

# INSIGHTS INTO ATOPIC DERMATITIS – FROM PATHOGENESIS TO THERAPY

K. Papadakis<sup>1</sup>, T. Handjieva-Darlenska<sup>2</sup>, R. Tafradjiiska-Hadjiolova<sup>1</sup>, H. Nocheva<sup>1</sup>

<sup>1</sup>Department of Physiology and Pathophysiology, Medical Faculty, Medical University – Sofia, Bulgaria

<sup>2</sup>Department of Pharmacology and Toxicology, Medical Faculty, Medical University – Sofia, Bulgaria

**Abstract.** Atopic dermatitis (AD), or eczema, is a common skin disease that is often associated with other atopic disorders, such as allergic rhinitis and asthma. The disease can develop both in infancy and adulthood, and characterizes with recurrent episodes impairing the quality of life. The review analyzes the genetical, immunological, and environmental factors in the pathogenesis of AD. The role of the skin barrier function is also considered in regard of the main hypotheses for AD development. Further elucidation of the mechanisms involved in the pathogenesis of AD could give interesting and useful clues for therapeutic protocols and prophylactic approaches.

**Key words:** atopic dermatitis, pathogenesis, genetics, environment, skin barrier

**Corresponding authors:** Hristina Nocheva – e-mail: hndimitrova@medfac.mu-sofia.bg; Radka Hadjiolova – e-mail: rhadjiolova@medfac.mu-sofia.bg

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## INTRODUCTION

Atopic dermatitis, or eczema, is a common skin disease that is often associated with other atopic disorders, such as allergic rhinitis and asthma [1].

Atopic dermatitis (AD) was once thought to be primarily a paediatric disease. In fact, 45% of all cases of atopic dermatitis begin within the first 6 months of life and, of note, 60% begin during the first year. Furthermore, 85% begin before 5 years of age. More than 50% of children who are affected in the first 2 years of life do not have any sign of IgE sensitization, but they become sensitized during the course of AD [2]. Up to 70% of these children have a spontaneous remission before adolescence.

However, recent epidemiologic studies showed that the disease is a common disorder also in adults. Emerging studies showed that genetic, immunologic,

and epidemiologic risk factors for AD differ in adults and children [3].

The prevalence of AD has doubled or tripled in industrialized countries during the past three decades: 15 to 30% of children and 2 to 10% of adults are affected. The disease can start in both early infancy (so-called early-onset atopic dermatitis) and adulthood (so-called late-onset atopic dermatitis). AD may represent a prelude to another atopic condition – e.g. asthma, even though in most patients no sign of IgE mediated sensitization has been confirmed [4].

It is believed that AD results from a combination of endogenous and exogenous factors. Endogenous factors include genetic, immunologic, and behavioural factors. Exogenous factors include different environmental entities capable to induce skin lesions in assemblance to endogenous predisposition.

The pathogenetic mechanisms underlying AD can be summarized in two broad groups:

- Disruption of the barrier function of the skin;
- Alterations in the normal immune response of the skin.

Such two groups generally correlate with the two main hypotheses for AD:

- The “outside-inside” hypothesis proposes that skin barrier disruption precedes, and predisposes to, skin inflammation;
- The “inside-outside” hypothesis suggests that skin inflammation due to an altered immunologic response precedes, and predisposes to, loss of the normal skin barrier function.

A unifying “inside-outside-inside” hypothesis has been also proposed, according to which altered immunologic reactivity accomplishes for the secondary barrier dysfunction that additionally promotes skin inflammation due to activation of type 2 immune responses [5].

## GENETIC FACTORS

Genetic inheritance plays an essential role in the predisposition to childhood AD. Monozygotic twins have a higher rate of AD concordance (77%) than dizygotic twins (15%) [6].

Null mutations in the filaggrin (FLG) gene are the most well-studied genetic determinant of AD. FLG codes for the protein filaggrin, which is broken down into a natural moisturizing factor in the stratum corneum and plays an integral role in skin-barrier function [7].

FLG null mutations lead to a deficiency of natural moisturizing factor and xerosis in AD, impairing epidermal barrier function. FLG loss-of-function mutations are associated with early childhood onset AD with greater severity and persistence into adulthood. Enhanced expression of IL 1 cytokines in the stratum corneum of patients with FLG loss-of-function mutations and type 1 interferon-mediated stress response are detected [8].

Filaggrin-dependent secretion of sphingomyelinase has also been found to protect against staphylococcal a-toxin-induced keratinocyte death [9]. This strongly suggests that patients with filaggrin mutations have a distinct endotype of AD with different mechanistic outcomes, which could be used to identify one subset of AD, particularly for the development of new therapies targeting skin barrier function.

