

## REVIEW ARTICLE

# Pathogenesis of Atopic Dermatitis: Current Paradigm

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## ABSTRACT

Atopic dermatitis (AD) is characterized by skin inflammation, barrier dysfunction and chronic pruritus. In this review, recent advances in the pathogenesis of AD are summarized. Clinical efficacy of the anti-IL-4 receptor antibody dupilumab implies that type 2 cytokines IL-4 and IL-13 have pivotal roles in atopic inflammation. The expression of IL-4 and IL-13 as well as type 2 chemokines such as CCL17, CCL22 and CCL26 is increased in the lesional skin of AD. In addition, IL-4 and IL-13 down-regulate the expression of filaggrin in keratinocytes and exacerbate epidermal barrier dysfunction. Keratinocytes in barrier-disrupted epidermis produce large amounts of thymic stromal lymphopoietin, IL-25 and IL-33, conducting to type 2 immune deviation via OX40L/OX40 signaling. IL-31, produced by type 2 T cells, is a cardinal pruritogenic cytokine. IL-4 and IL-13 also amplify the IL-31-mediated sensory nerve signal. These molecules are particularly important targets for future drug development for AD.

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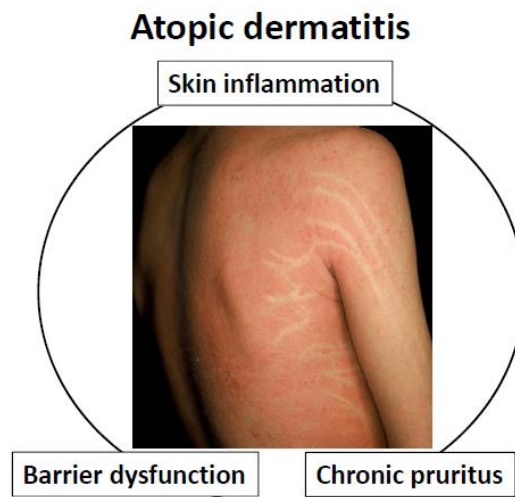
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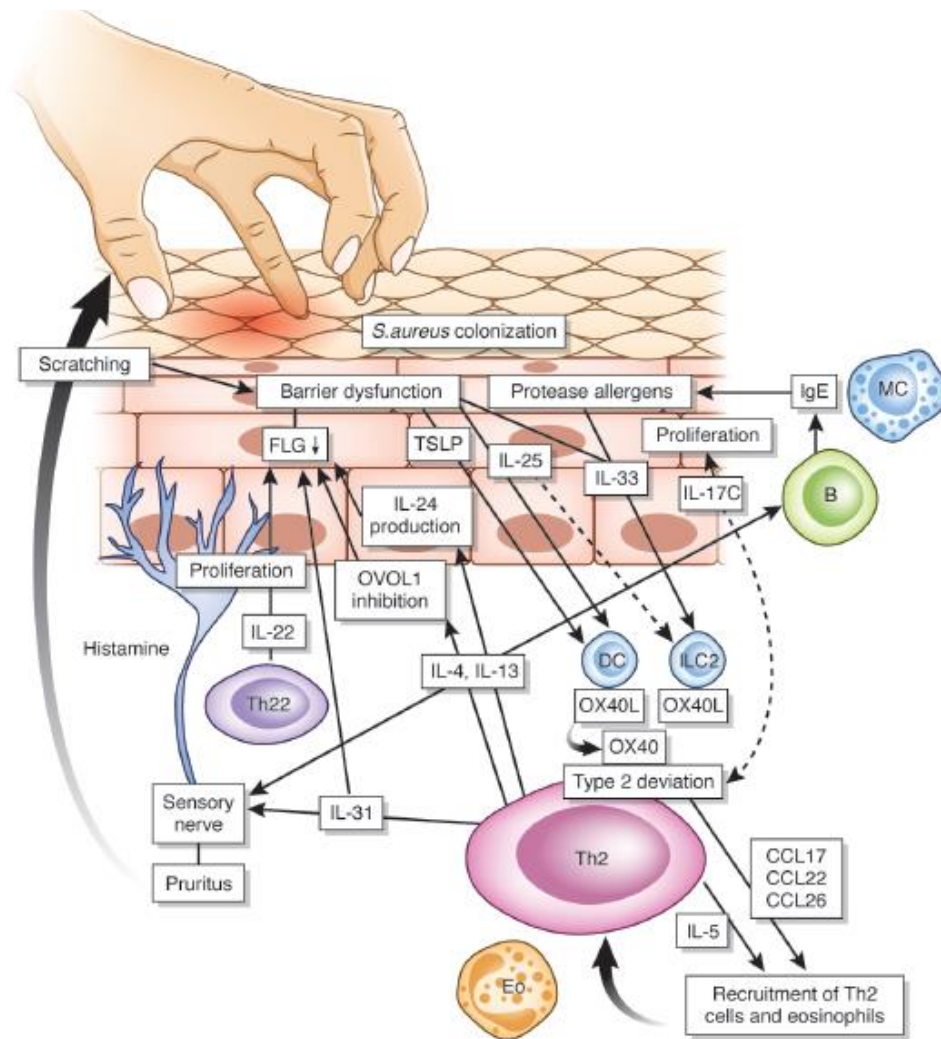
## INTRODUCTION

