

The interplay between genetic and environmental factors in the pathogenesis of atopic dermatitis

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Summary

Atopic dermatitis (AD) is a chronic skin disorder characterized by pruritus and recurrent eczematous lesions that are accompanied by T-helper (Th)2-dominated inflammation. AD Etiology is not yet completely understood, but it is multifactorial. Moreover, the disease is characterized by complex interactions between genetic and environmental factors, such as skin barrier dysfunctions, allergy/immunity, and pruritus. For example, filaggrin is a key protein involved in skin barrier function. Th2 cells produce interleukin (IL)-31, which provokes pruritus, and other Th2 cytokines decrease filaggrin expression by keratinocytes. Dupilumab has recently been developed for AD treatment; its mechanism of action is to bind to IL-4 receptor α and inhibit downstream signaling induced by IL-4 and IL-13. This review summarizes the etiopathogenesis of AD and provides the rationale for selecting a novel targeted therapy.

KEYWORDS

allergy, inflammation, skin

1 | OVERVIEW OF ATOPIC DERMATITIS (AD)

1.1 | Clinical features of AD

Atopic dermatitis (AD) is characterized by chronic, dry pruritic eczematous skin lesions.^{1,2} Because specific biomarkers or histological characteristics for AD are lacking, AD is diagnosed based on clinical symptoms, which include typical morphology, the distribution of skin lesions, and associated clinical signs, such as elevated serum immunoglobulin (Ig)E levels and a history of allergic rhinitis or asthma.² The onset of AD is, in most cases, between 3 and 6 months of age, and approximately 10% to 20% of children are affected by it.^{3,4} Although the majority of childhood AD spontaneously resolves by adulthood, the disease persists in 10% to 30% of cases.⁴ More rarely, the first symptoms develop in adulthood, and the prevalence of AD in adults is

approximately 1% to 3%.^{5–7} AD histology consists of epidermal hyperplasia (acanthosis) with inflammatory cell infiltration, including T cells and dendritic cells (DCs), in the superficial dermis. Non-specific immunosuppressants, such as topical steroids or systemic cyclosporine in severe cases, have been widely used for the treatment of AD.² However, as the pathogenesis of AD is gradually uncovered, novel, AD-specific therapies are being developed, and some of these therapies are almost ready for clinical use.^{8,9}

1.2 | The pathogenesis of AD

Barrier dysfunction and hyper-immune activation (Th2-type inflammation) are generally considered to underlie AD pathology.¹ A mutation in the gene that encodes filaggrin (FLG), a natural moisturizer, is one of the most well-known causal factors of barrier dysfunction.¹⁰ Approximately 10% to 30% of AD patients, depending on the population, have the mutation. Various studies have suggested that barrier dysfunction causes

the unregulated activation of proteases in the epidermis, leading to the production of Th2-type immune-inducing factors, such as thymic stromal lymphopoietin (TSLP).¹¹ Classically, Th2 cells are associated with the production of Th2 cytokines, such as interleukin (IL)-4 and IL-13, in AD lesions. However, recent studies have indicated that various innate-type immune cells, including innate-type 2 lymphoid cells (ILC2) and basophils, are also involved in the production of Th2-type cytokines in AD.^{12,13} TSLP acts on both Th2 cells and ILC2 and induces Th2-type cytokine production by these cells.^{12,14,15} TSLP may also indirectly induce Th2-cells by modulating cutaneous DCs, such as Langerhans cells (LCs) to promote differentiation of these cells.^{11,16} IL-4 and IL-13 in turn induce keratinocyte chemokine production and accelerate inflammatory cell infiltration into the skin. IL-4 and IL-13 also decrease FLG expression in keratinocytes, further impairing barrier function.^{17,18} Indeed, blocking IL-4R exhibits significant therapeutic efficacy and improves barrier function in AD patients.¹⁹ In addition to Th2-type cytokines, it has been suggested that IL-17 and IL-22 are involved in the development of AD, at least in a subset of patients,²⁰ based on the heterogeneous therapeutic effects of IL-23-targeted therapies.⁸

The daily application of moisturizing cream in infants significantly reduces the incidence of AD development, which strongly suggests the importance of barrier function in AD.²¹ Although pruritus is one of the most important features of AD, the mechanisms of pruritus in AD are less well understood than those of barrier dysfunction and immune activation. However, several cytokines, such as TSLP, IL-4/13, and IL-31, have recently been reported to be involved in AD-associated pruritus^{22–24} (Figure 1). Animal studies and translational research have demonstrated

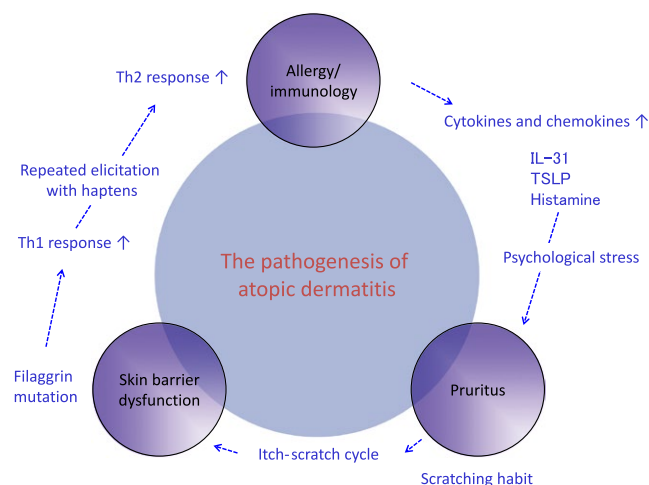


FIGURE 1 Barrier dysfunction, allergy, and pruritus. When the skin barrier is disrupted by, for example, filaggrin gene mutation and/or environmental factors, the skin is predisposed to penetration by external stimuli. Foreign antigens can be subdivided into two groups based on size: haptens (including metals) and protein antigens. A single hapten challenge initially provokes Th1 responses, but repeated elicitation with haptens results in a shift toward Th2-dominated responses. Conversely, exposure to protein antigens directly induces Th2-dominant conditions via the thymic stromal lymphopoietin (TSLP) receptor on LCs. Recently, Th2 cells were shown to produce IL-31, which provokes pruritus, and Th2 cytokines, which decrease filaggrin expression by keratinocytes

that multiple cytokines and diverse cell populations interact with each other and contribute to the pathogenesis of AD. Before discussing these, we must first consider that there are different types of AD.

2 | INTRINSIC VS EXTRINSIC AD

The clinical phenotypes of AD have been classified into extrinsic and intrinsic types, analogous to the classification of asthma.²⁵ Intrinsic or non-allergic AD is characterized by normal total IgE values and the absence of specific IgE.²⁵ Intrinsic AD composes 20% of AD cases and is predominant among female patients. Moreover, it is characterized by a relatively late onset and milder severity. Importantly, the skin barrier is not perturbed in intrinsic AD.²⁵

According to the European Academy of Allergy and Clinical Immunology, atopy is a tendency to produce IgE in response to low doses of allergens that results in the typical symptoms of asthma, rhinoconjunctivitis or eczema/dermatitis.²⁶ Thus, the suitability of the term “intrinsic AD” to describe patients with AD and normal IgE levels is under debate.²⁷ However, we will not pursue this controversy further in this review.

