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Invited Review Article

Interleukin-33 in atopic dermatitis

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ABSTRACT

Atopic dermatitis (AD) is characterized by pruritus, barrier disruption, and inflammationincluding type 2 cytokine production. Interleukin-33 (IL-33) is an inflammatory cytokine that is over-expressed in the keratinocytes of patients with AD. IL-33 transgenic mice, which express IL-33 specifically in keratinocytes, spontaneously develop AD-like eczema, suggesting that IL-33 is sufficient for the development of AD. IL-33 stimulates various cells, including group 2 innate lymphoid cells (ILC2s), to produce type 2 cytokines, such as IL-5 and IL-13, and IL-33-stimulated basophils activate ILC2s via IL-4. ILC2s are enriched in human AD skin lesions, and ILC2 isolated from AD lesions, are activated by IL-33, not by thymic stromal lymphopoietin (TSLP). IL-33 induces IL-31, thereby promoting pruritus and scratching behavior. Conversely, scratching the skin promotes IL-33 release from keratinocytes. IL-33 reduces the expression of filaggrin and claudin-1; it also reduces the skin barrier function. However, barrier destruction causes percutaneous exposure to allergens or IL-33 release. Thus, IL-33 is a common point of entry into the itch–scratch cycle of AD. These new findings can facilitate the development of novel therapeutic drugs targeting IL-33.

1. Introduction

Atopic dermatitis (AD) affects up to 15–20% of people in industrialized countries [1]. AD is one of the most common forms of inflammatory skin disease; it is characterized by chronic or recurrent eczema with pruritus, xerosis, and lichenification [2]. Recently, interleukin-33 (IL-33) has been shown to be involved in the pathophysiology of allergic disorders, including AD. There is no evidence that any one of the pathological conditions of AD is upstream. AD is a multifactorial, complex inflammatory skin disease; its pathogenesis includes impaired skin barrier function, excess type 2 cytokine production, and pruritus/excoriation [3]. In this review, we summarize how IL-33 is involved in the complex pathogenesis of AD. We begin by reviewing innate and acquired immune responses in AD. We then review the history of the discovery of IL-33 and the development of knowledge about it. Finally, we will provide an overview of animal models of IL-33-induced AD and human clinical trials of anti-IL-33 therapy for AD.

2. Adaptive and innate immunity in AD

The human immune system is divided into innate immunity and adaptive immunity. For example, asthma and allergic rhinitis are diseases in which acquired immunity is important, because there is strong evidence for the clinical efficacy of allergen immunotherapy for asthma and allergic rhinitis [4]. However, allergen immunotherapy is controversial in AD [4], and there are no validated tests to confirm the role of allergens in triggering AD [5]. Moreover, a diet that excludes the consumption of eggs and milk is not useful for patients with AD [6]. These studies suggest that AD may have aspects of antigen-independent inflammation as well as adaptive immune responses. In general, allergic reactions in acquired immunity require antigens, such as cedar pollen and house dust mites; however, IL-33, which is one of the inflammatory cytokines associated with innate immunity, can activate group 2 innate lymphoid cells (ILC2s) without antigen stimulation to induce type2 cytokines, such as IL-5 and IL-13 [7]. The innate immune system cells that correspond to Th1 cells (or CD8 + T cells), Th2 cells, and Th17 cells are ILC1s, ILC2s, and ILC3s, respectively. Thus, the cells of conventional acquired immunity require antigens to produce cytokines, whereas ILCs require cytokines instead of antigens.

3. Immunological characteristics of IL-33

3.1. IL-33 as an alarmin

IL-33 is one of the cytokines of the IL-1 inflammatory cytokine family; structurally, it is most closely related to IL-1β and IL-18 [8].

