Basophil: The cell that itches

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Basophils are myeloid cells characterized by the expression of basophilic granules in their cytoplasm and the high-affinity IgE receptor FcεRIa, but not c-kit, on their surface. Basophils normally constitute less than 1% of peripheral blood leukocytes in human and mice. They have been implicated in the pathogenesis of autoimmune diseases, inflammatory and allergic disorders, pruritic diseases, and cancer. Following activation by FcεRI ligation or cytokines, basophils secrete histamine, T42 cytokines (eg, IL-4, IL-13, and IL-31), proteases, and eicosanoids such as leukotrienes (LTs) and prostaglandins. Importantly, basophil-derived IL-4 promotes T42 cell differentiation. Basophil activation by cytokines can be IgE dependent or IgE independent. For instance, IL-3–mediated basophil activation is IgE dependent, whereas thymic stromal lymphopoietin (TSLP)-mediated basophil activation is IgE independent. Finally, basophils can acquire peptide–MHC II complexes from dendritic cells via trogocytosis and present these complexes to T cells.

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by intense itch episodes, epidermal barrier dysfunction, type 2–dominated immune responses, eosinophilia, and elevated serum IgE levels. Intense itch in AD interferes with sleep, affects the quality of life, and results in loss of productivity. Itch can be mediated by histaminergic and nonhistaminergic pathways. Type 2 cytokines, including IL-4, IL-13, TSLP, and IL-31, but not histamine, drive chronic itch by interacting with their receptors on sensory neurons. The mechanisms that drive acute itch flares are unknown.

In a recent report, Wang et al demonstrated that basophil-sensory neuron interactions are involved in acute itch flares. The authors analyzed self-reported daily acute itch severity scores from 2 clinical trials in patients with AD. They found that 46.5% of the patients (74 of 159) had an acute itch flare over a 2-month period. Using blood from this cohort, they demonstrated that the presence of allergen-specific IgE is correlated with acute itch episodes, indicating that allergen exposure might be driving acute itch flares. To investigate the mechanisms underlying acute itch flares, the authors established a mouse model of acute itch flares. Mice were sensitized on ear skin simultaneously with the allergen ovalbumin (OVA) with or without the irritant calcipotriol (MC903) for 10 days. Following challenge with intradermal injection of OVA at a separate skin site (the cheek), OVA plus MC903–sensitized mice, but not OVA-sensitized mice, developed acute itch flares at the site of antigen challenge. Acute itch was mast cell–independent but IgE dependent. This is in contrast to the chronic itch that occurred at the sensitization site (the ear), which was IgE independent. Intriguingly, MC903 plus OVA–sensitized mice displayed upregulation of murine basophil activation markers compared with OVA-sensitized controls. Basophils from patients with AD also demonstrated enhanced expression of activation markers such as CD203c and FcεRIa compared with that demonstrated by basophils from healthy controls. These observations prompted the authors to investigate the role of basophils in acute itch. They found that targeted activation of basophils alone via a chemogenetic approach induced itch in mice. Using both pharmaceutical and genetic approaches, the authors demonstrated that basophils are essential for the acute itch flares in their mouse model. Furthermore, they showed that basophils became elongated and localized with sensory neurons in the antigen-challenged skin of mice sensitized with OVA plus MC903. Importantly, intradermal injection of supernatants of blood basophils from sensitized mice activates sensory neurons and evokes acute itch flares in naive mice. To identify the responsible mediators, the authors first analyzed publicly available microarrays and found that compared with tissue-resident mast cells, mouse peripheral blood basophils demonstrate evidence of increased LT biosynthesis. Blocking of LT biosynthesis by pharmacologic inhibition or genetic ablation indicated that LTs play a crucial role in acute itch flares. Finally, the authors established that basophil-derived LTC4 acts on the CysLTR2 receptor on sensory neurons to mediate acute itching in a manner dependent on TRPV1 and TRPA1 calcium channels.

It is well established that basophils promote AD-like allergic skin inflammation. TSLP-elicited basophils are the dominant source of IL-4 in the inflamed skin in mouse models of AD. Depletion of basophils in these models results in a significant reduction of eosinophils and neutrophils, as well as in epidermal thickening. A recent report shows that basophils initiate skin barrier dysfunction through IL-4 but promote resolution of allergic skin inflammation through expansion of M2 macrophages and M-CSF in mice.

Patients with AD are often heavily colonized by Staphylococcus aureus, which adversely affects disease severity. Furthermore, colonization of skin by S aureus precedes the onset of AD in infants. Recent unpublished findings from our laboratory demonstrate that in mice, basophil-derived IL-4 promotes colonization skin by S aureus. Application of S aureus to tape-stripped skin causes recruitment of cutaneous basophils and enhanced basophil-derived IL-4 expression. Importantly, basophil-derived IL-4 inhibited IL-23 production by keratinocytes, blocked IL-17A production by TCRγδ cells, and suppressed IL-17A–
driven induction of neutrophil-attracting chemokines and antimicrobial peptides in keratinocytes, thereby promoting superficial skin infection with *S. aureus* (Fig 1). *S. aureus* has been reported to induce IL-31.10 The role of IL-31 in itch flares is well studied. Whether upregulation of IL-31 by *S. aureus* synergizes with basophil-derived LTC4 to magnify acute itch flares in AD remains to be investigated.

The study by Wang et al6 provides strong evidence of a novel additional pathway by which basophils participate in the pathogenesis of AD, namely, in the mediation of acute itch flares. Like all exciting studies, it raises a number of questions. What is the equivalent of MC903 that acts during antigen sensitization of patients with AD to result in acute itch flares? What are the underlying mechanisms for the activation of basophils and their recruitment at sites of itch flares? Does inhibition of FceRI-mediated basophil activation account for the improvement observed in some patients with AD treated with anti-IgE? Although the use of global LT synthesis inhibitors and CysLT inhibitors has had no consistent salutary effects on AD severity, is there a role for specific blockade of LTC4 or CysLTR2 in reducing itch flares in patients with AD? The answers to these questions are important, as not all patients with AD respond to currently available therapies in a satisfactory manner.

**REFERENCES**