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Atopic eczema: a disease modulated by gene and environment

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1. ABSTRACT

Atopic eczema (AE) is a chronic inflammatory skin disease that is mainly characterized by pruritus and epidermal barrier dysfunction. Between 15% and 20% of children and 1%–3% of adults are affected worldwide. AE is a complex disease triggered by multiple triggers, including gene and environmental factors. Impaired skin barrier function, modifications of the immune system, and hyper-reactivity to environmental stimulation directly cause and aggravate AE. In this review, we provide an overview of the recent developments and future directions in the pathogenesis of AE.

2. INTRODUCTION

Atopic eczema (AE), also known as atopic dermatitis (AD), is one of the most common chronic inflammatory skin diseases with a strong family predisposition occurring worldwide (1,2). Most of the patients with AE are infants; the onset is as early as 2–7 months of age (3). Many people outgrow AE by early adulthood, however, according to the theory of Atopic March, young children with AE may suffer from airway allergy, such as asthma or allergic rhinitis, later in life (4–7).

AE is a multifactorial skin disorder characterized by pruritus, epidermal barrier dysfunction, skin lesions, high susceptibility to allergens and microbes, and an ongoing course of relapse and remission (8–10). According to the nomenclature for AE by the Nomenclature Review Committee of the World Allergy Organization, the term AE should only be used for eczema patients with elevated total serum immunoglobulin E (IgE) levels >150kU/l and IgE-specific sensitization to allergens through an IgE-antibody determination or skin test (11). Other authorities use the term non-atopic eczema with chronic inflammation and skin disorder, but with less of a change in IgE antibody (12,13).

Complex factors contribute to the development of AE. With respect to the genetic aspect, a loss-of-function mutation of filaggrin, which is known as an important gene in the regulation of the epidermal barrier, may increase the risk of AE (14–17). People with AE often exhibit elevated interleukin (IL)-4, IL-5, IL-9, IL-13, and IL-17levels and high-affinity IgE receptors (18–22). In contrast, most AE patients have hyper-reactivity to food or aero allergens, and are always associated with allergic asthma, rhinitis, conjunctivitis, and allergic contact urticaria, and are more vulnerable to microbes and viruses (23,24).However, the exact pathogenesis and the link between other diseases are

far from understood. In this review we discuss the recent developments in the mechanism AE and future directions in this field.

3. EPIDEMIOLOGY OF AE

Different diagnostic guidelines have been proposed for the diagnosis of AE (25).The criteria established by Hanifin and Rajka are the most well-accepted and accurate (26,27); however, the criteria are infrequently used in large epidemiologic studies due to time constraints. Questionnaire studies, such as the International Study of Asthma and Allergies in Childhood (ISAAC), provide a worldwide method for estimation of the prevalence of AE. Although there may be slight deviation as the results vary based on the answers of the individual, the ISAAC questionnaire still has a strong correlation with the findings on clinical examination (28–31).

Currently, 15%–20% of children and 1%–3% of adults are affected with AE worldwide (32,33). According to the Scoring of Atopic Dermatitis (SCORAD), which was developed by the European Task Force of Atopic Dermatitis (ETFAD) to determine the severity of AE, the majority of patients are classified as 'mild,' whereas 10%–20% of patients are 'severe,' and this percentage seems to be higher in the adult AE population. Nearly 60% of patients experience remission (34).

The prevalence of AE has increased significantly in the last decade, reaching >10%of the population in developing countries, with a plateau at approximately 20% in Western countries (30,35). Nigeria, the United Kingdom, and New Zealand have the highest prevalence. Recent research has also shown an increase in AE in Korea, Japan, and India.

4. MOLECULAR BASIS OF AE

4.1 Genetic factors

Recent studies have shown that AE has a strong family predisposition with a phenotype concordance of 0.72–0.77 and 0.15–0.23 in monozygotic and dizygotic twin pairs, respectively, and is highly heritable (2,36).A number of single nucleotide polymorphisms (SNPs) have been described in genes associated with AE, thus highlighting the importance of the genetic component in the pathogenesis of AE. Moreover, genes involved in epidermal barrier differentiation and immune responses have been implicated in AE development.

