Current Topics

Recent Advances in Research on the Mechanisms and Regulation of Allergic Diseases

Review

Current Understanding of Pathophysiological Mechanisms of Atopic Dermatitis: Interactions among Skin Barrier Dysfunction, Immune Abnormalities and Pruritus

Masanori Fujii

Department of Pharmacology, Division of Pathological Sciences, Kyoto Pharmaceutical University;
Kyoto 607–8414, Japan.

Received February 1, 2019

Atopic dermatitis (AD) is a common chronic skin disease with multiple pathogenic factors including skin barrier dysfunction, immune abnormalities, and pruritus. This review summarizes components involved in these pathogenic factors. (1) Skin barrier dysfunction in AD could be due to the down-regulation of epidermal barrier components such as filaggrin, acylceramides, cornified envelope precursors, and claudin-1. (2) T helper type 2 (Th2) cell-derived cytokines, such as interleukin (IL)-4 and IL-13, and keratinocyte-derived cytokines, such as thymic stromal lymphopoietin (TSLP) and IL-33, contribute to Th2-mediated skin inflammation in AD. (3) IL-31, TSLP, IL-4, and IL-13 are able to directly activate primary sensory neurons to induce pruritus in AD, and increased susceptibility to itch (so-called *alloknesis*) is partly due to epidermal hyperinnervation. Importantly, the three key factors (skin barrier dysfunction, immune abnormalities, and pruritus) interact with each other, creating a positive feedback loop that leads to the induction and maintenance of AD. Therefore, a better understanding of not only each pathogenic factor but also their interactions is important to elucidate the complex pathophysiological mechanisms of AD, which will then lead to the development of new therapeutic strategies and drugs for the treatment of this common skin disease.

Key words atopic dermatitis; skin barrier dysfunction; immune abnormality; pruritus

1. INTRODUCTION

Atopic dermatitis (AD) is a common chronic skin disease that usually starts in infancy, disappears or subsides with age, but sometimes continues into adulthood with relapsing course. Abnormalities in the immune system have long been recognized as contributing to the development of AD.¹⁾ On the other hand, recent accumulating evidence has highlighted a primary pathogenic role of skin barrier dysfunction in AD.^{2,3)} Itch (or pruritus) is a hallmark of this disease and the main factor that impairs a patient's QOL.⁴⁾ Recent studies have demonstrated positive interactive effects among the three key factors: skin barrier dysfunction, immune abnormalities and pruritus. Therefore, at present, AD is assumed to result from the complex interactions of this trinity.⁵⁾ This review summarizes the current understanding of the pathophysiological mechanisms of AD focusing on these three key factors and their complex interactions (Fig. 1).

2. PATHOGENIC FACTORS

2.1. Skin Barrier Dysfunction The stratum corneum (SC), the outermost layer of the epidermis, is the most important structure for skin barrier function; it is formed during epidermal differentiation. SC consists of terminally differentiated keratinocytes (called corneocytes) and intercellular lipids, which together provide a physical and hydrophobic barrier.

Tight junction (TJ) proteins seal adjacent keratinocytes in the stratum granulosum, located beneath the SC, and these function as a second barrier. It has been well recognized that skin barrier function is impaired not only in lesional but also in non-lesional (*i.e.*, clinically normal) skin of patients with AD, which was often considered secondary to skin inflammation. However, recent emerging evidence suggests that the skin barrier dysfunction in AD is actually the primary event in disease development. In this section, components involved in skin barrier dysfunction in AD are reviewed.

2.1.1. Filaggrin (FLG)

FLG is a highly abundant protein expressed in differentiated epidermis. It functions to aggregate keratin filaments leading to keratinocyte compaction and SC formation. However, until just more than a decade ago, not much attention had been paid to the association of FLG with AD. Palmer *et al.* first reported in 2006 that a common loss of function mutation of the gene encoding FLG was highly associated with AD.⁶⁾ Since then, the role of this FLG deficiency in leading to the development of AD (*i.e.*, whether *via* skin barrier dysfunction) has been extensively studied. Several *in vitro* studies have shown that FLG deficiency indeed negatively affects epidermal permeability barrier function by perturbing epidermal differentiation or lipid composition and organization,^{7–9)} whereas a conflicting result has also been reported.¹⁰⁾ *In vivo* studies using FLG deficient mice have shown that the percutaneous penetration of hapten and protein antigens are enhanced on a

Fig. 1. Pathogenic Factors of AD and Their Interactions in the Lesional Skin

FLG: filaggrin, acylCer: acylceramide, CE: cornified envelope, IL: interleukin, IFN: interferon, TSLP: thymic stromal lymphopoietin, GM-CSF: granulocyte-macrophage colony-stimulating factor, AMPs: antimicrobial peptides, NGF: nerve growth factor. (Color figure can be accessed in the online version.)

C57BL/6 background,¹¹⁾ and eczematous dermatitis with skin barrier impairment spontaneously develops on a proallergic BALB/c background.¹²⁾ Furthermore, FLG metabolites, such as urocanic acid and pyrrolidone carboxylic acid, are shown to contribute to moisturization and maintenance of acidic pH of the SC, both of which may be crucial to epidermal barrier homeostasis by regulating the activity of multiple enzymes that control desquamation, lipid synthesis and inflammation in AD.^{5,13,14)} Therefore, FLG deficiency could lead to impaired skin barrier function through multiple pathways, which would then drive the development of AD.

2.1.2. Acylceramides (acylCer)

Ceramides (Cer) are the dominant SC lipids. Cer not only form the extracellular lamellar membrane bilayer, but also bind covalently to highly cross-linked insoluble proteins surrounding corneocytes (called the cornified envelope, or CE). The latter forms a lipid monolayer, called the cornified lipid envelope (CLE), which is considered to act as a scaffold for organization of the extracellular lamellae. Although there exist numerous Cer species in the SC, omega-*O*-acylCer (or acylCer), which are unique to the epidermis, are thought to be the most critical for SC barrier function.¹⁵⁾ Some studies have shown that the amounts of intercellular acylCer are significantly decreased in AD.^{16–19)} Covalently bound Cer, most of which are derived from acylCer, are also reduced in both the non-lesional and lesional skin of AD patients.^{20,21)} Furthermore, a functional deficit in acylCer may also contribute to skin barrier dysfunction in AD. Generally, acylCer contain linoleic acid, an essential fatty acid that is ester-linked to the omega-hydroxy group. Oxygenation of the linoleate by 12R-lipoxygenase and epidermal lipoxygenase-3 is a crucial step in forming CLE.²²⁾ Essential fatty acid deficiency is well known to cause severe skin barrier dysfunction, explained by the replacement of the linoleate by oleate and other non-essential fatty acids in acylCer.²³⁾ Importantly, Yamamoto *et al.* found increased levels of esterified oleate (instead of linoleate) in the acylCer in the SC of AD patients.¹⁷⁾ Abnormal Cer synthesis and metabolism, as well as essential fatty acid deficiency,

