Received: 3 June 2018 | Accepted: 6 June 2018

DOI: 10.1002/cia2.12023

REVIEW ARTICLE

WILEY Journal of Cutaneous Immunology and Allergy

T helper type 2 signatures in atopic dermatitis

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Funding information
The Ministry of Health, Labour and Welfare, Japan, Grant/Award Number: grant (H27-Shokuhin-Shitei-017) for Research on Food Safety

Abstract

T helper type 2 (Th2)-derived cytokines, such as IL-4, IL-13, and IL-31, play a fundamental role in the development and progression of atopic dermatitis (AD). In addition to gene mutations of filaggrin (FLG), the Th2-deviated microenvironment downregulates FLG expression and disrupts barrier function, resulting in *Staphylococcus aureus* colonization and increased penetration of external allergens. From lesional AD skin, the Th2 milieu helps to release Th2-related chemokines such as CCL17, CCL22, and CCL26, which augment recruitment of Th2 cells and eosinophils. IL-4 and IL-13 stimulate B cells to produce IgE that links AD to other atopic comorbidities. IL-31 is the major pruritogenic cytokine in AD. Notably, the anti–IL-4 receptor α antibody dupilumab and the anti–IL-31 receptor A antibody nemolizumab have proven to be effective for treatment of AD. In the present review, Th2 signatures in AD are examined and overviewed.

KEYWORDS
atopic dermatitis, CCL17, dupilumab, filaggrin, IgE, T helper type 2

1 | INTRODUCTION

Atopic dermatitis (AD) is a common, chronic or chronically relapsing, severely pruritic, eczematous skin disease that markedly deteriorates quality of life of the afflicted patients.[1–4] Clinical symptoms and signs of AD are characterized by skin inflammation, xerosis, and itching.[1,5,6] Severe pruritus induces sleep disturbance in AD patients and their caregivers.[7–9] The itch-sleepless circuit may increase attention-deficit/hyperactivity disorder in children as well as in adults with AD.[8,9] Their stress levels are also very high.[10]

Atopic dermatitis is more frequent in childhood, especially in the first five years of life.[11,12] The prevalence or incidence of AD in the first five years of childhood is 10%-16.5% and is generally considered to be increasing worldwide, at least from the 1980s to early 2000s.[13–15] Most pediatric AD cases are mild-to-moderate in severity, with 84% of cases considered mild, 14% moderate, and only 2% severe.[13] The number of patients with adult AD (over 40 years of age) has decreased rapidly,[14,16] but the occurrence of AD in senile or elderly patients is also currently an important issue.[17]

Atopic dermatitis is composed of heterogeneous pathophysiological groups regarding onset, persistence, genetics, seasonality, and IgE sensitization.[1,2,11,18–21] Eighty percent of childhood AD does not persist past eight years, but most patients remit by adulthood.[11,22,23] Less than 5% of childhood AD persists for 20 years after diagnosis.[11] Moreover, children who developed AD in the first two years of life have significantly lower risk of persistent disease than those who developed AD later in childhood or adolescence.[11] Children with moderate-to-severe AD at age 9-16 months are more likely to have persistent AD 6-12 years later compared to those with mild disease.[24] Fifty percent of subjects have at least one six-month symptom-/treatment-free period, but symptoms frequently recur until 20 years of age.[25] Therefore, AD is a lifelong illness.

As monozygotic twins have a higher co-occurrence of AD than dizygotic twins,[26] genetic factors are decisive in the development of AD. At least 31 gene loci have been identified as being associated with AD by genome-wide association studies.[18,27] Most of the gene loci such as filaggrin (FLG), OVOL1, and IL13 are ancestry-independent, but *NLRP10* and *CCDC80* are Japanese-specific loci.[18] The

strongest risk factors are null mutations of FLG gene, resulting in epidermal barrier deficiency.[18,27] In accordance, FLG expression levels have been reported to be reduced in lesional and nonlesional skin in AD patients.[28–30] Ichthyosis vulgaris is also known to be caused by a loss-of-function mutation of the FLG gene.[31] This may explain why AD is significantly comorbid with ichthyosis vulgaris.[32,33] Children with FLG mutations were more likely to have persistent AD.[25] However, FLG mutations are not found in all AD patients, and they are less common in southern Europeans[34] and are even absent in some African countries.[35,36] A humid atmosphere may reduce the contribution of FLG mutations to the onset of AD.[37] These studies reiterate the genetic heterogeneity of AD.

