


The IL-13–OVOL1–FLG axis in atopic dermatitis

Kazuhisa Furue,¹ Takamichi Ito,¹
Gaku Tsuji,¹ Dugarmaa Ulzii,¹
Yen Hai Vu,¹ Makiko Kido-
Nakahara,¹ Takeshi Nakahara^{1,2}
and Masutaka Furue^{1,2,3} 

¹Department of Dermatology, Faculty of Medical Sciences, Kyushu University, Higashi-ku, Fukuoka, Japan, ²Division of Skin Surface Sensing, Department of Dermatology, Faculty of Medical Sciences, Kyushu University, Higashi-ku, Fukuoka, Japan and ³Research and Clinical Center for Yusho and Dioxin, Kyushu University Hospital, Higashi-ku, Fukuoka, Japan

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Correspondence: Prof. Masutaka Furue, Department of Dermatology, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan.

Email: furue@dermatol.med.kyushu-u.ac.jp

Senior author: Takamichi Ito

Summary

Despite sharing interleukin-4 receptor α (IL-4R α) in their signaling cascades, IL-4 and IL-13 have different functions in atopic inflammation. IL-13 preferentially participates in the peripheral tissues because tissue-resident group 2 innate lymphoid cells produce IL-13 but not IL-4. In contrast, lymph node T follicular helper cells express IL-4 but not IL-13 to regulate B-cell immunity. The dominant microenvironment of IL-13 is evident in the lesional skin of atopic dermatitis (AD). The IL-13-rich local milieu causes barrier dysfunction by down-regulating the OVOL1–filaggrin (FLG) axis and up-regulating the periostin–IL-24 axis. Genome-wide association studies also point to the crucial involvement of the IL-13, OVOL1 and FLG genes in the pathogenesis of AD. Biologics targeting IL-13, such as the anti-IL-4R α antibody dupilumab and the anti-IL-13 antibody tralokinumab, successfully improve AD lesions and further highlight the importance of IL-13 in the pathogenesis of AD.

Keywords: atopic dermatitis; filaggrin; interleukin-13; OVOL1; Periostin.

Introduction

Atopic dermatitis (AD) is a common eczematous skin disorder characterized by skin inflammation, barrier disruption and chronic pruritus.¹ Its course involves chronic relapse with intense pruritus, which reduces quality of life and decreases treatment satisfaction of the afflicted patients.^{2–4} The lifetime incidence of AD is as high as 20% in the general population.⁵ Skin barrier dysfunction is associated with the reduced production of terminal differentiation molecules, such as filaggrin (FLG).^{6,7} Abnormal skin barrier integrity also causes the increased colonization of microbes, such as *Staphylococcus aureus*, which further exacerbates skin inflammation.⁸ In addition, some autoimmune diseases are co-morbid with AD.^{9,10}

The definition of ‘atopy’ is a diathesis for the overproduction of immunoglobulin E (IgE) antibodies or a personal and/or family history of asthma, allergic rhinitis, allergic conjunctivitis and AD.¹¹ With the help of interleukin-4 (IL-4) and/or IL-13 produced from type 2 helper T (Th2) cells, activated B cells produce IgE.¹² The diverse activation and differentiation of multiple B-cell subsets with significant correlation with circulating IgE levels

have been reported in AD but not in psoriasis or normal controls.¹³ Consistent with preponderant Th2 deviation in early childhood AD,^{14,15} elevated levels of total or allergen-specific IgE have been noted in infantile and early childhood AD.^{16,17} Skin barrier dysfunction with loss of function mutations of the filaggrin (FLG) gene contribute to disease progression and aberrant IgE production in AD.¹⁸

