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Advances in Atopic dermatitis

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Abstract

Atopic Dermatitis (AD) results from barrier defects combined with modified immune responses of the innate and the adaptive immune system to exogenous and endogenous factors. Recent research has continued to sort out the complex pathophysiologic puzzle of this frequent skin disease. However, the network of mechanisms leading to the manifestation of AD is far from being completely understood. Nonetheless, there is evidence that common mechanisms are shared by a majority of patients, while individual disease-triggering pathways might be dominant in particular subgroups of AD patients. Thus, detailed knowledge about the pathophysiologic pathways underlying this disease is essential for the development of mechanism-based, therapeutic approaches.

Introduction

The interplay of a multitude of factors leads to manifestations of the most frequent chronic inflammatory skin disease in the western world, called atopic dermatitis (AD). AD is characterized by acute flare ups as well as chronic eczematous pruritic skin lesions over dry skin. It is caused by an impaired skin barrier, complex immune dysregulation and amongst other factors, IgE-mediated mechanisms [1]. It has been a matter of debate for a long time, whether the disturbed skin barrier, which is a characteristic feature of AD, or the hyperreactive immune system on the other hand represent a primary or secondary cause of this disease. Arguments for a strong role of a genetically predetermined skin barrier disturbance came largely from the discovery of associations of loss-of function mutations in the pro-filaggrin (*FLG*) gene with AD. Pro-filaggrin is an important precursor of filaggrin, a key structural protein of the upper epidermal layer. Genetic associations of *FLG* mutations with AD were confirmed and further verified by many independent groups using numerous cohorts of Caucasian and Northern-American AD patients. These studies defined *FLG* mutations as the strongest genetic association with AD described so far. Furthermore, loss-of function mutations in the *FLG* gene predispose AD patients to sensitization with environmental factors, and leads to severe chronic AD, peanut allergy [2], hand eczema [3] or development of asthma in AD patients [4,5].

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In addition to the function of filaggrin in bundling keratin filaments and compaction of the upper epidermis, filaggrin degradation products are a source of natural moisturizing factor (NMF) in the stratum corneum. Although the level of NMF, including urocanic acid (UCA) and pyrrolidone carboxylic acid (PCA) is reduced in AD independently from *FLG* mutations, the *FLG* mutation status tightly determines the level of NMF reduction [6,7]. It has also been hypothesized that the lower acidification of the skin caused by reduced filaggrin metabolites acts on skin barrier impairment in AD as well. In this context it has been demonstrated that UCA and PCA reduce growth rates of *Staphylococcus aureus* (*S. aureus*) by lowering the secretion and expression of cell wall proteins necessary for its colonization and immune evasion [8]. Thus, reduced filaggrin levels due to *FLG* mutations might secondarily enhance the rate of *S. aureus* colonization and thereby increase the severity of AD.

However, since only one third of AD patients have been identified as *FLG* mutation carriers, other genetic and environmental co-factors might additionally act on skin barrier function [9]. In line with this assumption, a genome wide association study revealed the association of a common variant on chromosome 11q13 as well as a variant on chromosome 1q21 with AD [10]. The association of the chromosome 11q13.5 variant with AD has been confirmed in independent cohorts for childhood eczema [11] as well as allergic asthma and hay fever [12]. Since the same risk allele had been reported to be associated with Crohn's disease, this genetic modification might go along with chronic epithelial inflammation and barrier dysfunction in general. However, further functional analyses are required to elucidate the exact relevance of genetic modifications in AD. The second associated region on chromosome 1q21 encodes a protein important for keratinocyte differentiation, named hornerin, with quite similar functions to filaggrin. Recently, it has been demonstrated that hornerin is present in the epidermal cornified envelope, which together with presumed lower hornerin expression in AD skin points to another possible genetically predetermined skin barrier defect of the stratum corneum in AD [13]. In general, the physical skin barrier consists of two parts, the stratum corneum and tight junctions, which are important components for paracellular passage of soluble mediators and keratinocyte function. Reduced expression of claudin-1, which belongs to a family of transmembrane proteins in AD skin has been demonstrated and has been linked to AD by association of a single nucleotide polymorphism in the gene region encoding claudin-1 [13]. This genetic modification might lead to barrier dysfunction and predispose certain AD patients to disseminated viral skin infections [14].