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IL-1β and IL-18 are synthesized as an inactive precursor constitutively stored in many cells, including keratinocytes; they are then processed by caspase-1 into an active form when released from cells. Therefore, when IL-33 was first identified, it was believed that it was expressed as an inactive precursor (30-kDa full-length IL-33) and that caspase-1 led to the production of 18-kDa "mature" IL-33, such as amino acids "Ser109-Ile266″ [8], based on an *in vitro* study. However, this "Ser109-Ile266″ IL-33 does not exist *in vivo,* and 30-kDa full-length IL-33 does not possess a definite caspase-1 cleavage site; moreover, full-length IL-33 is biologically active [9]. IL-33 is constitutively expressed at the protein level in the nucleus of normal keratinocyte as alarmin [10]. Although Oppenheim et al. [11] proposed the novel term, alarmin, in 2005, there is no consensus regarding its definition. In the realm of dermatology, alarmins are endogenous, constitutively expressed in keratinocytes; they have danger-associated molecular patterns that activate innate immune responses. In general, stimulation first induces cytokine mRNA expression, followed by translation and then secretion of the cytokine from cells. Thus, in the case of most cytokines, such as IL-4 or IL-17A, the induced levels of mRNA and the subsequent protein secretion are correlated. In contrast, alarmins (e.g., IL-33) are stored as proteins inside cells, and they are rapidly released following pathogen challenge or cell death in order to alert the innate immune system [10]. However, the precise mechanism of IL-33 processing, and its localization, have not been fully elucidated. Disruption of the skin barrier is seen in patients with AD. Under such conditions, keratinocytes are triggered to produce IL-33. After secretion from cells, full-length mouse IL-33 is cleaved by proteases from environmental allergens and degraded within 10–20 min [9]. The mechanism of immediate secretion and immediate degradation upon stimulation seems to be ideal as an alarmin.

3.2. IL-33 as the ligand for the ST2 receptor

For a decade, the long form of serum STimulation-2 (ST2, also known as IL-33R alpha chain or IL-1RL1) [12] was thought to be an orphan receptor that expressed Th2 cells [13]. In 2005, IL-33 was identified as a functional ligand for ST2 [8]. The IL-33 receptor complex (heterodimer) is composed of ST2 and IL-1 Receptor Accessory Protein (IL-1RAcP) (Fig. 1). IL-1RAcP is a signaling receptor subunit that is also a member of the IL-1R complex.

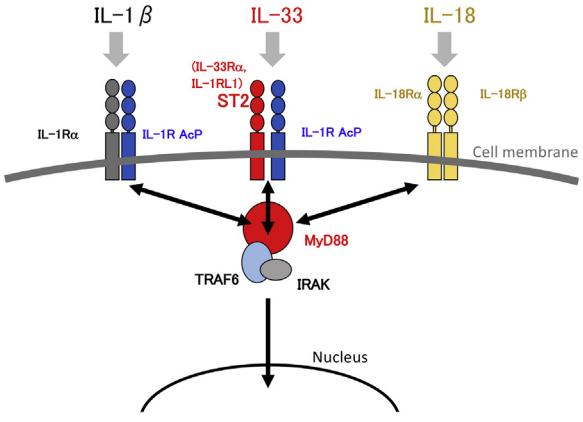

Fig. 1. IL-1β, IL-18, and IL-33 are related by receptor (R) structure and signal transduction pathways. IL-1Rα possesses a cytoplasmic domain, and interleukin-1 receptor accessory protein (IL-1RAcP) joins with IL-1Rα to form a complex that recruits myeloid differentiation factor 88 (MyD88), tumor necrosis factor receptor-associated factor 6 (TRAF6) and IL-1R-associated kinase (IRAK). The IL-18R complex is similar to the IL-1R complex. IL-33 binds to the receptor ST2 (IL-33Rα, also known as IL-1RL1) and IL-1RAcP joins with ST2 as a co-receptor.

Interestingly, in 2005, before the discovery of IL-33, Shimizu et al. reported that single nucleotide polymorphisms (SNPs) in the distal promoter of the ST2 gene are associated with AD [14]. IL-33 signaling activates myeloid differentiation primary response 88 (MyD88), and IL-33-induced cytokine production depends on MyD88 signaling, similar to the IL-1 cytokine family [15] (Fig. 1).

