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Understanding the Pathophysiology of Atopic Dermatitis – insights into Immune Dysregulation and Skin Barrier Dysfunction

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Abstract:

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by a disrupted skin barrier and immune dysregulation. The exact pathophysiology of atopic dermatitis despite extensive research remains complex. It includes genetic disorders, a defect in the epidermal barrier, an altered immune response, and disruption of the skin's microbial balance. Recent advances in research have provided deeper insights into the molecular mechanisms including the role of filaggrin mutations, Th2 cytokine-mediated inflammation, and the skin microbiome. Understanding the intricate interplay between these components is crucial for developing targeted therapeutic strategies.

Aim of the study: This review provides a comprehensive overview of the current knowledge on the pathophysiological mechanisms underlying AD, highlighting recent advances and areas for future research.

Material and methods: Comprehensive literature searches were performed across the main electronic databases of PubMed and GoogleScholar using the keywords: "atopic dermatitis", "eczema pathophysiology", "skin barrier".

Conclusions: Atopic dermatitis (AD) is a complex, chronic inflammatory skin disease with a multifaceted pathophysiology involving genetic, immunological, and environmental factors. Recent advances in understanding the molecular mechanisms underlying AD have highlighted the importance of skin barrier dysfunction, immune system dysregulation, and microbial interactions in the disease's progression.

Keywords: atopic dermatitis, skin barrier, eczema, pathophysiology

Introduction

Atopic dermatitis (AD), or atopic eczema, is a common chronic inflammatory skin disease affecting 15-20% of children and up to 1-3% of adults [1]. It is characterized by patches of dry, pruritic skin lesions usually accompanied by itch, erythema, papules, vesicles squames,

or lichenification. AD can manifest at any age in life. However, the onset of disease commonly presents before the fifth year of life (80% – 90%) [2] and is often the first step in the development of other atopic diseases ('atopic march'), characterized by a typical sequence of atopic diseases preceding the development of other allergic disorders later in life [3].

Although the pathophysiology of AD is not completely understood, numerous studies demonstrated that there is a strong genetic component, which leads to a compromised barrier function, resulting in increased transepidermal water loss (TEWL), and heightened permeability to allergens, irritants, and pathogens. This leads to immune activation that not only promotes inflammation but also further impairs barrier function, creating a vicious cycle of the disease. This article provides a comprehensive review of the pathophysiological mechanisms underlying AD, with a focus on recent advances. By elucidating such complex interactions, we aim to inform the development of targeted therapeutic strategies that address the causes of AD, ultimately improving patient outcomes and quality of life.

1. Genetic disorder

Recent research shows over 70 genes could be associated with AD in different populations [4]**.** Mutations in the human filaggrin gene (FLG) are among the most significant genetic mutations related to AD. Other variations associated with the disease include epidermal barriers, immune response mechanisms, and interleukin genes [5].

1.1 Filaggrin mutations

Filaggrin is a key protein involved in skin barrier function. During keratinocyte differentiation, profilaggrin is dephosphorylated and degraded into filaggrin monomers. Then it is aggregated in the keratin cytoskeleton to form a dense protein-lipid matrix, resulting in a fully differentiated epidermal barrier. During FLG deamination and breakdown, filaggrin monomers are degraded into amino acids, which contribute to the natural moisturizing factors (NMF), maintaining skin hydration, a low pH, and other aspects of the barrier function of the stratum corneum [6]. The less acidic pH caused by lack of NMF allows skin surface serine proteases to become activated leading to uncontrolled epidermis desquamation [7]. Moreover, there are research that shows that loss of NMFs affects the skin biome, because they favor adhesion of non-pathogenic bacteria, preventing the aggregation of *S. aureus* [8].

Because of its role in maintaining skin barrier FLG mutation currently stands out as a primary driver of atopic change. About half of the patients with moderate to severe AD have null mutations in the FLG gene [9]. Patients with AD who carry FLG mutations have more early-

onset, severe, and persistent disease [10,11]. It is important to remember that FLG mutations as such also represent a risk factor for other atopic manifestations, e.g., asthma, suggesting that FLG deficiency may have a broader systemic significance [12].

