

Previews

Basophils add fuel to the flame of eczema itch

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Children and adults with atopic dermatitis suffer from intractable chronic itch and can also experience acute itch flare ups that significantly increase itch intensity. In this issue of *Cell*, Wang et al. demonstrate that a subset of basophils activates sensory neurons to drive allergen-evoked itch flare ups in atopic dermatitis.

If you suffer from seasonal allergies, chances are you had eczema as a child. Atopic dermatitis (AD), or eczema, is the most common chronic itch disorder. In the United States alone, ~10% of adults and 20% of children suffer from the red, dry, itchy skin rashes characteristic of this disease (Silverberg, 2019). The intractable itch associated with AD can cause loss of sleep, inability to focus or work, and depression, all of which severely decrease quality of life. While AD is not typically caused by allergens, it is often followed by the development of food allergies, allergic rhinitis, and finally asthma, in a process called the atopic march. The disrupted skin barrier in AD leads to increased exposure to allergens, the acquisition of allergen-specific immunoglobulin E (IgE), and sensitization, which in turn, promotes the atopic march. Children with AD are six times more likely to develop allergies, and 50% will develop asthma (Silverberg, 2019). Individuals with AD can also suffer from acute itch “flare ups,” where the skin becomes intensely and unbearably itchy. Why some individuals experience itch flares and what mechanisms trigger the development of these flares are unknown. In this issue of *Cell*, Wang et al. (2021) show that AD patients with high levels of allergen-specific IgE are more likely to develop itch flares and that basophil-sensory neuron interactions may be the trigger for these atopic itch flares (Figure 1).

This study first examined mechanisms of AD itch flares by analyzing self-reported daily itch severity scores and blood previously collected from patients

in two clinical trials. The authors discovered a much higher than expected prevalence of itch flares and thus utilized blood samples from this cohort of patients to test the hypothesis that allergen exposure triggers these flares. In support of this hypothesis, they found that the presence of allergen-specific IgE in the blood correlates with acute itch flares. Previous studies have shown ~70% of patients with AD harbor allergen-specific IgE (Flohr et al., 2004; Mitchell et al., 1982; Zeller et al., 2009). However, the contribution of IgE to AD inflammation and itch was unknown.

To further investigate the mechanisms underlying AD itch flares, Wang et al. (2021) established a mouse model by sensitizing and challenging atopic mice to the allergen ovalbumin. This model phenocopies the clinical correlation between elevated allergen-specific IgE and itch flares. While mast cells are required for acute allergic itch, surprisingly, the authors show that mast cells are dispensable for AD itch flares (Steinhoff et al., 2018). This interesting finding led them to search for a new cellular mediator of AD itch flares.

To this end, the authors turned back to patient samples and compared circulating immune cells in AD versus healthy control subjects. They discovered that individuals with AD harbor a unique subset of basophils that display enhanced expression of the high-affinity IgE receptor FcεRI and CD203c and were previously associated with enhanced IgE sensitivity and acute allergy (Mitchell et al., 1982; James et al., 1993). Likewise, immune cell profiling in the mouse model

revealed the presence of these IgE-R⁺ basophils begins during the early development of AD, before allergen challenge (Figure 1, left). Together, these findings suggest that AD inflammation triggers a phenotypic switch in circulating basophils that are primed for enhanced allergen stimulation and mediate atopic itch flares.

Are IgE-R⁺ basophils necessary for the development of itch flares? Using both genetic and pharmacological depletion of basophils in mice, the authors demonstrate that basophils do not contribute to chronic AD itch but are essential for the itch associated with allergen-evoked AD flares. Following allergen-exposure, basophils display an elongated morphology and localize alongside free nerve endings in the skin. These results suggest degranulating basophils are functionally coupled to neurons that transmit itch signals and release inflammatory mediators in the skin. The authors performed three key experiments to test this model directly. First, they used molecular genetic tools to show that acute degranulation of basophils is sufficient to drive itch behaviors in naive mice. Second, they demonstrated that naive mice displayed itch-evoked scratching behaviors to injection of granule contents released from basophils purified from allergen-sensitized AD mice; this degranulate also directly activates a subset of cultured sensory neurons. Finally, the authors identify leukotriene C4 (LTC4) as the basophil mediator that activates its receptor, CysLTR2, on sensory neurons to drive atopic itch flares in mice (Figure 1, right). While AD basophils have been previously shown to release LTC4 (James