Even being characteristic for childhood, FLG loss-of-function mutation is not found in all children with AD

– it has not been described in South Africa, Ethiopia or the African-American population, nor does it seem to take part in the pathogenesis of AD after puberty and after 18 years of age [10].

Depending on the population, FLG mutations are found in up to 40% of patients with severe AD, but less than 20% of these patients with severe disease are homozygous or compound heterozygous for FLG mutations [11].

Genome wide scans have highlighted several possible atopic dermatitis-related loci on several chromosomes. A region of particularly high linkage was identified on chromosome 1q21, which harbours a family of epithelium-related genes called the epidermal differentiation complex. Even though the exact function and association with AD is not yet elucidated, existing data support the importance of serine protease inhibitors (e.g., SPINK5) for normal skin barrier maintenance. Most of the genetic regions associated with atopic dermatitis correspond to loci associated with psoriasis, although these two diseases are rarely linked [4].

Among other „candidates“ for mediators in the development of AD are a number of genes encoding cytokines that regulate the synthesis of IgE: IL-4, IL-5, IL-12, IL-13, granulocyte-macrophage-colony stimulating factor. IL-4, IL-5 and IL-13 (the synthesis of which is associated with Th-2 lymphocytes) increase IgE levels, while IL-12 (mainly produced by Th-1 lymphocytes) decreases them. Some patients with AD present with the so-called gain-of-function mutations associated with gene polymorphism (e.g. of the  $\alpha$ -subunit of the IL-4 receptor, or the IL-18 gene, which regulates the switch from a Th-1 to a Th-2 immune response) [4].

A genetic factor of clinical importance in patients over 18 years of age is the 1903/A-polymorphism of the mast cell chymase (MCC) gene, which is not associated with the development of allergic rhinitis or asthma. Its presence is inversely proportional to IgE levels in adults [10].

Other genetic factors associated with AD include vitamin D receptor gene polymorphisms [12].

## THE SKIN BARRIER FUNCTION

The skin is the frontier between the organism and the environment and has two key functions: 1. as a robust external barrier that is resilient against environmental stressors; and 2. as a watertight internal barrier that prevents trans-epidermal water loss (TEWL) and the colonization of the skin and underlying tissues by pathogens. Thus, the skin acts as a versatile

double barrier providing dual external-internal protection. The skin is also involved in regulatory functions in association with the organs of the body – serves as a common platform for signal exchange between internal organs and the environment via the cutaneous neuroendocrine system and the production of neuropeptides, biogenic amines, melatonin, opioids, cannabinoids, secosteroids, growth factors, and cytokines [5].

The stratum corneum (SC) resembles a brick wall comprising protein-enriched corneocytes ('bricks') embedded in an intercellular matrix of nonpolar lipids ('mortar') in between the granular and cornified layers. Corneocytes represent the cellular complement of the SC structure and contain a variety of enzymes, water, and keratin filaments, which give rise to the mechanical strength of the SC. They are encased in a cross-linked layer of proteins, such as filaggrin, loricrin, and involucrin, which anchor the cells with the lipid-rich extracellular matrix, the 'mortar'. This hydrophobic lipid matrix comprises approximately of 50% ceramides (CER) and 15% free fatty acids (FFAs), with the remaining 25% comprised of predominantly cholesterol and a small percentage of triacylglycerol (TAG) species, with FFAs and long-chain bases liberated from sebaceous TAG and epidermal CER, respectively, serving as potent antimicrobial agents. Improper epidermal permeability barrier formation contributes to TEWL and triggers the onset of inflammatory skin diseases, such as AD. This validates the crucial role of the SC in maintaining the dual barrier function of the skin. In addition, SC has potent antioxidant properties that help it to prevent oxidative damage to the skin via the secretion of enzymes, such as catalase, as well as nonenzymatic molecules, such as vitamin E, glutathione, and uric acid [5].

An intact epidermal compartment is a prerequisite for the skin to function as a physical and chemical barrier. The barrier itself is the SC with its brick and mortar-like structure described above. An alteration of the barrier that causes increased transepidermal water loss is a hallmark of AD. Intercellular lipids of the epidermal horny layers are provided by lamellar bodies, which are produced by exocytosis from upper keratinocytes. Alterations in the expression of enzymes involved in the subtle balance of epidermal adhesion structures are also likely to contribute to the breakdown of the epidermal barrier in patients with atopic dermatitis [4].