3.3. Target cells of IL-33

IL-33 binds to its receptor ST2, which is expressed on Th2 cells, basophils, mast cells, and ILC2s. IL-33 stimulates Th2-polarized CD4 + T cells to produce IL-5 and IL-13 [15]. IL-33 triggers mast cell degranulation [16]. IL-33 induces a significant amount of IL-4 production from basophils [15]. ILC2s are a population of lineage-negative lymphoid cells that lack surface markers for T cell, B cell, natural killer (NK) cell, macrophage, neutrophil, and eosinophil lineages. ILC2s produce very large amounts of type2 (Th2) cytokines, including IL-5 and IL-13, in response to IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), without antigen stimulation [7]. ILC2s have been classified as inflammatory ILC2s (iILC2s) and natural ILC2s (nILC2s) [17]. iILC2s are responsive to IL-25/TSLP, and nILC2s are responsive to IL-33. Skin-resident nILC2s are present in healthy human skin [18].

3.4. IL-33 in AD and other allergic disorders

In the epithelial cells, including keratinocytes, full-length biologically-active IL-33 is constitutively expressed, and it is normally stored in the cell nucleus. Upon cellular damage or stress, IL-33 is released rapidly as an alarmin to activate the innate immune system [10]. In human AD, IL-33 is abundant in the lesions of epidermal keratinocytes [19–21]. However, it is unclear whether IL-33 is the cause or the result of AD. We demonstrated that IL-33, up-regulated in keratinocytes, induces severe eczema in a transgenic mouse line expressing mouse IL-33 (IL33tg) driven by a keratin-14 promoter [22]. While the growth of the IL33tg mice was normal up to 5 weeks, all the mice spontaneously developed dermatitis. In the skin lesions of the IL33tg mice, the epidermis was thickened, and the mast cells and eosinophils were infiltrated. These mice showed severe scratching behavior and histamine, and their total Immunoglobulin E (IgE) concentrations in the blood were significantly increased. The concentration of type 2 cytokines and chemokines (e.g., IL-4, IL-5, IL-13, RANTES/CCL5, and Eotaxin 1/CCL11) were much higher in the serum and skin lesions of IL33tg mice than wild-type mice [22]. Those phenotypes closely resemble the features of human AD. Furthermore, an MC903-induced innate immune AD model is dependent on IL-33 at a later stage of inflammation [23]. However, in an ovalbumin-sensitized adaptive immune contact dermatitis mouse model, IL-33 and ST2 expressions are up-regulated in the skin [18] and antigen, in the presence of IL-33, stimulates Th2-polarized CD4 + T cells to produce IL-5 and IL-13 [15]. Thus, IL-33 is involved in both adaptive and innate immune responses. Still, we recently reported that the AD-like eczema that developed in IL33tg mice was not diminished in Rag2KO IL33tg mice that lack Th2 cells [24]. Hence, innate immunity may be a primary contributor to IL-33-induced AD-like inflammation. Etokimab, a humanized monoclonal antibody that targets IL-33, was proven to be efficacious for AD in a phase 2a trial [2,25], suggesting that the pathophysiology of AD may have an aspect of IL-33-dependent inflammation. Additionally, IL-33 has been reported to participate in allergic diseases, such as allergic conjunctivitis [26–28], urticaria [29,30], asthma [15], and allergic rhinitis [31]. Especially, in IL33tg mice, keratoconjunctivitis with blepharitis and corneal impairments were found to spontaneously develop between 18 and 22 weeks of age [28].

3.5. A role for IL-33–driven natural ILC2s in AD

IL-33 effectively induced the rapid expansion of ILC2s, which produce large amounts of type2 cytokines, such as IL-5 and IL-13 [7]. ILC2s were found to significantly increase in the skin lesions of IL33tg mice [22]; recently, we demonstrated that AD-like dermatitis is eradicated by ILC2 depletion [24]. Thus, IL-33-induced dermatitis is dependent on ILC2s. Several researchers have reported that ILC2s actually increased in human AD skin lesions [18,32,33]. Unlike in other organs, human skin-derived ILC2s are activated to produce type2 cytokines by IL-33, not by TSLP or IL-25 [18]. ILC2s are classified into two subgroups—natural ILC2s and inflammatory ILC2s [17]—which are responsive to IL-33 and IL-25/TSLP, respectively. Because IL-33 is a potent stimulus for the activation of human skin-derived ILC2s, ILC2s induced in human AD skin belong to the natural ILC2s subgroup. We demonstrated that ILC2s mainly infiltrate the dermis of Rag2 KO IL33tg mice, and basophils and ILC2s were co-localized in the dermis [24]. However, the localization of ILC2s in human AD is still unclear, because ILC2s can only be detected by flow cytometer, not by immunohistochemistry.

