

Immune Dysregulation in the Pathogenesis of Atopic Dermatitis

Tatyana Gavrilova, MD

Atopic dermatitis is a multifactorial disease. Epidermal barrier impairment often plays the initial role in the initiation of the disease. Immune dysregulation of the innate and adaptive immunity plays a central role in the pathogenesis of atopic dermatitis. Alteration of the epidermal microbiome-host interaction serves a catalytic role in propagating this immune response. The understanding of this disease pathogenesis is important in generating treatment options, especially those such as biologic agents that can target a specific immune pathway.

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by an impaired epidermal barrier, immune dysregulation, and epidermal flora dysbiosis. It presents clinically as intense pruritus, erythematous papules, vesicles, and, oftentimes, chronic lichenified plaques. Atopic dermatitis most frequently starts in infancy with a childhood prevalence of 15% to 30%¹ and an adult prevalence of 2% to 10%.^{1,2} Disruption of the skin barrier function is the result of multiple predisposing factors including susceptibility genes, defects in the skin barrier, immunologic aberrations, and alterations of the skin's host-microbiome interactions. Control of the course of disease progression is important not only from a clinical perspective but also for its social impact. Those with AD have significantly higher rates of mood and sleep disorders, as well as loss of work productivity.³ Translating the understanding of disease pathogenesis into practical treatment targets is important because this disease can be very impactful on one's quality of life.

Innate Immunity

Impaired recognition of pathogens secondary to defects in the innate immune system predisposes patients with AD to infections. Keratinocytes express pattern recognition receptors, which are intrinsic in the initiation of the immune response and recognition of pathogenic antigens. Pattern recognition receptors include Toll-like receptors (TLRs), NOD-like receptors, C-type lectin receptors, and RIG-I-like receptors.⁴ Activation of these receptors leads to the production of transcription factors that promote gene expression of proinflammatory proteins such as cytokines that are necessary for protection against pathogens.

For example, TLRs recognize bacterial and fungal components such as lipopolysaccharides (LPS), lipoteichoic acid, and zymosan. Toll-like receptor 2 directly interacts with peptidoglycan derived from *Staphylococcus aureus*, and TLR-2^{-/-} mice are very susceptible to *S. aureus* infection. A study of 78 adult patients with mild to severe AD identified that those carrying the TLR-2 R753Q allele variant exhibited moderate to severe AD as compared with control subjects.⁵

NOD2 is an intracellular receptor that recognizes muramyl dipeptide, a component of the *S. aureus* peptidoglycan cell wall. Expression of NOD2 was found to be significantly down-regulated in AD patients compared with control subjects. In these patients, there was also a lower ex vivo production of important inflammatory mediators such as tumor necrosis factor α , interleukin 6 (IL-6), and CXCL8 upon stimulation with *S. aureus*. NOD2 coactivation with TLR is effective in immunity against organisms such as *S. aureus*. NOD polymorphisms in patients with AD have been associated with an attenuated antibacterial response.⁴

Keratinocytes produce antimicrobial peptides (AMPs), such as defensins, cathelicidins, and calprotectins. The cationic AMPs interact with anionic components of bacteria, fungi, and viruses, resulting in the disruption of microbial membrane integrity and thus playing an important role in innate immunity.⁶ Antimicrobial peptides also induce the production of cytokines and chemokines, which contribute to the recruitment of other immune cells, such as neutrophils, monocytes, and T cells, into the epidermis.⁷ Decreased or dysfunctional AMPs play an important role in cutaneous infections that patients with AD experience.⁸

Interestingly, the commensal flora of skin produces AMPs that have anti-*S. aureus* function. Genome sequencing identified that *Staphylococcus hominis*-derived AMPs are present on the skin of non-AD subjects but diminished in those with AD. *Staphylococcus epidermidis*-derived AMPs were also found to have anti-*S. aureus* activity.⁹ Dysbiosis that is secondary to the skin's already impaired normal antibacterial response that is often present in AD therefore further diminishes a factor of innate immunity and normal skin flora.

Defensins have a broad spectrum of antimicrobial activity against gram-positive and gram-negative microbes. Whereas some

From the Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY.

Address reprint requests to Tatyana Gavrilova, MD, Montefiore Medical Center, Albert Einstein College of Medicine, 3415 Bainbridge Ave, Bronx, NY 10467. E-mail: tgavrilo@montefiore.org.

The author has no funding or conflicts of interest to declare.

