality) did not differ significantly (p=0.21). Erythema and edema were each observed once, both in the SOC group, and no infections occurred. At one and three months, questionnaire scores and satisfaction ratings remained comparable across groups (p>0.2). Recruitment is ongoing for a final sample size of 40. These preliminary findings suggest that TG may enhance early postoperative satisfaction with wound care for second-intention healing in high-mobility areas while maintaining similar complication rates to SOC. TG may offer a convenient, patient-friendly alternative to conventional dressings, particularly in the early healing period.

LB1131

VISIBLE: Significant serum cytokine reduction achieved with guselkumab in participants with psoriasis and skin of color

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Levels of disease-driving cytokines are typically elevated in the skin and blood of patients with psoriasis (PsO). VISIBLE, a Phase 3b study, is evaluating efficacy & safety of guselkumab (GUS) in participants (pts) with moderate-to-severe PsO across all skin tones. These post-hoc analyses evaluated the effects of GUS on targeted serum cytokines. VISIBLE pts with plaque (Cohort A) or scalp (Cohort B) PsO were randomized 3:1 to receive GUS 100mg at Week (W) 0, 4, and Q8W or PBO➞GUS at W16. Serum cytokine levels (IL-17A, IL-17F, IL-22, BD-2) were measured at baseline (W0) and W4/16/48 in 151 GUS and 50 PBO pts in both cohorts and up to 29 healthy controls (HCs). Serum IL-17F, IL-22, and BD-2 levels were significantly higher at W0 in VISIBLE pts vs HCs. GUS treatment led to significant reductions (log2 fold change from W0 ranging from -0.8 to –5.7) in serum IL-17F, IL-22, and BD-2 through W48 and in PBO➞GUS after W16. W0 IL-17F, IL-22, and BD-2 levels significantly correlated (p<0.05) with Psoriasis Area and Severity Index (PASI) and Psoriasis Scalp Severity Index (PSSI) scores. Greater reduction in BD-2 from W0 was associated with W16 PASI90 and PSSI90 response in Cohort A&B pts, respectively. Low PsO BSA (2%–<10%) at W0 in Cohort B was associated with significantly less reduction in IL-17F and BD-2 levels at W16 & W48. No significant differences in serum cytokine changes were noted in subgroups by BMI, sex, or psoriatic arthritis. This serum cytokine study in skin of color PsO pts showed that GUS provided early and sustained serum cytokine reductions through W48. Additional studies may inform our understanding on similarities & differences in pts with PsO from diverse backgrounds.

LB1132

Portable tools to quantify stiffness as an outcome measure for cutaneous neurofibroma in NF1

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Individuals with Neurofibromatosis Type 1 (NF1) share a clinically heterogeneous neurocutaneous disorder with >99% developing the hallmark tumor cutaneous neurofibroma (cNF). There is no effective drug therapy currently exists for cNF and mainstay treatment remains physical removal. However, clinical trials testing new drugs are ongoing, and quantitative techniques based on cNF biology are needed to measure changes in cNF following treatment. The cNF tumor bulk is composed of extracellular matrix, collagen and inflammatory cells that dictates their stiffness. No studies have reported measuring the stiffness change in neurofibromas, which would indicate shrinking of the tumor bulk. The goal of this study was to evaluate two different instruments: the Rex Gauge durometer (REX) and the Delfin SkinFibroMeter (DELFIN), in reproducibly measuring cNF stiffness. 97 neurofibromas from different skin areas of NF1 patients were measured at each of two visits about two weeks apart. The DELFIN had moderate within-tumor agreement (ICC = 0.607, 95% CI:0.512-0.691) and moderate within-visit agreement (ICC = 0.732, 95% CI:0.665-0.786), and the REX had moderate within-tumor agreement (ICC = 0.740, 95% CI:0.631-0.816) and excellent within-visit agreement (ICC = 0.937, 95% CI:0.913-0.953), while accounting for measurements clustered within a visit within a tumor within a patient. We found that both the Delfin SkinFibroMeter and the Rex Gauge Durometer are easy to use and reliable, providing consistent, objective quantification of cNF stiffness.

LB1133

Apremilast reduces epicardial adipose tissue in psoriasis patients

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Psoriasis is associated with increased risk of cardiometabolic morbidity and mortality as well as a greater burden of epicardial adipose tissue (EAT), an independent and modifiable risk factor for coronary artery disease and marker of cardiovascular risk. Little is known about the impact of existing psoriasis treatments on EAT. To address this evidence gap, we investigated the impact of apremilast, a phosphodiesterase-4 inhibitor shown to decrease visceral adiposity in psoriasis patients, on EAT burden. Using data from the VIP-A trial (NCT03082729), an open-label, single-arm, interventional trial of 70 patients with moderate to severe psoriasis treated with apremilast, we assessed changes in EAT volume on computed tomography images from baseline to 16 weeks and 52 weeks after apremilast initiation. Patients were 23% female, with mean age 48, psoriasis duration 19 years, PASI 19, BSA 22%, and PGA 3.2. Mean BMI was 30, 27% had hypertension, 23% had dyslipidemia, 9% had diabetes, and 76% currently or ever smoked. Baseline EAT (mean volume 108.5 cm^3) was positively associated with age (2.6 cm^3/year, p<0.001), BMI (9.3 cm^3/[kg/m^2], p=0.004), visceral adipose tissue (0.6 cm^3/cm^3, p<0.001), and serum biomarkers and indices for insulin resistance and dyslipidemia, including the Homeostatic Model Assessment for Insulin Resistance (3.4 cm^3/point, p=0.007), Diabetes Risk Index (1.2 cm^3/point, p=0.004), and large VLDL particles (2.6 cm^3/[nmol/L], p=0.018). EAT volume decreased by a mean of 6.3 cm^3 (95% CI: 1.8 to 10.7, p=0.009) or 4.3% from baseline after 16 weeks of treatment and by 11.4 cm^3 (95% CI: 5.9 to 17.0, p<0.001) or 9.0% from baseline after 52 weeks. These findings provide evidence that greater EAT burden in psoriasis patients is associated with worse biomarkers for cardiovascular risk and that apremilast may reduce EAT burden and associated cardiovascular risks in psoriasis patients.

LB1134

CB2 receptor activation as a novel therapeutic approach for inflammatory skin conditions

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The CB2 receptor modulates inflammation, immune responses, and pain perception. Unlike CB1, CB2 receptor activation offers peripheral anti-inflammatory effects without psychoactive consequences. Kado cream, a non-cannabis-derived CB2-receptor agonist, shows potential in neuropathic pain, musculoskeletal disorders, and inflammatory skin conditions. Case studies included patients with eczema, urushiol-induced dermatitis, and viral-induced urticaria. Patients showed rapid symptom resolution and reduced inflammation with minimal corticosteroid use. In a 2-year-old with eczema, corticosteroids ceased within a week. A 38-year-old with severe poison ivy dermatitis resolved within two weeks without prednisone. A 5-year-old with urticaria achieved symptom relief in four days, discontinuing antihistamines. These findings suggest CB2 activation reduces inflammation and immune overactivity, supporting its role as a non-steroidal alternative for inflammatory skin conditions. CB2 receptor activation showed analgesic effects in neuropathic and musculoskeletal pain. Patients with diabetic neuropathy, post-surgical pain, and osteoarthritis reported pain reduction within 15 minutes, with sustained relief and no adverse effects. A 71-year-old female with osteoarthritis and biceps tendonitis reduced opioid use by 50% after four weeks. These outcomes highlight the anti-inflammatory and opioid-sparing potential of CB2 activation in pain management. Preliminary data suggest CB2 activation mitigates UV-induced keratinocyte damage and suppresses pro-inflammatory cytokine release, supporting a role in skin barrier protection and photodamage prevention. By modulating inflammatory pathways, CB2 agonists like Kado cream may offer a novel approach for inflammatory skin diseases, neuropathic pain, and musculoskeletal disorders. Controlled trials are warranted to validate these findings and explore CB2-targeted therapies in dermatology and pain management.

LB1135

Risk factors associated with clinical-histopathologic discordance in keratoacanthoma diagnosis

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Keratoacanthomas (KA) are rapidly growing cutaneous tumors that closely resemble squamous cell carcinoma (SCC), leading to frequent diagnostic uncertainty. Same-day treatments such as ED&C are often performed on clinical suspicion alone. However, misclassification of SCC as KA can result in undertreatment of aggressive disease, while unnecessary excision of KA may lead to overtreatment. This study examines risk factors for clinical-histopathologic discordance in KA diagnosis to better guide treatment decision-making. We conducted a retrospective cohort study analyzing 477 consecutive tumors from a single academic medical center from 2010-2014 with KA listed in the clinical differential. Clinical and histopathologic diagnoses were compared, and univariate logistic regression identified risk factors for diagnostic discordance. Of the suspected KA cases, 122 (25.6%) were confirmed as KA, 223 (46.8%) were well-differentiated SCC, and 132 (27.7%) were non-well differentiated SCC. The non-well differentiated group included 66 well-moderate, 56 moderate, 8 moderate-poor, and 2 poorly differentiated SCC. KA and well-differentiated SCC were combined into a single reference group due to similar treatment guidelines and prognoses. Significant predictors of discordance included male sex (OR: 2.07, 95% CI: 1.38–3.15, $p < 0.001$), history of SCC (OR: 1.87, 95% CI: 1.24-2.83, $p = 0.003$), history of BCC (OR: 1.57, 95% CI: 1.05–2.36, $p = 0.027$), history of ≥2 SCC (OR: 1.76, 95% CI: 1.17–2.66, $p = 0.007$), and head/neck tumor locations (OR: 4.53, 95% CI: 2.90–7.11, $p < 0.001$). Given the risks of clinical-histopathologic discordance, clinicians should take a personalized approach to management and decision-making. For patients at high-risk for discordance, deferring same-day treatment until histopathologic confirmation may improve diagnostic accuracy and treatment outcomes.

LB1136

Dupilumab (DPL) for treatment of bullous pemphigoid (BP): Liberty-bp adept trial results

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BP is a potentially life-threatening, relapsing, autoimmune blistering skin disease. DPL, by blocking the shared receptor component for interleukin-4/13, targets underlying type 2 inflammatory drivers of BP pathogenesis. LIBERTY-BP ADEPT (NCT04206553), a randomized, double-blind, placebo (PBO)-controlled, 52-week (W) study evaluated DPL in moderate–severe BP patients. All patients started standard oral corticosteroids (OCS) on Day 1; OCS were tapered if BP was controlled. The primary endpoint, proportion of patients achieving sustained remission at W36, required complete remission and off OCS no later than W16, no relapse off OCS, and no rescue use through W36. Among 106 adult patients (DPL 300 mg Q2W/PBO, n=53/53), baseline characteristics were balanced (mean age, 71.3 years). At W36, 20.2% vs 4.0% of DPL vs PBO-treated patients achieved sustained remission (P=0.0114). More DPL-treated patients achieved ≥90% improvement in BP Disease Area Index activity score (40.5% vs 9.8%; P=0.0003) and ≥4-point reduction in Peak Pruritus Numerical Rating Scale score (39.8% vs 10.6%; P=0.0006). DPL patients had 1678 mg less mean cumulative OCS exposure over 36 weeks (P=0.0220) and 54% lower risk of rescue use (P=0.0016) vs PBO. Quality-of-life improvements favored DPL (nominal P=0.0463). Overall, 96.2% of patients reported treatment-emergent adverse events (TEAEs) with higher TE-serious AEs in PBO (30.2%) than DPL (22.6%). DPL showed significant benefits across multiple aspects of BP including sustained remission, reduced disease activity, itch, and OCS and rescue medication use. Overall safety was consistent with the known DPL safety profile. The first four authors are senior authors.

LB1137

Second-degree burn wounds treated in a phase 1/2a clinical study with mesenchymal stem cell-derived extracellular vesicles (EVs) exhibit enhanced regenerative healing

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Burn injuries pose challenges in immediate recovery and long-term scarring outcomes, leading to significant morbidity, and traditional treatments have yielded limited success in inhibiting burn wound conversion, restoring skin architecture, or preventing contractures. Mesenchymal stem cells (MSCs) have shown promise in wound healing, and recent research suggests that MSC-secreted extracellular vesicles (EVs) could be key to these regenerative effects. EVs deliver nucleic acids and proteins, reducing oxidative stress, inhibiting neutrophil activation, and preventing ischemia-reperfusion injury. A 47-year-old Hispanic male patient with gasoline fire burns was treated as part of a Phase 1/2a first-in-human, prospective, open-label study administering allogeneic MSC-derived EVs to deep second-degree burn wounds within 48 hours of injury. After just 1 treatment, the wound exhibited >99% closure at 1-week post-injury and remained durably closed through 1 year of follow-up. Furthermore, scores on the POSAS (Patient/Observer Scar Assessment Scale) markedly decreased over 52 weeks (week 4 - no pain; week 8 - no itch; no scarring). These results were in contrast with typical burn wounds which can take 4-6 weeks to close and result in poor scarring outcomes. The primary objective was to assess the safety of allogeneic MSC-derived EVs, and no adverse events were observed. Additionally, EVs prevented conversion of second-degree burns to third-degree burns as laser doppler imaging showed early restoration of skin perfusion after just 1 week. In summary, initial results from our study suggest that EVs can serve as a treatment to enhance burn recovery and reduce the long-term morbidity associated with burn scars.

LB1138

Rilzabrutinib attenuates inflammatory biomarkers in moderate-to-severe atopic dermatitis: A tape-strip proteomic analysis

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Rilzabrutinib, a selective oral Bruton's tyrosine kinase (BTK) inhibitor, was investigated in a placebo-controlled phase-2b trial (EudraCT: 2021-001704-15) in adult patients with moderate-to-severe atopic dermatitis (AD). We used a minimally invasive, tape-stripping approach, to evaluate the effect of Rilzabrutinib on the cutaneous proteomic profile of AD. We performed Olink Proteomic analysis on tape-strip skin samples from 24 AD patients treated with Rilzabrutinib BID (n=5), Rilzabrutinib TID (n=10) and placebo (n=9). Tape-strips were obtained from lesional (LS) and non-lesional (NL) skin at baseline and week 16. Differentially expressed proteins/DEPs were defined as fold changes/|FCH|>1.3, and p-value<0.05. At week 16, the LS proteome of patients receiving rilzabrutinib TID showed 100% improvement from baseline towards a NL profile compared to 40% in the placebo respectively (p<0.001), whereas no significant improvement was observed in the BID group. Rilzabrutinib TID also showed significant downregulation of key markers belonging to innate immunity (TNF/IL6/IL18), Th1 (CCL3/CXCL10/CXCL11/CXCL9/IL12B/CCL4), Th2 (CCL7/IL10), and Th17 (CCL20/CXCL1/ IL17A/S100A12/TGFB1), in LS skin at Week 16 (p<0.05), while no significant downregulation was observed in placebo. In rilzabrutinib-treated patients, changes in protein biomarker expression in LS skin were correlated with reductions in clinical severity scores indicating a relationship between specific modulation in key proteins and disease severity. BSA, EASI, and IGA improvements showed positive correlations with Th1 (TNF/CXCL10/CXCL11), Th2 (CCL7/IL33), and T-cell activation (CD38/CCL8) related markers (r>0.75, p<0.05). We showed significant modulation of the proteomic skin profile of patients treated with rilzabrutinib TID, highlighting its therapeutic potential in managing AD.

LB1139

AMP-303 injectable treatment for androgenetic alopecia: A multicenter, randomized, placebo-controlled feasibility study of a novel polysaccharide

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Background: AMP-303 is a proprietary novel polysaccharide designed for intradermal injection and developed to stimulate scalp hair growth in patients with Androgenetic Alopecia. Methods: In this randomized, within-subject controlled, double-blind, multicenter study, male subjects aged 18-45 with mild to moderate androgenetic alopecia (Group 1 (n=32): duration 3-5 years; Group 2 (n=29): ≥10 years) received AMP-303 injections on 1 side of the scalp and saline injections on the contralateral side. Treatments were administered to the frontotemporal scalp, with 2 mL injected on each side in ~20 locations spaced 0.5 cm apart. Hair count was analyzed from digital images for a representative 1 cm2 target area on each side of the scalp through 5 months. Results: The 61 subjects were fairly evenly divided among the 3 targeted classifications of alopecia (modified Norwood Hamilton III, III vertex, and IV). AMP-303 demonstrated a trend in increased non-vellus hair count. For the Group 1 responders, the mean percent increase in nonvellus hair count peaked at 60 days (14.5%) for AMP-303 and was significantly greater than saline through 5 months (p<0.005). AMP-303 showed durability of effect with 1 injection cycle and indicates hair terminalization. Local skin reactions (most commonly edema) were similar between AMP-303 and saline, with most being of minimal or mild severity and resolving by the 14-day visit. The most common treatment-related adverse events were mild headache (7.8%) and mild skin swelling (bilateral 3.1% and AMP-303 side 1.6%), and almost all adverse events resolved during the study period. Conclusion: AMP-303 was safe and well-tolerated and demonstrated a trend in increased nonvellus hair for males with mild to moderate androgenetic alopecia. Further studies are warranted to explore the effects of repeat cycle administration of AMP-303 on scalp hair growth.

LB1140

Effect of acitretin on Mohs surgery complexity, repair, and postsurgical outcomes in solid organ transplant patients: A TriNetX analysis from 2002 to 2022

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Purpose: Solid organ transplant (SOT) patients are at an increased risk of skin cancer, particularly cutaneous squamous cell carcinoma (cSCC). Acitretin serves as a chemopreventative agent in reducing future keratinocyte carcinomas in SOT patients. However, its chemotherapeutic effect and resultant impact on the complexity of Mohs surgery for existing cSCC has not been analyzed. We aim to characterize the effect of pre-operative acitretin on Mohs stages, repair size and complexity, and postoperative complications for the treatment of pre-existing cSCC in SOT patients. Methods: TriNetX was queried from 2002 to 2022. Cohort A included SOT patients on acitretin for at least 90 days prior to Mohs surgery for cSCC. Cohort B included SOT patients undergoing Mohs for cSCC who were not on acitretin during the study period. Results: There was no difference in invasive cSCC rates between acitretin (n=291, 59%) and non-acitretin groups (n=13567, 62%) (p>0.05). Acitretin patients underwent more Mohs stages, a greater percentage of large than small complex repairs for all anatomic sites other than the trunk, and more adjacent tissue transfers than did those not on acitretin (p<0.05 for all). Patients on acitretin had a 7.8x greater risk of graft failure (RR 7.76, CI 4.037, 14.929), 3.2x greater risk of surgical wound dehiscence (RR 3.14, CI 2.145, 4.584), and 3.9x greater risk of surgical site infection (SSI) (RR 3.88, CI 2.062, 7.306). Conclusions: Pre-operative acitretin is associated with increased complexity of Mohs surgery and greater postoperative complications for the treatment of cSCC in SOT patients. Higher rates of graft failure, dehiscence, and SSI likely stem from both the increased surgical complexity for acitretin patients as well as acitretin's inhibition of angiogenesis and collagen synthesis during the proliferative phase of wound healing.

LB1141

Signs of systemic inflammation (as detected by PET/CT imaging, transcription analysis, and neutrophil activation) in a moderately obese psoriasis patient are partially reversed by 6 weeks of dietary intervention with a healthy diet

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Skin, joint, and organ inflammation has been demonstrated in psoriasis (PsO) patients using older positron emission tomography (PET) devices. A diet containing high amounts of saturated fat and sugars - also known as Western diet (WD)- potentially increases the risk of inflammatory disease. We hypothesized that short term intervention with a healthy diet low in saturated fat and sugars can reduce PET-measurable skin and systemic signs of inflammation in PsO patients who consume a WD. The first subject underwent a dynamic FDG-PET/CT scan using an ultra-high resolution (3mm) PET /CT device. The patient's blood and non-lesional forearm skin samples were obtained at the time of the initial scan and then 6 weeks later at the PET/CT repeat scan following dietary intervention with healthy meals (3 meals/day) supplied by a research kitchen. The subject had PsO under good control with topical agents only. CT imaging showed increased liver density after intervention, indicating likely reduced liver fat content. FDG uptake was reduced in the gastroesophageal junction and right colon, potentially indicating amelioration of inflammation. Total bilirubin and some liver enzymes and lipid levels, which were elevated before intervention, were also reduced after the intervention. MRNA expression in non-lesional skin of TNF, IL6 and CCL20 was elevated at the first scan and reduced by ~70% at the final scan, whereas IL17A/F was not detected at either time point. At the end of the study, blood neutrophil inflammasome activation in response to ex vivo stimulation with TNFa was reduced by 2.6- fold. These preliminary results, including those obtained by PET/CT imaging, suggest that systemic inflammation may be measurably improved following even relatively short-term healthy diet intervention in a PsO patient.

LB1142

Phase 3 results from an innovative trial design of treating plaque psoriasis involving difficult-to-treat, high-impact sites with icotrokinra, a targeted oral peptide that selectively inhibits the IL-23–receptor

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Icotrokinra (ICO), a first-in-class, targeted oral peptide that binds and inhibits the IL-23R, was evaluated in ICONIC-TOTAL (NCT06095102). This Phase 3 trial included plaque psoriasis (PsO) severity of BSA≥1%/IGA≥2, and employed a novel basket-like design to evaluate 3 cohorts of adults & adolescents (≥12-<18y) with at least moderate, difficult-to-treat, high-impact skin sites: scalp (ss-IGA≥3), genital (sPGA-G≥3), and/or hand/foot (hf-PGA≥3). 311 randomized pts (ICO=208/placebo [PBO]=103) with scalp (n=252), genital (n=140), and/or hand/foot (n=71) PsO received once-daily ICO 200mg or PBO through Week (W)16. Primary (IGA0/1: clear [0]/almost clear [1] & ≥2-grade improvement) and key secondary (ss-IGA0/1, sPGA-G0/1, hf-PGA0/1) endpoints were assessed at W16. ICO vs PBO met primary (IGA0/1: 57% vs 6%; P<0.001) and secondary (ss-IGA0/1 [66% vs 11%], sPGA-G0/1 [77% vs 21%]; both P<0.001) endpoints, and showed higher hf-PGA0/1 (42% vs 26%; P=0.144). Pt-reported scalp/genital PsO improvements were statistically significantly superior to PBO. Proportions of ICO & PBO pts with ≥1 AE were 50% & 42% (most common=nasopharyngitis) and GI AE were 7.2% & 7.8%, respectively. ICO demonstrated significantly higher rates of overall skin, scalp, and genital PsO clearance vs PBO with a favorable safety profile. Basket-like trial designs can be used to efficiently study special skin sites in pts with PsO and other diseases.

LB1143

Is upadacitinib cardioprotective? An assessment of MACE and VTE risk in patients with atopic dermatitis

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Atopic dermatitis (AD) is a chronic inflammatory skin disorder linked to increased cardiovascular disease (CVD) risk. Ongoing systemic inflammation in moderate-to-severe AD may elevate risks of major adverse cardiovascular events (MACE) and venous thromboembolism (VTE). Upadacitinib (UPA), an oral selective Janus kinase 1 (JAK1) inhibitor, approved for multiple chronic inflammatory disorders, may have protective effects against cardiovascular and thrombotic events. This analysis evaluated MACE and VTE exposure-adjusted incidence rates in moderate-to-severe AD, comparing background incidence rates from real-world observational studies with long-term rates from UPA clinical trials up to 6 years of exposure. A literature search (PubMed, SCOPUS, EMBASE) identified studies reporting MACE and VTE rates in moderate-to-severe AD populations. Background MACE rates ranged from 0.3 to 1.2 (average 0.6) per 100 person-years. UPA-treated patients had lower MACE rates, with 0.2 per 100 person-years (15 mg) and <0.1 per 100 person-years (30 mg). VTE rates ranged from 0.1 to 0.7 (average 0.3) per 100 person-years, compared to 0.1 per 100 person-years for both 15mg and 30mg UPA doses. These findings show a reduction in MACE and VTE among UPA-treated patients with moderate-to-severe AD, indicating possible cardioprotective and thromboprotective effects of JAK1 inhibition beyond skin inflammation and itch control. Further cardiovascular outcome studies are needed to confirm these protective effects and explore underlying mechanisms.

LB1144

Treatment-free disease control after tralokinumab in patients with moderate-to-severe atopic dermatitis

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Tralokinumab, a monoclonal antibody targeting IL-13, is approved for treatment of moderate-to-severe AD in individuals ≥12 years of age. Enduring treatment-free disease control was assessed post hoc using pooled data from phase 3 ECZTRA 1 & 2 (NCT03131648 & NCT03160885) patients re-randomized to placebo after achieving primary endpoints (IGA 0/1 or EASI-75) at Week 16 with tralokinumab Q2W (n=73). Treatment-free disease control was defined as no use of rescue therapy (ie, TCS), no transfer to open-label arm (tralokinumab Q2W + optional TCS), and no permanent trial discontinuation due to lack of efficacy. Patients maintained treatment-free disease control for a median of 22.3 weeks. At 26 weeks off treatment, 38.4% (28/73) of patients maintained treatment-free disease control, with 32.1% (9/28) and 17.9% (5/28) of those patients meeting IGA 0 and Itch NRS 0/1, respectively. Patients who maintained treatment-free disease control had lower baseline mean BSA (33.6% vs 52.6%) and EASI (25.3 vs 31.4) and more robust Week 16 response (eg, IGA 0: 25% [7/28] vs 0% [0/45]) than those who did not. Of patients who transferred to open-label tralokinumab after experiencing a pre-determined decline from their Week 16 response (n=31), 69% regained IGA 0/1 or EASI-75 by 24 weeks of open-label treatment, with a median recapture time of 12.1 weeks. Approximately 40% of Week 16 responders maintained treatment-free disease control for six months with no rescue therapy, indicating that some patients may experience a remittive effect following specific neutralization of IL-13 with tralokinumab.

LB1145

Evaluating intralesional bleomycin for Kaposi sarcoma: A retrospective study

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This study evaluates the efficacy of intralesional (IL) bleomycin for treating Kaposi sarcoma (KS) and examines treatment response based on HIV/AIDS status. A retrospective cohort study was conducted on 20 patients (14 with HIV/AIDS and 6 without HIV/AIDS) treated with IL bleomycin at Northwestern Medicine. The final analysis included 95 lesions (58 from patients with HIV/AIDS and 37 lesions from patients without HIV/AIDS). Univariable logistic and Cox regression models identified predictors of complete resolution (CR) and time to CR. Papulonodular lesions were the predominant morphology (65.5%). 44.9% of lesions were ≤0.5 cm and 24.5% were 0.6-1.0 cm, with a median size of 0.5 cm (range: 0.1-3.0 cm). Lesion size did not significantly differ by HIV/AIDS status (p=0.102). CR was achieved in 63.6% of all lesions, with 74.1% resolving in patients with HIV/AIDS and 51.4% in patients without HIV/AIDS (p=0.622). Lesions in patients with HIV/AIDS took longer to reach CR, though this difference was not statistically significant (Median: 97.0 vs. 69.5 days, p=0.419). Lesion size was not significantly associated with CR or time to CR. Papulonodular lesions correlated with a shorter time to CR in the total cohort (HR: 4.68, 95% CI: 2.42-9.03, p<0.001). Lesions on the foot, ankle, or heel resolved faster in the total cohort (HR: 3.99, 95% CI: 2.12-7.5, p<0.001) and the HIV/AIDS-positive subgroup (HR: 6.0, 95% CI: 2.66-13.53, p<0.001). Lesions on the leg, hip, or buttock were associated with a longer time to CR for all lesions and both subgroups (All lesions: HR: 0.15, 95% CI: 0.08-0.31, p<0.001). Our findings support the use of IL bleomycin for KS, particularly for papulonodular lesions and those on the foot, ankle, or heel while highlighting a similar treatment timeline to CR in both HIV/AIDS-positive and negative patients. Further large-scale studies are warranted to optimize treatment protocols, revise relevant treatment guidelines, and inform patient counseling and expectations.

