Forum Minireview

Analysis of the Mechanism for the Development of Allergic Skin Inflammation and the Application for Its Treatment: Overview of the Pathophysiology of Atopic Dermatitis

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Abstract. It has been recognized that atopic dermatitis (AD) involves allergen-driven Th2 cell polarization. In patients with AD, cytokines induce allergic inflammatory responses and subsequently enhance IgE production. Recent reports revealed that a reduced barrier function as well as altered immunity are fundamental to the development of AD because barrier disruption due to aberrant filaggrin expression is a pathological factor. However, although recent studies have improved our understanding of the pathogenesis of AD, the overall pathophysiology remains elusive. I herein discuss it based on the natural history of AD.

Keywords: atopic dermatitis, nonatopic dermatitis, barrier dysfunction, filaggrin, IgE autoantibody, allergic inflammation

Clinical manifestations of atopic dermatitis (AD)

AD is a chronic inflammatory skin disease characterized by itchy dermatitis and susceptibility to cutaneous bacterial, viral, and fungal infections. Other hallmarks of AD are a defect in the barrier function, causing dry skin, and IgE-mediated sensitization to food and environmental allergens (1). The clinical manifestations of AD vary with age. There are three stages: 1) in infancy, the first eczematous lesions usually appear on the cheeks and scalp; 2) in childhood, lesions involve flexures and the extensor aspects of the limbs; and 3) in adolescence and adulthood, lichenified plaques affect the flexures, face, and neck. In each stage, itching worsens the skin lesions and impairs the patient's quality of life.

The prevalence of AD has markedly increased during the past three decades. A total of 45% of all cases of early-onset AD begin within the first 6 months of life, 60% begin during the first year, and 85% before 5 years of age. More than 50% of the children affected up to 2 years of age do not show any signs of IgE-sensitization, but they become sensitized during the course of the disease (2). Up to 70% of these children undergo spontaneous remission before adolescence.

Immunopathology of AD

AD is not a uniform disease entity. It frequently starts in early infancy, termed early-onset AD. This disease can also develop in adults (late-onset AD). More than 50% of infant-related AD cases show no signs of IgE-sensitization (“nonatopic” dermatitis or non-allergic form of AD), although some become sensitized during the course of the disease (“atopic” dermatitis or allergic form of AD) (2). In addition, inflammation in AD is biphasic. An initial Th2 phase precedes a chronic phase associated with Th0 and Th1 cells (3).

“Nonatopic” dermatitis may be induced by neurogenic factors, which will be reviewed later by A. Ikoma in this issue; irritation; and cytokines including a potent pruritogenic cytokine, IL-31, produced by epidermal keratinocytes (4). Thymic stromal lymphopoietin (TSLP) produced by stimulated epidermal keratinocytes causes Th2 polarization (5) (this topic is related to keratinocytes and will be discussed in this issue by M. Komine). Immune responses are mediated by both Langerhans cells (LCs) and inflammatory dendritic epidermal cells (IDECs) of myeloid dendritic cells (DCs) present in AD.
lesions (6). DCs express a high-affinity receptor (Fc epsilon RI) (7). On ligation of Fc epsilon RI by IgE, LCs produce IL-16, only a small number of different chemokines and proinflammatory cytokines (8). IDECs lead to Th1 polarization by producing IL-12 and IL-18 and by releasing proinflammatory cytokines.

**Structure and function of the epidermis and their alteration in AD**

The epidermis of the skin is composed of four layers (starting from the surface of the skin): the stratum corneum (SC), granular layer, spinous layer, and basal layer (Fig. 1A). The SC provides the essential attribute of a permeability barrier. The keratinocytes replace their plasma membrane with a cornified envelope (CE). Early steps in the formation of the CE result in the sequential expression of several major proteins. Among them, filaggrin is one of the final proteins to be incorporated. These structural proteins are extensively cross-linked by transglutaminases and act as a scaffold for the CE (9). The precursor profilaggrin is a large, highly phosphorylated polypeptide that is the main constituent of the keratin and granules in the granular layer. During the formation of CE, profilaggrin is dephosphorylated and proteolytically cleaved by serine proteases to release multiple copies of the functional filaggrin repeats. Each peptide is progressively degraded by the enzymes into hydrophilic amino acids, including pyrrolidone carboxylic acid, alanine, and trans-Urocanic acid. These amino acids and various ions, which are called natural moisturizing factors (NMF), play a pivotal role in maintaining hydration of the SC. trans-Urocanic acid also plays a critical role in the maintenance of the pH of the SC due to low filaggrin-breakdown products results in an increase in the amount of NMF (Fig. 1B). A decreased generation of NMF (Fig. 1B). A decreased generation of NMF (Fig. 1B). A decreased generation of NMF (Fig. 1B). A decreased generation of NMF (Fig. 1B). A decreased generation of NMF (Fig. 1B).