DOI: 10.1097/DER.0000000000000340

© 2018 American Contact Dermatitis Society. All Rights Reserved.

defensins are proinflammatory, stimulating keratinocytes to produce cytokines such as IL-6, recruiting dendritic cells and memory T cells, other defensins can attenuate the immune response. Defensins can also prompt the proliferation of keratinocytes, promoting wound healing.⁷ Cathelicidin is a peptide that disrupts bacterial membranes and viral envelopes. This protein also has antifungal activity.⁷ Cathelicidin and defensin deficiency contributes to severe cutaneous viral infections such as eczema vaccinatum and eczema herpeticum.^{10,11}

Calprotectin is a heterodimer of S100A8 and S100A9. It is expressed primarily by granulocytes but also by epithelial cells. This protein has antibacterial properties, but its expression has been found to be up-regulated in AD skin lesions, suggesting that it may be involved in AD inflammation.¹²

Dermcidin is an AMP that is constitutively expressed in eccrine sweat glands and released to the epidermal surface. Analysis of dermcidin in the sweat of patients with AD found that there is a decreased amount of this protein in the sweat of patients with AD as compared with control subjects. This deficiency might predispose patients with AD to skin infections.¹³

Filaggrin (FLG) is a protein produced by keratinocytes and necessary for the structural integrity of the epidermis. Degradation products of FLG contribute to the natural moisturizing factor that is necessary for the maintenance of the skin surface pH and water. Loss-of-function mutation of the *FLG* gene is associated with early-onset AD and a predisposition to bacterial infection.¹⁴ Other proteins have also been implicated in epidermal barrier dysfunction. The expression of loricrin and involucrin, structural proteins of the cornified envelope, is also down-regulated in AD skin.¹⁵

SPINK5 is a gene encoding lymphoepithelial Kazal-type-related inhibitor, a serine protease inhibitor that is necessary for epidermal structural integrity, as well as anti-inflammatory and antimicrobial protection of the epithelium. The autosomal recessive inheritance of this mutated gene results in Netherton syndrome. Heterozygous *SPINK5* mutations are associated with early-onset AD.^{16,17}

The stratum corneum contains an outer lipid layer consisting of long-chain ceramides, cholesterol, and free fatty acids.¹⁸ Ceramides provide a moisture-preserving function in the skin. Decreased lipid synthesis contributes to the barrier dysfunction of AD skin.¹⁹

Microbiome and Biofilm

The skin microbiome consists of a diverse commensal community, with *S. epidermidis* being the dominant gram-positive species. Disruption of this biodiversity allows for the expansion of *S. aureus* growth. The alteration of the skin microbiome is due to the disruption of the skin barrier and accompanying changes in innate immunity, such as decreased expression of AMPs by the commensal bacteria that are toxic to the pathogenic *S. aureus*, thereby predisposing to a shift in the skin flora.²⁰

Cutaneous dysbiosis is a risk factor for AD, with approximately 90% of patients with AD having *S. aureus* colonization²¹ and the methicillin-resistant *S. aureus* prevalence reported to be as high as 26%.²² Skin microbiomes differ between adults and children. The

microbiome of pediatric patients themselves differs drastically from site to site, as well as over time, and there are limited longitudinal studies with these populations. A previous analysis identified that 21% of infants with AD in the first year of life have *S. aureus* colonization. A recent study, however, found that, unlike with previously established AD patients, patients with infantile AD do not have significant skin dysbiosis. Interestingly, this same study found that commensal staphylococci were less abundant in infants with AD at month 12 as compared with control subjects, supporting the argument that early exposure to commensal bacteria is critical for immune regulation and skin homeostasis.²³

The premise of *S. aureus*-driven flares is related to the toxins and proteases produced by the organism that disrupt the immune balance of the epidermis. *Staphylococcus aureus* superantigens are potent polyclonal T-cell activators that generate proinflammatory cytokine release, resulting in AD flares. Although AMPs are an endogenous epidermal mechanism to combat pathogenic bacterial colonization, *S. aureus*-derived proteases can degrade these proteins, neutralizing an important barrier to infection. Biofilms are an added measure of protection that pathogenic bacteria use in evading detection. Biofilm is an extracellular matrix consisting of polysaccharides, proteases, and DNA that can inactivate AMPs. The degradation products of AMPs, such as LL-37, can themselves have proinflammatory effects on the epidermis.¹ Interestingly, although *S. aureus* may be part of the normal skin flora in non-lesional AD skin, specific subtype strains of this organism may be proinflammatory, causing a skewed T-cell proliferation and shifting the response to a T_H2 response, one that is especially important in driving the acute phase of AD.²⁴ This concept is reinforced by the fact that specific clonal staphylococcal species are isolated in lesional skin of flaring AD patients who have a more severe disease.²⁵