T helper type 2 cells were first reported by Mosmann *et al.* in 1988¹⁹ and are related to allergic inflammation in AD.^{15,20,21} The gene expression of IL-4 and IL-13 is up-regulated in the lesional skin of pediatric and adult AD patients compared with that in the normal skin of healthy controls.¹⁵ Type 2 predominance is likely to progress from non-lesional to lesional skin and from acute to chronic lesions in AD.²¹ Type 2 predominance has been confirmed in peripheral blood T helper cells.¹⁴ The number of IL-13-producing Th2 cells is significantly greater in the skin-homing cutaneous lymphocyte antigen (CLA)⁺ T helper cell population in both pediatric and adult AD patients than in healthy controls.¹⁴ The pathogenic importance of IL-4 and IL-13 has recently been reinforced by the excellent treatment response of

patients with AD to the anti-IL-4 receptor α (IL-4R α , *IL4R*) antibody dupilumab, which inhibits both IL-4 and IL-13 signals.²²

Notably, more recent, large-scale transcriptomic analysis revealed the specific and dominant role of IL-13 in the lesional skin of AD, because IL-4 expression was almost undetectable.²³ Consistent with this notion, the anti-IL-13 antibody tralokinumab successfully improved AD.²⁴ In this review, we focus on IL-13 as the major driving force of AD development.

IL-13 signaling

Interleukin-4 and IL-13 are encoded by adjacent genes and share a common receptor and signaling pathway.²⁵ However, IL-4 and IL-13 are differentially expressed *in vivo* by a number of different cells that regulate innate and adaptive immunity. For example, lymph node T follicular helper cells, which regulate B-cell immunity, express IL-4 but not IL-13.²⁵ Basophils and invariant natural killer T2 cells also express IL-4, whereas mucosal group 2 innate lymphoid cell (ILC2s) express mostly IL-13 and little IL-4.²⁵ Their differential cellular expression suggests that IL-4 and IL-13 have distinct and non-redundant functions in Th2 immunity; IL-4 plays an important role in humoral responses, whereas IL-13 mediates tissue responses, including the recruitment of eosinophils and parasite expulsion.²⁵ In addition to its production in Th2 cells, IL-13 is produced in ILC2s.²⁶ Mouse and human ILC2s are phenotypically comparable, lineage-negative, non-T and non-B lymphocytes that produce high levels of IL-13 and IL-5.^{26–28} Unlike IL-13, no or only negligible IL-4 is produced by ILC2s.^{26–29} The ILC2s reside in the skin and are increased in number in AD lesions.^{27,28}

Interleukin-13 signaling is regulated through a complex receptor system. In non-hematopoietic cells, IL-13 engages a heterodimeric receptor composed of IL-4R α and IL-13R α 1 (*IL13RA1*).²⁵ IL-13R α 1 binds IL-13 with low affinity, yet when it forms a complex with IL-4R α , it binds with a much higher affinity, inducing the effector functions of IL-13.²⁵ A second receptor, IL-13R α 2 (*IL13RA2*), is closely related to IL-13R α 1; IL-13R α 2 binds IL-13 with high affinity but lacks any significant cytoplasmic domain and does not function as a signal mediator.²⁵ Cells with high IL-13R α 2 expression rapidly and efficiently deplete extracellular IL-13.³⁰ In parallel, IL-13 responses were enhanced in mice lacking *Il13ra2*.³¹ These studies highlighted that IL-13R α 2 acts as a scavenger or decoy receptor of IL-13 that elicits antagonistic activity against IL-13.²⁵ Keratinocytes and fibroblasts express functional IL-4R α , IL-13R α 1 and IL-13R α 2.^{32–36}

The ligation of functional heterodimeric IL-4R α and IL-13R α 1 by IL-13 induces the activation of downstream

Janus kinase 2 (JAK2) and tyrosine kinase 2 (TYK2).³⁷ JAK2 activates signal transducer and activator of transcription 3 (STAT3), and TYK2 activates STAT6 and STAT1.³⁷ In contrast, IL-4 signaling proceeds via the IL-4R α and IL-2R γ heterodimer.³⁷ The ligation of IL-4R α and IL-2R γ by IL-4 induces JAK1/JAK3 and subsequent STAT3 and STAT6 activation.³⁷ Hence, different types of oral and topical JAK inhibitors are significantly therapeutic against AD.^{38,39} As IL-4R α is expressed on sensory nerves, and its activation is involved in the itch sensation, the administration of a JAK inhibitor reduces itch intensity.⁴⁰