2 | TH2 DEVIATION IN ATOPIC DERMATITIS

Compiling evidence has shown that acute AD lesions have a significantly greater number of T helper 2 (Th2) cells expressing interleukin-4 (IL-4) and IL-13 compared with normal skin or unaffected AD skin (Figure 1).[38,39] The Th2-deviated immune response is demonstrated both in pediatric and adult AD[40–42] and is more pronounced in chronic lesions than in acute lesions.[40,43] In addition to Th2 deviation, IL-22 produced by Th22 cells is also linked to the chronicity and amplification of atopic inflammation.[41,43,44] The pathogenic importance of IL-4/IL-13 and IL-22 signaling in AD has recently been demonstrated by the successful improvement in skin inflammation in patients with AD upon treatment with the specific anti–IL-4 receptor α antibody dupilumab and the anti–IL-22 antibody fezakinumab[45,46] Although a potential role for the IL-17–producing Th17 cells has been proposed in AD,[47,48] conflicting results have been reported.[49,50]

Despite a low phylogenetic homology of the IL-31 gene in mammals, administration of IL-31 causes an itch response in rodents, dogs, and cynomolgus monkeys.[51] IL-31 transgenic mice demonstrate continuous scratching behaviors and AD-like skin lesions.[52] IL-31 is preferentially expressed by Th2 cells after activation.[52,53] The expression of IL-31 is amplified in lesional skin and peripheral blood lymphocytes in AD compared with healthy controls.[51,54,55] The anti-canine IL-31 antibody (lokivetmab) significantly reduces scratching in dogs with canine AD.[56] More importantly, antihuman IL-31 receptor A antibody nemolizumab also reduces pruritus and sleep disturbance in patients with moderate-to-severe AD.[57]

3 | SKIN BARRIER DISRUPTION BY TH2 CYTOKINES

Skin barrier maturation is accomplished by sequential and coordinated expression of various terminal differentiation proteins such as FLG and loricrin (LOR) (Figure 1).[58] In addition to the loss-of-function mutations of FLG,[18,59] Th2-derived IL-4 and IL-13 inhibit FLG and LOR expression (Figure 1).[29,30] IL-22 and IL-31 also downregulate

