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Pathogenesis of atopic dermatitis: A short review

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Abstract: Atopic dermatitis (AD) is the most common inflammatory skin disease in children, may persist into adulthood, and is difficult to treat. Recent data in both experimental models and patients have shed new light on the multifactorial etiology of this chronic disease. In this review, we summarize the pathomechanism of AD in the following three sections: (1) defects in skin barrier including the role of filaggrin; (2) the immunological response of patients including key roles of T cells, dendritic cells, innate lymphoid cells, mast cells, and eosinophils; and (3) environmental factors such as the role of skin microbiota including *Staphylococcus aureus*.

Subjects: Allergology & Clinical Immunology; Dermatology; Immunology

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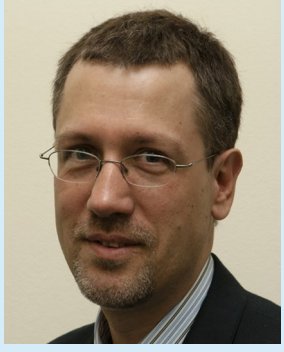
1. Introduction

Atopic dermatitis (AD), also known as atopic eczema, is a recurring inflammatory skin disease characterized by xerosis (dry skin), variably distributed eczematous lesions, intense pruritus, and high serum immunoglobulin (Ig) E levels (Dokmeci & Herrick, 2008; Leung, Boguniewicz, Howell, Nomura, & Hamid, 2004; Nutten, 2015). AD usually develops during early infancy, but sometimes persists into or starts in adulthood. It is evident that AD is the cutaneous manifestation of a systemic disorder; infant AD is often the initial indication of "atopic march" which leads to asthma, food allergy, and allergic rhinitis (hay fever).



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Wolfgang Weninger received his training in clinical dermatology at the Department of Dermatology, Medical University Vienna, Vienna, Austria. He then spent four years at Harvard Medical School, where he investigated the mechanisms of immune cell migration *in vivo*. Between 2003 and 2007, Weninger was a faculty member at the Wistar Institute and the Department of Dermatology, University of Pennsylvania, USA. In 2007, he was appointed Chair of the Discipline of Dermatology, Sydney Medical School, Sydney, Australia. He also heads the Immune Imaging Program at the Centenary Institute, Newtown, NSW, Australia. Weninger's research focuses on understanding the molecular basis of immune cell migration as well as immune cell interactions with pathogens and cancer cells. His group makes use of advanced imaging technology, primarily intravital two-photon microscopy, in a variety of infectious and tumor models.

PUBLIC INTEREST STATEMENT

Atopic dermatitis (AD) is a chronic, itchy skin disease that often starts in early childhood. The underlying causes of AD include genetic and immunologic factors. A lot of progress has been made in our understanding of these factors over the last few years. This review summarizes what we have learned about the pathogenesis of AD.

Clinically, the morphology and distribution of eczema in AD patients varies with age (Spergel & Paller, 2003): infants (birth to 2 years of age) typically present with erythematous papules and vesicles on the cheeks, forehead, and scalp, whereas children (2 years of age to puberty) exhibit dry skin and lichenified papules and plaques in flexural areas of the limbs. In adulthood, the predominant areas of eczema are the flexural folds, the face and neck, the upper arms and back, hands, feet, fingers, and toes. Pruritus, or itching, is another cardinal feature of AD. Patients often experience a characteristic itchy skin (alloknesis), an abnormal sensory state wherein normally innocuous stimuli elicit itching.

Over the last few years, a lot of insight has been obtained into the factors that contribute to the pathogenesis of AD. Here, we will review major developments in the dissection of the immunological, environmental, and intrinsic cues underlying this chronic skin disease.