IL-13 and periostin

Periostin (*POSTN*) is a matricellular, non-structural extracellular matrix protein that is highly expressed at sites of injury or inflammation.^{41,42} The main source of periostin is fibroblasts. Keratinocytes produce periostin but to a much lesser extent than fibroblasts.^{42–44} Periostin expression is enhanced by mechanical stress or skin injury; this is indicative of the physiologically protective function of periostin, which promotes wound repair by acting on keratinocytes and fibroblasts. Along with its physiological functions, periostin plays pathogenic roles in skin fibrosis and chronic allergic inflammation.⁴² In normal skin, periostin is mainly distributed in the subepidermal and perifollicular compartments.⁴²

The expression of periostin is induced by IL-4 and IL-13 in a STAT6-dependent manner.^{41,42} In parallel, the dermal expression of periostin is significantly up-regulated and correlated with disease severity in AD.⁴⁴ Periostin is also related to subepithelial remodeling in asthma and allergic rhinitis.⁴¹ In a mite-induced AD mouse model, epidermal thickening and dermal fibrosis were evident with *Il13* gene up-regulation and a marked increase in periostin expression.⁴⁴ All of these allergic manifestations were significantly attenuated in mice that were deficient in either *Stat6* or *Postn*.⁴⁴ Periostin stimulates the proliferation of keratinocytes and enhances their production of thymic stromal lymphopoietin (TSLP), a cardinal keratinocyte-derived cytokine that promotes the Th2 immune response.⁴⁴ Periostin signaling proceeds through integrin α_v ; therefore, anti-integrin α_v antibodies successfully improved mite-induced AD.⁴⁴

In addition to the mite-induced AD model, periostin deficiency inhibited epidermal hyperplasia in an imiquimod-induced psoriasis model without affecting the recruitment of inflammatory cells expressing IL-17, IL-22 and IL-23.⁴⁵ These results stress the cardinal role of the periostin–integrin α_v axis in the proliferative capacity of keratinocytes and are coincident with previous findings that the integrin α_v signaling axis is necessary for epidermal proliferation during cutaneous wound healing.⁴⁶ As epidermal thickening (acanthosis) is a striking feature in

the chronically lichenified lesional skin of AD, the increased expression of periostin may be a therapeutically important target for drug development.

AD and barrier dysfunction

Skin barrier function is disrupted in AD compared with that in normal controls.^{47–49} The epidermal barrier is formed by the coordinated and sequential cross-linking of epidermal differentiation molecules such as FLG and intercellular lipids and corneocyte adhesion.^{47–49} The expression of FLG and the other differentiation molecules loricrin and involucrin is down-regulated or expressed prematurely in the lesional and non-lesional skin of AD compared with their expression in the normal skin of healthy individuals.^{7,50,51} As the daily application of moisturizer during the first 32 weeks of life reduces the risk of AD in infants,⁵² skin barrier dysfunction is essential to the development of AD.

Although the strongest genetic risk factors for AD are loss of function mutations in the *FLG* gene,⁵³ *FLG* mutations were not found in all AD patients; they were less common in southern Europeans with AD⁵⁴ and were even absent in patients with AD from some African countries,⁵⁵ suggesting that *FLG* mutations only partly explain FLG protein down-regulation in AD. The *FLG* mutation was also not related to the development of AD in patients from a subtropical island in Japan.⁵⁶

