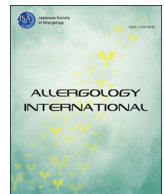




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Review Article

Atopic dermatitis: immune deviation, barrier dysfunction, IgE autoreactivity and new therapies

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AD, atopic dermatitis; α -NAC, α -nascent polypeptide-associated complex; AHR, aryl hydrocarbon receptor; CLA, cutaneous lymphocyte antigen; Fc ϵ RI, high affinity Fc IgE receptor; FLG, filaggrin; H4R, histamine H4 receptor; IFN, interferon; IL, interleukin; T22, interleukin-22 producing T; JAK, Janus kinase; Th, T helper; TrkA, tropomyosin receptor kinase A; TSLP, thymic stromal lymphopoietin

ABSTRACT

Atopic dermatitis (AD) is a chronic or chronically relapsing, eczematous, severely pruritic skin disorder mostly associated with IgE elevation and skin barrier dysfunction due to decreased filaggrin expression. The lesional skin of AD exhibits Th2- and Th22-deviated immune reactions that are progressive during disease chronicity. Th2 and Th22 cytokines further deteriorate the skin barrier by inhibiting filaggrin expression. Some IgEs are reactive to self-antigens. The IgE autoreactivity may precipitate the chronicity of AD. Upon activation of the ORAI1 calcium channel, atopic epidermis releases large amounts of thymic stromal lymphopoietin (TSLP), which initiates the Th2 and Th22 immune response. Th2-derived interleukin-31 and TSLP induce an itch sensation. Taken together, TSLP/Th2/Th22 pathway is a promising target for developing new therapeutics for AD. Enhancing filaggrin expression using ligands for the aryl hydrocarbon receptor may also be an adjunctive measure to restore the disrupted barrier function specifically for AD.

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Introduction

Atopic dermatitis (AD) is a common eczematous skin disorder affecting 2–20% of the general population with age and ethnic differences.^{1,2} AD is characterized by chronic cutaneous inflammation and dry skin with epidermal barrier dysfunction.^{3–5} Intense pruritus is the major and burdensome symptom of AD.^{6,7} Itch-induced scratching appears to exacerbate skin inflammation by accelerating cellular damage in the lesional skin.⁸

Approximately 80% of AD patients exhibit elevated levels of serum IgE.^{9,10} In contrast to normo-IgE and non-allergic intrinsic AD patients, extrinsic AD patients with hyper IgE levels are associated with increased disease severity,^{11,12} mutations in the *FLG* gene,¹³ and impaired skin barrier function.^{12,14} Recent genome-wide association studies and immunochip analyses indicate at least 19 significant susceptibility loci for AD, which emphasize the potential engagement of T helper 2 (Th2) cytokines (*KIF3A/IL-4/IL13*), IL-1 family receptors (*IL1RL1/IL18R1/IL18RAP*) and skin barrier proteins (*FLG*).^{15–20}

With regards to immune abnormalities, AD is currently considered as a biphasic T cell-mediated disease. A Th2 signal predominates in the acute phase, whereas a Th2 to Th1 switch promotes disease chronicity.^{21,22} However, recent studies have proposed a significant role for interleukin (IL)-22-producing T (T22)

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cells, and to a less extent IL-17-producing Th17 cells, in the initiation and maintenance of AD.^{22–24} Infiltrations of CD3+ T cells, CD11c+ dendritic cells and CD1c+ dendritic cells are accompanied with acute AD, and more intense infiltrations are associated with chronic AD.²²

In addition to the involvement of cellular immunity towards Th2 and T22 differentiation, elevated IgE is likely to be engaged in the development and severity of AD by manifesting IgE autoreactivity.^{25–27} Total IgE levels are strongly correlated with the prevalence of IgE autoreactivity.^{28–30} Some reports indicate a correlation between autoreactivity and disease severity in AD.^{28,31} In addition, numerous cells infiltrated in the lesional skin of AD are positive for IgE or the high affinity Fc IgE receptor (FcεRI).^{22,32–35}

Based on the pathogenetic role of barrier and immune abnormalities in AD, standard therapeutics include topical emollients for barrier dysfunction and topical steroids and calcineurin inhibitors for skin inflammation.⁶ These conventional treatments are more or less effective in reducing atopic inflammation and itch; however, patient satisfaction is generally low in daily clinics. Several targeting therapies are now emerging and being assessed in clinical trials.⁶

