



Atopic Dermatitis and Type 2 Immune Deviation

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This article is part of the Topical Collection on *Urticaria and Atopic Dermatitis*

Keywords Atopic dermatitis · Dupilumab · Type 2 immune deviation

Abstract

Purpose of the review To summarize recent topics on type 2 signatures in atopic dermatitis (AD).

Recent findings Therapeutic success of anti-IL-4 receptor antibody dupilumab does suggest that type 2 cytokines IL-4 and IL-13 have pivotal roles in the pathogenesis of AD. Lesional skin of AD expresses increased levels of IL-4 and IL-13. In parallel, type 2 chemokines such as CCL17, CCL22, and CCL26 are overexpressed in AD, and these chemokines recruit type 2 T cells and eosinophils. IL-4 and IL-13 downregulate the expression of filaggrin and exacerbate epidermal barrier dysfunction. Keratinocytes in barrier-disrupted epidermis produce thymic stromal lymphopoietin, IL-25 and IL-33, which enhance the type 2 immune response. IL-31, released from type 2 T cells, is an essential pruritogenic cytokine. IL-4 and IL-13 amplify the IL-31-mediated neuronal signal.

Summary Type 2 cytokines IL-4 and IL-13 are profoundly associated with three cardinal features of AD: barrier dysfunction, skin inflammation, and chronic pruritus. These findings explain the high efficacy of dupilumab in the treatment of AD.

Introduction

Atopic dermatitis (AD) is a common eczematous skin disorder characterized by skin inflammation, barrier disruption, and chronic pruritus [1]. Histopathological hallmarks of AD are epidermal spongiosis in acute vesicular lesions and irregular epidermal acanthosis and hyperkeratosis in chronic lichenified lesions [2, 3]. Immunohistologically, expression of epidermal differentiation molecules such as filaggrin (FLG), loricrin, and involucrin is downregulated in the lesional skin of AD

compared with the normal skin of healthy individuals [4, 5]. The comorbidity of autoimmune diseases is slightly increased in patients with AD [6, 7].

Type 2 cytokines (IL-4, IL-5, and IL-13) play a critical role in allergic inflammation in AD, as proved by their excellent treatment response to anti-interleukin 4 (IL-4) receptor α antibody dupilumab [8••] (Fig. 1). Acute and chronic AD skin lesions have a significantly greater number of infiltrated cells that are positive for IL-4 and

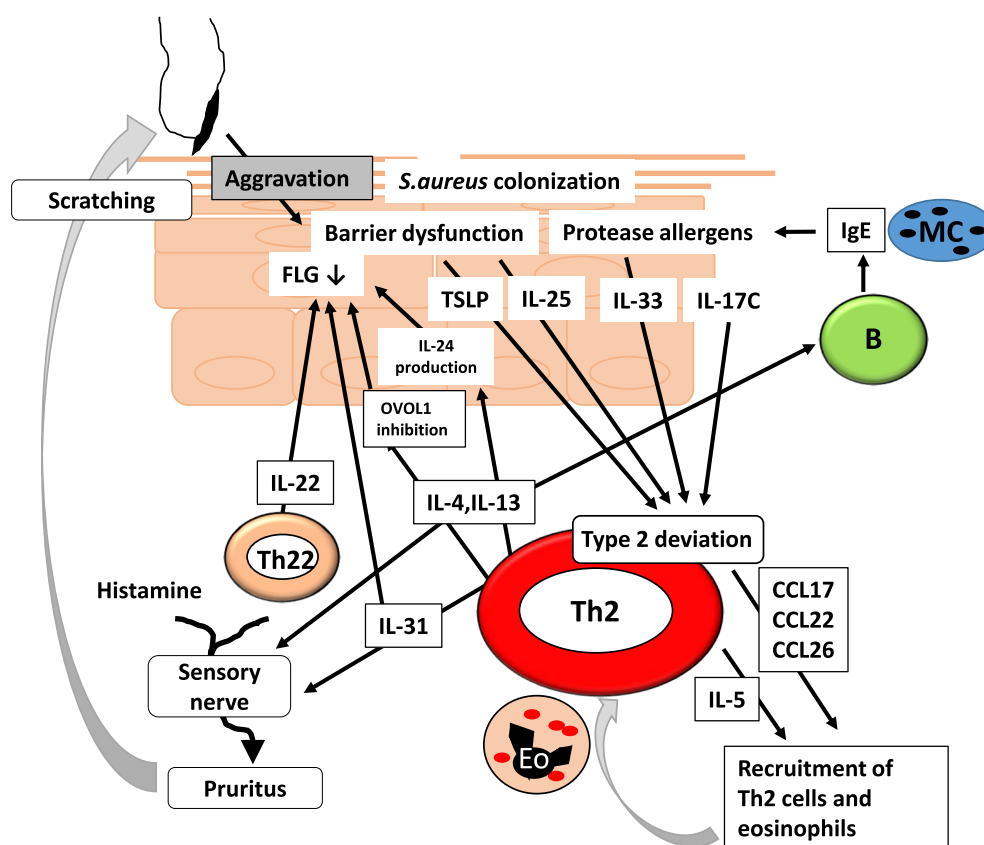


Fig. 1. Pathogenesis of atopic dermatitis. Barrier-disrupted keratinocytes are potent producers of immunoregulatory cytokines such as TSLP, IL-25, and IL-33. IL-17C is also involved in type 2 inflammation. These cytokines induce a type 2-deviated immune response. Most allergens possess protease activity. The protease allergens cleave full-length IL-33 to the active form and induce a type 2 immune response. Th2 cells produce IL-4, IL-13, IL-31, and IL-5. IL-4 and IL-13 inhibit barrier function by downregulating FLG expression via IL-24 induction or inhibition of OVOL1 function. IL-31 stimulates sensory nerves and mediates pruritus. IL-4 and IL-13 amplify the IL-31-induced pruritus. Pruritus evokes scratching, which aggravates barrier disruption. The barrier-disrupted epidermis is susceptible to colonization of *Staphylococcus aureus*, which further worsens barrier disruption. IL-4 and IL-13 stimulate B cells to produce IgE, which binds to mast cells and induces their degranulation upon binding to allergens. IL-4 and IL-13 upregulate the production of CCL17, CCL22, and CCL26. These chemokines as well as IL-5 recruit Th2 cells and eosinophils. FLG; filaggrin; Th2 cell, T helper type 2 cell; TSLP, thymic stromal lymphopoietin

