Pathogenesis of Atopic Dermatitis: New Developments

Thomas Bieber, MD, PhD, and Natalija Novak, MD

Corresponding author
Thomas Bieber, MD, PhD
Department of Dermatology and Allergy, Rheinische Friedrich-Wilhelms-University Bonn, Sigmund-Freud-Str. 25, D-53105 Bonn, Germany.
E-mail: Thomas.Bieber@ukb.uni-bonn.de

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Atopic dermatitis (AD) is a paradigmatic skin disease in which multiple gene–gene and gene–environment interactions play a pivotal role. Although the complex pathophysiologic network of AD explains the large spectrum of risk and trigger factors, it is far from being comprehensively understood. Hence, genetic modifications underlying the dysfunction of the epidermal skin barrier as well as the close interaction of innate and adaptive immune mechanisms were the focus of intensive research studies. This review aims to summarize the most recent findings in this field.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease, which results from the interaction of genetic, environmental, and immunologic factors. Based on the current disease concept, various deficiencies, modified activation stages, and functions of a plethora of cells (ie, keratinocytes/dendritic cells and their precursors T cells, B cells, effector cells, and eosinophils) in the skin and blood of AD patients act in concert and contribute to the manifestation, the severe course, and frequent flare-ups of the disease. Furthermore, an imbalance of T-helper type 2 and type 1 (Th2/Th1) immune responses as well as deficient defense machinery of innate and adaptive immunity represent additional pieces to the complex pathophysiologic puzzle of AD.

The Genes Behind the Epidermal Barrier Dysfunction

It is well accepted that AD emerges on the background of two different sets of genes. In principle, the first group of genes is linked to the target organ (ie, the epidermal compartment), whereas the second group of genes is related to the modulation of immune mechanisms (ie, T-cell responses, antigen presentation, or regulation of the IgE synthesis). The most exciting discovery concerning a genetic predisposition for AD was the identification of a series of loss-of-function mutations in the gene encoding (Pro-) filaggrin (*FLG*) [1••]. The strong and nicely reproducible associations of about 30 different *FLG* mutations with AD described subsequently in several studies around the world [2] clearly highlight the correlation of genetic variants in the *FLG* gene with subtypes of AD, in particular AD with early onset and a more severe, chronic course, a high number of allergic sensitizations [3,4], and AD-related asthma [2]. In this context, it is remarkable that the association between *FLG* mutations and asthma manifestation in patients with AD, but not in asthma patients without AD, represents one of the first genetic hints in support of the highly debated concept of the atopic march.

In addition, specific environmental factors are supposed to interact with the genetic predisposition determined by *FLG* mutations, such as early cat exposure, which was shown to increase the risk for eczema development during the first year of life exclusively in mutations carriers [5•].

Despite its impact on compaction of keratinocyte filaments to maintain the mechanical skin barrier in the stratum corneum, degradation products (ie, hygroscopic amino acids of filaggrin) can act as natural moisturizing factors [6•]. As a consequence, reduced amounts of filaggrin in the skin of mutation carriers may further impair dryness of the skin and thereby abet skin barrier defects. Moreover, it is important to mention that up to 7% of the normal population carries *FLG* variants [2]. Some evidence suggests a correlation between the occurrence of contact hypersensitivity reactions (ie, irritative hand eczema and sensitization to nickel) and the presence of *FLG* variants, even in individuals without AD or any atopic predisposition [7,8]. Furthermore, dry skin and skin barrier impairment promoted by a filaggrin deficiency does not only originate from genetic modifications, because inflammatory reactions and a Th2-dominated micromilieu in the skin may secondarily downregulate the expression of filaggrin proteins even in individuals without *FLG* mutations [9•]. Thus, there may be a synergistic effect of both the genetic predisposition and factors in the

skin environment related to AD, decreasing the filaggrin expression and thereby aggravating the dysfunction of the epidermal barrier, particularly in patients with AD. Together, these insights ultimately amend our knowledge about factors leading to skin barrier dysfunction and emphasize the role of the skin as a port of entry for allergens and subsequent development of allergic sensitizations and inflammation.