Filaggrin, derived from filament aggregation protein, is a major protein that facilitates terminal differentiation of the epidermis and formation of the skin barrier (16). A loss-of-function mutation in the filaggrin gene (FLG) has been demonstrated as the most significant genetic factor for the development of AE.

FLG is located in the epidermal differentiation complex on chromosome 1q21 (37), with other genes encoding loricrin and S100 calcium-binding proteins. The product of FLG is profilaggrin, a large, insoluble polyprotein which is expressed in terminally differentiating keratinocytes in the outermost layers of the human epidermis. Profilaggrin is the major constituent of keratohyalin granules in the stratum granulosum. Profilaggrin can be dephosphorylated and cleaved by several endoproteases to produce the functional monomeric filaggrin (38–41).

In mice, loss-of-function mutations of FLG result in the absence or reduction of the FLG protein and lead to a compromised skin barrier that allows the entry of allergens, then triggers immunologic responses. Previous studies have shown that nearly 25%–50% of AE patients have FLG loss-of-function mutations (42,43). The down regulation of FLG leads to a defective skin barrier, which allows external antigens to penetrate the epidermis and initiate immune responses. Since Smith *et al*. (44) first discovered the two loss-of-function mutations, R501X and 2282del4, in 2006, 3321delA, E2422X, S3247X, and R2447 mutations have been identified. The mutations vary within the population and geographic regions and can also occur in patients with ichthyosis vulgaris, psoriasis, asthma, and allergic rhinitis (45,46).

In addition, many AE-associated genes important for inflammation and atopy have been identified. Chromosome 5q31–33 harbors genes, including IL-3, IL-4,IL-5,and IL-13, and granulocyte-macrophage colony-stimulating factor (GM-CSF),which encode Th2 cytokines and regulate IgE production. The 590C/T mutation of the IL-4 gene promoter region increases the transcriptional activity of IL-4, resulting in upregulated pro-inflammatory factors, such as IL-19, IL-20, IL-1α, and IL-25, and downregulated antimicrobial factors, such as interferon (IFN)-γ, S100s, and Toll-like receptors. Polymorphic variants of IL-13 (R130Q and R110Q) have been shown to be associated with atopy.IL-4 and IL-13 can also downregulate FLG expression in patients with AE (47,48).

Signal transducer and activator of transcription 6 (STAT6), encoded on chromosome 12q13–24, is a downstream factor of IL-4 and IL-13.IL-4 and IL-13 can activate STAT6 by a phosphorylation process, making STAT6 able to translocate to the nucleus and bind to target genes to regulate its expression (49–51).Activation of STAT6in AE patients may contribute to the elevated serum IgE level and impaired epidermal barrier. Vladich et al. (52) demonstrated that an IL-13 (R130Q) mutation can induce the phosphorylation and activation of STAT6.Moreover, a very recent study showed SNPs in IL-13 (rs20541) and STAT6 (rs1059513) have a combined effect on the risk of eczema, which revealed the gene–gene interaction in AE.

Many other genes, such as SPINK5, NOD1,NOD2,CCL17,IL-18,CTLA4, and PHF11, also have strong relationships with AE development. There is still much work to be done to better understand the consequences of those mutations and the pathophysiology of AE.

4.2. Skin barrier dysfunction

The epidermis not only functions as a physical barrier, but also an active immunologic organ. It is the first barrier to protect individuals from microbes, allergens, viruses, and toxins from the outer environment. Dry skin and skin lesions, the most significant phenotypes of patients with AE, mainly result from lack of function of the epidermal barrier.

The stratum corneum (SC), the uppermost layer of the skin, consists of flattened keratinocytes, and lipids play a key role in the protective function of the skin. During epidermal differentiation, keratinocytes move from a proliferative cell type in the basal cell layer to flat, dead cell remnants (corneocytes) in the SC. Lipids, such as free fatty acids and cholesterol encompass the corneocytes and protect the skin from water loss (53).