1.2. SPINK5 mutations

In 1958 Earl W. Netheron described a rare monogenic disease with AD-like lesions in the skin [13] nowadays known as Netheron Syndrome. Research by S. Chavanas et al. [14] proved that it is caused by a loss-of-funcion mutation in the SPINK5 gene. This gene encodes the serine peptidase inhibitor lymphoepithelial Kazal-type trypsin inhibitor (LEKTI), which is crucial for epidermal homeostasis. LEKTI inhibits the activity of kallikreins (KLKs), the serine protease in the epidermis [15]. Netherton Syndrome is characterized by an excessive KLKs activity, which provokes permeability barrier defects. SPINK5 mutations are associated with AD in certain populations, especially eastern Asian populations [16], which suggest the role of serine protease imbalance in the pathogenesis of AD.

1.3 Other mutations

The above-described genetic mutations are not the only ones that are associated with an increased risk of atopic dermatitis. Besides FLG, other genes involved in maintaining skin barrier were identified to be associated with AD. Research has included so far genes for LAMA3, TMEM79, filaggrin-2(FLG2) and Late Cornified Envelope-like Proline-rich 1 (LELP1) [17-19]

Connection between atopic dermatitis and genes encoding the Th2 pathway has also been replicated by multiple independent studies. Genes whose polymorphisms contribute to the development of AD include IL-4, IL13 IL-31, IL-33, signal transducer and activator of transcription 6 (STAT6), thymic stromal lymphopoietin (TSLP) and its receptors: IL-7R and TSLPR [20-22]

Additionally, recent studies demonstrated that vitamin D receptor polymorphisms and cytochrome P450 variants are also associated with AD. In this regard, vitamin D receptor (VDR) polymorphisms and CYD27A1 were found to be associated with AD severity [23].

2. Lipids

The main lipid classes in human stratum corneum (SC) are ceramides (CERs), cholesterol (CHOL), and free fatty acids (FFAs). These lipid classes are present in an approximately equal molar ratio and constitute the lipid matrix that is organized in lamellar bodies and located between corneocytes [24] The introduction of liquid chromatography combined with

mass spectrometry provided a rapid boost in research leading to discovering and describing 12 different subclasses by 2010 [25]. Each CER consists of at least one acyl chain chemically linked to a sphingoid base of either sphingosine (S), phytosphingosine (P), 6-hydroxy-sphingosine, (H) or dihydrosphingosine (DS) base. The acyl chain is either a nonhydroxyfatty acid (N), an α-hydroxy fatty acid (A), or an esterified ω-hydroxy fatty acid (EO). The CER-EO subclass is often referred as acyl-CERs and contains an additional fatty acid attached to the acyl chain.

2.1. Lipid Composition

When focusing on the ratios between the various classes of lipids research [26] has reported a reduced CER/CHOL ratio in lesional AD skin. Imokawa et al. proved that the level of CER-EOS was decreased in lesional as well as in nonlesional skin [27]. Investigations of the CER composition led to the conclusion that all changes in nonlesional skin were also observed in lesional skin, but the changes were more aggravated [28]. A recent study showed that the average chain length in nonlesional skin in patients with AD was reduced compared with controls [29].

2.2 Lipid Organization

Not only lipid composition but also organization is crucial for the skin barrier function. Human SC lipids assemble in a dense, orthorhombic, lateral packing [30]. In the research on nonlesional AD skin significant increase in the level of lipids adopting the hexagonal lateral packing was observed [29]. As the hexagonal packing is less dense than the orthorhombic lateral packing, this change in lateral packing may result in a higher permeation through the lipid domains in the SC [31]. It was the first study to demonstrate that these modulations occur already in nonlesional AD skin.