2. Epidemiology

The International Study of Asthma and Allergies in Childhood is the most comprehensive worldwide survey of atopic diseases in childhood (covering 2 million children in 98 countries) (Mallol et al., 2013). The latest report in 2013 revealed that the world average prevalence for AD in the 6–7-year-age group was 7.9%, although there was a large variety in prevalence between regions; the lowest prevalence values were found in the Indian subcontinent (3.0%) and Eastern Mediterranean (4.8%), with intermediate values in North and Western Europe (6.0–8.6%), Africa (9.5%), Asia-Pacific (10.2%), and North America (10.3%), and the highest value in Oceania (17.0%). The prevalence of concurrent symptoms of AD also varies between world regions. The prevalence for the concurrence of asthma varied from 19.0% in Asia-Pacific to 37.8% in Oceania, while the concurrence of allergic rhinitis was ranging from 19.6% in Northern and Eastern Europe to 32.0% in Latin America. While the prevalence of AD appears to have reached plateau in most developed countries, it is still increasing in developing countries (Deckers et al., 2012). Importantly, wide variations in prevalence have been observed within countries inhabited by groups with similar genetic backgrounds, suggesting that environmental factors play a critical role in driving disease progression.

3. Intrinsic and extrinsic AD

Although most AD patients exhibit high serum level of IgE, a subgroup of AD patients represents normal IgE level. This subgroup is classified as “intrinsic AD” (other terms used are “non-allergic AD” or “non- atopic AD”) (Tokura, 2010). The term “intrinsic AD” has been proposed as a counterpart to the term “extrinsic AD,” in analogy to extrinsic and intrinsic types of bronchial asthma (Bruijnzeel, Hamelink, Prins, Remmert, & Meyling, 1988). The frequency of intrinsic AD is reported 10–40% of all AD patients (Simon, Simon, Akdis, & Wüthrich, 2001). Although the clinical manifestation of intrinsic AD is indistinguishable from that of extrinsic AD, intrinsic AD has the following main features: (1) normal serum IgE levels and (2) absence of other atopic disease. The two forms of AD might have a different pathomechanism, although this has not been fully elucidated.

4. Pathogenesis of AD

Various studies indicate that AD has a complex etiology. The clinical manifestation of AD is the product of manifold interactions between genetic, immunologic, and environmental factors. A precise understanding of the relative role of these factors in the pathogenesis of AD is critical for the development of effective management strategies.

4.1. Barrier dysfunction in AD

The main function of the skin is to form a physical and chemical barrier against external noxae. Thus far, at least three causes of barrier dysfunction in AD patients have been considered: (1) defect in the expression of the filaggrin gene, (2) decrease in skin ceramides, and (3) overactivation of epidermal proteases. Genome-wide association studies have identified several additional genetic risk loci relating to epidermal barrier function (reviewed in Tamari & Hirota, 2014). The role of these individual genes in the pathogenesis of AD requires further investigation.

4.1.1. Filaggrin deficiency in AD

In 2006, direct evidence of a strong link between the incidence of AD and loss-of-function variants in the FLG gene (encoding filaggrin protein) was discovered (Palmer et al., 2006; Smith et al., 2006). Up to 50% of AD patients carry FLG mutations, and more than 20 mutations in the FLG gene have been described so far (Irvine, McLean, & Leung, 2011). Filaggrin has a crucial role in skin barrier integrity; it cross-links keratin filaments into tight bundles and moisturizes stratum corneum (upper most layer of the epidermis) through its derivatives called natural moisturizing factors (Rawlings & Harding, 2004). Animal models of filaggrin deficiency have demonstrated an exacerbated percutaneous penetration of both hapten and protein antigens, which resulted in exaggerated immune responses (Kawasaki et al., 2012).

Of note, it was reported that patients with intrinsic AD lack barrier disruption and/or FLG gene mutation (Tokura, 2010; Weidinger et al., 2006). Thus, it is expected that barrier disruption, as represented by FLG gene mutations, is a feature of extrinsic AD.

4.1.2. Ceramide deficiency in AD

Ceramide is a lipid which is important for water retention in stratum corneum (Lampe et al., 1983). In AD patients, a marked reduction of ceramides in the lesional skin compared to healthy individuals was reported (Imokawa et al., 1991). Interestingly, non-lesional skin also exhibited a significant decrease of ceramides in AD patients. The significance of ceramides in cutaneous permeability barrier was evidenced by an inversed correlation between transepidermal water loss and the levels of ceramides in stratum corneum of AD patients (Imokawa, 2002). Consistently, impaired water-holding capacity and barrier function were reported in the skin of ceramide-deficient mice (Nakajima et al., 2013).