Ceramides, the dominant lipids, make up approximately 50% of the human SC. Lipids play an important role in determination of the permeability barrier and water reservoir of the epidermis. The balance of ceramides is regulated by three sphingolipid hydrolysis enzymes, in which β-glucocerebrosidase (GlcCDase) and sphingomyelinase (SMase) contribute to the synthesis, whereas ceramidase is for the degradation of ceramides (54,55). Thus, the expression and activity of these enzymes could be factors involved with AE. Researchers have discovered that AE patients exhibit reduced levels of ceramides, especially ceramide-1, although one study showed no change in ceramide levels in uninvolved atopic skin. Hara *et al.* (56) have shown that a deficiency in ceramides is linked to the high expression of sphingomyelin deacylase, which can compete with SMase or GlcCDase for a common substrate, sphingomyelin or glucosylceramide.In contrast, the skin of AE patients is frequently colonized by bacteria, especially *Staphylococcus aureus*. The bacteria are likely to secrete significantly more of the ceramidase, but less of the sphingomyelinase in all skin types of AE than healthy patients (57). Faster degradation results, but less synthesis of ceramides and thus a decreased amount of ceramides.

In addition, several proteases located in the SC are associated with AE patients. Proteases not only act as enzymes that conduct hydrolysis of peptide bonds, but also signaling molecules that contribute to increased desquamation and skin barrier dysfunction. Serine protease (SP) can mediate pro-inflammatory effects through protease-activated receptor-2 (PAR-2), induce the secretion of pro-inflammatory cytokines, and result in skin barrier disruption. Three SPs (stratum corneum chymotryptic enzyme [SCCE], stratum corneum tryptic enzyme [SCTE], and stratum corneum cathepsin-L-like enzyme [SCCL]) have been identified in SC and are important for desquamation (58,59). The mutation of an AACC insertion in the 3′UTR of the SCCE gene has been described in some patients with AE (60). This mutation may result in a change in SCCE activity and people with this mutation are more than two times as likely to develop AE as individuals with the normal allele. Moreover, soaps and other detergents can increase skin pH, leading to increased activity of both endogenous and exogenous proteases, which is suspected to induce abnormalities in SC integrity and permeability barrier homeostasis (61).

In contrast, the serine protease inhibitor, Karzal type 5 (SPINK5), is expressed in epidermis and the product of SPINK5, lymphoepithelial Kazal-type-related inhibitor (LEKTI), is a protease inhibitor which inhibits SCTE and SCCE. Mutation of SPINK5 has been implicated in Netherton syndrome, a rare skin disease characterized by greatly elevated IgE levels with atopic manifestations. Several studies have shown that SNPs of SPINK5 are associated with AE patients and the subsequent severe inflammation (62–64).

4.3. Immune system abnormalities

The deficient skin barrier of AE patients facilitates the entry of infectious microbes and allergens into the skin where they encounter immunocompetent cells and initiate rapid innate and adaptive immune responses. Alterations in both innate and adaptive immunity have been described in AE.

4.3.1. Innate immunity

Innate immunity is the first host barrier and antigen-non-specific defense mechanisms can be activated immediately or within several hours after exposure to virtually any foreign agent. The components of innate immune system always focus on pattern-recognition receptors (PRRs), pathogen-associated molecular patterns (PAMPs),and antimicrobial peptides (AMPs). PRRs play a pivotal role in the induction of the innate immune system, and can respond to highly conserved PAMPs shared by many classes of pathogens, including bacterial cell-wall products (such as LPS), peptidoglycan (PGN), and lipoteichoic acid (LTA), the fungal cell wall product zymosan, and viral double-stranded RNA. To discriminate these PAMPs, numerous PRRs have been identified and characterized, such as toll-like receptor (TLRs), C-type lectin receptors (CLRs), CD14, double-stranded RNA binding kinase, and nucleotide-binding oligomerization domain (NOD; 65–67).Stimulation of PRRs by PAMPs will initiate a signal transduction cascade that leads to the release of AMPs, cytokines, and chemokines, which are important for the recruitment of effector leukocytes or have direct antimicrobial effects to limit the infection.

