Atopic dermatitis as Th2 disease revisited

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1 INTRODUCTION

Atopic dermatitis (AD) is a chronic- intermittent, eczematous dermatitis that starts at infancy or early childhood and persists for a large part of life. A large number of clinical, laboratory, and experimental studies have been performed, but the pathophysiology of AD remains to be clarified.

Th1 and Th2 populations are a classical dichotomy to understand the immunological disorders, and this concept remains vital in atopic dermatitis (AD). While IL-4 and IL-13 are produced mainly by Th2 cells, mast cells, and basophils, these cytokines target these producers, indicating the presence of autocrine and paracrine stimulation. There are two types of receptors for IL-4 and IL-13, type I and type II. IL-4 binds to both type I and II receptors, while IL-13 has affinity to type II. Dupilumab is an IL-4Rx-antagonist that inhibits IL-4 and IL-13 signaling through blockade of the shared IL-4α subunit. The Th2-stimulating effect of thymic stromal lymphopoietin (TSLP) is triggered by its binding to TSLP receptor (TSLPR) on Th2 cells. The frequency of TSLPR^CD4^ T cells correlates with disease activity. CD4^ T cells directly interact with TSLP to produce a high amount of IL-4. Conversely, IL-4 induces TSLPR expression in T cells. Moreover, TSLP and IL-4 promote CCR4 expression, which is a chemokine receptor for CCL17/TARC. Langerhans cells initiate epicutaneous sensitization with protein antigens and induce Th2 cell-mediated immune responses via TSLP signaling. Filaggrin deficiency, which cornified layer-damaged skin allows protein antigens to penetrate through the stratum corneum, leads to allergy where IL-4 and IL-13 are overproduced. Subsequently, IL-4 and IL-13 further depress filaggrin expression with vicious cycle. AD is generally a Th2 disease, but there exist several exceptional and undeniable facts to be considered, including Th1-activated intrinsic AD, Th1-infiltrating chronic AD skin lesions, and Th17 involvement.

KEYWORDS
atopic dermatitis, barrier, dupilumab, filaggrin, keratinocytes, langerhans cell, T helper 2 populations

T helper 1 (Th1) and T helper 2 (Th2) populations are a classical dichotomy to understand the immunological disorders, and this concept remains vital in atopic dermatitis (AD). While IL-4 and IL-13 are produced mainly by Th2 cells, mast cells, and basophils, these cytokines target these producers, indicating the presence of autocrine and paracrine stimulation. There are two types of receptors for IL-4 and IL-13, type I and type II. IL-4 binds to both type I and II receptors, while IL-13 has affinity to type II. Dupilumab is an IL-4Rx-antagonist that inhibits IL-4 and IL-13 signaling through blockade of the shared IL-4α subunit. The Th2-stimulating effect of thymic stromal lymphopoietin (TSLP) is triggered by its binding to TSLP receptor (TSLPR) on Th2 cells. The frequency of TSLPR^CD4^ T cells correlates with disease activity. CD4^ T cells directly interact with TSLP to produce a high amount of IL-4. Conversely, IL-4 induces TSLPR expression in T cells. Moreover, TSLP and IL-4 promote CCR4 expression, which is a chemokine receptor for CCL17/TARC. Langerhans cells initiate epicutaneous sensitization with protein antigens and induce Th2 cell-mediated immune responses via TSLP signaling. Filaggrin deficiency, which cornified layer-damaged skin allows protein antigens to penetrate through the stratum corneum, leads to allergy where IL-4 and IL-13 are overproduced. Subsequently, IL-4 and IL-13 further depress filaggrin expression with vicious cycle. AD is generally a Th2 disease, but there exist several exceptional and undeniable facts to be considered, including Th1-activated intrinsic AD, Th1-infiltrating chronic AD skin lesions, and Th17 involvement.

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Recent use of anti-Th2 cytokine or receptor antibody therapies has been providing important information on Th2-skewing condition of AD. The clinical efficacies of these treatments are mandatory for evaluation of Th2 cytokines in AD pathogenesis. In this review, we revisit the essential role of Th2 cells for AD, but also several issues that are as yet unelucidated merely with Th2 dogma.

2 | PERTURBATION OF STRATUM CORNEUM BARRIER IN AD

The barrier function is usually assessed by transepidermal water loss (TEWL) and skin surface hydration. AD patients, especially common, serum IgE-high, extrinsic AD patients, have increased TEWL and lower skin surface hydration, compared with healthy subjects. Even at the non-lesional forearm and lower leg of patients and normal volunteers, the level of skin surface hydration was significantly lower in AD than in normal subjects.