LB1146

Safety and preliminary efficacy of a first-in-class DRIP inhibitor EN002 topical gel in non-melanoma skin cancer and actinic keratosis: An international phase I study

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Background: EN002 is an anticancer compound developed based on the novel anticancer targets, DNA Replication-Initiation Proteins (DRIPs). It selectively induces apoptosis of cancer cells but not normal cells, and leads to >90% tumor remission in mouse xenograft models. Here we report the Phase I dose escalation study data of EN002 in non-melanoma skin cancer (NMSC) and precancerous lesions. Methods: Subjects, mostly with recurrent or relapsed cutaneous basal cell carcinoma (BCC), Bowen's disease (BD), cutaneous squamous cell carcinoma (cSCC), or actinic keratosis (AK) were treated topically with EN002, to evaluate the safety, PK and preliminary efficacy. A BOIN design was used for dose escalation from 0.008 to 0.12 mg/cm^2. Subjects were treated q2d for 24 days and followed-up for 28 days. Results: 29 subjects completed the study, including 6 BCC, 1 cSCC, 6 BD and 16 AK cases in China and Australia. The adverse events (AEs) were Grades 1 and 2, without SAE or DLT. Treatment-related AEs were primarily local skin reactions, which were mild and transient. EN002 in subjects with NMSC had an objective response rate (ORR) of 62% (8/13) and disease control rate (DCR) of 100%. One case of invasive cSCC achieved PR at day 16. The ORR of BCC was 50% (3/6), while that in Australia was 75% (3/4). AKs were cleared to different degrees, from 0-100%. EN002 in most blood PK samples were very low and no increase in systemic exposure was observed with increasing dose. Conclusions: The phase 1 study provided preliminary clinical evidence of a favorable benefit-risk profile of a novel topical therapy for patients with naïve, recurrent or relapsed NMSC or AK, who represent unmet medical needs. In the ongoing Phase II study with expanded treatment duration, the first 4 enrolled patients all achieved 100% clearance in 9 weeks.

LB1147

Surgical treatment of hidradenitis suppurativa: Comparing wide local excision with secondary intent healing versus definitive closure outcomes

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Background: Hidradenitis suppurativa (HS) is a chronic follicular disorder affecting apocrine-rich areas, characterized by painful nodules, abscesses, and sinus tracts, leading to scarring and impaired quality of life. While surgical excision of lesions is a highly effective treatment modality, there is no standard approach. Objective: To compare various outcome measures associated with definitive closure (primary closure, split-thickness skin grafting (STSG), local tissue rearrangement (LTR)) versus wide local excision with secondary intent healing (WLE/SIH). Methods: A retrospective analysis of 45 HS patients with advanced disease undergoing WLE/SIH (n=29) or definitive closure (2009–2023) (n=44) were evaluated for healing time, complications, and recurrence rates. Results: A total of 45 patients underwent 73 surgical encounters for HS at a single institution. There were 44 sites treated by primary closure (n=18), STSG (n=21), or LTR (n=5); and 29 sites treated by WLE/SIH. There were no differences in comorbidities, mean body mass index, or length of hospital stay between cohorts (p>0.05). Healing time for WLE/SIH was similar to definitive closure techniques, ranging from 8-36 weeks (x=15.8 and 16.3 weeks, respectively). Primary closure had the highest complication rate (44.4%), followed by LTR (40%), STSG (8.3%), and WLE/SIH (20.7%). Recurrence was associated with 1 STSG procedure and 1 WLE/SIH procedure. While complete excision of affected tissue is the goal for HS patients, the most practical closure technique favors WLE/SIH because of the lower complication rate. Conclusion: Patients undergoing WLE/SIH demonstrated an equal healing time and recurrence rate with a lower overall complication rate. Based on these findings, WLE/SIH has become our institution's standard surgical technique for advanced HS.

LB1148

VISIBLE: pioneering transcriptomic analysis of psoriasis in skin of color

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VISIBLE is an ongoing Phase 3b study of guselkumab (GUS) in participants (pts) with moderate-to-severe plaque psoriasis (PsO) across the entire spectrum of objectively measured skin tones. Pts were randomized 3:1 to receive GUS 100 mg at Week (W) 0, 4, then every 8 W (Q8W), or placebo (PBO) with PBO crossover at W16. Participation in the biopsy substudy was optional. Bulk stranded RNA sequencing (RNA-seq) was performed on both non-lesional (NL) and lesional (LS) skin biopsies at W0 (n=31), and only LS biopsies at W16 (n=27) and W48 (n=20). At W0, 3635 genes (fold change cutoff 2, FDR 0.05) were observed to be differentially expressed in LS vs NL samples. Reduced expression of genes such as IL23A, IL12B, IL23R, IL17A, IL17C, IL17F, IL19, DEFB4A, and S100A7/8/9/11 in LS samples from GUS-treated pts was seen by W16 and maintained at W48. Similar patterns were seen in LS samples after PBO➞GUS crossover. Following GUS treatment, PsO disease-associated gene sets that showed elevated expression in PsO LS samples at W0 normalized to W0 NL levels. Significant differences in gene expression were observed between Psoriasis Area and Severity Index (PASI) 90 responders (R) vs nonresponders (NR) at W16. In W16 PASI90 NR LS samples, disease-driving gene sets related to Th17 cells, IL22 signaling, and inflamed keratinocytes remained differentially elevated, and less reduction in expression of genes associated with proliferating inflamed keratinocytes and inflammatory myeloid cells modules was seen by single-cell RNA-seq-derived cell type annotation. These gene expression findings in PsO pts with skin of color treated with GUS appear consistent with those in predominantly white PsO cohorts; further studies are needed to confirm these findings.

LB1149

Safety and efficacy of risankizumab in genital and scalp psoriasis in the UnIIMMited phase 4 randomized clinical trial at week 16

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Introduction: Scalp and genital psoriasis (PsO) are high impact PsO areas associated with increased patient burden and impact on quality of life. Risankizumab (RZB), an IL-23 inhibitor, is approved for the treatment of moderate to severe PsO. Here we present the first data for treatment of PsO in the genital region and scalp with RZB from dedicated studies. Methods: UnIIMMited (NCT05969223) is a Phase 4, multicenter, randomized, double-blind, placebo-controlled study for adult patients with moderate to severe genital or scalp PsO. Patients were randomized within either Study-G (genital PsO) or Study-S (scalp PsO) at 1:1 to receive either 150 mg RZB or placebo (PBO) at weeks 0 and 4. Efficacy was assessed at week 16 and reported using non-responder imputation. Efficacy was assessed for patients in Study-G by static Physician's Global Assessment-Genital (sPGA-G) and scalp Investigators Global Assessment (scalp IGA) for patients in Study-S. Safety and additional efficacy endpoints for symptoms and quality of life were also assessed. Results: At week 16, a significantly higher proportion of patients with genital PsO receiving RZB, versus patients receiving PBO achieved sPGA-G 0/1 (69.1% [38/55] vs 13.0% [7/54]; p<0.0001). For patients with scalp PsO, a significantly higher proportion of patients receiving RZB achieved scalp IGA 0/1 versus those receiving PBO (60.8% [31/51] vs 13.0% [7/54]; p<0.0001) at week 16. No new safety signals were reported. Conclusions: A significantly higher proportion of patients in Study-G with genital PsO achieved the primary endpoint of sPGA-G 0/1 treated with RZB, compared to PBO. Similarly, a significantly higher proportion of patients in Study-S with scalp PsO treated with RZB, compared to PBO, achieved the primary endpoint of scalp IGA 0/1. No new safety signals were identified.

LB1150

AX-158 proof-of-mechanism safety study: Evaluating a novel T cell receptor (TCR) signal modulator in patients with mild-to-moderate plaque psoriasis (NCT05725057)

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Background: Nck binding to TCRs directly amplifies T cell responses to low-affinity antigens, contributing to autoimmune diseases. AX-158 is a first-in-class oral candidate that inhibits the Nck-SH3.1 domain to selectively disrupt Nck-TCR interaction. AX-158 may help prevent self-reactive T cell responses that drive autoimmune pathobiology. Type of Study: A Phase 2a, prospective, randomized, double-blind, placebo-controlled safety and efficacy study of AX-158. Methods: Patients were randomized to receive AX-158 (N=21) or placebo (N=10). Safety and standard psoriasis efficacy endpoints were assessed. Histological markers, expression of psoriasis-related genes, and markers of immune activity were evaluated. Results: Few AEs were reported with a single incidence (4.8%) of Grade 2 neutropenia in the AX-158 arm. No serious AEs were reported. Moderate disease patients (PASI≥6) treated with AX-158 showed a positive response trend (34.6%). Using RT-PCR for expression of IL-17A and IL-17F, a group of 12/21 (57%) progressive responders (wk 4<wk2<baseline values) were identified different for drug vs. placebo treatment ($p = 0.04$). In extended RNAseq analysis, responder group showed 52% improvement in pathologic IL-17A levels; 281 genes of the psoriasis transcriptome were significantly down-regulated ($p< 0.05$). Using GSVA, multiple psoriasis-related gene sets were significantly modulated and by Ingenuity Pathway analysis, IL-17 pathways in psoriasis and neutrophil trap pathways were significantly modulated ($p< 0.0001$) in patients who received AX-158. Conclusion: AX-158 administration was found to be safe and well-tolerated, matching previous Phase 1 experience. Biomarker analyses revealed significant and consistent responses that validate Nck immunomodulation as a therapeutic approach to psoriasis with potential universal applicability to other autoimmune diseases.

LB1151

Facial aging analysis across four major Chinese cities using deep learning techniques

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Facial aging patterns exhibit significant inter-individual and regional variability, influenced by both intrinsic and environmental factors. Traditional methods for assessing facial aging often rely on subjective human evaluations, which are resource-intensive and prone to variability. In this study, we employed deep learning techniques to quantitatively analyze facial aging in 12,000 women aged 18-60 from four major Chinese cities—Beijing, Shanghai, Guangzhou, and Xi'an. Using an optimized U-Net architecture with multi-scale feature fusion, we quantified key aging features. Additionally, environmental factors such as climate and pollution were analyzed using Partial Least Squares Path Modeling (PLS-PM) to assess their impact on aging patterns. Results revealed distinct regional variations in facial aging patterns: Guangzhou exhibited milder wrinkle-related issues but more pronounced pigmentation concerns, while Xi'an displayed prominent dark circles and frown lines. Beijing was characterized by noticeable wrinkle-related aging, whereas Shanghai showed minimal overall facial aging issues but higher pore-related concerns. Environmental analysis identified air pollutants as a significant factor in Beijing (VIP=1.16), while ultraviolet radiation had a notable impact in Xi'an (VIP=1.12). Individual factors, such as marital and parental status, also correlated with aging severity, particularly in Beijing and Xi'an (VIP=0.84-1.48). Aging was categorized into three dimensions—structural change("Structure"), hyperpigmentation ("Color"), and sensitivity ("Sensitivity")—with pigmentation exerting the strongest overall influence on perceived aging (I=0.42). The PLS-PM model demonstrated a strong fit (R^2=0.81), highlighting robust relationships among these dimensions. This study not only advances the understanding of facial aging in Chinese women but also provides a foundation for targeted interventions, combining deep learning-based quantification with environmental and individual factor analysis.

LB1152

Effects of a fractional non-ablative 1940nm laser targeting the epigenetic MitraClock™ and clinical end-points: A longitudinal study

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Background: Skin aging results from intrinsic and extrinsic factors, altering DNA methylation and accelerating visible aging. Advances in epigenetic clocks now enable precise measurement of biological skin age, offering a quantitative tool to evaluate skin rejuvenation. This study investigates the impact of fractional non-ablative 1940 nm laser (Frax1940nm) on epigenetic aging and molecular pathways involved in skin homeostasis. Methods: A split-face pilot study (n=22, age 25-60, skin types II-III) involved three laser treatments 28 days apart. Non-invasive skin samples were collected at baseline, post-treatment 1, and 1/3/6-month follow-ups (MFU) from treated and untreated areas. DNA methylation profiling via enzymatic conversion and targeted Illumina sequencing was analyzed using MitraClock for age prediction. DMR analysis identified pathway-specific changes, and covariate analysis assessed menopause, age, and smoking effects. Paired t-tests and linear regression models adjusted for age and baseline methylation. Results: Epigenetic age decreased in treated skin at 6MFU (Δ -2.3 years, p≤0.05), with no significant change in untreated skin (Δ -0.4 years, p=0.21). Post-menopausal women exhibited greater short-term rejuvenation at 1MFU (Δ -1.9 years, p≤0.05). DMR analysis showed enrichment in FGFR3 and Notch signaling (adj p=0.007, p=0.02), suggesting epidermal differentiation and barrier restoration. Pigment severity reduction correlated with greater epigenetic age reversal (r=-0.72, p≤0.05), linking pigmentation improvement to molecular skin aging reversal. Conclusion: Frax1940nm reduces epigenetic skin age, with greater effects in post-menopausal women. Laser therapy modulates FGFR3 and Notch pathways, promoting skin differentiation, barrier repair, and rejuvenation. Non-invasive epigenetics offers a measurable tool for dermatological and aesthetic applications.

LB1153

Topical RE.D flavonoid, an extract of camellia japonica seeds, improves clinical features of photoaging without local skin irritation.

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Repetitive and chronic sun exposure leads to photoaging by increasing matrix metalloproteinase (MMP) production, which degrades dermal collagen. PDK1 (3-phosphoinositide-dependent kinase 1) inhibition reverses senescence by suppressing NF-κB and mammalian target of rapamycin (mTOR) signaling through inactivation of a positive feedback loop (PDK1, AKT, IKBKB, and PTEN), suggesting PDK1 inhibition may ameliorate skin aging. Extract of Camellia japonica seeds [RE.D Flavonoid] has MMP-1 and PDK1 inhibitory activities, thus may improve photoaging. We evaluated the effects of topical RE.D. Flavonoid (0.1%) on skin aging in 44 volunteers (37F, 7M, mean age 60.11 years, range 45 to 75). Subjects were randomized to use RE.D. Flavonoid cream or placebo for 24 weeks on the face and neck. Clinical grading, imaging, and subject surveys were completed. Compared to baseline, the active group saw all photoaging measures (fine lines, wrinkles, skin texture, pore appearance, luminosity, hyperpigmentation) significantly improved for the face and neck ($P < 0.05$). Furthermore, skin texture and luminosity for both sites showed significant improvement by as early as Week 8 ($P < 0.001$). In comparison, the placebo group had significant improvement only in skin texture, luminosity for the face and skin texture, pore appearance, luminosity, hyperpigmentation for the neck ($P < 0.05$). The mean percentage change from baseline for facial fine lines, wrinkles, skin texture, pore appearance, luminosity, and hyperpigmentation in the active group was 23%, 10%, 45%, 26%, 40%, and 29%, and for the neck was 25%, 19%, 45%, 25%, 35%, 28%, respectively. At Week 24, the active group had significantly positive responses to 9/19 questions on the self-assessment questionnaire compared to 0/19 positive responses for the placebo group ($P < 0.05$). Our data suggests that topical RE.D. Flavonoid is a well-tolerated option to combat multiple clinical features of photoaging.

LB1154

Rising antimicrobial resistance in chronic wounds

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Antimicrobial resistance (AMR) is a critical global public health threat, including multi-drug resistance in chronic wounds, and recently reported diminished efficacy of broadly used silver based dressings. We analyzed the prevalence of methicillin and mupirocin resistance genes in patients with chronic venous leg ulcers (VLU, n=24) without clinical infection signs. Methicillin-resistant Staphylococcus aureus was targeted due to its high AMR-related mortality, while mupirocin is the most prescribed topical wound antimicrobial. Results revealed a methicillin resistance rate of 66.67% and an alarming mupirocin resistance rate of 83.33%. We conducted a randomized controlled trial to compare efficacy of an antimicrobial silver-based dressing with a Dialkylcarbomoyl chloride (DACC)-based dressing, which eliminates bacteria through irreversible binding. 31 subjects were randomized to either group to receive 4 weeks of treatment, followed by a 2-week follow-up. Tissue samples were collected at weeks 0, 2, and 6, with bacterial load quantified using qPCR. DNA samples from week 0 and week 3 underwent 16s rRNA and metagenome sequencing. Inflammatory markers (CCL4, CXCL9, CXCL12, CCL13, ICAM-1, and VCAM-1) were analyzed in tissue. Subjects over 65 yo had a significantly higher bacterial load pre-intervention, correlating with increased AMR-related deaths in older adults. The silver-based dressing group showed a significantly higher bacterial load by third visit compared to the DACC, along with increased Staphylococcus and Streptococcus abundance. Healing rates were higher in the DACC group, with healers (≥50% wound size reduction) showing higher baseline tissue inflammation that reduced over time. Non-healers, particularly in the silver group, exhibited persistently low inflammation levels. Clinical data supported these findings, showing improved wound quality of life and pain in the DACC group. Our findings highlight the growing AMR in chronic wounds and the need for antimicrobial stewardship, accurate infection diagnosis, and novel treatment strategies to prevent AMR.

LB1155

Uncovering the genetic basis of therapy resistance in gorlin syndrome: A rare downstream mutation and the shift to second-line treatment

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This case describes the complex management of a patient with Gorlin syndrome who failed first-line therapy. A 40-year-old female with a history of chronic hypertension and obesity presented for dermatologic surgery evaluation of numerous facial lesions. On exam, there were multiple flesh-colored papules distributed across the face along with bilateral palmar pitting. Histopathological analysis of biopsies obtained from multiple sites at an external institution two years prior revealed infundibulocystic-type basal cell carcinomas (BCCs). Family history was significant for a brother with medulloblastoma at age 4 and a son with multiple BCCs at age 24. Clinicopathologic correlation led to a diagnosis of Gorlin syndrome. The patient's prior treatment included vismodegib for nine non-consecutive months; however, therapy was discontinued primarily due to lack of efficacy as well as the development of minor adverse effects. Given the patient's poor response to vismodegib and pertinent family history, a mutation downstream of PTCH1 in the sonic hedgehog pathway was suspected. Subsequent genetic sequencing confirmed the presence of a downstream SUFU (Suppressor of Fused) mutation. Due to the widespread distribution of BCCs, a localized surgical approach was not feasible. Instead, a multidisciplinary approach, including medical oncology, general dermatology, and cosmetic dermatology, was initiated. The patient is currently undergoing treatment with twice-daily topical 5-fluorouracil and monthly photodynamic therapy (PDT) and continues to show a good clinical response without significant adverse effects at monthly follow-ups. This case highlights the critical role of genetic testing in patients with suspected Gorlin syndrome, particularly in guiding treatment decisions and identifying mutations that may impact therapeutic response.

LB1156

Evaluation of antibiotic therapy in the treatment of hidradenitis suppurativa

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For mild to moderate hidradenitis suppurativa (HS), antibiotics are often prescribed, with oral doxycycline serving as a first-line treatment. However, other oral and topical antibiotics are also used, but studies investigating the efficacy of these therapies have not been conducted. To evaluate this, eleven cohorts were created within TriNetX using International Classification of Disease (ICD)-10 codes, each composed of patients prescribed either oral doxycycline, oral minocycline, oral and topical clindamycin, oral amoxicillin, oral and topical metronidazole, oral moxifloxacin, oral rifampin, or oral and topical dapsone within three years of HS diagnosis. Each cohort was excluded from usage of the other measured medications, adalimumab, secukinumab, or bimekizumab, and excluded from a history of deroofing procedures. The cohorts were evaluated for the need of adalimumab, secukinumab, or bimekizumab within three months to five years following the use of an antibiotic therapy, and a hazard ratio (HR) with 95% confidence intervals (CI) was calculated. Oral doxycycline showed an increased risk of requiring subsequent biologic therapy when compared against the oral amoxicillin cohort (HR= 3.35, 95% CI [2.173, 5.166]), the oral metronidazole cohort (HR= 2.709, 95% CI [1.387, 5.292]), and the oral minocycline cohort (HR= 5.74, 95% CI [1.284, 25.655]). There was no difference between the oral doxycycline and oral clindamycin cohort as well as between the oral and topical clindamycin cohorts. There were not enough measured outcomes to accurately evaluate the other antibiotics. These results question the efficacy of doxycycline monotherapy as a first-line therapy in the treatment of HS. Additional studies should be conducted to further analyze the efficacy of both oral and topical antibiotic monotherapies in the treatment of HS.

LB1157

Befriending the bugs: An updated meta-analysis on the efficacy of probiotic intervention in reducing scorad scores in atopic dermatitis

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We performed this updated meta-analysis to evaluate the efficacy of probiotics in reducing SCORAD scores (clinical tool used to assess the severity of atopic dermatitis) in individuals with atopic dermatitis. A systematic review was conducted across multiple databases, including PubMed, Google Scholar, EMBASE, MEDLINE, and Cochrane CENTRAL from inception to February 2025. The review included randomized controlled trials (RCTs) comparing probiotics with placebos in patients with atopic dermatitis. The primary outcome measured was the reduction in SCORAD scores during the treatment period. A random-effects meta-analysis was performed to calculate the mean difference (MD) with a 95% confidence interval (CI). The overall quality of the evidence was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. A total of four RCTs involving 248 patients, with 131 in the probiotic group and 117 in the placebo group, were included in the analysis. The results indicated a significant reduction in the SCORAD score in the probiotic group compared to the placebo group at the end of the treatment period (MD -6.23, 95% CI: -9.14 to -3.32; $p < 0.00001$). This updated meta-analysis concludes that probiotic use significantly reduces the severity of atopic dermatitis, with both statistical and clinical relevance, reinforcing the results of prior meta-analyses. As a result, the administration of probiotics can be regarded as an effective treatment option for atopic dermatitis.

LB1158

A novel more effective topical therapeutic approach for treatment of androgenetic alopecia: First in human trial results for topical ET-02

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Current pharmaceutical treatments for androgenetic alopecia (AGA) have limited efficacy, often with treatment-limiting side-effects, creating a demand for better therapies. ET-02 (which has not yet been assigned a generic name) is a novel topical small molecule suspension for the treatment of AGA that inhibits the molecular pathway causing hair follicle stem cells to become quiescent, reactivating them, resulting in renewed healthy hair growth. This double-blind, placebo-controlled trial evaluated the safety and efficacy of topical 5% ET-02; 1.25% ET-02, and ET-02's 0% vehicle. 24 healthy subjects diagnosed with moderate AGA were enrolled in the trial and were randomized to one of the three treatment groups for 28 days of daily treatment. Subjects returned one week later for final assessment. Safety and efficacy assessments using scalp photography automated image analysis for hair growth were made. A hair growth dose-response was noted, with minimal response from vehicle and 1.25% ET-02, but a significant response from 5% ET-02. For the analysis, vehicle and 1.25% ET-02 combined were considered a placebo group. 5% ET-02 had a 13.4% increase in non-vellus hair count vs. 2.3% for placebo at Day 35. For comparison, one month of 5% ET-02 treatment demonstrated more non-vellus hair growth (13.4%) than topical 5% minoxidil (12.0%) after four months of treatment as measured in separate trials (Berger 2003, Olsen 2007, Hillman 2015, weighted average, N = 230 in aggregate). 5% ET-02 also exhibited a 10.3% increase in hair width over placebo. ET-02 and its vehicle were found to be safe, including no skin adverse reactions such as irritation observed. There were no adverse events attributed to ET-02. The clinical trial results demonstrate the potential for 5% ET-02 to be much more effective and safer than existing products for the treatment of AGA. Further study of 5% ET-02 is warranted.

LB1159

First-in-human clinical trial evaluating AI-09, a novel long-lasting ready-to-use liquid injectable neuromodulator for the treatment of glabellar lines

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Neuromodulators are used to treat glabellar lines, but most require reconstitution with saline and have a typical duration of 3 to 4 months. A liquid ready-to-use product of longer duration would be preferred by patients. The objectives of this trial were to evaluate the safety, efficacy, and duration of effect of seven ascending dose levels of AI-09 (Eirion Therapeutics). AI-09 is a nanoemulsion formulation of a Type A botulinum holotoxin. 96 participants aged 20-70 were evaluated in this phase I/II, double-blind, vehicle-controlled trial, with moderate to severe glabellar lines. Patients were randomly assigned to receive one of 7 dose strengths of AI-09 (3.5U, 7U, 14U, 28U, 56U, 112U or 224U) or vehicle. Patients received a single treatment at baseline and were followed for 6 months. Efficacy on contraction was evaluated using a 4-point wrinkle scale (Absent, Mild, Moderate, Severe). AI-09 was found to be safe and well tolerated. A dose-response pattern was evident both in terms of efficacy and duration of response. The highest dose tested demonstrated clinically significant efficacy, with an investigator-rated improvement to Absent or Mild wrinkles having a response rate of 87% for active (N=15) vs 7% for vehicle (N=28) at Week 4 ($p<0.0001$). The median duration of response for this dose was 6 months, with 50% of responders maintaining a response of ≥1 point improvement. Overall, AI-09 and its vehicle were well tolerated. Adverse events were almost all mild or moderate, with only 3 of 38 considered related to the study drug or procedures. There was only one serious adverse event (stroke, 78 days after treatment) and it was not considered related to treatment by the investigator. There was no correlation between dose and frequency of adverse events. The findings of this first-in-man study indicate that injectable AI-09 is an effective and well-tolerated treatment for glabellar lines and offers an appealing alternative for those seeking a ready-to-use and longer-lasting neuromodulator product. Further study of AI-09 is warranted.

LB1160

Trephine ("punch-debridement") grattage: A definitive surgical approach for acute purulent inflammatory lesions of hidradenitis suppurativa

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Background: Trephine ("punch-debridement") grattage (TG) is an underutilized surgical procedure for treating purulent hidradenitis suppurativa (HS) lesions. While considered promising, the technique has not been standardized. Recurrence rates and aesthetic outcomes have not been studied (1). Objective: Investigating the value of TG for acute purulent lesions of HS. Methods: We performed TG on exudative inflammatory lesions. Under local anesthesia, a 6-8 mm trephine was used to enter the cavity; exudate manually drained; and, the cavity swabbed with a gauze-wrapped-probe. Once biofilm and blood clots were removed, the cavity walls/floor were scraped with a 5-6 mm curette to remove granulation tissue. A pressure dressing was applied for 36-48 hours. Nineteen patients underwent TG. Demographics, wound healing, complications, and recurrence rates were obtained from electronic medical records. All patients were surveyed with standardized questions addressing pre- and post-treatment mood, quality of life, pain, drainage, and measures of satisfaction. Results: Mean participant age was 35 years; 11 females/8 males; race/ethnic distribution: 8 Black, 6 Spanish/Hispanic /Latino, and 5 White. 15 patients were pain free one week after the procedure and the remaining four patients described minimal pain (1-2/10). 15 patients described complete healing in <2 weeks and the remaining patients healed within 2-4 weeks . Eighteen patients (95%) would undergo the procedure again. A majority of patients (14/19) rated their scar's aesthetic outcome as 5/5. There were no complications or recurrences. Other highly positive outcome measures included quality of life, mood, drainage, and itch. Pain level pre- and post-TG showed statistically significant decreases. Discussion: Incision and drainage, the standard of care for purulent HS lesions, has high recurrence rates (2). Using TG we encountered no complications or recurrence, high rates of satisfaction, and excellent aesthetic outcomes.

LB1161

CASZ1 and ZNF750 act redundantly to preserve differentiation programs in the developing mouse epidermis

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The epidermis is a constantly renewing stratified epithelial tissue that provides essential protective barrier functions. Disruptions to epidermal differentiation characterize various skin disorders. In search for regulators of epidermal differentiation, we have recently identified Castor zinc finger 1 (CASZ1) as a new transcription factor (TF) essential for in vitro keratinocyte differentiation program. Interestingly however, the epidermal deletion of murine Casz1 did not impair gross epidermal development and stratification, suggesting that in vivo loss of CASZ1 may be compensated for by other TF(s). Here, we uncover that such compensatory mechanism exists between CASZ1 and ZNF750 – a key driver of keratinocyte differentiation programs. We show that CASZ1-dependent genes are most significantly enriched for the co-binding of ZNF750 in epidermal keratinocytes. Importantly, we demonstrate that the co-ablation of both TFs in the developing mouse epidermis markedly aggravates the phenotypes of single knockout (KO) mice, impairs the induction of terminal differentiation genes such as filaggrin and loricrin otherwise expressed in single KOs, and leads to compromised inward and outward barrier functions, resulting in early postnatal lethality. Together, our studies highlight in vivo compensatory feedback mechanisms, in which two epidermal TFs can act redundantly to provide a regulatory safety net preserving epidermal development programs and the establishment of essential barrier functions.

LB1162

Advanced precision indoor farming boosts Red Shiso bioactives to strengthen the skin barrier against UV stress

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Sun exposure is a lifelong and universal phenomenon with both beneficial and harmful effects on human health. Among its adverse impacts, ultraviolet (UV) radiation remains a primary driver of skin aging. UV-induced disruption of the skin barrier is a well-documented mechanism in dermatology and cosmetology. To support the skin's barrier function, we developed a novel microgreen extract from Perilla frutescens (Red Shiso) using Precision Indoor Farming (PIF), an advanced, AI-controlled agronomic technology that enables full environmental optimization. This cutting-edge approach, combined with microwave-assisted extraction (MAE), allowed us to precisely enhance the total phenolic compounds (TPCs) content, particularly rosmarinic (RA) and caffeic acids (CA), and to boost specific flavonoids of great interest for cosmetic applications. In this study, we evaluated the effects of Red Shiso microgreen extract on key epidermal barrier proteins—filaggrin (FLG), claudin-1 (CLDN1), and aquaporin-3 (AQP3)—which are critical for skin integrity and hydration but are known to be altered following UV exposure. The antioxidant potential of the extract was also assessed. Experiments were conducted on reconstructed human epidermis (RHE) and ex vivo skin explants subjected to UVs irradiation for three days, followed by treatment with Red Shiso extract. In UV-treated RHE, 0.3% Red Shiso microgreen extract reduced UV-induced lipid peroxidation by 18% and restored AQP3 expression (+17.6%), which had been significantly diminished under UV stress. In UV-exposed skin explants, treatment with 0.3% extract enhanced barrier properties, increasing FLG expression by 139% and CLDN1 levels by 2.4-fold compared to untreated UV-exposed samples. These findings demonstrate that Red Shiso microgreen extract promotes skin barrier integrity and hydration, highlighting its potential as a new therapeutic strategy to mitigate UV-induced photodamage. They also confirm the powerful impact of AI-driven indoor precision agriculture on botanical ingredient development.