IL-5 mRNA compared with those of normal control skin or uninvolved AD skin by an in situ hybridization technique [9]. In addition, significantly greater numbers of eosinophils and IL-5-expressing T cells are detected in chronic lesions than in acute AD lesions [9]. The significant increase in IL-4, IL-5, and IL-13 mRNA levels is also confirmed in lesional skin compared with uninvolved skin in AD by Gittler et al. [10]. They also show stronger upregulation of IL-5 and IL-13 gene expression in chronic lesions than in acute AD lesions [10]. In addition to the type 2-dominated immune regulation, IL-22 is elevated especially in chronic lesions and is likely to be involved in the perpetuation of AD [10–13]. In accordance with the type 2-dominated immune regulation, blood levels of total IgE, and antigen-specific IgE are elevated along with functional B cell activation in most patients with AD [14].

Dry skin or xerosis is the most prominent clinical feature in AD [15]. Atopic dry skin results from skin barrier dysfunction as assessed by increased transepidermal water loss [16] and decreased corneal water content [17]. Abnormal microbial colonization, such as *Staphylococcus aureus*, is also associated with barrier dysfunction [18]. Barrier dysfunction is detected even in mild AD patients compared with healthy volunteers [19]. Therefore, moisturizers are important treatment modalities in AD [20]. Although pathogenesis underlying barrier dysfunction in AD are multidirectional and interconnected, genetic and type 2 immune-induced decreases in FLG have been extensively highlighted [5, 21, 22•]. Among 31 susceptible genes demonstrated by genome-wide association studies in AD, *FLG*, *OVOL1*, and *IL13* are listed as the top three responsible genes [22•]. Loss-of-function mutations of *FLG* are detected at varying frequencies in different ethnicities [21, 23]. *OVOL1* is an upstream transcription

factor for *FLG* and loricrin gene expression [4, 24, 25]. In addition to the genetic loss of *FLG*, the type 2 cytokines IL-4 and IL-13 potently inhibit *FLG* expression [4, 5, 25, 26] by interfering with *OVOL1* signaling [4] (Fig. 1). Other inflammatory cytokines, such as IL-22 and IL-25, also cause downregulation of *FLG* expression [27, 28]. Therefore, both genetic and acquired disruption of epidermal terminal differentiation leads to barrier dysfunction; in addition, barrier dysfunction promotes type 2 atopic inflammation, making a feed-forward loop toward type 2 dominance that will be discussed later [29–31]. In addition, keratinocytes in the barrier-disrupted skin accelerate the type 2 immune response by producing thymic stromal lymphopoietin (TSLP), IL-25 and IL-33, which are type 2-prone epithelial cytokines [28].

Chronic itch and itch-induced sleep disturbance are also characteristic symptoms in AD and profoundly harm the quality of life of afflicted patients [32–40]. Among various endogenous mediators, IL-4, IL-13, and IL-31 are particularly important for atopic itch because both the anti-IL-4 receptor antibody dupilumab and the anti-IL-31 receptor antibody nemolizumab potently improve pruritus in AD patients even 1 week after their administration [8, 41, 42] (Fig. 1). Cutaneous sensory neurons express IL-4 and IL-31 receptors [43, 44, 45••]. Preclinical studies have proved an itch-evoking property of IL-31, which is preferentially released from type 2 T cells [44]. The role of histamine in atopic itch is marginal considering the limited efficacy of antihistamines [46]. Chronic itch induces repetitive scratching, and this mechanical injury deteriorates barrier dysfunction and further increases the severity of dermatitis [47] (Fig. 1).

In this review, we summarize recent topics on the pathogenesis of AD focusing on type 2 immune deviation.

IL-4, IL-5, IL-13, and IL-22 are key drivers of atopic dermatitis

Gene expression of IL-4, IL-5, and IL-13 is upregulated in the lesional skin of pediatric and adult AD patients compared with the normal skin of healthy controls [9, 10, 12] (Fig. 1). Type 2 dominance is likely to be progressive from nonlesional to lesional skin and from acute to chronic lesions in AD [10, 12]. Increased expression of IL-22 is associated with type 2 dominance in AD and is also progressive from nonlesional to lesional skin and from acute to chronic lesion [10, 12]. Type 2 dominance is confirmed in peripheral blood T helper (Th) cells [11]. IL-13-producing type 2 T helper (Th) cells are significantly increased in the skin-homing cutaneous lymphocyte antigen (CLA)⁺ Th cell

population in both pediatric and adult AD patients compared with healthy controls [11]. An increased number of circulating IL-22+CLA+ Th cells is detected only in adult patients but not in pediatric patients with AD [11]. IL-4-induced, but not IL-2-induced, the proliferative response of peripheral T cells is significantly enhanced in AD patients compared with healthy controls [48].