In contrast to filaggrin, ceramide deficiency is not considered as an inherent factor of AD patients. In infant AD patients, ceramide levels are decreased in lesional skin but not in non-lesional skin compared to healthy controls (Imokawa & Ishida, 2014), perhaps indicating that the decreased level of ceramide in AD patients is a post-inflammatory event. Indeed, no loss-of-function mutation was reported in ceramide-related genes in AD patients.

4.1.3. Overactivation of epidermal proteases in AD

The human kallikrein (KLK)-related peptidases such as KLK5, KLK7, and KLK14 are key proteases for corneocyte desquamation (Suzuki, Nomura, Koyama, & Horii, 1994). The activity of these proteases is pH dependent and is enhanced when pH in the stratum corneum is elevated. In addition, their activity is strictly regulated by a cocktail of protease inhibitors, including lymphoepithelial Kazal-type 5 serine protease inhibitor (LEKTI) encoded by the serine protease inhibitor Kazal-type 5 (*SPINK5*). *SPINK5* is known as a responsible gene for Netherton syndrome in which patients display a broad range of allergic manifestations such as AD-like dermatitis, food allergy, asthma, hay fever, and markedly elevated serum IgE levels (Chavanas et al., 2000). In addition, *SPINK5* has been identified as being associated with AD (Moffatt, 2004). These observations suggest that overactivation of epidermal proteases and subsequent hyper-desquamation of corneocytes can induce AD-like dermatitis.

4.2. Immunological factors

Regarding immunological aspects, the pathogenesis of AD is quite complicated because the development of eczema is orchestrated by both the adaptive and innate immune systems. Skin-resident cells such as keratinocytes, dendritic cells (DCs), mast cells, macrophages, and innate lymphoid cells (ILCs) contribute to skin inflammation in AD patients (Tay, Roediger, Tong, Tikoo, & Weninger, 2014). In addition to these cells, T cells, plasmacytoid dendritic cells (pDCs), monocytes, and granulocytes, which are recruited from blood circulation, also contribute to eczema formation (Weninger, Biro, & Jain, 2014). Although complex interaction of immune cells mediates AD skin lesions, the immunopathogenesis of AD is characterized by the tendency toward Th2-skewed responses. Indeed, recent clinical trials demonstrated the potential benefit of dupilumab, a monoclonal antibody against IL-4 receptor-α, to the management of AD (Beck et al., 2014). In the next sections, we review some immune subsets which play a major role in the development of AD skin lesions.

4.2.1. T cells

T cells are one of the major players of adaptive immunity and have a critical role in the pathogenesis of AD. It is now considered that the pathomechanism of many immune-mediated diseases can in large part be explained by the relative balance of different types of T helper cells, such as Th1/Th2/Th17 cells (Wan, 2010). Th1 cells are induced by IL-12 and produce interferon (IFN)-γ, and contribute to cell-mediated immunity, while Th2 cells, producing IL-4, IL-5, and IL-13, are responsible for humoral immunity and antibody production. Th17 cells are induced by IL-23 and provide protection in certain infections via producing IL-17A, IL-17E, and IL-22.

The immune response observed during the course of AD is characterized by a biphasic inflammation (Grewe et al., 1998). A Th2-skewed immune response is predominant in the acute phase, but is then switched to a more Th1-like profile in the chronic phase. It was reported that both acute and chronic phases of AD lesions contain a significant amount of Th2 cytokines compared with normal skin; however, chronic lesions are associated with less IL-4 and IL-13 production and enhanced IL-5 and IL-12 production (Hamid et al., 1996). These observations suggest that maintenance of chronic AD lesions may be associated with the predominance of Th1 cells and eosinophils infiltration.