Immune deviation towards Th2 and T22 expansion in AD

Historically, acute AD lesions have a significantly greater number of Th2 cytokine (IL-4, IL-5 and IL-13) mRNA-expressing cells compared with normal skin or uninvolved AD skin.^{6,36} Compared with acute lesions, chronic AD lesions have fewer IL-4 and IL-13 mRNA-expressing cells but greater numbers of interferon (IFN)-γ mRNA-expressing Th1 cells.^{6,36} The Th2 to Th2/Th1 shift is also exemplified in an atopic patch test elicited by house dust mite antigen.^{37,38} In addition, the importance of Th2 deviation in AD is evidenced by the fact that the disease severity of AD is significantly correlated with IL-4/IL-13-related molecules, such as CCL17, perostin and galectin-9.^{39–41} Although the potential role of IL-17-

producing Th17 cells is proposed in AD,⁴² controversial results have been reported.^{43,44}

In addition to Th2 deviation, a series of recent studies by Guttman-Yassky *et al.* have stressed a critical role of IL-22 producing T22 cells in AD (Fig. 1).^{22,24,45} Unlike murine Th17 cells, which coproduce IL-22, human T cells harbor distinct T22 cells that lack IL-17 expression.^{45,46} Nogales *et al.* first demonstrated a significant accumulation of T22 cells in the lesional skin of AD compared with psoriasis and normal controls.⁴³ The infiltrated T22 cells included CD4+ helper (Th22) and CD8+ cytotoxic (Tc22) cells. Of note, the clinical severity of AD is correlated with the number of Tc22 cells rather than that of Th22 cells.⁴³ In a study comparing nonlesional skin with acute and chronic lesions in 10 patients with AD, the acute lesions exhibit a striking upregulation of genes related to Th2 (IL4, IL10, IL31 and CCL11) and T22 (IL22, S100A7, S100A8, S100A9, S100A12 and IL32).²² The increased Th2/T22 signatures in acute AD lesions are further enhanced in chronic lesions intermingled with upregulation of Th1-related genes (IFNG, CXCL9, CXCL10 and CXCL11).²² Multicolor flow cytometric analyses have revealed that circulating cutaneous lymphocyte antigen-positive (CLA+; skin homing receptor) Th2 cells are markedly expanded in both children (aged 5–70 months) and adults (aged 18–74 years) with AD compared with normal control subjects.²⁴ The number of CLA+Th1 cells is significantly decreased in childhood AD but not adult AD, whereas the number of both CLA+Th22 and CLA+Tc22 is significantly increased in adult but not childhood AD patients compared with normal controls.²⁴ The comparative study enrolling early (aged 0–3 years) and late (aged 3–6 years) childhood AD patients has elucidated a significant elevation of CLA+Th2 and a significant decrease of CLA+Th1 population in the early but not in late childhood AD patients compared with normal age-matched control subjects.⁴⁷ No significant difference is observed in the number of CLA+Th22 cells between AD patients and normal controls in either early or late childhood AD.⁴⁷ In parallel with the pivotal participation of Th2/T22 cells, the upregulation of chemokines and

