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Cytokine modulation of atopic itch

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Atopic dermatitis (AD) is an inflammatory skin disease characterized by two primary features: relapsing skin lesions and chronic itch. Major advances in our understanding of type 2 immunity have led to new insights into the critical factors that promote the development and persistence of AD-associated skin inflammation. Although inflammation is strongly associated with the development of atopic itch, the precise mechanisms by which itch arises in AD are poorly understood. In this review, we highlight recent studies that have started to unveil how various proinflammatory factors released within the skin can elicit sensations of itch and discuss the therapeutic potential of targeting these neuroimmunologic processes.

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have gained an increasing appreciation of the cellular and molecular mechanisms that drive AD-associated inflammation. However, while inflammation is broadly known to correlate with itch in AD, the mediators that underlie atopic itch have only recently begun to emerge.

Introduction

AD is a chronic and relapsing inflammatory skin disease that presents with red, crusted, and highly pruritic rashes [1]. In developed countries, AD affects up to 20% of children and 5% of adults, with an alarming increase in incidence worldwide [2,3]. Due to the incessant need to scratch, AD is highly debilitating. Yet despite the profoundly negative impact of AD on quality of life, therapeutic options have been historically very limited. However, recent advances in our understanding of the immunologic basis of AD have greatly accelerated therapeutic development and begun to expand treatment options.

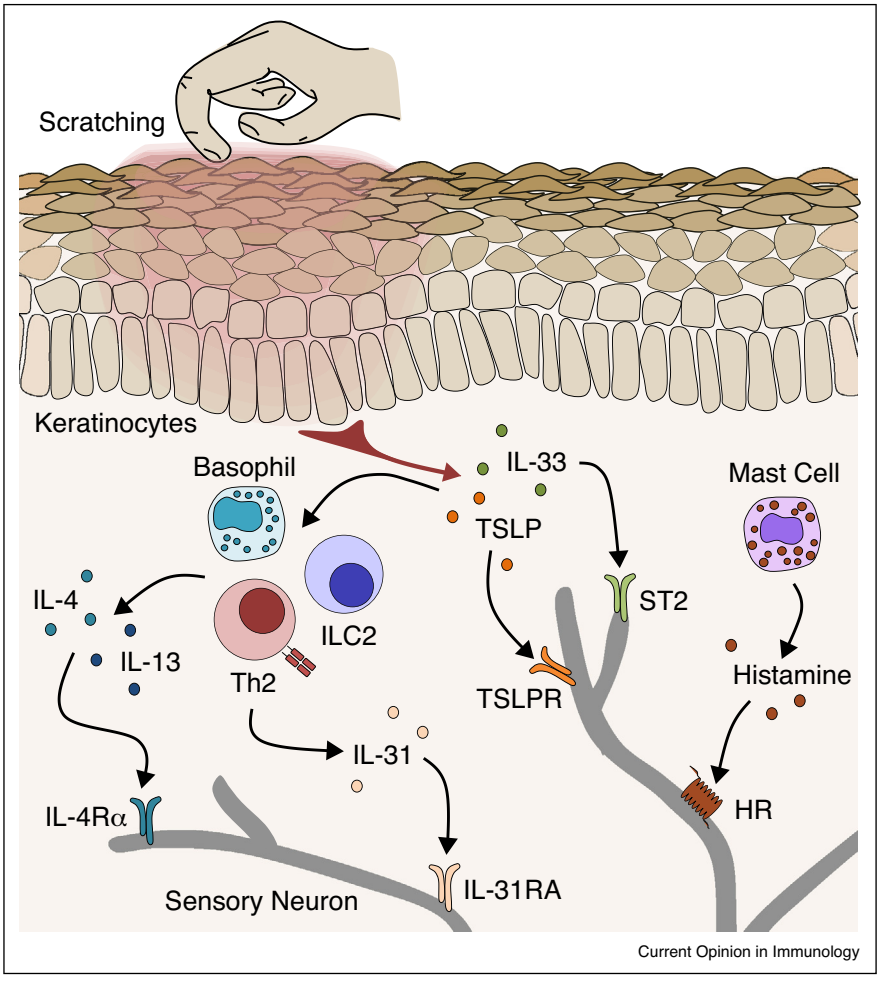
AD is characterized by an aberrant type 2 immune response as evidenced by elevated levels of IL-4, IL-5, and IL-13 in the skin. The importance of these cytokines in AD pathogenesis is further corroborated by the unprecedented efficacy of dupilumab, an anti-IL-4Rα monoclonal antibody (mAb) that blocks the shared receptor of IL-4 and IL-13, in treating moderate-to-severe AD. A critical upstream driver of the dysregulated type 2 immune response in AD is epidermal barrier dysfunction. Indeed, the discovery of the epithelial cell-derived cytokines IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) as potent promoters of type 2 inflammation demonstrates how a damaged or stressed epidermis can directly drive AD [4]. Specifically, these cytokines are able to induce a variety of immune cells, including T helper type 2 (Th2) cells, basophils, and group 2 innate lymphoid cells (ILC2s), to enhance their production of IL-4, IL-5, and IL-13 in order to further propagate AD-associated inflammation (Figure 1) [5,6]. Thus, over the past decade, we have gained an increasing appreciation of the cellular and molecular mechanisms that drive AD-associated inflammation. However, while inflammation is broadly known to correlate with itch in AD, the mediators that underlie atopic itch have only recently begun to emerge.

