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 treatment of atopic dermatitis 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 also recently shown promising results in clinical trials. The blockade 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 autoregions, antigen induced proliferation and cytokine production were measured after IL-4 and 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-IL-4ra 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.

Role of hippo signaling in apoptosis of lupus keratinocytes

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Hippo signaling is a highly conserved signaling network that is critical for maintaining organ size and tissue homeostasis. When activated, it induces cell cycle arrest or apoptosis, depending on the cellular context. In human skin, the signaling from various Hippo effectors is known to stimulate keratinocyte apoptosis in response to skin injury. However, our understanding of the role of Hippo signaling in human lupus keratinocytes is still limited. Using a combination of immunofluorescence microscopy, flow cytometry, and Western blotting, we analyzed Hippo signaling in keratinocytes from biopsies of lupus skin and healthy controls. We found a significant increase in the expression of the Hippo pathway components LATS1/2, YAP/TAZ, WW1, and WW2 in skin from lupus patients compared to controls. Furthermore, we observed a negative correlation between the expression of LATS1/2 and YAP/TAZ in skin from lupus patients (p = 0.17) and healthy controls (p = 0.15), suggesting that disruption of the Hippo pathway may be involved in the pathogenesis of lupus skin disease. Our findings suggest that Hippo signaling may play a role in the pathogenesis of lupus keratinocytes, furthering our understanding of the molecular mechanisms underlying this autoimmune disease.