Atopic dermatitis (AD) is a common eczematous skin disorder, the prevalence or incidence of which in the first 5 years of childhood is 10% to 16.5%. It is generally considered to have increased worldwide, at least from the 1980s to early 2000s (1). Clinical features of AD include skin inflammation, barrier disruption and chronic pruritus (Figure 1) (2). Abnormal microbial colonization, such as *Staphylococcus aureus*, is also associated with barrier dysfunction (3). The co-occurrence of autoimmune diseases is slightly increased in patients with AD (4). Since the discovery of type 2 helper T (Th2) cells by Mosmann *et al.* (5), type 2 cytokines such as interleukin (IL)-4 and IL-13 are highlighted as major players in allergic inflammation in AD (6-9). The pathogenic importance of IL-4 and IL-13 has recently been suggested by an excellent treatment response of AD to the anti-IL-4 receptor  $\alpha$  (IL4R) antibody dupilumab, which inhibits both IL-4 and IL-13 signals (Figure 2) (10).



**Figure 1. Characteristics of atopic dermatitis.**

Although the mechanisms responsible for barrier dysfunction in AD are multidirectional and interconnected, research has underscored loss-of-function mutations and/or a type 2 immune response-induced decrease in filaggrin (FLG) (11-13). In addition to the genetic loss of *FLG*, type 2 cytokines IL-4 and IL-13 potently inhibit FLG expression (11,14-16). In addition, keratinocytes in the barrier-disrupted skin accelerate the type 2 immune response by producing thymic stromal lymphopoietin (TSLP), IL-25 and IL-33, which are type 2-associated epithelial cytokines (17). Chronic pruritus and pruritus-induced sleep disturbances markedly deteriorate the life quality of the patients (18-23). Among various pruritogens, atopic itch is likely to be mediated by IL-31, which is produced by Th2 cells (24). In parallel, the anti-IL-31 receptor antibody nemolizumab potently improves pruritus in AD patients as early as one week following its administration (Figure 2) (25,26). In this review, the focus is on type 2 immune deviation as the major driving force of AD development.



**Figure 2. Pathogenesis of atopic dermatitis.** Barrier-disrupted keratinocytes are potent producers of immunoregulatory cytokines such as TSLP, IL-25 and IL-33. These cytokines induce a type 2 immune response. TSLP and IL-25 activate dendritic cells (DCs) to express OX40L. Most allergens possess protease activity. The protease allergens cleave full-length IL-33 to the active form and activate group 2 innate lymphoid cells (ILC2s) to express OX40L. Ligation of OX40L/OX40 initiates type 2 immune differentiation of T cells. IL-17C is also involved in keratinocyte proliferation and is a potential inducer of type 2 inflammation. Th2 cells produce IL-4, IL-13, IL-31 and IL-5. IL-4 and IL-13 inhibit barrier function by downregulating FLG expression via IL-24 induction or inhibition of OVOL1 function in keratinocytes. IL-22 induces keratinocyte proliferation and downregulates FLG expression. IL-31 stimulates sensory nerves and mediates pruritus. IL-4 and IL-13 amplify IL-31-induced and histamine-induced pruritus. Pruritus evokes scratching, which aggravates barrier disruption. IL-31 also downregulates FLG expression. The barrier-disrupted epidermis is susceptible to colonization of *Staphylococcus aureus*, which further worsens barrier disruption. IL-4 and IL-13 stimulate B cells to produce IgE, which binds to mast cells and induces their degranulation upon binding to allergens. Mast cells are a major source of histamine. IL-4 and IL-13 upregulate the production of CCL17, CCL22 and CCL26. These chemokines as well as IL-5 recruit Th2 cells and eosinophils. Thus, interconnected vicious cycles develop full-blown AD. FLG; filaggrin, Th2 cell; T helper type 2 cell, TSLP; thymic stromal lymphopietin.

