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The Roles of Th2-Type Cytokines in the Pathogenesis of Atopic Dermatitis

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1. Introduction

Atopic dermatitis (AD) is a chronic, relapsing, highly pruritic inflammatory skin disease (1, 2). Analyses of the cytokine expression profile in skin lesions of AD patients show that the Th2-type immune response is dominant in AD inflammation (3, 4). Interleukin-4 (IL-4), IL-5, and IL-13 are signature cytokines of the Th2-type immune response. Expression of IL-4 and IL-13 is significantly high in acute lesions of AD skin; however, it is down-regulated in chronic lesions. In contrast, expression of IL-5 is more elevated in chronic lesions than in acute lesions. High expression of IL-4, IL-5, and IL-13 in AD skins leads to high serum levels of IgE and eosinophilia, typical clinical features of AD. In addition to IL-5, expression of interferon-γ (IFN-γ) and IL-12 is elevated in chronic skin lesions of AD. IFN-γ and IL-12 are signature cytokines of Th1-type immune response. It has remained unclear why this immune milieu change occurs.
Based on observations of the predominant Th2-type immune responses in AD patients, many studies using model mice or involving genetic association have been performed to investigate the role played by Th2-type cytokines in the pathogenesis of AD. It is hoped that Th2-type cytokines will prove to be good targets to develop therapeutic agents for AD. In this chapter, we focus on these topics; we do not review the details of the structures, the signal pathways, or the biological functions of these Th2-type cytokines. Please refer to other articles regarding with these subjects (5-10).

2. Th2-type cytokines in model mice

Animal models are useful to understand the pathogenesis of AD and to develop therapeutic agents for AD. Among various species, mouse models have been primarily used, because genetically manipulated mice are available. Mouse models of AD can be categorized into three groups (2): (1) mice that spontaneously develop AD-like skin lesions, (2) mice epicutaneously sensitized with allergens, and (3) genetically engineered mice. It has been reported that several AD model mice that spontaneously develop AD-like skin lesions such as Nc/Nga mice (11) and DS-Nh mice (12) show a Th2-type–dominant immune milieu, suggesting that Th2-type cytokines are involved in pathogenesis in these mice. However, the situation is more complex, because it has been demonstrated that Nc/Nga mice deficient

in STAT6, a common critical transcription factor for IL-4 and IL-13 signals, exhibited skin lesions comparable to those of STAT6-positive littermates (13). Here, we summarize the results of analyses investigating the roles of Th2-type cytokines, using mice epicutaneously sensitized with allergens and genetically engineered mice (Table 1).

Category	Application	Phenotypes	References
Ovalbumin-sensitized mouse	IL-4–deficient mouse	Decreased eosinophils Decreased serum IgE No change in thickness of epidermis and dermis No change in chemokine expression No change in infiltration of CD45+, CD4+, or CD8+ cells	15
	IL-5–deficient mouse	No eosinophil Thinning of epidermis and dermis No change in chemokine expression No change in infiltration of CD45+, CD4+, or CD8+ cells	15
Genetically engineered mouse	IL-4 transgenic mouse	Xerosis Conjunctivitis Pruritis Presence of *Staphylococcus aureus* Spongiosis Acanthosis Infiltration of mononuclear cells and eosinophils in dermis and epidermis Degranulation of mast cells in dermis Increased expression of IL-5, IL-13,IL-12p40, IFN-γ, TNF-α, and IL-1β Increased serum IgE and IgG1 Increased T cell proliferation Increased dendritic cells, macrophages, and NK cells in skin and lymphoid organs	16-19
	IL-13 transgenic mouse	Pruritis Loss of hair Erythema Crusting Excoriation Bacterial pyoderma Erosions Dry lichenified skin lesion Infiltration of macrophages, dendritic cells, eosinophils, CD4+ cells, and mast cells Increased expression of CCL2/MCP-1, CCL5/RANTES, CCL11/Eotaxin, CCL17/TARC, CCL22/MDC, CCL27/CTACK, TSL, and VEGF Increased serum IgE and IgG1 Increased systemic immune responses	20

Table 1. Summary of effects of Th2-type cytokines in model mice

2.1 Ovalbumin (OVA)-sensitized mice

Geha's group established AD model mice by repeated epicutaneous sensitization to OVA (14). These mice manifest AD-like skin lesions including acanthosis, spongiosis, and infiltration of neutrophils, lymphocytes, mast cells, and eosinophils into the dermis. Expression of Th2-type (IL-4, IL-5 and IL-13) cytokines is up-regulated with little or no change of IFN-γ expression (2, 14). Furthermore, serum levels of total or OVA-specific IgE and IgG1 are elevated. This mouse model has been used to investigate involvement of various molecules associated with the pathogenesis of AD.