Biologic treatments with anti-IL-4 receptor α antibody dupilumab and anti-IL-22 antibody fezakinumab exhibit clear efficacy for AD [8••, 13]. Dupilumab significantly reduces clinical severity as well as total and specific IgE levels and IL-22 expression [13]. Patients expressing greater baseline levels of IL-22 show a better treatment response to fezakinumab [49]. IL-5 is crucial for eosinophil growth, differentiation, and migration [50]. Administration of anti-IL-5 antibody mepolizumab significantly reduces circulating eosinophils, whereas no significant improvement is observed in the severity score and pruritus in patients with AD [50]. These clinical studies emphasize the pivotal involvement of IL-4, IL-13, and IL-22, but not IL-5, in the pathogenesis of AD. In addition, fezakinumab is more efficacious in severe AD patients than in nonsevere AD patients, which suggests a critical role for IL-22 in the chronic phase of AD [13]. Topical steroids and tacrolimus are effective in downregulating the gene expression of IL-5, IL-13, and IL-22 and improving skin symptoms [51–53].

CCL17, CCL18, CCL22, and CCL26 are cardinal chemoattractants for type 2 T cells and eosinophils

CCL17, CCL18, CCL22, and CCL26 are type 2 chemokines that are overexpressed in the lesional skin of AD [54, 55••] (Fig. 1). CCL17, CCL18, and CCL22 are chemoattractive to type 2 T cells and are mainly produced from dendritic cells and other dermal cells in the presence of IL-4 and IL-13 [54, 55••, 56, 57]. For CCL17, platelets are probably the important source [58], and serum CCL17 levels become undetectable in a patient with AD comorbid with idiopathic thrombocytopenic purpura [59]. CCL26 is a potent chemotactic factor for eosinophils and is produced from endothelial cells stimulated by IL-4 and/or IL-13 [54, 55••, 60]. The expression levels of these type 2 chemokines are normalized by dupilumab and topical steroid [51, 55••].

Serum levels of CCL17 and CCL22 are significantly increased in patients with AD compared with healthy controls and are associated with disease severity in AD [61, 62]. Interstitial fluids contain significantly greater levels of IL-5, IL-13, and CCL17 in the lesional skin of AD patients compared with healthy individuals [63]. Increased levels of CCL17 and CCL22 as well as the proinflammatory chemokine CXCL8 are also reported in tape-stripped stratum corneum in AD [64–66].

The roles of TSLP, IL-24, IL-25, and IL-33 in type 2 immune deviation and barrier dysfunction

Epidermal keratinocytes are a rich source of various cytokines and chemokines [28, 67–69]. Skin barrier disruption caused by internal

and/or external stimuli induces phenotypic alteration of keratinocytes. Repeated barrier disruption by acetone treatment or tape stripping induces keratinocyte proliferation and epidermal acanthosis in mice and humans [70, 71]. Percutaneous sensitization with allergens through barrier-disrupted skin after tape stripping is known to elicit a type 2-dominant immune response [29, 30]. Epicutaneous sensitization with picryl chloride or mite antigen through barrier-disrupted site elicits greater IL-4 and IgE expression in the regional lymph node compared with sensitization through barrier-intact skin [29]. Tape stripping upregulates the expression of CCL17, CCL22, and CCL5 in epidermal cells and increases the recruitment of IL-4-producing cells and eosinophils [30].

Recent studies have proved that the barrier dysfunction-induced type 2 shift is driven, at least in part, by the keratinocyte-derived cytokines TSLP, IL-25, and IL-33 [28, 72] (Fig. 1). In the lesional skin of AD, the expression of TSLP, IL-25, and IL-33 is upregulated in epidermal keratinocytes [12, 73, 74]. Shaving and tape stripping cause a significant increase in TSLP levels in the skin [31]. A primary target for TSLP is likely to be dendritic cells. TSLP upregulates the expression of OX40L, CD80, and CD86 in murine dendritic cells, and TSLP-treated dendritic cells educate T cells to produce IL-4, IL-5, and IL-13 [75–77]. In humans, TSLP-treated dendritic cells also preferentially prime naïve T cells to produce IL-4, IL-5, and IL-13 [74]. TSLP upregulates the production of CCL17 and CCL22 from human dendritic cells [74].

IL-25, also called IL-17E, is a member of the IL-17 family [78]. Transgenic mice for IL-25 exhibit a Th2-biased response characterized by eosinophilia, increased serum levels of IgE and IgG1, and a Th2 cytokine profile including elevated serum levels of IL-13 and IL-5 and elevated gene expression of IL-4, IL-5, and IL-13 in many tissues [79]. Intranasal administration of IL-25 results in the expression of IL-4, IL-5, IL-13, and eotaxin in the lungs and marked eosinophilia in the bronchoalveolar lavage and lung tissue [80]. In addition to IL-25, the anti-IL-17C antibody may be efficacious for the treatment of AD [81]. In contrast, blockade of the IL-23 and IL-17A pathways may exacerbate AD [82].

IL-33 is a tissue-derived nuclear cytokine of the IL-1 family with critical roles in type 2 immunity, inflammation, and allergy [83••]. Tape stripping activates keratinocytes to produce IL-33 [84]. Herpes virus infection also induces IL-33 expression by keratinocytes [85]. Keratinocytes are activated by house dust mites through the toll-like receptor 6 and produce IL-25 and IL-33 [86]. Many potent allergens such as house dust mites, fungi, and pollens have intrinsic protease activity [83••, 87, 88]. Full-length IL-33 released from epithelial cells is cleaved to the mature form by various types of protease allergens, and cleaved IL-33 induces the production of IL-5 and IL-13 from immune cells and recruits eosinophils [83••]. Therefore, IL-33 acts as a sensitive sensor for external protease allergens [83••].

The roles of TSLP, IL-25, and IL-33 may be redundant, and their significance remains undetermined in the pathomechanism of AD. In *Schistosoma mansoni* infection, individual ablation of TSLP, IL-25, or IL-33 had no impact on the development of IL-4- and IL-13-dependent

inflammation or fibrosis [89]. However, simultaneous disruption of three cytokines ameliorates the type 2 deviation [89].