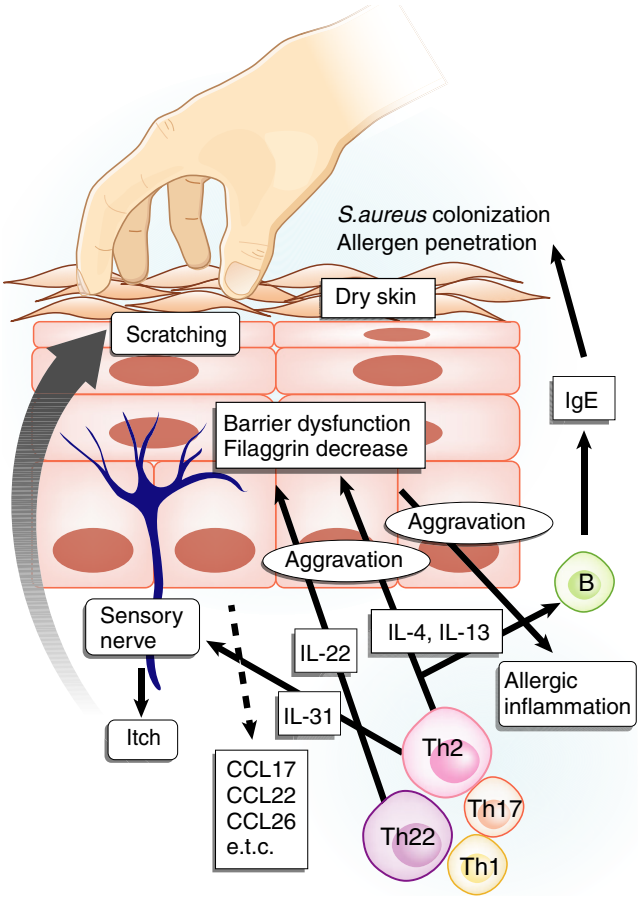

FIGURE 1 Simplified pathogenesis of atopic dermatitis (AD). Skin barrier dysfunction caused by genetic mutations of filaggrin (FLG) and Th2/Th22-deviated cytokines induces atopic dry skin, accelerates penetration of allergens, and increases colonization of *Staphylococcus aureus*. Skin barrier dysfunction and T helper type 2 (Th2)-skewed allergic inflammation mutually exacerbate each other. In response to IL-4 and IL-13, B cells produce high amounts of IgE and cutaneous resident and infiltrated cells release Th2-related chemokines such as CCL17, CCL22, and CCL26. Th2 cells also release IL-31, which stimulates sensory nerves and evokes the itch sensation leading to mechanical scratching and exacerbation of barrier dysfunction

FLG and LOR expression.[60,61] Therefore, the Th2- and Th22-polarized inflammatory milieus in AD interfere with coordinated epidermal differentiation and maturation and exacerbate barrier dysfunction. The barrier dysfunction is associated with atopic dry skin, increased penetration of allergens, and enhanced *Staphylococcus aureus* colonization.[62]

In line with this notion, topical steroids significantly improve clinical inflammatory signs and normalize transepidermal water loss in lesional AD skin because of the upregulation of FLG and LOR expression.[63] These improvements are associated with the downregulation of the Th2 signatures such as IL-13 and IL-31.[63] OVOL1 is an upstream transcription factor for FLG and LOR expression[29,64] and is one of the susceptibility genes for AD.[18] IL-4 is known to inhibit the activation of OVOL1 by interfering with its cytoplasmic to nuclear translocation.[29,65]

Coal tar and soybean tar were historically used for the treatment of AD.[30,66] Both agents are potent activators for the aryl hydrocarbon receptor (AHR), which is abundantly expressed in epidermal keratinocytes.[30,66,67] Notably, AHR is an upstream transcription factor for OVOL1/FLG and OVOL1/LOR signaling.[29,64,65] For example, soybean tar, Glyteer, activates AHR, which induces nuclear translocation of OVOL1 and upregulation of FLG and LOR expression.[29,64,65] AHR activation by soybean tar restores the inhibitory action of IL-4 on FLG expression.[29,65,66] In addition, recent clinical trials have revealed that a natural AHR agonist, tapinarof, improves AD skin lesions when used topically.[68,69]

4 | CHEMOKINES IN ATOPIC DERMATITIS

In parallel with the pivotal participation of Th2/Th22 cells, the upregulation of chemokines and chemokine receptors is also an integral component of atopic inflammation, that is, CCL1, CCL4, CCL13, CCL17, CCL18, CCL20, CCL22, CCL26, CXCL1, CXCL2, CXCL3, CXCL8, CXCL9, CXCL10, CCR1, and CCR7 (Figure 1).[70–73] Among them, CCL17, CCL22, and CCL26 are key Th2-related chemokines. Serum levels of CCL17 and CCL22 are elevated in patients with AD compared to healthy controls and are associated with disease severity.[74–76] Topical steroids are effective in normalizing the levels of CCL17 and CCL22.[63,77,78] Notably, serum TARC levels are inversely correlated with corneal water content not only in mild AD patients but also in healthy controls.[79] Dendritic cells, especially Langerhans cells, are one of the major sources of CCL17 and CCL22 production upon IL-4 stimulation.[80–82] CCL17 and CCL22 are potent attractants for CCR4-expressing Th2 cells.[83,84] Increased CCL17 is also evident in AD-like mouse models.[85]