have been suggested to be associated with acylCer deficits in AD.^{21,24–26)}

2.1.3. Epidermal Differentiation Complex (EDC)

Many genes encoding proteins involved in epidermal differentiation cluster on human 1q21 (mouse 3q), known as the “EDC.” The EDC contains three families of gene encoding: (1) “CE precursors” such as loricrin, (2) “S100 proteins” such as S100A8, and (3) “S100 fused type proteins” such as FLG. Like FLG, the CE precursor proteins are also structural proteins forming the SC barrier, whereas the S100 proteins act as an antimicrobial peptide or a chemoattractant which accompanies abnormal epidermal differentiation and barrier impairment.^{27,28)} A genome-wide linkage analysis has identified a genetic linkage of AD to chromosome 1q21.²⁹⁾ Furthermore, a microarray analysis of AD skin lesions has revealed the altered expression of EDC genes, such as the upregulation of S100A8 and S100A7 and the downregulation of loricrin and FLG.³⁰⁾ Although the EDC is also known as a susceptibility locus for psoriasis, another common inflammatory skin disorder with defective skin barrier, the expression patterns of EDC genes in AD and psoriasis are partly distinct; a comparison of gene expression profiles between psoriasis and AD skin lesions has shown that the genes encoding the CE precursor proteins are broadly defective in AD.³¹⁾ Interestingly, this broad terminal differentiation abnormality was observed even in the non-lesional skin of AD patients.³²⁾ Mutations in *FLG* (one of the EDC genes) are the most common risk factor for AD³³⁾; however, a genetic study on children with severe AD suggests that the *FLG* mutations are not solely responsible for the significant genetic linkage of AD to the EDC.³⁴⁾ Thus, the changes in other EDC genes may also contribute to AD development, possibly through multiple skin barrier defects.

2.1.4. Claudin-1

Claudin-1 is a TJ protein required for epidermal barrier integrity. It has been shown that mRNA and protein expression levels of claudin-1 are reduced in the skin of patients with AD, and polymorphisms in *CLDN1* (encoding claudin-1) are associated with AD susceptibility.³⁵⁾ Furthermore, a recent

study using conditional *Cldn1* knock-out mice has shown that at low expression levels of claudin-1, the mice exhibited an AD phenotype associated with the recruitment of neutrophils and macrophages; notably, the relationship between macrophage recruitment and reduced levels of claudin-1 was also observed in human AD patients.³⁶⁾

2.2. Immune Abnormalities AD has been generally considered a T helper type 2 (Th2)-mediated allergic disease because most patients with AD have increased numbers of circulating eosinophils and elevated serum immunoglobulin E (IgE), similar to allergic asthma and rhinitis. On the other hand, previous immunopathological studies of acute and chronic skin lesions of AD patients have revealed a biphasic switch from Th2 to Th1 responses.¹⁾ Which T cells are activated probably depends on the type of antigen-presenting cells or the size of the antigen. Other T cell subsets (*e.g.*, Th17 cells, Th22 cells, or regulatory T cells) are also thought to participate in the immune processes of AD, but are not discussed here (for more information, see the reviews⁵⁾). Furthermore, keratinocytes (KCs) at the interface between the skin and the environment can respond to both exogenous and endogenous signals to produce various proallergic and proinflammatory molecules that trigger Th2-mediated skin inflammation in AD. This section focuses on “Th2/Th1 immune responses” and “KC innate immune responses” in AD skin inflammation.

2.2.1. Th2/Th1 Immune Responses

Distinct cytokine expression patterns have been identified in the acute and chronic phases of AD skin lesions. Interleukin (IL)-4, IL-5, and IL-13 predominate in the acute lesions, whereas in the chronic lesions there is an increase of interferon (IFN)- γ , IL-12, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF).¹⁾ Thus, human AD skin is characterized roughly by Th2-cell activation in the acute phase, but by the activation of Th1 cells and/or Th0 cells (cells that share some activities of both Th1 and Th2) in the chronic phase. Animal studies using an AD model induced by the topical application of ovalbumin have shown that both Th2 and Th1 cytokines play important roles in skin inflammatory responses.³⁷⁾ Furthermore, it has been demonstrated that transgenic expression of either IL-4 or IL-13 in the skin induces AD-resembling phenotype in mice,^{38,39)} and that Th1-derived IFN- γ induces apoptosis of KCs through the cell death receptor Fas,⁴⁰⁾ which may perpetuate AD. Together, these findings indicate the importance of Th2 as well as Th1 responses in the induction and maintenance of skin inflammation in AD.

On the other hand, in some hapten-induced mouse models of skin inflammation, although a single challenge provokes Th1-type contact hypersensitivity in sensitized mice, repeated elicitation results in AD-like Th2-mediated skin inflammation.⁴¹⁾ This differential involvement of Th2 and Th1 responses in the disease stage between human and mouse models may reflect the complexity and heterogeneity of AD. Since human AD often follows a chronically relapsing course, Th2 and Th1 responses may indeed coexist in AD skin lesions. Alternatively, some Th1-dominant immune status may reflect skin pathology in a subgroup of AD. AD can be categorized into the major extrinsic (or IgE-associated) and the minor intrinsic (or non-IgE-associated) types. The latter type is immunologically characterized by the dominant Th1 response.⁴²⁾ The natural history of AD implies that AD manifests in the non-IgE-associated form, then shifts to an IgE-associated one.⁴³⁾

Several antigen-presenting cells in the skin are thought to play distinct roles in the induction of T-cell development. In the epidermis of patients with AD, two types of dendritic cells (DCs) are increased: Langerhans cells (LCs) and inflammatory dendritic epidermal cells (IDECs), both of which express the high-affinity IgE receptor Fc ϵ RI and are considered to contribute to sensitization against high molecular-weight protein antigens. On protein antigen capture, IgE-bearing LCs efficiently prime naïve T cells to differentiate into Th2 cells, whereas IDECs induce Th1 polarization by producing IL-12 and IL-18.^{1,43)} A recent study suggests that LCs, but not IDECs, extend dendrites through TJs, which are likely to actively capture antigens from outside the TJ barrier.⁴⁴⁾ On the other hand, upon exposure to low molecular-weight haptens that easily penetrate into the dermis, dermal DCs are activated, leading to Th1 polarization.⁵⁾

2.2.2. KC Innate Immune Responses

KC-mediated innate immune responses protect the host from microbial pathogens, but also drive Th2-mediated allergic diseases, including AD. KCs express pattern recognition receptors and are able to produce various chemokines and innate cytokines such as thymic stromal lymphopoietin (TSLP) and IL-33. KCs from AD patients show the abnormal production of chemokines, cytokines, and antimicrobial peptides (AMPs), suggesting some intrinsic and/or extrinsic (acquired) defects in the KCs of AD.