Features of lesional and non-lesional skin

Not only lesional, but also clinically non-lesional skin of AD patients is different from healthy skin. Lower hydration, modified lipid synthesis, decreased epidermal differentiation and infiltration of T cells have been described as characteristic features in the past. More detailed insights into the differences in terminal differentiation and immune responses have been reported in recent genomic and histologic profiling approaches, comparing lesional versus non-lesional AD skin within the same individuals [15]. Increased epidermal thickness and proliferation as well as a dermal infiltrate consisting of CD3⁺ T cells and CD11c⁺ DCs characterizes non-lesional AD skin. A panel of genes encoding proteins involved in the epidermal proliferation process are downregulated in lesional AD skin as opposed to healthy non-AD skin. Moreover, expression of Th1, Th2 and T22 proteins is increased even in non-lesional AD skin. In contrast, cytokine and chemokine genes consistent with allergic inflammation are directly related to severity of AD, and upregulated in non-lesional AD skin, but further induced in lesional AD skin. Additionally, epidermal skin barrier protein expression including filaggrin-2, coneodesmosin, desmoglein-1, desmocollin-1, transglutaminase-3 as well as arginase-1, caspase-14 and gamma-glutamyl-cyclotransferase

as components of natural moisturizing factor generation are lower in lesional than in non-lesional AD skin [16]. Beyond, the immunologic importance that allergens, such as mite allergens have in stimulating effector cells and antigen presenting cells, allergens also activate keratinocytes. House dust mite allergens activate caspase-1 related release of IL-1 β and IL-18 by skin keratinocytes and activate the inflammasome via the nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin-domain containing 3 (NLRP3) [17]. The inflammasome is a central part of the innate immune system, detecting and mediating danger signals. Based on this data, deficient signaling via the inflammasome pathway might be of pathophysiologic relevance in AD. Furthermore, attenuated toll-like receptor (TLR)2 mediated signaling and release of proinflammatory cytokines, chemokines or matrix metalloproteinases by primary keratinocytes from AD patients has been described. Together, modified functions of keratinocytes might promote inflammation in response to allergens or microbial components in AD [18]. Beyond, eczema formation it has been observed to go along with enhanced activation and apoptosis of keratinocytes. Among other factors, the tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK) has been shown to be overexpressed in keratinocytes in lesional AD skin [19]. Moreover, expression of the fibroblast growth factor-inducible 14, the receptor for TWEAK, was enhanced in AD skin as well. This suggests a role for TWEAK in keratinocyte death leading to spongiosis and eczema development.

A Role for Soluble Factors in the Circulation and the Skin

In a majority of AD patients, total serum IgE serum and allergen specific IgE are increased. It is still unclear, however, whether serum IgE represents just a co-factor of the disease or directly impacts relevant pathways in AD. Support for the latter hypothesis comes from observations gained in patients with Hyper-IgE syndrome (HIES), an immunodeficiency which is accompanied by frequent *S. aureus* infections as well as eczema. A high number of HIES patients carries STAT3 mutations and monocytes and monocyte-derived DCs generated from those patients display a reduced capacity to respond to IL-10. Consequently, they fail to induce a regulatory DC phenotype and Foxp3⁺ T regs from naïve T cells *in vitro*. This attenuated protolerogenic pathway exemplifies in which direction *S. aureus* driven superinfections might contribute to uncontrolled skin inflammatory mechanisms [20]. Another interesting connection between *S. aureus* and IgE-mediated mechanisms in AD arises from the identification of an IgE-reactive DNA clone, which encodes *S. aureus* derived fibronectin-binding protein [21]. Experiments with recombinant fibronectin binding protein revealed that induction of T cell reactivity requires antigen presentation of the fibronectin binding protein. The connection between IgE reactivity to *S. aureus* components mediated by antigen presenting cells further explains the multiple ways in which *S. aureus* and its products might serve as important amplifiers of the disease [22].

Since the discovery of increased TSLP expression in the epidermis of lesional AD, TSLP is regarded as another important co-factor, capable of enhancing the Th2 polarizing properties of DCs in allergic skin inflammation [23]. TSLP is expressed constitutively in epithelial cells such as keratinocytes. Interestingly, it has been shown recently that simple mechanical injury is capable of upregulating TSLP levels in the skin in mouse models, subsequently leading to an increased Th2 immune response driven by TSLP-activated skin DCs [24]. Based on this model, chronic skin injury, e.g induced by scratching, might elicit Th2 immune response. This further aggravates the course of AD causing a vicious circle between scratching, mechanical damage, TSLP activation and Th2 upregulation. Moreover, TSLP not only activates DCs and B cells but also invariant natural killer cells *in vitro*, which secrete enhanced levels of IL-4 and IL-13 in response to TSLP stimulation [25]. These T cells express both the semi-invariant T cell receptor (TCR) and the NK cell receptor

(CD161) linking innate and adaptive immunity by their cytotoxic functions [26]. However, whether invariant NK cells play a role in AD remains to be elucidated.