3.6. Basophils activate IL-33-induced ILC2s via IL-4

Basophils express ST2 on the cell surface and produce IL-4 and IL-13 in response to IL-33 without antigen stimulation [15,34]. ILC2s are activated by basophils via IL-4 in a mouse asthma model [35]. In humans, IL-4 also acts to induce the expansion of ILC2s [36].

The number of basophils increases in human AD skin lesions [33,37,38]. Basophils were found to accumulate in the inflamed skin of IL33tg mice, and AD-like inflammation was suppressed in basophil-depleted IL33tg skin [24]. Therefore, we speculate that basophils promote the activation of nILC2 via IL-4.

Based on the findings presented in a series of our studies and other reports, we propose a mechanism of IL-33-induced innate inflammation in AD (Fig. 2). However, it is still unclear whether this proposed mechanism is applicable to patients with AD. IL-33 produced by epidermal keratinocytes activates skin ILC2s to produce IL-5 and IL-13, resulting in eosinophil accumulation in skin lesions. IL-33 also stimulates basophils to produce IL-4, which promotes production of IL-5 and IL-13 from ILC2s. Dupilumab, an antibody against the IL-4 receptor alpha, is used to treat AD [39]. Considering the information presented above, its efficacy on AD might be due to blocking the activation of ILC2s via IL-4.

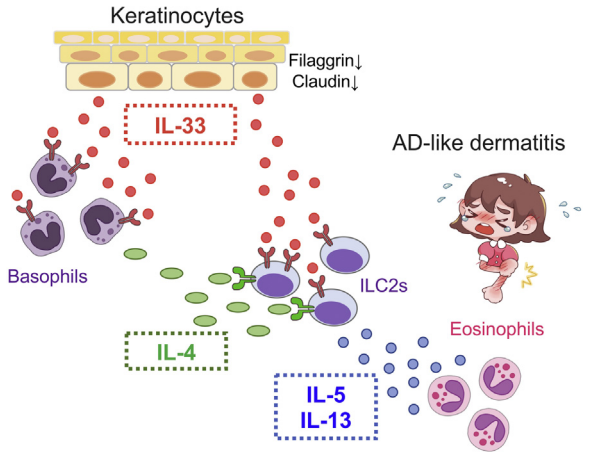

Fig. 2. The mechanism of IL-33-induced AD-like inflammation. Excess IL-33 produced by epidermal keratinocytes activates ST2+ cells, such as ILC2s and basophils in the skin. IL-33 stimulates the secretion of IL-5 and IL-13 from ILC2s, which leads to eosinophil accumulation in the skin lesions. IL-33 also stimulates basophils to produce IL-4, which promotes activation of ILC2s to produce more IL-5 and IL-13. IL-33 also directly down-regulates the expressions of claudin-1 and filaggrin, then exacerbates the dermatitis.

3.7. IL-33 induces IL-31 and promotes pruritus

As a mechanism of itching other than histamine, in humans, IL-31 induces itching by acting directly on itch-sensory neurons [40]. In a recent clinical trial, the anti-IL-31 receptor antibody demonstrated significant anti-pruritic effects [40]. IL-31 belongs to the IL-6 cytokine family, and it is mainly produced from leukocytes, such as Th2 cells, by stimulation with IL-33 [41]. A positive correlation has been reported between the serum levels of IL-31 and the severity of AD, and an anti–IL-31 receptor-A antibody improved pruritus and dermatitis in patients with AD [2]. It has also been noted that IL-4, IL-13, and IL-33 act directly on the peripheral nerves to cause pruritus [42]. IL-33 stimulates mast cells to produce histamine without an antigen [22]. These examples demonstrate that the immune response induces pruritus (Fig. 3a). However, when skin is disrupted by scratching because of itching, IL-33 is released from keratinocytes and inflammation is further triggered [30] (Fig. 3b).

