

Atopic dermatitis: from new pathogenic insights toward a barrier-restoring and anti-inflammatory therapy

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Current Opinion in Pediatrics 2011, 23:647–652

Purpose of review

Recent published work on atopic dermatitis focusing on the pathogenesis and epidemiology, which have a direct effect on treatment, is presented.

Recent findings

Worldwide, the incidence of atopic dermatitis is still increasing, although a plateau seems to be reached in certain industrialized countries. In addition to the filaggrin missense mutations, other mechanisms responsible for impaired skin-barrier function have been identified. These findings have a direct impact on therapy as well as behavior strategies. The barrier defect and the resulting inflammation in the skin, in particular interleukin (IL)-17-mediated responses, play an important role in promoting allergic airway responses and food allergy.

Summary

These recent findings on epithelial barrier defects, as well as cells and cytokines important for atopic dermatitis development, provide new insights into its pathogenesis, help to characterize patient subgroups, and identify new therapeutic strategies.

Keywords

atopic dermatitis, inflammation, quality of life, skin barrier

Curr Opin Pediatr 23:647–652
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1040-8703

Introduction

Atopic dermatitis is a common skin disease in children and adults. It is characterized by chronic skin inflammation and intense pruritus and, thus, has an immense impact on the quality of life of the patients as well as their families. Recent knowledge on the role of skin barrier defects in initiating and perpetuating skin inflammation has profoundly changed our understanding of atopic dermatitis pathogenic mechanisms. Progress in identifying epithelial barrier defects as well as cells and cytokines important for atopic dermatitis development has provided new insights into its pathogenesis, produced better tools for the characterization of patient subgroups, and identified new therapeutic approaches [1]. Here, we present recent published research on atopic dermatitis, focusing on concepts of pathogenic importance and that have implications for treatment and prevention.

Has prevalence reached a plateau?

The International Study of Asthma and Allergies in Childhood study revealed that the prevalence of atopic dermatitis in children at age 13–14 years has decreased in countries with former high prevalence. However, the prevalence in developing countries as well as in the age

group 6–7 years has been increasing worldwide over the past 6 years [2]. The plateau of maximum prevalence was around 20% [2]. Although the incidence of atopic dermatitis is highest in infancy, it is still 1.7% between ages 9–11 and 16–20 years [3^{••}]. The symptoms persist in 47.6% of adolescents with atopic dermatitis that develops in infancy [3^{••}]. Interestingly, besides genetic factors (parental history of atopic dermatitis and rhinitis) and sensitization to allergens at age 9–11, occupational exposure (working in high-risk jobs), even of limited duration and intensity, seemed a relevant factor for atopic dermatitis course over puberty [3^{••}]. These observations should be considered when adolescents are advised regarding job choice and training.

Besides genetics, a number of prenatal and postnatal factors might influence the development of atopic dermatitis. Children's atopic dermatitis was found to be determined by maternal atopic dermatitis independently of either maternal IgE or inflammatory cytokine expression during pregnancy [4]. Moreover, stress-related maternal factors increase the risk for atopic dermatitis in the first 2 years of life [5]. Day-care attendance during the first 2 years of life significantly increased the prevalence and incidence of atopic dermatitis up to 6 years of age [6]. Corresponding to the observations in asthma and

atopy, obesity is also associated with atopic dermatitis, in particular with onset at less than 2 years of age and when it persists for more than 5 years [7].

The interplay of skin barrier and immune response in atopic dermatitis

There is increasing evidence that a defective skin barrier plays a critical role in the development of atopic dermatitis as well as allergic airway diseases. Loss-of-function mutations of the *filaggrin* (*FLG*) gene have been detected in about 22% of atopic dermatitis patients. These mutations are associated with concomitant allergic sensitization or allergic asthma [8,9] as well as early-onset and persisting atopic dermatitis [10]. Moreover, loss-of-function variants of the *FLG* gene increase the risk of developing peanut allergy, suggesting a causative role of impaired barrier function in the pathogenesis of food allergy [11]. Insufficient cleavage of pro-FLG into FLG by proteases, for example, due to decreased protease activity because of missense mutations, results in thickened and dry skin [12]. Breakdown products of FLG, for example, urocanic acid (UCA) and pyrrolidone acid (PCA), are the major components of the natural moisturizing factor (NMF) in the stratum corneum. In atopic dermatitis patients carrying *FLG* mutations, the levels of NMF components in the stratum corneum are significantly lower compared with atopic dermatitis patients without *FLG* mutations and healthy controls [13[•]]. In addition, atopic dermatitis severity inversely correlated with NMF levels [13[•]]. Furthermore, UCA and PCA decrease the pH, resulting in reduced growth of *Staphylococcus aureus* due to a reduced expression of secreted and cell wall-associated proteins required for colonization and immune evasion [14]. Atopic dermatitis patients with *FLG* mutations were found to have significantly higher skin pH values as well as altered ceramide levels compared with those without *FLG* mutations [15].

