

# Immunological Implications in Atopic Dermatitis

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**Abstract** Both the inborn and acquired immune system plays an important role in the pathogenicity of atopic dermatitis (AD). The skin lesions are mostly due to the complex interaction of the cytokines, above all the ones secreted by the T helper 2 lymphocytes (Th2). In the acute phase of the disease, the most important cytokines are IL-4, IL-5 and IL-13, and also the subsequent activation of mastocytes and eosinophiles. The next step is the production of antigen-specific antibodies. The Th2 immune response is initiated by IL-1, IL-25, IL-17, IL-33 and by thymic stromal lymphopoietin (TSLP). Th2 cytokines block the expression of differentiation of certain proteins, like locrine, filaggrin, involucrin, and at the same time, they reduce the beta-antimicrobial peptide levels, disturbing the skin barrier in the process. In the chronic phase of the illness, the Th2 cytokines are predominant, with varying levels of T helper 17 cytokines.

**Keywords:** atopic dermatitis, allergic, immunological, factors, evaluation

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## 1. Introduction

The illness known as atopic dermatitis (AD) is a chronic relapsing non-contagious skin disease that produces extreme pruritus and affects children and adults alike. [1] The evolution of AD is characterized by remissions and relapses. [2] The disease has an annually increasing rhythm. It affects the rise, affecting 15-30% of children, and 2-10% of adults. The environmental factors influence the incidence of the illness. Also, the socio-economic burden is significant, but we cannot dismiss the impairment of the quality of life of the patient and the family as well. [3] In classic medicine AD was considered to be of allergic etiology, but lately, evidence emerged that immune processes play a more significant role in the pathogenesis of the disease. Allergic factors most likely are involved in the exacerbations of the illness. [4,5] The three major pathogenetic mechanisms that explain the symptoms are skin barrier dysfunction, disturbance of the immune response and the alteration of the skin microbiota. These components are also influenced by genetic and environmental factors. [6,7,8]

## 2. Pathogenetic Mechanisms

One of the immunological hypotheses is based on the existence of an imbalance between the Th1 and Th2 cells. The Th1 cells are excessively activated, producing

interleukins such as IL-4, IL-5 and IL-13, which in turn increase IgE production. [1,3,9,10]

The activation of eosinophiles cells, mastocytes and basophiles, usually mediated by T and B lymphocytes, also play an important role. It was also proven that basophiles are another source of IL-4, IL-5 and IL-13. The production of these cytokines are potentially regulated by another family of cytokines as well, produced by epithelial cells (thymic stromal lymphopoietin (TSLP), IL-25 and IL-33). [1,11,12]

The interaction between keratinocytes and immune cells is essential in producing pruritus. Both groups of cells secrete excessive amounts of mediators that stimulate sensitive nerve endings. TSLP, derived from keratinocytes, stimulates the sensory nerves, as well as the increased secretion of Th2 cytokines, such as IL-13 and IL-31, which ultimately results in neurogenic inflammation with all the consequences derived from it – activation of Th2 response, keratinocyte proliferation and epidermal damage. [1,2] The excessive production of IL-31 and the presence of pruritus are strongly correlated: patients with severe pruritus have increased serum levels of IL-31, while the ones with no pruritus complaints have physiologic levels of IL-31. Nemolizumab, a monoclonal antibody against IL-31 is a potential treatment in AD. Pruritus can be also diminished by blocking IL-4 and IL-13, using Dupilumab, another monoclonal antibody. These biological therapies represent some of the new directions in the treatment of AD. [13,14,15]

The loss of the skin barrier function can be considered both the result of the pathogenetic mechanisms and can

also lead to the aggravation of the lesions in AD. Alterations of the skin barrier allow the intrusion of self-antigens and environmental allergens into the body, with the consequent increase of the cytokine response and inflammation, and leads to transepidermal loss of water [1,15,16]. AD is commonly associated with xerosis and ichthyosis: around 50% of patients with vulgar ichthyosis present the atopic march and 37% of AD patients manifest this skin lesion. Recent studies prove the genetic baseline of the skin barrier dysfunctions, with mutations in the gene encoding filaggrin which were found in patients with vulgar ichthyosis. [1,17]

TARC (thymus and activation-regulated chemokine) plays a significant role in the pathogenesis, diagnostic and potentially the treatment of AD: it enhances the Th2 mediated inflammation, it can be used as a serological marker when following the short term evolution and also represents a potential molecular target in the treatment of AD. [16,18]

Epidermal barrier defects, along with immune system disorders and the changes of the antimicrobial peptides allow the bacteria in colonizing the epidermis, especially *Staphylococcus Aureus*. [16,19,20] Colonization with this bacteria increases, in turn, the inflammation and the production of proteases. Patients are also more susceptible to Herpes Simplex Virus which further compromises the skin barrier. [21,22]

In our case studies, we followed 87 patients with AD that met the definition criteria of the disease. One goal was observing the contribution of the allergic factor in the etiology of AD. Consequently, we found that 46% of the patients there could not be proven the existence of a type I hypersensitivity. Regarding the age of the patients, we found that in 81% of the cases, the onset of symptoms occurred in the first 5 years of life. We also noticed that exposure to allergic factors have aggravated the manifestations of AD or caused flare-ups by 67%. The study also highlighted that if both parents had a history of atopic march, the risk of developing AD was 3 times higher.

### 3. To Remember

- AD is a multifactorial disease, which is the combined result of the dysfunctionality of the skin barrier, the immune imbalance and the environmental and genetic factors.
- The treatment should target the maintenance of the skin barrier function, via topic treatments, interventions on the immunological imbalance and the autoimmune components, using monoclonal antibodies for IL-4, IL-31.
- Proactive use of topical corticosteroids and calcineurin inhibitors, for two consecutive days every other week, and the use of IL-4 blockers is a treatment scheme with an optimistic prognostic.
- The individualization of the treatment according to the age, the extension and the severity of the lesions, can represent the key to success in treating AD.

### 4. Conclusions

1. AD is a chronic skin condition that represents a challenge for the patients and relatives and also for their attending physicians because of the frequent treatment difficulties.

2. The immunological processes are essential for the perpetuation of lesions characteristic of AD.

3. Therapeutic interventions against these pathogenic mechanisms can lead to significant results concerning disease severity and progression.

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