The infiltration of Th17 cells in AD skin lesion has also recently been reported (Koga, Kabashima, Shiraishi, Kobayashi, & Tokura, 2008). Th17 cells infiltrate more markedly in acute than chronic lesions. IL-17 enhances the production of IL-6 and IL-8 from keratinocytes (Teunissen, Koomen, de Waal Malefyt, Wierenga, & Bos, 1998), induces neutrophil recruitment, and modulates fibroblast function (Kolls & Lindén, 2004). Although direct evidence has not yet provided, a role for IL-17 in AD is possible. Indeed, successful use of ustekinumb, a monoclonal antibody against IL-12 and IL-23, in severe AD has been reported (Shroff & Guttman-Yassky, 2015).

Regulatory T cells (Tregs) are another important modulator of skin immune responses. Previous studies reported marked increase of Tregs in the peripheral blood of AD patients (Ito et al., 2009; Samochocki et al., 2012) as well as in the skin lesions (Szegedi et al., 2009). One interesting notion is that Tregs in AD patients appear to decrease their immunosuppressive activity when they are activated by superantigens from *Staphylococcus aureus* (*S. aureus*) (Ou, Goleva, Hall, & Leung, 2004). This observation may contribute to *S. aureus*-mediated augmentation of skin inflammation in AD patients.

4.2.2. Dendritic cells

DCs play a crucial role in the early events of AD. Because of the impaired skin barrier function, foreign antigens readily penetrate into the epidermis and dermis, where they are taken up by cutaneous DCs. Two different types of epidermal DC populations have been described in AD lesions: Langerhans cells (LCs) and infiltrating inflammatory dendritic epidermal cells (IDECs) (Johnson-Huang, McNutt, Krueger, & Lowes, 2009). Both types of cells express high levels of Fc epsilon receptor I (FcεRI), the high affinity receptor for IgE, on their surface. Therefore, LCs and IDECs could potentially respond to numerous antigens in an antigen-specific manner, using the FcεRI-bound IgE molecules, leading to efficient capturing and processing of allergens/antigens.

After the initial contact of DCs with antigens in the skin, they migrate to the draining lymph nodes and present antigens to naïve T cells. In this process, DCs direct T cell differentiation by expressing specific surface molecules (MHC, co-stimulatory molecules) and producing cytokines. Indeed, it was shown that LCs activated by FcεRI drive naïve T cells into Th2 cells (Novak et al., 2004). In addition, a recent report demonstrated that LCs highly express the receptor for thymic stromal lymphopoietin, which plays a critical role in Th2-skewing, and mediate the development of AD (Nakajima, Miyachi, & Kabashima, 2011).

Of note, an additional type of DC, called pDC, has been described, which produces large amounts of type I interferon (IFN-α and IFN-β). Intriguingly, lesional skin samples from patients with psoriasis

vulgaris and contact dermatitis contained high numbers of both IDECs and pDCs, but only very few pDCs could be detected in AD lesions (Wollenberg et al., 2002). This selective lack of pDCs may predispose AD patients to cutaneous viral infections.

4.2.3. Innate lymphoid cells

ILC are newly identified innate immune cells involved in skin immunity (Kim et al., 2014; Roediger, Kyle, Le Gros, & Weninger, 2014). ILCs are currently categorized into three distinct populations based on their developmental requirements and cytokine production: group 1 ILCs (ILC1s) are T-bet-dependent IFN-γ- and TNF-α-producing ILCs; RORα-dependent, GATA3-expressing group 2 ILCs (ILC2s) producing IL-4, IL-5, and IL-13; and RORγt-dependent group 3 ILCs (ILC3s), producing IL-17A, and/or IL-22. These ILC groups are analogous to the relationship of Th1, Th2, and Th17 cells, although they can respond to innate signals in the absence of antigen specificity.

In the lesional skin of AD patients, ILC2s are highly enriched (Kim et al., 2013; Salimi et al., 2013) . In addition, ILC2s were found to be both necessary and sufficient for the development of AD-like disease in mice (Roediger et al., 2013). Their function is supposed to be regulated by keratinocyte-derived cytokines such as IL-25 (IL-17E), IL-33, and TLSP (Monticelli, Sonnenberg, & Artis, 2012). Furthermore, ILC2s express IL-4 receptor-α and basophil-derived IL-4 critically regulates ILC2 proliferation in the context of AD-like inflammation (Kim et al., 2014). Of note, ILC2s were found to selectively interact with mast cells *in vivo* and appear to suppress mast cell function via producing IL-13 in the steady state (Roediger et al., 2013). In contrast, activated ILC2s produce IL-5 and induce the recruitment of eosinophils to the skin. Taken together, these studies demonstrated novel regulatory and proinflammatory functions in AD pathogenesis.