Epidermal homeostasis is regulated by proteases, including kallikreins (KLK), which are important for skin desquamation and whose activity is tightly controlled by protease inhibitors. Mutations of the Kazal-type 5 (*SPINK5*) gene, which encodes for the protease inhibitor lymphoepithelial Kazal-type-related inhibitor (LEKTI), are responsible for an increased protease activity in Netherton syndrome [16]. Due to lack of LEKTI, unregulated protease KLK-5 was shown to directly activate proteinase-activated receptor-2; this results in an overexpression of thymic stromal lymphopoietin (TSLP) and proinflammatory cytokines including tumor necrosis factor (TNF)- α and interleukin (IL)-8 and, thus, may trigger atopic dermatitis-like lesions [17]. Recently, decreased expression of SPINK6 in the skin of atopic dermatitis patients has been reported [18]. Increased

Key points

- Defects of the skin barrier due to genetic and/or functional alterations of structural proteins, for example, filaggrin, proteases and their inhibitors, antimicrobial peptides, play a critical role in the pathogenesis of atopic dermatitis.
- Thymic stromal lymphopoietin provides a link between epidermal responses to environmental danger signals and Th2-biased inflammation in atopic dermatitis.
- IL-17 may contribute to local inflammation, auto-immune reactions and systemic allergic responses in atopic dermatitis patients.
- Treatment of atopic dermatitis is comprehensive and should focus on restoring epidermal barrier function, reducing skin inflammation as well as psychosocial aspects.

serine protease activities in the deeper layers of the stratum corneum in acute atopic dermatitis lesions are associated with reduced thickness of the stratum corneum as well as an impaired barrier function and skin irritation [19].

By producing antimicrobial peptides (AMP), keratinocytes may directly participate in innate immune responses after recognizing pathogenic organisms. In contrast to earlier published works, a systematic analysis revealed an enhanced expression of AMPs such as ribonuclease 7, psoriasin, human β -defensins (HBD)-2 and 3 in lesional skin of atopic dermatitis, which was even higher than that of psoriasis, compared with nonlesional skin and healthy controls [20]. However, it has been observed that keratinocytes from atopic dermatitis patients were unable to mobilize HBD-3 efficiently to kill *S. aureus* due to the inhibitory effects of IL-4 and IL-13 [21]. However, in lesions of eczema herpeticum, the increase of AMPs, including HBDs and cathelicidin, is less pronounced compared with lesions of atopic dermatitis and psoriasis [22[•]]. In-vitro data suggest that calcineurin inhibitors may enhance the expression of AMPs in keratinocytes and increase their functional capacity to inhibit growth of *S. aureus* [23]. The suppressing effects of calcineurin inhibitors on skin barrier and AMP expression observed in an animal model were neutralized by the application of a physiologic lipid mixture [24].

T helper 2 activation and beyond

TSLP plays a key pathogenic role in allergic diseases, including atopic dermatitis, by activating dendritic cells with subsequent proliferation of naive CD4⁺ T cells and their differentiation into T helper (Th)-2 cells, which produce the Th2 cytokines IL-4, IL-5 and IL-13 [25].

The expression of TSLP in keratinocytes is induced by mechanical injury as well as stimulation of Toll-like receptors-2, 5, and 6 [26^{••},27,28]. Thus, scratching of the pruritic skin and/or microbes might directly initiate TSLP production and skin inflammation in atopic dermatitis patients. In children, increased serum levels of TSLP have been detected [29]. The production of TSLP was found to occur as early as 1 h after cutaneous allergen challenge and clearly preceded the infiltration of dendritic cells [30]. IL-25, which is secreted by mast cells and eosinophils, may further enhance Th2 type responses in atopic dermatitis [31].

