PRURITUS

INTERLEUKIN-31 COUPLES ITCH SENSATION TO INFLAMMATION IN ALLERGIC SKIN DISEASE

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Background: Interleukin-31 (IL-31) is a powerful mediator of itch and rash. IL-31 administered to skin triggers dermatitis and activates sensory afferents to drive scratching behavior. Its receptor, IL31RA/OSMR, is expressed on myeloid cells in addition to TRPV1+ afferents. Therapeutic antibodies directed against IL31RA show promise in clinical trials for atopic dermatitis and other chronic pruritic disorders.

Objective: Our objective is to elucidate circuits IL-31 uses to regulate pruritoceptive sensory neurons and skin-infiltrating immune cells in the context of cutaneous inflammation. Our central hypothesis is that IL-31 couples itch and rash via direct effects on both pruritoceptive afferent circuits and Th2 cytokine-mediated inflammation.

Methods: We developed novel IL31-deficient mice (IL31KO), and challenged them with a panel of topical treatments known to stimulate dermatitis. Skin inflammation was assessed by flow cytometry, in situ hybridization, and RNA-sequencing. Pruritus intensity was determined by scoring the frequency of spontaneous hind-paw scratching bouts in treated animals.

Results: Observed effects of IL31KO on skin inflammation differed by inflammatory stimulus. Whereas most stimuli resulted in indistinguishable skin inflammation in WT and IL31KO animals, other treatments caused increased cytokine production in IL31KOs. IL31-dependent changes in skin inflammation after topical treatment did not correlate with scratching behavior, which was significantly diminished in IL31KO animals despite intact scratching responses to exogenous pruritogens.

Conclusion: In contrast to the hypothesis that IL-31 is pro-itch and pro-rash, our results demonstrate a complex dual role with important implications for anti-IL-31 therapy. Decreased scratching behavior was observed in IL31KO animals, consistent with pruritogenic effects of IL-31 on sensory nerves. However, IL31KO unexpectedly increased local and systemic Th2 inflammatory responses to some stimuli, suggesting a context-

specific anti-inflammatory role for IL-31. Taken together, these results demonstrate that IL-31 may have opposite effects on nerves and immune cells, and couples these two distinct biological circuits in dermatitis-affected skin.