Among these PRRs, TLRs are the most extensively studied, with 11 identified members (TLR1–11). TLRs are expressed on various cells of the innate immune system, including macrophages, dendritic cells (DCs), neutrophils, and mucosal epithelial and endothelial cells. TLRs not only bind to PAMPs, but also recognize newly discovered self-molecules released in response to tissue damage, which are collectively referred to as damage-associated molecular patterns (DAMPs). Ligand recognition induces signal transduction through a myeloid differentiation primary response gene-88 (MyD88)-dependent pathway, activating nuclear factor κB (NF-κB) and resulting in the production of pro-inflammatory cytokines. TLR3 and TLR4 use a MyD88-independent pathway and activate interferon regulatory factor 3, resulting in IFN-β gene expression.

Patients with AE have been shown to have reduced TLR function. TLR2, compared to most other TLRs, can recognize a remarkably broad range of PAMPs and is essential for the response to several pathogens. As TLR2 can recognize components of *S. aureus*, such as LTA and PGN, studies have indicated that TLR2 deficiency may contribute to susceptibility to *S. aureus* and severity of AE. A missense mutation (R753Q) of TLR2 occurs ata frequency of 12% in adult AE patients and is associated with a more severe phenotype, higher serum total IgE levels, and greater susceptibility to *S. aureus* colonization, although there is one study that showed opposite results (68–70). Patients with AE have a significantly lower expression of TLR2, and reduced IL-6, IL-8, and IL-1β pro-inflammatory cytokines released by macrophages. However, one study showed that monocytes/macrophages from AE patients with the TLR2 R753Q SNP produced significantly more IL-6 and IL-12, which may also act as important factors to stimulate T cells and thus initiate the adaptive immune response (71).

Furthermore, an A-16934T mutation in the TLR2 promoter region, which inhibits TLR2 transcription, was identified with an increased secretion of IL-6 and high total serum IgE levels (72). This mutation was significantly overrepresented in individuals with severe AE (SCORAD>50) and was associated with allergic asthma, hay fever symptoms, and recurrent bacterial infections. TLR9, which is found within the endosome, can recognize unmethylated CpG DNA and intracellular viral antigens. Still, no SNPs were found in TLR1, TLR3, and TLR6 with AE (71,73).

NOD, also known as caspase activation and recruitment domain (CARD) are intracellular receptors which can recognize PAMPs, particularly PGN through the C-terminal leucine-rich repeat (LRR) region and trigger the downstream signaling pathway via activation of NF-κB. The NOD family includes five members, among which NOD1 and NOD2 are the most prominent. Keratinocytes express NOD1 and NOD2 can produce IL-6 after stimulation with PGN and AMP, and human β-defensin (HBD) 2 after stimulation with NOD2-specific ligand muramyl dipeptide. Furthermore, NOD1 is located on chromosome 7p14–p15, a region linked to atopy, whereas NOD2 is located on chromosome 16q12, a locus associated with several autoimmune diseases. SNPs of NOD1 (rs2907748, rs2907749, and rs2075822) as well as a NOD2 variant (R702W)are significantly associated with AE and asthma. Moreover, NOD2-deficient mice have impaired clearance of *S. aureus* after subcutaneous or intraperitoneal infection (74–76). Whether or not NOD2 SNPs are correlated with increased susceptibility to epicutaneous *S. aureus* infections in patients with AE needs to be addressed.

In addition, CD14 and mannan-binding lectin (MBL) can respond to PAMPs and have also been shown to be associated with AE development (77). These factors not only contribute to the innate immune system in patients with AE, but also adaptive immunity, which highlights the importance of further study.