Secondary factors modifying DC function

Myeloid DC subtypes in the skin have been identified to play a key role in allergen uptake and antigen stimulation [27]. DC activated with wash fluid derived from AD lesions released several proinflammatory cytokines [28]. Lipoteichoic acid derived from *S. aureus* has been identified as the main component responsible for this effect. These results point to the role of bacterial infections in triggering AD by activating skin DCs. Moreover, the tetraspanins CD9 and CD81, which have been demonstrated to be highly expressed by epidermal DCs in lesional AD might amplify FcεRI activation on DC *in vivo* [29]. Tetraspanins exert their functions mainly by regulating cell-type specific protein-protein interactions, which might occur even independently and even without binding of exogenous ligands to the tetraspanins itself. Thus, association of CD9 and CD81 with FcεRI on human antigen presenting cell might co-regulate and amplify FcεRI mediated signals *in vivo* and explain in part the versatile functions of FcεRI on human DCs.

Lower IFN-γ receptor expression and attenuated IFN-γ response of skin DCs and their precursor cells might represent another important co-factor leading to attenuated Th1 driven immune responses in AD [30]. A modified responsiveness of skin DCs in AD to Th1 stimuli might in part explain the attenuated Th1 immune responses despite presence of a significant amount of Th1 cytokines as well as strong Th1 stimuli in the cellular microenvironment.

Experiments with enriched epidermal Langerhans cells, inflammatory dendritic epidermal cells as well as blood-dendritic cells antigen-1 positive and negative DCs from lesional AD skin, skin of psoriasis patients and healthy volunteers revealed a similar constitutive capacity of those cells to induce Th1, Th2, Th17 and Th22 driven immune responses in allogeneic responder cells *in vitro* [31].

The data suggests that unstimulated skin DCs might have the capacity to prime all types of T cell responses. Genetic background, factors in the microenvironment related to the respective skin disease and within the lymphatic organs, nature of stimulating antigens, concomitant FcεRI activation and numerous other factors might *in vivo* secondarily direct the nature of the T cell responses induced. Due to the constitutive capacity to induce various Th cell responses, this might be a target for therapeutic strategies with the aim of counteracting certain types of Th immune responses by inducing antagonistic T cells by the same source of skin DCs.

Nature of the T cell infiltrate

During eczema development, CD4⁺ Th cells have been regarded as key cells responsible for allergic inflammation of the skin, since high levels of these cells infiltrate into skin lesions. However, recent data from mouse models as well as biopsies taken from atopy patch test induced skin lesions in humans reveal that in addition to CD4⁺ T cells and natural killer T cells, CD8⁺ T cells might play a pivotal role for the development of eczema, since their number increases immediately after allergen application mostly in the dermis, but also in the epidermis [32]. Moreover, although a subpopulation of CD4 Th cells infiltrating the skin lesions expresses the forkhead-box transcription factor (Foxp)3, which is expressed by regulatory T cells as well, they are not immunosuppressive, but display functions of effector Th2 cells [33] after stimulation with *S. aureus* enterotoxins *in vitro*. Furthermore, the concept of Th1/Th2 driven immune responses in AD has been recently revised and extended to Th17 cells, which may play a role in allergic inflammation as well. IL-4⁺/IL-17⁺ T cells have been demonstrated to increase in acute AD, while IL-17 levels are low in chronic AD skin but IL-22 producing Th22 cells might play a role in this phase. In particular *S. aureus*

alpha toxins induce IL-17 and IL-22 production of T cells *in vitro* [34,35]. The relative absence of IL-17 in chronic AD might promote increased susceptibility to bacterial infections in AD. However, since constitutive capacity of keratinocytes in AD to upregulate antimicrobial peptide expression in response to IL-17 stimulation *in vitro* is not modified [36], cofactors in the skin microenvironment such as Th2 cytokines with antagonistic functions to IL-17 might contribute to the attenuated expression of antimicrobial peptides in AD. IL-22 has been demonstrated to contribute to the impaired skin barrier by reducing terminal keratinocyte differentiation and downregulating filaggrin and profilaggrin processing enzymes [37,38]. In this context, the cytokine IL-17E, also known as IL-25 has been demonstrated to be released by dermal DCs in AD. This is of critical immunological importance, since IL-25 enhances Th2 immune responses and reduces filaggrin synthesis thereby impairing the skin barrier [39]. Thus, IL-25 represents an important link between modified skin barrier function and dysfunction at the level of adaptive immune responses in AD.

A role for microRNAs, which are capable of regulating the expression of genes which encode proteins posttranscriptionally in AD skin has not yet been extensively studied. MicroRNAs are capable to mediate translational repression and to destabilize mRNA. A micro RNA which targets the cytotoxic T cell associated antigen (CTLA)-4, was demonstrated to be highly upregulated in lesional AD skin [40]. *In vitro*, expression of this microRNA was upregulated during T cell differentiation and by stimulation of T cells with *S. aureus* superantigens as well as nonspecific T cell activation [40]. Since CTLA-4 inhibits activation of T cells, microRNA induced suppression of CTLA-4 function may affect T cells in allergic skin inflammation.