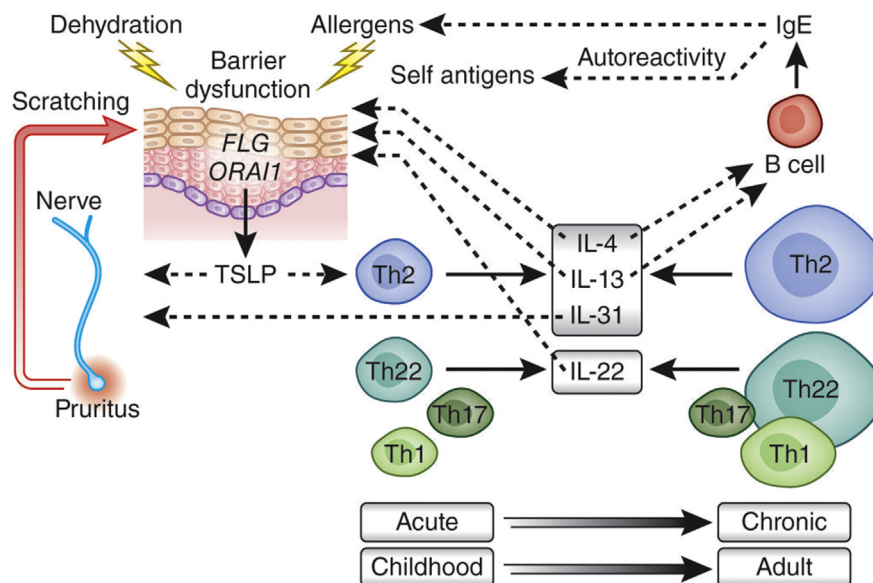


Fig. 1. Pathogenesis of atopic dermatitis (AD). Skin barrier dysfunction and Th2/Th22-deviated immune reactions are the fundamental abnormality in AD. Genetic mutations in filaggrin (FLG) cause barrier disruption and dehydration, which make the external allergens permeable. The barrier-disrupted epidermis abundantly releases thymic stromal lymphopoietin (TSLP), which triggers the Th2/Th22 immune response. The Th2/Th22 deviation is further accelerated during disease progression, for example, from acute to chronic or childhood to adult AD. In addition, Th1 but not Th17 cells tend to participate in the chronic phase of AD. Th2 cytokines (IL-4 and IL-13) stimulate B cells to produce IgE antibodies to allergens. Some IgEs react to self-antigens. IgE autoreactivity also contributes to disease activity. In addition, IL-4, IL-13 and IL-22 are strong suppressors of FLG expression. Pruritus is evoked by TSLP and Th2-derived IL-31, and the subsequent scratching further worsens skin barrier dysfunction. The release of TSLP from keratinocytes is dependent on calcium influx regulated by the Orai1 channel. Targeting TSLP/Th2/Th22 as well as Orai1 pathways is a promising strategy to overcome atopic inflammation.

chemokine receptors is also an integral component of atopic inflammation, i.e., CCL1, CCL4, CCL13, CCL17, CCL18, CCL20, CCL22, CCL26, CXCL1, CXCL2, CXCL3, CXCL8, CXCL9, CXCL10, CCR1 and CCR7 with increased expression of janus kinases (JAK) 1 and 3.^{48–51}

Disruption of barrier proteins by IL-4, IL-13 and IL-22

The epidermal barrier function is formed by coordinated and sequential cross-linking of various barrier proteins, such as filaggrin (FLG) and loricrin (LOR). The majority of human epidermal barrier proteins map to a 2.5-Mbp cluster termed the “epidermal differentiation complex” (EDC) located on chromosome 1q21.^{52,53} The expression of barrier protein genes in the EDC locus is up- and downregulated by various external and internal stimuli, including Th2 (IL-4 and IL-13) and T22 (IL-22) cytokines.^{43,53–57} Interleukin-4 and IL-13 significantly inhibit FLG and LOR mRNA and protein expression.^{53–56} FLG and LOR expression is also markedly downregulated by IL-22 (Fig. 1).^{43,57} In accordance with the loss of function mutation of *FLG* in AD,^{15–20} the downregulated action of Th2 and T22 cytokines explain the disrupted expression of FLG and LOR in the lesional skin of AD patients, leading to epidermal barrier dysfunction.^{10,54,55,58} In contrast to the decreased expression of FLG and LOR, the lesional skin of AD patients exhibited increased expression of S100A7, the gene of which is also located in the EDC locus.^{22,45,52,59} Although IL-4 and IL-13 inhibit the expression of S100A7 in keratinocytes, IL-22 is a strong inducer of S100A7 gene expression.^{22,45,59}

IgE autoreactivity in AD

The definition of “atopy” is a diathesis to overproduce IgE antibodies or to have a personal and/or family history of asthma, allergic rhinitis, allergic conjunctivitis and AD.⁶⁰ With the help of Th2 cytokines, activated B cells undergo IgE production.⁶¹ Diverse activation and differentiation of multiple B cell subsets are indeed reported in AD but not in psoriasis or normal controls, with a significant correlation with circulating IgE levels.⁶² Consistent with the preponderant Th2 deviation in early childhood AD,^{24,47} elevated levels of total or allergen-specific IgE are noted in infantile and early childhood AD.^{50,51,63} IgE levels specific for ovomucoid, wheat and mite allergens are correlated with serum levels of the Th2-related cytokines CCL17 and CCL22.^{50,51} The skin barrier dysfunction with *FLG* mutation and increased *Staphylococcus aureus* colonization contribute to disease progression and aberrant IgE production in AD.^{13,64–66}