2.1.1 Application of OVA-sensitized mouse model to IL-4–deficient mice

The role of IL-4 in OVA-sensitized AD model mice is complex (15). The eosinophil numbers decrease in the dermis of OVA-sensitized IL-4–deficient mice showing an important role of IL-4 for infiltration of eosinophils. However, the numbers of $CD45^+$, $CD3^+$, $CD4^+$, and $CD8^+$ cells and expression of MIP-2, MIP-1β, IP-10, and RANTES increase compared to wild type mice, suggesting that IL-4 has an inhibitory role in expression of chemokines to recruit T cells. It is of note that thickness of the epidermis and dermis are not changed compared to wild type mice showing that IL-4 has a subtle effect on skin thickening. In these mice, total or OVA-specific IgE levels significantly decrease, which argues against the roles of IgE in the pathogenesis of this mouse model. Correspondingly, OVA-sensitized IgE-deficient mice show no change in histological views of the skin tissues, infiltration of $CD45^+$, $CD3^+$, $CD4^+$, and $CD8^+$ cells and expression of IL-4, IL-5 and IFN-γ compared to OVA-sensitized wild-type mice (15), suggesting that this mouse model is independent of IgE. Furthermore, the redundancy of IL-4 and IL-13 *in vivo* may be the reason why the effects of IL-4–deficiency on skin thickening are subtle in this mouse model.

2.1.2 Application of OVA-sensitized mouse model to IL-5–deficient mice

IL-5–deficient mice had virtually no eosinophil (15). These mice sensitized with OVA had thinning of the epidermis and dermis compared with wild-type mice. However, infiltration of $CD45^+$, $CD3^+$, $CD4^+$, and $CD8^+$ cells and expression of chemokines were equivalent to wild-type mice. These results may suggest that IL-5 partially contributes to generating AD-like lesions in this mouse model.

2.2 Genetically engineered mice for Th2-type cytokines

Thus far, transgenic mice that express IL-4 or IL-13 specifically in keratinocytes have mainly been generated using keratin promoters. In contrast to the IL-4-deficient mice, these gain-of-function mice manifest overt skin lesions, which indicates topical overexpression of either IL-4 or IL-13 that is sufficient to induce phenotypes similar to AD patients.

2.2.1 IL-4 transgenic mice

Chan's group established and characterized IL-4 transgenic mice in which expression of IL-4 is controlled under the promoter of the keratin 14 gene (16-19). These mice are normal when they are newborn. However, almost four months after birth, they develop AD-like lesions such as xerosis (dry skin), conjunctivitis, and pruritic skin lesions (16). Many skin lesions appear in ears, necks, and eyes. Forty-three percent of the mice develop

skin lesions within 12 months. Inflammatory skin lesions show the presence of *Staphylococcus aureus*, a common infectious complication and exacerbating factor in human AD patients. Histological analyses of the lesions in these mice show spongiosis, acanthosis, dermal and epidermal infiltration of mononuclear cells and eosinophils, and degranulating mast cells in the dermis. Expression of Th2-type cytokines (IL-5, IL-13), Th1-type cytokines (IL-12p40, IFN-γ), and inflammatory cytokines (TNF-α, IL-1β) is up-regulated in the skin lesions of these mice. Enhancement of these cytokines except IL-12p40 is even observed in the skin, before the disease onset or in the intact skin (17). Correspondingly, serum levels of IgE and IgG1 are elevated even before the onset, which reflects high expression of IL-4 and IL-13. Afterward, up-regulated serum levels of IgG2a are observed, reflecting high expression of IFN-γ (19). T cells in these mice possess higher proliferating capacity *in vitro* spontaneously or induced by stimulants such as T cell receptor triggering or Staphylococcus enterotoxins A and B compared to T cells in wild-type mice (18). It is of note that the numbers of dendritic cells, macrophages, and NK cells increase in the skin tissues and lymphoid organs of these mice, which suggests that overexpression of IL-4 in skin tissues modulates antigen-presenting activity *in vivo*.