Special attention is paid to some specific components of the SC. CER comprises almost 50% of the total lipid component constituting SC. CER are related to the packing of corneocytes in the SC and were among the first lipids to be connected with skin barrier func-

tion deficiencies and AD. Later studies showed that deficient barrier function was associated with age-related decrease in the so-called 'ultra-long chain' ceramides (i.e., those with more than 26 carbons in length) and an increase in short-chain CER [5].

Experiments with topical application of different CER containing formulations seemed to improve the skin barrier function. These new insights hopefully will place in the basis of new therapeutic approaches [13].

Changes in skin ceramides that are secondary to variations in the pH of the SC can disturb maturation of lamellar bodies and impair the barrier [14].

Changes in FFAs and cholesterol content in AD have also been documented in relation to skin barrier function [15].

## THE INNATE SKIN BARRIER

Epithelial cells at the interface between the skin and the environment are the first line of defence of the innate immune system. They are equipped with a variety of sensing structures, which include the toll-like receptors (TLRs), C-type lectins, nucleotide-binding oligomerization domain-like receptors, and peptidoglycan-recognition proteins [16]. At least 10 different TLRs have been described in humans; they bind to bacterial, fungal (both cell walls), or viral structures (DNA or RNA), and to other microbial structures termed the pathogen-associated molecular patterns. TLR-mediated activation of epithelial cells induces the production of defensins and cathelicidins – families of antimicrobial peptides [4].

The inflammatory microclimate initiated by IL-4, IL-13, and IL-10 down-regulates these antimicrobial peptides in the skin of patients with atopic dermatitis. For these reasons, it is difficult to manage microbial infections of the skin in patients with AD. Lesional and normal looking skin is extensively colonized by bacteria such as *Staphylococcus aureus* or fungi such as *malassezia*. AD patients are predisposed to eczema herpeticum and eczema vaccinatum because of a reduced production of cathelicidin, which has potent antiviral activity [17].

## IMMUNOLOGIC MECHANISMS IN AD PATHOGENESIS

### *Skin sensitization – the beginning of atopic skin inflammation*

Location of allergic disease is determined in part by route of allergen sensitization, tissue chemokine expression, and tissue compartmentalization of the immune response. Studies in animal models have

demonstrated heterogeneity in the ability of memory T-cells to migrate to different tissues [18]. This tissue-selective homing is regulated by interaction of differentially expressed T-cell homing receptors with vascular endothelial cell surface antigens. The cell adhesion molecule that participates in T-cell homing to the skin is termed “cutaneous lymphocyte-associated antigen” (CLA). Importantly, T-cells migrating into the skin of allergen-induced reactions express significantly higher levels of CLA than do T-cells isolated from the airways of asthmatic subjects [19].

Th-2 and Th-1 cytokines contribute to the pathogenesis of skin sensitization/inflammation in AD with the relative contribution of each cytokine dependent on the duration of the skin lesion.

Early-onset atopic dermatitis usually emerges in the absence of detectable Ig E-mediated allergic sensitization, and in some children – mostly girls – such sensitization never occurs [20]. The initial mechanisms that induce skin inflammation in AD patients are unknown. They could entail neuropeptide-induced, irritation-induced, or pruritus-induced scratching, which releases proinflammatory cytokines from keratinocytes, or they could be T-cell-mediated but IgE-independent reactions to allergens present in the disturbed epidermal barrier or in food (so-called food-sensitive AD). Allergen-specific IgE is not a prerequisite, however, because the atopy patch test can show that aeroallergens applied under occluded skin induce a positive reaction in the absence of allergen-specific IgE [21].

In patients with early-onset AD, IgE-mediated sensitization often occurs several weeks or months after the lesions appear, suggesting that the skin is the site of the sensitization. In animal models, repeated epidermal challenge with ovalbumin-induces ovalbumin-specific IgE, respiratory allergy, and eczematous lesions at the application site [22]. A similar process is likely in humans. Epidermal-barrier dysfunction is a prerequisite for the penetration of high-molecular-weight allergens from pollens, house-dust-mite products, microbes, and food. Molecules in pollens and some food allergens drive dendritic cells to enhance Th-2 polarization [23]. There are numerous T-cells in skin (106 memory T-cells per square centimetre of body-surface area), nearly twice the number in the circulation [24]. Moreover, keratinocytes in atopic skin produce high levels of the IL-7-like thymic stromal lymphopoietin that signals dendritic cells to drive Th-2 polarization [25].