Commensal *S. epidermidis* also has an immunoregulatory role in inducing IL-10 secretion and promoting the activity of regulatory T cells, a role that is compromised with the expansion of pathogenic bacteria at the expense of the commensal flora.²⁶

Thymic Stromal Lymphopoietin

Epithelial cells are a major source of thymic stromal lymphopoietin (TSLP). Thymic stromal lymphopoietin is an IL-7-like cytokine that links the innate and adaptive arms of the AD response.²⁷ It is an IL-7-like cytokine due to the fact that its receptor is a heterodimer composed of a chain specific for TSLP and the IL-7R α chain. Its signaling, however, differs from a true IL-7 receptor in that it occurs via the non-JAK-dependent STAT5 phosphorylation pathway.

Thymic stromal lymphopoietin is expressed by epithelial cells at barrier surfaces of the skin, lung, and ocular and gastrointestinal tracts. The receptor for this protein is expressed on a variety of cells including dendritic cells, monocytes and macrophages, and T and B cells. Activated antigen-presenting cells (APCs) then migrate from the epidermis to the draining lymph node and further promote immune activation, particularly favoring the T_H2 response.^{28,29} Although TSLP is constitutively expressed, its up-regulation is

noted in the lesional skin of AD. In addition, this cytokine is also overexpressed in other atopic conditions such as asthma and allergic rhinitis.³⁰

The function of TSLP is varied, and although in AD it has a proinflammatory effect, it can also have a regulatory function such as when it promotes regulatory T-cell production in the gut. Its reduced expression or complete absence is found in the intestinal epithelial cells of those with Crohn disease.³¹

The dichotomy of TSLP function may be explained by its existence in 2 isoforms that have been identified in bronchial epithelial cells. The long isoform of TSLP (lfTSLP) is up-regulated in pathologic conditions. The short isoform of TSLP (sfTSLP), a 63-amino-acid portion of the long TSLP, is constitutively expressed on lung fibroblasts, and its expression is not changed despite antigenic stimulation.²⁷ The expression of sfTSLP has been found to be a stabilizing force in the integrity of airway epithelium, alleviating allergen-induced airway inflammation in contrast to the function of the lfTSLP, which actually damages the epithelial barrier.³² This duality in function was subsequently confirmed on lesional skin biopsies of AD. The sfTSLP is the constitutive and homeostatic isoform in nonlesional skin, whereas the lfTSLP is the proinflammatory isoform predominant in AD lesional skin.³³

Adaptive Immunity

Adaptive immunity is a specialized system of cells that functions in sensitization to antigens and mounting an effector and memory response to these antigens. B cells, T_H2 cells, basophils, eosinophils, and mast cells are some of its member cells, and IL-4, IL-5, IL-9, and IL-13 are the major cytokines of this immune system, as well as IL-25, IL-31, IL-33, and TSLP. Dendritic cells (DCs) are the primary APCs that internalize the antigen and transport it to the draining lymph node. Once in the lymph node, the antigen is processed and presented on major histocompatibility complex class II molecules to CD4⁺ T_H2 cells, which then produce IL-4 and IL-13. This cascade promotes immunoglobulin E (IgE)–isotype class switching of B cells, and this clonal expansion ensures the development of antigen-specific memory T_H2 and B cells.³⁴

Thymic stromal lymphopoietin and IL-33 are important players in initiating the adaptive immune response, linking the innate and adaptive immune systems. Thymic stromal lymphopoietin promotes the migration of DCs to the epidermis, which then induces T_H2 polarization. Langerhans cells are the specialized DCs of the epidermis that express TLRs, FcεRI, and FcγRIII/CD16 receptors. Whereas TLRs recognize antigens, FcεRI and FcγRIII/CD16 respond to antigen-driven antibodies cross-linking IgE and IgG, respectively. This explains how the AD pathogenesis involves both IgE and non-IgE pathways.³⁵