The IL-7-like cytokine TSLP is expressed mainly by barrier epithelial cells, and activates several cell types, particularly myeloid DCs, through the TSLP receptor (TSLPR). Soumelis *et al.* have demonstrated that (1) TSLP activates DCs to produce Th2-attracting chemokines, (2) TSLP-activated DCs prime naïve T cells to differentiate into Th2 cells, and (3) TSLP is highly expressed in the epidermis of lesional human AD skin, which is associated with LC migration and activation.⁴⁵⁾ In mice, KC-targeted transgenic expression of TSLP causes AD-like skin lesions accompanied by an increased infiltration of Th2 cells and elevated levels of serum IgE.⁴⁶⁾ Several studies have also shown that TSLP-TSLPR signaling on LC is critical for epicutaneous sensitization with protein antigens, as well as the development of AD-like skin inflammation in mice.^{47,48)} These findings implicate KC-derived TSLP and TSLPR-expressing LC as key players in the pathogenesis of AD.

IL-33, a novel cytokine of the IL-1 family, is produced primarily by cells of barrier tissues (*e.g.*, skin, gut, and lung) and mediates its biological effect *via* the receptor ST2. Increased expression of IL-33 and ST2 mRNA was observed in human AD skin after exposure to house dust mites or staphylococcal enterotoxin B.⁴⁹⁾ Imai *et al.* have demonstrated that (1) KC-specific overexpression of IL-33 in mice causes spontaneous itchy dermatitis resembling the features of AD, and (2) type 2 innate lymphoid cells (ILC2s), which produce large amounts of IL-5 and IL-13, are increased in the lesional skin and regional lymph nodes.⁵⁰⁾ Another study has further demonstrated that (1) IL-33 and ILC2s expressing ST2 are enriched in the lesional skin of AD patients, (2) IL-33-stimulated human skin ILC2s produce large amounts of type 2 cytokines, and (3) the house dust mite allergen challenge induces ILC2 infiltration into human and mouse skin.⁵¹⁾ These findings suggest that KC-derived IL-33 induces ILC2s in the skin and lymph nodes, and stimulates the production of type 2 cytokines from those

cells to induce AD-like skin inflammation.

A series of studies have shown that in response to proinflammatory cytokines, KCs from patients with AD produce higher concentrations of several proinflammatory chemokines and cytokines, such as GM-CSF, IL-1 α , tumor necrosis factor- α , and RANTES, compared with those from nonatopic control subjects.^{52,53} This enhanced KC response could promote inflammatory cell recruitment and maintain the inflammatory immune responses of AD skin.

AMPs, such as LL-37 and human beta defensin-3, are highly expressed by KCs during infection, inflammation, and wounds, which form an innate chemical barrier; however, the expression of AMPs is down-regulated by Th2 cytokines in AD.⁵⁴ Thus, the deficiency of AMPs in AD skin may lead to a higher propensity toward *Staphylococcus aureus* infection, which is known to contribute to the exacerbation of AD.

2.3. Pruritus Most AD patients show increased itch sensitivity to minimal and negligible stimuli (this phenomenon is called alloknesis).⁵⁵ Clinical studies have shown that emotional stress, sleep, and alcohol intake often trigger or enhance pruritus in patients with AD.⁵⁶ As these triggering factors seem to primarily affect brain function, unique brain mechanisms of itch may be involved in AD. However, the pathophysiology of itch in AD is still not fully understood. Non-sedative antihistamines are less effective in ameliorating itch in AD,⁵⁷ suggesting an involvement of non-histaminergic mechanism(s). This section focuses on itch mediators, alloknesis, and brain functions involved in AD itch.

2.3.1. Itch Mediators

IL-31 is a newly identified cytokine produced by Th2 cells, and acts on the IL-31 receptor A (IL-31RA) expressed in KCs and dorsal root ganglia (DRG) neurons. IL-31 is increased in the lesional skin of AD patients.⁵⁸ Skin-specific overexpression of IL-31 induces AD-like pruritic dermatitis in mice.⁵⁹ An intradermal injection of IL-31 evokes acute scratching in normal mice.⁶⁰ Cevikbas *et al.* have further demonstrated that IL-31 acts directly on a subpopulation of IL-31RA + /transient receptor potential (TRPV1) + /TRPA1+ DRG neurons to produce itch signals in mice.⁶¹ On the other hand, IL-31 does not induce immediate itch responses in humans, although about half of the subjects show late itch responses to an IL-31 challenge.⁶² This suggests an involvement of indirect mechanisms through other cells, such as KCs, in humans. A recent clinical study has shown that the anti-IL-31RA antibody nemolizumab significantly improves pruritus in AD patients,⁶³ indicating the importance of IL-31 in pruritus in human AD.