The skin acts as the point of entry for atopic sensitization and may even deliver signals required for allergenic sensitization in the lung or the gut. Wide-

spread skin inflammation can affect adaptive immunity, alter the phenotype of circulating monocytes, and increase the production of Pg E2 in AD. All these factors provide signals required for strong skin-driven Th-2 polarization [4].

There are two lineages of epidermal dendritic cells: plasmoid and myeloid. The first has strong antiviral activity due to significant IF $\alpha$ -production. This cell line is practically absent in AD. On the contrary, the second lineage of cells includes Langerhans and inflammatory dendritic epidermal cells, which are present in significant numbers in AD. Epidermal dendritic cells in AD bear IgE and express its high-affinity receptor (Fc $\epsilon$ RI). Langerhans cells can also be found in normal epithelium, while inflammatory dendritic epidermal cells are characteristic only for inflamed skin areas – they, in fact, transmit allergens to Th-1 and Th-2 cells, and possibly to other regulatory T-lymphocytes. Allergen-specific CD4+ and CD8+ T cells can be isolated from the skin lesions of patients with AD [4].

### ***The biphasic T-lymphocyte-mediated skin response***

In the acute phase of the lesions cytokines like IL-4, IL-5, and IL-13 predominate. Since they are part of the Th-2-mediated immune response, this initial Th-2 phase precedes the chronic phase in which Th-0 cells (cells that share some activities of both Th-1 and Th-2 cells) and Th-1 cells are predominant [26].

In the acute phase of AD, the skewed Th-2 response leads to increased activity of IL-4, IL-5, IL-13, IL-31, IL-18, thymus and activation regulated chemokine, TNF $\alpha$ , monokine induced by gamma interferon, and interferon  $\gamma$ -induced protein 10 kDa [27]. IL-4 and IL-13 are the only cytokines that induce germline transcription promoting isotype switching to IgE, also inhibiting the production of Th-1 cytokines.

Th-1 responses are upregulated in the chronic phase of AD. An increase of interferon- $\gamma$ , IL-12, and GM-CSF then characterises the Th-1- and Th-0-mediated immune responses. So, the peak of IL-12 expression is followed by increased expression of interferon- $\gamma$  messenger RNA by Th-1 cells, and inflammatory cells appear in the skin – normal-looking skin in AD patients presents a mild infiltrate, strongly suggesting the presence of residual inflammation between flares [27].

Inflammatory cells and keratinocytes in the skin lesions express high levels of chemoattractants. Additional amplification of the allergic response is sustained due to the generation of interferon- $\gamma$ -producing cytotoxic T-cells, implicated in the apoptosis of keratinocytes induced by the cell-death receptor Fas [28].



The complexity of the regulatory T-cell compartment is not yet fully understood, and the role of regulatory T-cells in the regulation of chronic inflammatory skin disease is elusive.

Children compared with adults with AD show comparable or greater epidermal hyperplasia and immune infiltration, and decreased filaggrin expression on histology and immunohistochemistry as well as activation of Th-2, Th-22, and Th-1 axes on quantitative real-time polymerase chain reaction. However, children showed higher induction of Th-17-related cytokines, antimicrobials, Th-9, IL-33, and innate markers than adults. These results suggest that the immune mechanisms of AD may differ between children and adults [29].

### **Autoimmune mechanisms in AD**

Some autoallergens in skin are also strong inducers of Th-1 responses. About 25% of adults with atopic dermatitis have IgE antibodies against self-proteins – proteins from keratinocytes and endothelial cells such as manganese superoxide dismutase and calcium-binding proteins. The serum levels of these IgE autoantibodies correlate with disease severity. Scratching probably releases intracellular proteins from keratinocytes. These proteins could be molecular mimics of microbial structures and thus could induce IgE autoantibodies. IgE antibodies against autoantigens in the skin can perpetuate the allergic inflammation – thus, AD seems to stand at the frontier between allergy and autoimmunity [30].

## **ENVIRONMENTAL FACTORS**

The term “atopic dermatitis” was first introduced in the 1930s in recognition of the close association between AD and respiratory allergy, as well as accumulating data that exposure to allergen plays an important role in its exacerbation. However, there remains considerable debate over whether allergens really have a critical role in AD. This is more than academic because it dictates whether the clinician should look for potential allergens in the AD patient’s environment and recommend allergen avoidance, the way it would have been done as part of the management of asthma and allergic rhinitis. Indeed, recent studies suggest that the immune mechanisms underlying asthma and AD have greater similarities than differences [31].