The expression of IL-33, whose role in AD has yet to be fully established, is up-regulated in keratinocytes and endothelial cells in AD. It is a member of the IL-1 family of cytokines whose role in AD has been suggested to function via activation of the ST2

(suppression of tumorigenicity 2)/IL-1 aR receptor on mast cells and T_H2 cells.^{35,36}

T cells, and particularly CD4⁺ T helper cells, play a key role in the continuation of the AD response, responsible for both its acute and chronic phases. T_H2, T_H22, and T_H17 cells are the primary drivers of acute AD, whereas T_H1, T_H2, and T_H22 cells drive the chronic phase of the disease.³⁷

T_H2 cells produce the proinflammatory cytokines that are seen in the initial phases of the acute adaptive response, namely, IL-4, IL-5, IL-13, and IL-31.³⁵ Interleukin 4, IL-13, and IL-5 genes are located on the 5q31 chromosome.^{38,39} Interleukin 4 has a sequence that closely resembles that of IL-13; hence, these 2 cytokines expectedly have overlapping functions. Interleukin 4 induces the differentiation of T_H2 cells and IgE-isotype-switched B cells. The positive feedback loop of this cycle promotes further IL-4 production, which in turn down-regulates the production T_H1 cells. IL-4 also attenuates the expression of the genes coding for FLG, loricin, and involucrin.³⁵ Interleukin 4 gene polymorphism is associated with AD.^{40,41} Single-nucleotide polymorphism of the IL-4 gene, resulting in a base codon substitution of C → T, was detected in the promoter region of the gene in patients with AD. This variant was associated with an increased production of IgE. TT homozygotes were more predisposed to AD than the CT and CC variants. The serum IL-4 levels were significantly higher in the CT and TT carriers as compared with a control group, and the TT variants were highest in the mild, moderate, and severe AD groups.⁴⁰

Interleukin 13 is primarily produced by T_H2 cells and promotes IgE isotype switching of B cells. Inflammation induced by IL-13 contributes to skin fibrotic remodeling and increased vasculature. It also promotes dermal infiltration of CD4⁺ T cells, mast cells, eosinophils, and macrophages.⁴² Murine models have demonstrated an increased number of fibrocytes in IL-13 transgene(+) skin lesions, and cessation of IL-13 transgene expression resulted in reduced skin inflammation.⁴³

Interleukin 4 and IL-13 have also been found to induce periostin expression. Periostin is an extracellular matrix protein that mediates cell activation, proliferation, and angiogenesis. Its role has been described in malignancies, as well as allergic inflammatory diseases such as AD, asthma, and allergic rhinoconjunctivitis. Recently, IL-4 and IL-13 have been found to induce periostin expression, which may also contribute to the tissue remodeling that is seen in the chronic stages of AD.⁴⁴

Interleukin 5 is produced by T_H2 cells and mast cells. This cytokine acts as a growth factor for B cells and eosinophils and is the primary modulator of eosinophil chemotaxis and survival. Interleukin 5 receptor polymorphisms have been found to be associated with an allergic subtype of AD in a Korean patient population.⁴⁵ Interleukin 5 levels were found to also be significantly higher in the serum, as well as skin lesions of patients with AD.

Interleukin 31 is produced by activated T_H2 cells. Its constitutively expressed receptor is expressed on epithelial cells, eosinophils, monocytes, and macrophages. This cytokine promotes the pruritic response that is very prevalent in AD.^{46–48}

Other helper T-cell subsets have been described in association with AD, namely, T_H17, T_H22, and T_H9. T_H17 cells are the source of IL-17, a cytokine that is known to be implicated in the pathogenesis of psoriasis. Recently, it has also been identified in acute and chronic AD lesions. Interleukin 22-producing T_H22 cells promote a similar inflammatory response as the IL-17/T_H17 cells. Increased IL-17 and IL-22 expression has been identified in acute and chronic AD lesions, with acute lesions being associated with a higher IL-22 profile.⁴⁹ Interestingly, pediatric patients showed a higher expression of T_H17 and T_H9 cytokines than adult patients with AD.⁵⁰

The chronic phase of AD is marked by a T_H1, T_H2, and T_H22 polarized response. Increased interferon γ production, a major cytokine produced by T_H1, is identified in chronic AD. This cytokine induces classically activated macrophages, also known as M1 cells that are potent APCs. Although the mechanism of macrophage dysregulation in AD is not yet fully understood, the persistence of proinflammatory cytokines and growth factors secreted by macrophages is described in chronic inflammatory lesions of AD.⁵¹