A recent study has revealed that TSLP functions as a pruritogen. Wilson *et al.* have demonstrated that TSLP acts directly on TSLPR-expressing DRG neurons to induce itch signals *via* TRPA1 in mice.⁶⁴ The authors have also shown that KC production of TSLP is mediated *via* protease-activated receptor 2 (PAR2).⁶⁴ In this regard, there is a correlation between PAR2 activity and TSLP expression in the skin of patients with Netherton syndrome with AD.⁶⁵

A very recent study has identified a direct role of the canonical Th2 cytokines IL-4 and IL-13 in itch. Oetjen *et al.* have reported that (1) mouse and human DRG cells express both IL-4 receptor α (IL-4R α) and IL-13 receptor α 1, and are directly activated by both cytokines; (2) interestingly, IL-4 enhances neuronal responsiveness to other pruritogens; and (3) the sensory neuron-specific deletion of IL-4R α or Janus

kinase 1 (JAK1) suppresses scratching and AD-like inflammation in mice.⁶⁶ These findings are consistent with a clinical study showing that a novel monoclonal antibody targeting the actions of IL-4 and IL-13 (dupilumab) significantly reduces the severity of pruritus in AD patients.⁶⁷

2.3.2. Alloknesis

Alloknesis seems to be due to increased epidermal innervation, a decreased itch threshold, or both. Sprouting of nerve fibers into the epidermis is found in AD.^{68,69} The epidermal nerve sprouting is shown to be regulated by the balance between nerve elongation factors (*e.g.*, nerve growth factor (NGF), amphiregulin) and nerve repulsion factors (*e.g.*, semaphoring 3A).⁷⁰ Recent studies have revealed that artemin and IL-31 also contribute to nerve sprouting to produce itch.^{71,72} Furthermore, NGF sensitizes primary sensory neurons that respond to cowhage,⁷³ which induces a non-histaminergic itch.

2.3.3. Brain Functions

Brain functional imaging studies have shown distinct brain activity induced by itch stimuli in patients with AD.⁷⁴ Visual and auditory stimulation are known to induce itch and scratching (so-called contagious itch). Contagious itch is profound in AD patients, which correlates with activity in the fronto-striatal circuit associated with the desire to scratch.⁷⁵ The molecular basis of brain mechanisms of itch in AD remains largely unclear, because there are few animal studies; however, we have shown that ethanol and barbiturates enhance scratching behavior in AD model mice through actions in the brain,^{76,77} and that allopregnanolone, an endogenous neurosteroid produced in the brain, also induces scratching in AD mice.⁷⁸ As ethanol, barbiturates and allopregnanolone exert a hypnotic effect, the unique scratching phenomenon may mimic unconscious nocturnal pruritus frequently observed in AD patients.⁷⁹

3. INTERACTIONS OF THESE PATHOGENIC FACTORS

Accumulating evidence suggests that the three pathogenic factors interact with each other, creating a positive feedback loop that contributes to the induction and maintenance of AD. In this section, their interactions are separately discussed.

3.1. Between Barrier and Immunology Skin barrier dysfunction allows the penetration of allergens into the skin, leading to immune activation (especially Th2 responses) and skin inflammation. Experimentally, acute skin barrier disruption induces the expression of Th2 and eosinophil chemokines by epidermal cells^{80,81} and promotes the activation of LCs to induce Th2 immune responses.⁸² As described, skin pH is partly increased by reduced FLG metabolites. The increase in skin pH directly modulates protease activity, leading to Th2-mediated inflammation *via* the PAR2-TSLP pathway.¹⁴

Conversely, IL-4, IL-13, and IL-33 down-regulate the expression of FLG.^{83,84} This could explain the fact that FLG expression is decreased, even in AD patients without *FLG* mutations. Other epidermal barrier components (CE, Cer, and TJs proteins) are also negatively regulated by these cytokines.^{35,85,86}

3.2. Between Barrier and Pruritus Skin barrier dysfunction also permits the entry of pruritogens, thereby easily inducing itch. In mice, acetone-induced skin barrier perturbation causes epidermal nerve sprouting with increased NGF

and amphiregulin levels,⁸⁷⁾ and tape stripping of the SC up-regulates the skin expression of TSLP.⁸⁸⁾ As mentioned, both nerve sprouting and TSLP induce itch.

Additionally, scratching directly damages the skin barrier. Furthermore, the pruritogenic cytokine IL-31 interferes with epidermal differentiation and FLG expression,⁸⁹⁾ whereas it promotes epidermal proliferation and thickening,⁹⁰⁾ which together could lead to impaired skin barrier function.

3.3. Between Immunology and Pruritus As described, activated Th2 cells produce several pruritogenic cytokines (*i.e.*, IL-4, IL-13, and IL-31). Furthermore, in the chronic stage of AD, IFN- γ -induced KC apoptosis may result in the release of some pruritogens such as TSLP.

Conversely, scratching exacerbates skin inflammatory immune responses. Mechanical injury to the KCs triggers pro-inflammatory cascades that contribute to the infiltration of immune cells into the skin.^{90,91)} The “butterfly sign” (sparing of the non-reachable area of the back) is often observed in AD patients, suggesting the importance of scratching itself in the development of skin inflammation.

4. CONCLUSION

This review summarizes the mechanisms of “skin barrier dysfunction,” “immune abnormalities,” and “pruritus” as the key pathogenic factors of AD. As these factors are linked to each other, the therapeutic approach should be comprehensive. However, current therapies for AD (*i.e.*, corticosteroids and calcineurin inhibitors) target the immune system, whereas emollients are used as an adjuvant to improve skin barrier function. There are few drugs available to treat itch in AD. Although several new medications targeting a more specific molecule (*e.g.*, dupilumab) have been approved for the treatment of AD, and some are undergoing clinical evaluation,⁹²⁾ further studies are needed to focus on strategies to restore skin barrier function and control itch. A better understanding of the molecular basis of AD would provide important implications for the development of new therapeutic drugs for AD.

Conflict of Interest The author declares no conflict of interest.