The Th2-axis is highly activated in both intrinsic and extrinsic AD. However, some differences between these two conditions should be noted. The scoring of atopic dermatitis (SCORAD) scores of patients with intrinsic AD positively correlate with Th17- and Th22-related molecules, such as IL-17A, IL-22, S100A12, and MMP12, whereas those of patients with extrinsic AD do not.²⁸ Instead, the SCORAD scores of patients with extrinsic AD positively correlate with the serum IgE and Th2 cytokine (IL-4 and IL-5) levels but negatively correlate with keratinocyte differentiation products, such as loricrin and periplakin.²⁸ The levels of Th1 and interferon-related products (such as IFN- γ , CXCL9, CXCL10, MX-1, IL-1 β , and IFN- α) also positively correlate with the SCORAD scores of patients with intrinsic AD.²⁸ In addition, the levels of certain cytokines (such as IL-9, IL-20, and IL-24) are significantly increased in intrinsic AD lesions.²⁸ IL-9 is produced by several immune cells, including Th9 cells,²⁹ and IL-20 and IL-24 are associated with epidermal hyperplasia.³⁰

Moreover, intrinsic AD has been associated with an SNP in the IL-31 gene.³¹ While the function of this SNP is not clear, an analysis of PBMCs from individuals homozygous for the risk haplotype showed a 4-fold induction of IL-31 upon stimulation with anti-CD3 and anti-CD28 *in vitro*.³¹

These lines of evidence indicate the following: First, a Th2 bias is not the sole cause for the high IgE levels in patients with extrinsic AD. Second, Th17, Th22, and Th9 appear to play roles in the pathogenesis of intrinsic AD. Finally, treatments targeting IL-31 or pruritus may be effective in controlling intrinsic AD.

3 | EARLY PHASE EXTRINSIC AD

3.1 | Initial events caused by skin barrier impairment

The impairment of the skin barrier, which may be caused by genetic or environmental factors, is suspected of initiating extrinsic AD (Figure 2).

Specifically, an impaired barrier allows the entry of allergens into the skin, and damaged keratinocytes produce cytokines, such as TSLP, IL-25, and IL-33. These cytokines stimulate ILC2, which promptly produce IL-5 and IL-13, both of which activate Th2 cells. TSLP enhances the maturation of CD11⁺ DCs and an epidermally located subset of DCs called LCs, allowing them to induce Th2 cells. Moreover, IL-25 is a cytokine of the IL-17 family and capable of amplifying the Th2-type immune response. IL-25 binds to IL17B, which is expressed on ILC2, iNKT, and Th2 cells. Lastly, IL-33 is a member of the IL-1 family that binds to ST2 (IL1RL1), which is highly expressed on ILC2, Th2, and mast cells.

In an inflammatory environment, keratinocytes produce chemokines, such as CCL17 (thymus- and activation-regulated chemokine; TARC), CCL20, and CCL27 (cutaneous T cell-attracting chemokine; CTACK), which bind to CCR4, CCR6, and CCR10, respectively. CCR4, CCR6, and CCR10 are expressed on Th2, Th17, and other skin-tropic T cells, respectively. Accordingly, corresponding T cells are recruited to the damaged skin. Th2 cells, which express CCR4, produce IL-4, IL-5, IL-13, IL-25, and IL-31, all of which induce the Th2-type immune response, as described in the next section. Th17 cells, which express CCR6, excrete IL-17A to further enhance the Th2-type response.³² However, the role of CCL27 in AD pathogenesis is not clear, and CCR10⁺CD4⁺ T cells in AD lesions express IL-2 and IL-4, suggesting that these cells are Th2 cells.³³ Infiltrating T cells in allergic delayed-type hypersensitivity and bacterial chancroid skin lesions express both CCR4 and CLA, whereas only 10% of these cells express CCR10.³⁴

Therefore, CCR10 is not important for skin homing but is required for recruiting certain cutaneous effector Th cells. To summarize, the events observed in the early phase of dermatitis are programmed to initiate a Th2-type response in the damaged skin.

3.2 | Amplification of the Th2-type immune response and further impairment of the skin barrier

Activated Th2 cells produce IL-4, IL-5, IL-13, IL-25, and IL-31, which reinforce the Th2-type reaction as follows: IL-4 and IL-13 bind to the receptors on keratinocytes and suppress FLG expression, and IL-4 promotes the production of IgE by B cells. However, the source of the IL-4 signal for differentiating B cells to become IgE-producing plasma cells is not known. Nevertheless, IgG1⁺ memory B cells have been shown to undergo class switch recombination to IgE and maturation to become plasma cells in response to IL-4 provided by Th2 cells and basophils in the periphery.³⁵

IL-5 activates eosinophils, which in turn excrete cytokines and leukotrienes. In a murine model of AD, CCR8⁺IL-25R⁺ Th2 cells produce large amounts of IL-5.³⁶ In human peripheral blood, the IL-5-producing Th2 subset is identified as the CD62L<low>CXCR3<low> cell population and referred to as "pathogenic effector" Th2 (peTh2) subset.³⁷ However, this population has not yet been identified in the skin lesions of patients with AD.³⁷ IL-5/IL-13-producing peTh2 cells are characterized by the expression of hematopoietic prostaglandin D

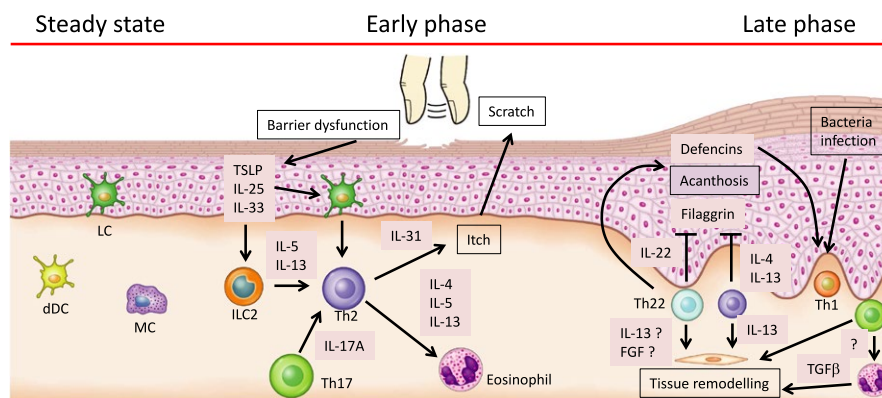


FIGURE 2 The early phase and late phase of AD. The priming event of extrinsic AD is suspected to be an impaired skin barrier, which can be caused by genetic or environmental factors. This impaired barrier allows entry of allergens into the skin, and damaged keratinocytes produce cytokines, such as TSLP, IL-25, and IL-33. These cytokines stimulate ILC2s. Responding ILC2s promptly produce IL-5 and IL-13, which both activate Th2 cells. TSLP enhances the maturation of CD11⁺ DCs and LCs, allowing these cells to induce Th2 cells. IL-25 is a cytokine of the IL-17 family and can amplify the Th2-type immune response, by binding to IL17B, which is expressed on ILC2, iNKT, and Th2 cells. IL-33 is a member of the IL-1 family and binds to ST2 (IL1RL1), which is highly expressed on ILC2, Th2, and mast cells. In the late phase, the affected skin becomes thick and leathery as a result of chronic inflammation and constant scratching and rubbing, a condition known as lichenification. The composition of infiltrating cells becomes complex in the late phase. IL-22 is a multifunctional cytokine that acts on epidermal cells, including keratinocytes. Its beneficial roles include enhancing the production of anti-microbial peptides by the epidermis, such as defensins. Defensins may contribute to the appearance of IFN- γ -producing Th1 cells in the lesions of late-phase AD. In response to IL-22, keratinocytes proliferate, resulting in diffuse epidermal hyperplasia, a condition called acanthosis. Together with Th2 cell-derived IL-4 and IL-13, IL-22 inhibits the expression of barrier-related genes, such as *FLG*, loricrin (*LOR*), and involucrin (*IVL*). The disruption of barrier function contributes to serious skin infections, such as eczema herpeticum (a viral infection caused by herpes simplex virus 1 or 2, also known as Kaposi varicelliform eruption) and impetigo contagiosa (a bacterial infection caused by *Staphylococcus aureus*). IL-17 induces the expression pro-fibrotic cytokines [e.g. transforming growth factor (TGF)- β and IL-11] in human eosinophils, and the number of Th17 cells correlates with tenascin C-expressing cells and metalloproteinase (MMP)-9-expressing eosinophils, which are both associated with tissue remodeling. Therefore, Th17 cells may also play a role in tissue remodeling in the late phase of AD

synthase (HPDS)⁺, the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2)⁺, and CD161⁺.