2.2.2 IL-13 transgenic mice

Zhu's group established IL-13 transgenic mice in which withdrawal of doxycycline induces expression of IL-13 under the control of the promoter region of the keratin 5 gene (20). Six to eight weeks after the withdrawal of doxycycline, AD-like skin lesions (i.e. pruritis, loss of hair, erythema, crusting, excoriation, bacterial pyoderma, and erosions, thereafter dry lichenified skin lesion) appear in these mice. All of the mice develop these features within four months. In the skin lesions, $F4/80^+$ cells including macrophages and dendritic cells, eosinophils, $CD4^+$ cells, and mast cells are accumulated. Expression of various chemokines (CCL2/MCP-1, CCL5/RANTES, CCL11/Eotaxin, CCL17/TARC, CCL22/MDC, CCL27/CTACK), TSLP (a critical cytokine correlated with AD at the interface of epidermis and immune cells), and VEGF (a potent cytokine for angiogenesis), is up-regulated in these mice. Serum levels of IgE and IgG1 are elevated. Furthermore, systemic Th2 skewing is enhanced because the lymphocytes in the lymph nodes of these mice produce more IL-4 and IL-13 upon stimulation of anti-CD3/CD28 antibody (Ab) than do those in the wild-type mice.

3. Genetic associations of Th2-type cytokines with AD

An initial linkage analysis in Amish families showed the association of 5q31.1 with serum IgE levels (21). This chromosome region contains a cluster of Th2-type cytokine genes. Therefore, much attention has been paid to the genetic association of Th2-type cytokine genes with atopy (defined as high serum IgE level) or with each specific phenotype of allergic diseases. As a result, several single nucleotide polymorphisms (SNPs) on the *IL4*, *IL5*, and *IL13* genes have been shown to be associated with atopy or AD (Table 2). Furthermore, SNPs located on the *IL4RA* and *IL13RA1* genes encoding the IL-4 receptor α chain (IL-4Rα) and the IL-13R α1 chain (IL-13Rα1) and on the *STAT6* gene encoding STAT6 were also reported to be associated with atopy or AD. IL-4Rα is a component of both type I IL-4R and type II IL-4R/IL-13, whereas IL-13Rα1 is a component of type II IL-4R/IL-13

(Figure 1). STAT6 is a transcriptional factor critical for IL-4 or IL-13 signals. The association of the *IL13*, *IL4RA*, and *STAT6* genes with IgE is confirmed by recent Genome Wide Association Studies (22, 23).

Gene	Variant	Association	Function	References
IL4	-590C/T	AD	Change in IL-4 production	24-26
IL13	Arg110Gln (Arg130Gln, G4257A)	AD Serum IgE specific anti-allergen IgE	Lower affinity with the IL-13R α2 chain Enhanced stability Transduction of stronger signal via IL-13Rα1	28-36
	-1055C/T ('-1111C/, -1024C/T)	AD Serum IgE specific anti-allergen IgE	Change in IL-13 production	34, 37-40
IL4RA	Gln576Arg (Gln551Arg)	Hyper IgE syndrome AD	Decreased binding to SHP-1 Increased STAT6 activation	41, 42
IL13RA1	1398A/G	Serum IgE		27
STAT6	2964G/A	Serum IgE		43
	in18SNP1C/T	Serum IgE Eosinophil number		44
	GT repeat in exon1	Serum IgE Eosinophil number		44
IL5	-703C/T	Serum IgE Eosinophil number		45

Table 2. Summary of genetic associations in Th2-type cytokines and their related molecules

3.1 IL-4 gene

There exists a SNP in the promoter of the *IL4* gene (-590C/T). This SNP was originally reported to be associated with bronchial asthma (24) and is thought to affect the binding activities to NFAT, resulting in modulating IL-4 production. Transmission disequilibrium testing shows a significantly preferential transmission of the T allele in AD patients (25). Another group confirmed the association of this SNP with AD (26).