3.8. IL-33 disrupts the skin barrier

Skin barrier proteins, such as filaggrin and claudin-1, are decreased in patients with AD [43]. It is known that filaggrin expression is reduced in AD, regardless of the presence or absence of the filaggrin gene mutation, because type 2 cytokines, such as IL-4, IL-13, and IL-33, directly reduce filaggrin expression in the skin [44,45]. IL-33 down-regulates the tight junction protein expression of claudin-1 through the signal transducer and activator of transcription 3 (STAT3) pathway in keratinocytes [46]. We also reported that levels of filaggrin and claudin-1 expression were reduced in the skin lesions of IL33tg mice [46]. Thus, IL-33 acts directly on keratinocytes to reduce the skin barrier function of the stratum corneum and the epidermis (Fig. 3c). In skin with barrier dysfunction, irritation easily promotes the secretion of alarmins, such as IL-33, from keratinocytes [30], and barrier destruction causes continuous percutaneous exposure to allergens, possibly promoting AD [47] (Fig. 3d).

3.9. ILC2s activated by IL-33 may be important for early AD lesions

Although the mechanism applicable to patients with AD is still unknown, recently, “stage-based” pathogenesis of AD has been proposed [2]. For example, the “double switch model” [48] is an *in silico* model of AD. The first switch is reversible innate immunity; epidermal barrier disruption stimulates keratinocytes to express alarmins, such as IL-33. Inflammation of AD begins when ILC2 is activated by IL-33 (Fig. 3e). The second switch is triggered by the first switch, causing irreversible acquired immunity; ILC2s promote the migration of Th2 cells into the skin lesions via IL-13 and thymus and activation-regulated chemokine (TARC) [49]. In the chronic phase, various inflammatory cell infiltrations, including Th17 and Th22 cells, can be observed, particularly in AD patients in Asia [2]. Thus, the cells that play a major role in the pathogenesis of AD depend on the stage of the disease: ILC2s play a role in the early lesions, Th2 cells play a role in the acute phase, and Th17 and Th22 play a role in the chronic phase [2].

3.10. Clinical applications of IL-33 inhibition therapy for AD

Based on the results mentioned above, inhibition of the IL-33-ILC2 axis appears to be a useful treatment for AD. Since no markers