Through the years investigators’ attention was directed towards different potential triggers of AD.

**Food allergens.** Even though some common allergens – eggs, milk, wheat, soy, peanuts, can pass

the placenta and can also appear in milk, there are no definitive data supporting the protective role of dietary restriction in development of AD. There are even some trials showing a potentially negative effect of maternal dietary antigen avoidance during pregnancy on the developing fetus. Statistically significant lower mean maternal pregnancy weight gain and a non-significant reduction in birth weight with an increased risk of preterm birth have been reported [32].

No definitive conclusions can be drawn from data comparing AD risk in new-borns on breast milk versus those on cow’s milk-based formula. The breastfeeding duration (3–4 month of exclusive breastfeeding versus 6 months or more) also seems irrelevant [33].

Several attempts were made to evaluate eventual advantage of hydrolyzed formulas versus cow’s milk-based ones. Extensively hydrolyzed casein-based, partially hydrolyzed whey containing, soy-based formula, and even oligosaccharides (prebiotic supplemented) formulas have been evaluated with conflicting results as to their protective effect on AD development [33].

**Aeroallergens.** With advancing age, inhaled allergens play an increasingly important role in the pathogenesis of AD in children with atopy. As early as 1918, an exacerbation of AD after exposure to horse dander, timothy (a type of grass) or bee pollen was documented. Over time, data accumulates on the pathogenic effect of *Alternaria* (pollen), dust mites, weeds, animal dander, molds [34].

These clinical studies suggest that inhalation or contact with aeroallergen may exacerbate AD. Laboratory data supporting a role for inhalants include the finding of IgE antibody to specific inhalant allergens in most patients with AD. The degree of sensitization to aeroallergens is directly associated with the severity of AD [34].

**Microorganisms.** Patients with AD have an increased tendency for the development of bacterial and fungal skin infections. *S. aureus* is found in more than 90% of AD skin lesions, while only 5% of healthy subjects harbour this organism. The density of *S. aureus* on inflamed AD lesions without clinical superinfection can reach up to 10<sup>7</sup> colony-forming units/cm<sup>2</sup> of the affected skin area. The importance of *S. aureus* is supported by the observation that even AD patients without superinfection show a reduction in severity of skin disease when treated with a combination of anti-staphylococcal antibiotics and topical corticosteroids [35]. The pathogenetic importance of *S. aureus* in the aggravation and/or maintenance of AD may be due to the toxins released by them with the effect of supe-

rantigens, stimulating the activation of T-lymphocytes and macrophages. Release of enterotoxins A and B and toxic shock syndrome toxin 1 has been experimentally demonstrated, as well as subsequent superantigen stimulation via T-cell receptors [36]. The formation of specific IgE against staphylococcal toxins in the skin has also been reported, as well as the release of histamine from mast cells carrying these specific antitoxin antibodies on their surface [37]. Last but not least, the above hypothesis of the relationship of AD with *S. aureus* skin infection is supported by the correlation data between the severity of AD and the levels of IgE anti-superantigens [36]. The investigators concluded that superantigens may induce an atopic process in the skin by stimulating epidermal macrophages or Langerhans cells to produce IL-1, TNF, and IL-12. Local production of IL-1 and TNF induces the expression of E-selectin on vascular endothelium, allowing an initial influx of T-cells; local secretion of IL-12 could increase cutaneous lymphocyte-associated antigen (CLA) expression on those T-cells activated by allergen or superantigen and thereby increase their efficiency of T-cell recirculation to the skin, perhaps including areas with only low levels of vascular E-selectin and minimal inflammatory activity. IL-12 secreted by toxin-stimulated Langerhans cells that migrate to skin-associated lymph nodes (and serve as antigen-presenting cells therein) could up-regulate the expression of CLA and influence the functional profile of virgin T-cells activated by the toxins, thereby creating additional skin-homing memory-effector T-cells. Together, these mechanisms would amplify the initial cutaneous inflammation in AD, creating conditions favouring staphylococcal skin colonization [34].

Some fungal infections are also of interest, e.g. with *Malassezia furfur* (*Pityrosporum ovale* or *Pityrosporum orbiculare*). *M. furfur* is a lipophilic yeast commonly present in the seborrheic areas of the skin. IgE antibodies against *M. furfur* is commonly found in AD patients and most frequently in patients with head and neck dermatitis. In contrast, IgE sensitization to *M. furfur* is rarely observed in healthy control subjects or asthmatic patients. The potential importance of *M. furfur* as well as other dermatophyte infections is further supported by the reduction of AD skin severity in such patients after treatment with antifungal agents [34].