IL-13 and OVOL1–FLG axis

The coordinated expression of FLG and other epidermal differentiation proteins is crucial for skin barrier protection.^{1,7} OVOL1 is an upstream transcription factor that regulates FLG expression.⁶ It is intriguing that *FLG*, *OVOL1* and *IL13* were the three genes most significantly associated with AD among 31 susceptible gene loci reported in a meta-analysis of genome-wide association studies.⁵² IL-4R α signaling by IL-14 and IL-13 significantly reduced the expression of FLG, loricrin and involucrin in keratinocytes.^{7,57–60} At least two mechanisms mediate the IL-4/IL-13-induced FLG down-regulation: OVOL1 inactivation and the periostin–IL-24 axis (Fig. 1).^{43,60} The activation of OVOL1 induces its cytoplasmic-to-nuclear translocation and up-regulates FLG and loricrin expression.^{6,61} Notably, IL-4 and IL-13 consistently inhibit FLG expression by interfering with OVOL1 signaling.⁶ Interleukin-13 also inhibits the involucrin expression but in an OVOL1-independent manner⁶¹ and exacerbates barrier dysfunction. Epidermal keratinocytes in barrier-disrupted skin produce large amounts of TSLP, IL-25 and IL-33, which promote the differentiation of Th2 cells and ILC2s and stimulate the production of IL-13.^{29,62} Hence, a vicious cycle is formed to develop atopic dry skin. These results suggest the

crucial involvement of the IL-13–OVOL1–FLG axis in the pathogenesis of AD.

IL-13 and periostin–IL-24 axis

In addition to the IL-13–OVOL1–FLG axis, IL-13-induced FLG down-regulation is partly mediated by the IL-13–periostin–IL-24 axis.⁴³ Interleukin-24 belongs to an IL-20 subfamily that includes IL-19, IL-20, IL-22 and IL-26.⁶³ Although gene and protein expression of IL-24 is up-regulated in the lesional skin of AD,^{23,43} its implication remains elusive. Interleukin-13 up-regulates the expression of periostin in keratinocytes through STAT6 activation.⁴³ Periostin stimulates keratinocyte to produce IL-24 and IL-24 down-regulates the FLG expression via STAT3 activation.⁴³ In a mite antigen-induced AD model, the *Flg* expression was decreased in the lesional murine skin. However, the decrease of *Flg* expression was not observed in mice deficient for *Stat6* or *Postn*.⁴³ Moreover, the phosphorylated forms of both STAT6 and STAT3 were abundantly expressed in the lesional epidermal keratinocytes of individuals with AD.⁴³ Like IL-13, IL-31 is a pruritogenic cytokine produced from Th2 cells.⁶⁴ Interleukin-31 stimulates keratinocytes to produce IL-24. Then, IL-24 contributes to down-regulate the expression of FLG.⁶⁵

Anti-IL-13 biologics for the treatment of AD

Standard therapeutics for AD include topical emollients for barrier dysfunction and topical steroids and calcineurin inhibitors for skin inflammation.^{11,66} These conventional treatments are more or less effective in reducing atopic inflammation and itch; however, patient satisfaction and adherence to conventional treatments are generally low, as reported in daily clinics.^{67–70}

The anti-IL-4R α antibody dupilumab inhibits the binding of IL-4 and IL-13 to IL-4R α and blocks IL-4R α signaling.²² Dupilumab significantly improved skin lesions and pruritus in patients with moderate to severe AD in two randomized, placebo-controlled phase 3 clinical trials.²² The severity of AD was authentically evaluated using the Eczema Area and Severity Index (EASI). A reduction in the EASI score of at least 75% (EASI75) was observed in 51% and 44% of patients in dupilumab monotherapy groups and only 15% and 12% of the patients in placebo groups, respectively, at 16 weeks post-treatment.²² Dupilumab also provided a clinically meaningful improvement in patient-reported outcome measures.⁷¹

Dupilumab therapy significantly reduced the lesional expression of *IL-13* and IL-13-regulated Th2 signature genes, such as *CCL17*, *CCL18* and *CCL26*, in AD patients.⁷² It also restored the down-regulation of FLG and loricrin and reduced epidermal acanthosis in the lesional skin of AD patients.⁷² In addition, dupilumab

