**Possible role of autophagy in sclerodema**

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Autophagy is an essential intracellular self-degradation system to maintain the homeostatic balance between the synthesis, degradation and recycling of cellular proteins and organelles. Recent experimental evidence suggests autophagy is involved in systemic lupus erythematosus (SLE), rheumatoid arthritis and idiopathic pulmonary fibrosis. The association with autophagy and scleroderma (SSc) is also suspected. However, the role of autophagy in the pathogenesis of tissue fibrosis is still unclarified, and the association of which phase of scleroderma is largely unknown. Therefore, we investigated the role of autophagy in the pathogenesis of SSc by using skin and lung samples of bleomycin (BLM)-induced SSc murine model and human SSc skin. BLM or phosphate-buffered saline (PBS) was injected into shaved back of C3H/HeJ mice for 2 or 4 weeks. Also, we used skin samples of edematous phase SSc and those of sclerotic phase SSc. We carried out haematoyxlin and eosin (HE) stain for evaluation of skin sclerosis and immunofluorescent stain by anti-microtubule-associated protein 1 light chain 3 (LC3) antibody, which is the most common autophagy marker. We evaluated the number of LC3-positive cells in the maeocyte, endothelial and lung and also the skin samples (both edematous and sclerotic phase). There was no clear difference between the number of LC3-positive dots of skin samples from PBS mice and those from BLM mice qualitatively. We are currently investigating the number of LC3-positive dots of mice lungs and human skin samples in more numbers.

**Recapitulation of ectopic lymphocytes aggregation and B cell phenotype in the skin lesions of patients with pemphigus**

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Ectopic lymphoid aggregates could be observed in several autoimmune diseases (e.g. rheumatoid arthritis). Pemphigus is an organ specific autoimmune disease and caused by circulating antibodies. Little is known about the features and function of lesional lymphocytes. The aim of this study is to illustrate the lymphoid neogenesis and B cell phenotype in pemphigus skin lesions. Methods: 197 HE-stained sections of pemphigus vulgaris (PV) and pemphigus foliaceus (PF) skin lesions in our department were collected. The histological grading of lymphoid aggregates was assessed according to a published grading system with grade 1 aggregates displaying a total cell number between 2 and 5 cells, grade 2 between 6 and 10 and grade 3 greater than 10. Immunohistochemistry staining for CD3, CD20 and CD138 was performed. B and T cells were stained by using CD20 and CD45 and plasmablasts by CD138. Results: Amongst the most decreased compounds in PP skin were cortisone and cortisol (357 and 1057-fold decreased, p < 0.001) and MIP-2 (p < 0.001) in ears of DNFB treated mice were significantly suppressed by oligo-HA application when measured by quantitative real-time PCR. The elevation of IgE levels in DNFB treated mice was reduced by p < 0.01). These data show that topical application of oligo-HA induces the suppressive effect to AD-like dermatitis by affecting the inflammatory status in skin and can influence clinical outcome.

**Metabolic profiling of psoriasis skin reveals localized cortisol deficiency resulting in maintenance of inflammatory state and disruption of epidermal differentiation**

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The factor involved in maintaining inflammatory state in psoriatic skin is poorly understood. To address this knowledge gap, we performed metabolic and transcriptomic profiling of skin from 6 lesional (PP) and non-lesional (PN) psoriatic skin, and 6 healthy (NN) individuals. We identified 377 RNA viruses altered between NN, PN and PP skin (p < 0.05). Amongst the most decreased compounds in PP skin were cortisone and cortisol (357 and 1057-fold decreased, p < 0.001). In contrast cortisol levels were similar in psoriatic (in the healthy controls (p = 0.2)). Genes involved in immune response and inflammation were expressed in NN skin but suppressed in PP skin (HSD11B1, p < 0.001, confirmed by HLC) consistent with decreased nuclear localization of the glucocorticoid receptor. Using a 3-D human epidermis culture model, we uncovered a differentiation-dependent increase in HSD11B1 expression (p < 0.05) and cortisol consumption (2.9-fold decrease compared to baseline, n = 3, p < 0.01). When starved of exogenous steroids, epidermal differentiation was markedly altered (COR, FLG, p < 0.05) and associated with increased mRNA expression and secretion of pro-inflammatory mediators including CXCL9 and CXCL10 (n = 3, p < 0.05). Notably, in vivo application of topical glucocorticoids led to rapid restoration of glucocorticoid biosynthesis gene expression coincident with normalization of epidermal differentiation (n = 3). These data demonstrate that steroids have a dual role in the epidermis acting as a co-factor in facilitating epidermal differentiation and as a suppressor of inflammatory responses. The localized steroid deficiency in PP skin is likely to maintain inflammatory state and impede restoration of normal epidermal differentiation.

**Aggregation of Dsg-specific lymphocytes and antibody production in the lesions of pemphigus vulgaris patients**

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Recent experimental evidence suggests that Tregs may influence tissue-specific stem cell functions. To address this knowledge gap, we performed metabolomic and transcriptomic profiling of skin from 6 lesional (PP) and non-lesional (PN) psoriatic skin, and 6 healthy (NN) individuals. We identified 377 RNA viruses altered between NN, PN and PP skin (p < 0.05). Amongst the most decreased compounds in PP skin were cortisone and cortisol (357 and 1057-fold decreased, p < 0.001). In contrast cortisol levels were similar in psoriatic (in the healthy controls (p = 0.2)). Genes involved in immune response and inflammation were expressed in NN skin but suppressed in PP skin (HSD11B1, p < 0.001, confirmed by HLC) consistent with decreased nuclear localization of the glucocorticoid receptor. Using a 3-D human epidermis culture model, we uncovered a differentiation-dependent increase in HSD11B1 expression (p < 0.05) and cortisol consumption (2.9-fold decrease compared to baseline, n = 3, p < 0.01). When starved of exogenous steroids, epidermal differentiation was markedly altered (COR, FLG, p < 0.05) and associated with increased mRNA expression and secretion of pro-inflammatory mediators including CXCL9 and CXCL10 (n = 3, p < 0.05). Notably, in vivo application of topical glucocorticoids led to rapid restoration of glucocorticoid biosynthesis gene expression coincident with normalization of epidermal differentiation (n = 3). These data demonstrate that steroids have a dual role in the epidermis acting as a co-factor in facilitating epidermal differentiation and as a suppressor of inflammatory responses. The localized steroid deficiency in PP skin is likely to maintain inflammatory state and impede restoration of normal epidermal differentiation.