013  Different effects of combined blockade of IL-4/IL-13 and selective inhibition of IL-13 in in vitro model systems for atopic dermatitis with allergen stimulated lymphocytes

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New treatments for atopic dermatitis have been focussed on the development of humanized antibodies directed against Th2 cytokines for the last few years. Dupilumab is the only antibody approved for the treatment of AD so far and blocks the IL-4Rα receptor subunit, inhibiting IL-4/IL-13 signaling pathways. Two specific anti-IL-13 antibodies have shown promising results in clinical trials. The mechanism of IL-4 and IL-13 has similarities, in part because they share the same receptor subunits and thus signal through similar pathways. Our work focuses on the question of whether combined blockade of IL-13 and IL-4 or selective inhibition of IL-13 have different functional effects on lymphocytes from sensitized patients with atopic dermatitis. After stimulation of mononuclear cells from the blood of patients sensitized via IgE against house dust mite or against autoantigens, antigen induced proliferation and cytokine production were measured after IL-4 and/or IL-13 blockade. T cell subtypes were determined and IL-lymphocytes were examined with regard to IgE production. Surprisingly, combined IL-4/IL-13 blockade led to an increase in antigen-specific growth of mononuclear cells in short-term cultures over 7 days. This effect was not caused by IL-11 inhibition alone. The investigations with long-term cultures over 3 weeks showed a suppressive effect on the growth of the antigen-specific T cell lines by both the selective IL-11 and the combined IL-4/IL-13 blockade. Moreover, specific IL-11 treatment had an effect on IL-5 and IL-17 levels whereas ALL-4Rα treatments affected IL-5 levels only. IgE monitoring showed that both forms of IL-4/IL-13 inhibition reduced in vitro IgE production in anti-CD40 plus IL-13 stimulated cells by more than 70%. Our work shows different functional effects by combined IL-4/IL-13 resp. by selective IL-11 blockade raising the question of the benefit of additional IL-4 inhibition in Th2 directed treatments of AD.

015  Role of hippo signaling in apoptosis of lupus keratinocytes

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Skin inflammation and photosensitivity are common manifestations of systemic lupus erythematosus. Yet mechanisms underlying heightened cell death and epidermal inflammation following UV light remain unclear. We performed genome-wide DNA methylation analyses on keratinocytes (KCs) DNA from non-lesional, non-sun-exposed skin of SLE patients and healthy controls and identified Hippo signaling as the top canonical pathway. Hippo signaling is a conserved developmental and cellular stress response pathway with the potential for cell death. KCs in SLE show evidence of increased proliferation, hyperplasia, and epidermal hyperplasia. To determine functional relevance of our methylation data, we compared paried RNA-seq samples stimulated with IFNγ and IFNg. We found a negative correlation between IFN induced genes and methylation signatures, suggesting methylation changes result in functional expression differences in vivo. To further evaluate in situ, we analyzed expression data and localization of these proteins using immunofluorescence microscopy of lesional biopsies and found a significant increase in cytoplasmic retention of phosphorylated Yap in SLE compared to controls. Collectively, our work describes a new mechanistic paradigm for how Hippo signaling through restriction of Yap transcriptional activity is a mechanism of dysregulated apoptosis and photosensitivity in lupus skin.

016  Three North American cases of cutaneous Pemphigus vulgaris with no history of mucosal disease

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Pemphigus vulgaris (PV) is a group of autoimmune blistering diseases including Pemphigus (PV) and Pemphigus foliaceus (PF). Explanation of lesion morphogenesis has been elegantly proffered by the Desmoglein Compensation Hypothesis (DCH) based on the epidermal distribution of desmogleins (DGs) and autoantibody profiles. In this theory, PV is characterized by subcorneal lesions in the presence of only anti-Dg1 antibodies, while PV lesions are suprabasal and associated with anti-Dg1 and -Dg3 in mucocutaneous PV. However, logical inconsistencies in the DCH have emerged and exceptions have been published in multiple small-scale studies. One of these inconsistencies described by our group and others is that some PV patients present with solely cutaneous PV and no history of mucosal disease. In this study, we report three cases of clinically and histologically confirmed PV without any history of mucosal lesions. One of these patients, two do not carry the most common PV associated HLA alleles, DRB1*04:02 or DQB1*05:03. The same two patients also tested negative for the primary PV associated autoantibodies, anti-Dg3 and anti-Dg1, while in active disease status. We confirm the first documented individual cases of PV without any history of mucosal disease. We also confirm cPV without any history of mucosal disease, further challenging the fidelity of the DCH. The two of the 3 patients reported did not type for the common PV associated HLA genes or display anti-Dg autoantibodies while in active disease, suggesting some cPV patients may display PV via genetic and immune mechanisms that differ from typical mucosal or mucocutaneous PV.

017  Endotypes of mucous membrane pemphigoid predict disease severity

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Mucous membrane pemphigoid (MMP) is an autoimmune bullous disease predominantly involving mucosa and is caused by autoantibodies directed against BP180. Collagen VII, Laminin 332, or β4 integrin. Oral/opharyngeal lesions are the most common, but any mucosal membrane can be involved. The potential long-term consequences are devastating, including blindness, airway compromise, loss of dentition and strictures. Despite its morbidity and mortality, MMP have not been well characterized. The goal was to determine if MMP can be resolved into distinct disease endotypes based on the autoantibody target. Seventy-one patients who met clinical, histological and immunological criteria for MMP were enrolled. Hindgut biopsies, clinical status and lesional lesional lesional lesional lesional lesional lesional lesions was 3-4-fold higher than the nares for unaffected skin from the same patient (p<0.0001). The absence of autoantibodies to these targets does not fully explain disease ac-

018  TSS1-1: Staphylococcus aureus in bullous pemphigoid

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Bullous pemphigoid (BP) is an autoimmune blistering disease that is treated with high dose immunosuppression due to lack of specific targets. Staphylococcus aureus is a communal bacterium implicated inflammatory and autoimmune disorders because of its secretion of multiple superantigen effects. We prospectively evaluated S. aureus colonization and its production of toxic shock syndrome toxin-1 (TSS1-1) in 28 new onset BP patients. Inclusion criteria were active blistering and linear basement membrane IgG/C3 or a serum ELISA >14 for BP180 IgG. Bacterial swabs were collected from the lesion interior, nares and healthy skin from the same patient. Swabs were cultured for S. aureus and the same two patients also tested negative for the primary PV associated autoantibodies, anti-Dg3 and anti-Dg1, while in active disease status. We confirm the first documented individual cases of PV without any history of mucosal disease. We also confirm cPV without any history of mucosal disease, further challenging the fidelity of the DCH. The two of the 3 patients reported did not type for the common PV associated HLA genes or display anti-Dg autoantibodies while in active disease, suggesting some cPV patients may display PV via genetic and immune mechanisms that differ from typical mucosal or mucocutaneous PV.

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