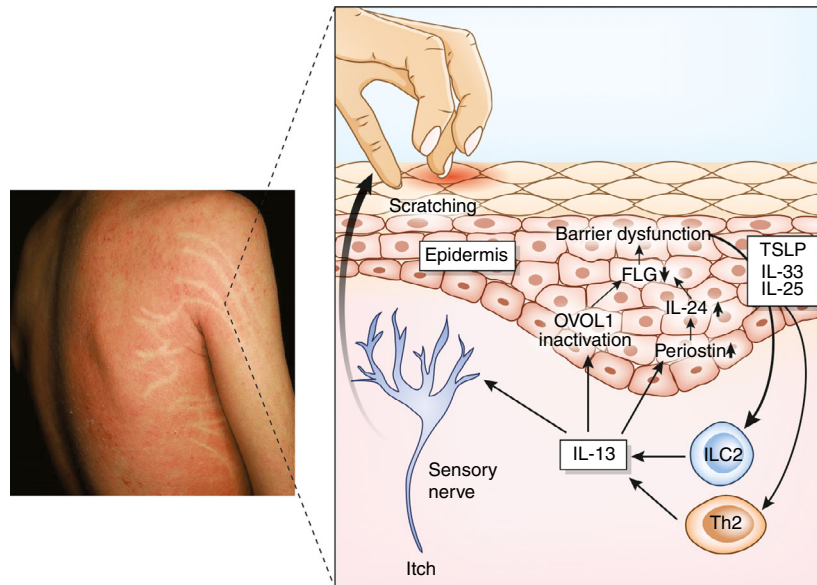


Figure 1. Simplified pathogenesis of atopic dermatitis. In the lesional skin of atopic dermatitis, T helper type 2 (Th2) cells and innate lymphoid cells (ILCs) produce high amounts of interleukin-13 (IL-13). IL-13 induces OVOL1 inactivation and up-regulates the periostin–IL-24 axis, which down-regulates filaggrin (FLG) and induces subsequent barrier dysfunction. Barrier dysfunction augments the epidermal production of thymic stromal lymphopoietin (TSLP), IL-25 and IL-33. These cytokines promote the differentiation of Th2 cells and group 2 ILCs (ILC2) and facilitate their production of IL-13. IL-13 also stimulates the sensory nerve and evokes the itch sensation. Itch-induced scratching further deteriorates barrier dysfunction.

normalized the type 2 serum biomarkers CCL17, CCL18 and periostin.⁷²

Tralokinumab is a fully human monoclonal antibody that potently and specifically neutralizes IL-13.²⁴ In a phase 2b study, 42.5% of patients injected with 300 mg tralokinumab every 2 weeks for 12 weeks achieved EASI75, which was significantly higher than that in the placebo control group (15.5%).²⁴ Tralokinumab inhibits serum type 2 signature biomarkers such as periostin, CCL17 and IgE, but only the periostin level is a predictive biomarker for a good treatment response to tralokinumab in AD.²⁴ Dipeptidyl peptidase-4 (DPP-4), a regulator of glucose metabolism, is also a type 2 signature biomarker.^{24,73} Similar to the results of periostin treatment, patients with AD with high serum levels of DPP-4 showed a greater treatment response to tralokinumab.²⁴ In a phase 2b clinical trial of tralokinumab for severe asthma, high serum periostin and DPP-4 levels were also significant biomarkers to predict a good treatment response to tralokinumab.⁷³

Conclusion

Interleukin-4 and IL-13 share IL-4R α in their signaling cascades and induce similar biological responses. However, IL-13 likely preferentially participates in peripheral tissues, including the skin, because tissue-residing ILC2s produce IL-13 but not IL-4.^{26–28} An IL-13-dominant

microenvironment is evident in the lesional skin of AD,²³ and the IL-13-rich local milieu causes barrier dysfunction by the down-regulation of the OVOL1–FLG axis.^{6,7} The linkages among IL-13–OVOL1–FLG may be particularly crucial for the development of AD, because genes encoding these three molecules are the three most susceptible genes for the development of AD.⁵³ The successful improvement of AD by treatment with the anti-IL-4R α antibody dupilumab and the anti-IL-13 antibody tralokinumab further highlights the importance of IL-13 in the pathogenesis of AD.

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Disclosures

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