Memory-type pathogenic Th2 (Tpath2) cells are also considered a key cell population in the pathogenesis of allergic inflammatory disorders.³⁸ Several studies have reported phenotypically and functionally distinct memory Th2 cell subsets that produce large amounts of IL-5, IL-17, or IFN- γ in addition to IL-4 and IL-13.^{36,39–41} High-level IL-5-producing memory Th2 cells have been reported as a novel pathogenic population that induces eosinophilic inflammation in allergic diseases including AD.³⁹ Recent studies have demonstrated a novel subset of Th2 memory/effector cells that simultaneously produce both IL-4 and IL-17.^{40,42} The IL-17-producing Th2 cell subset can be induced in chronic airway inflammation such as asthma and thought as another type of Tpath2 cell population.

In addition, infiltrating Th17 cells appear to enhance the pathological Th2-type reaction. For example, IL-17A synergistically enhances Th2 polarization in a murine model⁴³ and down-regulates FLG to mediate skin barrier dysfunction, in a similar manner to Th2-cytokines.⁴⁴ Th17 cells may also play a role in tissue remodeling in the late phase of AD, as described in the next section. Th17 cell dysfunction results in hyper-IgE syndrome, which resembles the skin lesions of AD,⁴⁵ and further analysis is needed to specify the role of Th17 cells in AD.

4 | THE LATE PHASE OF EXTRINSIC AD

4.1 | Appearance of diverse T cell subsets

In the late phase, the affected skin becomes thick and leathery as a result of chronic inflammation and constant scratching and rubbing, a condition known as lichenification. Moreover, the composition of infiltrating cells becomes complex in this phase.

4.2 | The role of IL-22

In addition to Th2 cells, a number of IL-22-producing T22 cells are observed in the skin during the late phase of AD.^{46–48} The T22 cell population includes CD4⁺ Th22 and CD8⁺ Tc22 cells,^{29,46,49} and T22 cells express CCR4, CCR6, CCR10, and platelet-derived growth factor receptor (PDGFR).⁴⁹ Transcripts for *IL13* and fibroblast growth factor (*FGF*) have also been detected in T22 cells, suggesting that they play a role in skin remodeling, as described below. Moreover, IL-22 is a member of the IL-10 family and can also be produced by Th1, Th2, Th17, NKT, and $\gamma\delta$ T cells.^{29,46}

IL-22 is a multifunctional cytokine that acts on epidermal cells, including keratinocytes. Its beneficial roles include enhancing the production of anti-microbial peptides by the epidermis, such as defensins. Defensins may contribute to the appearance of IFN- γ -producing Th1 cells in the lesions of late-phase AD.⁵⁰ In response to IL-22, keratinocytes proliferate, resulting in diffuse epidermal hyperplasia, a condition called acanthosis. Together with Th2 cell-derived IL-4 and IL-13, IL-22 inhibits the expression of barrier-related genes, such as *FLG*, *loricrin* (*LOR*), and *involucrin* (*IVL*).^{44,46} The disruption of barrier function contributes to serious skin infections, such as eczema herpeticum (a

viral infection caused by herpes simplex virus 1 or 2, also known as Kaposi varicelliform eruption) and impetigo contagiosa (a bacterial infection caused by *Staphylococcus aureus*).

4.3 | Tissue remodeling in the skin

IL-13 appears to play a role in the fibrotic remodeling of skin. For example, inducible skin-specific IL-13 transgenic mice (K5-tTA-IL-13) on a C57BL/6 background develop AD-like dermatitis and exhibit fibrotic skin remodeling,⁵¹ and abrogating transgenic IL-13 expression reduces the severity of skin inflammation but does not affect the further progression of fibrosis, which depends on TLSP. Moreover, the number of TLSP-receptor expressing CD34⁺/procollagen⁺ fibroblast-like cells is increased in the skin lesions of patients with AD.⁵¹ In airway inflammation, IL-13 induces VCAM-1 expression in blood vascular endothelial cells, activates eosinophils/basophils, induces chemokine production in epithelial cells, and promotes fibrosis by activated macrophages.⁵¹ However, a similar pathogenic mechanism remains to be identified in AD skin lesions.

IL-17 induces the expression of pro-fibrotic cytokines, such as transforming growth factor (TGF)- β and IL-11, in human eosinophils,⁵² and the number of Th17 cells correlates with tenascin C-expressing cells and metalloproteinase (MMP)-9-expressing eosinophils, which are both associated with tissue remodeling.⁵³ Therefore, Th17 cells may also play a role in tissue remodeling in the late phase of AD.

5 | THE ROLE OF CD8⁺ T CELLS IN AD

CLA⁺CD8⁺ T cells infiltrate the lesions of patients with AD,⁵⁴ as observed soon after allergen exposure during atopy patch reaction tests in patients with AD.⁵⁵ A similar event occurs in mice, and the depletion of CD8⁺ T cells attenuates their infiltration at the site of dust mite application.⁵⁶ In NC/Nga mice, the depletion of CD4⁺ T cells does not ameliorate AD-like dermatitis because the cytokine environment changes from a Th1/Th2 response to a Tc17 cell-mediated response. Tc17 cells produce IL-17 and are the CD8⁺ counterpart of Th17.

6 | THE ROLE OF $\gamma\delta$ T CELLS IN AD

In mice, V γ 5/V δ 1-expressing $\gamma\delta$ T cells are localized in the skin and produce various humoral factors, including IL-17, IL-22, IFN- γ , and TNF- α .⁵⁷ In a murine AD model (flaky tail mice, Flg^{ft/ft ma/ma}), dermal V γ 5⁺ $\gamma\delta$ T cells are the main source of IL-17A.⁴³ In humans, V δ 1⁺ $\gamma\delta$ T cells exist in the skin, and NK cells and $\gamma\delta$ T cells are functionally defective due to apoptosis in patients with AD.⁵⁸ However, the precise function of $\gamma\delta$ T cells in human skin requires further investigation.

7 | TH9 CELLS

IL-9 promotes the development of allergic and autoimmune diseases,⁵⁹ and Th2 cells were originally thought to be the main source

of IL-9. However, a subset of CD4⁺ T cells was subsequently found to preferentially produce IL-9, and these cells were named Th9 cells.⁶⁰ IL-4 can induce T cells or Th2 cells to become Th9 cells, whereas IL-2, TGF- β , and anti-GITR antibody can induce naive T cells to become Th9 cells in vitro.⁶¹

In humans, most memory-type Th9 cells are skin-tropic or skin-resident memory T cells,⁶² and most of these cells are specific to *Candida albicans* and produce IL-9, TNF- α , and granzyme B.⁶² The number of Th9 cells is increased in the skin lesions of AD and psoriasis,⁶² and IL-9 is known to induce the expression of IL-9, IL-13, and IL-17 by T cells in the skin.⁶² V δ 2 T cells are another source of IL-9 in humans, but their role in AD has not yet been studied.⁶³ Thus, the precise contribution of Th9 cells to AD remains to be studied further.

8 | REGULATORY T CELLS

Regulatory T cells counterbalance inflammatory conditions,²⁹ and this designation can indicate FOXP3⁺CD25⁺CD4⁺ T cells, IL-10-producing CD4⁺ T cells, TGF- β -producing CD4⁺ T cells, and lymphocyte activation gene-3 (LAG3)⁺CD25⁺ T cells, which are referred to as FOXP3⁺ Tregs, Tr1 cells, Th3 cells, and LAG3⁺ Tregs, respectively.