LB1163

Psoriasiform dermatitis after keratinocyte-restricted deletion of centrosomal protein Cep43

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Polymorphisms in the locus containing centrosomal protein 43 (Cep43) are highly associated with autoimmune diseases, including Crohn's disease and primary biliary cholangitis, as well as cutaneous autoimmune diseases including psoriatic arthritis, oral lichen planus, and vitiligo. To address the relevance of Cep43 to cutaneous autoimmunity, we sought to define its role in the epidermis. We found that induced deletion of Cep43 in adult mouse keratinocytes in vivo led to a psoriasiform rash and lymphadenopathy, with robust p53 pathway activation. Cep43-deleted keratinocytes showed signs of DNA damage with micronuclei formation ex vivo and in vivo, and upregulated the DNA damage marker gH2AX. Micronuclei were recognized by cyclic GMP-AMP synthase (cGAS), linking DNA damage to the immune response. Our data are the first report of micronuclei arising in keratinocytes in vivo and shed light on novel mechanisms of immune activation in the skin.

LB1164

Marked depletion of non-canonical sphingolipids in atopic dermatitis reveals an understudied lipid class with potential roles in skin barrier function

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Sphingoid bases, particularly long-chain free forms, are an underexplored lipid class, yet their dysregulation may underlie atopic dermatitis (AD), a chronic inflammatory disease characterized by barrier dysfunction, immune dysregulation, and microbial dysbiosis. This study examines the abundance and diversity of long-chain sphingoid bases (LCBs) in healthy and AD skin. Using D-Squame tape discs, we collected stratum corneum samples from five AD patients (lesional and non-lesional skin) and four healthy controls, followed by methanol-based lipid extraction and LC-MS/MS analysis. In healthy skin, these non-canonical LCBs were highly abundant, exceeding canonical species by over 90-fold ($p < 0.01$). These novel LCBs were predominantly free rather than intermediates in sphingolipid biosynthesis, unlike typical sphingoid bases, suggesting a distinct functional role. In AD, levels of these non-canonical LCBs were significantly reduced, with certain classes of free LCBs showing up to a sevenfold decrease in lesional skin compared to non-lesional skin ($p < 0.05$). These findings identify a previously understudied class of LCBs as a novel, abundant, and free lipid class in healthy skin, with marked depletion in AD lesions, highlighting their potential role in barrier integrity and expanding our understanding of AD pathogenesis.

LB1165

American hair research society mentorship grant program: Short term training opportunities with experts

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Students training in clinical dermatology practice, dermatopathology, or basic research focused on skin and specifically hair diseases often find that the institutions where they are training have limited to no resources in this area. The American Hair Research Society Mentorship Grant Program was developed in 2002 to address this challenge. Since its inception, it has provided $440,398 to 252 physicians, veterinarians, and basic scientists to acquire additional academic or research skills to further their careers as leaders in hair research with a focus on establishing mentoring relationship. Here, we describe the history of the grant and basic steps in applying for funding. Workforce studies indicate a growing demand for qualified personnel in dermatology over the coming decade. Those entering the field will benefit greatly from the relationships fostered by programs like the AHRS Mentorship Grant Program.

LB1166

Identification of an activated langerhans cell population and its role in cutaneous immunity

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Langerhans cells (LCs) are a specialized subset of epidermal antigen-presenting cells that form a dense network essential for wound healing and immune homeostasis in both mice and humans. However, what attracts LCs to wounded areas remains unclear and whether a distinct LCs population exists in the injured epidermis, separate from steady-state and migratory stages. In this study, we utilized transgenic mice, intravital imaging, single-cell mRNA sequencing, and advanced data analysis techniques to characterize distinct stages of LCs activation. To induce local inflammation, we applied both physical and chemical skin treatments, and at the transcriptional level, LCs exhibited a similar response to both stimuli. We identified a previously unrecognized activated LCs stage through data integration, characterized by specific surface markers, which we validated using FACS analysis. A key feature of this activated stage was the upregulation of various complement system components and their receptors. Using C3 knockout mice, we observed reduced LCs accumulation at the edges of wounds, suggesting that C3 plays a critical role in recruiting activated LCs to the wound site. Furthermore, inducing LCs activation with ovalbumin led to enhanced early CD4+ T cell activation in draining lymph nodes and an increased B cell response, supported by elevated levels of anti-OVA IgG antibodies. These findings provide deeper insight into LC-mediated immune responses and wound healing mechanisms. Additionally, they may contribute to the development of novel non-invasive vaccines that leverage LCs activation for enhanced antigen uptake and immune priming.

LB1167

Efficacy of camellia chrysantha extract in repairing the skin barrier and managing sensitive skin

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Skin barrier dysfunction is a key mechanism underlying sensitive skin (SS), characterized by decreased barrier proteins, loss of hyaluronic acid, and delayed epidermal healing, resulting in clinical symptoms of SS. Therefore, identifying an effective strategy for repairing the skin barrier and improving SS is essential. Camellia chrysantha is a rare medicinal and edible plant, and its extract (CCE) is rich in flavonoids, polyphenols, and polysaccharides, suggesting its potential to promote skin health. This is the first study to report the efficacy of CCE in managing SS. We established a UV-induced HaCaT keratinocyte damage model to evaluate the skin barrier repair effects of CCE. Compared to the model group, the levels of FLG and LOR in the CCE group increased by 1.3-fold and 1.2-fold, respectively ($P<0.01$). Similarly, the effect of CCE on HaCaT cell migration was assessed using a scratch assay. Compared to the control group, the migration rate of cells following CCE intervention increased by 38.99% ($P<0.001$) at 24 h. Moreover, the inhibitory effect of CCE on hyaluronidase was tested to evaluate its skin-soothing efficacy. The IC_{50} value of CCE was 1.96 mg/mL, comparable to that of vitamin C (1.02 mg/mL). Furthermore, a double-blind, split-face, placebo-controlled clinical trial was conducted, enrolling 30 subjects with SS. An emulsion containing 1% CCE was formulated, and its safety was evaluated through patch testing. Skin parameters were measured using non-invasive instruments, and capsaicin-induced stinging scores were assessed using questionnaires. CCE showed no skin irritation and significantly improved TEWL, erythema, and stinging scores after 28 days of application. These results provide valuable insights into the effects of CCE on skin health, highlighting its beneficial role in skin barrier repair and the improvement of SS.

LB1168

A fomulation containing fomes officinalis extract improved skin barrier function through optimizing sebum composition in oily sensitive skin

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Sebum plays a crucial role in maintaining skin barrier integrity. However, oily sensitive skin presents a paradoxical condition, where elevated sebum production coincides with compromised barrier function. Recent lipidomic studies revealed that this phenomenon may be attributed to an imbalance in sebum composition of oily sensitive skin, characterized by increased oxidized lipids, lower degree of lipid unsaturation, and reduced chain length of fatty acids. This study aimed to develop a cream containing Fomes officinalis extract to address both the excessive sebum and impaired barrier function in oily sensitive skin, and elucidate the underlying mechanism. A clinical trial was conducted with 33 female participants with oily sensitive skin, who applied the cream twice daily for 28 days. Instrumental measurements showed significant reductions in facial sebum content by 21.5% and 46.2% after 7 and 28 days of application, respectively (both $P < 0.001$). Despite the decrease in sebum levels, transepidermal water loss was surprisingly improved by 17.1% and 30.9% on days 7 and 28, respectively (all $P < 0.001$), without being negatively affected by the reduction in sebum content. To further explore the mechanisms underlying this contradiction, a lipidomic analysis was performed and revealed that the 28-day application of the cream effectively reduced the content of oxidized lipids, increased the proportion of unsaturated fatty acids, and promoted the synthesis of long-chain ceramides, resulting the improvement of skin barrier function. In conclusion, the formulation containing Fomes officinalis extract not only inhibited facial sebum secretion but also improved skin barrier function through optimizing sebum composition, providing a safe and effective approach for managing oily sensitive skin.

LB1169

Galactomyces ferment filtrate maintains skin firmness through actin stabilization and upregulation of anchoring junctions

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Focal adhesions and adherens junctions are anchoring junctions which connect the actin cytoskeleton to the extracellular environment. We investigated how these cellular structures contributed to skin cell firmness and if they could be modulated by Galactomyces ferment filtrate (GFF). Proteomic and transcriptomic analysis was used to identify changes in cellular components in skin biopsies and skin equivalents. Keratinocyte firmness was measured using nanoindentation. Immunofluorescence and confocal microscopy were used to visualize protein changes. Proteomics revealed that actin cytoskeleton and focal adhesion cellular components were decreased in sun-exposed aged skin whilst, in skin equivalent models, GFF upregulated both components and adherens junction. Nanoindentation measurements identified that destabilizing the actin cytoskeleton with Latrunculin B decreased cell firmness by 35%. GFF pretreatment was able to prevent loss of cell firmness. Immunofluorescence confirmed GFF upregulated integrins and the actin stabilizer calponin 2 in basal keratinocytes and demonstrated increased localization with basement membrane collagen IV. Biological processes involved in actin reorganization and cell adhesion mediated by integrins were significantly lower in the under-eye epidermis compared to other facial sites such as cheek and nasolabial folds. Our data establishes the actin cytoskeleton and anchoring junctions as important cellular structures which not only decline with age but are required for keratinocyte firmness. Furthermore, these cellular structures are upregulated by GFF in vitro to increase actin stabilization, maintain keratinocyte firmness, and promote cell-cell and epidermal-dermal anchoring.

LB1170

Overcoming clonal expansion barriers in primary human keratinocytes in a chemically defined and animal component-free culture system.

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The expansion of single-cell clones from primary human keratinocytes is inherently challenging due to their limited proliferative capacity, early differentiation, and senescence. These constraints hinder the use of primary keratinocytes for applications that rely on single cell cloning, such as genome editing, ex vivo gene therapy, or lineage tracing. Consequently, researchers often resort to immortalized keratinocyte cell lines. Such cell lines support extended culture but exhibit drawbacks such as incomplete differentiation and tumorigenic potential. We report the successful long-term expansion of single cell clones derived from primary non-transformed human adult keratinocytes. A total of 120 keratinocytes were plated as single cells by dilution in passage 2. After two weeks, 96 single cells (80 %) exhibited successful clonal expansion. Of 21 clones harvested and propagated until growth stop, 18 clones sustained proliferation beyond 20 population doublings (PD) post-plating, while three of these clones exceeded 40 PD and 50 days of culture, which corresponds to a potential yield of 1.1 × 10^12 (over a trillion) cells derived from one single cell. Epidermal models constructed in passage 8 confirmed full stratification into all four epidermal layers in three out of four clones, indicative of functional differentiation capacity. Preliminary data from single-cell clones of primary keratinocytes from a second donor confirmed reproducibility. We established a robust cell culture system using CELLnTEC's fully defined, animal and human component-free CnT-NX-EX Epithelial Extended Proliferation Medium without the need for surface coating or feeder cells, making it highly suitable for clinical translation. The system allows for expansion of single cell clones from primary keratinocytes, which makes it a valuable enabling tool for genetic modification, such as transfection, transduction, and genome editing. This underlines its versatility for applications in basic and translational research, gene therapy, and regenerative medicine.

LB1171

Galactomyces ferment filtrate stimulates a wound healing response that can facilitate overcoming a response plateau

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Human skin is the first line of defense from factors such as solar radiation and is susceptible to premature aging. One hallmark of premature aging in the epidermis is diminished proliferation of keratinocytes. The ability to validate technologies that can restore a proliferative index in aged skin is an intervention strategy to impact skin health and appearance. Galactomyces Ferment Filtrate (GFF) is a natural extract that has been shown to impact epidermal biology, response to oxidative stress, and inflammation. To further understand the impact of GFF on hTERT keratinocyte proliferation, we used bulk RNAseq and a scratch wound model to simulate a reduced proliferative state by utilizing low-nutrient modified media. Under these conditions, keratinocytes exhibited a plateau in proliferation, achieving only 39% wound closure. While the addition of HB-EGF enhanced proliferation, resulting in a maximum closure of 61%, significant proliferation limitations persisted. In contrast, GFF demonstrated a remarkable capacity to overcome this plateau and restore keratinocyte proliferation. In the modified media wound healing assay, the inclusion of 1.25% and 2.5% GFF facilitated wound closures of 92% and 97%, respectively, indicating its role in supplying essential nutrients for maintaining cellular proliferation. A dose-response curve at lower doses of GFF also supports the positive effects of increasing concentrations of GFF on activating wound closure. Bulk RNAseq of hTERT keratinocytes treated with GFF for 24 hours show a significant induction of "wound healing" associated genes. These genes include EREG, HMOX1, S100A9, SAA1, PLA2G4A, VAV3, PLSCR1, HSPB1, KRT6A, KRT6B, CLDN4, EDN1, CLDN1, ENTPD2, SERPINB2, TNFAIP3, GRHL3, and IL6R. These findings were corroborated by a robust wound healing gene signature observed in human skin treated ex vivo with GFF at 6 and 24 hours. In conclusion, GFF emerges as an anti-aging technology that significantly enhances keratinocyte proliferation capacity, offering promising implications for restoring skin health.

LB1172

A method to screen exfoliation capacity of topical chemical peels

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Skin exfoliation with chemical peels is a means to desquamate surface dead skin cells, remove dirt from pores and improve absorption of subsequent treatments. In terms of the clinical benefits, concentration of acid and pH of the chemical peel either used alone, or in combination with additional treatments, can reduce the appearance of mild dyschromic skin, photodamaged skin, enlarged pores and blemishes, revealing more even toned and smoother skin (1-4). To identify if an optimal blend, concentration of acid or pH could maximize exfoliation capacity, within the regulatory constrained use limits of commercial acids, we developed a human ex vivo skin exfoliation assay where we were able to compare and quantify corneocyte removal after treatment with a series of amino acids, alpha-hydroxy acids, beta-hydroxy acids, polyhydroxy acids, proteolytic enzymes, and combinations thereof (5). Our human ex vivo skin exfoliation assay was optimized from previously reported methods and employed a stain to dye corneocyte debris and measured the optical density of the debris after extraction by UV/VIS spectroscopy (6). The method allowed for a rapid, highly reproducible and cost-effective way to compare and optimize blends of individual exfoliants and to identify several blends with high exfoliation capacity. In addition, we confirmed that some cosmetically available proteolytic enzymes had, in as fast as 30 minutes, a measurable exfoliation capacity in our human ex vivo skin exfoliation assay. References: Rendon MI, Berson DS, Cohen JL, Roberts WE, Starker I, Wang B. J Clin Aesthet. Dermatol. 2010;3(7):32-43. Han A, Chien AL, Kang S. Dermatol. Clin. 2014;32(3):291-299. Dong J, Lanoue J, Goldenberg G. Cutis. 2016 Jul;98(1):33-36. Kim SJ, Baek JH, Koh JS, Bae MI, Lee SJ, Shin MK. Int. J. Cosmet. Sci. 2015;37(5):519-525. Ahn B, Lee SH, Kim JH, Goh A, Park SG, Lee CK, Kang NG. J. Cosmet. Dermatol. 2019. Lebeau PF, Chen J, Byun JH, Platko K, Austin RC. MethodsX. 2019; 6:1174-1180.

LB1173

Cell-state-specific regulatory roles of the H2AZ-SRCAP chromatin remodeling axis in epidermal tissue homeostasis

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Dysregulation of chromatin remodeling has been increasingly recognized in the pathogenesis of various diseases such as cancer, yet the roles of chromatin remodeling in skin epidermal homeostasis and carcinogenesis remain under-explored. In this study, we focus on the chromatin remodeling process of depositing the histone variant H2AZ in epidermal homeostasis. Epidermal homeostasis requires both progenitor maintenance and the activation of terminal differentiation process. In the progenitor state, H2AZ is highly expressed, and requires the actions of the chromatin remodeler SRCAP to be deposited into chromatin. We found that the high H2AZ expression as well as the intact function of SRCAP are both essential for maintaining the regenerative capacity of epidermal progenitors. High H2AZ levels not only modulate the genes related to extracellular matrix organization and cell adhesion, but also play essential roles in maintaining nuclear-envelope integrity and counteracting DNA damage. Using a targeted inhibitor screen, we identified both MEK/ERK and AKT/mTOR as key upstream pathways sustaining the high expression of both H2AZ and SRCAP in the progenitor state. Inhibition of these pathways drastically reduced H2AZ's chromatin incorporation, with disrupted nuclear integrity and increased DNA damage foci. In the differentiation process, H2AZ is downregulated at both the mRNA and protein levels. H2AZ's chromatin incorporation is also drastically reduced. Surprisingly, we found that the residual levels of H2AZ as well as its remodeler SCRAP play essential roles in the differentiation process, by modulating largely distinct sets of genes as compared to the progenitor state, including the activation of epidermal barrier-function genes. Taken together, our findings demonstrate the cell-state-specific roles of the essential SRCAP-H2AZ axis in both progenitor maintenance and the terminal differentiation process. As SRCAP is frequently mutated in both cSCC and BCC, our findings provide new insights into understanding the impact of SRCAP mutations in these two types of skin cancers.

LB1174

Therapeutic potential of YAP1 activation in nagashima-type palmoplantar keratosis: Rescue of epidermal pathology in human skin organoid models

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Nagashima-type palmoplantar keratosis (NPPK) is an autosomal recessive genetic skin disorder characterized by keratosis of the palmar and plantar regions, due to mutations in the SERPINB7 gene. However, the precise mechanisms underlying the pathogenesis of NPPK remain elusive. This study found no direct interaction between SERPINB7 and proteolytic enzymes. However, our findings demonstrated that SERPINB7 mutation significantly impaired keratinocyte proteolysis by downregulating the expression of kallikreins (KLKs) and matrix metalloproteinases (MMPs) in the epidermis of NPPK patients. Mechanistically, SERPINB7 mutations inhibited keratinocyte glycolysis by suppressing hexokinase 1 (HK1) activity, disrupting the activation and nuclear translocation of the transcription factor YAP1, and ultimately leading to decreased expression of KLKs and MMPs in keratinocytes. Furthermore, we established a pioneering three-dimensional skin organoid model carrying the SERPINB7 c.796C>T mutation that faithfully recapitulates human NPPK pathology at molecular and histological levels. Pharmacological YAP1 activation in this preclinical model significantly attenuated disease-associated phenotypic and biochemical abnormalities. These findings delineate a novel metabolic-transcriptional axis underlying NPPK pathogenesis and identify YAP1-targeted intervention as a promising therapeutic strategy for this dermatological disorder.

LB1175

New insight into keratin 16 function in palmoplantar epidermis and the pathophysiology of pachyonychia congenita

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Pachyonychia congenita (PC) is a rare genetic disorder with palmoplantar keratoderma (PPK) as its most debilitating symptom, manifesting as painful, thick calluses on palmar and plantar skin. The disorder is caused by dominantly-acting variants in the KRT6A, KRT6B, KRT6C, KRT16, and KRT17 genes. Previous studies in our laboratory demonstrated that Krt16 null mice develop PC-like PPK in footpad skin, at a histological and molecular levels. Unfortunately, the Krt16 null strain is not genetically representative of most PC cases, which predominantly involve missense variants. To address this limitation, we utilized CRISPR-Cas9 to introduce a R123C variant, which is implicated in over 20% of KRT16-related PC cases, in the mouse Krt16 gene. Whole genome sequencing confirmed the successful knock-in of the R123C mutation. Beginning at 15-16 weeks post-birth, homozygous mutant mice ($Krt16^{R123C^*/R123C^*}$) exhibit footpad skin lesions that closely resemble those seen in Krt16 null mice and the PPK lesions arising in individuals with PC. Notably, these lesions display an upregulation of K16 protein, paralleling observations in PC individuals. In vitro studies further revealed that cells transfected with an epitope-tagged mutant K16 plasmid form distinct aggregates or puncta, as opposed to the extensive filament arrays forming in cells expressing wildtype K16. This $Krt16^{R123C^*}$ mouse model uniquely expresses the mutant Krt16 mRNA and K16 protein, representing an advanced tool for developing mutant allele-specific treatments beyond palliative care. Furthermore, it provides a valuable biological context to explore the role of K16 and the contributions of its structural domains in skin physiology and pathology.

LB1176

Highly efficient correction of three recurrent pathogenic variants in COL7A1 using base editing to treat recessive dystrophic epidermolysis bullosa

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We explored the therapeutic potential of Base editing mediated correction of three recurrent pathogenic COL7A1 variants in patient-derived cells with Recessive Dystrophic Epidermolysis Bullosa (RDEB), a life-threatening genetic disease of the skin and mucosa. We report highly efficient correction of c.425A>G (p.Lys142Arg); c.6187C>T (p.Arg2063Trp) and c.6508C>T (p.Gln2170*) in primary keratinocytes (KC) and fibroblasts (FC) from RDEB subjects. Fourteen candidate gRNAs were designed and tested. mRNAs encoding Cytosine Base Editors (CBE) and Adenine Base Editors (ABE) were synthesized by in vitro transcription and were delivered by nucleofection to RDEB KCs and FCs. For the c.425A>G variant, gRNA-N1 and gRNA-N2 achieved 73% and 91% editing, respectively, with minimal bystander effects and without apparently affecting protein sequence, as evaluated by high-throughput sequencing. mRNA analysis confirmed correct transcript expression. C7 protein levels were restored using gRNA-N2 together with TAD-CBED_V106W. Similarly, gRNA-N2 and gRNA-N3 in combination with ABE8eSprY achieved up to 79% of correction in patient' cells homozygous for the c.6187C>T variant. For the c.6508C>T variant, six gRNAs were tested together with different ABEs (ABE8e, ABE-Max and ABE8e-NG) and results showed up to 91% of correction when using gRNA-N5 or gRNA-N6 in combination with ABE8e-NG. Other conditions showed up to 86% of correction, but were associated with up to four bystanders ranged from 95% at its highest to 13% at its lowest. Currently, genetically corrected 3D skin equivalents are being generated to validate functionality of this approach for future ex vivo clinical applications. At least 16.5% of patients (harboring one of these mutations) could benefit from this approach. Overall, by evaluating the feasibility and efficacy of base-editing of selected COL7A1 recurrent variants, this project has the potential to accelerate clinical translation of gene-correcting strategies to treat RDEB.

LB1177

Lipid nanoparticle-mediated mRNA transfection in multiple cell types within human skin

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Transient expression of epigenetic reprogramming factors is an investigative approach for rejuvenating aged skin and other tissues, but delivery of these factors has been a major challenge. Delivery of mRNA encoding these factors offers a potential solution. The purpose of this ex vivo study was to determine which areas and cell types in skin are transfected following the administration of lipid nanoparticle (LNP)-encapsulated mRNA by various methods. Novel LNPs loaded with eGFP mRNA were administered to adult human skin explants by several methods: 1) intradermal (i.d.) bolus injection; 2) i.d. microinjections; 3) i.d. bolus injection after microneedling; and 4) topical application after microneedling. In addition to eGFP, LNPs were also formulated with a lipophilic fluorescent dye (DiD) in order to track the distribution of LNPs. At 24 and 72 hrs after administration, cultures were fixed and analyzed by immunofluorescence (IF) microscopy. Whole mount imaging showed that i.d. injections resulted in expression in the dermis while topical application with microneedling resulted in expression in the epidermis. Additionally, i.d. microinjections resulted in a greater distribution compared to a single i.d. bolus injection of the same total volume. Further analysis using IF demonstrated that in explants that were administered with i.d. microinjections, there was a gradient of transfection efficiency across the skin that ranged up to a maximum of 30.7% cells transfected, with an overall average of 8.4%. Colocalization of eGFP with K15 in the bulge area of hair follicles suggest there was transfection of hair follicle stem cells, and colocalization with K14 confirmed transfection in the basal epidermis. Taken together, these findings highlight the potential to use LNP-mediated transfection of mRNA as a method to deliver proteins to different areas/cell types of the skin, which can be applied towards epigenetic reprogramming of skin as well as gene therapy for skin diseases.

LB1178

High resolution Hi-C map defines regulatory mechanism for atopic dermatitis associated signals

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Three-dimensional (3D) genome architecture modulates gene regulation by altering DNA-DNA interactions, frequently linking regulatory elements to promoters. We aim to investigate how 3D genome reorganization of atopic dermatitis (AD) skin underlies gene dysregulation. We perform Hi-C experiments on paired lesional and non-lesional skin samples from 7 AD patients, utilizing ~1.8 billion reads per condition to achieve a resolution of 1,750bp. We identify 10,414 lesional and 13,171 non-lesional differential abundant loops (DALs) overlapping gene promoters. Multi-omics integration reveals that >60% of DALs link to promoters of skin expressed genes, and >75% of them also coincide with open chromatin regions defined by single nucleus multiome data. Notably, 9.6% of lesional DALs link to promoters of upregulated differentially expressed genes (DEGs), exceeding the 7.9% expected outcome. Single-cell RNA-seq integration indicates lesional DALs linked to upregulated DEGs are more enriched in T cells (3.48% vs 0.59%) and myeloid cells (6.47% vs 0.30%), but less in fibroblasts (4.14% vs 9.76%), compared to non-lesional DALs linked to downregulated DEGs. Furthermore, our recent GWAS suggests that 43.3% of AD associated loci are found in the DALs. Among the loci we highlight three which overlap with lesional DALs encompassing up-regulated genes (SOCS1, IL6R, TRAF3), and one with down-regulated DEG BACH2 (FC = 0.53, p-adjust < 0.001) associated with 5 non-lesional DALs spanning across 500kb in chromosome 6. These DALs, located within open chromatin regions, narrow down the pool of potential causal variants from 580 significant variants to 34 within the four loci, 27 of which are also eQTL for the connected genes. Our study thus reveals 3D chromatin reorganization in AD skin that correlates with transcriptional and immunological changes providing mechanistic insights into disease biology.

LB1179

Combination therapy with losartan and RTA-408 in a recessive dystrophic epidermolysis bullosa (RDEB) mouse model

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Recessive Dystrophic Epidermolysis Bullosa (RDEB) is a severe skin disorder caused by COL7A1 mutations, leading to chronic skin fragility, fibrosis, and inflammation. This study explores the therapeutic potential of combining Losartan, an angiotensin II receptor antagonist with previously described antifibrotic properties, and RTA-408 (omaveloxolone), a powerful Nrf2 activator that helps reduce oxidative stress in cells with previously described efficacy in a murine model of junctional epidermolysis bullosa. To optimize treatment strategies, we tested the effects of single and dual-drug therapies on symptom severity in hypomorphic collagen VII mice. Five-week-old mice were treated with either Losartan (0.6 g/L in drinking water), RTA-408 (3% in corn oil, applied topically), corn oil control, or combination therapy with both Losartan and RTA-408. Treatments were administered for four weeks, followed by a four-week observation period. Anatomical evaluation revealed no consistent benefits in fibrosis, ear folding, or paw digit loss with combination therapy when compared with controls. However, immune cell infiltration analysis of ear skin showed a notable increase in CD45 expression with monotherapy for RTA-408 treated animals (68% increase, P-Value 0.0204), whereas combination therapy mitigated this response, suggesting a possible modulation of the immune response with losartan treatment. Our findings indicate that the combination of Losartan and RTA-408 had limited therapeutic benefits compared with single-drug treatment. These results support the continued exploration of multi-drug approaches to mitigate fibrosis and inflammation in RDEB and related disorders.

LB1180

Gene expression or mutational profile for psoriasis in guiding treatment

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Psoriasis is a chronic inflammatory skin disease characterized by scaly erythematous plaques, typically on the scalp and extensor surfaces. Genome-wide studies have advanced understanding of its pathogenesis, but small sample sizes have limited consistent identification of upregulated genes. This study systematically reviewed gene expression profiles in psoriatic lesions to recognize consistent molecular patterns that may point to potential therapeutic targets. A PubMed search identified 3,063 studies, with 10 meeting inclusion criteria based on comparative gene expression analysis between psoriatic lesional, psoriatic nonlesional, and healthy control skin from 2010–2023. Across 275 psoriasis patients and 248 healthy controls, 74 genes were upregulated in psoriatic lesions, most frequently S100A7 and CXCL8 (five studies); and CCL20, DEFB4A/B, S100A9, CXCL1, and IL-36A (four studies). DEFB4A/B exhibited the highest expression increase (log2 fold change up to 5.8), while COL1A1 and CCL27 were the most downregulated. The variability in methodologies, including differences in biopsy versus tape-strip sampling and comparator groups, limited direct cross-study comparisons. However, the consistent upregulation of S100A7, CXCL8 and DEFB4A/B suggests their potential as therapeutic targets or biomarkers. These findings reinforce the inflammatory roles of CXCL, S100, and DEFB4 family proteins in psoriasis and underscore the need for further research to determine whether these differentially expressed genes drive disease progression or reflect secondary inflammation. Standardized approaches to gene expression profiling in psoriasis could enhance the development of targeted treatments, particularly for patients resistant to current therapies.