This is an important observation as this may implicate that a normalization of the lipid composition in nonlesional skin may contribute to the restoration of the barrier function and thus reduce the reoccurence of lesional skin in AD patients.

3. Microbiome

3.1 Staphylococcus aureus

It has been proven that the composition and diversity of microorganisms on the skin differ between people with eczema and those healthy ones. In atopic skin, there has been a reduction in commensal bacteria of the genera *Streptococcus, Corynebacterium, Cutibacterium*, and the type *Proteobacteria* with the increase towards the genus *Staphylococcus* (*S. aureus* in

particular) [32]. Also, the total bacterial load is significantly greater on AD skin compared with healthy control skin.

Staphylococcus aureus colonized the skin in 60–100% of AD patients compared with 5–30% of healthy controls [33]. There is evidence of a loss of community diversity preceding flares of AD. Moreover, a higher colonization index and increased pathogen density show a positive correlation between the skin lesions' severity and the severity of the disease [34].

Research has proven that *S. aureus* damages and penetrates the epidermal barrier [35]. Staphylococcal enterotoxin B increases the expression of IL-31, which lowers the level of fillagrin and can induce T-cell–independent B-cell expansion, upregulate proinflammatory cytokines, and stimulate mast cell degranulation [36]. Moreover, by realising proteases it can affect and deformed corneocytes leading to stratum corneum dissolution. All of the above contribute to Th2 overexpress, skin inflammation, and itching leading to further *S. aureus* colonization.

3.2 Commensal bacteria

Studies suggested that normal microbiota commensals may modulate skin resistance and protect against AD development. For example, *Staphylococcus epidermidis* causes keratinocytes to produce antimicrobial peptides, and these suppress cytokine release after minor epidermal injury. Thus*, S. epidermidis* contributes as a barrier against colonization of pathogenic microbes [37].

Therapeutic interventions such as topical treatments with corticosteroids, calcineurin inhibitors, or even moisturizers and emollients in patients with atopic eczema may restore barrier function and normalize the skin microbiome.

4. Immunological dysregulation

The impaired skin barrier allows for the penetration of allergens and microbes, which activate the innate immune system and subsequently the adaptive immune system. This leads to the production of cytokines and chemokines that perpetuate the inflammatory response, recruit more immune cells, and further damage the skin barrier.

4.1. Innate Immune Response

The innate immune system is the first line of defense against pathogens and is crucial for maintaining skin homeostasis. It consists of the epidermal barrier, cells of the immune system, cytokines, pattern recognition receptors (PRR), antimicrobial peptides and skin microbes [38]. A recent study showed that the skin of AD patients has an over-representation of innate immunity and angiogenesis markers [39]. There is a three to four times increased percentage

of proliferating Langerhans cells in atopic skin than in healthy control. On the contrary, patients with AD have reduced levels of Antimicrobial Peptides (AMPs), contributing to an increased risk of skin infections, which induce pro-inflammatory cytokines by activating TLR2 [40]. They can also enhance the upregulation of FcεRI (high-affinity IgE receptor), which binds immunoglobins on skin dendritic cells and enhances the immune response and the skin's inflammatory reaction.

The skin barrier disruption activates inflammatory epidermal dendritic cells and stimulates keratinocytes to produce proinflammatory cytokines such as TSLP (Thymic stromal lymphopoietin), IL-25, L-33, and type 2 mediated responses [41]. TSLP activates immature dendritic cells and enhances the maturation of antigen-presenting cells (APCs). Research shows that TSLP is highly expressed in the skin of patients with AD, and its production is triggered by exposure to environmental factors such as allergens, microorganisms, diesel exhaust, cigarette smoke, and chemical irritants [42]. Korean birth cohort study showed elevated expression of TSLP in the skin of 2-month-old infants before the development of clinical AD at 24 months of age [43]. IL-25 induces the expression of various chemokines: eotaxin, CCL17, (thymus and activation-regulated chemokine), and MDC (macrophage-derived chemokine), which are necessary for the recruitment of eosinophils and Th2 cells. IL-33 activates NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) and MAP (mitogen-activated protein kinases), which stimulates the production of cytokines related to Th2 response (such as IL-4, IL-5, and IL-13) [38].