REFERENCES

- 1) Leung DY. Atopic dermatitis: new insights and opportunities for therapeutic intervention. *J. Allergy Clin. Immunol.*, **105**, 860–876 (2000).
- 2) Elias PM, Steinhoff M. “Outside-to-inside” (and now back to “outside”) pathogenic mechanisms in atopic dermatitis. *J. Invest. Dermatol.*, **128**, 1067–1070 (2008).
- 3) Cork MJ, Danby SG, Vasilopoulos Y, Hadgraft J, Lane ME, Moustafa M, Guy RH, Macgowan AL, Tazi-Ahnini R, Ward SJ. Epidermal barrier dysfunction in atopic dermatitis. *J. Invest. Dermatol.*, **129**, 1892–1908 (2009).
- 4) Koblenzer CS. Itching and the atopic skin. *J. Allergy Clin. Immunol.*, **104**, S109–S113 (1999).
- 5) Kabashima K. New concept of the pathogenesis of atopic dermatitis: interplay among the barrier, allergy, and pruritus as a trinity. *J. Dermatol. Sci.*, **70**, 3–11 (2013).
- 6) Palmer CN, Irvine AD, Terron-Kwiatkowski A, *et al.* Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat. Genet.*, **38**, 441–446 (2006).
- 7) Mildner M, Jin J, Eckhart L, Kezic S, Gruber F, Barresi C, Stremnitzer C, Buchberger M, Mlitz V, Ballaun C, Sterniczky B, Födinger D, Tschachler E. Knockdown of filaggrin impairs diffusion barrier function and increases UV sensitivity in a human skin model. *J. Invest. Dermatol.*, **130**, 2286–2294 (2010).
- 8) Vávrová K, Henkes D, Strüver K, Sochorová M, Školová B, Witting MY, Friess W, Schreml S, Meier RJ, Schäfer-Korting M, Fluhr JW, Küchler S. Filaggrin deficiency leads to impaired lipid profile and altered acidification pathways in a 3D skin construct. *J. Invest. Dermatol.*, **134**, 746–753 (2014).
- 9) Pendaries V, Malaisse J, Pellerin L, Le Lamer M, Nachat R, Kezic S, Schmitt AM, Paul C, Poumay Y, Serre G, Simon M. Knockdown of filaggrin in a three-dimensional reconstructed human epidermis impairs keratinocyte differentiation. *J. Invest. Dermatol.*, **134**, 2938–2946 (2014).
- 10) van Drongelen V, Alloul-Ramdhani M, Danso MO, Mieremet A, Mulder A, van Smeden J, Bouwstra JA, El Ghalbzouri A. Knockdown of filaggrin does not affect lipid organization and composition in stratum corneum of reconstructed human skin equivalents. *Exp. Dermatol.*, **22**, 807–812 (2013).
- 11) Kawasaki H, Nagao K, Kubo A, Hata T, Shimizu A, Mizuno H, Yamada T, Amagai M. Altered stratum corneum barrier and enhanced percutaneous immune responses in filaggrin-null mice. *J. Allergy Clin. Immunol.*, **129**, 1538–1546.e6 (2012).
- 12) Saunders SP, Moran T, Floudas A, Wurld F, Kaszlikowska A, Salimi M, Quinn EM, Oliphant CJ, Núñez G, McManus R, Hams E, Irvine AD, McKenzie AN, Ogg GS, Fallon PG. Spontaneous atopic dermatitis is mediated by innate immunity, with the secondary lung inflammation of the atopic march requiring adaptive immunity. *J. Allergy Clin. Immunol.*, **137**, 482–491 (2016).
- 13) Thyssen JP, Kezic S. Causes of epidermal filaggrin reduction and their role in the pathogenesis of atopic dermatitis. *J. Allergy Clin. Immunol.*, **134**, 792–799 (2014).
- 14) Jang H, Matsuda A, Jung K, Karasawa K, Matsuda K, Oida K, Ishizaka S, Ahn G, Amagai Y, Moon C, Kim SH, Arkwright PD, Takamori K, Matsuda H, Tanaka A. Skin pH is the master switch of kallikrein 5-mediated skin barrier destruction in a murine atopic dermatitis model. *J. Invest. Dermatol.*, **136**, 127–135 (2016).
- 15) Uchida Y, Holleran WM. Omega-O-acylceramide, a lipid essential for mammalian survival. *J. Dermatol. Sci.*, **51**, 77–87 (2008).
- 16) Imokawa G, Abe A, Jin K, Higaki Y, Kawashima M, Hidano A. Decreased level of ceramides in stratum corneum of atopic dermatitis: an etiologic factor in atopic dry skin? *J. Invest. Dermatol.*, **96**, 523–526 (1991).
- 17) Yamamoto A, Serizawa S, Ito M, Sato Y. Stratum corneum lipid abnormalities in atopic dermatitis. *Arch. Dermatol. Res.*, **283**, 219–223 (1991).
- 18) Di Nardo A, Wertz P, Giannetti A, Seidenari S. Ceramide and cholesterol composition of the skin of patients with atopic dermatitis. *Acta Derm. Venereol.*, **78**, 27–30 (1998).
- 19) Ishikawa J, Narita H, Kondo N, Hotta M, Takagi Y, Masukawa Y, Kitahara T, Takema Y, Koyano S, Yamazaki S, Hatamochi A. Changes in the ceramide profile of atopic dermatitis patients. *J. Invest. Dermatol.*, **130**, 2511–2514 (2010).
- 20) Macheleidt O, Kaiser HW, Sandhoff K. Deficiency of epidermal protein-bound omega-hydroxyceramides in atopic dermatitis. *J. Invest. Dermatol.*, **119**, 166–173 (2002).
- 21) Danso M, Boiten W, van Drongelen V, Gmelig Meijling K, Gooris G, El Ghalbzouri A, Absalah S, Vreeken R, Kezic S, van Smeden J, Lavrijsen S, Bouwstra J. Altered expression of epidermal lipid bio-synthesis enzymes in atopic dermatitis skin is accompanied by changes in stratum corneum lipid composition. *J. Dermatol. Sci.*, **88**, 57–66 (2017).
- 22) Muñoz-García A, Thomas CP, Keeney DS, Zheng Y, Brash AR. The importance of the lipoxygenase-hepoxilin pathway in the mam-