Downregulation of FLG expression by IL-4, IL-13, IL-20, IL-22, IL-24, IL-25, IL-31, and IL-33

Among the 31 susceptible gene loci reported by a meta-analysis of genome-wide association studies, *FLG*, *OVOL1*, and *IL13* are the top 3 significant genes associated with AD [22•]. Activation of *OVOL1* induces its cytoplasmic to nuclear translocation and upregulates FLG expression [4, 24]. The expression of FLG is downregulated in the lesional skin of AD [4, 5] (Fig. 1). Type 2 cytokines IL-4 and IL-13 potentially inhibit FLG expression [4, 5, 24–26] by interfering with *OVOL1* signaling [4, 24, 90].

IL-13 also stimulates keratinocytes to produce IL-24, which inhibits FLG expression in autocrine and paracrine fashions [91]. Other cytokines, such as IL-20, IL-22, IL-25, IL-31, and IL-33, also cause downregulation of FLG expression [27, 92–95]; however, their molecular mechanisms leading to FLG downregulation are not fully understood. IL-20 and IL-24 are partly responsible for IL-31-mediated FLG downregulation [92].

Atopic pruritus is induced by IL-31, IL-4, and IL-13

Chronic itch is the characteristic symptom of AD [36, 96]. Antipruritic effects of antihistamines are limited in the treatment of AD and are appreciated by patients when antihistamine is added over topical steroids [46]. IL-31 is likely to be the cardinal pruritogenic cytokine in AD [44] (Fig. 1). Administration of IL-31 induces an itching sensation in mice, dogs, monkeys, and humans [44]. Anti-IL-31 receptor antibody nemolizumab significantly and rapidly reduces the pruritus of patients with AD [41, 42]. Anti-canine IL-31 antibody (lokivetmab) has already been commercially available in the treatment of dogs with canine AD [97].

The major source of IL-31 is type 2 Th cells [44, 98]. The expression of IL-31 is increased in the lesional skin of AD [55••]. IL-31 promotes elongation and branching of sensory nerve fibers [43]. Murine and human sensory neurons express IL-4 and IL-13 receptors, while simple injection of IL-4 and/or IL-13 does not induce acute itch [45••]. However, IL-4 and IL-13-pretreated neurons respond to subthreshold concentrations of histamine or IL-31, suggesting that IL-4 and IL-13 amplify the itch sensation [45••]. Both IL-31 receptor and IL-4 receptor α activate downstream JAK1/JAK2 and JAK1/JAK3 signaling pathways, respectively [44, 99]. Targeted disruption of neuronal JAK1 signaling pathway reduces chronic itch, which supports the success of JAK inhibitors in treating chronic itch [45••, 100].

Conclusion

AD is characterized by three cardinal features: type 2-deviated immune response, skin barrier disruption, and chronic pruritus. The therapeutic success of dupilumab appears to verify that the elevated IL-4 and/or IL-13 signal,

namely, type 2 deviation, is the essential pathogenesis in AD [55••, 101]. An increase in IL-4 and/or IL-13 signal accelerates the barrier dysfunction by inhibiting FLG expression. Type 2 pruritogenic cytokine IL-31 induces itching and scratching. Scratching deteriorates epidermal barrier disruption, and dry skin enhances the production of type 2 keratinocyte-derived cytokines TSLP, IL-25, and IL-33, resulting in amplification of type 2 immune deviation. The IL-4/IL-13 signal exacerbates IL-31-induced pruritus by reducing the threshold of IL-31. Further mechanistic investigation is warranted to develop new efficacious drugs for AD.

Compliance with ethics guidelines

Conflict of interest

The authors declare that they have no conflict of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
 - Of major importance
1. Furue M, Chiba T, Tsuji G, Ulzii D, Kido-Nakahara M, Nakahara T, et al. Atopic dermatitis: immune deviation, barrier dysfunction, IgE autoreactivity and new therapies. *Allergol Int*. 2017;66(3):398–403.
 2. Hanifin JM. Atopic dermatitis. *J Allergy Clin Immunol*. 1984;73(2):211–26.
 3. Mihm MC Jr, Soter NA, Dvorak HF, Austen KF. The structure of normal skin and the morphology of atopic eczema. *J Invest Dermatol*. 1976;67(3):305–12.
 4. Tsuji G, Hashimoto-Hachiya A, Kiyomatsu-Oda M, Takemura M, Ohno F, Ito T, et al. Aryl hydrocarbon receptor activation restores filaggrin expression via OVOL1 in atopic dermatitis. *Cell Death Dis*. 2017;8(7):e2931.
 5. van den Bogaard EH, Bergboer JG, Vonk-Bergers M, van Vlijmen-Willems IM, Hato SV, van der Valk PG, et al. Coal tar induces AHR-dependent skin barrier repair in atopic dermatitis. *J Clin Invest*. 2013;123(2):917–27.
 6. Cipriani F, Marzatico A, Ricci G. Autoimmune diseases involving skin and intestinal mucosa are more frequent in adolescents and young adults suffering from atopic dermatitis. *J Dermatol*. 2017;44(12):1341–8.
 7. Furue M, Kadono T. “Inflammatory skin march” in atopic dermatitis and psoriasis. *Inflamm Res*. 2017;66(10):833–42.
 8. •• Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med*. 2016;375(24):2335–48.
- This paper is the result of phase 3 trials of dupilumab in atopic dermatitis.
9. Hamid Q, Boguniewicz M, Leung DY. Differential in situ cytokine gene expression in acute versus chronic atopic dermatitis. *J Clin Invest*. 1994;94(2):870–6.
 10. Gittler JK, Shemer A, Suárez-Fariñas M, Fuentes-Duculan J, Gulewicz KJ, Wang CQ, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. *J Allergy Clin Immunol*. 2012;130(6):1344–54.
 11. Czarowicki T, Esaki H, Gonzalez J, Malajian D, Shemer A, Noda S, et al. Early pediatric atopic dermatitis shows only a cutaneous lymphocyte antigen (CLA)(+) TH2/TH1 cell imbalance, whereas adults acquire CLA(+) TH22/TC22 cell subsets. *J Allergy Clin Immunol*. 2015;136(4):941–51.
 12. Esaki H, Brunner PM, Renert-Yuval Y, Czarowicki T, Huynh T, Tran G, et al. Early-onset pediatric atopic dermatitis is T(H)2 but also T(H)17 polarized in skin. *J Allergy Clin Immunol*. 2016;138(6):1639–51.