The identification of loss-of-function mutations in filaggrin gene (FLG) has shed new light on the mechanisms of AD. When we examined the amount of filaggrin in stratum corneum of AD patients, ichthyosis vulgaris patients, and normal subjects, we confirmed that filaggrin is apparently reduced in ichthyosis vulgaris and AD compared with normal subjects. Patients with FLG mutations have various extents of ichthyosis vulgaris (Figure 1), palmar hyperlinearity (Figure 2), and atopic dermatitis. Different FLG mutations were

![Barrier impairment vs. Allergic disorder](image1)

**Figure 1** Vicious cycle between barrier impairment and allergic disorder in atopic dermatitis. Filaggrin deficiency is a typical cause of barrier impairment (as seen in ichthyosis vulgaris), which allows protein antigens to penetrate through stratum corneum, leading to Langerhans cell-mediated Th2 allergic responses. The resultant upregulation of IL-4/IL-13 production reduces filaggrin expression, resulting in further reduction in barrier and promotion of allergic reaction.

![Palmar hyperlinearity](image2)

**Figure 2** Palmar hyperlinearity associated with FLG mutations. The intensity of hyperlinearity depends on the age of patients.
reported depending on races, and the frequency of FLG mutations is 24.3% in AD patients in Hamamatsu University Hospital. Profilaggrin is the major component of the keratohyalin granules within epidermal granular cells. During epidermal terminal differentiation, the profilaggrin polyprotein is dephosphorylated and rapidly cleaved by serine proteases, such as kallikrein-5, to form monomeric filaggrin, which is further degraded into natural moisturizing factors. Perturbation of skin barrier function as a result of reduction or complete loss of filaggrin expression enhances percutaneous transfer of allergens (Figure 1). The association of the FLG mutations in particular with the extrinsic type of AD was observed.

Thus, the skin barrier is perturbed in AD, and FLG mutation represents a typical cause of barrier impairment. The allergic conditions of AD may be preceded by skin barrier impairment, which allows protein antigens to penetrate through disrupted barrier.

### 3 | TH2-POLARIZED IMMUNOLOGICAL STATE OF AD

In general, skin responses to exogenous antigens can be divided into three types, depending on the evoked timing after exposure, the eruption type, and the immunocompetent participants (Figure 3). The responses comprise immediate-, late-phase, and delayed-type reactions. AD is well known as a Th2-polarized disease. Th2 cells are involved mainly in the late-phase reaction, but the Th2 reaction may extend to parts of the immediate- and delayed-type hypersensitivity, because of graduation between these three categories. In the chronic lesion of AD, Th1 cells (additionally Th22 and Tc1 cells) are considered to induce chronic eczema with thick epidermis.

As expected with elevated total serum IgE and circulating eosinophils, AD patients show high levels of Th2 cytokines, such as IL-4, IL-5, and IL-13. Along with the elevation of IL-5, eosinophil counts and eosinophil cationic protein levels are increased in AD. In addition to AD, there are many Th2-polarized skin diseases such as eosinophilic pustular folliculitis, prurigo, angioiyymphoid hyperplasia with eosinophilia (Kimura’s disease), eosinophilic cellulitis (Wells’ syndrome), bullous pemphigoid, and cutaneous T-cell lymphoma. Among them, AD is a disorder where the epidermis and dermis afford Th2-associated inflammatory sites.

To identify Th2 cells, several methods are used. Intracellular cytokine staining and subsequent flow cytometry are a standard method, and IL-4- or IL-5-positive CD4+ cells represent Th2 cells. The surface marker of CD4+CD7+CCR4+ phenotype is also employed. Chemotaxis toward CCL17/TARC represents functional identification.

### 4 | IL-4/IL-13 AND THEIR RECEPTORS

IL-4 and IL-13 are representative Th2 cytokines and are structurally and functionally related. While IL-4 and IL-13 are produced mainly by Th2 cells, mast cells, and basophils, these cytokines target Th2 cells, mast cells, basophils, eosinophils, M2 macrophages, keratinocytes, smooth muscle, fibroblasts, and endothelial cells. Therefore, the producers and the targets of the IL-4/IL-13 are virtually same, indicating the presence of autocrine and paracrine stimulation with IL-4/IL-13. In this sense, it is an issue which cell type is the initial producer of IL-4. One candidate for this "early IL-4" producer is basophil. It is noted that IL-33 stimulates basophils to secrete IL-4.