LB1181

WITHDRAWN

LB1182

Multi-ancestry genome-wide association meta-analysis identifies novel systemic sclerosis loci and elucidates cell-type specific regulatory mechanisms

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Systemic Sclerosis (SSc) is a rare autoimmune disease with complex hereditary components. Genetic factors significantly influence disease susceptibility, and the prevalence of the disease varies across populations. Recent studies have identified variants in 35 loci associated with SSc, but fine-mapping causal variants and elucidating their biological functions remain critical challenges. In this study, we performed a multi-ancestry meta-analysis, integrating data from 1,849 African American and European ancestry SSc cases, along with 1,350,382 controls, into existing cohorts from European ancestry and Japanese ancestry populations. This comprehensive analysis included a total of 12,372 cases and 1,478,438 controls. We identified five novel loci reaching genome-wide significance ($p \leq 5 \times 10^{-8}$). These loci encompass genes involved in pathways related to adipogenesis (MBNL1), lipid metabolism (JAZF1), integrin function (SPOCK2), cytokine receptor activity (CD44), and the cell growth, differentiation and migration (PDGFB). Remarkably, we were able to identify five or fewer causal variants within the 99% Bayesian Credible Sets (BCS) for 12 out of the 40 (30%) SSc loci and noted a reduced number of variants in the BCS for the five novel loci. To further clarify the cell types and biological roles associated with these signals, we generated single-nuclei multiomic data (ATAC-seq and RNA-seq) from eight SSc patients and four controls. We found that 17 (42.5%) of the SSc loci overlap with ATAC peaks, with 16 exhibiting cell type specificity with myeloid cells, fibroblasts, and T cells being most prominent. Additionally, overlapping BCSs from 14 loci were identified as eQTLs for genes including IRF7 and DNASE1L3 from the established loci and SPOCK2 and PDGFB from the new loci.

LB1183

Absence of insertional oncogenesis and RCR in clinical and pre-clinical experience with prademagene zamikeracel, a retrovirally delivered cell-based gene therapy, in recessive dystrophic epidermolysis bullosa patients

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Introduction:Prademagene zamikeracel(pz-cel) is an autologous gene-modified cellular sheet for recessive dystrophic epidermolysis bullosa(RDEB) made using the LZRSE-COL7A1 retroviral vector. Since retroviral vectors used for gene therapy stably integrate into the host genome, we analyzed integration profiles in preclinical studies and assessed the presence of provirus or replication-competent retrovirus(RCR) in pz-cel trial patients who developed SCC. Methods:In subjects who developed SCC, biopsy samples were analyzed for proviral genome sequences, and RCR testing was conducted via whole blood analysis. During pz-cel manufacturing, proviral genome copy number(PGCN) was limited to ≤3 to mitigate oncogenic risk. Oncogenic risk was assessed using a list of human oncogene representing 7.23% of all genes. In pre-clinical studies, insertional analysis was performed on RDEB keratinocytes six days post-transduction. Results:In clinical trial subjects, no SCC was observed at 144 pz-cel-treated sites yet occurred exclusively in untreated areas. In SCC cases, RCR and proviral genome testing results were negative. In an ex-vivo non-clinical study, six RDEB samples were retrovirally transduced yielding 3,203,395 reads, 193,317 inferred cells, and 184,931 unique integration sites. Increased oncogenic risk was not observed, and no clone exceeded 5.5% of the total cell population, indicating highly polyclonal integration. Discussion:No insertional oncogenesis or RCR was observed in our clinical studies with pz-cel. SCCs, which in natural history occur in ~95% of RDEB patients by age 55, were not seen at pz-cel-treated sites in our trial subjects and were seen exclusively in non-treated areas. Ex vivo analysis confirms lack of oncogene-proximal integration or clonal expansion, suggesting that stringent control of PGCN may limit oncogenesis risk. Taking into consideration the high baseline risk of SCCs in RDEB patients, pz-cel maintains a favorable benefit-risk profile in treating RDEB patients.

LB1184

Imsidolimab, a novel IgG4 IL36 receptor antagonist, was effective and well tolerated in patients with GPP

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Generalized pustular psoriasis is a rare, severe disease characterized by debilitating flares of non-infectious pustular and erythematous skin lesions, with systemic impacts that can be life threatening. The pathogenesis of GPP is attributed to excessive activity of interleukin 36 pathway, often caused by mutations in the IL36RN gene. Imsidolimab is a novel high affinity humanized immunoglobulin IgG4 mAb that antagonizes IL36 signaling. The efficacy of imsidolimab was investigated in GPP patients in 2 global Phase 3 studies, GEMINI-1 and GEMINI-2. In GEMINI-1, a randomized, double-blind, placebo (PBO) controlled, GPP patients received a single IV dose of 300mg or 750mg imsidolimab, or PBO. Primary efficacy at Wk 4 was achievement of GPPPGA score of clear/almost clear (0/1) across GPP disease attributes. GPPPGA responders, partial responders, or those needing rescue therapy could enroll in GEMINI-2. GPPPGA 0/1 was achieved in 53.3% of patients in the 300mg and 750mg groups, vs 13.3% of patients on PBO. Among PBO patients that received RT in GEMINI-2, 55.6% attained GPPPGA of 0/1 at Wk 4. No responders re-randomized to imsidolimab had a GPP flare through Wk 24, and all maintained GPPPGA score of 0/1, vs 62.5% flared and 75.0% lost GPPPGA 0/1 response in PBO. No PBO cross-over patients had a flare. There were no SAEs leading to discontinuation nor treatment-related SAEs. Both single IV and monthly SC imsidolimab demonstrated clinically meaningful results and prevented GPP flares. In GEMINI-1, the most common TEAE observed in 2 patients in the 750mg treatment group was headache. In GEMINI-1 a total of 1 case of ADA (1/30, 3.3%) was reported. In contrast, a total of 23 cases of ADAs (23/50, 46%) were reported among patients who had received at least 1 dose of spesolimab. Imsidolimab has demonstrated effectiveness in GPP with a well tolerated and safe profile after a single dose. Targeting IL36 signaling with imsidolimab represents a promising therapeutic option.

LB1185

Single-cell transcriptomic analysis uncovers keratinocyte- and immune-specific long non-coding RNAs in psoriasis epidermis

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Psoriasis is a chronic inflammatory skin disease characterized by disrupted crosstalk between keratinocytes and immune cells, leading to epidermal dysfunction and immune infiltration. Long non-coding RNAs (lncRNAs) are crucial regulators, often with cell- or tissue-specific functions, yet their role in epidermal dysfunction and activation in psoriasis remains poorly understood. Here, we aimed to create an atlas delineating cell subsets and their cell type-specific lncRNA signatures in psoriasis epidermis using single-cell RNA sequencing with $CD45^-$ and $CD45^+$ epidermal cells from psoriasis and healthy skin. Our analysis identified three keratinocyte subpopulations with elevated activation markers and seven immune cell subsets exclusively present in lesional psoriatic epidermis. We identified 1447 consistently expressed epidermal lncRNAs, including 332 keratinocyte-specific and 411 immune cell-expressed lncRNAs. Notably, we identified lncRNAs preferentially expressed in activated keratinocyte subsets in psoriasis. One of these, LINC01137, a previously poorly characterized lncRNA, showed increased expression in psoriasis epidermis by single-molecule in situ hybridization. Additionally, several lncRNAs were identified in distinct epidermal immune cell subsets in psoriasis. Among these, LINC00892 was preferentially expressed in T cells, and in situ hybridization with immunofluorescence staining showed its increased expression in psoriatic epidermis. Collectively, our study unveils the non-coding transcriptomic landscape of the psoriatic epidermis and highlights distinct lncRNA signatures in keratinocytes and immune cells, suggesting their involvement in pathogenic processes in psoriasis.

LB1186

MEFV variants contribute to eosinophil-dominant refractory atopic dermatitis and enhance the therapeutic response to JAK inhibitors

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Atopic dermatitis (AD) is an inflammatory skin disorder influenced by genetic and environmental factors. To explore genetic factors contributing to refractory AD, we performed whole-exome sequencing on 13 patients with moderate-to-severe AD. Five harbored MEFV variants (rs150819742, rs201766654, rs190705322, rs11466023, rs11466024, rs11466018), with three heterozygous and two compound heterozygous cases. MEFV encodes pyrin, crucial for innate immunity, and its mutations cause familial Mediterranean fever (FMF) and PFAPA syndrome. Eight patients received upadacitinib (JAKi), including four with MEFV variants. Baseline characteristics and treatment responses were compared. Despite no significant differences in age, sex, disease severity, or prior treatments, patients with MEFV variants had significantly higher eosinophil counts (1913 vs. 454.6 cells/μL, $P = 0.0228$, unpaired t-test). After 3 months of JAKi, eosinophil counts significantly decreased in patients with MEFV variants (mean reduction: -1623 cells/μL, 95% CI: -2701 to -545.4, $P < 0.01$, two-way ANOVA with Bonferroni posttests), whereas no significant reduction was seen in those without variants (-96.57 cells/μL, $P > 0.05$). Two of four patients without MEFV variants developed MSSA infections, including impetigo, erysipelas, and abscesses within 3 months, whereas none occurred in those with variants except for one pre-existing folliculitis case. MEFV encodes pyrin, expressed in neutrophils, eosinophils, and monocytes. Pyrin inflammasomes activate IL-1 and IL-18, and IL-18 is essential for eosinophil maturation, like IL-5. Our findings suggest that MEFV variants contribute to eosinophil-dominant refractory AD and may enhance JAK inhibitor response by modifying immune activation.

LB1187

Loss of CD103 reduces chronic inflammation by decreasing the retention of IL-17a-secreting γδ T cells in mouse model of psoriasis

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CD103-positive γδ T cells accumulate in psoriasis-like inflamed skin and serve as a major source of IL-17A, leading to Th1/Th17-mediated inflammation. The study investigates the role of CD103 in regulating IL-17A-secreting γδ T cells and its impact on chronic inflammation. Using a K14CreER-Ube2l3f/f mouse model simulating psoriatic dermatitis and a CD103-deficient mouse model, we evaluated the infiltration and persistence of γδ T cells in inflammatory tissue and the expression of CD103 by flow cytometry and immunofluorescence. Our results demonstrate that CD103 deficiency significantly reduces the population of tissue-resident γδ T cells secreting IL-17A compared to wild-type controls ($p < 0.01$). The absence of CD103 impairs the ability of γδ T cells to secrete IL-17A, weakens their adhesion to epithelial cells, and limits their retention in inflammatory tissue. These findings highlight CD103 as a key regulator of γδ T cell retention and chronic inflammation.

LB1188

In silico analysis of genetic alterations in breast cancer associated skin lesions to guide 3D flipwell co-culture system performance in screening immunomodulatory therapies.

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Breast cancer associated inflammatory skin rash (BCIR) presents a unique challenge in therapeutic screening due to its distinct phenotypic and genetic differences. This study focuses on leveraging computational models to explore genetic modifications in the skin of patients with breast cancer-associated cutaneous lesions. We aim to identify key genetic drivers that influence the development and progression of the skin lesions. By using the Chan Zuckerberg CELL by GENE Discover Differential Expression database, we have identified several robustly co-expressed genes. Cytokeratin genes KRT7 (CK7), KRT5 (CK5), KRT19 (CK19), but not KRT20 (CK20) or KRT6 (CK6), were more differentially expressed together with ATP1A1, CD14, CD19, as well as macrophage associated genes CD86, STAT1, IL1B. By further analyzing specific genetic alterations in breast cancer associated lesions, we aim to enhance performance of the 3D Flipwell co-culture system - a novel co-culture system designed to model gut microbiome, epithelial and immune cell crosstalk - in screening immunomodulatory therapeutics. This integrated approach promises to refine the screening process for immunomodulatory treatments and could lead to more targeted and effective therapies for managing breast cancer-associated cutaneous lesions.

LB1189

Growth and biofilm formation potential of Malassezia species in an in vitro artificial sebum model

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Malassezia yeast overgrowth is linked to multiple skin disorders, yet its growth dynamics and virulence traits remain poorly understood. This study aimed to evaluate the growth, biofilm formation, and virulence potential of Malassezia species using an optimized in vitro artificial sebum model that closely mimics sebum-rich skin conditions. The model was specifically adapted to support Malassezia growth by modifying the pellet composition. Biofilm formation was assessed using confocal microscopy with Calcofluor and FUN1 staining to visualize cell wall structures and metabolic activity, while growth was quantified via conventional plating and quantitative PCR. Multiple Malassezia species, including M. furfur, M. pachydermatis, M. sympodialis, and M. restricta, demonstrated robust growth and biofilm formation. Indole production and extracellular lipase activity were also examined, though results were inconclusive. This study introduces a tailored in vitro artificial sebum model for Malassezia biofilm research, providing a valuable tool for studying its growth dynamics and potential role in skin disorders.

LB1190

Skin testosterone fuels MRSA pathogenesis via quorum sensing and reveals testosterone antagonism as a therapeutic strategy

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Skin cells have the capacity to secrete testosterone, with greater amounts of testosterone secreted at the skin surface in males compared to females. Males are also more susceptible to skin infections that females. We now find that mice engineered with testosterone-deficient skin are resistant to methicillin resistant S. aureus (MRSA) skin infections. Moreover, testosterone directly stimulates MRSA to express virulence factors that are required for skin colonization through the activation of a bacterial communication system called quorum sensing. Testosterone stimulation of bacterial quorum sensing is concentration dependent and can circumvent other inhibitory signals in the environment. Notably, we have also uncovered that an isomer of testosterone, enantiomer-testosterone, blocks bacterial quorum sensing and inhibits the pathogenesis of MRSA. Taken together, these findings are a mechanistic advance of our understanding of how the skin regulates bacteria and provides a novel therapeutic strategy for the management of antibiotic-resistant bacterial infections.

LB1191

Skin microbiome dysbiosis drives pathogenesis in murine models of hidradenitis suppurativa

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Hidradenitis suppurativa (HS) is a chronic inflammatory dermatosis with a complex pathogenesis influenced by both genetic and environmental factors, many of which remain poorly understood. Mutations in Ncstn, frequently observed in familial HS, disrupt Notch signaling- a pathway which is critical for maintaining skin homeostasis. To address the limitations of existing in vivo models, we developed two novel murine systems: keratin 17-driven Ncstn knockout (NEKO) mice and keratin 17-expressing tissue Rbpj knockout (REKO) mice. Both models recapitulated key HS phenotypes, including epidermal hyperplasia, follicular occlusion, and inflammatory cell infiltration. Histological analysis revealed a cellular infiltrate resembling human HS lesions, characterized by macrophages, IL-17$^+$ T lymphocytes, and neutrophils. Given the emerging role of microbial dysbiosis in inflammatory skin conditions, we performed 16S rRNA gene sequencing on the skin microbiomes of these murine models. The analysis revealed significant dysbiosis in both models, with a marked enrichment of Corynebacterium mastitidis. Subsequent antibiotic treatment reduced cutaneous inflammation in both NEKO and REKO mice, suggesting that C. mastitidis and associated dysbiosis may drive HS pathogenesis. The phenotypic similarities between the NEKO and REKO models further suggest that Rbpj dysregulation likely operates downstream of Ncstn loss within the Notch signaling cascade. These findings underscore the pivotal roles of Ncstn and Rbpj in HS pathogenesis and highlight the skin microbiome as a promising therapeutic target. Further studies are needed to elucidate the precise mechanisms by which C. mastitidis contributes to HS inflammation in these murine models.

LB1192

Integrating nutrition and the gut-skin axis into dermatology: A holistic approach to skin health and rejuvenation

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Recent studies show that the gut-skin axis is significant in maintaining skin health, particularly in anti-aging, collagen synthesis, and rejuvenation. The gut microbiome regulates inflammation, immune responses, and skin barrier function, all critical in supporting youthful, healthy skin. Diets rich in vitamins, minerals, antioxidants, and omega-3 fatty acids help reduce oxidative stress, support collagen production, and combat inflammation. A balanced diet can help maintain the skin's structure and external appearance by supporting internal processes that regulate skin health. The gut-skin axis suggests that a healthy gut microbiome influences skin conditions. Diets high in fiber, fermented foods, and prebiotics support beneficial gut bacteria, reducing inflammation and improving skin barrier function. In contrast, diets rich in processed foods and unhealthy fats contribute to gut dysbiosis, which can exacerbate conditions like acne, rosacea, and eczema. Many species, such as Cutibacterium acnes, Staphylococcus epidermidis, and Malassezia, on the skin are affected by gut health imbalances, influencing skin inflammation and irritation. Probiotics, found in foods like yogurt and kefir, can help restore balance to the gut microbiome, further supporting skin health. Integrating nutrition-focused therapies into dermatology offers a holistic approach to skincare. This review explores how personalized nutrition and microbiome-focused therapies can enhance dermatological treatments, offering an integrative approach to skin rejuvenation. As research continues, evidence-based nutritional guidelines will play a pivotal role in optimizing skin health, addressing both internal health and external appearance for more sustainable, effective skincare solutions.

LB1193

A single m^{6}A motif in HPV16 regulates circular E7 (circE7) RNA expression, viral replication, and keratinocyte immortalization

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High-risk human papillomaviruses (HPV), including HPV16, produce circular RNAs containing the E7 oncogene (circE7). CircE7 is N^6-methyladenosine (m^{6}A) modified, associated with polysomes, and translated into the E7 oncoprotein. Here, we identified a single m^{6}A motif, distal to the circE7 back-splice acceptor, that is essential for circE7 formation. A splicing reporter assay confirmed that mutation of this m^{6}A motif inhibited circE7 formation, while it enhanced E6*I forward splicing. In keratinocytes transfected with an HPV16 genome containing silent mutations in the circE7 m^{6}A motif (mut2), we observed significantly decreased circE7 and HPV16 genome copy number when compared with the wild-type genome. Mut2-transfected cells expressed elevated levels of Rb and p53, consistent with their inhibition by E6 and E7. Surprisingly, mut2-tranfected cells showed more efficient immortalization, indicating a complex relationship between circE7, viral replication, and cell immortalization. METTL3, the primary m^{6}A methyltransferase, was critical for circE7 biogenesis as siMETTL3 reduced circE7 recovery in m^{6}A RNA IP assays, confirming its essential role in circRNA methylation and back-splicing. Moreover, knockdown of the nuclear m^{6}A reader YTHDC1, which has previously been implicated in circRNA formation, decreased circE7 levels and translation. However, silencing m^{6}A-readers YTHDF3 and hnRNPA1 resulted in increased circE7 expression, indicating an intricate regulatory network regulating circE7 back-splicing and expression. In summary, our studies highlight the central role of a single m^{6}A motif and several m^{6}A regulatory proteins in the regulation of circE7 back-splicing and translation. The striking impact of a single m^{6}A motif mutation on circE7 expression, viral genome replication, and keratinocyte immortalization suggests a critical, unanticipated role for circE7 in the regulation of the viral life cycle.

LB1194

Real-world eczema phenotypes: Evaluation of longitudinal severity trends from an eczema mobile health app

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This study evaluated longitudinal patterns of eczema severity among EczemaWise users between March 12, 2019 and March 1, 2025 and classified users into real-world eczema phenotypes of disease expression. EczemaWise is a mobile health app (mHealth) that supports patient and caregiver monitoring of eczema symptoms and care conversations with healthcare providers through the collection of patient-reported data. A total of 885 users, each with more than three POSCORAD data points over at least two months, were analyzed. The identified cohort was predominantly female (77.29%), white (62.15%), metropolitan (87.34%), and patient users (88.70%, vs. caregivers). Patients were classified as 'mild' (85 users), 'moderate' (121 users), or 'severe' (51 users) if all recorded scores remained within those respective categories. Users were categorized as 'mild with moderate flares' (126 users) or 'moderate with severe flares' (71 users) if their scores were mostly in the lower category but spiked at least twice into the higher category. 'Seasonally mod-severe' users exhibited recurring seasonal fluctuations between moderate and severe (118 users). Users whose data did not fit these classifications were labeled 'uncategorized' (313 users). Notably, the uncategorized group comprised the largest subset, suggesting that many individuals exhibit fluctuating or atypical patterns that defy conventional classification; this sizable segment may indicate an unmet need for refined or additional metrics to capture the full spectrum of disease variability. Statistical analyses revealed significant differences in severity distribution across demographic subgroups, with race being statistically significant ($p<0.05$), highlighting potential disparities in disease expression and management. These findings underscore the utility of mHealth platforms not only in monitoring disease progression but also in contributing to a re-evaluation of current categorization frameworks to better understand disease journeys, tailor interventions, and improve patient outcomes.

LB1195

Sleep and activity in skin of color patients with autoinflammatory conditions

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Chronic inflammatory and autoimmune skin conditions are associated with sleep disturbances and decreased physical activity, which can significantly impact quality of life. Skin of color (SOC) patients with these conditions have lower quality of life even after controlling for disease severity and body surface area affected. Our study uses biometric data to compare sleep and activity quality in SOC vs. non-SOC patients with these conditions. A secondary objective is to determine if biometric data is correlated to patient reported data. Biometric data from wearable devices and patient questionnaire data for patients with psoriasis, hidradenitis suppurativa, atopic dermatitis, vitiligo, lupus, alopecia areata and acne were extracted from the All of Us database. Sleep data were reviewed for 567 white patients and 72 SOC patients. In comparison to SOC patients, white patients spent 35 more minutes asleep (401 vs 365, $p<0.001$) and spent more minutes in light sleep (258 vs 223, $p< 0.001$). SOC patients spent a greater percentage of the night in deep sleep (17.3 vs 15.3, $p<0.001$) and a greater percentage of time in REM sleep (21.2 vs 19.9, $p=0.02$). Among activity data for 636 white patients and 81 SOC patients, there were no statistically significant differences in time spent being very active, fairly active, lightly active, or sedentary among these groups. Among patient reported data, white patients reported better overall health, quality of life, physical health, mental health, social ability, and physical ability (on a scale 1-5, all p values<0.001). SOC patients also reported higher pain scores (5.56 vs 4.06, $p< 0.01$). Our analysis demonstrates no difference in activity levels between the two groups despite white patients having better self-reported measures of health. While white patients spent more time asleep, SOC patients spent a higher percentage of the night in deep sleep and REM sleep. Further investigation is needed to explore sleep quality and impact on quality of life in these patients.

LB1196

Evaluating the diagnostic accuracy of AI models in dermatology: Addressing skin tone bias to improve outcomes for ethnic skin types

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Artificial intelligence (AI) is increasingly integrated into dermatology for diagnostic support, yet its effectiveness across diverse skin tones remains limited. This study evaluates the diagnostic performance of AI dermatology models in detecting conditions across different Fitzpatrick skin types (FST) and assesses the representation of skin of color (SOC) in AI training datasets. A scoping review was conducted using PubMed and Google Scholar, focusing on studies that examined AI performance across FSTs and the demographic composition of AI training datasets. Findings indicate that AI models exhibit significantly lower diagnostic accuracy for darker skin tones, which may exacerbate existing disparities in dermatology education, undermining AI's potential to improve equity. For instance, evaluations using the Diverse Dermatology Images (DDI) dataset revealed reduced area under the curve (AUC) scores for FST V–VI compared to FST I–II (0.55 vs. 0.64 for DeepDerm; 0.50 vs. 0.61 for ModelDerm; 0.57 vs. 0.72 for HAM 10000). Additionally, many commonly used AI training datasets underrepresent SOC, with databases such as the Lesion Image Database containing only 4.3% images of Black or African American skin. Incorporating the Stanford DDI dataset (65% SOC images) into model training significantly improved diagnostic accuracy, closing the performance gap between light and dark skin tones and nearly equalizing their ROC-AUC values ($p = 9.33 \times 10^{-5}$ for DeepDerm, $p = 5.91 \times 10^{-10}$ for HAM10000; one-sided t test). These results underscore the need for diverse and representative training datasets to improve AI's diagnostic accuracy for SOC. Strategies such as synthetic data augmentation, transfer learning, and transparency in dataset curation can enhance model reliability and reduce disparities in dermatologic care. For AI-driven dermatology to bridge healthcare disparities and improve diagnostic outcomes, it must incorporate underrepresented populations at inception.

LB1197

Readability of sun protection education materials for dermatology patients

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This study evaluated the readability of online sun protection materials to assess their accessibility for both English- and Spanish-speaking populations. A Google search for "sun protection" was conducted in December 2024, and the first seven websites—American Academy of Dermatology (AAD), Skin Cancer Foundation, Centers for Disease Control and Prevention (CDC), U.S. Food and Drug Administration (FDA), Johns Hopkins Medicine, Visit Florida, and MedlinePlus—were reviewed. Readability was analyzed using nine validated calculators: Automated Readability Index (ARI), Flesch-Kincaid Grade Level, Coleman-Liau Index, Gunning Fog Index, Simple Measure of Gobbledygook (SMOG), and Linsear Write Formula for English materials, and Flesch-Kincaid Grade Level (SOL), Spanish SMOG, and Crawford-Score for Spanish materials. A total of 73 web pages were reviewed—54 in English and 19 in Spanish. Readability levels ranged from 5th grade to college-entry, with most materials exceeding the sixth-grade reading level recommended by the National Institutes of Health (NIH) and American Medical Association (AMA). English materials typically required 8th to 10th grade reading levels, with the FDA website requiring the highest reading level. Spanish materials ranged from 5th to 8th grade, but many websites, including Skin Cancer Foundation and Johns Hopkins, lacked Spanish translations, while others used interactive translation tools that could compromise accuracy. These findings underscore significant readability barriers to accessing sun protection information, particularly for Spanish speakers, and emphasize the need for simplified, culturally appropriate, multilingual materials to improve health literacy and promote equitable access to care.

LB1198

A comprehensive characterization of the Hispanic, Black, Asian, and Caucasian atopic dermatitis phenotype via RNAseq in skin tape strips

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Atopic dermatitis (AD) is a heterogeneous disease characterized by various endotypes. However, there is still limited understanding of the molecular phenotypes of AD across different ethnicities, particularly among Hispanic patients, who are often categorized as either White or Black, without independent characterization through bulk-omics methods. To address this gap, we aim to conduct a comprehensive study comparing multiple ethnicities using RNAseq in skin samples. We enrolled 52 AD patients (9 Hispanic, 15 Black, 13 Asian, 15 White) and 42 matched controls (9 Hispanic, 10 Black, 11 Asian, 12 Caucasian) and collected tape strips for RNAseq analysis. Differentially expressed genes/DEGs were defined by fold change/FCH>1.5 and false discovery rate/FDR<.05.RNAseq showed a universal upregulation of Th2- and Th1-related genes across all ethnicities (CCL17/22, IL10/13/IL12B, TNF, INFGR2) with a stronger OX40 skewing observed in Hispanic AD patients. While Th17 was differentially driven in different ethnicities, such as CXCL3/IL6 in White and Black AD patients, while S100As were prominent in Hispanic AD, and CXCL1/2/IL6 in Asian AD. Key terminal differentiation (FLG/LCEs), keratins, and lipids (FA2H/FASN) were downregulated across all groups but several downregulated barrier genes found in White, Black, and Asian AD were not observed in Hispanic AD (CERS4/GJB2/RPTN). Lipid-associated barrier genes (UGT8/FABP4) were uniquely attenuated in Asian AD.The shared and unique features of Hispanic AD compared to Black and Caucasian AD represented a "bridging" phenotype between the two that may be explained by the ethnic vs racial categorization underscoring AD as a heterogenous disease that necessitates targeted and individualized therapeutics.