- malian epidermal barrier. *Biochim. Biophys. Acta*, **1841**, 401–408 (2014).
- 23) Melton JL, Wertz PW, Swartzendruber DC, Downing DT. Effects of essential fatty acid deficiency on epidermal *O*-acylsphingolipids and transepidermal water loss in young pigs. *Biochim. Biophys. Acta*, **921**, 191–197 (1987).
 - 24) Murata Y, Ogata J, Higaki Y, Kawashima M, Yada Y, Higuchi K, Tsuchiya T, Kawainami S, Imokawa G. Abnormal expression of sphingomyelin acylase in atopic dermatitis: an etiologic factor for ceramide deficiency? *J. Invest. Dermatol.*, **106**, 1242–1249 (1996).
 - 25) Horrobin DF. Essential fatty acid metabolism and its modification in atopic eczema. *Am. J. Clin. Nutr.*, **71** (Suppl.), 367S–372S (2000).
 - 26) Jensen JM, Fölster-Holst R, Baranowsky A, Schunck M, Winoto-Morbach S, Neumann C, Schütze S, Proksch E. Impaired sphingomyelinase activity and epidermal differentiation in atopic dermatitis. *J. Invest. Dermatol.*, **122**, 1423–1431 (2004).
 - 27) Eckert RL, Broome AM, Ruse M, Robinson N, Ryan D, Lee K. S100 proteins in the epidermis. *J. Invest. Dermatol.*, **123**, 23–33 (2004).
 - 28) Abtin A, Eckhart L, Gläser R, Gmeiner R, Mildner M, Tschachler E. The antimicrobial heterodimer S100A8/S100A9 (calprotectin) is upregulated by bacterial flagellin in human epidermal keratinocytes. *J. Invest. Dermatol.*, **130**, 2423–2430 (2010).
 - 29) Cookson WO, Ubhi B, Lawrence R, Abecasis GR, Walley AJ, Cox HE, Coleman R, Leaves NI, Trembath RC, Moffatt MF, Harper JJ. Genetic linkage of childhood atopic dermatitis to psoriasis susceptibility loci. *Nat. Genet.*, **27**, 372–373 (2001).
 - 30) Sugiura H, Ebise H, Tazawa T, Tanaka K, Sugiura Y, Uehara M, Kikuchi K, Kimura T. Large-scale DNA microarray analysis of atopic skin lesions shows overexpression of an epidermal differentiation gene cluster in the alternative pathway and lack of protective gene expression in the cornified envelope. *Br. J. Dermatol.*, **152**, 146–149 (2005).
 - 31) Guttman-Yassky E, Suárez-Fariñas M, Chiricozzi A, Nogales KE, Shemer A, Fuentes-Duculan J, Cardinale I, Lin P, Bergman R, Bowcock AM, Krueger JG. Broad defects in epidermal cornification in atopic dermatitis identified through genomic analysis. *J. Allergy Clin. Immunol.*, **124**, 1235–1244.e58 (2009).
 - 32) Suárez-Fariñas M, Tintle SJ, Shemer A, Chiricozzi A, Nogales K, Cardinale I, Duan S, Bowcock AM, Krueger JG, Guttman-Yassky E. Nonlesional atopic dermatitis skin is characterized by broad terminal differentiation defects and variable immune abnormalities. *J. Allergy Clin. Immunol.*, **127**, 954–964.e4 (2011).
 - 33) Barnes KC. An update on the genetics of atopic dermatitis: scratching the surface in 2009. *J. Allergy Clin. Immunol.*, **125**, 16–29.e11, 11, quiz, 30–31 (2010).
 - 34) Morar N, Cookson WO, Harper JJ, Moffatt MF. Filaggrin mutations in children with severe atopic dermatitis. *J. Invest. Dermatol.*, **127**, 1667–1672 (2007).
 - 35) De Benedetto A, Rafaels NM, McGirt LY, *et al.* Tight junction defects in patients with atopic dermatitis. *J. Allergy Clin. Immunol.*, **127**, 773–786.e7 (2011).
 - 36) Tokumasu R, Yamaga K, Yamazaki Y, Murota H, Suzuki K, Tamura A, Bando K, Furuta Y, Katayama I, Tsukita S. Dose-dependent role of claudin-1 *in vivo* in orchestrating features of atopic dermatitis. *Proc. Natl. Acad. Sci. U.S.A.*, **113**, E4061–E4068 (2016).
 - 37) Spengel JM, Mizoguchi E, Brewer JP, Martin TR, Bhan AK, Geha RS. Epicutaneous sensitization with protein antigen induces localized allergic dermatitis and hyperresponsiveness to methacholine after single exposure to aerosolized antigen in mice. *J. Clin. Invest.*, **101**, 1614–1622 (1998).
 - 38) Chan LS, Robinson N, Xu L. Expression of interleukin-4 in the epidermis of transgenic mice results in a pruritic inflammatory skin disease: an experimental animal model to study atopic dermatitis. *J. Invest. Dermatol.*, **117**, 977–983 (2001).
 - 39) Zheng T, Oh MH, Oh SY, Schroeder JT, Glick AB, Zhu Z. Transgenic expression of interleukin-13 in the skin induces a pruritic dermatitis and skin remodeling. *J. Invest. Dermatol.*, **129**, 742–751 (2009).
 - 40) Trautmann A, Akdis M, Kleemann D, Altnauer F, Simon HU, Graeve T, Noll M, Bröcker EB, Blaser K, Akdis CA. T cell-mediated Fas-induced keratinocyte apoptosis plays a key pathogenetic role in eczematous dermatitis. *J. Clin. Invest.*, **106**, 25–35 (2000).
 - 41) Kitagaki H, Fujisawa S, Watanabe K, Hayakawa K, Shiohara T. Immediate-type hypersensitivity response followed by a late reaction is induced by repeated epicutaneous application of contact sensitizing agents in mice. *J. Invest. Dermatol.*, **105**, 749–755 (1995).
 - 42) Tokura Y. Extrinsic and intrinsic types of atopic dermatitis. *J. Dermatol. Sci.*, **58**, 1–7 (2010).
 - 43) Bieber T. Atopic dermatitis. *N. Engl. J. Med.*, **358**, 1483–1494 (2008).
 - 44) Yoshida K, Kubo A, Fujita H, Yokouchi M, Ishii K, Kawasaki H, Nomura T, Shimizu H, Kouyama K, Ebihara T, Nagao K, Amagai M. Distinct behavior of human Langerhans cells and inflammatory dendritic epidermal cells at tight junctions in patients with atopic dermatitis. *J. Allergy Clin. Immunol.*, **134**, 856–864 (2014).
 - 45) Soumelis V, Reche PA, Kanzler H, Yuan W, Edward G, Homey B, Gilliet M, Ho S, Antonenko S, Lauerma A, Smith K, Gorman D, Zurawski S, Abrams J, Menon S, McClanahan T, de Waal-Malefyt Rd R, Bazan F, Kastelein RA, Liu YJ. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat. Immunol.*, **3**, 673–680 (2002).
 - 46) Yoo J, Omori M, Gyarmati D, Zhou B, Aye T, Brewer A, Comeau MR, Campbell DJ, Ziegler SF. Spontaneous atopic dermatitis in mice expressing an inducible thymic stromal lymphopoietin transgene specifically in the skin. *J. Exp. Med.*, **202**, 541–549 (2005).
 - 47) Elentner A, Finke D, Schmuth M, Chappaz S, Ebner S, Malissen B, Kissenpfennig A, Romani N, Dubrac S. Langerhans cells are critical in the development of atopic dermatitis-like inflammation and symptoms in mice. *J. Cell. Mol. Med.*, **13** (8B), 2658–2672 (2009).
 - 48) Nakajima S, Igyártó BZ, Honda T, Egawa G, Otsuka A, Hara-Chikuma M, Watanabe N, Ziegler SF, Tomura M, Inaba K, Miyachi Y, Kaplan DH, Kabashima K. Langerhans cells are critical in epicutaneous sensitization with protein antigen *via* thymic stromal lymphopoietin receptor signaling. *J. Allergy Clin. Immunol.*, **129**, 1048–1055.e6 (2012).
 - 49) Savinko T, Matikainen S, Saarialho-Kere U, Lehto M, Wang G, Lehtimäki S, Karisola P, Reunala T, Wolff H, Lauerma A, Alenius H. IL-33 and ST2 in atopic dermatitis: expression profiles and modulation by triggering factors. *J. Invest. Dermatol.*, **132**, 1392–1400 (2012).
 - 50) Imai Y, Yasuda K, Sakaguchi Y, Haneda T, Mizutani H, Yoshimoto T, Nakanishi K, Yamanishi K. Skin-specific expression of IL-33 activates group 2 innate lymphoid cells and elicits atopic dermatitis-like inflammation in mice. *Proc. Natl. Acad. Sci. U.S.A.*, **110**, 13921–13926 (2013).
 - 51) Salimi M, Barlow JL, Saunders SP, Xue L, Gutowska-Owsiak D, Wang X, Huang LC, Johnson D, Scanlon ST, McKenzie AN, Fallon PG, Ogg GS. A role for IL-25 and IL-33-driven type-2 innate lymphoid cells in atopic dermatitis. *J. Exp. Med.*, **210**, 2939–2950 (2013).
 - 52) Pastore S, Fanales-Belasio E, Albanesi C, Chinnini LM, Giannetti A, Girolomoni G. Granulocyte macrophage colony-stimulating factor is overproduced by keratinocytes in atopic dermatitis. Implications for sustained dendritic cell activation in the skin. *J. Clin. Invest.*, **99**, 3009–3017 (1997).
 - 53) Pastore S, Corinti S, La Placa M, Didona B, Girolomoni G. Interferon-gamma promotes exaggerated cytokine production in keratinocytes cultured from patients with atopic dermatitis. *J. Allergy Clin. Immunol.*, **101**, 538–544 (1998).
 - 54) Nomura I, Goleva E, Howell MD, Hamid QA, Ong PY, Hall CF, Darst MA, Gao B, Boguniewicz M, Travers JB, Leung DY. Cy-