There are two types of receptors for IL-4 and IL-13 (Figure 4). Both receptors are comprised of heterodimers. Type I consists of IL-4Ra and Common γ, and type II is composed of IL-4Rα and IL-13Rα1. IL-13Rα2 is another IL-13 receptor, serving as either a decoy or a key mediator of fibrosis. IL-4 binds to both type I and II receptors, while IL-13 has affinity to type II and IL-13Rα2. Dupilumab is an IL-4Ra antagonist that inhibits IL-4 and IL-13 signaling through blockade of the shared IL-4Ra subunit.

In addition to allergy, IL-4/IL-13 regulates the immune microenvironment in cancer. Signaling via type II receptor induces tumor proliferation, cell survival, cell adhesion, and metastasis. Thus, type II expression in tumors is associated with poor prognosis.

IL-4Ra activates JAK1, whereas γc and IL-13Rα1 activate JAK3 and JAK2/TYK2, respectively. Activated JAKs phosphorylate STAT6, and then, dimerized STAT6 migrates to nucleus encoding genes that promote Th2 differentiation and production of cytokines.

### 5 | PROMOTION OF IL-4 STIMULATION/PRODUCTION BY AD-AGGRAVATING FACTOR THYMIC STROMAL LYMPHOPOIETIN IN TH2 CELLS

Th2 cells are activated by IL-4/IL-13 in an autocrine/paracrine manner. Various AD-exaggerating factors promote this autocrine/paracrine system. One of the representative factors is TSLP, which is produced by epidermal keratinocytes via PAR-2 expressed on them.

**FIGURE 3** Allergic skin responses to exogenous antigens. The responses consist of immediate-, late-phase, and delayed-type reactions.
Proteinases, such as mite antigens and keratinocyte-derived kalikrein-5, function as ligands for PAR-2 and stimulate keratinocytes to release TSLP. TSLP has two actions, functional promotion of epidermal LCs and activation of Th2 cells. Although the initiative role of TSLP-activated dendritic cells (DCs) in AD has gained much attention in the past few years, we found that TSLP also has a stimulatory action on Th2 cells.

The Th2-stimulating effect of TSLP is triggered by its binding to TSLP receptor (TSLPR) on Th2 cells (Figure 5). CD4+CCR4+CXCR3+CCR7−CCR10+CLA+ Th2 cells in AD patients exhibit enhanced TSLPR expression. The frequency of TSLPR+CD4+ T cells correlates with disease activity.

Protein antigens induce Th2 responses, while metals and haptens usually evoke Th1 responses. In the sweat, Malassezia antigen may deteriorate Th2 aspect of AD, while nickel, cobalt, and chromium are usually Th1 inducers. Mental stress or anxiety is associated with Th2 status. In addition, future studies on microbiota might shed light for its association with Th2 condition.

Protein antigens can penetrate through disrupted barrier, and epidermal LCs serve as antigen-presenting cells to Th2 cells. It is assumed that epidermal LCs in the barrier-disrupted skin produce high amounts of Th2 and eosinophil chemokines, whereas Th1 chemokines are produced by keratinocytes. Upon external stimulation, epidermal keratinocytes produce TSLP, which stimulates LCs possessing TSLP receptors. Protein antigen is more essential than hapten as the cause of the extrinsic type of AD. Upon the epicutaneous application of ovalbumin (OVA), conditional LC depletion attenuated the development of clinical manifestations as well as serum OVA-specific IgE increase, OVA-specific T-cell proliferation, and IL-4 mRNA expression in the draining lymph nodes. Consistently, even in the steady state, permanent LC depletion resulted in decreased serum IgE levels, suggesting that LCs mediate the Th2 local environment. Thus, LCs initiate epicutaneous sensitization with protein antigens and induce Th2 cell–mediated immune responses via TSLP signaling, further suggesting that LCs play a mandatory role in AD.

Regarding epidermal chemokines of the barrier-disrupted skin, the mRNA expression levels of Th1 chemokines (CXCL10, CXCL9, and CXCL11), Th2 chemokines (CCL17 and CCL22), and eosinophil chemoattractant (CCL5) are high in the epidermal cells from Th2 response-prone mice. In particular, CCL17/TARC, CCL22, and CCL5 are remarkably elevated in BALB/c mice. Tape stripping induced dermal infiltration of eosinophils, and the late-phase reaction was increased with infiltration of Th2 cells as well as eosinophils, when challenged via the tape-striped skin. It is notable that Th1 chemokines (CXCL9 and CXCL10) and Th2 chemokines (CCL17 and CCL22)
are derived mainly from keratinocytes and LCs, respectively. Thus, it is thought that LCs attract Th2 cells and eosinophils chemotactically in AD.