13. Guttman-Yassky E, Brunner PM, Neumann AU, Khattri S, Pavel AB, Malik K, et al. Efficacy and safety of fezakinumab (an IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by conventional treatments: a randomized, double-blind, phase 2a trial. *J Am Acad Dermatol*. 2018;78(5):872–81.
14. Czumowski T, Esaki H, Gonzalez J, Renert-Yuval Y, Brunner P, Oliva M, et al. Alterations in B-cell subsets in pediatric patients with early atopic dermatitis. *J Allergy Clin Immunol*. 2017;140(1):134–44.
15. Chu H, Shin JU, Park CO, Lee H, Lee J, Lee KH. Clinical diversity of atopic dermatitis: a review of 5,000 patients at a single institute. *Allergy Asthma Immunol Res*. 2017;9(2):158–68.
16. Werner Y, Lindberg M. Transepidermal water loss in dry and clinically normal skin in patients with atopic dermatitis. *Acta Derm Venereol*. 1985;65(2):102–5.
17. Werner Y. The water content of the stratum corneum in patients with atopic dermatitis. Measurement with the Corneometer CM 420. *Acta Derm Venereol*. 1986;66(4):281–4.
18. Furue M, Iida K, Imaji M, Nakahara T. Microbiome analysis of forehead skin in patients with atopic dermatitis and healthy subjects: implication of *Staphylococcus* and *Corynebacterium*. *J Dermatol*. 2018;45(7):876–7.
19. Furue M, Matsumoto T, Yamamoto T, Takeuchi S, Esaki H, Chiba T, et al. Correlation between serum thymus and activation-regulated chemokine levels and stratum corneum barrier function in healthy individuals and patients with mild atopic dermatitis. *J Dermatol Sci*. 2012;66(1):60–3.
20. Komura Y, Kogure T, Kawahara K, Yokozeki H. Economic assessment of actual prescription of drugs for treatment of atopic dermatitis: differences between dermatology and pediatrics in large-scale receipt data. *J Dermatol*. 2018;45(2):165–74.
21. Egawa G, Kabashima K. Barrier dysfunction in the skin allergy. *Allergol Int*. 2018;67(1):3–11.
22. Paternoster L, Standl M, Waage J, Baurecht H, Hotze M, Strachan DP, et al. Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. *Nat Genet*. 2015;47(12):1449–56.
- This paper is the meta-analysis of genome-wide association studies for atopic dermatitis.
23. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet*. 2006;38(4):441–6.
24. Hashimoto-Hachiya A, Tsuji G, Murai M, Yan X, Furue M. Upregulation of FLG, LOR, and IVL expression by *Rhodiola crenulata* root extract via aryl hydrocarbon receptor: differential involvement of OVOL1. *Int J Mol Sci*. 2018;19(6):pii: E1654.
25. Hirano A, Goto M, Mitsui T, Hashimoto-Hachiya A, Tsuji G, Furue M. Antioxidant *Artemisia princeps* extract enhances the expression of filaggrin and loricrin via the AHR/OVOL1 pathway. *Int J Mol Sci*. 2017;18(9):pii: E1948.
26. Takei K, Mitoma C, Hashimoto-Hachiya A, Uchi H, Takahara M, Tsuji G, et al. Antioxidant soybean tar Glyteer rescues T-helper-mediated downregulation of filaggrin expression via aryl hydrocarbon receptor. *J Dermatol*. 2015;42(2):171–80.
27. Gutowska-Owsiak D, Schaupp AL, Salimi M, Taylor S, Ogg GS. Interleukin-22 downregulates filaggrin expression and affects expression of profilaggrin processing enzymes. *Br J Dermatol*. 2011;165(3):492–8.
28. Han H, Roan F, Ziegler SF. The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines. *Immunol Rev*. 2017 Jul;278(1):116–30.
29. Kondo H, Ichikawa Y, Imokawa G. Percutaneous sensitization with allergens through barrier-disrupted skin elicits a Th2-dominant cytokine response. *Eur J Immunol*. 1998;28(3):769–79.
30. Onoue A, Kabashima K, Kobayashi M, Mori T, Tokura Y. Induction of eosinophil- and Th2-attracting epidermal chemokines and cutaneous late-phase reaction in tape-stripped skin. *Exp Dermatol*. 2009;18(12):1036–43.
31. Oyoshi MK, Larson RP, Ziegler SF, Geha RS. Mechanical injury polarizes skin dendritic cells to elicit a T(H)2 response by inducing cutaneous thymic stromal lymphopoietin expression. *J Allergy Clin Immunol*. 2010;126(5):976–84.
32. Arima K, Gupta S, Gadkari A, Hiragun T, Kono T, Katayama I, et al. Burden of atopic dermatitis in Japanese adults: analysis of data from the 2013 National Health and Wellness Survey. *J Dermatol*. 2018;45(4):390–6.
33. Cai L, Kaneko S, Morita E. Changes in salivary chromogranin A levels in adults with atopic dermatitis are correlated with changes in their condition. *J Dermatol*. 2018;45(5):554–9.
34. Chang YS, Chiang BL. Sleep disorders and atopic dermatitis: a two-way street? *J Allergy Clin Immunol*. 2018; pii: S0091-6749(18)31176-X.
35. Jung HJ, Bae JY, Kim JE, Na CH, Park GH, Bae YI, et al. Survey of disease awareness, treatment behavior and treatment satisfaction in patients with atopic dermatitis in Korea: a multicenter study. *J Dermatol*. 2018;45(10):1172–80.
36. Kido-Nakahara M, Furue M, Ulzii D, Nakahara T. Itch in atopic dermatitis. *Immunol Allergy Clin N Am*. 2017;37(1):113–22.
37. Silverberg JL, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, et al. Patient-burden and quality of life in atopic dermatitis in US adults: a population-based cross-sectional study. *Ann Allergy Asthma Immunol*. 2018; pii: S1081-1206(18)305672.
38. Takeuchi S, Oba J, Esaki H, Furue M. Pruritus of patients with atopic dermatitis in daily life and their experience of therapeutic effects: results of a web-based questionnaire survey. *Br J Dermatol*. 2015;173(1):250–2.