Besides the issue of *FLG*, it is supposed that a genetically driven imbalance of the qualitative and quantitative nature of proteases and antiproteases in the skin, such as the serine peptidase inhibitor, kazal type 5 (*SPINK5*) or the kallikrein-related peptidase 7 (*KLK7*), exists [10,11]. More recent evidence also emerged for the involvement of other epidermal structures, such as the epithelial tight junction protein Claudin-1 in the epidermal barrier function [12]. Claudins control the permeability of epithelial cells for water and other soluble components or immune cells. Reduced expression of Claudin-1 has been observed in AD, and polymorphisms in the gene region encoding Claudin-1 (*CLDN1*) were shown to be associated with AD [12]. Therefore, we may have to reconsider our conceptual view of factors leading to disturbed physical barrier function in AD, which were so far mainly limited to components located in the upper stratum corneum, but should potentially also include components located in deeper parts of the skin. In addition, the relevance of recently described associations of genes encoding other structures putatively involved in the skin barrier function, such as epidermal collagen 29 (*COL29*) [13] or a genetic variant on chromosome 11q13 (previously shown to be associated with Crohn's disease [14•]), needs to be further evaluated on the genetic and functional level. Additionally, many novel genetic and epigenetic modifications, which may act in concert with mechanisms involved in the disturbed epidermal skin barrier function in AD, are expected to be identified soon, in part due to a high range of upcoming innovative technologies in this field.

Disturbance of the Innate Immune System of the Skin

Major progress has been made in the past few years concerning the dissection of mechanisms of the innate immune system involved in the control of microbial attacks. It became clear that keratinocytes are able to produce several antimicrobial peptides (AMPs), which may potentially cover a wide range of protective effects against microbes of relevance in AD, including *Staphylococcus aureus*, *Candida albicans*, herpes simplex, or vaccinia virus [15,16]. At the first line of defense, recognition of microbes is mediated by the Toll-like receptors (TLRs) and other pattern recognition receptors expressed by different skin cells. In this regard, it represents a plausible hypothesis that genetic modifications leading to functional changes of these structures may profoundly alter the capacity of the organism to sense the environment for foreign structures, which may impede protective immune functions. Variants in gene regions encoding some of these recognition receptors and their downstream signal transduction pathways have been highlighted in AD. For example, associations of polymorphisms of the *TLR2* gene with AD and increased risk for staphylococcal infections were described by some authors, whereas no association of *TLR2* polymorphisms with AD was observed in another study [17–19]. Furthermore, a polymorphism in the gene region encoding *TLR9* was shown to be associated with pure AD and may impact on the promoter activity [20].

As previously mentioned, numerous keratinocyte-derived AMPs have been described, including S100 proteins, cathelicidin (LL-37), human defensins (hBD1-3), sphingosine, and dermcidin, and also expressed, in part, in normal skin but released in high amounts by skin cells after stimulation with inflammatory mediators [21]. Whereas the antimicrobial protein psoriasin (S100A7) was shown to be upregulated after mechanical damage in AD [22], reduced levels of AMPs have been detected in acute and chronic skin lesions of AD compared with one other inflammatory skin disease, such as psoriasis or contact dermatitis [21,23]. This downregulation was most likely induced by high levels of interleukin (IL)-10 and Th2 cytokines in the skin microenvironment of AD [21]. Another important aspect in the regulation of the synthesis and production of LL-37 by keratinocytes discovered recently is the level of vitamin D3, which is known to be induced by inflammation and infections and promotes upregulation of LL-37. Considering the debate about a putative pathophysiologic relevance of a vitamin D3 insufficiency in AD, vitamin D3 level in the skin and therapeutic vitamin D3 supplementation could represent critical cofactors modulating antimicrobial activity of AMPs in AD [24•]. Overall, it is important to note that some of the AMPs such as LL-37 need to be cleaved by proteases in order to become biologically active. This highlights the role of a critical balance between proteases and antiproteases (which are produced by keratinocytes and by *S. aureus*) such as aureolysin, which inactivates LL-37 [25,26•]. Finally, AMPs are not only involved in the control of microbial infections, but display chemotactic activities and thereby link innate and adaptive immune responses [27,28].