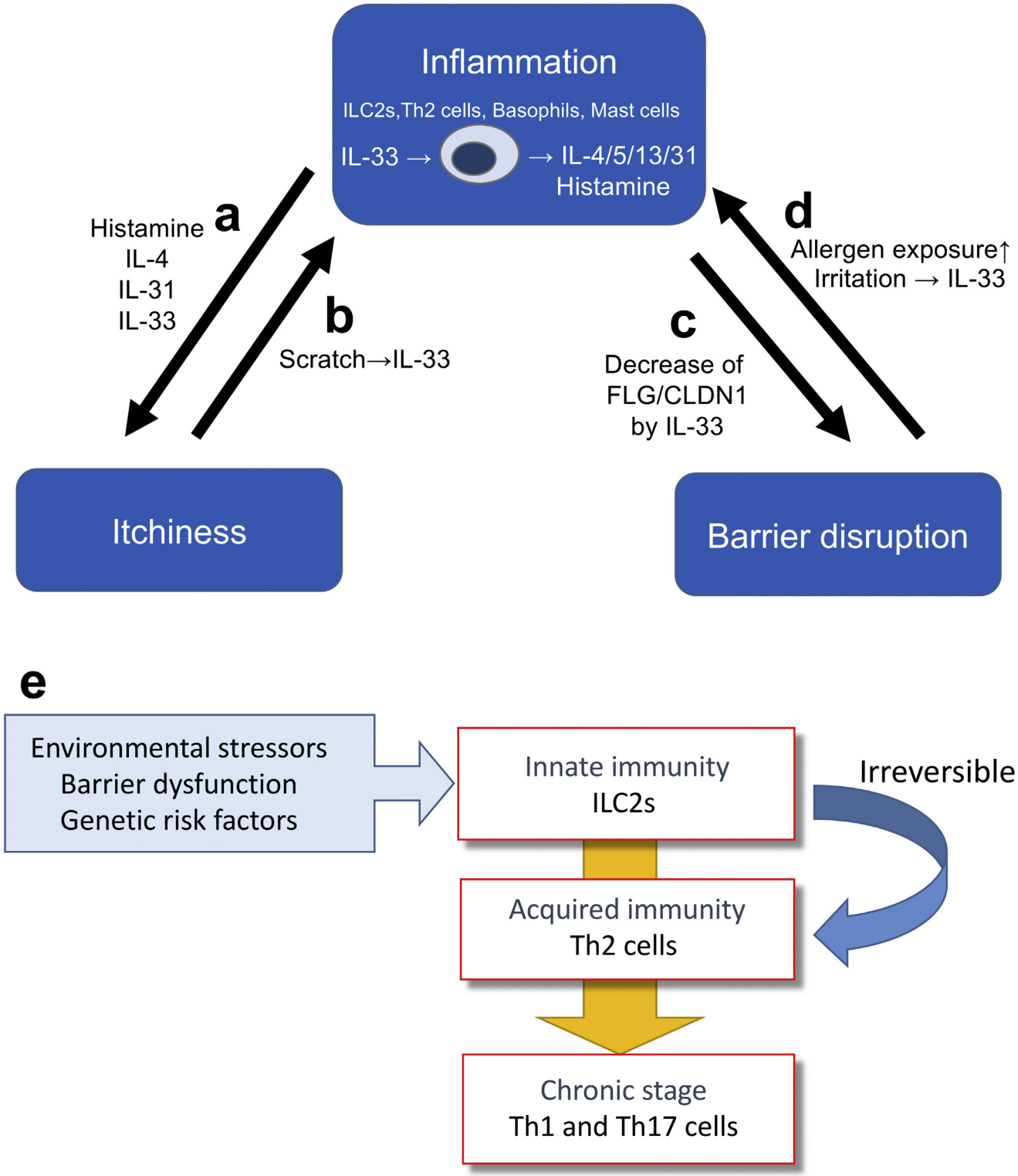

Fig. 3. Main mechanisms of AD. (a) Inflammation induces pruritus. IL-33 stimulates various cells to produce type 2 cytokines, which induces pruritus. (b) Itchiness induces skin inflammation. Scratching behavior promotes IL-33 release from keratinocytes. (c) Inflammation disrupts skin barrier function. Type 2 cytokines, including IL-33, down-regulate skin barrier proteins, such as filaggrin and claudin-1. (d) Barrier disruption causes skin inflammation. Irritation promotes the secretion of IL-33 from keratinocytes, and barrier destruction promotes antigen sensitization and Th2-acquired immunity. (e) Double-switch, stage-based mechanism AD. Environmental stressors or genetic risk factors (e.g., filaggrin or other barrier dysfunction) cause the onset of the first reversible switch of innate immunity, including ILC2. This switch leads to dermatitis, which can be reversed. Long-lasting inflammation can trigger the second irreversible switch of acquired immunity, including Th2. When the disease progresses in the chronic phase, mixed T cells (Th1/2/17/22) infiltrate and perpetuate AD and promote skin remodeling and lichenification.

have been found that are only expressed in human ILC2s, it is difficult to only eliminate ILC2s. Therefore, blocking IL-33 signaling is a more realistic approach. A rare (0.65%) sequence variant in the IL33 gene (loss-of-function mutations) has been reported, and this mutation causes a reduced number of eosinophils in blood and protects against asthma [50]. The anti-IL-33 (or ST2) monoclonal antibodies, registered at www.clinicaltrials.gov, are Etokimab (previously known as ANB020), AMG282, REGN3500, and GSK3772847. Etokimab, a humanized IgG1 antibody that targets IL-33, has been proven to be efficacious for AD in a phase 2a trial [2,25]. Therefore, clinical applications of those antibodies are expected.

4. Conclusion

IL-33 is involved in the pathogenesis of AD through a variety of mechanisms, and the IL-33-ILC2s axis might represent a central mediator for human AD. IL-33 is secreted extracellularly from keratinocytes by pruritus or by reduced skin barrier function. IL-33 activates ILC2 to produce type2 cytokines and forms AD lesions. IL-33 reduces skin barrier function, and IL-31, induced by IL-33, causes itching of the skin. Furthermore, with regard to IL-4, which is an important cytokine for ILC2 activation, the anti-IL-4R antibody, dupilumab, has already been clinically applied to AD [39]. Similarly, treatments targeting IL-33 may be approved in the near future. Thus, elucidation of the pathophysiology of AD is facilitating the identification of new therapeutic strategies using AD biologics.

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Declaration of Competing Interest

The author states no conflict of interest.

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