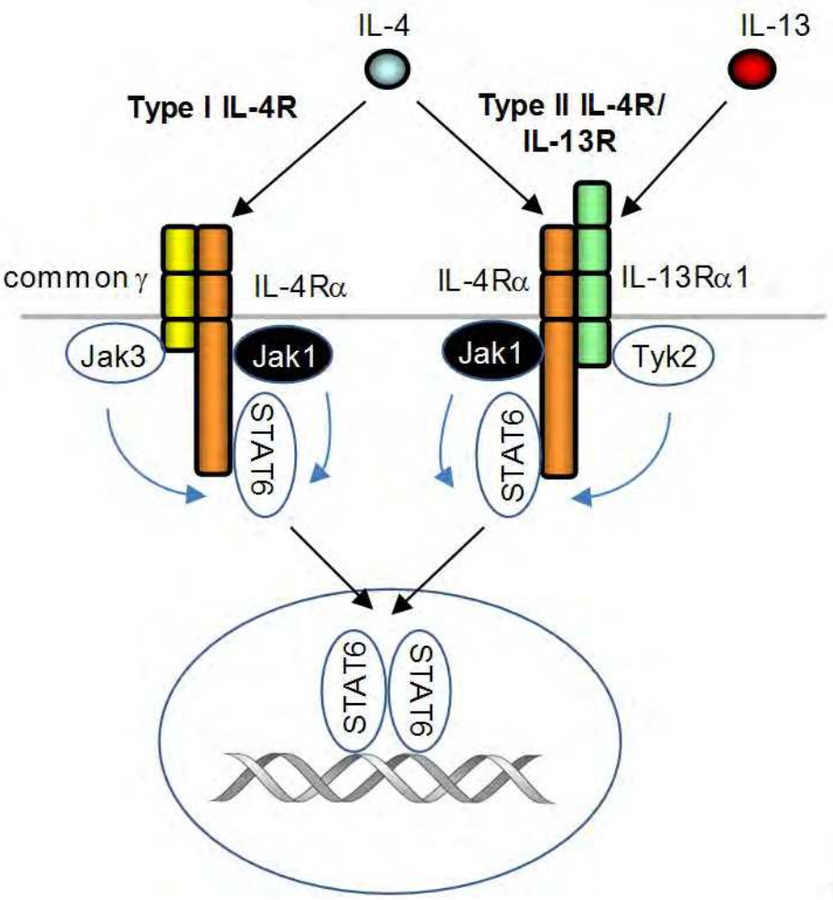

Fig. 1. The receptor structures and signal pathways of IL-4 and IL-13.
IL-4 binds to type I IL-4R or type II IL-4R/IL-13R, and IL-13 binds to type II IL-4R/IL-13R. Type I IL-4R and type II IL-4R/IL-13R are composed of IL-4Rα and the IL-2R γ chain (common γ) or IL-4Rα and IL-13Rα1, respectively. Engagement of the receptors activates Jak kinases followed by activation of STAT6.

3.2 IL-13 gene

There exist several SNPs on the *IL13* gene. Thus far, two of them (Arg110Gln, also referred to as Arg130Gln or G4257A; and -1055C/T, also referred to as -1111C/T or -1024C/T) are reported to be associated with atopy or AD. We and other groups reported the genetic association of Arg110Gln with bronchial asthma (27), serum IgE levels (28, 29), and AD (29). This SNP causes exchange of arginine at the 110 (130) amino acid for glutamine. Several functional differences between the arginine type and the glutamine type have been demonstrated (30-32): (1) The glutamine type has lower affinity with the IL-13R α2 chain, a decoy receptor for IL-13, than the arginine type. (2) The glutamine type has enhanced stability over the arginine type (3). The glutamine type transduces a stronger signal via IL-13Rα1, a functional receptor for IL-13, than the arginine type. All of these results suggest that the glutamine type acts more potently *in vivo* than the arginine type. It has been reproducibly demonstrated that this SNP is genetically associated with serum total IgE levels (33-35), specific anti-allergen IgE (33, 35), or AD (36).

-1055C/T was originally found to be associated with bronchial asthma and positive skin tests (37, 38). This SNP is adjacent to the biding site for NFAT; hence, this variant may affect the complex formation of transcriptional factors. Reproducible genetic associations of this SNP with serum total IgE levels (34, 39), specific anti-allergen IgE (35, 40), or AD (39) have been observed.

3.3 IL-4Rα gene

The type II IL-4R or the IL-13R is composed of IL-4Rα and IL-13Rα1. Both IL-4 and IL-13 bind to this receptor on cell surface, transducing their signals intracellularly (5, 6). Several SNPs on the *IL4RA* gene are known to be genetically associated with atopy or allergic diseases. The genetic association of Gln576Arg, also referred as Gln551Arg, was originally found in hyper IgE syndrome patients, some of who had severe AD (41). Position 576 is adjacent to the tyrosine residue at 575, a binding site for SHP-1, a phosphotyrosine phosphatase. Exchange of glutamine for arginine decreases the binding activities for SHP-1, resulting in up-regulation of STAT6 activation. The genetic association of this SNP with AD was confirmed by another group (42).