FOXP3⁺ Tregs are a subset of CD4⁺ T cells that suppress the activation and proliferation of effector T cells. FOXP3 is the key transcription factor that endows Tregs with their suppressive function, and a lack of FOXP3 gene expression causes an autoimmune disease named IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked).^{64,65} Patients with IPEX exhibit spontaneous dermatitis, excessive IgE levels, and food allergy, indicating that FOXP3⁺ Tregs play a role in suppressing allergic responses.^{29,66} These lines of evidence suggest the presence of allergen-specific FOXP3⁺ Tregs in humans.⁶⁷⁻⁷¹

The number of FOXP3⁺ Tregs in the skin can be increased by activated dermal DCs, which are stimulated by RANKL expressed on keratinocytes.⁷² TSLP, a keratinocyte-derived proinflammatory cytokine, activates FOXP3⁺ Tregs. Thus, keratinocytes directly or indirectly control the number and the function of FOXP3⁺ Tregs. The number of FOXP3⁺ Tregs was found to be low in AD lesions,⁷³ and an imbalance between Th17 cells and FOXP3⁺ Tregs has been identified in patients with AD, indicating that suppression by FOXP3⁺ Tregs is defective.⁷⁴ However, anti-inflammatory cytokines, such as IL-10 and TGF- β , were expressed, indicating the presence of Tr1 cells.⁷³ On the other hand, corticotropin-releasing hormone down-regulates IL-10 production by Tr1 cells in patients with AD.^{75,76}

The suppressive functions of regulatory T cells are also influenced by the skin flora. *S. aureus* produces super-antigens that worsen the severity of AD by stimulating Th2 cells.⁷⁷ For example, Staphylococcal enterotoxin B (SEB), one such super-antigen, inhibits the function of CD25⁺CD4⁺ regulatory T cells (mostly FOXP3⁺ Tregs) in vitro.⁷⁸

These data indicate that regulatory T cells in the skin are not always poised to suppress inflammation. Recently, a clinical study indicated that the lidocaine-mediated expansion of FOXP3⁺ Tregs ameliorated AD,⁷⁹ but further investigation is required to reveal the role of regulatory T cells in AD.

9 | INNATE LYMPHOID CELLS

Innate lymphoid cells (ILCs) consist of a heterogeneous population of innate immune cells that mediate immunity, tissue homeostasis, and inflammation. ILCs include a helper T cell-like population and cytotoxic natural killer (NK) cells. The helper T cell-like population is further divided in three groups: group 1 or type 1 ILCs (ILC1s); group 2 or type 2 (ILC2s); and group 3 or type 3 (ILC3s). ILC3s include lymphoid tissue inducer (LTi) cells, which are found in developing lymphoid organs. ILCs interact with lymphocytes and influence adaptive immune responses.^{80,81}

The ILC-family immune cells are of lymphoid origin. They develop from the common lymphoid progenitor (CLP) in the bone marrow, as do B and T cells.⁸¹ In contrast to lymphocytes, ILCs develop in the absence of recombinant activated gene (RAG) 1 and 2 expression and lack a rearranged antigen receptor.⁸⁰ Practically, ILCs are defined as cells lacking known lineage markers for lymphocytes while expressing the alpha chain of the IL-7 receptor.^{80,81}

ILC2s are activated in response to keratinocyte-derived IL-33 and produce IL-5, IL-13, and amphiregulin in the skin lesions of AD.⁸² Skin-resident ILC2s are negative for lineage-markers, CD45hi, IL-7R α ⁺, CRTH2⁺, CCR4⁺, and CCR10⁺.⁸² E-cadherin can down-regulate the gene expression of AREG, IL13, IL5, and GATA3 of ILC2s in vitro⁸² by binding to KLRG-1 on ILC2s. However, this feedback system may be ineffective because keratinocytes express less E-cadherin under inflammatory conditions. In addition to the Th2-type cytokines, the E-cadherin-KLRG-1 axis may also be a novel target for controlling AD.

10 | THE ROLES OF CUTANEOUS DCS IN AD

10.1 | DC subsets in the skin

Several subsets of DCs exist in the skin of both mice and humans under physiological conditions.^{83,84} Furthermore, inflammatory DCs appear in the skin during inflammation.

LCs are a skin-specific DC subset that reside in the epidermis in mice and humans. LCs are usually found below tight junction barriers and extend their dendrites to capture antigen above the junction.⁸⁵ LCs constitutively express several markers, such as langerin/CD207, E-cadherin, epithelial-cell adhesion molecule (EpCAM), and CD205. Human LCs highly express CD1a, a member of the group 1 CD1 protein family, which can present microbial lipid antigens to T cells.⁸⁶ In AD lesions, inflammatory DCs, called inflammatory epithelial DCs (IDECs), are also detected in the epidermis.⁸⁷

In the dermis, at least two subsets of DCs (dermal DCs, dDCs) have been identified in both mice and humans. In mice, dDCs are classified into langerin-positive dDCs (langerin⁺ dDCs) and langerin-negative dDCs (langerin⁻ dDCs).⁸⁴ Langerin⁺ dDCs compose 10 to 20% of the total dDC pool; they express integrin α E β 7 (also called CD103) and low levels of integrin CD11b but lack E-cadherin and EpCAM. Langerin⁻ dDCs compose the majority (up to 70%) of the dDC pool and express

high levels of integrin CD11b. In humans, dDCs are also classified into at least two subsets (CD1a⁺ dDCs, and CD141⁺ dDCs) depending on the expression pattern of surface molecules, although their functional differences remain unclear.⁸³ During inflammation, two additional subsets of DCs can be found: a DC population derived from blood monocytes and pDCs. Specifically, monocyte-derived DCs arise from inflammatory Ly6C^{hi} monocytes recruited from blood.⁸⁸

10.2 | Cutaneous DCs in the pathogenesis of AD

Among the cutaneous DC subsets, LCs are the most extensively investigated DC subset in the pathogenesis of AD. In a murine AD model induced by epicutaneous sensitization with protein antigen (ovalbumin), LC depletion significantly attenuated the induction of IgE/IgG1, impaired Th2 cell induction, and decreased skin inflammation, suggesting that LCs mediate Th2-type immune responses in AD.^{89,90} Although protein antigens of large molecular size usually cannot permeate the size-selective barrier formed by tight junctions, activated LCs extend their dendrites through the tight junctions and take up protein antigens in a langerin-dependent manner.⁸⁵

TSLP has been suggested to be responsible for endowing LCs with their Th2-inducing capacity. In the skin, TSLP is mainly produced by keratinocytes in response to various stimuli, including tape stripping, cytokines and proteases. TSLP-activated DCs, including LCs, express OX40L, which is an important molecule for Th2 differentiation.¹⁶ The Th2-polarizing capacity of cutaneous DCs increases after tape stripping,⁹¹ and the depletion of TSLP receptor on LCs attenuates Th2-type immune responses in a murine AD model.⁹⁰ These results suggest that TSLP produced by keratinocytes activates nearby LCs, which induce Th2-type immune responses in AD.

In accordance with these mouse studies, LCs in the lesional skin of AD reportedly exhibit an activated phenotype,⁹² and TSLP is highly expressed in AD lesions.¹¹ Moreover, mutations in the FLG gene may influence the activation of LCs not only in AD patients but also non-AD healthy controls.⁹³ These results suggest that LCs also induce Th2-type immune responses in human AD.

In addition to LCs, HLA-DR⁺CD206⁺langerin⁻ DCs (IDECs) have been detected in the epidermis of human patients with AD.⁸⁷ IDECs express FcεRI on their surface, which has been assumed to enable specific allergen uptake via IgE-dependent antigen capture. However, the physiological significance of this pathway remains unknown.

Taken together, these data identify LCs as the most important cutaneous DCs for the induction of Th2 responses in the pathogenesis of AD. However, because dDCs can also induce Th2-type immune responses,⁹⁴ they may also participate in the induction of AD.

11 | THE ROLE OF MAST CELLS IN AD

Mast cells are generally assumed to contribute to skin inflammation because most studies have shown increased mast cell numbers in the skin lesions in human patients with AD and mouse AD models.⁹⁵ For example, a recent study showed that Trim32 knockout (KO) mice

exhibited an AD-like inflammatory skin condition in response to imiquimod (IMQ) treatment,⁹⁶ and IMQ application usually results in psoriasis-like dermatitis in murine model.⁹⁷ Trim32 is a member of the Trim E3-ubiquitin ligase family, and the Trim proteins in this family are mainly involved in innate antiviral immunity. Specifically, IL-4, IL-5, and CC chemokine ligand 5 (CCL5) were increased, but the expression levels of IL-17A, CCL20, and S100A9 were reduced. Interestingly, the number of mast cells was also increased, whereas FLG protein expression was attenuated.

