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REVIEW ARTICLE

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A new autoimmune disease: atopic dermatitis in children

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Abstract
Atopic dermatitis (AD) is mainly considered an allergy, exacerbated by allergic factors. Is there evidence to suggest the existence of autoimmune components in the pathophysiology of the illness? Studies in the literature that dealt with the occurrence of autoimmunity in children with AD were analyzed. We followed the studies published in PubMed for 10 years, from 2001 to 2021. Clinical signs and symptoms were similar to other autoimmune diseases, having periods of remission and relapses. Other correlations between AD and autoimmune diseases have been described, and patients with AD can also present with a wide range of autoimmune comorbidities. Three major factors contribute to the pathogenesis of AD: damage of the skin barrier, disorders of the immune response, and imbalances of the skin microbiome—all based on genetic changes and influenced by environmental factors. Predominant activation of Th 2 cells, with the increase of Th 1, Th 17, and Th 22 subsets, promotes skin inflammation. All this evidence suggests that AD might be classified as an autoimmune disease, not just as an allergic reaction.

Introduction

Atopic dermatitis (AD) is a chronic relapsing skin disease manifested trough extreme itching along with other symptoms.[1] The inflammation in AD is complex, with remissions and relapses and a clinical course that strikingly resembles autoimmune diseases.[1,2] The condition was first designated as AD in 1933 by Wise and Sulzberger. The prevalence of the illness is rising, affecting about 15-30% of children and 2-10% of adults. It is important to take into consideration

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the socioeconomic impact as well as the impairment of quality of life for patients and their families.[3] The etiology is not fully known, even though there have been attempts to tie the symptoms to allergic factors. Several studies emphasized the allergic factors which are more likely implicated in the exacerbations of AD.[4] However, concerning the physiopathogenesis of this complex disease, there are three major mechanisms: (1) skin barrier dysfunction, (2) disturbance of the immune response, and (3) alteration of the skin microbiota.[2,5] These mechanisms are influenced by genetic as well as environmental factors.

One of the most studied aspects of AD is skin barrier dysfunction. Considered as a barrier between the internal and external environments, the skin provides protection and support to the organism. Primary functions of the epidermal barrier include limiting passive water and preventing environmental chemical absorption and microbial infection.[6] Keratinocytes are the main cells that sustain the skin. After mitosis, keratinocytes differentiate and migrate from the stratum basale toward the stratum corneum. This differentiation process forms the following keratinocyte layers: stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum.[7] The corneocytes are responsible for protection against mechanical and chemical injury. The lipid matrix provides the essential component of the water barrier.[8] Most of the mechanical strength provided by the epidermal barrier is due to corneocytes. A protein shell surrounds each corneocyte, consisting of loricrin, involucrin, and filaggrin. In immediate contact with the corneocyte sits the corneocyte lipid envelope, a structure of specialized lipids which is important for the formation of the functional skin barrier.

AD has been linked to genetic abnormalities related to filaggrin. Filaggrin deficiency has been found to have an important role in AD in children, increasing the severity of allergies, infection rates, and vulnerability. Filaggrin can be broken down into free amino acids, forming the urocanic acid, which is responsible for the acidity level in the skin, and pyrrolidine carboxylic acid, a natural moisturizer. Filaggrin abnormalities are related to dry skin in patients with AD because of transepidermal water loss. Skin barrier dysfunction leads to an inflammatory response and autoimmune reactions that result in the production of IgE by B cells and interleukins (ILs) by Th2 cells.[9]

We studied PubMed articles that were found from keywords autoimmunity and atopic dermatitis. We analyzed the articles that described elements of autoimmunity in AD and the occurrence of autoimmunity in children with the disease.

Immune Mechanisms that Initiate and Sustain Inflammation

Th2 lymphocytes also represent an important source of pruritus-generating cytokines, such as IL-31. Studies show that there is a strong correlation between the presence of pruritus and IL-31 secretion; individuals with severe forms of pruritus have increased serum levels of IL-31, while those with mild symptoms have normal or low levels of IL-31.[2,10,11] In an average individual, the different types of T cells, specifically Th1 and Th2 cells, are in balance. One of the immunological hypotheses suggests an imbalance between the Th1 and Th2 cells, the former being excessively activated and producing interleukins such as IL-4, IL-5, and IL-13, which results in increased IgE production.[11,12]

The T and B lymphocytes play an important role in the activation of eosinophiles (Eo), mastocytes, and basophiles. It has been proven that basophiles are another important source of IL-4, IL-5, and IL-13. These cytokines are potentially regulated by another family of cytokines, produced by epithelial cells, for example, thymic stromal lymphopoietin, IL-25, and IL-33.[4,13] Nemolizumab, a monoclonal antibody that targets IL-31 specifically, can be potentially used as a treatment for AD. Dupilumab, also a monoclonal antibody, may influence the production and intensity of pruritus by blocking IL-4 and IL-13.[14] Biological therapies represent a new direction in the treatment of AD.[2,15,16]