39. Takeuchi S, Oba J, Esaki H, Furue M. Non-corticosteroid adherence and itch severity influence perception of itch in atopic dermatitis. *J Dermatol.* 2018;45(2):158–64.
 40. Wei W, Anderson P, Gadkari A, Blackburn S, Moon R, Piercy J, et al. Extent and consequences of inadequate disease control among adults with a history of moderate to severe atopic dermatitis. *J Dermatol.* 2018;45(2):150–7.
 41. Nemoto O, Furue M, Nakagawa H, Shiramoto M, Hanada R, Matsuki S, et al. The first trial of CIM331, a humanized antihuman interleukin-31 receptor A antibody, in healthy volunteers and patients with atopic dermatitis to evaluate safety, tolerability and pharmacokinetics of a single dose in a randomized, double-blind, placebo-controlled study. *Br J Dermatol.* 2016;174(2):296–304.
 42. Ruzicka T, Hanifin JM, Furue M, Pulka G, Mlynarczyk I, Wollenberg A, et al. Anti-interleukin-31 receptor A antibody for atopic dermatitis. *N Engl J Med.* 2017;376(9):826–35.
 43. Feld M, Garcia R, Buddenkotte J, Katayama S, Lewis K, Muirhead G, et al. The pruritus- and TH2-associated cytokine IL-31 promotes growth of sensory nerves. *J Allergy Clin Immunol.* 2016;138(2):500–8.
 44. Furue M, Yamamura K, Kido-Nakahara M, Nakahara T, Fukui Y. Emerging role of interleukin-31 and interleukin-31 receptor in pruritus in atopic dermatitis. *Allergy.* 2018;73(1):29–36.
 - 45.●● Oetjen LK, Mack MR, Feng J, Whelan TM, Niu H, Guo CJ, et al. Sensory neurons co-opt classical immune signaling pathways to mediate chronic itch. *Cell.* 2017;171(1):217–28
- This paper reveals that IL-4 is also important for chronic itch.
46. Kawashima M, Tango T, Noguchi T, Inagi M, Nakagawa H, Harada S. Addition of fexofenadine to a topical corticosteroid reduces the pruritus associated with atopic dermatitis in a 1-week randomized, multicentre, double-blind, placebo-controlled, parallel-group study. *Br J Dermatol.* 2003;148(6):1212–21.
 47. Takeuchi S, Yasukawa F, Furue M, Katz SI. Collared mice: a model to assess the effects of scratching. *J Dermatol Sci.* 2010;57(1):44–50.
 48. Furue M, Ohtsuki M, Ogata F, Ishibashi Y. Responsiveness to interleukin 4 and interleukin 2 of peripheral blood mononuclear cells in atopic dermatitis. *J Invest Dermatol.* 1991;96(4):468–72.
 49. Brunner PM, Pavel AB, Khattri S, Leonard A, Malik K, Rose S, et al. Baseline IL22 expression in atopic dermatitis patients stratifies tissue responses to fezakinumab. *J Allergy Clin Immunol.* 2018. pii: S0091-6749(18)31141-2. <https://doi.org/10.1016/j.jaci.2018.07.028>.
 50. Oldhoff JM, Darsow U, Werfel T, Katzer K, Wulf A, Laifaoui J, et al. Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. *Allergy.* 2005;60(5):693–6.
 51. Guttman-Yassky E, Ungar B, Malik K, Dickstein D, Suprun M, Estrada YD, et al. Molecular signatures order the potency of topically applied anti-inflammatory drugs in patients with atopic dermatitis. *J Allergy Clin Immunol.* 2017;140(4):1032–42.
 52. Nakahara T, Morimoto H, Murakami N, Furue M. Mechanistic insights into topical tacrolimus for the treatment of atopic dermatitis. *Pediatr Allergy Immunol.* 2018;29(3):233–8.
 53. Ohtsuki M, Morimoto H, Nakagawa H. Tacrolimus ointment for the treatment of adult and pediatric atopic dermatitis: review on safety and benefits. *J Dermatol.* 2018;45(8):936–42.
 54. Esaki H, Ewald DA, Ungar B, Rozenblit M, Zheng X, Xu H, et al. Identification of novel immune and barrier genes in atopic dermatitis by means of laser capture microdissection. *J Allergy Clin Immunol.* 2015;135(1):153–63.
 - 55.●● Guttman-Yassky E, Bissonnette R, Ungar B, Suárez-Fariñas M, Ardeleanu M, Esaki H, et al. Dupilumab progressively improves systemic and cutaneous abnormalities in atopic dermatitis patients. *J Allergy Clin Immunol.* 2018. pii: S0091-6749(18)31266–1, 2019. <https://doi.org/10.1016/j.jaci.2018.08.022>.
- This paper shows how dupilumab affects molecular signatures of atopic dermatitis.
56. Shoda T, Futamura K, Kobayashi F, Saito H, Matsumoto K, Matsuda A. Expression of thymus and activation-regulated chemokine (TARC) by human dermal cells, but not epidermal keratinocytes. *J Dermatol Sci.* 2014;76(2):90–5.
 57. Takemura M, Nakahara T, Hashimoto-Hachiya A, Furue M, Tsuji G. Glyteer, soybean tar, impairs IL-4/Stat6 signaling in murine bone marrow-derived dendritic cells: the basis of its therapeutic effect on atopic dermatitis. *Int J Mol Sci.* 2018;19(4):pii: E1169.
 58. Fujisawa T, Fujisawa R, Kato Y, Nakayama T, Morita A, Katsumata H, et al. Presence of high contents of thymus and activation-regulated chemokine in platelets and elevated plasma levels of thymus and activation-regulated chemokine and macrophage-derived chemokine in patients with atopic dermatitis. *J Allergy Clin Immunol.* 2002;110(1):139–46.
 59. Ozawa M, Sasahara Y, Aiba S. Case of atopic dermatitis concurrent with idiopathic thrombocytopenic purpura, whose serum thymus and activation-regulated chemokine level remained undetectable. *J Dermatol.* 2018;45(5):606–8.
 60. Shinkai A, Yoshisue H, Koike M, Shoji E, Nakagawa S, Saito A, et al. A novel human CC chemokine, eotaxin-3, which is expressed in IL-4-stimulated vascular endothelial cells, exhibits potent activity toward eosinophils. *J Immunol.* 1999;163(3):1602–10.
 61. Kakinuma T, Nakamura K, Wakugawa M, Mitsui H, Tada Y, Saeki H, et al. Thymus and activation-regulated chemokine in atopic dermatitis: serum thymus and activation-regulated chemokine level is closely related with disease activity. *J Allergy Clin Immunol.* 2001;107(3):535–41.
 62. Kakinuma T, Nakamura K, Wakugawa M, Mitsui H, Tada Y, Saeki H, et al. Serum macrophage-derived