In addition to autoimmune diseases, Th17 cells, which are CD4⁺ T cells that produce IL-17A and IL-17F, are thought to be involved in the pathogenesis of atopic dermatitis. An increased percentage of Th17 cells in the peripheral blood correlates with disease severity [32]. Moreover, Th17 cells are present in acute inflamed skin lesions of atopic dermatitis patients [32]. In atopy patch-test reactions, up to 10% of infiltrating T cells express IL-17 [33]. FLG deficiency leads to Th17-dominated skin inflammation and susceptibility to epicutaneous allergen sensitization [34]. Keratinocytes stimulated by IL-17 produce proinflammatory cytokines, for example, TNF- α , IL-8, granulocyte macrophage colony-stimulating factor, as well as the AMP HBD-2 [32,33]. However, IL-4 and IL-13 partially inhibit HBD-2 production upon IL-17 stimulation [33]. Staphylococcal toxins are able to induce IL-17 production in T cells [33,35]. In animal models, cutaneous antigen sensitization induced both local and systemic IL-17 responses, resulting in inflammation after inhalative allergen challenge independently of IL-4 and IL-13 [36,37]. T-cell clones isolated from the skin of atopic dermatitis patients and stimulated with the autoallergen Hom s 2 produce IL-17 [38]. Furthermore, IL-17 directly stimulates B cells to produce IgE [39]. Thus, IL-17 immune responses may contribute to local skin inflammation and autoimmune reactions, as well as to allergen sensitization and systemic inflammation involving the airways of atopic dermatitis patients.

Evidence of a pathogenic role of IL-18 in atopic dermatitis came from a mouse model demonstrating that overexpression of IL-18 resulted in the spontaneous development of atopic dermatitis-like inflammation [40]. Serum levels as well as epidermal production of IL-18 correlate with the severity of atopic dermatitis [41,42]. IL-18 constitutively expressed by keratinocytes and cleaved into its active form by caspase-1 exerts dual functions. It promotes the differentiation of Th1 cells producing IFN- γ , but, in the absence of IL-12, it stimulates the production of IL-4 by CD4⁺ T cells and, thus, may contribute to the Th2 milieu and enhanced IgE production in atopic dermatitis [43].

The role of bugs and mites

Because of the impaired barrier and ongoing inflammation, the skin of atopic dermatitis patients is very susceptible to environmental triggers, in particular microbial factors. *S. aureus* colonizes both lesional and nonlesional skin in about 90% of atopic dermatitis patients. It can exacerbate or perpetuate skin inflammation by secreting toxins with superantigenic properties leading to the proliferation and activation of T cells, by stimulating keratinocytes to release proinflammatory cytokines, for example, in response to lipoteichoic acid, and by stimulating basophil histamine release via specific IgE antibodies to toxins [44]. Atopic dermatitis patients with eczema herpeticum tend to have more severe disease, a higher rate of sensitizations to environmental allergens, asthma and food allergy, as well as more frequent infections with *S. aureus* and molluscum contagiosum, compared with those without eczema herpeticum [45]. The susceptibility of atopic dermatitis patients to eczema herpeticum is associated with an impaired barrier, for example, R501X mutation of the *FLG* gene, genetic variants of TSLP, as well as reduced IFN- γ production and IFN- γ receptor expression [46–48]. In addition to their pathogenic role in atopic dermatitis by inducing specific IgE or stimulating specific T cells, house dust mites provide danger signals to keratinocytes resulting in caspase-1 activation and release of the proinflammatory cytokines IL-1 and IL-18 [49[•]].

The itch-scratch cycle

Severe pruritus is the main and usually most disturbing symptom in atopic dermatitis patients. Recently, progress has been made in elucidating the mechanisms responsible for itch in the skin. Nerve growth factor (NGF) and substance P levels are elevated in the plasma of atopic dermatitis patients and correlate with disease activity as well as eosinophil count [50,51]. In atopic dermatitis patients, the content of NGF in eosinophils, which store NGF as a preformed mediator, is markedly increased compared with healthy individuals [52]. High levels of NGF in cord blood as well as maternal blood have been found to be associated with pediatric atopic dermatitis [53]. Immunohistochemistry revealed an intense expression of NGF in the epidermis and cells in the papillary dermis of lesional atopic dermatitis skin in association with neurohyperplasia and NGF receptor expression [54]. In an atopic dermatitis mouse model, stress induced an increase of NGF expression in the skin, whereas treatment with neutralizing NGF antibodies reduced stress-induced epidermal thickening and eosinophil infiltration and NGF expression by mast cells [55[•]]. Effective treatment of atopic dermatitis, for example, with topical steroids, results in decreased NGF

expression in the skin, suggesting a crucial pathogenic role of NGF [51].