- tokine milieu of atopic dermatitis, as compared to psoriasis, skin prevents induction of innate immune response genes. *J. Immunol.*, **171**, 3262–3269 (2003).
- 55) Ikoma A, Steinhoff M, Ständer S, Yosipovitch G, Schmelz M. The neurobiology of itch. *Nat. Rev. Neurosci.*, **7**, 535–547 (2006).
 - 56) Ständer S, Steinhoff M. Pathophysiology of pruritus in atopic dermatitis: an overview. *Exp. Dermatol.*, **11**, 12–24 (2002).
 - 57) Wahlgren CF, Hägermark O, Bergström R. The antipruritic effect of a sedative and a non-sedative antihistamine in atopic dermatitis. *Br. J. Dermatol.*, **122**, 545–551 (1990).
 - 58) Sonkoly E, Muller A, Lauerma AI, Pivarsci A, Soto H, Kemeny L, Alenius H, Dieu-Nosjean MC, Meller S, Rieker J, Steinhoff M, Hoffmann TK, Ruzicka T, Zlotnik A, Homey B. IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J. Allergy Clin. Immunol.*, **117**, 411–417 (2006).
 - 59) Dillon SR, Sprecher C, Hammond A, *et al.* Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat. Immunol.*, **5**, 752–760 (2004).
 - 60) Arai I, Tsuji M, Takeda H, Akiyama N, Saito S. A single dose of interleukin-31 (IL-31) causes continuous itch-associated scratching behaviour in mice. *Exp. Dermatol.*, **22**, 669–671 (2013).
 - 61) Cevikbas F, Wang X, Akiyama T, Kempkes C, Savinko T, Antal A, Kukova G, Buhl T, Ikoma A, Buddenkotte J, Soumelis V, Feld M, Alenius H, Dillon SR, Carstens E, Homey B, Basbaum A, Steinhoff M. A sensory neuron-expressed IL-31 receptor mediates T helper cell-dependent itch: Involvement of TRPV1 and TRPA1. *J. Allergy Clin. Immunol.*, **133**, 448–460 (2014).
 - 62) Hawro T, Saluja R, Weller K, Altrichter S, Metz M, Maurer M. Interleukin-31 does not induce immediate itch in atopic dermatitis patients and healthy controls after skin challenge. *Allergy*, **69**, 113–117 (2014).
 - 63) Ruzicka T, Hanifin JM, Furue M, Pulka G, Mlynarczyk I, Wollenberg A, Galus R, Etoh T, Mihara R, Yoshida H, Stewart J, Kabashima K. Anti-interleukin-31 receptor A antibody for atopic dermatitis. *N. Engl. J. Med.*, **376**, 826–835 (2017).
 - 64) Wilson SR, Thé L, Batia LM, Beattie K, Katibah GE, McClain SP, Pellegrino M, Estandian DM, Bautista DM. The epithelial cell-derived atopic dermatitis cytokine TSLP activates neurons to induce itch. *Cell*, **155**, 285–295 (2013).
 - 65) Briot A, Deraison C, Lacroix M, Bonnart C, Robin A, Besson C, Dubus P, Hovnanian A. Kallikrein 5 induces atopic dermatitis-like lesions through PAR2-mediated thymic stromal lymphopoietin expression in Netherton syndrome. *J. Exp. Med.*, **206**, 1135–1147 (2009).
 - 66) Oetjen LK, Mack MR, Feng J, *et al.* Sensory neurons co-opt classical immune signaling pathways to mediate chronic itch. *Cell*, **171**, 217–228.e13 (2017).
 - 67) Beck LA, Thaçi D, Hamilton JD, Graham NM, Bieber T, Rocklin R, Ming JE, Ren H, Kao R, Simpson E, Ardeleanu M, Weinstein SP, Pirozzi G, Guttman-Yassky E, Suárez-Fariñas M, Hager MD, Stahl N, Yancopoulos GD, Radin AR. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N. Engl. J. Med.*, **371**, 130–139 (2014).
 - 68) Tobin D, Nabarro G, Baart de la Faille H, van Vloten WA, van der Putte SC, Schuurman HJ. Increased number of immunoreactive nerve fibers in atopic dermatitis. *J. Allergy Clin. Immunol.*, **90**, 613–622 (1992).
 - 69) Sugiura H, Omoto M, Hirota Y, Danno K, Uehara M. Density and fine structure of peripheral nerves in various skin lesions of atopic dermatitis. *Arch. Dermatol. Res.*, **289**, 125–131 (1997).
 - 70) Tominaga M, Takamori K. Sensitization of itch signaling: itch sensitization–nerve growth factor, semaphorins. *Itch: Mechanisms and Treatment*. (Carstens E, Akiyama T, eds.) Chapter 17. Frontiers in Neuroscience, CRC Press/Taylor & Francis, Boca Raton, FL (2014).
 - 71) Murota H, Izumi M, Abd El-Latif MI, Nishioka M, Terao M, Tani M, Matsui S, Sano S, Katayama I. Artemin causes hypersensitivity to warm sensation, mimicking warmth-provoked pruritus in atopic dermatitis. *J. Allergy Clin. Immunol.*, **130**, 671–682.e4 (2012).