3.4 IL-13α1 gene

IL-13Rα1 is another component of type II IL-4R/IL-13R, together with IL-4Rα. A SNP in the coding region of the *IL13RA1* gene, 1398A/G, was reported to be genetically associated with serum IgE levels (27). The function of this SNP is unclear because this SNP is a silent one.

3.5 STAT6 gene

STAT6 is a transcriptional factor, critical for both IL-4 and IL-13 signals (5, 6). Heterodimerization of type I IL-4R or type II IL-4R/IL-13R by binding of IL-4 or IL-13 activates Jak1, Jak3, or Tyk2, tyrosine kinases associated with IL-4Rα, common γ, and IL-13Rα1 respectively, followed by activation of STAT6. Several SNPs on the *STAT6* gene, 2964G/A, in18SNP1C/T, and GT repeat in exon1 were reported to be associated with serum IgE levels or with eosinophil numbers (43, 44).

3.6 IL-5 gene

A SNP on the IL5 gene (-703C/T) was reported to be associated with the numbers of eosinophils in blood and serum IgE levels, but not with AD (45).

4. Th2-type cytokine – Targeted treatment for AD

Because of the importance of Th2-type cytokines in the pathogenesis of AD, it has been thought that Th2-type cytokines have the potential to be targeted to develop novel agents against AD. A clinical trial to administer a humanized anti–IL-5 monoclonal Ab (mepolizumab) to AD patients was performed, with a disappointing result (46). To the best of our knowledge, no trial targeting IL-4 or IL-13 for AD patients has thus far been performed.

4.1 Antagonist of IL-5 for treatment of AD

AD patients received 750 mg of humanized anti–IL-5 monoclonal Abs (mepolizumab) intravenously twice (at day 0 and 7) (46). Efficacy assessed by SCORAD was observed at

day 14 but was not statistically significant. There was no difference in pruritis score between mepolizumab- and placebo-administered groups. Even when efficacy was assessed by PGA (the Physician's Global Assessment of Improvement), the numbers showing 'marked improvement' were not statistically significant. However, it is of note that 4 of 18 (22.2%) patients receiving mepolizumab showed 'marked improvement'. These results can be interpreted two ways: one is that the overall efficacy of mepolizumab is not as good as expected. The other is that mepolizumab is effective only for limited patients. The latter is likely when mepolizumab is administered to patients with bronchial asthma. In the first clinical trial, mepolizumab yielded a disappointing result (47, 48). However, it turned out that mepolizumab is quite effective for the patients with sputa containing large numbers of eosinophils (49, 50). It is important to select patients who are sensitive to certain molecular target drugs by so-called 'companion diagnostics': in this case, numbers of eosinophils in sputum. A companion diagnostic should be found to treat AD effectively with mepolizumab.

5. Conclusion

In this chapter, we summarized the studies concerned with Th2-type cytokines in the pathogenesis of AD from the standpoint of the model mice and genetic association. Furthermore, we mentioned a trial in which AD patients were treated by administration of neutralizing Abs against IL-5. We hope the information in this review will be useful in developing new treatments for AD patients in the future.

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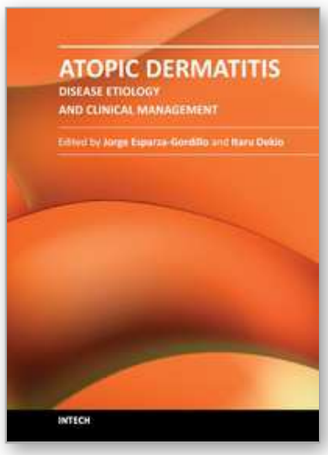

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Atopic Dermatitis is a common disease characterized by inflamed, itching and dry skin. This relapsing allergic disorder has complex etiology and shows a remarkably high clinical heterogeneity which complicates the diagnosis and clinical management. This book is divided into 4 sections. The first section (Disease Etiology) describes some of the physiological mechanisms underlying Atopic Dermatitis, including alterations in the immune system and the skin-barrier function. The important role of host-microorganism interactions on the pathophysiology of Atopic Dermatitis is discussed in the second section (Microorganisms in Atopic Dermatitis). An overview of the clinical diagnostic criteria and the disease management protocols commonly used is given in the third section (Diagnosis and Clinical Management). The last section (New Treatments) describes new therapeutic approaches that are not widely used but are currently being studied due to preliminary evidence showing a clinical benefit for Atopic Dermatitis.

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