Interleukin 12 is an interleukin that is produced primarily by APCs, such as DCs and macrophages, in response to antigenic stimulation. It induces interferon γ production, and the expression of IL-12 mRNA was found to be significantly elevated in lesional skin from AD and down-regulated with the use of topical corticosteroids.⁵²

Allergens in AD

Immunoglobulin E sensitization is present in most patients with AD, and it is suggested that this antibody may play a role in the pathogenesis of AD, potentially implicating food allergen sensitization, a possible exacerbating factor of AD. However, as opposed to solely IgE-mediated disease, it is likely that the interplay between IgE and IgE-primed immune cells contributes, at least in part, to the pathogenesis of AD.

The epidermis serves as an important point of contact with external antigens. Animal models have demonstrated that an impaired epidermal barrier predisposes to allergen sensitization and development of protein-specific IgE. Application of ovalbumin (OVA) to disrupted epidermal barrier of mice leads to OVA-reactive T cells in the inguinal lymph nodes and spleen. In addition, OVA-specific IgE and IgG1 antibodies were detected in the sera of these mice 2 weeks after sensitization.⁵³ This suggests that food sensitization occurs via an impaired epidermal barrier, with AD therefore predisposing to a higher risk of food allergen sensitization even without previous food ingestion. Evidence for food elimination diets as a mode of treatment of AD is limited. Many of the studies evaluating food elimination diets in AD are small and poorly designed. This, coupled with heterogeneity of study designs, limits evidence-based conclusions that can be derived from such studies. There is little evidence to support food elimination in unselected AD patients.⁵⁴ There is, however, level 1 evidence that suggests that there is potential for AD improvement when specific

elimination diets are implemented based on food allergy identification based on either percutaneous skin tests (PST), serum IgE levels, or oral provocation tests.⁵⁵

The significance of allergen-specific IgE, however, in mediating the pathogenesis of AD is yet to be fully elucidated because allergen-specific T-cell responses seem to play a direct role in disease pathogenesis. Epicutaneous administration of Bet v 1 allergen was found to induce an allergen-specific cutaneous T-cell response as a positive atopy patch test response, and those subjects who were Bet v 1 IgE positive had a larger increase of allergen-specific T-cell proliferation as compared with Bet v 1 IgE-negative subjects.⁵⁶ Antigen-driven lymphocytic and IgE-mediated reactions therefore may have synergistic roles.

Of note, a subgroup of patients with AD has IgE autoreactivity to human antigens, and this autoreactivity has been reported to be present in a third of study patients with AD.⁵⁷ Although the pathogenic role of this autoimmunity has yet to be determined, the development of autoreactive IgE may be the result of the inflammation and scratching that take place in AD. Self-antigen epitopes are exposed and then identified as new antigens by the host's own immune system, leading to an autoreactive IgE response.

Immune Targets of Pharmacologic Therapy

The mainstay of current AD treatment center on optimizing barrier function with frequent emollient use and the application of topical agents such as corticosteroids and calcineurin inhibitors. Antimicrobial treatments such as topical and systemic antibiotics are beneficial in treating *S. aureus*-associated flares. A recent meta-analysis found limited utility in using bleach baths in reducing AD severity, as compared with regular water baths.⁵⁸

Expansion of the knowledge of the immune mechanisms involved in AD has resulted in the development of new treatment modalities that target specific immune mediators. Crisaborole is a topical phosphodiesterase-4 inhibitor that has shown to be of clinical benefit in mild to moderate AD.⁵⁹

Dupilumab has recently been approved for the treatment of AD. Dupilumab is a human monoclonal antibody against the IL-4 receptor α that inhibits IL-4 and IL-13 signaling pathways. Two phase 3 clinical trials demonstrated its efficacy in improving symptoms of moderate to severe AD in patients 18 years or older.⁶⁰ A clinical trial is currently underway studying its effects in pediatric patients.

Interleukin-31, a potent pruritus-inducing cytokine, has become another target for pharmacologic therapy. Nemolizumab is a humanized antibody against the IL-31 receptor A. A phase 2 trial found that nemolizumab significantly improved pruritus in patients with moderate to severe AD.⁶¹

Tezepelumab is a human monoclonal antibody specific for the epithelial-cell-derived TSLP. It has recently shown success in lowering rates of clinically significant asthma exacerbations for those patients on moderate- to high-dose inhaled corticosteroids.⁶² Tezepelumab is presently in clinical trials being studied for the treatment of AD.