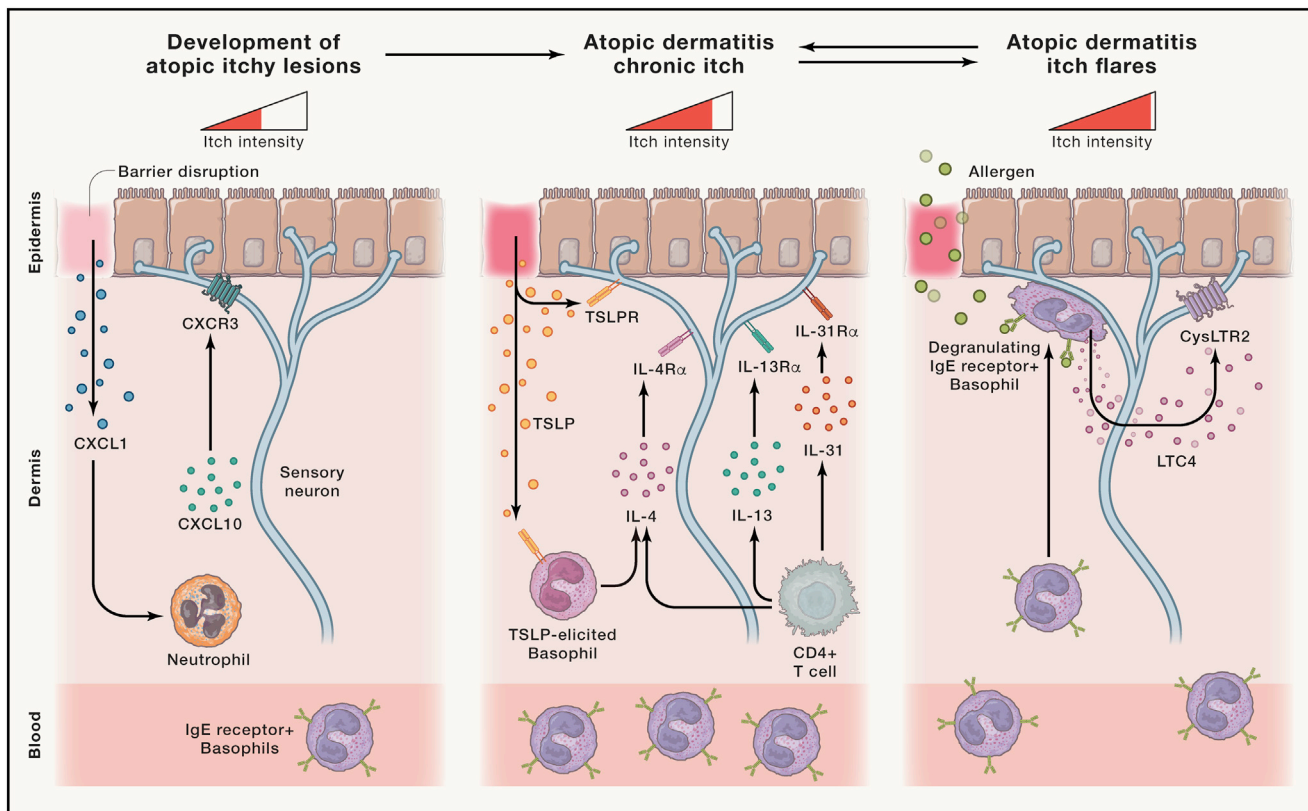


Figure 1. The cellular and molecular players of atopic dermatitis

Distinct neuroimmune interactions drive three key phases of atopic dermatitis (AD) itch: (1) development of atopic itch and lesions begins with skin barrier disruption and release of inflammatory cytokines, including CXCL1 (light blue dots), that recruit neutrophils, which trigger the release of CXCL10 (dark blue dots) and activation of CXCR3-expressing sensory neurons that transmit itch signals (left; [Walsh et al., 2019](#)). This phase also displays an increase in high-affinity IgE-R⁺ basophils circulating in the blood (left; [Wang et al., 2021](#)). (2) During chronic itch and inflammation, AD skin lesions are characterized by infiltration of TSLP receptor-expressing basophils, which release IL-4 (purple dots) and CD4⁺ T cells, which also release IL-4, as well as IL-13 (green dots) and IL-31 (pink dots). Sensory neurons expressing receptors for TSLP, IL-4, IL-13, and IL-31 are consequently activated and drive itch sensation (middle; [Oetjen et al., 2017](#); [Walsh et al., 2019](#); [Yamanishi et al., 2020](#)). (3) During allergen-stimulated AD itch flares, the disruption of the skin barrier allows increased allergen infiltration (large green dots). IgE-R⁺ basophils are recruited to the skin, localize near free nerve endings of sensory neurons, and degranulate to release leukotriene C4 (LTC4) (purple dots). Sensory neurons expressing the LTC4 receptor, CysLTR2, are activated and transmit itch signals that drive itch sensations and scratching behaviors during these itch flare ups ([Wang et al., 2021](#)).