Disturbances of the epidermal functions can lead to the apparition of signs and symptoms characteristic of AD. Destruction of the skin barrier increases antigen penetration into the body and also cytokine production.[17] Xerosis and ichthyosis are common manifestations associated with AD, although it has been proven that half of the patients with vulgar ichthyosis have other atopic diseases as well, and 37% of AD patients present this skin lesion.[17,18] According to recent findings, mutations in the gene encoding filaggrin are also responsible for skin barrier dysfunctions and are thus implicated in the pathogenesis of vulgar ichthyosis. Other consequences of skin barrier lesions are transepidermal water loss and increased permeability to environmental allergens. These allergens lead to increased levels of inflammatory cytokines and other inflammatory processes, and their increased penetration into the body also represents an important step in the atopic march.[19,20]

Thymus and activation-regulated chemokine (TARC) have an important role in the pathogeny of AD by enhancing the inflammation mediated by Th2 lymphocytes. TARC can be used as a marker of the short-term evolution of AD. It may represent a potential molecular target in the treatment of AD, and blocking it significantly reduces epithelial inflammation.[9,21] Immune system dysfunction, along with changes in the epidermal barrier function, facilitates lesions with the possibility of bacterial colonization, especially of *Staphylococcus aureus*. Colonization with Staphylococcus increases inflammation, hyperkeratinization, and the production of proteases. The persistence of chronic inflammation, even after allergic factors have been eliminated, is caused by *Staphylococcus aureus* infection. *Staphylococcus aureus* colonization was identified in 90% of patients with severe clinical forms of the disease.[22-24]

It also involves the innate defense system: T cells activate superantigens through enterotoxins. There can be direct stimulation of the mast cell (MC) degranulation. Susceptibility to herpes simplex virus infection is also a result of the combination of the defects in the epidermal barrier and those of the innate defense system and adaptive immune response.[25] The cross talk between immune cell disorders and keratinocytes produces an intensification of pruritus. Excess mediators secreted by both cell groups stimulate sensitive nerve endings. Thymic stromal lymphopoietin, which is derived from keratinocytes, plays a role in the effect on the sensory nerves and the increased production of Th2 cytokines such as IL-31 and IL-13, resulting

in neurogenic inflammation with numerous and important consequences.[26]

Autoimmune Mechanisms in AD

Even if, historically, the pathogenesis of AD is considered to be allergic and inflammatory, there is accumulating evidence that hints at the existence of an autoimmune component of the disease.[2,21,23] There are more than 30 studies that associate the presence of autoantibodies with AD, by identifying IgE autoantibodies in AD patients. Most of these studies focus on the identification of autoantigens in epithelial cell extracts, which are targeted by IgE.[27] All of the studies included in this review concluded that IgE autoantibodies are more frequent in patients with AD compared to control groups.[6,28]

Other studies following up on the autoimmune nature of AD have identified antinuclear antibody (ANA) as a potential indicator. Eight studies have shown that ANA are significantly more frequent in patients with AD, compared to the control group.[16,29] Some studies tried to associate IgG autoantibodies with the illness, but there were no quantitative measurements conducted, and so they did not yield statistically significant conclusions.[4,18]

Concerning the association of autoantibody levels and disease severity, 16 studies managed to prove the existence of a positive correlation between IgE autoantibody levels and the severity of clinical symptoms.[10,30] It was also proven that there was an increased autoreactive response of the T lymphocytes in patients with AD.[8,31] It is hypothesized that there is a modified ratio of CLA+/CLA− and CCR4+/CCR4− cells involved in the process.[32] Studying these autoimmunity indicators can lead to promising results concerning the correlation with AD. Other studies have shown that the suppressive effect of regulatory T lymphocytes on the proliferation of CD8+ CLA+ T lymphocytes is absent in AD.[33,34] This mechanism is similar to other autoimmune conditions, such as psoriasis.[2,24]

Skin barrier damage and the consequent release of self-peptides that play the role of autoantigens can lead to three activation pathways.[9,32] In the first path, the epidermal autoantigens are presented by the dendritic cell to the naïve T cell. The naïve T cells can differentiate into Th2 cells through IL-4, IL-5, IL-13, and IL-31, and into Th1 cells through interferon (IFN) gamma.[2,18,35] Of these two, in AD, Th2 cells play the main role. Activated Th2 cells stimulate the Eo through IL-5 and, through IL-4, they stimulate B cells which secrete excessive amounts of IgE autoantibodies.[32-34,36,37] These IgE autoantibodies get attached to the MC membrane, as well as the epidermal self-peptides, through the second activation pathway, leading to MC degranulation and histamine release.[15,31] Histamine and IL-31, also secreted by Th2 cells, act on the nervous fibers, producing pruritus.[9] In the third activation pathway, the self-peptides act on the skin T cells, producing a cytotoxic reaction.[28,32] Because of the skin damage, the keratinocytes secrete IL-33, which stimulates the innate immune response. The interface of autoimmunity with AD is presented in Figure 1.