The SC is composed of flattened corneocytes surrounded by multiple lamellae sheets enriched with highly hydrophobic lipids such as ceramides, cholesterol, and free fatty acids (FFAs). These lipids are delivered to the intercellular spaces of the SC as their precursors through the secretion of the lamellar body (LB). This organelle delivers not only lipid constituents and lipid precursors, but also the enzymes required to generate ceramides and FFAs. In parallel, LB-derived proteases and inhibitors orchestrate the digestion of corneodesmosomes, transient intercellular junctions between the corneocytes, and their shedding at the skin surface (Fig. 1A). Antimicrobial peptides are also delivered to the intercellular spaces of the SC.

Both defective permeability and defective antimicrobial barriers are well-recognized features of AD (Fig. 1B), which often cause secondary infection.

**Genetics of AD**

Two hypotheses regarding the mechanism of AD have been proposed: 1) the primary defect is an immunologic disturbance with epidermal barrier dysfunction as a consequence of local inflammation; 2) a primary defect in the epidermal keratinocytes that leads to barrier dysfunction, while the immunologic aspects are considered to be an epiphenomenon.

The development of AD in a bone marrow recipient after the engraftment of hematopoietic stem cells from an atopic donor (10) supports the former hypothesis. However, recent studies revealed the strongest evidence for the latter, whereby a primary structural abnormality of the SC underlies the pathogenesis of AD, caused by the link between loss-of-function mutations in the gene encoding filaggrin and AD. The two most common mutations (R501X and 2282del4) account for the majority of cases, while over 10 different mutations have been reported. Overall, between 18% and 48% of individuals with AD carry filaggrin gene (FLG)–null alleles (11). The initial effect of filaggrin deficiency in AD cases is decreased SC hydration due to a reduced amount of NMF (Fig. 1B). A decreased generation of filaggrin-breakdown products results in an increase in the pH of the SC due to low trans-Urocanic acid levels (Fig. 1B).

Recent reports showed the relationship between loss-of-function mutations in the FLG predisposing to AD and bronchial asthma in association with AD, as well as strong evidence for an association between FLG mutations and other allergic phenotypes that occur in the context of the atopic march (12). These results support the role of filaggrin in the pathogenesis of AD and in the subsequent progression to other allergic diseases that is called the atopic march. This suggests that the maintenance and repair of the epidermal barrier in infants with AD may prevent the subsequent development of allergic airway disease.

**Natural history of AD**

One classification distinguishes an IgE-associated form (“atopic” dermatitis) from a non–IgE-associated form (“nonatopic” dermatitis) (13). This implies that they might be two different diseases. However, in both forms, dry skin due to barrier dysfunction is an important characteristic, and the absence of IgE-sensitization is only a transient factor in most cases.

The natural history of AD suggests that there may be three phases in most early-onset AD (14) (Fig. 2): 1) the
A: Structure and function of the skin

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<tr>
<th>Structure</th>
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<tr>
<td>The epidermis</td>
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<tr>
<td>Stratum corneum (SC)</td>
<td>Filaggrin</td>
<td>Breakdown-product of filaggrin</td>
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<td></td>
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<td>NMF Water-holding capacity</td>
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<td>trans-UC Control of pH</td>
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<td></td>
<td>Cornified envelope</td>
<td>Permeability barrier</td>
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<td>Granular layer (GL)</td>
<td>Keratohyalin granules</td>
<td>Permeability barrier</td>
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<td>Pro-filaggrin</td>
<td>Precursor of filaggrin</td>
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<td>Lamellar body</td>
<td>Anti-microbial peptides</td>
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<td></td>
<td>Precursor of lipids</td>
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<td>Spinous layer (SL)</td>
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B. Schematic comparison between normal skin and AD lesional skin