As previously demonstrated in the autoimmune diseases, such as systemic lupus erythematosus and bullous pemphigoid,²⁷ IgE autoreactivity is given increasing attention in AD (Fig. 1).^{25–27} A positive skin test to human dander and sweat had suggested the presence of IgE autoreactivity to unknown auto-antigens in the 1940s.^{67–71} In addition, the fungal protein MGL_1304, which is derived from *Malassezia globosa*, is identified as the major antigen for the sweat-targeting IgE antibodies from AD.⁷² However, some autoreactive IgE antibodies in AD patients potentially bind to cell membrane and intracellular structures of cultured human keratinocytes.²⁹ Natter *et al.*, Zeller *et al.* and other researchers have examined human cDNA clones coding for auto-antigens targeted by IgE autoantibodies from AD patients and have found a variety of plausible self-antigens, including manganese superoxide dismutase, ribosomal P2 protein, profilin 1, cyclophilin B, thioredoxin, α -nascent polypeptide-associated complex (α -NAC), keratin 6A, actin α 2 and tubulin α 1A, some of which have high homology to environmental allergens.^{30,73–77} It is intriguing that the titers of anti-manganese superoxide dismutase IgE autoantibodies correlate with AD disease severity.²⁸ Some of these auto-antigens activate

basophils via Fc ϵ RI and induce a positive skin reaction of the immediate or delayed type.^{28,30,75}

The transcriptional coactivator α -NAC is an intracellular protein that is involved in sorting of newly synthesized polypeptides without any homology with environmental known allergens.⁷⁸ Peripheral blood mononuclear cells (PBMC) from AD patients with anti- α -NAC IgE antibodies produce significantly increased amounts of IL-17, IL-22 and IFN- γ compared with normal control PBMCs *in vitro* in the presence of α -NAC and IL-2. The cytokine production is cancelled by the depletion of antigen-presenting monocytes from PBMC, demonstrating that the α -NAC self-antigen is presented by monocytes to T cells by the ordinary immune system.⁷⁸ The autoreactive T cells specific for α -NAC are CLA+ and CCR4+.⁷⁹ Recently, α -NAC-specific autoreactive CD8+ T cells are also detected in AD patients. These α -NAC-specific CD8+ T cells coproduce IL-4 and IFN- γ .⁸⁰ These studies highlight the potential role of autoreactive IgE and T cell responses in exacerbating and perpetuating AD disease severity.

New therapies for atopic dermatitis

First-line treatments of AD include the application of emollients for dry skin, topical steroids and tacrolimus for skin inflammation, and oral antihistamines for pruritus, followed by second-line adjunct therapies, such as systemic cyclosporine, short-term oral steroids, and ultraviolet radiation.⁶⁰ Although many reports confirm the effects of conventional treatments, the satisfaction and adherence to treatments are typically very low in AD patients.⁸¹ Considering the recent progress in the understanding of the pathomechanisms of AD, there is room for new strategies and therapies in the management of AD.

Dupilumab

Dupilumab is a fully human monoclonal antibody directed against the α subunit of the IL-4 receptors that blocks signaling from both IL-4 and IL-13. In phase I and II studies of adults with moderate-to-severe AD, administration of dupilumab resulted in significant improvements in inflammation and pruritus with no dose-limiting toxicity.^{82–84} Significant decrease in mRNA expression of genes related to Th2-associated chemokines (*CCL17*, *CCL18*, *CCL22* and *CCL26*) is detected without significant modulation of Th1-associated genes (*IFNG*).⁸² Dupilumab also significantly improves the disturbance of sleep and quality of life at 16 weeks of treatment.⁸⁵ These findings indicate that dupilumab is a promising new anti-inflammatory and anti-pruritic treatment for AD.

Anti-IL-31 A receptor antibody (CIM331)

An anti-IL-31 receptor A antibody may be another promising agent to inhibit atopic itch. In humans and mice, IL-31 is predominantly produced by Th2 cells, and its cutaneous injection induces pruritus.⁸⁶ A recent clinical trial has revealed that a single injection of an anti-IL-31 receptor A antibody (CIM331) significantly inhibits pruritus in patients with moderate to severe AD for up to 4 weeks after administration without any serious adverse events.⁸⁷ CIM331 also increases sleep efficiency and decreases the use of topical hydrocortisone butyrate.⁸⁷ Notably, IL-31 receptor A is defined as a downstream molecule of Fc ϵ RI activation.⁸⁸