IL-31, a 4-helix-bundle cytokine, is a new candidate mediator of pruritus preferentially produced by Th2 cells.²³ Specifically, it was reported that the number of IL-31-positive mast cells was increased in the lesional skin of patients with AD, and the lymphocytes of patients with AD expressed significantly higher IL-31 levels than did those of control subjects. In addition, the serum IL-31 levels correlate with disease activity in AD.^{98–100} Furthermore, human mast cell lines upregulated IL-31 in the presence of anti-microbial peptides that are abundant in AD skin lesions.^{101,102} These results suggest that mast cells and IL-31 are involved in the pathogenesis of AD.

In a murine model, AD-like dermatitis is induced by repeated epicutaneous exposure to antigens.¹⁰³ Skin inflammation induced by cutaneous sensitization with cedar pollen antigens was abolished in c-kit deficient mice (*Kit*^{W/W^{-v}),¹⁰⁴ but skin inflammation induced by epicutaneous application of ovalbumin (OVA) is comparable in wild-type and *Kit*^{W/W^{-v} mice.¹⁰⁵ This cedar pollen dermatitis model was found to be independent of signal transducer and activator of transcription 6 (Stat6) and IgE but dependent on CRTH2 (chemoattractant receptor homologous molecule expressed on Th2 cells), a PGD₂ receptor. However, mast cell reconstitution experiments were not performed in either study. Interestingly, a recent study showed that FcεRI and FcγR are involved in a cutaneous OVA patch model.¹⁰⁶}}

Epithelial cell-derived TSLP plays an essential role in the pathogenesis of asthma or AD by inducing a dendritic cell-mediated Th2-type allergic inflammation, and allergic rhinitis is also pathologically characterized by Th2-type allergic inflammation. Mast cells reportedly regulate epithelial TSLP expression in allergic rhinitis.¹⁰⁷ In an OVA-sensitized mouse model of allergic rhinitis, inflammation was abolished in mast cell-deficient mice compared with control mice. Therefore, mast cells may regulate epithelial TSLP expression in AD. In addition, a recent study demonstrated that mouse and human mast cells express 25-hydroxyvitamin D-1α-hydroxylase, which enables them to convert inactive 25OHD3 to biologically active 1α,25(OH)2D3. Mast cell-CYP27B1 activity and mast cell-VDRs represent important mechanisms by which the vitamin D3 metabolites 25OHD3 and 1α,25(OH)2D3 can repress overt IgE-mediated mast cell activation in a cutaneous allergic model.¹⁰⁸

The lesional skin of most patients with AD is colonized by *S. aureus*. Interestingly, δ-toxin, the mast cell degranulation-inducing factor produced by *S. aureus*, induced allergic cutaneous inflammation in a murine model.¹⁰⁹ The δ-toxin-mediated increases in IgE production and dermatitis were abrogated in mast cell-deficient mice. This study provided evidence of the correlation between bacteria, mast cells and AD. In accordance with these findings, another group reported that

the skin microbiome drives stem cell factor (SCF) production in keratinocytes, which triggers the differentiation of dermal mast cells.¹¹⁰ This SCF production depends on the stimulation of lipoteichoic acid (LTA), a Toll-like receptor 2 ligand.

Further studies are needed to clarify the mechanism of mast cells in the pathogenesis of AD using mast cell-deficient models. Classic models of mast cell functions are based on Kit-mutant mouse strains. In addition to their mast cell defect, the Kit-mutant mouse strain *Kit^{W/W^v}* exhibits multiple hematopoietic abnormalities that include compromised hematopoietic stem and progenitor cell fitness,¹¹¹ severe macrocytic anemia,¹¹² impaired T cell development in the thymus,¹¹² and a shift in intraepithelial T cells in the gut in favor of T cell receptor (TCR) $\alpha\beta^+$ cells and against TCR $\gamma\delta^+$ cells.¹¹³ In addition, the Kit mutant is neutropenic, which may affect the immune response of this strain.¹¹⁴ New mouse models that have marginal effects on other immune cells have recently been developed, such as mice expressing Cre recombinase under the control of mast cell protease genes.^{115–117} Nevertheless, the role of mast cells in the pathogenesis of AD has not yet been studied in these models.

12 | THE ROLE OF BASOPHILS IN AD

The number of basophils is reportedly increased in AD lesions,¹¹⁸ but the role of these cells in AD pathogenesis remains unknown. AD is a common inflammatory disorder of the epithelial surface that classically involves antigen-driven Th2 lymphocyte polarization and the coordinate production of cytokines, such as IL-4, IL-5, and IL-13. Basophils are recognized as immune modulators based on their ability to produce IL-4 and TSLP, a key cytokine required for Th2 immunity. In mice, basophils were also recently reported to migrate into draining LNs from the site of papain injection or helminth infection and act as antigen-presenting cells (APCs) by taking up and processing antigens.^{119–121} Basophils can express MHC class II and costimulatory molecules, such as CD40, CD80, and CD86. In addition, basophils can also induce Th2 upon exposure to OVA proteins complexed with specific IgE.¹²¹ Thus, basophils alone can induce Th2 production by naïve T cells in the absence of DCs under certain conditions. We previously demonstrated that basophils play a role in Th2 skewing in response to haptens and peptide antigens, but not protein antigens, because of the lack of processing ability.¹²² Because basophils cannot take up or process protein antigens efficiently, DCs may prepare peptides from protein antigens for antigen presentation by basophils or may promote IL-4 production from basophils to skew Th2. Consistently, LCs play an essential role in epicutaneous sensitization with OVA protein antigen to induce Th2-type immune responses via TSLP production.⁹⁰ A recent study demonstrated that coculture of basophils and DCs revealed that basophils acquired peptide–MHC-II complexes from DCs via cell contact-dependent trogocytosis which is dynamic transfer of membrane patches that occurs within minutes of conjugate formation of two live cells.¹²³ Once basophils acquired peptide–MHC-II complexes from DCs, they could function as APCs and stimulated T cells to proliferate and produce IL-4. These findings appear to reconcile

the discrepancy observed in previous studies demonstrating that basophils play an essential role as APC in driving Th2 differentiation.

Several studies show that murine basophils can serve as APCs, although this phenomenon is less clear for human basophils. Human basophils express MHC class II^{124,125} but are not able to induce antigen-specific T cell activation or proliferation in response to exposure to house dust mite allergen.¹²⁵ Another group reported that human leukocyte antigen-antigen D related (HLA-DR) is upregulated by IL-3 and IFN- γ in human basophils, but the basophils could not act as APCs for pollen allergen.¹²⁶ Accordingly, human basophils have been confirmed to lack some features of APCs.^{127,128} Thus, additional studies are needed to assess the ability of human basophils to act as APCs under various pathophysiological conditions.

Basophils and ILC2 play an essential role in Th2-type inflammation in a murine model. Specifically, they infiltrate AD-like lesional skin in a TSLP-dependent manner,^{12,129} and we previously reported that basophils secrete IL-4 and TNF- α in contact with fibroblasts and promote the expression of eotaxin/CCL11 by fibroblasts, which promotes the infiltration of innate immune cells, such as eosinophils.¹³⁰ Moreover, ILC2s express IL-5 and IL-13 but not IL-4, except in certain situations.^{129,131} The differential effector cytokine expression profiles of basophils and ILC2s define their specialized functions in vivo.¹³² Specifically, IL-13 production was largely confined to Th2 cells and ILC2 cells in the lungs, and the cellular transcription factor GATA-3 was associated with IL-13 production. Conversely, follicular helper T cells (T_{FH} cells) and basophils only produced IL-4 in vivo and did not express high levels of GATA-3.¹³² In addition, recent studies have demonstrated that basophils and ILC2s accumulate adjacent to each other in the lesional skin of patients with AD and in AD-like murine models.¹² Moreover, basophil–ILC2 clusters significantly accumulated in AD-associated skin compared with the skin of healthy controls. In murine AD-like dermatitis, basophils accumulated into the lesional skin, which was followed by the infiltration of eosinophils into this area. Basophils and IL-4 are necessary for the accumulation of ILC2s and the induction of AD-like dermatitis. In addition, ILC2s express IL-4R α and depend on IL-4 produced by basophils for their proliferation in AD-like inflammation. Collectively, these studies demonstrate that basophils are early regulators of ILC2 responses in AD-like dermatitis.