**IL-4R Signaling Plays a Crucial Role in Atopic Dermatitis.**

The anti-IL4R antibody dupilumab significantly improved skin lesions and pruritus in patients with moderate to severe AD in two randomized, placebo-controlled clinical trials (10). The severity of AD is authentically evaluated using Eczema Area and Severity Index (EASI). At 16-week post-treatment, a reduction in the EASI of at least 75% was observed in 51% and 44% of patients in the dupilumab monotherapy groups, and in only 15% and 12% of patients in placebo groups, respectively (10). Dupilumab also provides clinically meaningful improvement in patient-reported outcome measures (27). IL-4 and IL-13 have historically been the focus of much attention in AD. As IL4R receives signals from both IL-4 and IL-13, the therapeutic success of dupilumab testifies to the pivotal roles of IL-4 and IL-13 in the pathogenesis of AD (Figure 2), a notion supported by a series of studies. Gene expression of IL-4 and IL-13 is upregulated in the lesional skin of pediatric and adult AD patients compared to that in the normal skin of healthy controls (7-9). Type 2 predominance is likely to be progressive from nonlesional to lesional skin and from acute to chronic lesions in AD (7,8). Type 2 predominance is corroborated in peripheral blood Th cells (28). IL-13-producing Th2 cells are significantly increased in the skin-homing cutaneous lymphocyte antigen (CLA)+ Th cell population in both pediatric and adult AD patients in comparison to those in the healthy controls (28). CCL17, CCL18, CCL22 and CCL26 are type 2 chemokines overexpressed in the lesional skin of AD (6,29) (Figure 2). CCL17, CCL18 and CCL22 are chemoattractive to Th2 cells and are mainly produced by dendritic cells and other dermal cells activated by IL-4 and IL-13 (6,29,30). Concerning CCL17, platelets are probably the important source (31), and serum CCL17 levels became undetectable in a certain patient with AD comorbid with idiopathic thrombocytopenic purpura (32). CCL26 is a potent chemotactic factor for eosinophils and is generated by endothelial cells stimulated by IL-4 and IL-13 (6,29). The expression levels of these type 2 chemokines are normalized by dupilumab and topical steroids (29,33). Serum levels of CCL17 and CCL22 are significantly augmented in patients with AD compared to those in healthy controls and are associated with disease severity in AD (34,35). Interstitial fluids contain significantly higher levels of IL-13 and CCL17 in the lesional skin of AD patients compared to those in healthy individuals (36). Increased levels of CCL17 and CCL22 are further reported in tape-stripped stratum corneum in AD (37). IL-5 is also a type 2 cytokine crucial for eosinophil growth, differentiation and migration (38). Gene expression of IL-5 is upregulated in the lesional skin of pediatric and adult AD patients compared to the normal skin of healthy controls (7-9). Administration of the anti-IL-5 antibody mepolizumab significantly reduces circulating eosinophils; however, no significant improvement is observed in the severity score or pruritus in patients with AD (38). These clinical results suggest that IL-5 plays a major role in the recruitment of eosinophils, but its pathogenic significance is limited in AD.

**IL-22 Perpetuates the Chronicity of Atopic Dermatitis.**

In addition to IL-4 and IL-13, the increased expression of IL-22 is associated with type 2 dominance in AD, and is also progressive from nonlesional to lesional skin and from acute to chronic lesions (7,8). Serum levels of IL-22 are significantly correlated with serum levels of CCL17 (39). IL-22 is a potent inducer of keratinocyte proliferation (40). An increased number of circulating IL-22+CLA+ Th cells were detected in adult patients but not in pediatric patients with AD (28). Notably, the anti-IL-22 antibody fezakinumab exhibits clear efficacy for AD and is more efficacious in severe AD patients compared with non-severe AD patients (41). Patients expressing higher baseline levels of IL-22

show a better treatment response to fezakinumab (42). Topical steroids and tacrolimus are effective in downregulating the gene expression of IL-13 and IL-22 and improving skin symptoms (33,43,44). These results underline the critical role of IL-22 in AD, particularly in the chronic phase (41).