The Role of the Epidermal Compartment in the Induction of the IgE Response

There is evidence from animal models for a critical role of the skin in the outcome of the T-cell response in the context of IgE-mediated allergic reactions. It is assumed that acute and chronic inflammation in the skin impacts the adaptive immune system and may be responsible for the initiation and continuation of a Th2 response. Thereby, the thymic stromal lymphopoietin (TSLP)—an IL-7–like cytokine produced in high amounts by keratinocytes in response to microbes, trauma, and inflammation—plays

an important role [29]. Dendritic cells (DCs) primed by TSLP may convert to strong inducers of T-cell responses of the Th2 type [30]. Together, enhanced TSLP release triggered by frequent allergen challenge, microbial infections, and inflammation may initiate and perpetuate Th2 immune responses in AD. Therefore, TSLP represents a promising new therapeutic target of immunopharmacologic developments. Besides TSLP, mediators produced by pollen grains, the so-called PALMs (pollen-associated lipid mediators), are suspected to affect DCs by reducing their ability to produce the Th1 immune responses driving cytokine IL-12 upon antigen presentation [31]. Therefore, it is tempting to speculate that TSLP, the pollen-derived PALMs, and other signals act in concert to enforce a Th2-driven immune reaction in AD. Furthermore, IL-21 and IL-21R expression was demonstrated to be upregulated in skin lesions of mice and humans after allergen application or mechanical damage and was shown to play role in the trafficking of DCs to the draining lymph nodes and initiation of the allergic immune response [32•]. This novel pathway may represent another target for therapeutic approaches aimed at attenuating the allergic inflammatory reaction in the skin.

Among T cells infiltrating the inflamed skin, it has been suggested that the so-called Th17 cells may be operative not only in psoriasis but also in AD. Indeed, some reports from animal models and studies using atopy patch tests in humans have suggested that Th17 may be induced in the skin by the topical application of allergens and could also in part contribute to skin infection in AD [33,34]. However, the role of Th17 cells remains controversial because it has been shown that compared with psoriasis, the contribution of Th17 cells to AD is rather weak.

It is well accepted that histamine is not instrumental in inducing pruritus in AD. In contrast, IL-31 has been proposed to be one of the key cytokines, able to induce itch in AD and other diseases such as allergic contact dermatitis [35,36]. IL-31 is mainly produced by skin-homing T cells expressing cutaneous lymphocyte antigen, and IL-31 production can be aggravated by stimulation of these T cells by *S. aureus* superantigens in vivo and in vitro [35]. In addition, a polymorphism of the *IL31* gene has been reported to be associated with the intrinsic form of AD [37]. Interestingly, in animal models the administration of anti–IL-31 improves the scratching behavior but does not impact the clinical phenotype (ie, erythema and infiltration) [38]. Overall, IL-31 will certainly be considered as a new target for strategies aimed at controlling pruritus, not only in AD, but also in various other chronic inflammatory skin diseases.

The Natural History of Atopic Dermatitis: Revised

Attempts have been made to subdivide AD in extrinsic/IgE-mediated and intrinsic/nonatopic dermatitis according to the presence or absence of sensitization in these patients. However, in view of epidemiologic studies, which highlight the fact that in more than 50% of infants affected by the disease, sensitization is absent but emerges after several months or years after the onset of skin inflammation, this binary view has to be carefully reconsidered [39]. One approach to redefine AD subtypes could be to create a more chronological classification of AD [40] consisting mainly of three different disease stages/subtypes: 1) in early infancy, the disease starts as nonatopic dermatitis without detectable sensitizations [39]; 2) in 60% to 80% of the cases, development of sensitization and production of specific IgE to food and/or environmental allergens follows, which reflects the classical form of AD; and 3) it cannot be excluded that IgE to self-proteins is the hallmark of a third state of the disease, in which IgE-autoreactivity is of major pathophysiologic relevance as a kind of intrinsic trigger factor. The emergence of autoreactive mechanisms may explain, in part, why some patients suffering from very severe forms of AD typically fail to improve under allergen avoidance strategies.

Conclusions

AD is one of the most important subjects in dermatologic research, with many pathogenic pathways still left to be elucidated. Skin barrier impairment and disturbance of the innate immune system seem to be key factors, which promote development of sensitizations to allergens in early childhood. On the other hand, systemic immune deviation represents an important prerequisite for sensitization and disease development. Therefore, future research will have to consider the complex interplay of epidermal components with the adaptive immune system. Rapidly increasing knowledge about the molecular basis of AD will hopefully allow the development of novel, rational-based therapeutic strategies, with a high benefit for the patients.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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