- chemokine (MDC) levels are closely related with the disease activity of atopic dermatitis. *Clin Exp Immunol.* 2002;127(2):270–3.
63. Szegedi K, Lutter R, Res PC, Bos JD, Luiten RM, Kezic S, et al. Cytokine profiles in interstitial fluid from chronic atopic dermatitis skin. *J Eur Acad Dermatol Venereol.* 2015;29(11):2136–44.
64. Amarbayasgalan T, Takahashi H, Dekio I, Morita E. Interleukin-8 content in the stratum corneum as an indicator of the severity of inflammation in the lesions of atopic dermatitis. *Int Arch Allergy Immunol.* 2013;160(1):63–74.
65. Morita E, Takahashi H, Niihara H, Dekio I, Sumikawa Y, Murakami Y, et al. Stratum corneum TARC level is a new indicator of lesional skin inflammation in atopic dermatitis. *Allergy.* 2010;65(9):1166–72.
66. Hulshof L, Hack DP, Hasnoe QCJ, Dontje B, Jakasa I, Riethmüller C, et al. Stratum corneum analysis provide a minimal invasive tool to study immune response and skin barrier in atopic dermatitis children. *Br J Dermatol.* 2018 Jul 10;180:621–30. <https://doi.org/10.1111/bjd.16994>.
67. Asahina R, Maeda S. A review of the roles of keratinocyte-derived cytokines and chemokines in the pathogenesis of atopic dermatitis in humans and dogs. *Vet Dermatol.* 2017;28(1):16–e5.
68. Nedoszytko B, Sokołowska-Wojdyło M, Ruckemann-Dziurdzińska K, Roszkiewicz J, Nowicki RJ. Chemokines and cytokines network in the pathogenesis of the inflammatory skin diseases: atopic dermatitis, psoriasis and skin mastocytosis. *Postepy Dermatol Alergol.* 2014;31(2):84–91.
69. Uchi H, Terao H, Koga T, Furue M. Cytokines and chemokines in the epidermis. *J Dermatol Sci.* 2000;24(Suppl 1):S29–38.
70. Denda M, Wood LC, Emami S, Calhoun C, Brown BE, Elias PM, et al. The epidermal hyperplasia associated with repeated barrier disruption by acetone treatment or tape stripping cannot be attributed to increased water loss. *Arch Dermatol Res.* 1996;288(5–6):230–8.
71. Hatta N, Takata M, Kawara S, Hirone T, Takehara K. Tape stripping induces marked epidermal proliferation and altered TGF- α expression in non-lesional psoriatic skin. *J Dermatol Sci.* 1997;14(2):154–61.
72. Hamad H, Lambrecht BN. Barrier epithelial cells and the control of type 2 immunity. *Immunity.* 2015;43(1):29–40.
73. Aktar MK, Kido-Nakahara M, Furue M, Nakahara T. Mutual upregulation of endothelin-1 and IL-25 in atopic dermatitis. *Allergy.* 2015;70(7):846–54.
74. Soumelis V, Reche PA, Kanzler H, Yuan W, Edward G, Homey B, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat Immunol.* 2002;3(7):673–80.
75. Gilliet M, Soumelis V, Watanabe N, Hanabuchi S, Antonenko S, de Waal-Malefyt R, et al. Human dendritic cells activated by TSLP and CD40L induce proallergic cytotoxic T cells. *J Exp Med.* 2003;197(8):1059–63.
76. Ito T, Wang YH, Duramad O, Hori T, Delespesse GJ, Watanabe N, et al. TSLP-activated dendritic cells induce an inflammatory T helper type 2 cell response through OX40 ligand. *J Exp Med.* 2005;202(9):1213–23.
77. Liu YJ, Soumelis V, Watanabe N, Ito T, Wang YH, Malefyt Rde W, et al. TSLP: an epithelial cell cytokine that regulates T cell differentiation by conditioning dendritic cell maturation. *Annu Rev Immunol.* 2007;25:193–219.
78. Kolls JK, Linden A. Interleukin-17 family members and inflammation. *Immunity.* 2004;21(4):467–76.
79. Pan G, French D, Mao W, Maruoka M, Risser P, Lee J, et al. Forced expression of murine IL-17E induces growth retardation, jaundice, a Th2-biased response, and multiorgan inflammation in mice. *J Immunol.* 2001;167(11):6559–67.
80. Hurst SD, Muchamuel T, Gorman DM, Gilbert JM, Clifford T, Kwan S, et al. New IL-17 family members promote Th1 or Th2 responses in the lung: in vivo function of the novel cytokine IL-25. *J Immunol.* 2002;169(1):443–53.
81. Guttman-Yassky E, Krueger JG. IL-17C: a unique epithelial cytokine with potential for targeting across the spectrum of atopic dermatitis and psoriasis. *J Invest Dermatol.* 2018;138(7):1467–9.
82. Ishiuchi Y, Umezawa Y, Asahina A, Fukuta H, Aizawa N, Yanaba K, et al. Exacerbation of atopic dermatitis symptoms by ustekinumab in psoriatic patients with elevated serum immunoglobulin E levels: report of two cases. *J Dermatol.* 2018;45(6):732–4.
- 83.●● Cayrol C, Duval A, Schmitt P, Roga S, Camus M, Stella A, et al. Environmental allergens induce allergic inflammation through proteolytic maturation of IL-33. *Nat Immunol.* 2018;19(4):375–85
- This paper reveals how environmental allergens trigger type 2 immune response via IL-33.
84. Dickel H, Gambichler T, Kamphowe J, Altmeyer P, Skrygjan M. Standardized tape stripping prior to patch testing induces upregulation of Hsp90, Hsp70, IL-33, TNF- α and IL-8/CXCL8 mRNA: new insights into the involvement of ‘alarmins’. *Contact Dermatitis.* 2010;63(4):215–22.
85. Jin M, Komine M, Tsuda H, Oshio T, Ohtsuki M. Interleukin-33 is expressed in the lesional epidermis in herpes virus infection but not in verruca vulgaris. *J Dermatol.* 2018;45(7):855–7.
86. Jang YH, Choi JK, Jin M, Choi YA, Ryoo ZY, Lee HS, et al. House dust mite increases pro-Th2 cytokines IL-25 and IL-33 via the activation of TLR1/6 signaling. *J Invest Dermatol.* 2017;137(11):2354–61.
87. Palm NW, Rosenstein RK, Medzhitov R. Allergic host defences. *Nature.* 2012;484(7395):465–72.
88. Sokol CL, Barton GM, Farr AG, Medzhitov R. A mechanism for the initiation of allergen-induced T helper type 2 responses. *Nat Immunol.* 2008;9(3):310–8.
89. Vannella KM, Ramalingam TR, Borthwick LA, Barron L, Hart KM, Thompson RW, et al. Combinatorial targeting of TSLP, IL-25, and IL-33 in type 2 cytokine-