Although ILC2s have been reported to be independent of IL-33,¹² another study demonstrated that the skin-specific expression of IL-33 in transgenic mice causes AD-like dermatitis accompanied by the accumulation of eosinophils and ILC2s.¹³³ Specifically, IL-33 stimulates the production of IL-4 by eosinophils,¹³⁴ which can consequently promote the proliferation of ILC2 via IL-4R α .

IL-4 from basophils is also considered to play an essential role in allergic asthma. Proteases, including papain, can disrupt the epithelial cell barrier, which leads to the production of multiple cytokines, such as IL-25, IL-33, and TSLP, due to the stress of tissue injury. Accordingly, a recent study showed that the conditional deletion of basophils resolved papain-induced eosinophilia and mucus production in an allergic asthma model,¹³⁵ and basophil-derived IL-4 enhanced the expression of the chemokine CCL11 as well as IL-5, IL-9, and IL-13 in ILC2s, leading to the accumulation of eosinophils. Moreover,

IL-33-deficient mice, but not TSLP receptor-deficient mice, failed to develop papain-induced lung inflammation.¹³⁶ In addition, the antibody neutralization of IL-33 blocked IL-13 production.¹³⁷ It has therefore been speculated that lung ILC2 cells respond to activated lung stromal cell-derived IL-33 by producing IL-5 and IL-13, resulting in lung eosinophilia, goblet cell hyperplasia, and mucus production.^{136,137} Most importantly, basophil-derived IL-4 appears to be the main regulator of ILC2s in allergic conditions, and the mechanism underlying the induction or accumulation of ILC2s may depend on the organ specificity or the stimulus.

13 | SKIN BARRIER DEFECTS IN AD

The main function of the skin is to form a protective barrier from external stimuli, such as irritants and allergens. In the epidermis, the terminal differentiation of keratinocytes leads to the formation of the stratum corneum (SC), an impenetrable physical barrier consisting of flat anucleated corneocytes embedded in an intercellular matrix rich in non-polar lipids.¹³⁸ FLG is formed and stored as profilaggrin polymers in keratohyalin granules in the stratum granulosum (SG). At the interface between the SG and SC, profilaggrin polymers are cleaved into FLG monomers by several proteases, such as CAP1¹³⁹ and SASPase.¹⁴⁰ These monomers then assemble with keratin intermediate filaments to strengthen the SC. In the upper layers of the SC, proteases called natural moisturizing factors (NMFs), which play a major role in SC hydration, further process FLG monomers into hygroscopic amino acids and their derivatives^{141,142} (Figure 3).

Barrier dysfunction and continuous percutaneous exposure to antigens might initiate and drive AD development.^{10,143,144} A strong

link between the incidence of AD and nonsense mutations in the gene encoding FLG has been reported,⁵ and FLG-null mutations are found in approximately 20%–30% of patients with AD.^{10,145–147} In addition, FLG expression is down-regulated in almost all cases of moderate to severe AD, irrespective of FLG mutations.¹⁸ These findings suggest that barrier dysfunction is a primary cause of AD. Accordingly, several studies demonstrated that FLG-deficient flaky tail mice develop a severe contact hypersensitivity reaction compared with wild-type mice and exhibit spontaneous AD-like skin lesions.^{148–152} However, flaky tail mice have a frameshift mutation not only in the FLG gene but also in the *matted* gene, and *matted*, but not FLG, is reportedly responsible for the dermatitis phenotype and corresponds to a Tmem79 gene nonsense mutation.¹⁵³ Specifically, Tmem79 is mainly expressed in SG cells in the epidermis in both mice and humans. Therefore, the *matted* mutation also alters SC barrier function.

Both haptens and protein antigens can penetrate the SC of FLG-deficient mice, which exacerbates the immune response.¹⁵⁴ Moreover, a large-scale study demonstrated that intragenic copy number variation (CNV) within FLG, with alleles encoding 10, 11, or 12 repeats of FLG monomers, contributes to the risk of AD.¹⁵⁵ We recently screened a library of bioactive compounds using an FLG reporter assay and identified candidates that promoted FLG mRNA expression in a human immortalized keratinocyte cell line (HaCaT). Among these candidates, JTC801 promoted FLG expression in normal human epidermal keratinocytes (NHEKs), and the human skin equivalent model revealed that JTC801 promotes FLG expression but does not affect other differentiation markers of keratinocytes. Interestingly, the oral administration of JTC801 increased FLG protein expression and suppressed the development of AD-like skin inflammation in NC/Nga mice. Thus, modulation of FLG expression may be a new therapeutic target for AD.

A recent highlight in the allergy field was the finding that the mutations in the FLG gene are not only associated with AD but also with the atopic march. Thus, a therapeutic strategy based on modulating FLG expression is promising not only for the control of AD but also to prevent the development of other allergic diseases. The data show that epicutaneous antigens are strong sensitizers of allergic disorders, and mouse studies have demonstrated that food allergy and asthma can be induced by epicutaneous sensitization and are enhanced by the disruption of the skin barrier.^{148,156,157} In human subjects, the sequential acquirement of allergic diseases (atopic march) is frequently observed in both patients with AD and some genodermatoses, such as Netherton syndrome (mutation in SPINK5),¹⁵⁸ peeling skin syndrome 1 (corneodesmosin),¹⁵⁹ and SAM syndrome (desmoglein 1),¹⁶⁰ which strongly suggests that skin barrier deficiency contributes to the development of the atopic march. In the presence of barrier dysfunction in the SC, foreign antigens readily penetrate the epidermis and activate innate immune receptors and pattern recognition receptors, which results in the production of Th2-promoting cytokines, including IL-33, IL-25, and TSLPs, by skin-resident cells. Animal studies have demonstrated an essential role for TSLP in the epicutaneous induction of food allergy with AD-like dermatitis. Increased TSLP levels in the epidermis elicit the accumulation of basophils in the skin, which promote Th2 cytokine responses.¹⁵⁷ In addition, TSLP signaling in epidermal LCs may

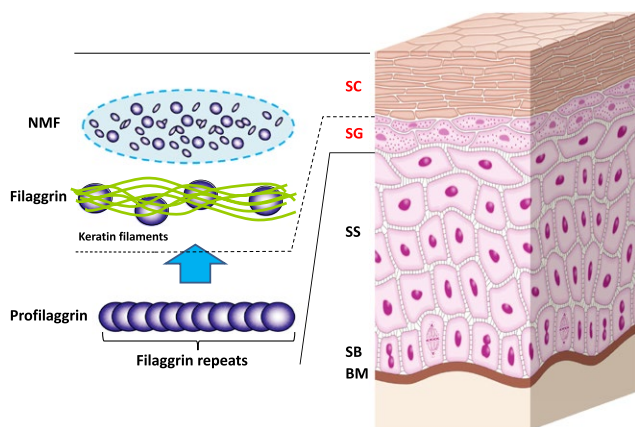


FIGURE 3 The role of filaggrin. FLG protein is localized in the granular layers of the epidermis. Profilaggrin is the main component of keratohyalin granules. During keratinocyte differentiation, profilaggrin is dephosphorylated and cleaved into 10–12 FLG molecules, which aggregate in the keratin cytoskeleton system to form a dense protein-lipid matrix. These FLG monomers are further degraded into natural moisturizing factors, which are important for maintaining skin hydration and a low pH. SC, stratum corneum; SG, stratum granulosum; SS, stratum spinosum; SB, stratum basale; BM, basement membrane; NMF, natural moisturizing factor

be important for IgE production during the epicutaneous sensitization to food allergens.⁹⁰

14 | PRURITUS IN AD

Itch or pruritus is one of the most irritating symptoms that characterizes AD and can significantly impair the quality of life of affected individuals.¹⁶¹ Pruritus in AD is the result of a complex interplay between many factors. Although the exact pathogenesis remains unknown, recent studies have shown that the hyperinnervation of the epidermis, an increase in several itch mediators/pruritogens, and the central sensitization of itch are evident in AD.