 - 72) Feld M, Garcia R, Buddenkotte J, Katayama S, Lewis K, Muirhead G, Hevez P, Plesser K, Schruppf H, Krjtskov K, Sergeeva O, Müller HW, Tsoka S, Kere J, Dillon SR, Steinhoff M, Homey B. The pruritus- and TH2-associated cytokine IL-31 promotes growth of sensory nerves. *J. Allergy Clin. Immunol.*, **138**, 500–508.e4 (2016).
 - 73) Rukwied RR, Main M, Weinkauff B, Schmelz M. NGF sensitizes nociceptors for cowhage- but not histamine-induced itch in human skin. *J. Invest. Dermatol.*, **133**, 268–270 (2013).
 - 74) Mochizuki H, Schut C, Nattkemper LA, Yosipovitch G. Brain mechanism of itch in atopic dermatitis and its possible alteration through non-invasive treatments. *Allergol. Int.*, **66**, 14–21 (2017).
 - 75) Schut C, Mochizuki H, Grossman SK, Lin AC, Conklin CJ, Mohamed FB, Gieler U, Kupfer J, Yosipovitch G. Brain processing of contagious itch in patients with atopic dermatitis. *Front. Psychol.*, **8**, 1267 (2017).
 - 76) Fujii M, Nakamura T, Fukuno S, Mizutani N, Nabe T, Kohno S. Ethanol aggravates itch-related scratching in hairless mice developing atopic dermatitis. *Eur. J. Pharmacol.*, **611**, 92–99 (2009).
 - 77) Fujii M, Takeuchi K, Umehara Y, Takeuchi M, Nakayama T, Ohgami S, Asano E, Nabe T, Ohya S. Barbiturates enhance itch-associated scratching in atopic dermatitis mice: A possible clue to understanding nocturnal pruritus in atopic dermatitis. *Eur. J. Pharmacol.*, **836**, 57–66 (2018).
 - 78) Fujii M, Ohgami S, Asano E, Nakayama T, Toda T, Nabe T, Ohya S. Brain allopregnanolone induces marked scratching behaviour in diet-induced atopic dermatitis mouse model. *Sci. Rep.*, **9**, 2364 (2019).
 - 79) Ebata T, Aizawa H, Kamide R, Niimura M. The characteristics of nocturnal scratching in adults with atopic dermatitis. *Br. J. Dermatol.*, **141**, 82–86 (1999).
 - 80) Kondo H, Ichikawa Y, Imokawa G. Percutaneous sensitization with allergens through barrier-disrupted skin elicits a Th2-dominant cytokine response. *Eur. J. Immunol.*, **28**, 769–779 (1998).
 - 81) 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.*, **18**, 1036–1043 (2009).
 - 82) Kubo A, Nagao K, Amagai M. Epidermal barrier dysfunction and cutaneous sensitization in atopic diseases. *J. Clin. Invest.*, **122**, 440–447 (2012).
 - 83) Howell MD, Kim BE, Gao P, Grant AV, Boguniewicz M, De Benedetto A, Schneider L, Beck LA, Barnes KC, Leung DY. Cytokine modulation of atopic dermatitis filaggrin skin expression. *J. Allergy Clin. Immunol.*, **120**, 150–155 (2007).
 - 84) Seltmann J, Roesner LM, von Hesler FW, Wittmann M, Werfel T. IL-33 impacts on the skin barrier by downregulating the expression of filaggrin. *J. Allergy Clin. Immunol.*, **135**, 1659–1661.e4 (2015).
 - 85) Sawada E, Yoshida N, Sugiura A, Imokawa G. Th1 cytokines attenuate but Th2 cytokines attenuate ceramide production in the stratum corneum of human epidermal equivalents: an implication for the disrupted barrier mechanism in atopic dermatitis. *J. Dermatol. Sci.*, **68**, 25–35 (2012).
 - 86) Kim BE, Leung DY, Boguniewicz M, Howell MD. Loricrin and involucrin expression is down-regulated by Th2 cytokines through STAT-6. *Clin. Immunol.*, **126**, 332–337 (2008).
 - 87) Tominaga M, Ozawa S, Tengara S, Ogawa H, Takamori K. Intraepidermal nerve fibers increase in dry skin of acetone-treated mice. *J. Dermatol. Sci.*, **48**, 103–111 (2007).
 - 88) 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.*, **126**, 976–984.e5 (2010).
 - 89) Cornelissen C, Marquardt Y, Czaja K, Wenzel J, Frank J, Lüscher-

- Firzlauff J, Lüscher B, Baron JM. IL-31 regulates differentiation and filaggrin expression in human organotypic skin models. *J. Allergy Clin. Immunol.*, **129**, 426–433.e8 (2012).
- 90) Singh B, Jegga AG, Shanmukhappa KS, Edukulla R, Khurana Hershey GH, Medvedovic M, Dillon SR, Madala SK. IL-31-Driven skin remodeling involves epidermal cell proliferation and thickening that lead to impaired skin–barrier function. *PLOS ONE*, **11**, e0161877 (2016).
- 91) Nickoloff BJ, Naidu Y. Perturbation of epidermal barrier function correlates with initiation of cytokine cascade in human skin. *J. Am. Acad. Dermatol.*, **30**, 535–546 (1994).
- 92) Paller AS, Kabashima K, Bieber T. Therapeutic pipeline for atopic dermatitis: end of the drought? *J. Allergy Clin. Immunol.*, **140**, 633–643 (2017).