### 7 | RELATIONSHIP BETWEEN BARRIER STATUS AND TH2 RESPONSES IN AD

The skin immune status is closely associated with the disordered condition of skin barrier. Barrier disruption induces Th2 cytokine production and eosinophil infiltration in mice. Topical protein antigen application further promotes Th2 responses. Therefore, barrier impairment results in elevation of Th2 status.

Filaggrin deficiency, which cornified layer-damaged skin allows protein antigens to penetrate through the stratum corneum, leads to allergy where IL-4 and IL-13 are overproduced. Subsequently, IL-4 and IL-13 further depress filaggrin expression. This cascade yields vicious cycle, and therefore, even heterozygous FLG mutations may result in development of AD. In addition, IL-4 suppresses the enhancement of ceramide synthesis and cutaneous permeability barrier functions, which further aggravates the barrier. Neutralization of the normally acidic stratum corneum has deleterious consequences for permeability barrier homeostasis and stratum corneum integrity/cohesion attributable to serine proteases activation, leading to deactivation/degradation of lipid-processing enzymes and corneodesmosomes.

### 8 | LACK OF PURITY OF TH2 POLARIZATION IN AD

Although several criteria for its definition have been widely approved, there still exist variations in the diagnosis of AD because of its heterogeneous aspects. AD is generally a Th2 disease, but there exist several exceptional and undeniable facts to be considered.

#### 8.1 | Intrinsic AD and Th1 activation

The first issue is the presence of intrinsic type among AD patients. AD can be categorized into the IgE-high, extrinsic type and the IgE-normal, intrinsic type. While extrinsic AD is the classical type with high prevalence, the incidence of intrinsic AD is approximately 20% with female predominance. The skin barrier is perturbed in the extrinsic, and FLG mutation represents a typical cause of barrier impairment. Intrinsic AD is immunologically characterized by the higher expression of IFN-γ and non-protein antigens, such as metals and haptons, may induce dermatitis. The overproduction of IFN-γ may further downregulate IgE production in intrinsic AD, as suggested by our in vitro study, and intrinsic AD is linked with much lower levels of IL-4 and IL-13.

#### 8.2 | Chronic AD lesion and Th1 infiltration

It is known that Th2 cells infiltrate in the acute lesion of AD, but Th1 cells, and presumably Tc1 cells, are involved in the chronic lesion. The acute skin lesion corresponds to the late-phase reaction evoked by Th2 cells and eosinophils, while the chronic skin lesion corresponds to the delayed-type hypersensitivity induced by Th1/Tc1 cells. Accordingly, IFN-γ generally plays an essential role for occurrence of dermatitis. Clinically, the therapeutic effectiveness of systemic IFN-γ, which suppresses Th2 cells in vitro, is limited, further supporting the notion that AD does not have a pure Th2 property.

#### 8.3 | Involvement of Th17 cells

Th17 cells, producing IL-17A and IL-22, are increased in the peripheral blood of AD, and Th17 cells infiltrate in the acute skin lesion...
more markedly than in the chronic lesion. There is a tendency that the frequency of circulating Th17 cells is higher in intrinsic AD than in extrinsic AD. In the lesional skin, another group of investigators found positive correlations between Th17-related molecules and SCORAD scores in patients with intrinsic AD, whereas only patients with extrinsic AD show positive correlations between SCORAD scores and Th2 cytokine (IL-4 and IL-5) levels. Asian patients may be more prone to have Th17-participating AD.

9 | THERAPIES FOR IMMUNOMODULATION OF AD

Recent cytokine-targeting biologic therapies have been proving the disease mechanisms underlying atopic dermatitis as well as psoriasis. The essential involvement of IL-4 and IL-13 in AD pathogenesis is strongly supported by the therapeutic effectiveness of anti-IL-4Ra antibody dupilumab, which block IL-4 binding to type I and type II IL-4 receptors and IL-13 binding to type II receptor (Figure 4). Dupilumab depresses Th2-centered inflammatory axis and exerts a high clinical efficacy. Dupilumab was approved in Japan in 2018, and the number of patients treated with this biologic has been increasing. Before dupilumab was marketed, many patients with refractory AD had been treated with cyclosporine A. However, because of its renal toxicity, careful attention is necessary for its long term use. Dupilumab is beneficial for such cases.

There are possible Th2 cytokine-targeting therapies, including anti-IL-13 antibody and anti-IL-31 antibody. Furthermore, semi-Th2 targeting JAK inhibitors are promising therapeutic modalities for AD. Further clarification of the immunological mechanism of AD may lead to development of novel therapies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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