[et al., 1993](#)), this is the first study to show that basophil-derived LTC4 is a mediator of AD-associated itch. These results reveal an exciting new role for basophils in atopic itch flares.

Overall, the findings from Wang et al. (2021) expand our understanding of AD and open several new directions for future studies in the lab and clinic. First, what mechanisms prime basophils to take on this IgE-R⁺ phenotype? Second, what factors trigger the transitions between the different clinical phases of AD? Early AD itch and lesion development is mediated by neutrophil-neuron signaling via CXCR3 ([Figure 1](#), left), while chronic AD skin inflammation and itch is mediated by TSLP-elicited basophils and T cells and TSLP, IL-4, IL-13, and IL-31- acti-

vated sensory neurons, respectively ([Figure 1](#), middle) ([Oetjen et al., 2017](#); [Walsh et al., 2019](#); [Yamanishi et al., 2020](#)). This study now reveals that cross-talk between IgE-R⁺ basophils and CysLTR2⁺ sensory neurons is essential for atopic itch flares ([Figure 1](#), right). Third, how common are IgE-mediated itch flares in individuals with AD? Here, the authors found that 43% of AD patients experienced itch flares over 2 months. This is likely an underestimate as AD and allergen exposure are highly dynamic. Finally, is inhibition of IgE signaling a potential therapeutic for AD-associated itch? As the authors discuss, anti-IgE therapy was not effective in reducing chronic skin inflammation, but itch relief and flares were not specifically addressed

in clinical trials. Answering these questions will lead to a better understanding of the complex roles of basophils in atopic disease and may lead to new therapeutics.

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DECLARATION OF INTERESTS

D.M.B. is on the scientific advisory board of eS-cient Pharmaceuticals. She has patents pending on inhibiting neuronal signaling to treat development of chronic itch.

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Breathing new life into the rational design of Alzheimer's therapeutics

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γ -secretase is a promising therapeutic target for Alzheimer's disease, but all inhibitors and modulators have failed due to toxicity or low efficacy. In this issue of *Cell*, Yang et al. provide cryo-EM structures of γ -secretase bound to three inhibitors and a modulator, giving new promise to targeting γ -secretase therapeutically.

Alzheimer's disease (AD) has been one of medicine's most notoriously intractable diseases. Human genetics and biochemical experiments have identified key players in AD pathogenesis and advanced the amyloid hypothesis for the etiology of the disease. With central players and a mechanism in hand, pharmaceutical companies have invested in small molecules that target the central proteolytic machinery responsible for the disease. Many of these putative therapeutics failed in clinical trials due to challenges including low efficacy and poorly tolerated side effects. Slowly, drug companies have begun to chase other AD pathways instead. Recent advances in structural biology, such as Yang et al. (2020) in this issue of *Cell*, give new promise to the design of AD therapeutics.

The holy grail of rational drug design—an all-atomic model of the drug target—

had challenged structural biologists for decades. The rise of cryoelectron microscopy (cryo-EM), however, has provided unprecedented structural information about the proteolytic complex at the core of AD pathogenesis: γ -secretase. One hallmark pathological feature of AD brains is dense neuritic plaques composed of the neurotoxic peptide, β -amyloid. γ -secretase is responsible for the proteolytic generation of β -amyloid from the amyloid precursor protein (APP; Figure 1A) (Dries and Yu, 2008). A large, multisubunit, transmembrane complex, the structure of γ -secretase has been refractory to study through nuclear magnetic resonance spectroscopy and X-ray crystallography. Recently, however, Shi and colleagues have used cryo-EM to determine atomic structures for the free and substrate-bound γ -secretase complex (Bai et al., 2015; Zhou et al., 2019).

Now, they provide structures of γ -secretase bound to two types of therapeutics: γ -secretase inhibitors (GSIs) and modulators (GSMs) (Yang et al., 2020; Figures 1B and 1C).

One of the first GSIs was L-685,458 (L458), a peptidomimetic whose hydroxyethylene was predicted to serve as a transition-state analog (TSA) (Shearman et al., 2000). Although L458 never entered clinical trials, the compound served as a critical tool for dissecting γ -secretase structure and function. In this issue, Yang et al. (2020) show that L458 is indeed a TSA, occupying the active site aspartyl residues of the subunit Presenilin (PS). The authors also describe two interactions that were not predicted during the development of L458: hydrogen bonding to the conserved GxGD motif of PS1 and completing a hybrid three-stranded β