**Autoallergens.** The majority of sera from patients with severe AD contain IgE antibodies directed against human proteins. Evidence exists to support the idea that human skin dander could trigger immediate hypersensitivity reactions in the skin of patients with severe AD, suggesting that they made IgE against

autoantigens in the skin. These data suggest that, although IgE immune responses are initiated by environmental allergens, allergic inflammation can be maintained by human endogenous antigens, particularly in severe AD [34].

## RELEVANCE OF THE PATHOGENETIC MECHANISMS FOR THE THERAPY

The clinical approaches also depend on presumed pathogenesis. Since patients with established AD have skin barrier dysfunction and skin inflammation, skin barrier repair is among the primary goals of therapeutic attempts. Even during periods of remission and in cases with nonlesional AD, there is transepidermal water loss, and skin hydration is necessary. Emollient therapy is also helpful in improving the skin barrier repair.

Anti-inflammatory medications (corticosteroids or calcineurin inhibitors) can be locally applied (for control of frequent relapses and subclinical inflammation). Medium- and high-potency corticosteroids can be used for short periods of time to control the disease in occasions of acute AD exacerbations.

Elimination of factors (including allergens, irritants, and emotional triggers) that might exacerbate the scratch-itch cycle should also be taken in consideration.

Some patients may not properly respond to conventional approaches. In such refractory cases alternative options can be helpful: immunosuppressants (cyclosporine), cytostatics (methotrexate, azathioprine), IL-6 blockade, dust mite immunotherapy [34].

Topical Janus kinase (JAK) and phosphodiesterase-4 (PDE4) inhibitors are novel treatment approaches for AD [38]. The Janus kinase (JAK) – signal transducer and activator of transcription (STAT) pathway is utilized by numerous cytokines and growth factors for signal transduction [39]. JAKs are promising targets for both topical and systemic treatment of AD [40]. Phosphodiesterase-4 (PDE4) is a key regulator of inflammatory cytokine production in AD through the degradation of cyclic adenosine monophosphate [41]. PDE4 activity is increased in circulating inflammatory cells of patients with AD [42], and the inhibition of PDE4 in monocytes in vitro has been demonstrated to reduce the release of proinflammatory cytokines. Topical PDE4 inhibitors demonstrated a favourable safety profile and remarkable improvement in efficacy, including overall disease severity and skin score.

New therapeutic strategies are also under development: given the importance of the Th-2 immune response, Th-2 antagonists (i.e., anti-IL-4/13 receptor

antibodies and anti-IL-13 antibodies to reduce the systemic Th-2 inflammation reported in severe AD) have been tested with promising results [43].

## **PATHOGENESIS AND PREVENTION**

Dietary allergens are secreted in breast milk and have the potential to affect an infant's immune system. Interestingly, recent data support earlier introduction of potentially allergenic foods in children [44].

On the other hand, most of the studies support the beneficial effect of breastfeeding in decreasing the risk for AD [45], even though some studies reveal increased risk [46].

It seems that regardless of the generally accepted lower allergenic potential of hydrolysed formulas and soy-based formulas, there isn't enough substantial prove of their advantage compared to cow milk-based formulas regarding the risk for AD development [47].

Other searches were directed to omega-3 or omega-6 fatty acids, vitamins (vitamin D), antioxidants (vitamin C, vitamin E), minerals (zinc, selenium) supplementation, but no clinical study had led to decisive clinical beneficial effect [47].

A recent systematic review and meta-analysis concluded that, specifically for infants, probiotics might have a protective effect [48], and *Lactobacillus* seems to be a favourite – colonization of *Lactobacillus* enhances IL-10 production, which has significant anti-inflammatory effects [49].

## **CONCLUSION**

The highlighted elements in the pathogenesis of AD emphasize its complexity.

Endogenous predisposition seems to be essential for disease unclatching, but clarification of exogenous factors allows prophylaxis of exacerbations and alleviation of the symptoms.

Many novel biologic and small molecule agents that are clinically effective in AD treatment have emerged. More data regarding ongoing development programs can be expected in the future. In addition to the ability to alter the natural history of AD, drug safety and cost-effectiveness should be considered.