- driven inflammation and fibrosis. *Sci Transl Med*. 2016;8(337):337–65.
90. Tsuji G, Ito T, Chiba T, Mitoma C, Nakahara T, Uchi H, et al. The role of the OVOL1-OVOL2 axis in normal and diseased human skin. *J Dermatol Sci*. 2018;90(3):227–31.
 91. Mitamura Y, Nunomura S, Nanri Y, Ogawa M, Yoshihara T, Masuoka M, et al. The IL-13/periostin/IL-24 pathway causes epidermal barrier dysfunction in allergic skin inflammation. *Allergy*. 2018;73(9):1881–91.
 92. Cornelissen C, Marquardt Y, Czaja K, Wenzel J, Frank J, Lüscher-Firzlaff J, et al. IL-31 regulates differentiation and filaggrin expression in human organotypic skin models. *J Allergy Clin Immunol*. 2012;129(2):426–33.
 93. Gutowska-Owsiak D, Ogg GS. Cytokine regulation of the epidermal barrier. *Clin Exp Allergy*. 2013;43(6):586–98.
 94. Hvid M, Vestergaard C, Kemp K, Christensen GB, Deleuran B, Deleuran M. IL-25 in atopic dermatitis: a possible link between inflammation and skin barrier dysfunction? *J Invest Dermatol*. 2011;131(1):150–7.
 95. Seltmann J, Roesner LM, von Hesler FW, Wittmann M, Werfel T. IL-33 impacts on the skin barrier by down-regulating the expression of filaggrin. *J Allergy Clin Immunol*. 2015;135(6):1659–61.
 96. Furue M, Kadono T. New therapies for controlling atopic itch. *J Dermatol*. 2015;42(9):847–50.
 97. Souza CP, Rosychuk RAW, Contreras ET, Schissler JR, Simpson AC. A retrospective analysis of the use of lokivetmab in the management of allergic pruritus in a referral population of 135 dogs in the western USA. *Vet Dermatol*. 2018 Aug 23;29:489–e164. <https://doi.org/10.1111/vde.12682>.
 98. Yamamura K, Uruno T, Shiraishi A, Tanaka Y, Ushijima M, Nakahara T, et al. The transcription factor EPAS1 links DOCK8 deficiency to atopic skin inflammation via IL-31 induction. *Nat Commun*. 2017;8:13946.
 99. Kurgonaite K, Gandhi H, Kurth T, Pautot S, Schwille P, Weidemann T, et al. Essential role of endocytosis for interleukin-4-receptor-mediated JAK/STAT signalling. *J Cell Sci*. 2015;128(20):3781–95.
 100. Nakagawa H, Nemoto O, Yamada H, Nagata T, Ninomiya N. Phase 1 studies to assess the safety, tolerability and pharmacokinetics of JTE-052 (a novel Janus kinase inhibitor) ointment in Japanese healthy volunteers and patients with atopic dermatitis. *J Dermatol*. 2018;45(6):701–9.
 101. Sastre J, Dávila I. Dupilumab: a new paradigm for the treatment of allergic diseases. *J Invest Allergol Clin Immunol*. 2018;28(3):139–50.

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