Normal pregnancy is associated with Th2 skewing of the immune system. This is most pronounced at the maternal-fetal interface and affords protection to the "semi-allogeneic" fetus.[86–88] This Th2 bias persists in the neonates and infants, and it is likely to promote onset of infantile atopic diseases such as AD and food allergies.[86,89,90] Consistent with this notion, the levels of CCL17 and CCL22 are highest in neonates and then decrease over the course of the following two years.[91–93] Umbilical cord blood CCL22 levels were positively associated with IgE sensitization at age 2.[94] Cord blood levels of CCL17 from neonates destined to develop AD in infancy are higher than those from neonates who show no signs of AD during infancy. Moreover, high umbilical cord serum levels of CCL17 are associated with infantile AD development in neonates born to mothers without AD.[95] Serum levels of CCL17 are higher in childhood AD patients with egg allergy than those without egg allergy.[73,96]

CCL26 is also a Th2-associated chemokine, which potently attracts eosinophils.[97] Levels of CCL26 are elevated in the sera and lesional skins of patients with AD and are correlated with their disease activity.[98] Notably, administration of dupilumab significantly diminishes the lesional expression of CCL26 as well as CCL17 and CCL22 in AD.[99]

5 | IGE IN ATOPIC DERMATITIS

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.[6] With the help of Th2 cytokines, activated B cells undergo IgE production (Figure 1).[100] Diverse activation and differentiation of multiple B cell subsets are indeed reported in AD, with a significant correlation with circulating IgE levels, but not in psoriasis or normal controls.[101] Approximately 80% of AD patients exhibit elevated levels of serum IgE.[19] In contrast to normo-IgE and nonallergic intrinsic AD patients, extrinsic AD patients with hyper IgE levels are associated with increased disease severity,[102] mutations in the FLG gene,[20] and impaired skin barrier function.[102,103] Some IgE antibodies are known to be reactive to autoantigens such as α-nascent polypeptide-associated complex.[104,105] In accordance, autoimmune diseases involving skin and intestinal mucosa are frequently associated with AD.[106,107]

Consistent with the preponderant Th2 deviation in early childhood AD (Czarnowicki, Esaki),[40,41] elevated levels of total or allergen specific IgE are noted in infantile and early childhood AD.[71,73,108] Cord blood IgE levels are apparently associated with onset of food allergies in infants.[109] IgE levels specific for ovomucoid, wheat, and mite allergens are correlated with serum levels of the Th2-related chemokines CCL17 and CCL22 in childhood AD.[71,73,110] The skin barrier dysfunction with FLG mutation and increased *S. aureus* colonization contribute to disease progression and aberrant IgE production in AD.[20,111,112]

6 | CONCLUSION

T helper type 2 deviation appears to affect immune function and epidermal barrier integrity in AD by forming an IL-4/IL-13–dominant milieu. Moreover, it induces atopic itch because of IL-31, which is preferentially released by Th2 cells.[51,53] Itch-induced scratching is a cardinal factor in the exacerbation of AD.[113] In parallel, recent clinical trials have revealed that blockade of IL-4/IL-13 signaling by anti–IL-4 receptor α antibody dupilumab significantly improves atopic inflammation.[45,114] In addition, the anti–IL-31 receptor A antibody nemolizumab successfully resolves atopic itch.[57,115] Despite the safety and the considerable effectiveness of these biologics, there still exists high and low responders. This fact reiterates the heterogeneity of AD. Search for relevant biomarkers that dictate treatment response is warranted for these targeted biologic therapies.

ACKNOWLEDGEMENT

This work is partly supported by a grant (H27-Shokuhin-Shitei-017) for Research on Food Safety from The Ministry of Health, Labour and Welfare, Japan.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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How to cite this article: Furue M. T helper type 2 signatures in atopic dermatitis. *J Cutan Immunol Allergy*. 2018;1:93–99. https://doi.org/10.1002/cia2.12023