## **REFERENCES**

1. Akdis CA, Akdis M, Bieber T, et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. *J Allergy Clin Immunol*, 2006, 118:152-169.
2. Illi S, von Mutius E, Lau S, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol*, 2004, 113:925-931.
3. Silverberg JI. Atopic Dermatitis in Adults. *Med Clin North Am*. 2020 Jan; 104(1):157-176. doi: 10.1016/j.mcna.2019.08.009).
4. Bieber T. Atopic Dermatitis. *N Engl J Med*, 2008, 358:1483-1494.
5. Bhattacharya N, Sato WJ, Kelly A, et al. Epidermal Lipids: Key Mediators of Atopic Dermatitis Pathogenesis. *Trends Mol Med*, 2019, 25(6):551-562. <https://doi.org/10.1016/j.molmed.2019.04.001>
6. Schultz LF. Atopic dermatitis: a genetic-epidemiologic study in a population-based twin sample. *J Am Acad Dermatol*, 1993, 28(5 Pt 1):719-723.
7. Rawlings AV, Harding CR. Moisturization and skin barrier function. *Dermatol Ther*, 2004, 17(Suppl 1):43-48.
8. Kezic S, O'Regan GM, Lutter R, et al. Filaggrin loss-of-function mutations are associated with enhanced expression of IL-1 cytokines in the stratum corneum of patients with atopic dermatitis and in a murine model of filaggrin deficiency. *J Allergy Clin Immunol*, 2012, 129:1031-1039.
9. Brauweiler AM, Bin L, Kim BE, et al. Filaggrin dependent secretion of sphingomyelinase protects against Staphylococcal alpha toxin-induced keratinocyte death. *J Allergy Clin Immunol*, 2013, 131:421-427.
10. Silverberg JI. Atopic Dermatitis in Adults. *Med Clin N Am*, 2020, 104:157-176. <https://doi.org/10.1016/j.mcna.2019.08.009>
11. Mohiuddin M, Ramamoorthy P, Reynolds PR, et al. Increased compound heterozygous filaggrin mutations in severe atopic dermatitis in the United States. *J Allergy Clin Immunol Pract*, 2013, 1:534-536.
12. Heine G, Hoefer N, Franke A, et al. Association of vitamin D receptor gene polymorphisms with severe atopic dermatitis in adults. *Br J Dermatol*, 2013, 168(4):855-858.
13. Berker T, Visscher D, Gooris GS, et al. Topically applied ceramides interact with the stratum corneum lipid matrix in compromised ex vivo skin. *Pharm Res*, 2018, 35(3):48. doi: 10.1007/s11095-017-2288-y
14. Schmid-Wendtner MH, Korting HC. The pH of the skin surface and its impact on the barrier function. *Skin Pharmacol Physiol*, 2006, 19:296-302.
15. Schafer L, Kragballe K. Abnormalities in epidermal lipid metabolism in patients with atopic dermatitis. *J Invest Dermatol*, 1991, 96:10-15.
16. McGirt LY, Beck LA. Innate immune defects in atopic dermatitis. *J Allergy Clin Immunol*, 2006, 118:202-208.
17. Howell MD, Wollenberg A, Gallo RL, et al. Cathelicidin deficiency predisposes to eczema herpeticum. *J Allergy Clin Immunol* 2006;117: 836-41.
18. Butcher EC, Picker LJ. Lymphocyte homing and homeostasis. *Science*, 1996, 272:60-66.
19. Picker LJ, Martin RJ, Trumble A, et al. Differential expression of lymphocyte homing receptors by human memory/effector T cells in pulmonary versus cutaneous immune effector sites. *Eur J Immunol*, 1994, 24:1269-1277.
20. Novak N, Bieber T. Allergic and nonallergic forms of atopic diseases. *J Allergy Clin Immunol*, 2003, 112:252-262.
21. Kerschenlohr K, Darsow U, Burgdorf WH, et al. Lessons from atopy patch testing in atopic dermatitis. *Curr Allergy Asthma Rep*, 2004, 4:285-289.
22. Spergel JM, Mizoguchi E, Brewer JP, et al. Epicutaneous sensitization with protein antigen induces localized allergic dermatitis and hyperresponsiveness to methacholine after single exposure to aerosolized antigen in mice. *J Clin Invest*, 1998, 101:1614-1622.
23. Traidl-Hoffmann C, Mariani V, Hochrein H, et al. Pollen-associated phytoprostanes inhibit dendritic cell interleukin-12

