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Assessment of psoriasis using label-free ultra-broadband optoacoustic mesoscopy

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Psoriasis is one of the most prevalent widespread chronic inflammatory skin disease but modern imaging methods provide only limited view on the disease specific hallmarks. In clinical practice, standard tools to assess disease severity and drug efficacy are based on visual scores that are subjective and inconsistent among different examiners. Here, we introduce paradigm shifting ultra-broadband optoacoustic mesoscopy (OPAM) for visualizing psoriatic skin beyond the reach of current dermatological imaging. Implemented in handheld mode, we show visualization of optical absorption contrast resolving for the first time vascular morphology in the dermis and quantifying inflammatory landmarks such as blood volume, epidermal thickness and characterization of capillary architecture in label free mode. Investigating the mesoscopic appearance of psoriasis in six different patients, we found that OPAM cross sectional images and 3D reconstructions examined for morphological skin alterations, capillary loop elongation, acanthosis and changes in dermal vasculature correlated with the values obtained from histopathological skin samples of the respective patients. Besides, we established a multidimensional computational analysis combining the OPAM parameters of increased dermal blood volume, capillary loop density, acanthosis and vessel structure complexity which significantly correlated with Psoriasis Area Severity Index. Thus, we confirm that obtained imaging data reflected the main clinical signs of psoriatic inflammation namely erythema, scaling and induration of plaques. The method has enormous implications in non-invasive accurate staging, treatment evaluation and assessing a larger spectrum of diseases towards precision medicine.

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The efficacy of 1% hydrogen peroxide cream for acne vulgaris treatment

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Acne vulgaris most commonly occurs during adolescence, affecting an estimated 80−90% of teenagers. However we observe increasing number of acne vulgaris in adults as well. The purpose of this study was to evaluate the safety and anti-inflammatory, anti-bacterial and soothing effects of topical use of 1% hydrogen peroxide cream. Hydrogen peroxide is a chemical compound that finds use as a strong oxidizer, bleaching agent and disinfectant. Cosmetic industry offers a wide range of products for this condition, however hydrogen peroxide has not been very popular so far. The study was conducted on 19 volunteers with acne vulgaris between ages 16-61 years old. The product was used daily for a week. Skin condition was analyzed using VISIA system as well as by dermatologists according to the Hellgren and Vincent scale and via a questionnaire survey completed by volunteers after one week of product usage. Skin assessment revealed the reduction in the amount of pustules by 63% and reduction of the severity of seborrhea by 32%. Instrumental skin analysis revealed significant decrease of porphyrins, pores and spots. Moreover skin texture was improved by 22%. Results of the presented study demonstrated that systematic application of 1% hydrogen peroxide cream significantly reduces skin inflammation, soothes and accelerates healing process as well as demonstrates great product tolerance. 1% hydrogen peroxide can supplement pharmacological treatment of acne vulgaris with mild to moderate course of disease.

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Characterization of multiple B cell subsets in peripheral blood of psoriasis patients identifies a correlation of regulatory B cells and disease severity

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Imbalances of T cell subsets have been demonstrated as hallmarks of disease-specific inflammation in psoriasis. However, the role of B cells as important counterparts of T cell function remains poorly investigated. Here, we analysed a broad set of B cell subsets and immunoglobulins in psoriasis patients and correlated their distribution in peripheral blood with disease severity. Surface staining and flow cytometry was performed on leucocytes from whole blood of 100 psoriasis patients and 20 individuals without history of skin disease. The severity of psoriasis was determined by Psoriasis Area and Severity Index (PASI) and patients were classified as PASI low (< 5) or PASI high (> 10). Five developmentally different B cell subsets defined by their CD24 and CD38 expression were characterized as well as the distribution of CD138 and CD27. The humoral immunologic profile was complemented by serum parameters including immunoglobulins. We found a significant increase of plasma cells ($CD19^+$, $CD38^{high}CD24^-$) accompanied by increased IgA serum levels in patients with higher severity scores (PASI high) as compared to patients of the PASI low group and healthy volunteers. Moreover, frequencies of regulatory B cells, defined as $CD19^+CD24^{high}CD38^{high}$, were upregulated in psoriasis patients and showed positive correlation with PASI. These data suggest a contribution of B cell subsets to the severity of psoriasis with increased frequencies of regulatory B cells representing a possible compensatory mechanism to increased frequencies of plasma cells and IgA serum levels observed in psoriasis patients.