#### **IL-4R Signaling Downregulates Filaggrin Expression.**

Skin barrier formation is a sophisticated biochemical sequence composed of epidermal differentiation molecules such as FLG, intercellular lipids and corneocyte adhesion (12). The expression of FLG is downregulated in the lesional and nonlesional skin of AD compared with the normal skin of healthy individuals (11,14). Among the 31 susceptible gene loci reported by meta-analysis of genome-wide association studies, *FLG*, *OVOL1* and *IL13* are the top 3 significant genes associated with AD (13). The most potent risk factors are null mutations of the *FLG* gene in AD (13). However, *FLG* mutations are not found in all AD patients, are less common in Southern Europeans (45), and are even absent in certain African countries (46,47), suggesting that *FLG* mutations only partly explain FLG protein downregulation in AD. *OVOL1* is an upstream transcription factor for FLG expression (14,48) (Figure 2). Activation of *OVOL1* induces its cytoplasmic-to-nuclear translocation and upregulates FLG expression (14,48). Notably, type 2 cytokines IL-4 and IL-13 consistently inhibit FLG expression by interfering with *OVOL1* signaling (11,14-16,48,49). IL-4 signaling also disrupts barrier permeability (50) and modulates E-cadherin distribution (51). Therefore, the IL-4/IL-13-induced FLG downregulation is likely to be more meaningful compared with the genetic mutation of *FLG*. IL-13 also stimulates keratinocytes to produce IL-24, inhibiting FLG expression in autocrine and/or paracrine fashions (52). Other cytokines, such as IL-20, IL-22, IL-25, IL-31 and IL-33, also entail the downregulation of FLG expression (53-56); however, the molecular mechanisms leading to FLG downregulation by these cytokines are not fully fathomed. IL-20 and IL-24 are partly responsible for IL-31-mediated FLG downregulation (54).

#### **Skin Barrier Dysfunction Induces Type 2 Immune Deviation by Producing TSLP, IL-24, IL-25 and IL-33.**

Epicutaneous application of picryl chloride or mite antigen on barrier-disrupted skin, upregulates IL-4 and IgE expression in the regional lymph node, compared to sensitization through barrier-intact skin (57). Barrier disruption by tape stripping upregulates the expression of CCL17, CCL22 and CCL5 in epidermal cells, and induces the recruitment of IL-4-producing cells and eosinophils (58). Current studies suggest the crucial roles of TSLP, IL-25 and IL-33 in the type 2 immune deviation induced by barrier dysfunction (17,59) (Figure 2). In the lesional skin of AD, the expression of TSLP, IL-25 and IL-33 is upregulated by epidermal keratinocytes (7,60,61). Tape stripped skin expresses an increased level of TSLP (62). TSLP upregulates the expression of OX40L in murine dendritic cells, and TSLP-treated dendritic cells induce OX40+ T cells to produce IL-4, IL-5 and IL-13 (63,64). OX40L/OX40 interaction works as a type 2 immune checkpoint (64,65). Additionally, TSLP-treated human dendritic cells are preferentially prime naïve T cells producing IL-4, IL-5 and IL-13 (61). In addition, TSLP upregulates the production of CCL17 and CCL22 by human dendritic cells (61). IL-25, also called IL-17E, is a member of the IL-17 family (66). Th2 immune responses characterized by eosinophilia, increased serum levels of IgE, and an elevated expression of IL-4, IL-5, and IL-13, are observed in transgenic mice that overexpress IL-25 (67). Intranasal administration of IL-25 upregulates the expression of IL-4, IL-5, IL-13 and