Fig. 1. Structure and function of the skin. Barrier and immunological dysfunction in AD. A: Structure and function of the skin. 1Intercellular lipids: ceramide, cholesterol, free fatty acids. B: Schematic comparison between normal skin and AD lesional skin. NMF: natural moisturizing factors, trans-UC: trans-urocanic acid;
initial phase is “nonatopic” dermatitis in early infancy without IgE-sensitization; 2) in about two-thirds of patients, genetic factors influence the induction of IgE-mediated sensitization to food and/or environmental allergens (“atopic” dermatitis); 3) scratching damages epidermal keratinocytes of the skin, leading to their release of autoantigens, which induce IgE autoantibodies in a large number of patients with AD.

Serum obtained from patients with severe AD often contains IgE antibodies against autoantigens such as manganese superoxide dismutase and a calcium-binding protein (12, 15). The serum levels of these IgE autoantibodies correlate with the disease severity. About 25% of adults with AD have IgE antibodies against the self-proteins. The hallmarks of these patients are an early-onset, intense pruritus, recurrent bacterial skin infections, and high serum IgE levels.

Thus, initial IgE-independent inflammation in AD induces IgE-sensitization caused by environmental allergens. The proteins secreted from keratinocytes during itch-scratch cycles could be molecular mimics of microorganisms such as Malassezia, a fungal flora component of the skin, inducing IgE autoantibodies (16). The IgE antibodies could aggravate and perpetuate the allergic inflammation.

**Animal models of AD and its treatment with oligodeoxynucleotides containing CpG motifs**

To identify an effective treatment for severe cases of AD, new animal models are required. N. Inagaki and H. Nagai will introduce the several animal models of AD in this issue. Here I would like to explain our reproducible murine model of protein Ag–induced eosinophilic inflammation that is accompanied by epidermal acanthosis and increased serum IgE levels, as seen in severe AD showing diffuse edematous erythema (17).

Oligodeoxynucleotides (ODN) containing CpG motifs (CpG-ODN) have been highlighted as immunomodulators that reduce Th2-mediated responses. Using our established model of Th2-mediated eosinophilic inflammation, we found that treatment with CpG-ODN during epicutaneous sensitization in previously i.p.-primed mice prevented the development of Th2-mediated responses. Furthermore, to evaluate the therapeutic effect of CpG-ODN on established eosinophilic inflammation, mice were treated with a course of immunotherapy at a skin site remote from the area of Ag application prior to the second 1-week epicutaneous exposure to Ag. Therapeutic treatment with CpG-ODN plus Ag, but not that with CpG-ODN alone, could reverse the established eosinophilic inflammation (17).

CpG-ODN is known to activate cells such as B cells, macrophages, and DCs through TLR9. Signaling through TLR9 leads to the secretion of proinflammatory cytokines. Among them, IL-12 acts on T and NK cells, inducing the production of cytokines, primarily IFN-γ. It has also been reported that CpG-ODN–activated DCs induce the generation of regulatory T cells (Treg) with a strong immunosuppressive function (18) and that blocking the suppressor activity of Treg and increasing the Th2 cell frequency enhance allergen-specific Th2 cell activation ex vivo (19).

These results provide strong evidence for the feasibility of a novel Ag-specific immunomodulator like CpG-ODN to treat cutaneous eosinophilic inflammation such as that characteristically found in patients with severe AD.
Conclusion

Recent insights into the genetic and immunologic mechanisms that drive cutaneous inflammation in AD have led to a better understanding of the natural history of this disease and have highlighted the critical role of the epidermal-barrier function and immune system. Both contribute to IgE-mediated sensitization and should be considered as major targets for therapy.

New developments aimed specifically at the molecular defects in the stratum corneum could provide a tailor-made therapy to improve the barrier function. Early treatment and preventive management could improve the outcome and quality of life of patients with AD and could also prevent the progression to bronchial asthma and allergic rhinitis.

References