Atopic itch

Chronic itch is the most debilitating aspect of AD and can be incredibly difficult to manage. In addition to being the central morbidity of AD, itch also directly promotes the pathogenesis of the disease through a process called the 'itch-scratch cycle'. This phenomenon occurs when the sensation of itch evokes the scratching reflex, which results in skin damage and thus further exacerbates barrier dysfunction and inflammation. In addition to exacerbating the skin rash, scratching also stimulates the release of a variety of itch-inducing factors called pruritogens, which act directly on sensory neurons to drive additional itch sensation, further perpetuating this destructive cycle.

Chronic itch results in an equivalent reduction in quality of life as chronic pain [7]. Yet compared to pain, studies

Figure 1



The immune network in atopic itch. Mast cell-derived histamine can act on sensory neurons to mediate acute itch but has historically been a poor therapeutic target in AD. TSLP and IL-33, released upon perturbation of the epidermis (e.g. scratching), promote the accumulation of type 2 immune cells (e.g. Th2 cells, ILC2s, and basophils) in the inflamed skin but can also act directly on sensory neurons. The Th2 cell-derived cytokine IL-31 is a well-known pruritogen while neuronal signaling through IL-4Rα, the shared receptor for IL-4 and IL-13, modulates the responsiveness of sensory neurons to other pruritogens in order to promote chronic itch. IL-4Rα, IL-4 and IL-13 shared receptor subunit; IL-31RA, IL-31 receptor subunit; HR, histamine receptor; ILC2, group 2 innate lymphoid cell; ST2, suppressor of tumorigenicity (IL-33 receptor subunit); Th2, T helper type 2 cell; TSLP, thymic stromal lymphopoietin; TSLPR, TSLP receptor subunit.

have just begun to unravel the molecular and cellular mechanisms that mediate itch. A distinct population of sensory neurons, called pruriceptors, is now recognized to transmit itch. Critical to the identification of these specialized neurons were several landmark discoveries of receptors that specifically and potently regulate itch sensation, including the gastrin-releasing peptide receptor (GRPR) and the Mas-related G protein-coupled receptor (Mrgpr) family [8,9]. While the role of these specific receptors in AD remains unknown, this body of work helped to establish the rapidly growing field of itch biology and subsequently paved the way for the identification of key mediators of chronic itch in AD (Table 1).

Histamine: a canonical pruritogen

Histamine, a small molecule predominately released by tissue-resident mast cells, was one of the earliest identified pruritogens. Initially, research on the pruritogenic capacity of histamine focused on its ability to activate the histamine type 1 receptor (H_1R) on sensory neurons (Figure 1) [10]. While histamine is very effective at inducing acute itch and histamine levels are elevated in lesional AD skin [11], H_1R antagonists have proven widely ineffective in treating chronic itch such as in AD [12]. However, another histamine receptor, H_4R, which is also expressed on sensory neurons, has emerged as a new potential therapeutic target in AD with H_4R antagonists currently in clinical trials (Table 1) [10,13]. While