LB1199

Generational and cultural influences on the discrepancy between patient-reported and physician-assessed atopic dermatitis severity: A Japanese single-center study

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The utilization of patient-reported outcomes (PROs) in chronic conditions such as atopic dermatitis (AD) is increasingly common; however, discrepancies with physician assessments, such as the Eczema Area and Severity Index (EASI), are often observed. This study aimed to investigate whether generational differences influence these discrepancies among Japanese patients, as no prior research has addressed this topic in Japan despite findings from a European study indicating generational effects on PROs. We conducted a retrospective analysis of 81 AD patients (38 males, 43 females; aged 11-59) attending our clinic from December 2022 to December 2024. EASI was used for physician evaluations, while PROs included the Atopic Dermatitis Control Tool (ADCT) and pruritus Numerical Rating Scale (NRS). Data from mild-to-moderate severity and peak EASI periods were analyzed. Patients were categorized into Generation Z (born 1997-2012), Millennials (1981-1996), and Generation X (1965-1980). Statistical analyses examined differences in ADCT and NRS responses based on generation, disease duration, and onset age (infancy, school age/adolescence, or adulthood). While no significant differences were found in EASI, NRS, or ADCT scores across generations, there was a trend of higher ADCT scores among Millennials and the adult-onset group, particularly in mood-related aspects (ADCT Q6). Multiple regression analysis identified Generation Z as significantly associated with lower ADCT scores and higher NRS scores, suggesting varying response patterns by generation across PRO instruments. Although limited to a northern Japanese cohort, our findings suggest generational factors may influence PRO responses. These results differ from European studies, indicating potential cultural differences in patient reporting. Understanding these generational influences can enhance PRO interpretation and promote patient-centered AD management.

LB1200

Knowledge, attitudes, and practices of anal cancer screening among dermatologists

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Dermatologists' awareness and involvement in HPV-related cancer screening are crucial for early detection and improved outcomes in patients at a disproportionate risk of anal cancer. This study aimed to assess dermatologists' knowledge, attitudes, and practices regarding anal cancer screening. Members of the American Academy of Dermatology's LGBTQ/SGM Expert Resource Group were surveyed on their perspectives, knowledge of anal cancer risk factors and screening guidelines, and current clinical practices. Seventeen respondents completed the survey (response rate 45%). The median respondent age was 43 (IQR 38-53), 76.5% self-identified as lesbian or gay, 82.4% were male, and 52.9% practiced in an academic institution. Most respondents correctly noted 90% of anal squamous cell carcinomas in the U.S. are attributable to HPV (88.2%), but only 41.2% correctly identified digital anal rectal exam plus anal cytology and/or HPV testing as the appropriate screening method for eligible populations. Most respondents agreed dermatologists should counsel (82.4%) and refer (76.5%) eligible patients for anal cancer screening, while 41.2% believed dermatologists should perform screenings themselves. In practice, most respondents reported counseling (64.7%) and referring eligible patients (70.6%), yet only 5.9% performed screenings. This study was limited by a modest response rate and non-representative sampling. These findings highlight gaps between dermatologists' perceived role and actual practices in anal cancer screening, and knowledge deficits even among those with expertise in SGM health. Expanding dermatology-specific training on anal cancer risk assessment, counseling, and referral may enhance early detection efforts in patients at a disproportionate risk of anal cancer and lessen the increasing disease burden.

LB1201

Skin care kits for people unhoused: Pilot study and dermatological care needs assessment

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Over the past few years, the Dermatology Interest Group (DIG) at Yale School of Medicine has been assembling and donating skin care kits to support people who are unhoused in the New Haven community. In this pilot program, we surveyed kit recipients (n = 63) to assess the most needed skin care products, as well as dermatological care needs and barriers. The most helpful product in our kit was dry skin cream (74%). Participants also frequently reported the need for deodorant (67%), oral care products (61%), clean underwear and socks (75%), and athlete's foot cream (48%). Additionally, we found that 38% of participants have ever needed but were unable to have a skin condition evaluated. Among these participants, the top barriers to accessing dermatological care were lack of transportation (71%), lack of information on where to go or who to contact (63%), and concern that they may not be treated with respect by healthcare providers (50%). These results show that a significant proportion of people who are unhoused require dermatological care, which may be overlooked in this population. This study highlights the importance of expanding access to dermatological care and skin care products to people who are unhoused.

LB1202

Perceived barriers to atopic dermatitis care among adults

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Barriers to medical care for atopic dermatitis (AD) lead to suboptimal outcomes and contribute to disparities in disease burden. This study aimed to identify perceived barriers to care among an urban population of adults with AD. We performed a qualitative study of adults with AD in Philadelphia using freelisting, a method that identifies how individuals with similar experiences think about a topic. Participants listed things that prevent them from getting medical care for their AD. The most salient responses were identified using Smith's Salience index (S). Relative salience (RS) was calculated by dividing the S of each response by the S of the most salient response, expressed as a percentage. We interviewed 46 adults with AD (15 White, 16 Black, 15 Hispanic). Median (interquartile range) age was 34 (28, 41) years; 72% were female; 63% had moderate/severe AD. "Nothing" (i.e., no reported barriers) was the most salient response among all participants and those with mild and moderate/severe disease. Among those with moderate/severe disease, additional salient barriers included "insurance" (e.g., no insurance; RS 93%), "finances" (e.g., visit costs; RS 77%), and "competing priorities/time" (e.g., work schedule; RS 76%). "Nothing" was also the most salient response among White and Black participants; however, among Hispanic participants, "insurance" was the most salient response followed by "nothing" (RS 72%). This aligned with quantitative data identifying the highest percentage of uninsured among Hispanic participants (13.3% White, 0% Black, 33.3% Hispanic). Notably, "lack of knowledge" (e.g., misdiagnosis) was the least salient response among White participants (White RS 7%, Black RS 30%, Hispanic RS 36%). Our study reveals differences in perceived barriers to care for AD by disease severity and race/ethnicity. The perceived absence of barriers was surprising among our study population that experiences a large burden of disease and suggests learned helplessness that will be examined in additional interview responses.

LB1203

Smoking prevalence and cessation in skin cancer survivors: A cross-sectional survey

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Smoking is associated with poor prognosis among melanoma survivors, but smoking prevalence and cessation in skin cancer survivors are not well characterized. This cross-sectional study aimed to estimate smoking prevalence and cessation in US adult skin cancer survivors aged 18-84 years using the nationally representative 2020 and 2022 National Health Interview Survey. Weighed prevalence of current smoking within 30 days of survey, smoking at the time of first cancer diagnosis, and smoking cessation after first cancer diagnosis were estimated and compared with internal cancer using Rao-Scott chi-squared tests and multivariable logistic regression. Survivors of multiple cancers were excluded. Compared to internal cancer survivors (n=3782), skin cancer survivors (n=1908) were older (mean age 64.7 vs 62.8 years) and more college educated (46.6% vs 32.6%). Comparing skin cancer survivors with internal cancer survivors, current smoking was less common (9.0% vs 12.9%, p<0.001), smoking at the time of cancer diagnosis did not significantly differ (34.8% vs 40.2%, p=0.06), and post-diagnosis smoking cessation was more prevalent (42.3% vs 31.0%, p=0.01). Prevalence odds of current smoking (OR 0.99, 95% CI 0.66-1.35), smoking at time of diagnosis (1.19, 0.86-1.66), or cessation after diagnosis (1.04, 0.61-1.80) did not differ in skin cancer survivors as compared to internal cancer survivors after adjusting for age, race/ethnicity, sex, household income, health insurance, and education. Limitations include self-reported smoking outcomes. A substantial minority of skin cancer survivors smoke at the time of and after diagnosis. Dermatologists should provide smoking cessation counseling and facilitate referral to evidence-based smoking cessation interventions to skin cancer survivors who smoke.

LB1204

A retrospective analysis of emergency and inpatient care of patients hospitalized for hidradenitis suppurativa

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The aim of this retrospective study was to analyze treatment course and clinical outcomes of patients admitted to the hospital for hidradenitis suppurativa (HS). The Epic SlicerDicer tool was used to identify all patients admitted at an academic health center between September 1st, 2013 and September 1st, 2023 with a primary diagnosis of HS. Of 98 patients identified, 61% were female, 80% were black, and 68% were insured with Medicaid/Medicare or uninsured. Mean age at diagnosis was 32 years and mean age upon admission was 42 years. The most common concerns at emergency department (ED) presentation were pain (90%), drainage (48%) and abscess (38%). In the ED, 68% received pain medication, 62% received intravenous (IV) antibiotics and 17% underwent incision and drainage (I&D). The average hospital length of stay was 6 days. The most frequently consulted specialties during admission were general surgery (53%), dermatology (42%), and infectious disease (30%), and the most common therapies received were oral antibiotics (90%), pain medication (82%), IV antibiotics (81%), and I&D (38%). A mean of 3 imaging studies and 35 labs were ordered for each patient. Only 59% of those admitted were instructed to follow-up with dermatology post-discharge with an average length of time between discharge and dermatology appointment of 63 days. Within this cohort, 72% sought emergency care more than once with an average of seven HS-related ED visits and 52% were hospitalized more than once with an average of five HS-related admissions. The average length of time between HS-related hospitalizations was 9 months. Our results suggest HS patients who seek care in the ED utilize significant resources, frequently return, and have lengthy hospital admissions. Optimization of outpatient HS management is required to decrease the physical and financial burden of frequent admissions for HS.

LB1205

Outcome measures in pseudofolliculitis barbae: A scoping review

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Pseudofolliculitis barbae (PFB) is a dermatological condition primarily affecting the hair follicle, resulting in extrafollicular and transfollicular penetration of spiraled hair, painful papules, and potential scarring, particularly along the jawline and neck. Despite various treatment approaches used to address PFB, there is a lack of uniform grading scales and outcome measures to determine the effectiveness of treatments. We conducted a scoping review of the literature to evaluate the outcome measures used when treating PFB. MEDLINE, Embase, Web of Science, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov were searched for a combination of keywords and database-specific controlled vocabulary terms related to PFB. The searches were conducted on December 5, 2024, and independently peer-reviewed using a modified PRESS checklist. Citations were imported into Covidence, a systematic review screening software. After the removal of duplicates, 443 studies were screened for title and abstract, and full text review was completed for 59 studies. Excluded articles lacked outcome measures, published data, correct disease indication, or were written in non-English language. Sixteen studies were included in the scoping review and demonstrated clinician and/or patient- reported outcome measures. Most physician-reported outcome measures focused on papule count, dyspigmentation and hair density reduction. Patient-reported outcome measures were centered on patient satisfaction with treatment and side effects. Only one study attempted validating the physician-reported outcomes, specifically papule and hair counts. This review highlights various grading scales and outcome measures utilized in PFB assessment. Additional effort is required in the development of a standardized global severity assessment and outcome measures for PFB to ensure the accurate assessment of treatment efficacy in future clinical trials.

LB1206

Spatial transcriptomic analysis reveals increased myofibroblast localization in patients with central centrifugal cicatricial alopecia

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Previous transcriptomic and proteomic studies in central centrifugal cicatricial alopecia have identified several genes and canonical pathways associated with fibroblast activation, adaptive immune response, and dysregulated wound healing. However, key spatial information is lost using the aforementioned methods of analysis, limiting the ability to localize gene expression within the skin. To investigate gene expression patterns in CCCA patients while preserving the in-situ transcript localization, 3 treatment naive CCCA patients treated at a tertiary center were recruited. Two scalp biopsy samples were obtained from each patient: 1 from lesional scalp and 1 from non-lesional scalp. Spatial transcriptomic analysis was performed using Visium 10x Genomics. Spatial transcriptomic analysis of 8,410 genes identified 95 upregulated genes and 534 downregulated genes in lesional vs non-lesional scalp ($p<0.05$, absolute log2 fold changes [FC]>0.5). Gene set analysis revealed upregulation of pathways related to B cell activation, leukocyte differentiation, and Th17 cell lineage commitment. Downregulated pathways included those involved with keratinization, metabolic processes, hair cycle regulation, and epithelial cell differentiation ($q<0.25$). Notably, smooth muscle actin positive myofibroblasts, noted by ACTA2 expression, showed similar expression patterns in lesional and non-lesional scalp. However their distribution within the tissue differed, localizing around scarred hair follicles in lesional scalp and epithelial wall of blood vessels in non-lesional scalp. This study further supports the role of adaptive immunity in CCCA, while also highlighting the spatial differences of myofibroblasts in active disease. Increased myofibroblast localization around hair follicles instead of the vessels may offer key insights in disease pathogenesis. Future studies exploring fibroblast heterogeneity and localization patterns in CCCA may provide new insights into targeted therapies aimed at mitigating fibrosis.

LB1207

Racial and ethnic representation in clinical trials of janus kinase inhibitors for dermatologic conditions: A systematic review

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Janus kinase (JAK) inhibitors represent promising therapies for various dermatologic conditions, and adequate racial representation in clinical trials is essential to ensure generalizability. We conducted a systematic review of published JAK inhibitor clinical trial results for dermatologic indications and evaluated demographic representation. Trials were identified via PubMed and ClinicalTrials.gov. Studies from 2000 to 2025 were included. Animal studies, review papers, and duplicated studies were excluded. Of 401 identified studies, 206 clinical trials were included for review. 57,112 study participants were evaluated. Among studies reporting race (57.5%), representation was predominantly White (75.1%), followed by Asian (13.2%), Black (6.6%), American Indian/Alaska Native (0.48%), Native Hawaiian (0.11%), and Multiple races (0.43%). White participant representation closely aligned with their U.S. population proportion (75.3%), while Asian participants were overrepresented (13.2% vs. 6.4%), and Black participants were underrepresented (6.6% vs. 13.7%). Underrepresentation was pronounced among Black participants in psoriasis (1.3%), SLE (1.0%), and vitiligo trials (5.1%), although higher in HS (27.9%). Differences in racial representation in trials across conditions differed significantly from the U.S population ($p=0.021$). Representation in these trials significantly differed from the racial distribution of U.S. patients with vitiligo ($p = 0.012$) and AD ($p = 0.00088$). White patients were overrepresented in vitiligo and AD trials (Pearson's residual=2.71, 0.99), and Black patients were underrepresented in vitiligo and AD trials (Pearson's residual=-2.41, -1.84). These findings highlight a critical need for improved recruitment strategies targeting underrepresented populations to enhance the inclusivity and applicability of dermatologic clinical research.

LB1208

Expanding access to dermatological and wound care for underserved communities through a free clinic in rural Illinois

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Disparities in care and outcomes in dermatology are rising, particularly in rural and underserved areas. Despite comprising a large portion of the general population, under- and uninsured individuals are often underrepresented in dermatology practice, resulting in delays in diagnosis, management, and treatment. There is a high incidence and prevalence of dermatological conditions affecting the population of rural Illinois. According to the Illinois Department of Public Health, the incidence of skin cancers, bacterial, viral, fungal, and parasitic skin infections, STIs, acne, dermatitis, and psoriasis, as well as superficial and open wounds secondary to chronic conditions and tool and machine use, injury, or trauma, continues to rise. Increasing access to dermatological and wound care in under- and uninsured individuals may help reduce the risk and burden of these skin conditions in rural Illinois. To address the pressing and critical need for dermatological and wound care in rural Illinois, we created the first-ever free dermatology and wound care facility in Urbana-Champaign, Champaign County, IL. It offers dermatological and wound care services that are 100% free to residents. On stratification, our patients encompass Hispanic 33.3%, Caucasian 33.3%, African American 11.1%, and those that declined to respond 22.2%. The conditions we have managed include benign growths (38.89%), foot-related conditions (5.57%), dermatitis (22.2%; all types), malignant/at risk growths (5.56%), appendage-related (11.11%), and pigmentation disorders (16.67%). 77.7% of patients treated don't have medical insurance; while 22.3% don't know/are unsure. 11.1% of patients speak a primary language other than English. We discuss the establishment and operationalization of the clinic, highlighting its impact on patient dermatological and wound healthcare outcomes and its role in fostering and empowering student involvement in dermatology.

LB1209

Publication characteristics of successful dermatology applicants from 2020 through 2022

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This study aimed to determine the publication characteristics and trends of successful dermatology applicants from 2020 to 2022. The analysis included all dermatology residents who began their training between 2020 and 2022 in a retrospective cohort study. Dermatology residencies were collected from FREIDA and demographic data was collected from each program's website. Publication data was obtained from SCOPUS. During the study period, there were a total of 1395 successful dermatology applicants with 2766 publications included in final analysis. There was a statistically significant trend for increased total publications ($p=0.004$), dermatology publications ($p=0.005$), the publication of original research ($p=0.013$) and review articles ($p=0.002$) and serving as either the first ($p=0.019$) or second ($p=0.015$) author amongst successful dermatology applicants. Those applicants who attended a medical school ranked in the top 20 for NIH grant funding had statistically significant more total publications ($p<0.001$), publications on research outside of dermatology ($p<0.001$), original research publications ($p<0.001$), and acted in the first ($p<0.001$) or other author positions ($p=0.025$) as compared to applicants who did not attend a top 20 school in NIH grant funding. Those who match at a university-based program also have statistically significant more total publications ($p<0.001$), dermatology publications ($p<0.001$), original research ($p<0.001$), and first authorship manuscripts ($p<0.001$) as compared to those who match at a community-based residency program. From 2020 through 2022, an upward trend in publications has been seen amongst successful dermatology applicants. Those who attend a medical school who rank in the top 20 for NIH funding have more publications than those applicants who attend a school outside of this ranking. Applicants who match at a university based residency are also more likely to have more publications than those who match at a community based residency.

LB1210

Aggregating Hispanic patients with cutaneous T-cell lymphoma obscures survival differences compared to non-Hispanic white patients

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Comparisons of survival outcomes between Hispanic patients with cutaneous T-cell lymphoma (CTCL) and Non-Hispanic White (NHW) patients have yielded conflicting results. However, prior studies have classified all Hispanic populations as one group, despite considerable heterogeneity in national origin. To disaggregate Hispanic patients, we queried the National Cancer Database (NCDB) for patients diagnosed with CTCL from 2004-2020. Overall survival (OS) was compared using the log-rank test, and hazard ratios (HRs) were calculated using a multivariable Cox proportional hazard model. Missing data were handled with multiple imputation by chained equations. Out of 15,276 patients with CTCL, we identified 14,264 NHW and 1,012 Hispanic patients, of whom 111 were Mexican, 87 were South/Central American, 115 were Caribbean, and 699 were Other Hispanic. Compared to NHW patients, aggregated Hispanic patients had higher rates of OS (log-rank test, $p < .001$). In a multivariable Cox model, there were no differences in OS among aggregated Hispanic patients and NHW patients (HR 0.93; 95% CI, 0.80-1.10), but after disaggregation, Caribbean patients had significantly greater OS than NHW (HR 0.64; 95% CI, 0.41-0.99). There were no significant differences between other Hispanic populations and NHW patients. We demonstrate that Caribbean patients with CTCL in the NCDB may have significantly improved OS compared to NHW patients, even after adjusting for covariates. Our findings challenge the assumption that Hispanic populations with CTCL can be aggregated in clinical research. More studies are needed to investigate other potential contributors to survival differences not captured in NCDB, such as genetic ancestry, the immigrant health effect, and environmental mediators.

LB1211

Reddit-based thematic analysis of patient preferences in non-melanoma skin cancer treatments

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Superficial radiation therapy (SRT) is utilized to treat low risk cutaneous non-melanoma skin cancers (NMSCs). Dermatologists are increasingly fielding questions as to the utilization of SRT rather than undergoing Mohs micrographic surgery (MMS). While both target NMSCs with different risk profiles, SRT's growing use suggests patient appeal. This study examines attitudes, preferences, and satisfaction with SRT compared to MMS. Reddit was searched using "Superficial Radiation Therapy Mohs," "SRT Mohs," and "GentleCure." The first 50 posts from each search were screened for relevance. Posts discussing MMS or SRT for NMSCs were included. Two medical students independently identified themes, created a codebook, and applied it to all posts, resolving discrepancies by consensus. Mixed-methods analysis incorporated qualitative themes and quantitative content. Fifteen Reddit threads and 196 subthreads from 94 unique users were analyzed, revealing 20 themes. Common topics included independent treatment research (n=24), cosmetic concerns (n=22), and satisfaction/dissatisfaction with results (n=20). Many users were dissatisfied with the information provided by their care teams, prompting inquiries about SRT's efficacy (n=19) and cost (n=8). Fears of facial scarring from MMS (n=22) led some to prefer SRT for its perceived cosmetic benefits, though concerns about SRT-related dyspigmentation, atrophy, and scarring (n=5) were noted. This is the first study to assess patient perspectives on SRT versus MMS for NMSCs. Frustration with inadequate SRT information drives some patients to unreliable sources like Reddit, emphasizing the need for thorough education. The focus on cosmetic outcomes highlights its importance in treatment discussions.

LB1212

XPC gene variation in an individual with generalized eruptive keratoacanthomas of grzybowski

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Generalized eruptive keratoacanthomas of Grzybowski (GEKA) is a rare variant of keratoacanthoma (KA) that is characterized by development of hundreds of KAs and has no known germline genetic cause. A 64-year-old white male was referred to our dermatology department in 2023. He had developed frequent keratoacanthoma type squamous cell carcinomas since 2016 and was diagnosed with GEKA in 2018. His physical exam was notable for several widely distributed, solitary, dome-shaped, skin-colored nodules with a central keratinous plug, which were confirmed as KAs on biopsy. Treatments included topical 5-fluorouracil, 5-fluorouracil + calcipotriene cream, imiquimod, triamcinolone cream, and clobetasol ointment; injected 5-fluorouracil and triamcinolone; and oral nicotinamide, acitretin, methotrexate, and cyclophosphamide. These treatments were variably effective in reducing but not eliminating additional KAs. To investigate the genetic cause of his predisposition to KAs, library preparation and next-generation sequencing (NGS) of coding regions of approximately 4800 medically relevant genes was conducted with targeted gene analysis planned. Initial referral for sequencing targeted the TGFBR1 gene which was negative. Expanded analysis identified two variants of uncertain significance in XPC. TGFBR1 has been shown to play a role in KA development and Multiple Self-Healing Squamous Epithelioma and Loeys-Dietz Syndrome. Prior studies have shown an association between XPC germline mutations and KA development as well as decreased XPC expression levels in KAs, but no studies have linked it directly to GEKA. Similarly, GEKA has been linked to HPV 39 infection, and sporadic keratoacanthomas have shown positivity with multiple HPV subtypes, but this testing is not currently available at our institution. Further testing is indicated to determine the significance of these genetic findings and to explore the role of HPV in GEKA.

LB1213

KIF18A expression is increased in cutaneous squamous cell carcinoma regardless of immune status

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Immuno-oncology has revolutionized the treatment of both melanoma and non-melanoma malignancies. In unresectable cutaneous squamous cell carcinoma(CSCC), however, the objective response rate is between 30 and 50%. Moreover, in solid organ transplant recipients(SOTRs) the use of immunotherapy remains a major challenge. Further investigation of anti-tumor agents that are mechanistically distinct from checkpoint inhibitors and can trigger an anti-tumor but not allograft immunity is urgently needed in patients with advanced skin cancers to improve survival. A hallmark of skin cancer is chromosomal instability. KIF18A is an important mediator of mitosis in chromosomally aberrant cancer cells but is not required for cell division in normal diploid cells. KIF18A overexpression has been shown in a variety of solid tumors including breast, colorectal, renal, and liver cancer. To investigate the expression of KIF18A in CSCC, we stained paraffin embedded sections of CSCC from both SOTRs (n=5) and immunocompetent patients (n=6) against KIF18A. Compared to normal adjacent epidermis, tumor tissue has a significantly higher level of KIF18A expression (2.8 vs. 17.3% KIF18A-positive cells, $p<0.0001$). Expression was also significantly higher in poor vs well-differentiated tumors (27.5 vs 14.8 % KIF18A-positive cells, $p= 0.0072$), which is consistent with previous data on increased level of somatic copy number aberrations observed in tumors with high-risk histology. The level of expression of KIF18A was not different in CSCCs of SOTRs vs immunocompetent patients, consistent with prior studies which show that when adjusted for T stage, metastatic risk is similar between SOTRs and immunocompetent. Here we demonstrate that KIF18A is highly expressed in CSCC and correlates with aggressive histology. KIF18A inhibitor is currently in clinical trials for advanced malignancies. Its lack of mechanistic dependency on adaptive immunity makes it a promising treatment target for CSSC in SOTRs and patients failing immunotherapy.

LB1214

Topical imipramine and amitriptyline: Potential treatments for UVB-triggered redness in rosacea

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Rosacea is a chronic inflammatory condition with limited therapeutic options. It is typically exacerbated by stimuli such as sunlight and alcohol use. Functional inhibitors of acid sphingomyelinase (FIASMs) such as amitriptyline and imipramine have been shown to inhibit the production of microvesicle particles (MVPs) which are membrane-bound mediators of cell signaling and biological activity. It is hypothesized that FIASMs, through their ability to inhibit the release of MVPs, may reduce the erythema response associated with ultraviolet B light exposure in rosacea patients. This study was conducted as a single-center, double-blinded, placebo-controlled randomized clinical trial. Patients with rosacea and non-rosacea controls were recruited, de-identified, and then randomized to receive 4% amitriptyline or 4% imipramine on either the left or right side of their face and a placebo medication on the other. Baseline erythema, photography, pain, and itch measurements were taken. Respective topical medications were applied, then 300Joules/m^2 of artificial UVB light was administered and subsequent measurements were taken after UVB administration at 10 min, 60 min, 120 min, and 24 hours. UVB-induced erythema in patients with rosacea had a statistically significant reduction from baseline in 4% topical amitriptyline and 4% imipramine compared to vehicle (one-tailed t-test, $p= 0.043$). In conclusion, topical FIASMs such as amitriptyline and imipramine work by blocking the release of microvesicle particles and thus reducing the erythema associated with rosacea. These medications may serve as an adjunct treatment to UVB exposure in rosacea patients without adverse events or safety concerns.

LB1215

Advanced glycation end products induced M1-like macrophages exacerbate photoaging via PTX3

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Introduction: Advanced glycation end-products (AGEs) accumulate in photoaged skin and play a pivotal role in accelerating skin aging. However, the precise role of AGEs in macrophage polarization and their impact on photoaging remains largely unclear. Objectives: This study aims to elucidate the role and underlying mechanism of AGEs-induced M1-like macrophages in photoaging, as well as how PTX3 secretion exacerbates photoaging during this process. Materials and Methods: Macrophage-depletion mice were used to assess the role of macrophages in AGEs-induced skin aging. In vitro, THP-1-derived macrophages were treated with AGEs. Macrophage polarization and inflammation were evaluated by flow cytometry, ELISA, PCR, WB, and RNA sequencing. Single-cell and bulk RNA-seq data were analyzed to examine macrophage polarization and PTX3 expression, which were further verified by immunohistochemistry and immunofluorescence in photoaged skin. Additionally, the molecular mechanisms underlying these processes were explored. Results: (1) Macrophage depletion significantly alleviated AGEs-induced skin aging in mice, indicating the critical role of macrophages in this process. (2) M1 polarization markers in the skin were elevated and positively correlated with AGEs. AGEs promoted M1-like polarization in macrophages, which subsequently induced senescence in co-cultured fibroblasts. (3) The expression and secretion of PTX3 were markedly increased in macrophages treated with AGEs. PTX3 was mainly expressed in macrophages and increased with age in sun-exposed areas, and it could induce fibroblast senescence in vitro. (4) AGEs-induced M1-like macrophages secrete PTX3 via activation of the NFκB pathway. Quercetin suppresses the NFκB pathway, thereby reducing M1 polarization and PTX3 secretion in vitro, and subsequently alleviates AGEs-induced skin aging in mice. Conclusions: Our study reveals that AGEs-induced M1-like macrophages exacerbate skin photoaging through PTX3 secretion, and that inhibition of macrophage M1 polarization may offer a potential therapeutic strategy for photoaging.

LB1216

Apobec3a expression accelerates chemical carcinogenesis in murine skin

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Dysregulated activity of the human cytidine deaminase APOBEC3A is a prevalent contributor to human cancer. Signatures of APOBEC3A activity are found in approximately 10% of cutaneous squamous cell carcinoma (cSCC) where APOBEC3A mutagenesis targets driver genes critical to pathways regulating cell state, growth, and apoptosis. Tumors with enriched APOBEC3A activity have increased heterogeneity, increased resistance to therapy and a higher risk of metastasis. To determine the contribution of APOBEC3A to DMBA/TPA chemical carcinogenesis in the skin, we utilized the A3A10 mouse model, characterized by constitutive, low copy number expression of human APOBEC3A driven by the chicken beta actin promoter. Mice positive for human APOBEC3A that received DMBA and TPA had significantly higher average tumor burden ($p < 0.0001$) over the course of the experiment, with final average tumor burden being 8.35 times higher than their negative counterparts. APOBEC3A expression also led to a significantly higher number of tumors ($p < 0.0001$), with the final average tumor count being 3 times higher, and increased histological and morphological features of progressive cSCC. Overall, our data demonstrates that low level, constitutive expression of human APOBEC3A accelerates chemical carcinogenesis in the skin.