Food allergens are important triggers of AD particularly in children. Both ingestion of food as well as epicutaneous food application are capable of inducing eczematous skin lesions. A recent mouse model of orally immunized mice provided evidence that antigen-specific gut homing T cells can be reprogrammed to express skin homing molecules in order to be recruited to the skin in response to contact of food allergens with the skin [41]. These data introduce a model in which the plasticity of tissue specific homing receptors on T cells modifies the migratory properties and direction of T cells, so that epicutaneous antigen challenge might be capable of promoting the infiltration of T cells primed in the gut.

Despite reactivity to aeroallergens and food allergens, hyperreactivity to human proteins is regarded as another trigger factor in a subgroup of AD patients. This mechanism is based on cross-reactivity between exogenous and endogenous proteins. T cells cross reactive to *Malassezia sympodialis* thioredoxin derived from a skin colonizing lipophilic yeast and human thioredoxin has been proposed to be of pathophysiologic relevance in AD [42]. *Malassezia sympodialis* specific T cell clones generated from the skin and blood of sensitized AD patients were cross reactive to human thioredoxin, expressed CD4 and the cutaneous lymphocyte antigen and secreted Th1, Th2, Th17 and T22 cytokines [42]. Thus, the allergic hyperreactivity to human proteins might promote chronic skin inflammation in AD even in the absence of exogenous triggers.

Factors promoting viral spreading in the skin

A subgroup of AD patients develops one or more episodes of a severe, disseminated herpes simplex virus skin infection, called eczema herpeticum (EH). Several co-factors have recently been identified, which predispose a subgroup of AD patients to viral skin infections. These include enhanced Th2-polarity, higher number of sensitizations and increased severity of AD [43]. Strong Th2 polarity is of critical immunological importance, since Th2 cytokines dampen several components of the innate and adaptive immune system required for effective viral defense and reduces the expression of proteins in the epidermal

differentiation complex such as filaggrin and proteins crucial for keratinocyte differentiation including S100/A11 *in vitro*. Data from mouse models provide evidence for deficient functioning of Foxp3 expressing regulatory T cells in the skin as another putative cause for uncontrolled viral spreading and disseminated virus infections in AD skin [44]. Whether allergen specific IgE against the virus plays a role as a cofactor, as recently demonstrated for varicella zoster virus specific IgE, which is higher in vaccinated children with AD [45], remains to be determined.

Moreover, transcriptional differences in the interferon (IFN) superfamily were detected in PBMC from patients with AD and history for EH including lower IFN- γ R expression and IFN- γ release. In line with this observation, genetic variants in *IFNG* and *IFNGR1* were reported to be associated with EH and were shown to go along with disseminated viral skin infections in knockout mice [46]. Other genetic modifications shown to be more frequent in the subgroup of AD patients with EH were SNPs in the gene regions encoding thymic stromal lymphopoietin (*TSLP*), an IL-7 like cytokine which promotes the differentiation of Th2 cells via DCs and the respective IL-7 receptor (*IL7R*) [47]. On the functional level, some of those genetic modifications might enhance TSLP promoter activity by increasing binding of the activator protein 1 to the regulatory element in the *TSLP* gene, thereby enhancing TSLP mediated Th2 immune responses certain AD patients.

In addition to a defective adaptive immune response characterized by enhanced Th2, and defective Th1 responses, comparative proteomic profiling of biopsies from non-lesional and lesional skin of patients with AD with and without a history for EH revealed reduced protein levels of filaggrin-2 in tape stripped skin from patients with a history of EH [16]. This is consistent with the concept that defective skin barrier predispose to increased risk for EH [48]. Patients with a history of EH also have an attenuated induction of the antimicrobial peptides human beta-defensin 2, 3 and cathelicidin under inflammatory conditions [49]. Thus propensity to EH results from a combination of enhanced viral penetration into the skin as the result of skin barrier dysfunction, combined with an inadequate antimicrobial response and impaired adaptive anti-viral immune response.

Concluding remarks

Recent studies suggest a multitude of cofactors impact at different levels on the pathophysiology and clinical phenotype of AD. However, the key question, which of those factors could be regarded as the hen, and which of them as the egg in this network of events remains still to be answered. In fact, more and more data support a complex pathophysiologic picture of AD supporting a disease model of skin barrier impairment interacting with components of a hyperreactive allergic response concomitantly with a defective anti-microbial immune system modified by genetic variants [50]. As a consequence, one approach for the future would be to differentiate between factors driving the disease in general from a more individual constellation of trigger factors and mechanisms in particular subgroups of patients. This would hold true for both, preventive as well as mechanism-based therapeutic measures [51].

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Highlights

- Atopic Dermatitis is the most common inflammatory skin disease in the general population
- Atopic Dermatitis is a genetic disease triggered by infection, allergens and stress
- Atopic dermatitis results from barrier defects combined with abnormal innate and adaptive immune responses