Conclusions

AD is a chronic inflammation of the skin, manifested mainly by pruritus and dry skin, and is more prevalent in pediatric

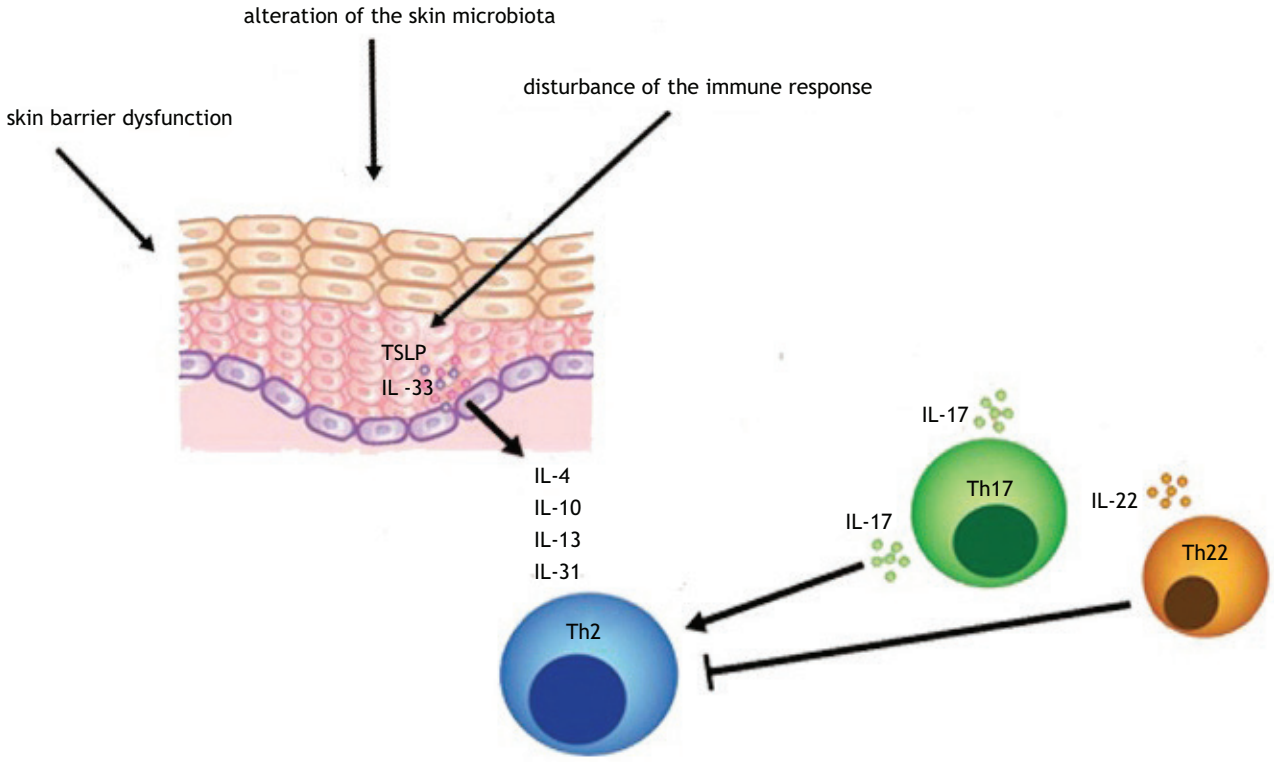

Figure 1 Interface of autoimmunity with atopic dermatitis.

patients. Three major factors contribute to the pathogenesis of AD: damage of the skin barrier, disorders of the immune response, and imbalances of the skin microbiome—all based on genetic changes and influenced by environmental factors. Predominant activation of Th 2 cells, with the increase of Th 1, Th 17, and Th 22 subsets, promotes skin inflammation. Our study highlights the fact that an autoimmune component exists in the pathogenesis of AD, upheld by the association of other autoimmune conditions with AD and the similar clinical course of autoimmune diseases and AD.

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Conflicts of Interest

The authors declare no conflicts of interest.

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