LB1217

Probing the potential origin of virus-driven merkel cell carcinoma using a novel mouse model

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Over 80% of Merkel cell carcinomas (MCCs) carry integrated Merkel cell polyomavirus (MCPyV), leading to expression of oncogenic small T (sT) and truncated large T (tLT) viral antigens which drive tumorigenesis. The MCPyV non-coding control region (NCCR) contains DNA regulatory elements that drive expression of sT and tLT viral oncogenes in MCC tumor cells, and presumably also in skin cells that give rise to MCC. To map NCCR-driven gene expression in vivo we generated mice carrying a randomly integrated NCCR-RFP transgene with a red fluorescent protein reporter molecule to identify cells in which the MCPyV viral promoter is active. NCCR-RFP mice exhibited RFP in rare dermal cells, but these were infrequent, and RFP expression was weak. To improve our ability to detect and manipulate NCCR+ cells, we generated a modified construct containing i) the MCPyV NCCR, ii) a nuclear-localized RFP (nRFP), and iii) an rtTA3 cDNA for inducible expression of tetO-driven transgenes. The NCCR-nRFP-rtTA3 construct was inserted into the ROSA26 safe harbor genomic locus to mimic the open chromatin landscape associated with integrated NCCRs in human MCC tumor cells. In contrast to NCCR-RFP mice, R26-NCCR-nRFP-rtTA3 mice consistently exhibited nRFP expression in a subset of epidermal and dermal cells, and most strikingly and consistently, in hair follicle stem cells localized to the bulge region. NCCR activity/nRFP expression in follicle stem cells is particularly interesting since early-stage tumors in our MCC mouse models are first detected in the bulge region. These findings point to follicle stem cells as potential cells of origin for MCC, addressing a long-standing question that has been difficult to tackle using other approaches. In addition, our data show that targeted insertion of promoters into the ROSA26 locus can override the confounding effects of flanking sequences on faithful expression of randomly-integrated transgenes, providing a more reliable way to map promoter activity.

LB1218

Persistence of residual basal cell carcinoma (BCC) cells in vismodegib-treated Ptch1$^{+/-}$/SKH-1 mice is associated with treg accumulation

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Hedgehog (Hh)-targeted therapies effectively reduce BCC burden in patients with Gorlin syndrome (GS). However, a major challenge with targeted Hh inhibitors (HHi) is their inability to fully eliminate tumor cells, thus driving significant tumor recurrence. Preclinical and clinical studies suggest that residual tumor cells refractory to HHi persist, underscoring the need for developing novel therapeutic strategies to achieve sustained remission. Prior research has revealed a complex immune landscape within the BCC tumor microenvironment in both humans and Ptch1$^{+/-}$/SKH-1 mice, a murine model that mimics multiple features of GS-associated BCC, suggesting that an altered immunogenic landscape may enhance tumor progression and inhibit treatment response. To further investigate BCC-associated immune cell composition, we conducted high-dimensional spectral flow cytometry using an optimized immune profiling panel. Compared to non-tumor-bearing Ptch1$^{+/-}$/SKH-1 skin, BCC-bearing skin exhibited substantial T cell infiltration, including CD8+ T cells, conventional CD4+ T cells, CD4+ regulatory T cells (Tregs), and γδT cells. Notably, immune profiling of Ptch1$^{+/-}$ skin harboring residual microscopic BCCs revealed pronounced accumulation of CD4+ Tregs within the skin, whereas Treg levels in the draining lymph nodes were unchanged. Further analysis identified two distinct Treg subclusters enriched for activation markers including ICOS, CD39, and KLRG1, with substantial increases in ICOS+FOXP3+ cells in vismodegib-treated Ptch1$^{+/-}$/SKH-1 mice with residual BCCs. These findings highlight specific immune correlates that support the persistence of residual BCCs, pointing to Treg-mediated immunosuppression as a potential mechanism of HHi resistance. Our results suggest that combinatorial targeting of Tregs and the Hh pathway may enhance anti-tumor immunity, reduce residual disease, and enhance therapeutic GS efficacy.

LB1219

Upper lip invasion in primary buccal mucosa squamous cell carcinoma: A case report

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Introduction: Squamous cell carcinoma (SCC) is the most prevalent form of cancer affecting the oral cavity. Most cases arise in the tongue, with other rare sources being the lip and buccal mucosa. Buccal mucosa SCC commonly spreads to adjacent oral subsites, including the Stensen duct, but less frequently involves the upper lip. This case presents a treatment refractory case of primary buccal mucosa squamous cell carcinoma with direct extension to the upper lip that resulted in a highly expanding tumor burden and ultimately, metastasis. Case Presentation: A 51-year-old-woman with a past dermatological history of hidrotic ectodermal dysplasia and psoriasis first noticed a small, 0.5 cm lesion in her right buccal mucosa, that within a three month period grew into her right oral commissure and upper lip. The lip lesion was small yet exophytic, firm and painful. A series of two biopsies were performed which confirmed the diagnosis of p53 positive squamous cell carcinoma of the buccal mucosa with direct extension to the upper lip. The lesion was initially treated with focal tumor resection and a two month course of radiotherapy until remission was reached. Following three years after remission, the squamous cell carcinoma reappeared in the upper lip, having already metastasized to adjacent lymph nodes and lung tissue. The patient was deemed a nonsurgical candidate and platinum-based chemoradiotherapy regimen was then pursued as management. The patient experienced severe chemotherapy induced dermatological complications including rashes, xerosis and psoriatic flares, after which therapy was halted. Over a course of three months without active chemoradiation, the lesion grew exponentially, becoming ulcerated, hypervascular and, ultimately, necrotic. Patient prognosis was deemed poor and palliative measures were pursued. Conclusion: Aggressive oral cavity squamous cell carcinoma prognosis is largely based on early tumor recognition, extensive surgical intervention and combined cancer therapy. In addition, immunotherapy with immune checkpoint inhibitors are viable options in the management of treatment-resistant SCC.

LB1220

The role of the microbiome in topical treatment efficacy for non-melanoma skin cancer in a UV-induced non-melanoma skin cancer mouse model

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Non-melanoma skin cancer (NMSC) lesions are effectively treated with surgical therapies; however, patients with multiple lesions benefit from topical therapies that provide a field treatment effect. Topical therapies, such as 5-fluorouracil (5-FU) and imiquimod (IMQ), have significant inflammatory side effects that result in poor treatment adherence and suboptimal clinical outcomes. We showed topical application of N-phosphonacetyl-L-aspartate (PALA) reduced tumor numbers and area of tumor tissue, without inducing inflammation in a clinically relevant, murine UVB-induced NMSC model. Head-to-head comparisons of PALA to 5-FU and IMQ in this model demonstrate that local skin inflammation is not required for an effective anti-tumor response. Skin microbiome profiling showed distinct treatment-dependent shifts in microbiome diversity and composition. Of note was a substantial increase in the Cutibacterium: Staphylococcus genus ratio and large decreases in the prevalence of pro-inflammatory genera uniquely on PALA treated mice indicating a less inflammatory local microbiome. Reduction of the pro-inflammatory microbiome of IMQ treated mice by topical antiseptic treatment improved therapeutic outcomes, while perturbation of the anti-inflammatory microbiome of PALA treated mice resulted in larger tumors. In vitro antimicrobial testing demonstrated that 5-FU ointment was toxic to many skin commensals, while IMQ and PALA topicals had minimal direct antimicrobial activity. These results indicate that topical NMSC therapies modify the skin microbiome by different mechanisms and microbial modulation impacts therapeutic efficacy. This study provides a foundation for future research into the cross-talk of immune responses and the skin microbiome to improve treatment of skin cancers.

LB1221

Subtype of macrophages and its clinical significance in Riehl's melanosis

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The phagocytosis of melanin granules by macrophages and the subsequent formation of melanophages are key histopathological features of Riehl's melanosis. However, the role and underlying mechanisms of macrophages and phagocytes in disease progression remain unclear. To elucidate this, we performed single-cell RNA sequencing to characterize the immune landscape of Riehl's melanosis and analyze the phenotypic and functional diversity of macrophage and melanophage subtypes. Our analysis identified seven macrophage subpopulations, among which MFI-FOLR2+ and MFI-CCR7+ macrophages may actively interact with melanocytes and T/NK cells. Histological examination using H&E and immunofluorescence staining of skin lesion samples revealed that infiltrating macrophages predominantly localize in the dermal papillae, sites of melanin deposition, and around the superficial capillary network. These macrophages exhibit a CD68+ CD86− CD206+ phenotype. Functionally, M1-conditioned medium inhibited melanin synthesis in melanocytes, whereas M2-conditioned medium promoted it. Furthermore, macrophages were more likely to undergo classical and alternative activation in a high LA/ALA ratio environment, whereas a low LA/ALA ratio favored a resting state. In conclusion, macrophage infiltration may serve as an auxiliary indicator for assessing pigmentation severity and prognosis in patients with Riehl's melanosis.

LB1222

Potential of FAK/PYK2 inhibition in overcoming immune checkpoint inhibitor resistance

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Immune checkpoint inhibitors (ICIs) have transformed cancer therapy, yet many patients ultimately develop acquired resistance. IFNγ-mediated induction of PD-L1 and STAT1 has been implicated in this resistance, but the underlying signaling pathways remain incompletely understood. Phosphoproteomic analyses of IFNγ-stimulated melanoma cells provided significant enrichment of phosphorylation events associated with the cytoskeleton and cell adhesion—processes in which FAK and PYK2 play central regulatory roles. To determine whether these kinases contribute to IFNγ-driven responses, we stimulated cells with IFNγ in the presence of the FAK/PYK2 inhibitor VS6063. Under these conditions, IFNγ-induced PD-L1 and STAT1 expression was suppressed by more than 90%, pinpointing FAK as a central regulator of IFNγ-driven signaling. In 470 TCGA melanoma samples, gene set enrichment analysis comparing samples with high and low FAK expression revealed significant enrichment of ICI resistance-related terms in the high FAK expression group. Furthermore, a re-analysis of existing RNA sequencing data from 56 human melanoma specimens showed that FAK levels were significantly elevated in ICI non-responders compared to responders ($p<0.05$). In co-culture assays with human $CD8^+$ T cells, FAK/PYK2 inhibition significantly enhanced tumor cell killing ($n=4$, $p<0.05$). Network analysis identified paxillin (PXN) as a key IFNγ-responsive signaling hub, suggesting that PXN-related pathways further support immune suppression. These findings demonstrate that dual blockade of FAK and PYK2 effectively suppresses IFNγ-driven PD-L1 and STAT1 expression, offering a promising strategy to overcome ICI resistance in melanoma. Importantly, similar results were observed in breast cancer and glioblastoma models, suggesting that this approach could have broader applications in cancers with immune checkpoint resistance.

LB1223

Development of statin-loaded microneedle patch for anti-tumor immune modulation in melanoma

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Introduction: Statins, established cholesterol-lowering drugs, are being investigated as anticancer agents and immune modulators. Cholesterol modulates several cellular functions e.g regulation of programmed death-ligand 1 (PD-L1) expression, checkpoint used by many cancers to evade immune surveillance. The goal of the study is to identify the dose of Simvastatin to modulate the function of macrophages and melanoma cells and to load in microneedle patches (MNPs) to target melanoma. Method: Mouse melanoma (B16F10, YUMM3.3) and macrophage cell lines were used for the study. PD-L1 expressions were assessed by flow cytometry and western blot techniques. Silicon molds (ST-07, array 8 × 8, height = 700 µm, base = 200 µm, pitch = 500 µm, shape = pyramid) were used to prepare MNPs. Statin-loaded MNPs were prepared by mixing simvastatin (20 mg/ml) with polymeric solution of chitosan (CS), polyvinyl alcohol (PVA), and polyvinyl pyrrolidone (PVP) K30. Patches were characterized for chemical interactions (FTIR), tensile strength, elongation (%), and penetration capabilities using confocal microscopy. Loading efficiency was evaluated via HPLC. Result: Statins treatment significantly reduced PD-L1 expression in melanoma and macrophage cell lines dose-dependently. Macrophages showed higher sensitivity to statin-induced cell death and immune modulation. FTIR analysis demonstrated compatibility between statins and polymers with no direct interactions. MNPs exhibited optimal properties for transdermal delivery, including excellent tensile strength (103.021±2.06 mPa), elongation (42±1.414%), and penetration depth (430±46.05 µm). Conclusions: MNPs represent a promising platform for localized statin delivery as an immune modulator for melanoma. This approach circumvents rapid liver metabolism, minimizes systemic side effects, and enables sustained, controlled drug release. Additional in-vitro and mouse studies are ongoing to optimize statin-loaded MNPs as an adjuvant for melanoma immunotherapy.

LB1224

Single-cell analysis deciphered a pivotal role of SPP1-mediated interactions contributing to lymph node metastasis in acral melanoma

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Background: Acral melanoma (AM), a highly aggressive cutaneous malignancy with frequent lymph node metastasis, remains poorly understood in terms of myeloid-driven immunosuppression and metastatic niche formation. Objectives: To delineate myeloid cell heterogeneity and SPP1-mediated interactions driving lymph node metastasis in AM. Methods: We performed single-cell RNA sequencing from tumor and adjacent normal tissues of 13 treatment-naïve AM patients (3 with lymph node metastasis, 6 without and 4 from adjacent normal tissues). Prognostic and experimental validation utilized an independent cohort of 51 AM patients data. Results: Through an unbiased analysis of 106 pathways, myeloid-derived SPP1 signaling emerged as predominant driver in LN^+. SPP1-high myeloid subcluster was more abundant in LN^+ and displayed elevated expression of FTL and CCL2. This subcluster promoted formation of self-sustaining niches and directed interactions with melanoma cells through SPP1-CD44 axis, maintaining $DPEP3^+$/$S100A8^+$ melanoma subsets. Moreover, comparative cellchat mapping highlighted SPP1 signaling shifting from melanocyte-driven interactions in LN^- to myeloid-dominated networks in LN^+, engaging five distinct cellular subsets. Clinically, the SPP1 axis was associated with $CD8^+$ $LAG3^+$ T cell exhaustion and a significant reduction of $CD8^+$ T cell infiltration in LN^+. Spatial analysis further revealed mutually exclusive distribution patterns of $SPP1^+$ myeloid cells and $CD8^+$ T lymphocytes. In addition, high SPP1 expression independently predicted poorer 5-year survival. Conclusions: Our study uncovers an SPP1-driven immunosuppressive axis in AM metastasis, characterized by myeloid-melanoma cell cooperativity and $CD8^+$ T cell dysfunction. Targeting SPP1 signaling may restore anti-tumor immunity and synergize with existing immunotherapies, providing a rationale for $SPP1^+$myeloid-directed therapeutic strategies in advanced AM.

LB1225

Utility of prame ihc staining in the clinical management of pigmented lesions of varying severity

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A survey study was conducted with the objective of assessing the utility of PRAME IHC staining in the clinical management of pigmented lesions of varying levels of severity. Not all melanomas are PRAME positive and benign nevi may also demonstrate PRAME expression. PRAME staining poses significant patient costs, thus determining its clinical utility is warranted. An Epic SlicerDicer search was used to identify all pigmented lesion biopsy specimens with PRAME IHC staining between January 1st, 2023 and December 31st, 2023. Pigmented lesion biopsies with PRAME staining were divided into five categories: 1) Invasive melanoma, 2) Melanoma in situ, severely dysplastic nevi 3) Moderately dysplastic nevi 4) Mildly dysplastic nevi 5) Benign nevi. Three cases were chosen from each category. Twelve clinicians provided their clinical management strategy for each case in three passes. The first pass included non-PRAME IHC and H&E stain interpretation and omitted both PRAME staining results and final histopathologic diagnosis, the second pass included PRAME staining results, and the third pass revealed final histopathologic diagnosis. For all lesions, a smaller percent change in excision rate was seen following the addition of PRAME staining results versus the addition of final histopathologic diagnosis. The greatest difference in excision rate percent change was seen in cases describing severely dysplastic nevi (12.5% change following PRAME staining; 67% change following final diagnosis). Interestingly, the addition of PRAME staining and final histopathologic diagnosis in cases describing melanoma did not alter clinical management (100% excision). Our results highlight the limitations of IHC studies interpreted in isolation for benign and dysplastic nevi and suggest that PRAME staining may not offer as much additional information in the clinical management of melanomas. Limitations include sample size and varied physician comfort in making clinical management decisions without final histopathologic diagnosis.

LB1226

Defining the clinical characteristics of BRAF V600K melanoma mutations

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Background: The BRAF V600K mutation is the second most common mutation in cutaneous melanoma, after V600E, and as a result, less is known about its defining characteristics. While both mutations lead to constitutive activation of the MAPK/ERK pathway, their clinical implications, including patient demographics, tumor characteristics, and treatment responses, differ.[1] Understanding these differences is crucial for optimizing patient management and therapeutic strategies. Methods: A set of 72 patients with V600K mutations and 46 patients with V600E were obtained and stratified by mutation type, age, gender, and stage of disease, with a particular emphasis on treatment modalities and outcomes. This study received institutional review board approval. Results: V600K mutations were more frequently observed in an older population than in V600E (66 vs. 57, p = 0.001). They also presented with advanced melanoma, with V600K patients more often presenting with metastasis compared to V600E (31% vs. 9%, p = 0.03). These patients required more aggressive treatment involving multiple agents with differing mechanisms of action, seen in 25% of cases compared to 6% in V600E (p = 0.03). Patients with V600K mutations were also often seen in a male population, more often found on the head and neck as compared to the trunk in V600E and often with a higher staging, although this data was not significantly significant. Extensive sun exposure was seen in both mutations. Discussion: V600K mutations are associated with an older, male population and advanced melanoma stages compared to V600E. This mutation may necessitate more complex treatment regimens potentially due alternative pathways taken by the mutation.[1] Our findings were limited by sample size and future directions include further histological comparison as well as the comparison of V600K mutations and other codon changes such as V600M, V600R, and V600G. References: 1. Nepote A, Avallone G, Ribero S, et al. Current Controversies and Challenges on BRAF V600K-Mutant Cutaneous Melanoma. J Clin Med. 2022;11(3):828.

LB1227

Synergizing ASOs unveil MAPK pathway associated vulnerabilities in drug resistant melanoma

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Synergistic drug combinations enhance therapeutic efficacy and reduce side effects, a key goal in cancer research. Dual treatments targeting the MAPK pathway are critical in melanoma therapy, often combining MEK (MEKi) and BRAF inhibition. However, resistance mechanisms frequently limit their efficacy. RNA-targeted therapies using Antisense Oligonucleotides (ASOs) effectively inhibit MAPK-dependent melanoma growth, but little is known about dual ASO treatments in treatment-naïve or drug-resistant MAPK-driven melanoma. This study explored dual ASO treatments targeting NRAS mRNA, T-RECS lncRNA, and MALAT1 lncRNA across melanoma cell lines with MAPK-hyperactivating mutations and mechanisms of MEKi-resistance, simulating various clinical conditions. In treatment-naïve and resistant cells not exposed to chronic MEK inhibition, combinations showed antagonistic or additive effects. However, in MEKi-resistant cells, dual ASO therapy combined with MEKi exposure produced synergistic responses. To understand these effects, we analyzed MAPK-pathway-associated kinase expression, and transcriptional interdependencies of NRAS, T-RECS, and MALAT1. MEKi-resistance profoundly altered MAPK-signaling activity and the transcriptional dynamics of NRAS, T-RECS, and MALAT1. These findings reveal how resistance mechanisms reshape oncogenic lncRNA expression and identify patient groups who may benefit from dual ASO therapies targeting MAPK-pathway-associated RNA.

LB1228

***Ex vivo* and *in vitro* analysis of epidermal progenitors using flow cytometry**

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In this study, we use flow cytometric analysis to characterize the expression patterns of CD90, a proposed marker of epidermal stem cells. We find that CD90+ cells in human epidermal samples are evenly split between keratinocyte and melanocyte lineages, suggesting this is a marker for both types of progenitors. Similarly, both melanocytes and keratinocytes dividing in culture also express CD90. While keratinocytes can maintain a stem-like phenotype in vitro, we find that all melanocytes begin to express the differentiation marker CD117 after the first passage. Growing melanocytes on collagen, in the presence of melanogenesis inhibitors, or co-cultured with keratinocytes, can all increase CD90 expression, yet none of these conditions are able to prevent the universal differentiation that occurs. Further, we find that all pre-passaged melanocytes have intermediate levels of both CD117 and melanosomes, but after the first passage a second population emerges with high expression of both. These CD117-high cells are significantly less likely to co-express CD90, highlighting loss of proliferative capacity. Though cells double positive for both CD90 and CD117 appear to drive population growth in vitro, we find these cells to be extremely rare ex vivo, suggesting they more likely represent a transitional state in the skin, rather than a proliferative pool as seen in culture. Lastly, we find that aging increases the percentage of CD90 positive epidermal cells, though we suspect this to be due to age-related thinning of the upper epidermis, as other basal cell markers are also overrepresented with age.

LB1229

Understanding pregnancy's pigmentary puzzle: The role of demarcation lines

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Pigmentary Demarcation Lines (PDL) are natural, distinct borders between areas of differing skin pigmentation that may become more visible during pregnancy due to hormonal changes affecting melanin distribution. Recent classification of PDL includes eight types (A-H) and is commonly linked to inheritance and cutaneous mosaicism. Distinguishing PDLs from pregnancy-related pigmentation (e.g., melasma, linea nigra) is crucial for accurate diagnosis and avoiding unnecessary invasive tests, especially in patients with skin of color, where cosmetic concerns are more pronounced. We present a case involving a dermatologist who experienced pigmentary changes, likely attributable to PDL. A 41-year-old primigravida of South Asian heritage developed asymptomatic well-demarcated pigmentation on the posterior aspect of lower limbs bilaterally during her second trimester. These symmetrical linear changes had lighter skin medially, transitioning to darker pigmentation laterally, with no changes on the anterior aspect. The obstetric team initially suspected this was an underlying deep vein thrombosis (DVT). However, the patient, a dermatologist by profession, was certain of the clinical diagnosis of PDL and therefore further investigations were not pursued. Where the pigmentation gradually faded over two years, it is likely that these demarcated lines are consistent with type B PDL, which often develops in the third trimester of pregnancy and regresses spontaneously post-delivery. This case report emphasizes the importance of recognizing PDL as a key differential for pigmentary changes in pregnancy, characterized by abrupt, well-demarcated lines, typically on the lower limbs. Prompt recognition of this self-limiting condition prevents unnecessary tests and treatments. Counselling patients on the benign course of these changes helps ease anxiety and address psychosocial and cosmetic concerns, especially in skin of color patients.

LB1230

Macrophage dysregulation plays a pathogenic role in melanocyte death in mouse models of vitiligo and canities

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Vitiligo and canities are caused by melanocyte death. The pathogenesis of these conditions is not clearly understood at the present. Epidemiological studies revealed a significant correlation between these two diseases, suggesting they share an overlapping pathogenic mechanism. The objective of this study is to investigate the role of innate immune cells, especially macrophages in the pathogenesis of vitiligo and canities. We employed transcriptome sequencing-based cellular deconvolution to profile the immune cells in the skin microenvironment of vitiligo patients, revealing enrichment of M1 ($p=0.009$) and depletion of M2 macrophages ($p=0.044$) in vitiligo skin. These changes were confirmed by flow cytometry. In C57BL/6J mice, maresin 1, the main functional mediator and autocrine polarization factor of M2 macrophages, not only augmented skin-resident M2 macrophages but also decreased melanocyte death after vitiligo induction using TRP2-immunization ($p=0.0086$). Reduced M2 macrophage function (reduced maresin 1 levels) was also observed in mice with canities ($p=0.26$). In addition, treatment with exogenous maresin 1 abolished spontaneous development of canities in mice ($P=0.0125$). Further, in vitro maresin 1 treatment suppressed oxidative stress-induced death of cultured melanocytes ($p<0.01$). In conclusion, dysregulated macrophage function contributes to melanocyte death in vitiligo and canities. Thus, treatment with maresin 1 or other M2 agonists, may be effective for the treatment and prevention of these depigmentation diseases.

LB1231

Transcriptional network regulating meibomian gland resident stem cells during morphogenesis and homeostasis

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The Meibomian Glands (MGs) are located in the eyelids and secrete meibum, an oily substance that prevents the tear film from evaporation. MGs are holocrine glands, meaning their cells –meibocytes – release meibum upon cell rupture. Thus, these cells must be replenished throughout life. Dysfunction of MGs results in one of the most common eye conditions, Dry Eye Disease, highlighting the importance of elucidating the molecular mechanisms underlying MG morphogenesis and homeostasis. In our studies, we found that loss of Krox20 led to a significant reduction of MGs, whereas its overexpression resulted in enlarged MGs, indicating the critical role of Krox20 in MG resident stem cells. Using Krox20 lineage tracing and ablation studies, we investigated the processes that govern lineage commitment during MG morphogenesis and homeostasis. We found that Krox20 marks MG stem/progenitor cell pools, and regulates cellular contributions to the glands. We also found that Notch1 signaling is regulated by Krox20 and that ablation of the Notch1 gene in Krox20-expressing cells leads to gland atrophy, while Notch1 overexpression partially rescues MG atrophy caused by the loss of Krox20. Together, these results reveal a critical interaction between Krox20 and the Notch1 pathway in MG resident stem cells. Activation of Notch1 signaling offers a potential novel approach to preventing and treating dry eye disease caused by the depletion of the MG stem cell pool that happens with normal aging and in some disease states.

LB1232

Presence of large progenitor cell populations in pz-cel autologous gene-corrected epidermal sheets

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Background: Recessive Dystrophic Epidermolysis Bullosa (RDEB) is a rare genetic disorder caused by biallelic mutations in the COL7A1 gene, resulting in deficient or absent collagen VII (Col7) protein, leading to fragile skin and chronic wound formation under mechanical stress. Pz-cel (prademagene zamikeracel) was developed to address large, chronic wounds in RDEB patients. Epidermal cells isolated from patient skin biopsies are expanded ex vivo and genetically corrected by retroviral vector transduction to restore Col7 expression. The corrected cells are cultured and differentiated into epidermal sheets. A long-term follow-up study from a Phase 1/2a clinical trial demonstrated sustained wound closure for some wounds up to eight years. Additionally, a two-year follow-up on Col7 expression at the grafted sites revealed detectable Col7 in treated areas at 24 months. Methods: Pz-cel sheets dissociated and analyzed by flow cytometry. Cells were assessed using antibodies against key markers associated with progenitor cell populations, including K14, integrin α6, CD71, CD29 and K15. Results: Analysis confirmed that the cell sheets are primarily composed of basal keratinocytes (K14+:82%± 19% SD, N=10), which serve in vivo as a reservoir of epidermal stem cells and progenitors. Integrin α6bright expression was observed at a mean of 75.5% ± 22% SD, while K15 expression was detected at a mean of 32% ± 25% SD (N=6) in the epidermal sheets. Additionally, analysis showed 85.9% ± 15% SD of the cells were CD29+, and 88% ± 13% SD exhibited an CD28+/CD71dim/- phenotype. The Integrinα 6bright/CD29+/CD71dim/- subpopulation was estimated at 67% ± 21% SD. Conclusions: These results confirm the presence of a significant population of progenitor cells within the graft. The large proportion of these cells in the drug product may increase the likelihood of wound site repopulation by long-lasting, genetically corrected cells, consistent with the detection of Col7 at grafted sites at 24 months.

LB1233

Closing old wounds- a systematic review of the role of vitamin c in procedures and biopsies

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Vitamin C, also known as ascorbic acid, has been found to be involved in wound healing pathogenesis. From the inflammatory phase by acting as a free radical scavenger to reduce oxidative stress, to the proliferative phase in which the synthesis, maturation and secretion of collagen takes place, to the maturation phase during which collagen production occurs throughout, vitamin C's role in wound healing is inextricably linked to improved wound recovery [1]. Despite the abundance of well-documented evidence supporting vitamin C use in procedures and surgeries, its use in dermatology is mainly reserved for cosmetic purposes [2]. In dermatological and surgical specialties, vitamin C is not typically recommended as a post-procedural agent for improved recovery[3], even though studies suggest that scar appearance and wound healing would benefit from vitamin C: an online search on three academic databases within Google Scholar, PubMed and Cochrane was conducted using the search terms "Vitamin C", "Wound healing", "Surgery", "Post-operative" "Dermatology", "Dermatology biopsies", and "Melanoma" and a combination of these words to be able to capture the clinical and procedural landscape in which vitamin C is utilized, and where there is room for improvement in its utility. A total of 93 articles were initially screened, with the exclusion of 42 works that were out of scope and 4 articles that were not in English, leaving a total of 47 articles. Of the included articles, 40% involved vitamin c in cosmetic procedures, 25.5% in outpatient surgical procedures, 13% in skin care regimens, 8.5% in inpatient surgical procedures and 13% in wound healing. No articles discussed vitamin c use in biopsies or diagnostic tests within dermatology. The results suggest a significant opportunity for vitamin c to be employed in different practices within dermatology and healthcare. Consequently, the favorable properties of vitamin c in wound healing and in improved procedural outcomes are not being benefited from as a result of under utility and potential gaps in clinical practice.