4.3.2. Adaptive immunity

The adaptive immune system, also known as the acquired immune system, which consists of highly specialized, systemic cells and processes, eliminates or prevents pathogen growth (78).Acquired immunity is triggered when a pathogen evades the innate immune system in vertebrates (79,80). Acquired immunity creates immunologic memory after an initial response to a specific pathogen, leading to an enhanced response to subsequent encounters with that same pathogen.The cells functioning in the acquired immune system are T and B lymphocytes (81).T cells are intimately involved in cell-mediated immune responses, whereas B cells play a large role in the humoral immune response. Immediately after recognizing foreign antigen in the cellular context, the acquired immune response is activated. The foreign antigen presented by DCs or macrophages induces a complex response, in which $CD8^+$ T lymphocytes directly kill the pathogens, the helper T cells secrete numerous cytokines, such as IFN-γ, to clear the pathogens (82), and B cells produce antibodies to recognize and neutralize specific pathogens.

Many inflammatory skin diseases are thought to be mediated by T cell activation and proliferation in the skin (83). T cells are one of the major elements of adaptive immunity and have acritical role in the pathogenesis of AE (84).The migration of memory and effector T cells to the inflamed skin plays an essential role in the development of atopic skin inflammation. The initial phase of AE is predominated by T helper type 2 (Th2) cytokines, then switches to a more chronic Th1-dominated eczematous phase (85). As such, AE is a biphasic disease. It has been shown that AE patients exhibit characteristic features of dramatic Th2 polarization with high levels of IL-4, IL-5, and IL-13 in the acute phase in both lesional and non-lesional skin in combination with a predominance of Th2 cytokines in the blood (86,87). Increased mRNA expression of IFN-γ, IL-5, IL-12, and GM-CSF is observed in patients with chronic AE, whereas mRNA expression for Th1 cytokines, such as IFN-γ and IL-12,is not detectable in acute AE skin lesions. Based on the different cytokines elaborated during the chronic phase of disease, biphasic AE suggests the initiation of acute skin inflammation by Th2 cytokines and maintenance of chronic inflammation by Th1 cytokines. DCs contribute to allergic sensitization and maintenance of inflammation with the Th2-to-Th1 switch.

An increase number of peripheral blood $CD4^+CD25^+$regulatory T (Treg) cells have been demonstrated in AE patients compared to healthy controls (88,89). Treg cells control the activation of autoreactive and T effector cells and are crucial for the maintenance of peripheral tolerance to self-antigens.The balance between Th2 cells and allergen-specific Treg cells appears to be decisive in the development of

allergy. It has been shown that Treg cells from AE patients markedly inhibit the activation of IL-4-secreting Th2 cells and IFN-γ-secreting Th1 cells stimulated with antigen *in vitro* (90,91).

In addition to T cells, B cells are also involved in the process. Enhanced IgE production by B cells occurs in AE patients. The effective production of IgE in atopic disease by B cells depends on support by Th2 cells. B cells play a critical role in antigen-specific $CD4^+$ T-cell proliferation and Th2 and IL-17 responses in a murine model of AE (86,87). CD19 expression of B cells has been found to play an important role in AE. Compared to T cells, however, the role of B cells in AE needs further exploration. Taken together, the important role of the adaptive immune system in AE has been clarified, which provides targeted therapies for the treatment of AE (86,87).

5. MICROBES AND FOOD ALLERGY IN AE

AE is frequently complicated by recurrent skin infections with bacterial, viral, and mycotic pathogens. The role of microbial superinfections has not been fully elucidated, but there is a general consensus that bacterial superinfections, in part due to impaired innate immunity, play a critical role in the clinical course of skin lesions (92).*S. aureus* colonization of both lesional and clinically uninvolved skin in AE has been demonstrated to increase significantly and exacerbate the disease (57). Greater than 90% and 76% *S. aureus* colonization has been demonstrated in lesional and non-lesional skin of AE patients, respectively, whereas <10%*S. aureus* colonization is associated with healthy skin (93–95).A previous study concluded that *S.aureus* colonization is both a cause and a consequence o allergic skin inflammation. Patients developing AE exhibit impaired skin barriers, increased synthesis of extracelluar matrix adhesions for *S.aureus*, reduced skin lipid content, increased skin surface pH, and defective innate immune responses, which lead to a significant increase in *S.aureus* colonization (96). In contrast, the exotoxins secreted by *S.aureus* are superantigens which could be recognized by large numbers of different T cells via interaction with the major histocompatibility complex (MHC) II and β-chain of the T cell receptor. Skin immune response activating and cytokines releasing (tumor necrosis factor (TNF)-α, IFN-γ, IL-1, IL-4, and IL-12) can in turn cause severe inflammation (97). Moreover, anti-inflammatory agents can reduce skin *S.aureus* colonization and is recommended for AE control.