eotaxin with marked eosinophilia in lung tissues (68). IL-25 further upregulates OX40L in dendritic cells and promotes IL-4 and IL-13 production in T cells (69). Among other IL-17 family members, mention can be made of IL-17C, potentially important in AD because the anti-IL-17C antibody may be efficacious in the treatment of AD (70). IL-17C may be related to epidermal proliferation and thickening (71). In contrast, the blockade of the IL-17A pathways may exacerbate AD (72). IL-33 is a tissue-derived IL-1 family cytokine which also facilitates type 2 immune responses (73). Barrier disruption by tape stripping induces IL-33 production in keratinocytes (74). IL-33 expression by keratinocytes is markedly augmented by herpes infection, which, more often than not, aggravates AD and results in distinct eruptions, known as Kaposi's varicelliform eruptions (75). House dust mites activate keratinocytes via toll-like receptor 6 and induce IL-25 and IL-33 production (76). Many potent allergens such as house dust mites, fungi and pollens have intrinsic protease activity (73,77,78). Full-length IL-33 released from epithelial cells is cleaved to the mature active form by various sorts of protease allergens, and cleaved IL-33 generates IL-5 and IL-13 by immune cells, and recruits eosinophils (73). Therefore, IL-33 acts as a sensitive sensor of external protease allergens (73). IL-33, but not TSLP, upregulates OX40L in group 2 innate lymphoid cells (ILC2s) and stimulates OX40+ T cells towards type 2 immune deviation (65). IL-25 also induces OX40L in ILC2, but to a lesser extent compared with IL-33 (63). Mouse and human ILC2s are phenotypically comparable, lineage negative, and non T-, non B-lymphocytes and are high producers of IL-13 and IL-5, but not IL-4 (79,80). ILC2 resides in the skin and is increased in number in AD lesion (80). IL-33 as well as IL-25 stimulates ILC2 and promotes Th2 response by enhancing their release of IL-13 and IL-5 (80). In *Schistosoma mansoni* infection, individual ablation of TSLP, IL-25, or IL-33 had no impact on the development of IL-4- and IL-13-dependent inflammation or fibrosis (81). However, simultaneous disruption of all three cytokines ameliorates the type 2 deviation (81). Further studies are warranted to elucidate the significance and redundancy of TSLP, IL-25 and IL-33. Notably, a clinical trial of the anti-TSLP antibody tezepelumab failed to show the efficacy of AD (82), while the anti-IL-33 antibody ANB020 was efficacious in all 12 AD patients in a phase 2a clinical trial (83).

#### **Atopic Pruritus and IL-31, IL-4 and IL-13.**

Pruritus is the fundamental symptom of AD (21). Histamine is virtually not a key pruritogenic mediator of AD because the antipruritic effect of antihistamine is limited, and is only appreciated by patients when antihistamine is used in combination with topical steroids (84). IL-31 is also a Th2-associated cytokine (24,85) (Figure 2) whose expression is increased in the lesional skin of AD (29). IL-31 promotes the elongation and branching of sensory nerve fibers (86). Administration of IL-31 induces pruritus in mammals such as mice, dogs, monkeys and humans (24). A single shot of the anti-IL-31 receptor antibody nemolizumab significantly and rapidly reduces pruritus in patients with AD (25,26). Monthly injection of nemolizumab effectively reduces pruritus in AD for at least 52 weeks (87). The anti-canine IL-31 antibody lokivetmab is already commercially available in the treatment of dogs with canine AD (88). These results point to the crucial role of IL-31 in atopic pruritus. Murine and human sensory neurons express IL-4 and IL-13 receptors, but a simple injection of IL-4 and/or IL-13 does not induce acute itch (89). However, IL-4 and IL-13-pretreated neurons respond to subthreshold concentrations of histamine or IL-31, suggesting that IL-4 and IL-13 amplify histamine- and IL-31-induced pruritus (89). Both IL-31 receptor and IL-4 receptor  $\alpha$  activate downstream JAK1/JAK2

and JAK1/JAK3 signaling pathways, respectively (24). Targeted disruption of the neuronal JAK1 signaling pathway reduces chronic pruritus, corroborating the success of JAK inhibitors in treating chronic pruritus (89,90).

## DISCUSSION

The therapeutic success of dupilumab underpins the pivotal role of IL-4 and IL-13 signaling in the pathogenesis of AD (29). Another type 2 cytokine, IL-31, is a potent pruritogenic mediator of atopic pruritus. IL-4, IL-13 and IL-31 inhibit FLG expression and conduce to barrier dysfunction. The vicious itch-scratch cycle further exacerbates epidermal barrier disruption which releases TSLP, IL-25 and IL-33, initiating and perpetuating type 2 immune deviation. The IL-4/IL-13 signal further exacerbates IL-31-induced pruritus by reducing the threshold of IL-31. Current advances in understanding the pathogenic mechanism may facilitate new drug development in AD.

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