LB1234

Suppression of de-novo lipogenesis via Wnt-Dpp4 activation: A critical factor in the onset and recovery of fibrotic lipodystrophy

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Skin fibrosis is characterized by lipodystrophy in the dermal white adipose tissue (DWAT), followed by accumulation of extracellular matrix (ECM) and a hallmark of diseases such as systemic sclerosis and keloids. It impacts 1 in 5,400 individuals worldwide annually, yet there are no effective treatments to prevent or reverse skin fibrosis. While many profibrotic factors and processes are implicated in dermal ECM expansion, the mechanisms underlying lipodystrophy in fibrotic DWAT remain unclear. Our inducible-reversible model of Wnt activation in fibro-adipoprogenitors of the skin showed that DWAT lipodystrophy was dependent on sustained activation of Wnt signaling and its downstream mediator dipeptidyl peptidase 4 (DPP4). Here, we test the hypothesis that the Wnt/DPP4 axis induces the early downregulation of de novo-lipogenesis (DNL) axis enzymes leading to fibrotic lipodystrophy in the skin. RNA-seq profiling of mature mouse dermal adipocytes in vivo revealed that all the key enzymes in the de novo lipogenesis axis were downregulated by two and also five days of Wnt activation in vivo. We showed that the protein expression of FASN, a key DNL enzyme, was highly dependent on Wnt activation in mature dermal adipocytes in vivo and in vitro. Wnt activation in the DPP4-/- mouse background led to dramatic rescue of FASN expression in the protected dermal adipocytes. Withdrawal from Wnt activation led to the recovery of lipodystrophic adipocytes, which was attenuated by a pharmacological blockade of FASN in vivo. Thus, WNT/DPP4 mediated downregulation of the DNL axis contributes to the onset and recovery from fibrotic lipodystrophy, opening new avenues for therapeutic targets in skin fibrosis.

LB1235

Comparison of healing characteristics between dehydrated human amnion/chorion membrane and acellular dermal matrix following mohs micrographic surgical excision for cutaneous malignancies

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This study presents the comparison of healing times following Mohs surgery with the adjunct utilization of dehydrated human amnion/chorion membranes (Epifix) and acellular dermal matrices (ACell-Cytal). This study evaluated a cohort of 77 patients who underwent Mohs surgery. 46 patients received Epifix treatments following surgery and 31 received ACell-Cytal treatments. A retrospective chart review from September 2017 to September 2023 of patient characteristics included: age, race, smoking history, body mass index, wound location, wound size, wound depth, healing time, number of treatments, graft usage, and graft size. Of the 77 patients, 36 were women and 41 were men. The mean age was 74 years. The mean wound size was 2.67cm^2. Patients had a mean of 2.26 treatments in the Epifix cohort and 1.42 treatments in the ACell-Cytal cohort. Both cohorts had a graft usage rate of 74%. The mean healing time from the date of Mohs surgery was 42 days for the Epifix cohort and 31 days for the ACell-Cytal cohort. Statistical analysis using Fisher's exact test comparing the cohorts showed significantly shorter healing times ($p < 0.05$) and significantly less treatments used ($p < 0.001$) in the ACell-Cytal cohort, and no significant differences in wound size ($p = 0.46$). We found patients treated with ACell-Cytal following Mohs surgery had significantly shorter healing times compared to treatment with Epifix. The ACell-Cytal group required significantly less treatments with no significant differences in mean wound size between the two cohorts. Future studies will include larger cohorts controlled for anatomic wound site and depth, comparison of aesthetic outcomes, as well as a cost analysis between the two biological agents as well as secondary healing.

LB1236

Investigating the role of endothelial Rac1 towards skin vascular maturation and maintenance via 4D imaging of live mice

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The coordinated morphogenesis of developing vasculature informs the organotypic architecture of specialized vascular beds. Utilizing our longitudinal imaging platform, we have recently delineated the principles that orchestrate vascular maturation and maintenance in the skin of live mice. To understand the molecular mechanisms driving these processes, we probed the role of the cytoskeletal regulator, Rac1, towards the remodeling of skin vessels. While it has been shown that endothelial cell (EC) Rac1 regulates developmental angiogenesis, little is known of the impact of Rac1 loss upon existing vessels and its long-term effects in vivo. We found that neonatal Rac1 mutants displayed angiogenic defects but surprisingly, had little effect upon vessel regression dynamics. Interestingly, tracking Rac1 mutants into adulthood revealed varied phenotypes across vessel subtypes. Mutants displayed vessel fraying in capillaries, leading to network rarefaction, while in venules, exhibited the development of severe malformations. In contrast, Rac1 mutant arterioles did not display any overt morphological changes. Utilizing a multispectral reporter of EC morphology, we found that both Rac1 mutant capillaries and venules possess abnormally small and rounded ECs. Conversely, arteriole EC morphology was unaffected, leading to ongoing investigation of whether differential responses to shear stress could account for the protection of arteriole ECs. Lastly, to assess the functional consequences of EC Rac1 loss, we assessed the regenerative capacity of the skin epidermis and surrounding hair follicles. Surprisingly, epidermal architecture was unaffected by the severe vascular defects of mutants. Intriguingly, mutants displayed hair growth defects due to a delayed entry into the follicle growth phase, revealing a divergent regulation of skin appendages by blood vessel remodeling. Our work reveals previously unknown roles for EC Rac1 towards the long term maintenance of vascular and organ homeostasis.

LB1237

Quantifying exosomes and characterizing their tetraspanin expression in platelet-poor plasma, platelet-rich plasma and following platelet activation

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Exosomes are extracellular vesicles secreted by most cells in our body following an endosomal pathway. Exosomes measure 30-150 nm in diameter and contain large number of GFs, cytokines, chemokines, lipids, metabolites and RNA. Exosomes are heterogenous based on the cellular source, quantity, size and molecular content. There is now a great focus to develop exosome-based therapy for regenerative medicine. We quantified exosomes and characterized their tetraspanin expression in clinical samples of platelet-rich plasma (PRP) used to treat patients with hair loss. We similarly analyzed exosomes in PRP following platelet activation (APRP) and in platelet-poor plasma (PPP). We hypothesized that PRP is enriched in platelet-derived exosomes while PPP, a by-product of autologous PRP preparation that is discarded, contains exosomes derived from blood lymphocytes. We selected tetraspanins, CD9, CD41, CD63 and CD81, to detect and quantify exosomes in PPP, PRP and APRP. Exocarta, an online database of exosomal contents curated based on their cellular source, highlighted CD9 and CD63 as markers on exosomes derived from both platelets and lymphocytes while CD81 as being specific to lymphocyte-derived exosomes. CD41 is a platelet maker and therefore is specific to platelet-derived exosomes. We detected differential tetraspanin expression on exosomes with a majority expressing CD41 followed by CD81 and CD63. The exosomes with CD9 expression were the fewest. There was no difference in the quantity of tetraspanin-positive exosomes between PPP, PRP and APRP, which ranged between 10^{11}-$2x10^{12}$ per ml, suggesting a lack of segregation of exosomes based on cellular source in PPP and PRP samples. There is also an increase in median size of CD9 and CD41 positive exosomes following platelet activation. We show that PRP and PPP contain exosomes derived from platelets and lymphocytes. The diversity among plasma-derived exosomes suggests their versatility and potential for varied clinical applications.

LB1238

An *ex vivo* co-culture model of murine skin and lymph nodes to represent psoriatic inflammation and identify novel treatments

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Psoriasis is driven by the IL23-IL17 pathway and involves an amalgamation of cells, such as Th17 cells, keratinocytes, and dendritic cells. In vivo mouse models, such as direct IL23 injection and minicircle DNA are effective tools for translational research; however, the development of ex vivo/in vitro models would enable more focal studies of immune mechanisms involved in Th17 cell activation in the IL23-IL17 pathway. Whole ears are removed from C57BL/6 mice, gently split into dorsal and ventral layers, and immersed in culture medium in a 24-well plate with the inner side facedown, comprising the resident skin cells of the co-culture. Cervical lymph nodes are collected from the same mouse for single-cell suspension and aliquoted to make up the immune cells of the co-culture. Either IL23, TNF, or both are then added. After 4-24 hours incubation, IL17A is measured by ELISA. RT-PCR and flow cytometry are performed for the skin and lymph node samples, respectively, to determine inflammatory markers. Psoriasis initiation is linked to dendritic cells stimulating T cells, which migrate to the epidermis and drive lesion growth. Our co-culture model, simulating this in vivo network, showed high IL17a expression upon IL23 stimulation (50ng/ml) and over 450-fold increase in IL17a mRNA in the skin. In individual cultures, ear skin showed a 60-fold increase in IL17a, while lymph node cultures only showed a 2.5-fold increase. Other Th17-related genes, IL17f and IL22, displayed similar responses, with IL22 absent in lymph node cultures. IL17a mRNA changes began as early as 4 hours post-IL23 stimulation. TNF-α alone did not significantly affect IL17 production, but a synergistic increase was seen with IL23 and TNF-α combined. NBA, a TRPM4 inhibitor, reduced IL17 levels in the presence of IL23 and TNF-α ($p<0.001$). The ex vivo co-culture model of murine skin and lymph node tissue under cytokine stimulation offers a controlled, reproducible platform for studying psoriasis immunopathology and testing therapeutic interventions.

LB1239

Proteomic analysis of serum from brepocitinib-treated cicatricial alopecia patients reveals downregulation of key biomarkers of inflammation and fibrosis

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Cicatricial alopecias (CA) are progressive scarring hair loss disorders that significantly impact patient quality of life and lack effective treatments. Given the putative role of Th1/JAK activation in CA pathogenesis, brepocitinib, a TYK2/JAK1 inhibitor, was recently evaluated in a Phase 2A, double-blind, placebo-controlled trial (NCT05076006). Patients with lichen planopilaris (LPP, n=16), frontal fibrosing alopecia (FFA, n=9), and central centrifugal cicatricial alopecia (CCCA, n=24) were randomized 3:1 to receive 45 mg brepocitinib or placebo daily for 24wks, followed by an additional 24wks of open-label brepocitinib. Serum samples collected at baseline, wk24, and wk48 were analyzed using the inflammation, cardiovascular, and neurology panel of Olink Proteomics Analysis. Differentially expressed proteins were identified based on fold changes ($|FCH|>1.2$, $p<0.05$). Proteomic analysis of serum from FFA/LPP and/or CCCA patients treated with brepocitinib revealed significant downregulation of key biomarkers associated with Th1 (CXCL9/CXCL10/CXCL11/IL2RA), T-cell activation (TNFRSF9/XCL1/CD8A/CCL19), and fibrosis (SPP1/COL1A1) at wk24, with sustained reductions through wk48 ($p<0.001$). No significant downregulation of the proteome was observed in the placebo at wk24. Spearman correlation analysis at wk48 demonstrated positive associations between clinical severity scores (FFASI/LPPAI/CHLG) and multiple immune-related markers, including Th1 (IL8/CCL4), Th2 (CCL17/CCL13), and Th17 (PI3/CXCL1) and negative correlation with lipid biomarkers (AMBP/CTSD) ($|r|>0.5$, $p<0.05$ for all). Brepocitinib was well tolerated and consistent with safety reported in prior studies. Overall, the reduction of inflammatory and fibrotic serum biomarker expression paralleled clinical improvement in brepocitinib-treated CA patients, further supporting its role in targeting key drivers of CA disease pathogenesis.

LB1240

Human skin-on-chip atopic dermatitis model for biomarker identification and therapeutic evaluation

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Atopic dermatitis (AD) is a complex inflammatory skin disease affecting a large subset of the population (7.3% US adults). Current therapies have limited efficacy, highlighting the need for innovative human models, such as microfluidic devices, to uncover new therapeutic approaches and better understand the disease. In this study, skin biopsies from patient-matched lesional and non-lesional skin obtained from patients diagnosed with mild to moderate to severe AD were cultured in microfluidic devices. Subsequently, conditioned media was collected to identify AD-specific inflammatory biomarkers through secretome analysis. Additional AD hallmarks were evaluated in vivo through skin health assessments such as skin hydration, pH, and trans-epidermal water loss (TEWL), as well as in vitro through histological and immunofluorescence analysis to assess epidermal morphology and local inflammation. This prototype skin-on-chip model maintained its viability for up to 7 days while preserving the epidermal structure. Patient-matched lesional and non-lesional skin fragments showed immune infiltration in lesional skin, consistent with AD. Analysis of conditioned media at day 3 of culture revealed differential secretion of local inflammatory biomarkers, such as IL33, TNF-α, and TSLP, associated with AD and atopy-related pathways. These biomarkers were then correlated with systemic secretome from whole blood to distinguish local and systemic AD inflammatory signature. In conclusion, this human skin-on-chip approach offers new insights into the AD pathogenesis. Beyond identifying biomarkers, we envision using this device for targeting AD therapies and deeper understanding of the disease.

LB1241

Immune dysregulation and CCL3-induced neuronal sensitization underlie chronic pruritus of unknown origin

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Chronic pruritus of unknown origin (CPUO) is a debilitating condition that significantly affects quality of life, yet the underlying mechanisms remain poorly understood. Single-cell sequencing and Luminex multiplex protein analysis of patient samples were used to unravel the immune landscape of CPUO, with subsequent mechanistic validation by mouse itch behavioral assays, immunofluorescence, and calcium imaging. We showed that CPUO patients (n = 35) manifested a wide age range without notable elevation in IgE or eosinophil levels. Furthermore, single-cell transcriptional analysis revealed distinct immune cell function and interactions in CPUO compared to controls. Circulating classical monocytes were significantly reduced in CPUO patients but exhibited enhanced tissue migration, chemotaxis, and antigen presentation capabilities. Natural killer (NK) and T cells displayed increased proportions and prominent senescence signatures compared to controls, with NK cells showing mitochondrial dysfunction and enhanced stress responses. Analysis of the T cells highlighted a notable shift towards T helper 2 predominance and reduced regulatory T cells. Consistently, plasma protein profiling identified several elevated inflammatory mediators in CPUO patients compared to HCs. Among these, CCL3 showed robust upregulation and contributes to pruritus through CCR1-dependent sensitization of pruriceptive neurons. In conclusion, our characterization of CPUO as a distinct entity driven by systemic immune dysregulation and CCL3-mediated neuronal sensitization provides mechanistic insights into its pathophysiology and opens new avenues for therapeutic intervention.

LB1242

STAT6 signature is not detectable in AD skin T-cells

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IL-4 and IL-13 have unique and overlapping roles in different disease indications. IL-4 signals through both the type I (IL-4Ra & y chain), and type II receptors (IL-4Ra & IL-13Ra1). IL-13 however, only signals through the type II receptor. The type I receptor is primarily expressed by immune cells (B-cells, T-cells, monocytes) whereas the type II receptor is expressed by structural cells (keratinocytes, fibroblasts) and myeloid cells, but not by T-cells. AD was traditionally thought to be driven by the classical Th2 mechanism, in which IL-4 stimulates Th2 T-cells to produce IL-13. However, recent studies have failed to detect IL-4 expression in AD skin, while IL-13 is highly expressed by skin-infiltrating T-cells. In addition, the clinical data from IL-13 blocking antibodies lebrikizumab and tralokinumab, suggest a dominant role of IL-13 in AD. We hypothesized because T-cells only express the type I receptor, and thus can only be stimulated by IL-4 and not IL-13, a lack of STAT6 signature in these T-cells in AD skin, would further suggest that IL-4 is not stimulating T-cells, likely due to its low to no expression. A STAT6-signaling transcriptomic signature was created by stimulating PBMCs and keratinocytes with IL-13 in the presence or absence of lebrikizumab. This signature was screened against two AD skin RNA single cell datasets (Zhang et al, Allergy 2023 & Bangert et al Sci Immunol 2021). In both datasets, T-cells in AD skin showed no increase in STAT6 signature, as compared to healthy and Psoriasis skin T-cells. In AD skin, myeloid cells and keratinocytes showed an increase in STAT6 signature vs healthy skin and psoriasis lesions, suggesting that these cell types are stimulated by IL-13. In conclusion, our analysis showed no evidence for STAT6 signaling in AD skin T-cells, implying no local stimulation by IL-4. This finding further highlights the dominant role of IL-13, and not IL-4, in AD.

LB1243

Single-cell and bulk-RNA transcriptomics reveal nemolizumab effects on pruritus, hyperplasia, and fibrosis markers

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Nemolizumab is an anti-IL-31Ra monoclonal antibody tested in two phase III clinical trials (ARCADIA1:NCT03985932/ARACADIA2:NCT03989349) for the treatment of moderate-to-severe atopic dermatitis in patients aged>12 years. This study characterizes transcriptomic changes in a subset of patients from ARCADIA1 pre- and post-nemolizumab treatment using single-cell (scRNA-seq) and bulk RNA-seq. Tape strips were collected from the lesional(LS) and nonlesional(NL) skin of 72 patients with AD at baseline and after 16 weeks of nemolizumab (+topical corticosteroids with or without topical calcineurin inhibitors[TCS/TCI]) and of 39 patients receiving placebo (+TCS/TCI). RNAseq analysis identified differentially expressed genes (|FCH|>1.5, FDR<0.05). scRNA-seq of LS and NL skin of 6 patients with AD and 15 healthy controls were integrated with bulk-RNAseq data from patients treated with nemolizumab. At 16 weeks, 142 genes were upregulated and 797 downregulated in LS skin compared to baseline. Nemolizumab downregulated key markers related to pruritus (TRPV1/3, OSMR), epidermal hyperplasia/fibrosis (KRT6C, SERPINB, COL10A1/12A1, IGFBP3), Th1 markers (CCL2, MX1, OASL), and Th17/Th22 (S100A7/8/9/12, IL36G, PI3). scRNA-seq mapping revealed nemolizumab attenuated genes associated with inflammatory, follicular, and supraspinous keratinocyte subpopulations (IL-18+, IVL+, KRT10+), profibrotic fibroblasts (COL11A1+, APOE+, SFRP2/4+), and endothelial and nerve cell-associated genes (FN1+, PGF+, BDNF+, MAP2+). These findings suggest nemolizumab modulates keratinocyte, fibroblast, and nerve cell-associated pathways, reducing fibrosis, pruritus, and inflammation, supporting its potential for patients with itch dominant and hyperplastic AD phenotypes.

LB1244

Spatial transcriptomics analysis of Merkel cell carcinoma reveals novel immune cell subsets and hypoxia as correlates of immunotherapy response

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Immune checkpoint blockade remains the standard of care for advanced Merkel cell carcinoma (MCC); however, approximately 50% of patients develop either primary or acquired resistance. Although the tumor microenvironment (TME) is implicated in mediating therapeutic outcomes, the specific cell types involved, and the impact of their spatial organization remain largely undefined. To address this gap, we applied Xenium spatial transcriptomics (ST) to 27 treatment-naive MCC tumors from a clinical trial of retifanlimab in advanced MCC, with the goal of uncovering TME correlates of immunotherapy response. Our analysis revealed the presence of CXCL9 and SPP1 macrophages that have not been previously reported in MCC. These macrophages were not detectable in several single cell RNA-sequencing (scRNA-seq) MCC datasets, suggesting ST can uncover cell populations missed by traditional scRNA-Seq. Other immune subsets were also observed, including CD4 and CD8 T cells expressing hallmarks of tumor reactivity such as CXCL13, NK cells, B cells, and plasma cells. The tumor compartment contained distinct subpopulations of hypoxic and proliferating tumor cells with unique spatial organization. Cellular neighborhood analysis revealed 3 types of tissue domains: immune rich, tumor rich, and stromal rich regions. Higher levels of hypoxic and proliferating tumor cells were associated with poor outcomes. Interestingly, overall immune cell composition was relatively homogeneous between responders and non-responders, suggesting that immune cell spatial relationships, rather than abundance, may be more strongly associated with immunotherapy response.

LB1245

Brepocitinib improves inflammation and fibrosis in cicatricial alopecias through transcriptomic changes

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Cicatricial alopecias (CA) are scarring hair loss disorders characterized by inflammation and progressive scalp fibrosis. In a recent phase 2 trial (NCT05076006), brepocitinib, a dual TYK2/JAK1 inhibitor, demonstrated clinical improvement in CA patients. In order to better characterize the potential molecular targets of brepocitinib in CA, transcriptomic analysis using RNA sequencing was conducted on scalp samples obtained from the same trial. Patients with frontal fibrosing alopecia/lichen planopilaris (FFA/LPP, n=22) and central centrifugal cicatricial alopecia (CCCA, n=22) were randomized to receive brepocitinib 45 mg daily or placebo for 24 weeks, followed by placebo cross-over, open-label treatment with brepocitinib for an additional 24 weeks. Biopsies were collected from nonlesional and lesional scalp at baseline, and from lesional scalp at week 24 and week 48. RNA sequencing was performed, with differential gene expression identified using fold-change/|FCH|>1.5 and false-discovery-rate/FDR<0.05 thresholds. At week 24, brepocitinib significantly downregulated markers of Th1 (MX1, CXCR3, IL2RA, OASL, CCR2, TNF, IRF1, CXCL9/10/11, STAT1, CCR5), Th2 (IL10, CCL13, OX40, IL7R), Th17/22 (IL32, IL6R, S100A7/8) and fibrosis (CXCR3, IL2RA, IL7R, CCL2, CCR2, TNF) pathways in lesional scalp from FFA/LPP and/or CCCA patients. These effects persisted at week 48, with stronger modulation observed in the FFA/LPP group. Notably, clinical scores (FFASI/LPPAI/CHLG) correlated positively with JAK/STAT-related markers and fibrosis markers (COL12A1, COL8A2, ITGB1BP1, COL5A3, JAKMIP3) (r>0.7; p<0.05). Brepocitinib was well tolerated and consistent with safety reported in other clinical studies. Taken together, brepocitinib significantly reduced markers of inflammation and fibrosis in the lesional scalp of FFA/LPP and CCCA patients, supporting its potential as a therapeutic option in CA patients.

LB1246

Immune profiling of eosinophilic fasciitis by single cell rna sequencing

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Eosinophilic fasciitis (EF) is a rare inflammatory condition characterized by fibrosis of the fascia and subcutaneous tissue accompanied by variable degrees of eosinophilic infiltration. Although disease etiology remains unclear, T cells have been implicated in pathogenesis in histopathological studies.[1] Using single cell RNA sequencing (scRNAseq), we characterized the immune cell populations from three EF patients as compared to healthy controls. Preliminary data revealed a trend towards increased presence of T cell, B cell, and plasma in EF samples relative to healthy controls. Further characterization of T cells in EF samples revealed a predominance of two CD8 T cell phenotypes. Furthermore, natural killer cells populations also appear increased in EF specimens. TCR repertoire analyses demonstrated clonal expansion in one CD8 T cell population. Overall, these early findings suggest a dominant type 1 cytotoxic response in EF. While the significance of the observed expansion of B cells and plasma cells remains unclear, the clinical improvement of improvement in one patient with the addition of rituximab, a therapy targeting CD20-expressing B cells, warrants further investigation into their role in disease progression.

LB1247

Blue light entrains circadian rhythm via peropsin in keratinocytes of skin organotypic cultures

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The epidermis possesses its own independent circadian rhythm (CR), whose primary environmental cue is light. Various opsins, proteins responsible for light detection, have been observed in different differentiation states of keratinocytes. Peropsin (RRH), in particular, detects near-ultraviolet blue light and is highly expressed in differentiated keratinocytes. Here, we use a differentiated skin organotypic culture to examine the effect of blue light in keratinocyte circadian rhythm, and investigate its effect on inflammatory cytokines such as IL-13. To examine CR, we established N/TERT cell cultures and maintained 2D and 3D skin equivalent in dark-dark (DD) cycle. One group was moved under 12h:12h light-dark (LD) conditions to an incubator equipped with a lighting panel. Both groups were treated with all-trans-retinal (an opsin chromophore), and mRNA was analyzed. A 3D full-thickness skin equivalent culture model for atopic dermatitis (AD) was developed using IL-13 treatment for 21 days. Finally, to examine BMAL1/CLOCK binding to IL-13 recognition sites, promoter pulldown assays and electrophoretic mobility shift assays (EMSA) were performed. The skin organotypic cultures exhibited typical clock gene oscillations when exposed to LD cycles. Deletion of RRH in keratinocytes abolished light-induced CR, indicating that peripheral light induced CR, and Bmal1 (a key CR player) relies on RRH activation and blue light. We also demonstrated that the pro-inflammatory cytokine IL-13 is expressed in keratinocytes, and IL-13 expression underwent a circadian pattern when exposed to LD cycle. Finally, we demonstrated BMAL1/CLOCK binding to IL-13 gene promoters. These results show that peropsin is a functional photoreceptor in keratinocytes and visible light alone may entrain CR in the epidermis. Our preliminary data also suggests that activation of RRH triggers an inflammatory state in the epidermis, allowing for a better understanding of diurnal symptoms in atopic dermatitis.

LB1248

Improving the therapeutic potential of intravenous recombinant collagen VII as a protein replacement therapy for recessive dystrophic epidermolysis bullosa

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We assessed the disease-modulating efficacy of intravenous infusion of PTR-01, a recombinant type VII collagen (C7) expressed in Chinese Hamster Ovary (CHO) cells, in a Phase 2 clinical trial involving 6 patients with recessive dystrophic epidermolysis bullosa (RDEB). While PTR-01 was well-tolerated and resulted in improvements in wound healing, no anchoring fibrils (AFs) were detected at the basement membrane zone of the skin, despite intact PTR-01 accumulation at the dermal-epidermal junction (DEJ). To understand why no AFs formed, we compared PTR-01 to C7 purified from dermal fibroblasts. On non-reducing western blots, additional bands of lower molecular weight were visible in PTR-01, suggesting reduced stability of CHO-derived PTR-01. Under reducing conditions, PTR-01 appeared as a doublet, and domain-specific antibodies revealed significant proteolytic maturation at the C-terminus. Proteomics of PTR-01 revealed altered glycosylation and a mixture of 40% wildtype C7 and 60% C7 with a D1033Y substitution in the FN type III domain of the NC1 domain. This variant acted dominantly negative, reducing the thermal stability of C7 and impairing binding to laminin-332 and collagen IV. Collectively, our data indicate that systemic delivery of C7 to the skin can be achieved and confer benefit in RDEB. However, the reduced affinity for DEJ ligands, lower thermal stability, and premature NC2 maturation likely impaired the ability of PTR-01 to assemble into AFs. We have since identified CHO clones that express only wild-type C7 and plan to develop this as an improved alternative to PTR-01.

LB1249

Differential expression of splice variants between responders and non-responders to immunotherapy in merkel cell carcinoma

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Post-transcriptional splicing of mRNA leads to a variety of protein isoforms of a gene, each with distinct functions. Although alternative splicing events have been studied in many cancers and associated with outcomes, the role of alternative splicing in Merkel cell carcinoma (MCC) is not well understood, especially in the context of resistance to immune checkpoint inhibition (ICI). We evaluated bulk RNA-seq data from 9 primary MCC tumors from patients treated with neoadjuvant nivolumab (4 tumors that completely resolved complete response and 5 tumors that persisted at 4 weeks after ICI start) for differential expression of alternative splicing events. We used the well-established bioinformatic tool called Replicate Multivariate Analysis of Transcript Splicing (rMATS)-turbo bioinformatic tool. Our analysis focused on skipped exon events, because these splice variants can be detected with highest confidence. 215 splice variants were significantly more highly expressed in responders to ICI, while 172 splice variants were more highly expressed in non-responders. To further eliminate false positive, we filtered by difference in expression of ≥25% with FDR ≤ 0.01 and focused on genes specifically expressed in tumor cells in single cell RNA-Seq data from primary MCC tumors. This filtering yielded 10 gene variants. Non-responders showed higher expression of a 130 bp exon in PLEKHA5, a phosphorylation target of MET receptor tyrosine kinase involved in metastasis of various cancers, including melanoma. MET antagonism is a treatment for melanoma though not explored in MCC. Samples with complete response, on the other hand, showed higher expression of a 50 bp exon in ITGB3BP, which is upregulated by TGF-beta pathway and associated with poor prognosis in several cancers. Our results suggest alternative splicing plays a role in MCC ICI resistance and there may be existing therapeutic strategies that could overcome the identified resistance mechanisms.

