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 and keratinocyte dissociation

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New therapeutic approach of atopic dermatitis (AD) has been focused 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 been shown to provide promising results in clinical trials. The kinetics of IL-4 and IL-13 have 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 IL-13 blockade. T-cell subsets were determined and IL-13 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-IL-13 treatments affected IL-5 only. IL-11 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-11 inhibition in Th2 directed treatments of AD.

014 Role of hippo signaling in apoptosis of lupus keratinocytes

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Skin inflammation and photosensitivity are common manifestations of systemic lupus erythematosus (SLE), yet mechanisms underlying heightened cell death and epidermal inflammation following UV light remain unclear. We performed genome-wide DNA methylation analysis on keratinocyte (KC) DNA from non-lesional, non-sun-exposed skin of SLE patients and healthy controls and identified Hippo signaling as the top canonical pathway. Hippo mutations increase cell proliferation in oncogenesis models, including in UV-induced neoplasms. However, this pathway has not been studied in inflammatory skin disease. YAP is a critical component in the regulation of the Hippo pathway. Through a kinase cascade that critical component in the regulation of the Hippo pathway. Through a kinase cascade that involves LATS1/2, TAZ and WW1C, the Hippo pathway targets YAP for phosphorylation, preventing nuclear translocation and transcriptional activity of YAP. We aimed to explore the role of Hippo signaling in skin diseases and to investigate the potential of pharmacological and genetic inhibition of YAP as a novel therapeutic strategy for the treatment of lupus.

015 Role of lipopolysaccharide (LPS) in the pathogenesis of lupus

DCH. Two of the 3 patients reported did not type for the common PV-associated HLA genes (HLA-A2 and HLA-B7). A third patient typed HLA-A2, HLA-B7 and HLA-B18. cPV patients reported in the literature have been classified as such based on their lesion morphology. Explanation of lesion morphology has been elegantly proffered by the Desmoglein Compensation Hypothesis (DCH) based on the epidermal distribution of anti-Dsg3 in mucosal PV, or anti-Dsg1 and -Dsg3 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 disease. This phenomenon of mucocutaneous PV is the cause of a novel patient-derived antibody in the skin with potential disease relevance.

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

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Pemphigus is a group of autoimmune blistering diseases including Pemphigus vulgaris (PV) and Pemphigus foliaceus (PF). Explanation of lesion morphology has been elegantly proffered by the Desmoglein Compensation Hypothesis (DCH) based on the epidermal distribution of desmoglein (Dsg) proteins and autoantibody profiles. In this theory, PF is characterized by subcorneal lesions in the presence of only anti-Dsg1 antibodies, while PV lesions are suprabasilar and associated with anti-Dsg1 in mucosal PV, or anti-Dsg1 and -Dsg3 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 disease. This phenomenon of cutaneous PV is the cause of a novel patient-derived antibody in the skin with potential disease relevance.

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, and 4 College of Dentistry University of Iowa, Iowa City, Iowa, United States

Skin inflammation and photosensitivity are common manifestations of systemic lupus erythematosus (SLE), yet mechanisms underlying heightened cell death and epidermal inflammation following UV light remain unclear. We performed genome-wide DNA methylation analysis on keratinocyte (KC) DNA from non-lesional, non-sun-exposed skin of SLE patients and healthy controls and identified Hippo signaling as the top canonical pathway. Hippo mutations increase cell proliferation in oncogenesis models, including in UV-induced neoplasms. However, this pathway has not been studied in inflammatory skin disease. YAP is a critical component in the regulation of the Hippo pathway. Through a kinase cascade that involves LATS1/2, TAZ and WW1C, the Hippo pathway targets YAP for phosphorylation, preventing nuclear translocation and transcriptional activity of YAP. We aimed to explore the role of Hippo signaling in skin diseases and to investigate the potential of pharmacological and genetic inhibition of YAP as a novel therapeutic strategy for the treatment of lupus.

018 TSS1-S: Staphylococcus aureus in bullous pemphigoid

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Bullous pemphigoid (BP) is an autoimmune bullous disease that is treated with high dose immunosuppression due to lack of specific targets. Staphylococcus aureus is a common bacterium implicated inflammatory and autoimmune disorders because of its secretion of both superantigen effects. We prospectively evaluated S. aureus colonization and its production of toxic shock syndrome toxin-1 (TSS1-T1) 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 obtained from the lesion interior, nares and uninvolved skin. S. aureus was matched in skin of 28 age- and sex-matched controls. Staphylococcal growth was assessed on blood agar, and TSS1-T1 production by cultured S. aureus isolates and in blister fluid was evaluated by immunoblot. S. aureus was cultured from the lesion interior in 13 (46%) patients. TSS1-T1 was 3.4-fold higher than the nose for uninvolved skin from the same patients (p<0.0030) and 6-fold higher than control nares or skin (p=0.0015). Evaluation of superantigen gene profiles using PCR indicated that 96% of BP patients are colonized with S. aureus. TSS1-T1 produced by S. aureus isolates identified in BP was neutralized by C20/20 and reduced by C2, while ELISA did not correlate. Interestingly, S. aureus colonization was not observed in patients who had received prior antibiotics. In colonized patients with severe disease, addition of anti-staphylococcal antibiotics resulted in clinical improvement and reduced TSS1-T1 production. These findings show that Staphylococcus aureus is an important determinant of TSS1-T1 producing S. aureus that is not evident in the general elderly population. Thus, immunosuppressive therapies should be balanced with the knowledge that S. aureus is likely the primary source of TSS1-T1 production in BP and the knowledge that antibiotics may play an important therapeutic role through bacterial clearance.