Malassezia is a monophyletic genus of fungi that belongs to the normal cutaneous flora. Fourteen species are currently recognized, among which *M. sympodialis* has been reported to be associated with AE and can also cause systemic infections (98). Of adult AE patients, 30%–80% are reactive to *M. sympodialis* in terms of specific IgE and T cell reactivity. Products, such as zymosan, can be recognized by TLR2 and activate mast cells, leading to the release of potent inflammatory mediators, such as histamine, proteases, chemotactic factors, cytokines, and arachidonic acid metabolites (99). In addition, *M. sympodialis* can activate mast cells to release cysteinyl leukotrienes, enhance the mast cell IgE response, modulate MAPK activation, and alter IL-6 production by signaling through the TLR2/MyD88 pathway. Thus, it may have effects on inflammation and itching in AE (100,101).

In contrast, extracelluar vesicles secreted by *M. sympodialis* containing antigens and allergens from the fungi can induce a significantly higher IL-4 response in AE patients. All of this evidence indicates *M. sympodialis* may have a role in pathogenesis and severity of AE (102).

In addition, clinical studies have revealed that >50% of all children with AE can experience exacerbations triggered by certain foods (103–105).Food allergy and AE often occur in the same patient. While different foods affect people differently, it has been shown that foods, such as cow's milk and hen's eggs, can directly provoke flares of AE, particularly in sensitized infants, whereas inhaled allergens and pollen-related foods are of greater importance in older children, adolescents, and adults. Three patterns of cutaneous reactions to food may occur in patients with AE upon oral challenge. The first pattern commonly occurs a few minutes after ingestion of food, without exacerbation of AE, with the onset of gastrointestinal, respiratory, and cardiovascular symptoms. In the second pattern, pruritus occurs soon after ingestion of food, with subsequent scratching leading to an exacerbation of AE. In the third pattern, exacerbations of AE occur after 6–48 h; these exacerbations are termed late reactions (106-109). Reliable markers for the identification of patients with food-responsive eczema are still lacking. Based ona straightforward history, diagnosis of immediate symptoms provoked by a food may be evident, which is further confirmed by diagnostic tests to detect food-specific IgE antibody. Determination of the role played by food allergy in patients with AE is more difficult and may require additional diagnostic maneuvers, including elimination diets and oral food challenges (107,110). Further investigations and clinical studies need to be conducted to clarify the relationships between foods and AE.

6. CONCLUSION

AE is a common skin inflammatory disease with complex genetic and environmental factors that affects an increasing number of people worldwide. Fortunately, efforts from scientists have provided us much evidence in understanding this disease. Gene mutations, skin barrier abnormalities, dysfunction of the innate and adaptive immune systems, microbes, and allergens are important factors for the development and exacerbation of AE (Figure 1).These findings not only allow us to develop a precise definition of AE, but also have a great impact on clinical therapy. However, more studies are needed to discover interactions between those factors and the