4.2.4. Mast cells

The role of mast cells in AD pathogenesis is controversial. Mast cells express the high-affinity IgE receptor (FcεRI) and release various kinds of proinflammatory mediators upon activation. Increased mast cell numbers and activation were reported in the chronic skin lesion of AD (Kawakami, Ando, Kimura, Wilson, & Kawakami, 2009). Although they are generally considered effector cells of skin inflammation, immunosuppressive roles of mast cells have also been demonstrated in mouse AD models. Hershko et al. (2011) reported that mast cell-deficient ($Kit^{W-sh/W-sh}$) mice showed exacerbated dermatitis in oxazolone-induced AD model compared to mast cell-sufficient controls. They also revealed that the immunosuppressive function is mediated by mast cell-derived IL-2. This observation is consistent with the notion that mastocytosis (an aberrant systemic proliferation of mast cells) is not associated with higher incidence of AD (Gonzalez de Olano et al., 2007).

4.2.5. Eosinophils

Although eosinophilia is often observed in AD patients, the role of eosinophils in the pathogenesis of AD has not been established. The Th2 cytokine IL-5 induces chemotaxis and activation of eosinophils. During flares of AD, the serum levels of IL-5 and eosinophil chemoattractants, such as eotaxin, are elevated (Hossny, Aboul-Magd, & Bakr, 2001). In addition, the presence of high amounts of eosinophil-associated cytokines such as eosinophil cationic protein and major basic protein deposits in AD lesion suggest eosinophil degranulation in the skin (Kay, Barata, Meng, Durham, & Ying, 1997). A recent study demonstrated that keratinocyte-specific overexpression of IL-33 is sufficient to induce AD-like skin lesion in mice (Imai et al., 2013). Intriguingly, in addition to the accumulation of ILC2s in the skin, marked skin infiltration of eosinophils was observed in this model. This observation implies that ILC2s play a role in eosinophil recruitment to the skin.

4.3. Environmental factors

Significant variations in the prevalence between world regions suggest that environmental factors, such as climate, diet, obesity, smoking rates, and microbial exposure, could influence the development of AD.

4.3.1. Microbial exposure

Recent studies highlighted the impact of skin microbiota on AD because microbiota have been revealed to be involved both in the homeostasis and pathogenic conditions of the skin (Naik et al., 2012). In AD patients, temporal dybiosis dominated by *S. aureus* during disease flares was reported (Kong et al., 2012; Leyden, Marples, & Kligman, 1974). The skin commensal *S. epidermidis* also significantly increased during flares. In contrast, *Streptococcus*, *Propionibacterium*, and *Corynebacterium* species were increased post-therapy. In addition, in a mouse model which presents AD-like skin lesions, significant dysbiosis with prominent *S. aureus was* observed (Kobayashi et al., 2015). Furthermore, antibiotic treatment specific for *S. aureus* almost completely reversed dysbiosis and eliminated skin inflammation in this model. These studies suggest that an important role of *S. aureus* and/or dysbiosis during active atopic inflammation. This exacerbation of skin inflammation may be mediated by superantigens, such as staphylococcus enterotoxins-A and -B, and toxic shock syndrome toxin (TSST)-1, which cause polyclonal activation of T cells (Baker, 2006).

Several studies showing that the early gut microbiota of children who develop AD later in life are different from that of children who do not develop AD, both in terms of composition and diversity (Wang et al., 2008; Watanabe et al., 2003). In addition, systemic antibiotic treatment was reported to increase the risk of AD (Tsakok, McKeever, Yeo, & Flohr, 2013), which may be linked to microbiota changes in the intestine. These observations suggest that gut microbiota might be involved in AD pathogenesis, potentially through stimulation and education of immune cell populations.