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Addition of interleukin-17 alters the healthy keratinocyte secretome and causes inhibition of Langerhans' cell migration

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Langerhans' cells (LC), the dendritic cells of the epidermis, are responsible for regulating the cutaneous immune response. Migration of LC is impaired in the uninvolved skin of patients with chronic plaque psoriasis. We have recently demonstrated that: (i) addition of recombinant interleukin (IL)-17 (a cytokine over-expressed in psoriasis), and; (ii) conditioned medium generated from psoriasis primary keratinocytes (KC), are each able to inhibit LC migration in an ex vivo healthy epidermal explant model. Here we examine whether IL-17 can induce healthy KC to acquire a 'psoriasis-like' phenotype and to inhibit LC migration in this model. Punch biopsies (6 mm) acquired from 10 healthy volunteers were used to isolate KC or epidermal sheets. KC conditioned media was generated in the presence of IL-17 or vehicle control (n=3). Epidermal sheets were isolated, and one from each volunteer was fixed immediately (T0). The others were floated on either control or IL-17 KC conditioned media for 24h before fixing (T24, n=7). A neutralising anti-IL-17 antibody was added to both cultures to ensure that any effect in the explant model was due to downstream effects of IL-17 on KC and not residual IL-17 in the conditioned media. The frequency of LC was compared between the T0 and T24 groups. The mean frequency of LC in the T0 epidermal sheets was 864±136 LC/mm^2. Epidermal sheets cultured with conditioned media from control treated KC had a significant reduction (p=0.0156) in LC frequency to 695±138 LC/mm^2 (the proportion of LC migration being consistent with previous observations). In contrast, when epidermal sheets were cultured with conditioned media from IL-17 treated healthy KC, LC migration was impaired and there was no significant difference in LC frequency in the T24 group (792±142 LC/mm^2). We therefore propose that the impaired LC migration observed in uninvolved psoriasis skin is associated with alterations in the KC secretome in response to overexpression of IL-17.

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Levels of IgE anti-BP180 and anti-BP230 autoantibodies in bullous pemphigoid patients

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Bullous pemphigoid (BP) is characterized by subepidermal blistering caused by IgG autoantibodies (autoAb) against the hemidesmosomal proteins, BP180 and BP230. Whereas IgG autoAbs play a primary role in the pathogenesis, there is a growing number of evidences coming from several mouse models suggesting that also IgE autoAbs are pathogenic. However, only a percentage of BP patients ranging from 18 to 44% shows IgE deposition in the dermo-epidermal junction and the significant relation between circulating IgE levels against BP antigens and disease severity is not always present. To measure the levels of IgE anti-BP180 and anti-BP230 antigens and investigate their clinical relevance we have set up two specific (100%) and sensitive ELISAs. In a cohort of 52 BP patients a comparable frequency of circulating IgE autoAbs anti-BP180 (67%) and anti-BP230 (62 %) was found. However, the levels of IgE reactivity against BP230 was higher than that measured for BP180. The assays showed a combined sensitivity of 85% and no BP sera IgG negative for both BP180 and BP230 possessed IgE autoAbs specific for BP antigens. In 2 of 4 BP patients monitored over time the levels of IgE anti-BP180 were associated with disease severity, while anti-BP230 IgE autoAbs weakly correlated with disease severity in 4 of 6 BP patients. Of note, in 26 of 52 BP patients at diagnosis the presence of IgE anti-BP180 or anti-BP230 autoAbs was not related with disease severity. These findings show that i) the detection of anti-BP antigens IgE does not improve the diagnostic performance of IgG ELISAs and (ii) IgE autoAbs could have a limited role in the pathogenesis of BP.

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Targeting type 2 immunity: Therapeutic perspectives for fibrotic skin diseases

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Activation of the immune response is a critical early event during injury that determines the outcome of tissue restoration towards regeneration or replacement of the damaged tissue with a scar. The mechanisms by which immune signals control these fundamentally different regenerative pathways are largely unknown. In this study we have demonstrated that during skin repair in mice interleukin-4 receptor a (IL-4Rα)-dependent macrophage activation controlled collagen fibril assembly, and that this process was important for effective repair while having adverse pro-fibrotic effects. We could show that in mice with myeloid cell-restricted IL-4Rα-deficiency (*Il4ra*^{MKO}) skin repair was associated with delayed wound closure, massive hemorrhages in the granulation tissue, and disturbances in extracellular matrix architecture. Ultrastructural analysis of wound tissue in *Il4ra*^{MKO} mice revealed an abnormal collagen fibril assembly. Intriguingly, HPLC-based analysis of the granulation tissue revealed an altered collagen cross-link pattern when compared to control mice. Whereas granulation tissue in control mice was characterized by dihydroxy lysinonorleucine (DHLNL) collagen cross-links, a typical feature of fibrotic tissue, these crosslinks were significantly reduced in *Il4ra*^{MKO} mice. Interestingly, wound macrophages in *Il4ra*^{MKO} mice revealed significantly reduced expression of Relm-a, a small cysteine-rich secreted molecule that is a hallmark of alternatively activated macrophages and has been associated with experimental fibrosis and pro-fibrotic conditions in human diseases. By using an *in vitro* macrophage-fibroblast co-culture system we identified Relm-a released from macrophages as inducer of lysyl hydroxylase 2 (LH2) expression in fibroblasts. LH2 is known to play a pivotal role directing DHLNL collagen cross-links. Collectively, our findings provide novel mechanistic insights in the link between type 2 immunity and initiation of pro-fibrotic pathways, and offer interesting perspectives for therapeutic innovation.