IL-31 provides a link between inflammation and pruritus in atopic dermatitis. This cytokine is produced by Th2 cells and its receptor is expressed in dorsal root ganglia, in which the cell bodies of the primary sensory neurons reside [56,57]. In both children and adults with atopic dermatitis, serum IL-31 levels are increased compared with healthy individuals and correlate with disease severity [58,59]. IL-31 expression correlates with the itch-associated scratching behavior in mice, which is suppressed by anti-IL-31 antibodies [60,61]. In addition to the role in the development of itch, IL-31 may stimulate keratinocytes, eosinophils and macrophages and, thus, may contribute to skin inflammation in atopic dermatitis [62–64]. Interestingly, stimulation of T cells, which express functional histamine H4 receptors, leads to the release of IL-31 [65]. In an animal model, blocking of H4 receptors by a specific antagonist resulted in a reduction of skin inflammation as well as pruritus [66].

Over the last years, psychosocial aspects of atopic dermatitis have been addressed in a number of epidemiologic studies. Children with atopic dermatitis are at increased risk to develop hyperactivity/attention-deficits, particularly in association with sleeping problems [67,68^{••}]. Compared with healthy children, the quality of life is significantly poorer in infants with atopic dermatitis, mainly due to itch-associated sleep disturbances and treatment difficulties [69].

Patient-oriented medicine is an emerging concept to get patients involved in the management of chronic diseases. In order to provide patients with atopic dermatitis a tool for self-assessment of disease activity, the patients-oriented scoring atopic dermatitis (POS-CORAD) has been validated, demonstrating a good correlation with the SCORAD assessed by the physician [70[•]]. Interventions by structured educational programs result in an improvement of coping behavior in children, and in better handling the affected children by their parents [71].

Practical aspects for treatment

Because skin barrier impairment is considered the initial pathogenic event in atopic dermatitis, all measures restoring the defect barrier should not just be considered cosmetic, but are essential for an effective treatment and prevention. In children with moderate-to-severe atopic dermatitis, a ceramide-dominant triple-lipid barrier repair formulation significantly decreased skin symptoms and pruritus after 1 month; this decrease was comparable with fluticasone cream, although

fluticasone showed a faster improvement [72]. In addition to its positive medical effects, for example, reduction of flare-ups, maintenance therapy with moisturizing cream has positive health–economic effects [73,74]. The first study on primary prevention of atopic dermatitis by emollient therapy starting at birth showed promising results [75]. Application of substances that establish an acidic pH on the skin surface might be helpful for barrier homeostasis such as antimicrobial function, lipid processing, regulating protease activity and inhibition of corneodesmosome degradation [76,77]. Although there is evidence that increased protease activity is involved in atopic dermatitis, a clinical trial with a novel protease inhibitor failed to improve atopic dermatitis [78]. Textiles made of silver-loaded seaweed-based cellulosic fibers significantly reduced *S. aureus* colonization without affecting the normal flora, and decreased transepidermal water loss in patients with mild-to-moderate atopic dermatitis [79]. In addition to their anti-inflammatory effects by inhibiting T-cell proliferation and cytokine production, topical calcineurin inhibitors were found to affect keratinocyte activity [80]. Topical pimecrolimus cream may be helpful in children intolerant of or dependent on topical corticosteroids [81]. So far, no association between topical pimecrolimus and tacrolimus and increased risk in cancer rate in atopic dermatitis patients has been observed [82[•]].

The effects of probiotics assumed to regulate Th1/Th2 dysbalance in prevention and treatment of atopic dermatitis are controversial. Recent published articles report that supplementation of probiotics to mothers prenatally and postnatally during breastfeeding decreased the incidence of atopic dermatitis in infants in the first 2 years of life but had no effect on atopic sensitization [83,84].

Conclusion

The discovery of *FLG* mutations as primary genetic defects in atopic dermatitis has opened a new era in atopic dermatitis research, focusing on understanding the constituents and function of the skin barrier and their pathology leading to skin inflammation and promotion of atopic sensitization. Promising new therapeutic approaches are seen in restoring the skin barrier by regulating protease and protease inhibitor activation, optimizing the function of AMPs, normalizing the imbalance between T cell subtypes with monoclonal antibodies and reduction of itch by targeting histamine H4 receptor and/or cytokines such as IL-31.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 704–706).

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