4.3.2. Climate factors and smoking habit

Previous studies provide evidence that climate factors such as temperature, humidity, and UV exposure influence on the prevalence of eczema in AD patients. In particular, combined high UV exposure and temperature appear to have protective effects in eczema development, whereas combined high humidity and precipitation are associated with more eczema (Silverberg, Hanifin, & Simpson, 2013).

It was reported that smoking habit is not a risk factor of AD (Mills et al., 1994). On the other hand, passive smoking is known to increase bronchial responsiveness and symptoms in children. Indeed, maternal smoking appears to be a risk factor for wheezy illness in children with AD (Murray & Morrison, 1990).

4.3.3. Skin pH

The skin has an acidic pH (known as acid mantle) which contributes to the barrier function of this tissue (Cork et al., 2006). It has a strong antibacterial effect and controls corneocytes' desquamation. Previous reports showed that a total body pH increases in the patients with AD (Ring et al., 2000; Seidenari & Giusti, 1995), which might exacerbate AD skin lesions. The most common environmental agents that affect skin pH are soap and other detergents. Washing the skin with soap causes elevation of skin pH, emulsification of skin surface lipids, enhancement of skin proteases, and subsequent thinning of stratum corneum (White, Jenkinson, & Lloyd, 1987).

5. Interaction between pathogenetic factors

As described above, AD is a multifactorial, heterogeneous skin disorder resulting from complex interactions between genetic, immunologic, and environmental factors. Therefore, it is important to consider how these pathogenic factors are influenced by each other and modify AD symptoms (Figure 1).

Impaired epidermal barrier allows enhanced penetration of external antigens and readily induces skin inflammation. This facilitates the interaction of external antigens with the local antigen-presenting cells and immune effector cells and may lead to the elicitation of systemic immune responses. This line of thought is called the "outside-in hypothesis," explaining the association between AD and an increased risk of developing asthma, food allergy, and allergic rhinitis (atopic march).

On the other hand, human keratinocytes differentiated in the presence of Th2 cytokines such as IL-4 and IL-13 exhibited significant reduction of FLG gene expression (Howell et al., 2007). In addition,

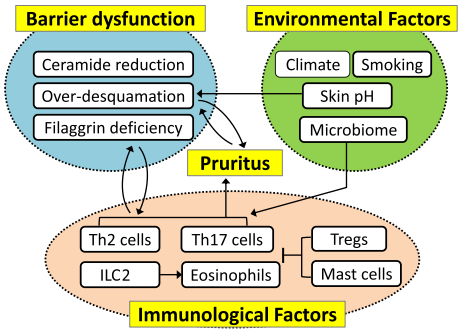

Figure 1. Interplay among barrier dysfunction, immunological factors, environmental factors, and pruritus in AD pathogenesis.

IL-17A treatment also downregulates the expression of FLG *in vitro* (Gutowska-Owsiak et al., 2012). Consistently, the level of FLG expression in AD patients was decreased even without carrying FLG mutations (Howell et al., 2007). These reports suggest that the atopic inflammatory state induces an acquired barrier dysfunction via, at least in part, FLG downregulation ("inside-out hypothesis"). This positive feedback loop between Th2/Th17 inflammation and barrier dysfunction might explain the chronic inflammatory feature of AD.

Interaction between pruritus and barrier dysfunction is evident since scratching directly disrupts skin barrier functions. In addition, barrier dysfunction, in turn, induces growing of intraepidermal nerve fibers via increasing epidermal nerve growth factor levels (Tominaga, Ozawa, Tengara, Ogawa, & Takamori, 2007). Pruritus is also influenced by skin immunological factors. It is well known that cyclosporine efficiently suppresses the pruritus in AD patients, probably by suppressing the production of IL-31, a pruritogenic Th2 cytokine, from T cells (Sonkoly et al., 2006).

6. Conclusion

AD has become a significant public health issue because of its increasing prevalence and increasing evidence showing that it may progress to "atopic march." A better understanding of its pathogenesis must be imperative for better treatment and prevention of AD.

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Competing interests
The authors declare no competing interest.

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