Phosphodiesterase 4 inhibitors

Phosphodiesterase 4 inhibitors exhibit immunosuppressive activity by enhancing the intracellular concentration of cyclic AMP and inhibit IL-4 and tumor necrosis factor α in experimental

animals.⁸⁹ In clinical trials, several topical phosphodiesterase 4 inhibitors, including E6005,^{90,91} OPA-15406,⁹² and crisaborole,⁹³ have demonstrated effectiveness against inflammation and pruritus in AD. Although the oral phosphodiesterase 4 inhibitor apremilast is effective in the treatment of AD and psoriasis, a higher dose may be necessary to obtain significant improvement in AD compared with psoriasis.^{94,95}

Histamine H4 receptor antagonist

Based on its anti-pruritic and anti-inflammatory effects in experimental animals, a clinical trial of the oral administration of histamine H4 receptor (H4R) antagonist (JNJ-39758979) was conducted in Japanese patients with AD.⁹⁶ Although the H4R antagonist significantly reduced day- and night-time pruritus in AD patients, the clinical study was terminated due to the severe adverse effects of agranulocytosis. In addition to its neural expression,⁹⁷ H4R is involved in the CCL17 and CCL22 production from monocyte-derived dendritic cells and the Th2-deviated inflammation in atopic model mice.^{98,99}

Janus kinase inhibitor (tofacitinib)

Cytokines exert their effects by activating intracellular signaling pathways, such as the JAK family. Tofacitinib is a pan-JAK inhibitor that preferentially inhibits JAK1 and JAK3, and to a lesser extent, JAK2 and tyrosine kinase 2.¹⁰⁰ Both oral and topical tofacitinib significantly improve the skin inflammation and pruritus of AD.^{101,102} The mean percent changes from baseline at week 4 in eczema area and severity index (EASI) score are significantly greater ($p < 0.001$) for topical tofacitinib (−81.7%) vs. vehicle (−29.9%).¹⁰² Significant improvements in EASI are observed by week 1 and pruritus by day 2.¹⁰² Although tofacitinib is a promising agent, its potential adverse events due to immunosuppression should be carefully evaluated in a long-term clinical trial.

Topical tropomyosin receptor kinase A inhibitor

Tropomyosin receptor kinase A (TrkA) is a high-affinity NGF receptor. Nerve fibers positive for TrkA are detected in human epidermis, dermis, and dorsal root ganglion.¹⁰³ A recent clinical trial by Roblin *et al.* demonstrates that the topical TrkA kinase inhibitor CT327 is an effective treatment for pruritus due to psoriasis.¹⁰³ Further trials are necessary to prove the anti-pruritic effects of CT327 in AD.

Conclusion

The expression of FLG is upregulated by the specific activation of aryl hydrocarbon receptor (AHR), which senses various external and internal chemical ligands.^{53,55,56} Ligation of AHR by coal tar, soybean tar or certain phytochemicals cancels the inhibitory action of Th2 cytokines on the FLG expression, which may partly account for the medicinal use of these agents to treat inflammatory skin disease.^{53,55,56,104} Exploring the safe and effective ligands for AHR is one of the potential methods to develop new adjunctive therapeutics for barrier-disrupted skin diseases. AHR is also a key molecule in establishing the intestinal microbial community by influencing the balance between Th17 cells and regulatory T cells.¹⁰⁵ Therefore, one can also hypothesize that spontaneous regression of infantile AD¹⁰⁶ may be related to the restoration of FLG expression by endogenous and exogenous AHR ligands supplied from skin microbiota⁶⁶ together with the normalization of immune deviation.

As revealed in psoriasis,¹⁰⁷ epidermal and immune interactions also play critical roles in the pathogenesis of AD.¹⁰⁸ Thymic stromal lymphopoietin (TSLP) is strongly expressed in the lesional epidermis in AD and acts as a master switch that triggers the Th2 and Th22 response (Fig. 1).^{108,109} In addition, TSLP directly activates sensory nerves to induce pruritus.¹¹⁰ The production of TSLP by epidermal keratinocytes is highly dependent on an increase in intracellular Ca^{2+} regulated by the activation of ORAI1, which is the major subunit of a store-operated Ca^{2+} channel in keratinocytes.^{110–112} Knockdown of ORAI1 significantly attenuates TSLP release by keratinocytes.¹¹⁰ Of interest, an *ORAI1* genetic polymorphism is associated with the susceptibility of AD in Japanese and Taiwanese populations.¹¹³ Taken together, targeting TSLP/Th2/Th22 as well as ORAI1 pathways is a promising strategy to overcome atopic inflammation.

Conflict of interest

MF serves as a consultant of P&G and receives research funds from P&G and Sunstar. The rest of the authors have no conflict of interest.

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