Lebrikizumab, a humanized anti-IL-13 monoclonal antibody, has also demonstrated clinical improvement in patients with asthma⁶³ and is currently in phase 2 clinical trials being studied for its applicability in the treatment of moderate to severe AD.

CONCLUSIONS

Atopic dermatitis is a multifactorial disease for which immune dysregulation plays an important role in its pathogenesis. The aberrant function of the innate immune response, normally a sentinel for the body's immune homeostasis, initiates an inflammatory cascade that is then propagated by the adaptive immunity. A more developed understanding of these pathways yields potential for the development of new treatment agents, some of which are already in use.

REFERENCES

1. Sonesson A, Przybyszewska K, Eriksson S, et al. Identification of bacterial biofilm and the *Staphylococcus aureus* derived protease, staphopain, on the skin surface of patients with atopic dermatitis. *Sci Rep* 2017;7(1):8689.
2. Silverberg JJ, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allergy Clin Immunol* 2013;132(5):1132–1138.
3. Eckert L, Gupta S, Amand C, et al. Impact of atopic dermatitis on health-related quality of life and productivity in adults in the United States: an analysis using the National Health and Wellness Survey. *J Am Acad Dermatol* 2017;77(2):274.e3–279.e3.
4. Bitschar K, Wolz C, Krismer B, et al. Keratinocytes as sensors and central players in the immune defense against *Staphylococcus aureus* in the skin. *J Dermatol Sci* 2017;87(3):215–220.
5. Tsybikov NN, Petrisheva I, Fefelova EV, et al. Expression of TLR2 and TLR4 on peripheral blood monocytes during exacerbation of atopic dermatitis. *Allergy Asthma Proc* 2015;36(6):e140–e145.
6. Aoki W, Ueda M. Characterization of antimicrobial peptides toward the development of novel antibiotics. *Pharmaceuticals (Basel)* 2013;6(8):1055–1081.
7. Marcinkiewicz M, Majewski S. The role of antimicrobial peptides in chronic inflammatory skin diseases. *Postepy Dermatol Alergol* 2016;33(1):6–12.
8. Di Meglio P, Perera GK, Nestle FO. The multitasking organ: recent insights into skin immune function. *Immunity* 2011;35(6):857–869.
9. Nakatsuji T, Chen TH, Narala S, et al. Antimicrobials from human skin commensal bacteria protect against *Staphylococcus aureus* and are deficient in atopic dermatitis. *Sci Transl Med* 2017;9(378).
10. Wollenberg A, Rawer HC, Schaubert J. Innate immunity in atopic dermatitis. *Clin Rev Allergy Immunol* 2011;41(3):272–281.
11. Hata TR, Kotol P, Boguniewicz M, et al. History of eczema herpeticum is associated with the inability to induce human β -defensin (HBD)-2, HBD-3 and cathelicidin in the skin of patients with atopic dermatitis. *Br J Dermatol* 2010;163(3):659–661.
12. Jin S, Park CO, Shin JU, et al. DAMP molecules S100A9 and S100A8 activated by IL-17A and house-dust mites are increased in atopic dermatitis. *Exp Dermatol* 2014;23(12):938–941.
13. Rieg S, Steffen H, Seebert S, et al. Deficiency of dermcidin-derived antimicrobial peptides in sweat of patients with atopic dermatitis correlates with an impaired innate defense of human skin in vivo. *J Immunol* 2005;174(12):8003–8010.
14. Manti S, Amorini M, Cuppari C, et al. Filaggrin mutations and molluscum contagiosum skin infection in patients with atopic dermatitis. *Ann Allergy Asthma Immunol* 2017;119(5):446–451.
15. Kim BE, Leung DY, Boguniewicz M, et al. Loricrin and involucrin expression is down-regulated by T_H2 cytokines through STAT-6. *Clin Immunol* 2008;126(3):332–337.