14.1 | Hyperinnervation of AD skin

The sprouting of nerve fibers is influenced by a balance between nerve sprouting factors [e.g. nerve growth factor (NGF), amphiregulin and gelatinase] and nerve retraction factors [e.g. semaphorin 3A (Sema3A) and anosmin-1].¹⁶² An increase in nerve fiber density in the epidermis is well reported in AD,^{163,164} and this increase is partly explained by increases in NGF, which can be observed in the plasma of patients with AD,¹⁶⁵ and a decrease in Sema3A, which is detected in the lesional AD epidermis.¹⁶⁶ Consistently, topically applied Sema3A ointment is known to inhibit scratching behavior and improves AD-like skin inflammation in NC/Nga mice.¹⁶⁷ In addition, the acetone-induced hyperinnervation was significantly decreased by phototherapy in accordance with the normalization of the abnormal expression of NGF and Sema3A in the epidermis.¹⁶²

In addition to the hyperinnervation of skin, a lower threshold for activation of the sensory nerve fibers has also been well documented in AD, and these changes synergistically increase the excitability of sensory nerves.²² Furthermore, the hypersensitivity of primary itch-sensing neurons may contribute to allodynia (i.e. pruritus resulting from non-pruritogenic stimuli),¹⁶⁸ which is common in AD patients.¹⁶⁹ Interestingly, artemin, a member of the glial cell-derived neurotrophic factor (GDNF)-related family, is reportedly important in heat-induced itching. Dermal fibroblasts secrete artemin in response to substance P, leading to abnormal peripheral innervation and thermal hyperalgesia.¹⁷⁰ It is probable that artemin lowers the threshold of temperature-dependent itch sensation in pruritic skin disorders, including AD. In addition, a recent study demonstrated that artemin is responsible for epidermal hyperinnervation via aryl hydrocarbon receptors (AhRs) on keratinocytes.¹⁷¹ Various organic components of pollutants activate the transcription factor AhR, and AhR therefore links AD and air pollution via induction of artemin.

14.2 | Pruritogens

Several itch mediators and their corresponding receptors are reportedly responsible for itching in AD. Histamine is a well-known pruritogen, because anti-histamines are effective at controlling pruritus in several skin diseases, especially in urticaria. However, pruritus in

AD is not controlled well by anti-histamines, suggesting that other itch mediators exist. In addition to histamine and its receptors, the H1 and H4 receptors,^{22,172} several other pruritogens are reported to be increased/involved in AD such as proteases (including tryptase, dust mites, and *S. aureus*¹⁶¹); substance P^{1,161}; IL-31^{23,173}; TSLP²⁴; and endothelin-1.¹⁷⁴

A recent study demonstrated that epithelial cells directly stimulate cutaneous sensory neurons via TSLP to promote itching.²⁴ Specifically, TSLP acts on a subset of TRPA1-positive sensory neurons to trigger robust itch behaviors. In addition, IL-31 receptor α (IL-31RA) and oncostatin M receptor β (OSMR β) are expressed in peripheral nerve fibers, dorsal root ganglia (DRGs) and keratinocytes.^{173,175} Upon ligand binding, IL-31 signaling is mediated by the activation of the JAK-signal transducer and activator of transcription (STAT) (STAT-1/5 and ERK-1/2), mitogen-activated protein kinase, and phosphoinositide-3-kinase (PI3K) signaling pathways.^{176,177} Clinical trials of anti-IL-31 receptor (nemolizumab) and anti-IL-31 (BMS-981164) agents as treatments for AD are currently underway.³² A recent study revealed endothelial PAS domain protein 1 (EPAS1) as an important transcription factor for IL-31 induction in CD4⁺ T cells.¹⁷⁸ EPAS1 mediates *IL31* promoter activation, but DOCK8, whose mutation causes the elevated serum IgE, negatively regulates nuclear translocation of EPAS1.^{178,179} EPAS1 therefore links DOCK8 deficiency to atopic skin inflammation via IL-31 induction.

14.3 | Central sensitization of pruritus in AD

The role of the central nervous system in causing the itch associated with AD has been investigated to a lesser extent compared with the role of peripheral innervation. However, a study based on functional magnetic resonance imaging with arterial spin labeling demonstrated an increase in the activation of the anterior cingulate cortex and dorsolateral prefrontal cortex in human subjects with AD compared with healthy controls.¹⁸⁰ This result suggests that individuals with AD are centrally sensitized. Importantly, cognitive and affective processes play a pivotal role in the interpretation and perception of pruritus.¹⁶¹ For example, several psychotropic drugs, including anti-depressants, can attenuate the itch severity in some patients with AD.¹⁸¹

In addition to the brain itself, STAT3 activation in astrocytes of the spinal dorsal horn has been shown to be involved in chronic pruritus. Astrocytes are a subtype of glial cells that reside in the central nervous system¹⁶¹ and this activation results in the production of lipocalin-2, which enhances itching and may lead to the vicious itch-scratch cycle.¹⁸²

15 | NEW DRUGS FOR THE TREATMENT OF AD

Effective treatments with minimal side effects for AD are still lacking, which makes the management of the disease very challenging. Recent understandings in the complex pathogenesis of AD have broadened the treatment options with the new era of targeted therapy. Novel

drugs, developed to target pathways important in AD pathogenesis, have yielded promising results in recent clinical trials. Table 1 displays the summary of these novel therapeutic strategies.^{8,9,32,183,184}

15.1 | Treatments directed against pathogenic molecules

15.1.1 | JAK inhibitors

JAK-STAT is an indispensable signaling pathway for up to 40 different cytokines, and many of them are involved in AD pathogenesis including IL-4/IL-13.¹⁷

The JAK inhibitor has been reported to be effective in many inflammatory dermatoses, such as psoriasis and alopecia areata.¹⁸⁵ For AD, a recent study demonstrated that topical application of JTE052, a JAK inhibitor, can improve the skin barrier by up-regulating filaggrin and NMF expression in murine AD models via suppressing STAT3 activation.¹⁷ A reduction in Eczema Area and Severity Index (EASI) score could be achieved with the use of topical tofacitinib in AD patients in a phase II clinical trial.¹⁸⁶ PF-04965842, another oral JAK inhibitor is also under investigation for AD (NCT02780167). Moreover, orally administered JTE052 was able to inhibit antigen-specific T cell activation and subsequent skin inflammation in a contact hypersensitivity model.¹⁸⁷

15.1.2 | Phosphodiesterase (PDE)-4 inhibitors

The cyclic adenosine monophosphate (cAMP) pathway is one of the important intracellular signaling pathways. Activation of G protein-coupled receptors results in production of cAMP by adenylyl cyclase. cAMP then converts protein kinase A into its active form. The downstream effects of cAMP activation vary between cell types and include both the suppression of proinflammatory cytokines, and the induction of inhibitory cytokines. cAMP is broken down by PDE; therefore, the intracellular level of cAMP is increased by inhibiting PDE.¹⁸⁸ A variety of cell types express PDE-4; T and B cells, macrophages, monocytes, neutrophils, and eosinophils.^{189,190} Interestingly, AD mononuclear leukocytes demonstrate increased cAMP-PDE activity, which perpetuates cutaneous inflammation.¹⁹¹ A recently developed PDE-4 inhibitor was shown to diminish inflammatory cytokines such as TNF- α , IL-2, IL-5, and IFN- γ .¹⁹²

PDE-4 inhibitors will be available in both topical and oral forms. Topical PDE-4 inhibitors, that is, Crisaborole,¹⁹³ E6005¹⁹⁴ and DRM02 (ClinicalTrials.gov Identifier: NCT01993420) show promising results in clinical studies (details are shown in Table 1). In addition, apremilast, an oral PDE-4 inhibitor, achieved a decrease in EASI in a phase II study for AD.¹⁹⁵

15.1.3 | TSLP inhibition

TSLP is one of the central cytokines responsible for Th2 skewing, is crucial for ILC2 activation and is pruritogenic.¹⁹⁶ A strategy to down-regulate this cytokine may improve AD and allergic disorders. Tezepelumab (AMG 157), an anti-TSLP monoclonal antibody, has

been investigated for asthma.¹⁹⁷ The study of the drug for AD is currently being conducted (NCT02525094).