subsequent signaling

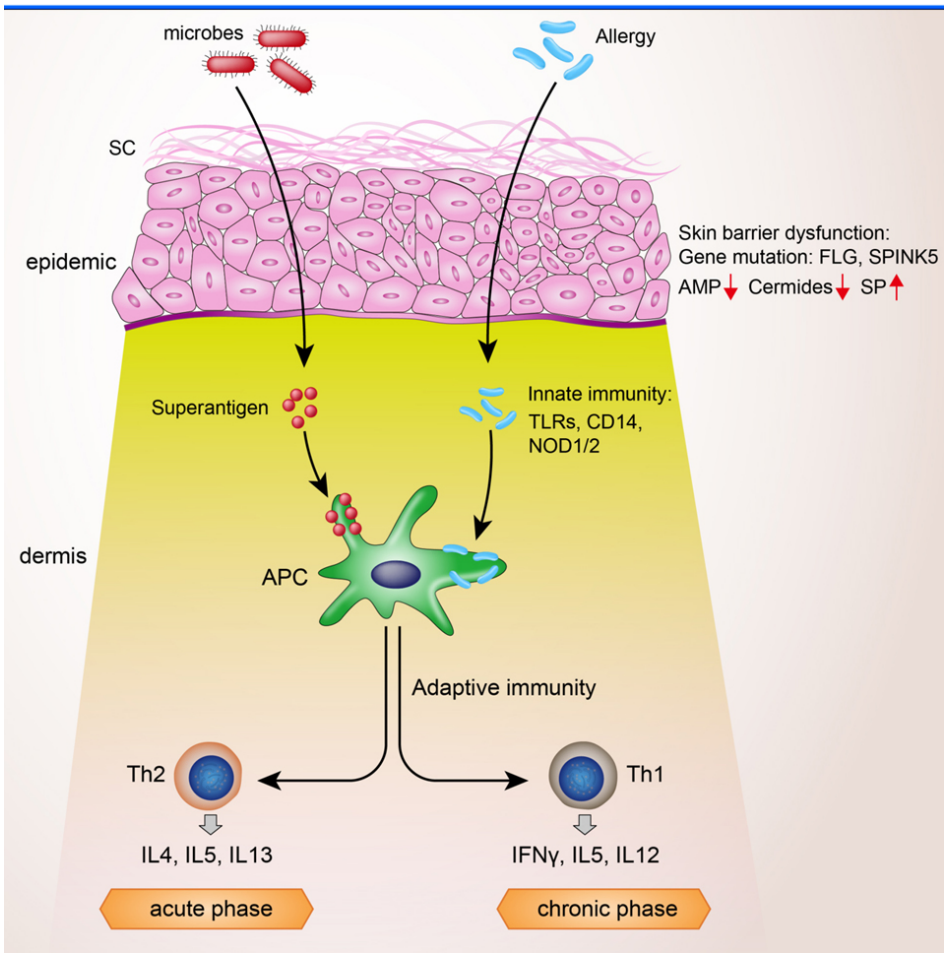

Figure 1. Important factors for the development and exacerbation of AE: Gene mutations, skin barrier abnormalities, dysfunction of the innate and adaptive immune systems, microbes, and allergens.

transduction pathways. It is hoped that specific biomarkers can be identified to reflect the detailed pathogenesis for AE, which is important in providing an early diagnostic strategy and targeted therapy for affected individuals.

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Abbreviations: AE, atopic eczema; AD, atopic dermatitis; IgE, immunoglobulin E; IL, interleukin; ISAAC, International Study of Asthma and Allergies in Childhood; SCORAD, Scoring of Atopic Dermatitis; SNPs, single nucleotide polymorphisms; FLG, filaggrin gene; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon;PAR-2, protease-activated receptor-2; SPINK5, Karzal type 5;SCCE, tratum corneum chymotryptic enzyme; SCTE, stratum corneum tryptic enzyme; SCCL, stratum corneum cathepsin-L-like enzyme; PRRs, pattern-recognition receptors; PAMPs, pathogen-associated molecular patterns; AMPs, antimicrobial peptides; PGN, peptidoglycan; LTA, lipoteichoic acid; TLRs, toll-like receptors; CLRs, C-type lectin receptors; DCs, dendritic cells; DAMPs, damage-associated molecular patterns; NF-κB, nuclear factor κB; MyD88, myeloid differentiation primary response gene-88; CARD, caspase activation and recruitment domain; HBD, human β-defensin; MBL, mannan-binding lectin; MHC, major histocompatibility complex; TNF, tumor necrosis factor

Key Words: Atopic eczema, Skin Diseases, Genetic Factors, Immune System Abnormalities, Microbes, Review

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