16. Dezman K, Korosec P, Rupnik H, et al. SPINK5 is associated with early-onset and CHI3L1 with late-onset atopic dermatitis. *Int J Immunogenet* 2017;44(5):212–218.
17. Di WL, Hennekam RC, Callard RE, et al. A heterozygous null mutation combined with the G1258A polymorphism of SPINK5 causes impaired LEKTI function and abnormal expression of skin barrier proteins. *Br J Dermatol* 2009;161(2):404–412.
18. Feingold KR. The outer frontier: the importance of lipid metabolism in the skin. *J Lipid Res* 2009;50(Suppl):S417–S422.
19. Danso MO, Boiten W, van Drongelen V, et al. Altered expression of epidermal lipid bio-synthesis enzymes in atopic dermatitis skin is accompanied by changes in stratum corneum lipid composition. *J Dermatol Sci* 2017;88(1):57–66.
20. Schommer NN, Gallo RL. Structure and function of the human skin microbiome. *Trends Microbiol* 2013;21(12):660–668.
21. Wollina U. Microbiome in atopic dermatitis. *Clin Cosmet Investig Dermatol* 2017;10:51–56.
22. Cavalcante FS, Abad ED, Lyra YC, et al. High prevalence of methicillin resistance and PVL genes among *Staphylococcus aureus* isolates from the nares and skin lesions of pediatric patients with atopic dermatitis. *Braz J Med Biol Res* 2015;48(7):588–594.
23. Kennedy EA, Connolly J, Hourihane JO, et al. Skin microbiome before development of atopic dermatitis: early colonization with commensal staphylococci at 2 months is associated with a lower risk of atopic dermatitis at 1 year. *J Allergy Clin Immunol* 2017;139(1):166–172.
24. Iwamoto K, Moriwaki M, Niitsu Y, et al. *Staphylococcus aureus* from atopic dermatitis skin alters cytokine production triggered by monocyte-derived Langerhans cell. *J Dermatol Sci* 2017;88(3):271–279.
25. Byrd AL, Deming C, Cassidy SKB, et al. *Staphylococcus aureus* and *Staphylococcus epidermidis* strain diversity underlying pediatric atopic dermatitis. *Sci Transl Med* 2017;9(397).
26. Laborel-Préneron E, Bianchi P, Boralevi F, et al. Effects of the *Staphylococcus aureus* and *Staphylococcus epidermidis* secretomes isolated from the skin microbiota of atopic children on CD4⁺ T cell activation. *PLoS One* 2015;10(10):e0141067.
27. Tsilingiri K, Fornasa G, Rescigno M. Thymic stromal lymphopoietin: to cut a long story short. *Cell Mol Gastroenterol Hepatol* 2017;3(2):174–182.
28. Indra AK. Epidermal TSLP: a trigger factor for pathogenesis of atopic dermatitis. *Expert Rev Proteomics* 2013;10(4):309–311.
29. Soumelis V, Reche PA, Kanzler H, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat Immunol* 2002;3(7):673–680.
30. Yi L, Cheng D, Zhang K, et al. Intelectin contributes to allergen-induced IL-25, IL-33, and TSLP expression and type 2 response in asthma and atopic dermatitis. *Mucosal Immunol* 2017;10(6):1491–1503.
31. Aubry C, Michon C, Chain F, et al. Protective effect of TSLP delivered at the gut mucosa level by recombinant lactic acid bacteria in DSS-induced colitis mouse model. *Microb Cell Fact* 2015;14:176.
32. Dong H, Hu Y, Liu L, et al. Distinct roles of short and long thymic stromal lymphopoietin isoforms in house dust mite-induced asthmatic airway epithelial barrier disruption. *Sci Rep* 2016;6:39559.
33. Fornasa G, Tsilingiri K, Caprioli F, et al. Dichotomy of short and long thymic stromal lymphopoietin isoforms in inflammatory disorders of the bowel and skin. *J Allergy Clin Immunol* 2015;136(2):413–422.