15.1.4 | Chemoattractant-receptor homologous molecule expressed on Th2 lymphocytes (CRTh2) inhibition

Recent studies revealed that prostanoid receptors play a role in AD.¹⁹⁸ CRTh2 is a prostaglandin D2 (PGD₂) receptor that is expressed by Th2 cells, ILC2, neutrophils, eosinophils and basophils.^{199,200} The interaction between PGD₂ and CRTh2 causes cellular chemotaxis, activation, recruitment, and cytokine production.^{199,201} An inhibitor of CRTh2 has been investigated as a treatment strategy for asthma. Additional trials for AD have been initiated (NCT01785602 and NCT02002208).

15.2 | Treatments directed against pathogenic cytokines and their receptors

15.2.1 | The anti-IL-4 receptor dupilumab

Dupilumab is a fully humanized monoclonal antibody against the IL-4 receptor α subunit (IL-4R α), which is shared by IL-4 and IL-13. Thus, dupilumab can inhibit both IL-4 and IL-13, the Th2 cytokines that drive allergic diseases.²⁰² Earlier studies have proved the benefit of dupilumab for AD, asthma and chronic sinusitis with nasal polyposis.^{202–205} Additionally, two randomized, placebo-controlled, phase III studies have confirmed these findings in a larger number of patients. In these studies, more patients achieved EASI-75 (75% improvement of EASI compared with the baseline value) in the dupilumab treatment arm.²⁰⁶ Though studies with longer duration of treatment to monitor the long-term effects of dupilumab are necessary, dupilumab seems to be a promising option for AD patients who have failed standard treatment regimen.

15.2.2 | IL-13 antagonists

Functions of IL-13, another Th2 cytokine, share some redundancy with those of IL-4.⁸ B cell activation, differentiation and IgE production are mediated through the IL-13 signaling pathway.¹⁸³ Therefore, treatments that aim to down-regulate IL-13 may improve the clinical manifestations of AD. Lebrikizumab and tralokinumab are monoclonal antibodies targeting IL-13. Their efficacy in improving AD is currently being explored (NCT02340234 and NCT02347176).

15.2.3 | IL-23p40 antagonists

Ustekinumab is a monoclonal antibody against p40, a subunit of IL-12 and IL-23. Both are required for Th17 and Th1 induction and maintenance.¹⁸⁴ Based on a study demonstrating the importance of Th1 and Th17 cells in cutaneous inflammation in AD, ustekinumab has been tested in AD patients. However, no significant differences in the clinical efficacy (SCORAD50) between the ustekinumab- and

TABLE 1 Novel AD treatments. Potential therapeutic approaches for AD, modified from Heratizadeh et al.¹⁸³, Lauffer et al.¹⁸⁴, Noda et al.⁹, Nomura et al.³², and Werfel et al.⁸

Agent	Company	Route	Target	Clinical trial phase	Outcome of the trial
Tofacitinib	Pfizer	Topical	JAK inhibitor	IIa	Decreased in EASI, BSA of involvement, pruritus, better PGA
Pf-04965842	Pfizer	Oral	JAK inhibitor	II	Unpublished
Crisaborole	Anacor	Topical	PDE-4 inhibitors	III	Achieved ISGA success and greater percentage of patients with clear and almost clear
E6005	Eisai	Topical	PDE-4 inhibitors	II	Decreased in EASI and SCORAD
DRM02	QLT	Topical	PDE-4 inhibitors, protein kinase inhibition, IL-1 and TNF- α antagonist	II	Unpublished
Tezepelumab	Amgen	SC, IV	TSLP antagonist	II	Unpublished
Cipamfylline	Discontinued	Topical	PDE-4 inhibitors	II	Decreased in TSS
Apremilast	Celgene	Oral	PDE-4 inhibitors	II	Decreased in EASI, DLQI
ODC-9101	Oxagen	Oral	CRTh2 antagonist	II	Unpublished
Fevipirant	Novartis	Oral	CRTh2 antagonist	II	Unpublished
OC000459	Atopix	Oral	CRTh2 antagonist	II	Unpublished
Dupilumab	Regeneron	SC	IL-4/IL-13 receptor α -chain antagonist	III	Decrease in EASI, pruritus and better quality of life
Lebrikizumab	Roche	SC	IL-13 antagonist	II	Unpublished
Tralokinumab	AstraZeneca	SC	IL-13 antagonist	II	Unpublished
Mepolizumab	GlaxoSmithKline	IV	IL-5 antagonist	II	Did not result in clinical success with the regimen used in the study
Ustekinumab	Janssen	SC	IL-23p40 antagonist	II	Unpublished
Secukinumab	Novartis	SC	IL-17 antagonist	II	Unpublished
Fezakinumab	Pfizer	IV	IL-22 antagonist	II	Unpublished
Nemolizumab	Roche	SC	IL-31 receptor antagonist	II	Decrease in EASI and pruritus
BMS-981164	Bristol-Myers-Squibb	SC, IV	IL-31 antagonist	I	Unpublished
Anakinra	Sobi	SC	IL-1R1 antagonist	I	Unpublished
Tocilizumab	Genentech	SC, IV	IL-6	Case series	Decrease in EASI
Omalizumab	Novartis	SC	IgE antagonist	Stopped	Heterogeneous results
Ligelizumab	Novartis	SC	IgE antagonist	Phase II	Unpublished

PDE, Phosphodiesterase; CRTh2, Chemoattractant-receptor homologous molecule expressed on Th2 lymphocytes; JAK, Janus kinase; TSLP, thymic stromal lymphopoietin; SC, subcutaneous injection; IV, intravenous; TSS, Total Severity Score; ISGA, Investigator's Static Global Assessment; SCORAD, SCORing Atopic Dermatitis; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; PGA, Physician's Global Assessment.

placebo-treated groups were observed.²⁰⁷ An additional trial is currently being conducted (NCT01806662).

significant itch and EASI reduction²⁰⁸ and BMS-981164 is in phase I trial (NCT01614756).

15.2.4 | IL-31 receptor antagonists and IL-31 antagonists

IL-31 is one of the principal pruritogenic cytokines responsible for itch and inflammation observed in AD. The level of IL-31 parallels with AD disease severity.⁹⁸ IL-31 signaling can be reduced through the use of Nemolizumab, an IL-31 receptor antagonist, and BMS-981164, an IL-31 antagonist. A study involving Nemolizumab has shown a

15.2.5 | Treatments that target IgE and B cells

Increases in IgE and B cell levels are observed in AD patients²⁰⁹ indicating that these immune components may be important therapeutic targets. Results of Omalizumab (a monoclonal anti-IgE antibody) use for the treatment of AD in multiple case reports and few control trials remain inconclusive.^{210–212} Moreover, studies regarding rituximab, an anti-CD20 chimeric monoclonal antibody also demonstrate

inconsistent outcomes.^{213–215} A newer anti-IgE antibody, ligelizumab, which exerts a robust IgE suppression,²¹⁶ is currently undergoing a phase II trial (NCT01552629).

16 | CONCLUSION

The skin barrier and innate and adaptive immunity all orchestrate skin inflammation in AD. Although the pathogenesis of the disease is complex, many aspects need to be further clarified. Based on the detailed evidence available to date, certain disease mechanisms can be selected as treatment targets, and many clinical trials of biological agents targeting these mechanisms are currently being conducted. Overall, a deeper understanding of the mechanism of barrier damage and immune dysregulation will lead to the development of more specific regimens to control and prevent AD.

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CONFLICT OF INTEREST

None declared.

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