LB1250

RNA-sequencing of plucked hair follicles identifies gene expression signatures of chemotherapy-induced alopecia

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Chemotherapy-induced alopecia (CIA) is one of the most common and distressing side effects for cancer patients. Scalp cooling (SC) is effective at minimizing CIA and promoting hair regrowth, but its efficacy in patients with skin of color and varying hair textures remains understudied. This study aimed to elucidate the effects of SC on CIA and identify predictive biomarkers through hair follicle transcriptomics. We conducted a prospective, open-label clinical study including cancer patients with Type 3 or 4 hair undergoing taxane-based chemotherapy. Ten hair follicles were collected at baseline and one month post-treatment. Total RNA was extracted from four follicles, mRNA sequencing was performed at an outside laboratory, and data were analyzed using Kallisto and DESeq2 in R. After bulk comparison of gene expression at baseline compared to one month, we found a statistically significant difference, with a low number of upregulated compared to downregulated genes. Principal component analysis revealed two patients exhibited significantly altered gene expression from baseline. Interestingly, these two patients clinically demonstrated substantial loss of hair. In contrast, the remaining two patients exhibited minimal CIA. Downregulated pathways at one month included phosphorylation and growth factors in beta cell proliferation, T-helper 2 differentiation, and interleukin-4 (IL-4) production. Notably, IL-4 has been thought to contribute to the immunopathogenesis of an alopecia areata phenotype. Upregulated genes included Keratin 14, a marker of dividing basal keratinocytes, and Cornifelin, associated with hair anchoring and cyclic alopecia. These results suggest that hair follicles one month post-chemotherapy may be initiating recovery and restarting the anagen cycle. These results support the use of non-invasive hair follicle sampling for gene expression profiling of alopecia.

LB1251

Longitudinal multimodal characterization of radiation dermatitis in a C57BL/6J mouse model

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Radiation dermatitis (RD) is a common sequela of radiation therapy (RT), affecting over half of cancer patients. Its cutaneous manifestations—ranging from erythema and desquamation to ulceration and fibrosis—can hinder oncologic treatment completion. Despite its prevalence, RD's pathogenesis remains poorly understood. As such, we aim to develop a temporal murine model of RD using clinical grading, objective skin parameters, histopathology, and gene expression analysis of inflammatory markers. Ten-week-old female C57BL/6J mice were radiated with 35 Gy to the left flank. Mice (n=19) were split into five groups: sham (no RT), and four post-RT groups with weekly data collection for four weeks. Data included clinical grading, measurements for erythema, fibrosis, and transepidermal water loss (TEWL), biopsies, and serum samples. Blinded clinical images were graded from 1-4 and blinded histologic images with variables on a 1-5 scale. Expression of selected pro-inflammatory cytokines were assessed using RNA extraction and quantitative PCR. Clinical grading increased from zero at baseline to two by week four across all groups, mirroring progression of skin lesions. Objective probe measurements for erythema and fibrosis significantly increased over the four weeks, while TEWL peaked at week three. Certain histologic variables (epidermal ulceration and follicular loss) increased significantly over the four weeks, while others (dermal and hypodermal inflammation, dermal fibrosis, glandular loss, and total score) peaked at week one, decreased, then progressed through week four. Pro-inflammatory markers IL-17A and IL-1b were significantly upregulated at week four, while IL-6 peaked at week three. TGF-B1 showed an increasing trend but did not reach significance. Our murine model provides a clinical, histologic, and molecular framework for understanding RD progression over time. Additional studies are needed to further validate this model, potentially supporting future research on therapeutic interventions.

LB1252

Investigating sex-related differences in skin cell cultures for tissue engineering applications

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Over the last four decades, our laboratory has produced over 800 lots of cultured autologous skin substitutes for burned patients. While sex-specific medicine has advanced in various fields, the influence of biological sex on cell therapies remains largely unexplored. Our project aims to assess the impact of biological sex on key parameters of the Self-Assembled Skin Substitutes (SASS): the proliferation of keratinocytes and the thickness of the epidermis. We analyzed the records of 282 burn patients treated between 1994 and 2025. To isolate the effect of sex on the studied outcomes, we explored statistical models using a brute force approach to systematically evaluate all possible combinations of variables potentially associated. Our findings revealed that biological sex was not a significant predictor of keratinocyte doubling time, despite being included in some of the most robust predictor sets. While its presence in the models improved the overall model precision, it did not independently influence keratinocyte proliferation rate. For epidermal thickness, biological sex was ranked as the least influential predictor and was not identified as a statistically significant factor. A strength of this study is that the culture data were obtained through a rigorously controlled production process: use of standardized culture protocols performed by trained personnel, selection of serum to limit inter-lot variability, etc. Even though the sample size is relatively important compared to in vitro studies conducted on specimen obtained from skin resection surgeries, it is possible that more subtle effect of sex was not detected due to lack of power and highlights the need for further research.

LB1253

M2 macrophages secrete oncostatin M to facilitate pruritus in primary cutaneous amyloidosis

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Primary cutaneous amyloidosis (PCA) is a chronic dermatosis in which amyloid protein is deposited in the superficial dermis without involvement of other organs. Intense itching is a typical complication symptom in PCA.We sought to determine the specific pruritogenic cytokine and its related signal pathway in PCA lesions trough immunofluorescence and immunohistochemical staining. Inflammatory cells were detected by immunofluorescence and HE staining. To elucidated the correlation among inflammatory cells, pruritogenic cytokine and pruritus, we ask patients to self-evaluate their pruritus severity by NRS score.<br _mstmutation="1" /> Increased secretion of Oncostatin M (OSM) which was observed in PCA lesions had correlation with pruritus severity (r=0.6656, <i _mstmutation="1">P<0.05) while the generations of Interleukin-4, Interleukin-13, Interleukin-31 and Interleukin-33 are similar in healthy skin (<i _mstmutation="1">P<0.05). A number of macrophages (<i _mstmutation="1">P<0.001) and CD4<sup _mstmutation="1">+ T cells (<i _mstmutation="1">P<0.01) infiltrated in PCA lesions. Pruritus severity in PCA was correlated with the number of macrophages (r=0.7320, <i _mstmutation="1">P<0.05) rather than CD4<sup _mstmutation="1">+ T cells (r=0.2102, <i _mstmutation="1">P>0.05). In PCA, CD163<sup _mstmutation="1">+CD68<sup _mstmutation="1">+ M2 macrophages (77.28%±16.21%) are the major type of macrophages. OSM production in Primary cutaneous amyloidosis is largely secreted by macrophages. Dermal OSMRβ<sup _mstmutation="1">+ cells are increased (<i _mstmutation="1">P<0.05). Macrophages showed the activation of JAK-STAT, PI3K-AKT signal pathway. OSM appeared to induce pruritus in primary cutaneous amyloidosis lesions. It largely secreted by macrophages trough the activation of JAK-STAT, PI3K-AKT signal pathway.<br _mstmutation="1" />

LB1254

Establishing predictive models for NB-UVB treatment efficacy and safety in psoriasis through a genome-wide association study

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Background: NB-UVB phototherapy is an effective, cost-efficient, and safe treatment for patients with plaque psoriasis. However, the predictors of NB-UVB treatment response remain limited. Objective: We aimed to detect relevant SNPs in order to establish predictive models for the efficacy and safety of NB-UVB phototherapy. Methods: A total of 252 patients with moderate-to-severe plaque psoriasis were enrolled in this study and underwent 12 weeks of NB-UVB phototherapy. Extracted DNA from whole blood samples was genotyped using Infinium Global Screening Array-24 v3.0 BeadChip. GWAS was performed to identify SNPs related to NB-UVB treatment response. Predictive models for the efficacy and safety of NB-UVB therapy, which involved SNPs along with clinical parameters, were developed utilizing logistic regression and further evaluated by ROC curve and calibration curve. Results: After 4 weeks of NB-UVB phototherapy, 40.8% of patients achieved PASI 50. Through GWAS, we discovered that SLC7A13 rs35314286 TA allele and DYNC1H1 rs941636 A allele were significantly correlated with better efficacy of 4-week NB-UVB treatment. After 12 weeks of treatment, 61.4% of patients achieved PASI 75. Seven ATP2B2 SNPs and ten PSMB7 SNPs significantly impacted 12-week PASI 75 achievement. During the treatment, 29.8% of patients experienced AEs. Two KCNA2 SNPs, seven THSD7B SNPs and one TENM4 SNP were considerably associated with the occurrence of AEs. Based on the clinical parameters and NB-UVB relevant SNPs, predictive models for the efficacy and safety of NB-UVB phototherapy were established, demonstrating excellent predictive capacities with AUC value being 0.81 for 4-week efficacy, 0.80 for 12-week efficacy, and 0.85 for AE development. Conclusion: Multiple gene SNPs were identified to be correlated with the efficacy and safety of NB-UVB phototherapy. Moreover, predictive models of NB-UVB treatment response were subsequently established. Our findings might contribute to the advancement of precision phototherapy in psoriasis.

LB1255

Novel inhibitors of the scaffolding function of BTK selectively and potently block BTK signaling and are efficacious in preclinical models of chronic spontaneous urticaria

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BTK signaling in multiple immune cell types is important in immunological diseases such as chronic spontaneous urticaria (CSU), rheumatoid arthritis, and multiple sclerosis. BTK supports pro-inflammatory signaling downstream of the Fc receptor and B cell receptor through formation of a signaling complex dependent on the BTK SH2 domain. Achieving clinical efficacy with BTK tyrosine kinase inhibitors (TKIs) has been compromised by failure to maintain deep and durable inhibition of BTK's kinase activity. Additionally, off-target inhibition of TEC kinase has resulted in adverse events related to platelet dysfunction, such as bleeding and petechiae. Although no BTK inhibitors are yet approved for dermatologic diseases, LOU064 (remibrutinib, Novartis) has demonstrated Phase 3 efficacy in CSU and encouraging Phase 2 data in hidradenitis suppurativa. We have identified the first small molecule inhibitors targeting the previously undruggable SH2 domain of BTK (BTK SH2i). BTK SH2i are highly potent in biochemical (<1 nM) and cellular assays (<10 nM) and chemically differentiated from BTK TKIs. By inhibiting the scaffolding function of BTK, SH2 domain inhibitors potently block access to substrates such as PLCγ2 and inhibit downstream signaling and immune cell activation. Best-in-class selectivity is achieved for BTK over both safety-related off-targets (>85,000× over TEC) and the SH2ome (>5,000× over other SH2 domains). BTK SH2i prodrugs enable prolonged intracellular pharmacokinetics that achieve deep and durable target engagement in PBMCs for at least 48 hours. In a clinically-relevant mouse model of CSU, BTK SH2 inhibitors achieve efficacy equivalent to BTK TKIs. Selective, potent, and durable inhibitors of BTK's scaffolding function have the potential to safely enable broader clinical efficacy in dermatologic disease.

LB1256

TRIV-509, a dual inhibitor of KLK5 and KLK7, rapidly improves barrier integrity and markers of epidermal differentiation in atopic dermatitis skin explants

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Impaired barrier integrity and disordered epidermal differentiation are hallmarks of atopic dermatitis (AD). KLK5 and KLK7, serine proteases involved in the natural desquamation process, are dysregulated in AD and contribute to these pathologies along with independently driving inflammation (KLK5-PAR2 pathway) and itch (KLK7-dependent pathway). In diseased skin, KLK5 and KLK7 are hyperactive and aberrantly expressed in layers below the stratum corneum, where they can cleave crucial epidermal structural proteins such as DSG1, DSC1, CDSN. Cleavage of essential junctional proteins permits penetration of allergens, irritants, and bacteria which triggers a vicious cycle of inflammation, pruritus, and further barrier loss. TRIV-509 is a dual-targeting monoclonal antibody, in early clinical development for AD, that potently and selectively inhibits KLK5 and KLK7. To further elucidate the mechanism of KLK5 and KLK7 inhibition in AD, lesional and/or peri-lesional biopsies were collected from 3 patients with a clinical diagnosis of AD (IGA (Investigators Global Assessment) ≥2) and treated with TRIV-509 or vehicle control ex vivo. After 72 hours, the biopsies were processed for histological and protein analysis. In all three patients, TRIV-509 significantly reduced epidermal thickness and parakeratosis in active AD skin. Furthermore, TRIV-509 blunted (≥80% reduction) cell proliferation in the epidermis as measured by Ki-67. Finally, TRIV-509 significantly increased the number of DSG1+ cells in the appropriate layers of the epidermis. Together this data demonstrates that KLK5 and KLK7 inhibition rapidly improves the barrier integrity and markers of epidermal differentiation ex vivo, thereby highlighting the therapeutic potential of TRIV-509 in AD.

LB1257

Evaluation of transcriptome capture and stability from dermal biomarker patches

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Psoriasis affects around 3% of the population of the United States and is predominately a chronic condition that often requires a recurring treatment regime using targeted biologics. Administering the optimal biologic for a patient's biology directly affects their quality of life in a profound way, as there is no prolonged diagnostic odyssey. Recently, a dermal biomarker patch (DBP) platform has been developed (Mindera Health, Vista, CA) for the minimally invasive extraction of biomarkers from the epidermis and the dermis. Using this platform, a test (Mind.Px) has been reported that uses a set of machine-learning derived algorithms to predict if a patient will respond to each class of biologic used in the treatment of psoriasis. The kit consists of the DBP, along with a single use applicator and vial for shipment containing a preservation buffer. In this study, we have examined >1,800 samples from psoriasis patients and healthy subjects to assess the analytical validity of the DBP platform. Samples were analyzed for reproducibility as well as stability over time. Of the data set, only 0.48% (9 samples of 1,864 total) required reanalysis for low concentration (<0.2 ng/μL) and importantly, reanalysis of the initially extracted biomarkers could be achieved without the need for recollection of sample. Interestingly, samples were found to be stable while biomarkers were bound to the patch for at least 14 days with no appreciable deterioration of quality or quantity of the extracted transcriptomes. This finding is particularly surprising given the known lability of RNA biomarkers, independent of temperature, particularly over extended storage times. Limited dependence was also observed with sample collection site, with all body sites yielding assessable samples. Further study of this phenomenon is needed to understand the molecular mechanism of stability, however, it is clear that the dermal biomarker patch platform is a reproducible and robust method for collecting biomarkers from the skin.

LB1258

Investigation of the role and mechanism of pigment epithelium-derived factor (PEDF) in androgenetic alopecia

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Background: Androgenetic alopecia (AGA) is the most common type of hair loss, characterized by follicular miniaturization and hair shedding. Identifying differentially expressed genes and pathways in hair follicles is crucial for elucidating disease mechanisms and developing effective treatments. Previous studies, including those by our group based on transcriptomic data, have highlighted the pivotal role of the Wnt signaling pathway in AGA. Pigment epithelium-derived factor (PEDF) is a gene closely associated with the Wnt pathway. Therefore, this study aimed to investigate PEDF expression in the hair follicles of AGA patients and to explore its role and underlying mechanisms using in vitro–cultured hair follicles and cells. Methods: Hair follicles from the balding and non-balding regions of AGA patients were collected. PEDF mRNA and protein levels were examined by real-time PCR and immunohistochemistry, respectively. In vitro–cultured hair follicles were subjected to siRNA transfection to knock down PEDF expression. A stereomicroscope was used to capture morphological changes and evaluate the effects of PEDF on hair growth and the hair cycle. Additionally, dermal papilla cells and epithelial cells were cultured in vitro to assess how PEDF influences cell proliferation and viability. Results: Quantitative PCR and immunohistochemical analyses revealed higher PEDF expression in hair follicles from balding regions compared to non-balding regions in AGA patients. siRNA-mediated knockdown of PEDF in cultured hair follicles effectively reduced PEDF levels, which promoted hair shaft elongation and prolonged the anagen phase. In vitro cell experiments further demonstrated that PEDF knockdown significantly enhanced dermal papilla cell proliferation and increased cell viability. Conclusion: PEDF is upregulated in hair follicles from balding regions in AGA and is associated with aberrant hair follicle growth and cycling. These findings suggest that PEDF may serve as a promising therapeutic target for the treatment of AGA.

LB1259

Ambient shipping of immobilized mRNA on dermal biomarker patches

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RNA stability is central to processing of samples in the laboratory and the central dogma is that stability is difficult to achieve. This is further exacerbated by the fact that the clinics are located in different geographies, have different collection personnel, ambient temperatures and variation in shipping handling. These factions have a direct impact on the quality and stability of collected mRNA samples. Data from our collections using the Mindera Health Dermal Biomarker Patch (DBP) have displayed longer than expected stability at 2-8°C of up to 14 days without showing a discernible effect on assay result. This indicates that the binding to the DBP in combination with the storage buffer has a protective function on the attached mRNA. The purpose of this study was to evaluate the stability of RNA in transit from collection site to the laboratory in various conditions and ambient temperatures. Previous evaluation of this theory within the laboratory environment demonstrated that samples were stable in the range from -20°C to +40°C with current stabilization buffer as well as a modified buffer. To evaluate this further and in real world conditions, a clinical study was initiated. The study was performed by collection of 3 samples from each of 200 patients at 4 independent sites throughout the US over a period of 2 months. The first sample was returned under the current shipping mechanism, chilled and priority overnight. The second and third samples used the same collection buffer or modified buffer, respectively, and returned using 2-day shipping and at ambient conditions. Quantity and quality of collected RNA was assessed using insert size as a measure of integrity. Good parity was observed between the three samples within patients, despite significant variations in shipping conditions. As previously observed with the DBP platform, a range of RNA concentration was obtained, however, all samples yielded interpretable data by RNA-Seq. The results suggest that the binding of RNA to the DBP imparts sufficient stability to allow for ambient shipping.

LB1260

Redefining alopecia diagnostics: 3D histologic reconstruction and morphometric classification

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Alopecia diagnosis is challenging due to follicular complexity and the limitations of 2D histology. This study integrates digital pathology, machine learning (ML), and volumetric image reconstruction to generate the first 3D histologic maps of scarring and non-scarring alopecias. We digitally scanned 319 alopecia biopsies, including lichen planopilaris (LPP), central centrifugal cicatricial alopecia (CCCA), androgenetic alopecia (AGA), and alopecia areata (AA). Using CODA, a robust image registration and segmentation algorithm, we reconstructed high-resolution 3D histologic volumes from serial H&E-stained sections. In these volumes, we quantified follicular morphometrics—density, size, eccentricity, and spatial distribution—across four anatomical levels: bulb, suprabulbar, isthmus, and infundibulum. Tissue composition, including sebaceous glands, sweat glands, vasculature, adipose tissue, and immune infiltrates, was mapped at each level. Immune cells were further classified into lymphocytes, neutrophils, and plasma cells. Preliminary 3D reconstructions (n=3 per subtype) reveal architectural and immune infiltration differences between scarring and non-scarring alopecias. Scarring subtypes (CCCA, LPP) exhibit a 20% increase in peribulbar fibrosis, an 81% reduction in sebaceous gland density, and a 48% rise in immune cell clustering at the isthmus and infundibulum. Non-scarring forms show follicular miniaturization, with a 44% increase in single-hair follicles (AGA) and a 51% rise in bulbar immune infiltration (AA). We plan to expand our analysis to 10 samples per subtype for statistical validation and further insights. This study establishes the first comprehensive 3D histologic framework for alopecia diagnosis, offering a novel spatial perspective on follicular pathology. By integrating volumetric morphometrics with ML-driven classification, our approach aims to enhance diagnostic precision, improve subtype differentiation, and overcome traditional 2D histology limitations—potentially transforming alopecia diagnostics.

LB1261

Therapeutic effects of nano-encapsulated anandamide on skin inflammation in a novel PD-1H knock-out lupus mouse model

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Cutaneous lupus erythematosus (CLE) is an autoimmune skin disease involving immune cell accumulation, cytokines, immune complexes, and complement in skin lesions. The endocannabinoid system, including Anandamide (AEA), a key endocannabinoid, has demonstrated therapeutic potential in modulating immune responses and maintaining skin barrier function. Our pilot study explored the therapeutic effects of AEA on spontaneous lupus skin lesions in a newly developed lupus mouse model with programmed death-1 homolog (PD-1H) knockout (KO) mice in a BALB/c background. Fourteen mice, matched for skin plaque scores, were divided into two groups and treated topically with either 4% AEA-ZP (AEA encapsulated in a novel silica-based particle delivery system, treatment) or 0% AEA-ZP (control) on skin lesions twice weekly for 8 weeks. Our preliminary data, analyzed by repeated measures two-way ANOVA, showed significant time x treatment interaction ($p<0.001$), indicating the effect of time on lesional scores depended on the treatment group. Post-hoc analysis showed that 4% AEA-ZP treatment progressively reduced lesional scores compared to baseline, with significant improvement from week 5 onward until the end of treatment period (1.47±0.39 at week 8 vs 3.50±0.42 baseline, $P<0.01$). In contrast, the control group (0% AEA-ZP) showed only minimal and insignificant reduction in skin scores over the same period of time. H&E stained lesion skin showed reduced epidermal skin thickness and attenuated inflammatory cell infiltration in the dermis in 4% AEA-ZP treated compared to control mice. The observed clinical and immune-modulating effects of AEA suggest it may be a viable efficacious new treatment for CLE. Encapsulation of AEA appears to enhance skin penetration and efficacy. Further studies with IMC analysis will help to elucidate the mechanism for the therapeutic potential of AEA-ZP in a novel lupus model.

LB1262

Sustained epithelial alarmin contribute to persistent hyperpigmentation after psoriasis remission by biologics.

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Post-inflammatory hyperpigmentation (PIH) can develop following various skin conditions, external factors, and dermatological treatments. PIH after psoriasis can be particularly bothersome for patients, as the pigmentation may persist even after the complete resolution of psoriatic plaques. Our study aimed to examine the histopathologic and molecular characteristics of persistent hyperpigmentation following the clearance of psoriasis lesions. Two psoriasis patients treated with IL-23 monoclonal antibodies and reached PASI 100 underwent skin biopsies on both recovered lesions without PIH and lesions with persistent PIH. Compared to lesions that recovered without PIH, persistent PIH lesions showed more pronounced hyperkeratosis, epidermal acanthosis, and increased melanin deposition in the basal layer of the epidermis. Using spatial transcriptomics analysis, we observed heightened alarmin and cytokine signaling in the epidermis of persistent PIH lesions compared to non-PIH lesions. Furthermore, the alarmins were associated with increased expression of melanin-related proteins, suggesting a role for residual inflammatory signaling in the persistence of PIH. Together with our previous research, these findings indicate that persistent PIH in psoriasis patients represents an epidermal type of hyperpigmentation characterized by increased basal melanin and sustained hyperkeratosis, despite the absence of clinically visible scaling. Our data suggest that persistent hyperpigmentation may result from prolonged alarmin signaling. Targeting the alarmin signaling pathway could be a promising strategy for improving recalcitrant PIH.

LB1263

WITHDRAWN

LB1264

Treatment of murine atopic dermatitis with a CCL11 antibody and a topical CCR3 inhibitor

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We reported previously that Ikkb deletion in Prx1+ fibroblasts blocks NF-kB activation and surprisingly promotes myelocytic and leukocytic dysregulation in the skin, mimicking atopic dermatitis characterized by eosinophilia and a type II immune response. In this model, skin lesions were associated with dermal and subcutaneous inflammation associated with fibrosis and alopecia. Experiments showed that upregulation of CCL11 and CCR3 drove the inflammatory phenotype. This study aims to determine whether blocking CCR3 and CCL11 signaling with a topical CCR3 inhibitor and systemic CCL11 antibody can induce regression of the spontaneous atopic dermatitis (AD)- like skin lesions in this model. We analyzed Prx1Cre+Ikkbf/f mice that had developed atopic dermatitis-like lesions at 9-10 weeks of age and were subjected them to a combination of a topical CCR3 inhibitor and a systemic CCL11 antibody for 10 weeks. Control mice received vehicles only. Rat anti-mouse CCL11 antibody (approximately 1.0 ug/ul) was administered twice weekly via subcutaneous injection into inflamed lesions with the animal under anesthesia. The CCR3 inhibitor GW766944 was applied topically in a gel daily to the inflamed lesions at a concentration of 25 mM for 10 weeks. Administration of the topical CCR3 inhibitor and systemic CCL11 antibody induced regression of lesional area by approximately 70% compared to controls ($P<0.05$). Our initial results indicate that blocking the CCR3 with a topical small molecule inhibitor combined with a systemic CCL11 antibody inhibited the formation of atopic dermatitis-like lesions in Prx1Cre+Ikkbf/f mice. These findings indicate that inhibition of CCL11 and CCR3 signaling may be useful for inhibiting maintenance of skin lesions and Th2 inflammation in this murine model of AD.

LB1265

Natural product-based compounds demonstrate potent anti-inflammatory and anti-itch effects in a mouse model of atopic dermatitis

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Atopic dermatitis (AD) is a common and debilitating skin disease characterized by inflammation and itch. While the precise molecular pathogenesis of AD is not fully understood, multiple cytokines have been discovered that mediate AD inflammation (such as IL4, IL5, and IL13) and itch (IL31). Despite recent approval of systemic and topical therapies, there is still a significant unmet need for additional safe and effective therapies for AD. To meet this need, our team has developed a group of novel natural-product based small-molecule compounds including DB007-5. In a MC903-induced mouse model of AD, DB007-5 demonstrated strong and concentration dependent inhibition of inflammation score ($p<0.05$ for 0.5%, 0.75% and 1% concentrations). Further, at 0.75%, DB007-5 reduced scratching (itch) score at Day 12 from 7.2+/-2.70 in vehicle treated group to 0.70+/-0.33, $p<0.05$), while ruxolitinib 1.5% reduced the scratching score to 1.7+/-0.62, $p<0.05$). In summary, DB007-5 demonstrated strong anti-inflammatory effects as well as potent inhibition of the primary symptom of AD, namely itch. Further studies are underway to evaluate the potential of DB007-5 as a therapy for AD.

LB1266

Menstrual cycle matters: How hormonal fluctuations could impact skin immunity in health and disease

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Our study explores the relationship between hormonal changes during the menstrual cycle and their effects on skin health, focusing on Hidradenitis Suppurativa (HS) and healthy individuals. To study the effects of cyclic hormonal changes on the skin, we collected site-matched healthy-donor skin from five healthy women, and lesional and non-lesional skin from ten women with HS during the early follicular and luteal phases of the menstrual cycle. We used RNA-sequencing to identify differentially expressed genes between these phases that met the significance criteria (FDR < 0.05 and log2fold-change > 1.5). In healthy-donor skin, several upregulated genes, were involved in suppressing T cell and lymphocyte proliferation and activation, inhibiting cytokine-mediated signaling, and promoting regulatory T cell differentiation during the early follicular phase compared to the luteal phase as indicated by gene ontology (GO) overrepresentation analysis. In contrast, lesional HS skin showed a different set of upregulated genes related to innate immunity, microbial defense responses, and humoral responses during the early follicular phase compared to the luteal phase by GO terms. In non-lesional skin, no genes met the same significance criteria. Notably, the immunoregulatory pathways upregulated in healthy skin during the early follicular phase were not similarly activated in HS skin. While validation is ongoing, our transcriptome data suggest that the failure to activate immune regulatory pathways in HS may contribute to increased severity of skin lesions during the early follicular phase of the menstrual cycle. Our findings have implications for clinical trial design and insights into identifying new therapeutic targets for hormone-mediated inflammatory pathways in skin.

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Deruxtecan-based antibody-drug conjugate targeting TCR-Vβ2 for the treatment of cutaneous T cell lymphoma

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A challenge in the development of effective and safe immunotherapies for T cell lymphomas and leukemias malignancies is the lack of a unique marker on malignant vs healthy T cells. We observed that malignant T cells from advanced cutaneous T cell lymphoma (CTCL) patients express a clone-defining T cell receptor (TCR), with Vβ2 being the most common Vβrepresented variable region of the >20 Vβ families. Since each Vβ gene is expressed by only a small fraction (~3–9%) of the overall T cell population, a patient-matched Vβ-specific immunotherapy may be a safer strategy for eliminating CTCL cells. [MG1] We have previously generated anti-Vβ2 chimeric antigen receptor (CAR)-T cells using purified T cells from healthy donors as a potential patient-matched Vβ-specific immunotherapy. However, to overcome the production cost and logistical challenges of generating CAR-T immunotherapies, we have now developed antibody-drug conjugate (ADC) prototypes using different conjugation strategies and payloads. Using a Lysolight internalization assay, we show that a Fc-dead inactivated humanized anti-Vβ2 antibody is readily internalized in any target cells Lysolight internalization assay. We then conjugated deruxtecan (Dxd), a topoisomerase 1 inhibitor and a derivative of exatecan, to the anti-Vβ2 antibody via lysine modification at a drug-antibody ratio of ~2.5. We show that these anti-Vβ2-Dxd ADC prototype can effectively and specifically kill Vβ2 Jurkat cells in vitro. Finally, to assess the anti-Vβ2-Dxd ADC prototype in vivo, a complimentary mouse xenograft models using NSG mice was were generated by intravenous (retro-orbital) or subcutaneous injection of luciferase-expressing Vβ2+ Jurkat cells. In vivo preclinical imaging revealed that tumor burden growth was substantially suppressed in mice treated with the anti-Vβ2-Dxd ADC prototype (1 or 2 mg/kg i.p.) when compared to untreated mice. Overall, we demonstrate a potential strategy to rapidly generate and assess Dxd ADCs targeting TCRVβs for the treatment of Vβ+ clonal CTCL and other T cell malignancies.

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