34. Palomares O, Akdis M, Martin-Fontecha M, et al. Mechanisms of immune regulation in allergic diseases: the role of regulatory T and B cells. *Immunol Rev* 2017;278(1):219–236.
35. Brandt EB, Sivaprasad U. T_H2 cytokines and atopic dermatitis. *J Clin Cell Immunol* 2011;2(3).
36. Cevikbas F, Steinhoff M. IL-33: a novel danger signal system in atopic dermatitis. *J Invest Dermatol* 2012;132(5):1326–1329.
37. Guttman-Yassky E, Krueger JG, Lebwohl MG. Systemic immune mechanisms in atopic dermatitis and psoriasis with implications for treatment. *Exp Dermatol* 2017;00:1–9.
38. Matsunaga MC, Yamauchi PS. IL-4 and IL-13 inhibition in atopic dermatitis. *J Drugs Dermatol* 2016;15(8):925–929.
39. Yao X, Zha W, Song W, et al. Coordinated regulation of IL-4 and IL-13 expression in human T cells: 3C analysis for DNA looping. *Biochem Biophys Res Commun* 2012;417(3):996–1001.
40. Shang H, Cao XL, Wan YJ, et al. IL-4 gene polymorphism may contribute to an increased risk of atopic dermatitis in children. *Dis Markers* 2016; 2016:1021942.
41. Narozna B, Hoffmann A, Sobkowiak P, et al. Polymorphisms in the interleukin 4, interleukin 4 receptor and interleukin 13 genes and allergic phenotype: a case control study. *Adv Med Sci* 2016;61(1):40–45.
42. Zheng T, Oh MH, Oh SY, et al. Transgenic expression of interleukin-13 in the skin induces a pruritic dermatitis and skin remodeling. *J Invest Dermatol* 2009;129(3):742–751.
43. Oh MH, Oh SY, Yu J, et al. IL-13 induces skin fibrosis in atopic dermatitis by thymic stromal lymphopoietin. *J Immunol* 2011;186(12):7232–7242.
44. Izuhara K, Nunomura S, Nanri Y, et al. Periostin in inflammation and allergy. *Cell Mol Life Sci* 2017;74(23):4293–4303.
45. Namkung JH, Lee JE, Kim E, et al. IL-5 and IL-5 receptor alpha polymorphisms are associated with atopic dermatitis in Koreans. *Allergy* 2007;62(8):934–942.
46. Furue M, Yamamura K, Kido-Nakahara M, et al. Emerging role of interleukin-31 and interleukin-31 receptor in pruritus in atopic dermatitis. *Allergy* 2018;73(1):29–36.
47. Otsuka A, Nomura T, Rerknimitr P, et al. The interplay between genetic and environmental factors in the pathogenesis of atopic dermatitis. *Immunol Rev* 2017;278(1):246–262.
48. Saito S, Aoki A, Arai I, et al. Regulation of T_H2 responses by different cell types expressing the interleukin-31 receptor. *Allergy Asthma Clin Immunol* 2017;13:23.
49. Gittler JK, Shemer A, Suarez-Farinas M, 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): 1344–1354.
50. Esaki H, Brunner PM, Renert-Yuval Y, et al. Early-onset pediatric atopic dermatitis is T_H2 but also T_H17 polarized in skin. *J Allergy Clin Immunol* 2016;138(6):1639–1651.
51. Kasraie S, Werfel T. Role of macrophages in the pathogenesis of atopic dermatitis. *Mediators Inflamm* 2013;2013:942375.
52. Yawalkar N, Karlen S, Egli F, et al. Down-regulation of IL-12 by topical corticosteroids in chronic atopic dermatitis. *J Allergy Clin Immunol* 2000;106(5):941–947.
53. Han H, Roan F, Ziegler SF. The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines. *Immunol Rev* 2017;278(1):116–130.
54. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000;4(37):1–191.
55. Lim NR, Lohman ME, Lio PA. The role of elimination diets in atopic dermatitis—a comprehensive review. *Pediatr Dermatol* 2017;34(5):516–527.
56. Campana R, Moritz K, Neubauer A, et al. Epicutaneous allergen application preferentially boosts specific T cell responses in sensitized patients. *Sci Rep* 2017;7(1):11657.
57. Altrichter S, Kriehuber E, Moser J, et al. Serum IgE autoantibodies target keratinocytes in patients with atopic dermatitis. *J Invest Dermatol* 2008;128(9):2232–2239.
58. Chopra R, Vakharia PP, Sacotte R, et al. Efficacy of bleach baths in reducing severity of atopic dermatitis: a systematic review and meta-analysis. *Ann Allergy Asthma Immunol* 2017;119(5):435–440.
59. Zane LT, Chanda S, Jarnagin K, et al. Crisaborole and its potential role in treating atopic dermatitis: overview of early clinical studies. *Immunotherapy* 2016;8(8):853–866.
60. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med* 2016;375(24): 2335–2348.
61. Ruzicka T, Mihara R. Anti-interleukin-31 receptor A antibody for atopic dermatitis. *N Engl J Med* 2017;376(21):2093.
62. Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med* 2017;377(10):936–946.
63. Hanania NA, Noonan M, Corren J, et al. Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies. *Thorax* 2015;70(8):748–756.