4.2. Adaptive Immune Response

The adaptive immune response in the early phases of the disease process in AD is predominantly characterized by a Th2 signal. Switching from Th2 to Th1 seems to promote chronicity of the disease [44].

External irritants and damage to the epidermal barrier lead to the stimulation of the Th2 response. Activated Th2 cells secrete cytokines such as IL-4, IL-5, and IL-13. IL-4 and IL-13 promote IgE class switching in B cells via the signal transducer and activator of the transcription (STAT) pathway [45], leading to elevated serum IgE levels. IL-5 is involved in the recruitment and activation of eosinophils in peripheral blood and tissues [46]. In addition mentioned earlier cytokines also regulate the proteins needed in the epidermal barrier. IL-4 and IL-13 stimulation were both shown to inhibit FLG function and production, with an effect

strong enough to simulate a loss of function mutation in FLG already discussed above [47]. Another study demonstrates how IL-4 upregulates, via the JAK/STAT pathway, the expression and function of the histamine receptor 4, expressed on peripheral eosinophils [48].

5. Skin barrier dysfunction

Numerous studies have demonstrated that skin barrier dysfunction is a critical component of atopic dermatitis. An impaired barrier allows external antigens and toxins to penetrate the skin and induce inflammation. This defect causes degradation of intercellular connections, higher protease activity, increased epidermal permeability, infiltration of antigens, and stimulation of proinflammatory cytokines [49].

Keratinocytes of patients with AD show an increase in the apoptosis process. Genes related to apoptosis such as NOD2, DUSP1, and ADM were all induced by the IFN-γ. The loss of skin cells due to apoptosis may cause gaps in the skin barrier allowing increased water loss and antigen penetration [50].

5.1. Tight junctions

Tight junctions are groups of adhesive proteins placed on opposing membranes of keratinocytes in SC. They are crucial in maintaining skin barrier integrity as they control the passage of fluids and solutes paracellularly acting as a selective barrier. The components of tight junctions include claudins, occludins, tricellulin, zonula occludens, and junction adhesion molecules [51] Study conducted by De Benedetto et al. [52] shows a striking reduction in expression of TJ skin proteins in AD patients. Moreover, the expression of claudin-1 correlated with Th 2 cytokines, serum IgE, and serum eosinophils [53]. In another study on animal models, it was revealed that upregulation of claudin-1 attenuated the severity and natural course of AD. Furthermore, reduced expression of tight junction proteins such as claudin-1 and 4 may be caused by cytokines such as IL-17 and bacterial infection [54].

5.2. Increase TEWL

Cutaneous barrier lesion leads to a significant increase in transepidermal water loss (TEWL) [55]. Stratum corneum hydration declines in both lesional and nonlesional AD skin, moreover it is suggested that a high TEWL may correlate with disease severity. Dry skin promotes the survival and replication of invasive staphylococci and inhibits the growth of commensal organisms, which leads to disruption of the skin microbiome [56]. It also stimulates epidermal hyperplasia and early evidence of inflammation (eg, mast cell degranulation), even in normal skin.

Regular application of emollients has been reported to reduce TEWL, enhance skin hydration, and improve general skin barrier function.

6. Conclusion

Atopic dermatitis is the most common inflammatory skin condition that affects both children and adults. Multiple factors, including epidermal gene mutations, skin barrier dysfunction, immune dysregulation, altered lipid composition, and microbial imbalance, can contribute to the development of the disease. Recently, there has been substantial progress in understanding the pathogenesis of AD. These new insights related to the genetic, immunologic, and environmental impacts have paved the way for future novel treatments. Early diagnosis and treatment may help decrease the morbidity of the disease and prevent progression to other associated atopic diseases. Further advances in this matter will allow us to achieve a precision medicine approach to the prevention and treatment of AD.

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