- production and augment T helper type 2 cell polarization. *J Exp Med*, 2005, 201:627-636.
24. Clark RA, Chong B, Mirchandani N, et al. The vast majority of CLA+ T cells are resident in normal skin. *J Immunol*, 2006, 176:4431-4439.
  25. Soumelis V, Reche PA, Kanzler H, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat Immunol*, 2002, 3:673-680.
  26. Grewe M, Walther S, Gyufko K, et al. Analysis of the cytokine pattern expressed in situ in inhalant allergen patch test reactions of atopic dermatitis patients. *J Invest Dermatol*, 1995, 105:407-410.
  27. Tazawa T, Sugiura H, Sugiura Y, et al. Relative importance of IL-4 and IL-13 in lesional skin of atopic dermatitis. *Arch Dermatol Res*, 2004, 295(11):459-464.
  28. Trautmann A, Akdis M, Kleemann D, et al. T cell-mediated Fas-induced keratinocyte apoptosis plays a key pathogenetic role in eczematous dermatitis. *J Clin Invest*, 2000, 106:25-35.
  29. Esaki H, Brunner PM, Renert-Yuval Y, et al. Early-onset pediatric atopic dermatitis is TH2 but also TH17 polarized in skin. *J Allergy Clin Immunol*, 2016, 138(6):1639-1651.
  30. Aichberger KJ, Mittermann I, Reininger R, et al. Hom s 4, an IgE-reactive autoantigen belonging to a new subfamily of calcium-binding proteins, can induce Th cell type 1-mediated autoreactivity. *J Immunol*, 2005, 175:1286-1294.
  31. Leung DYM. Pathogenesis of atopic dermatitis. *J Allergy Clin Immunol*, 1999, 104 (Suppl):S99-108.
  32. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Evid Based Child Health*, 2014, 9:447-483.
  33. Khan A, Adalsteinsson J, Whitaker-Worth DL. Atopic dermatitis and nutrition. *Clin Dermatol*, 2022, 40(2):135-144. <https://doi.org/10.1016/j.clindermatol.2021.10.006>
  34. Leung DYM, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: Shifting paradigms in treatment approaches. *J Allergy Clin Immunol*, 2014, 134(4):769-779. doi: 10.1016/j.jaci.2014.08.008
  35. Lever R, Hadley K, Downey D, et al. Staphylococcal colonization in atopic dermatitis and the effect of topical mupirocin therapy. *Br J Dermatol*, 1988, 119:189-198.
  36. Bunikowski R, Mielke M, Skarabis H, et al. Prevalence and role of serum IgE antibodies to the Staphylococcus aureus-derived superantigens SEA and SEB in children with atopic dermatitis. *J Allergy Clin Immunol*, 1999, 103:119-124.
  37. Nickoloff BJ, Naidu Y. Perturbation of epidermal barrier function correlates with initiation of cytokine cascade in human skin. *J Am Acad Dermatol*, 1994, 30:535-546.
  38. Nakajima S, Igyarto BZ, Honda T, et al. Langerhans cells are critical in epicutaneous sensitization with protein antigen via thymic stromal lymphopoietin receptor signaling. *J Allergy Clin Immunol*, 2012, 129:1048-1055.
  39. Ghoreschi K, Laurence A, O'Shea JJ. Janus kinases in immune cell signaling. *Immunol Rev*, 2009, 228(1):273-287.
  40. Suga H, Sato S. Novel topical and systemic therapies in atopic dermatitis. *Immunol Med*, 2019, 42(2):84-93.
  41. Jimenez JL, Punzon C, Navarro J, et al. Phosphodiesterase 4 inhibitors prevent cytokine secretion by T lymphocytes by inhibiting nuclear factor-kappa B and nuclear factor of activated T cells activation. *J Pharmacol Exp Ther*, 2001, 299(2):753-759.
  42. Grewe SR, Chan SC, Hanifin JM. Elevated leukocyte cyclic AMP-phosphodiesterase in atopic disease: a possible mechanism for cyclic AMP-agonist hyporesponsiveness. *J Allergy Clin Immunol*, 1982, 70(6):452-457.
  43. Nakajima S, Igyarto BZ, Honda T, et al. Langerhans cells are critical in epicutaneous sensitization with protein antigen via thymic stromal lymphopoietin receptor signaling. *J Allergy Clin Immunol*, 2012, 129:1048-1055.
  44. Dominguez O, Plaza AM, Alvaro M. Relationship Between Atopic Dermatitis and Food Allergy. *Curr Pediatr Rev*. 2020;16(2):115-22.
  45. Kajosaari M. Atopy prophylaxis in high-risk infants. Prospective 5-year follow-up study of children with six months exclusive breastfeeding and solid food elimination. *Adv Exp Med Biol*, 1991, 310:453-458.
  46. Bergmann RL, Diepgen TL, Kuss O, et al. Breastfeeding duration is a risk factor for atopic eczema. *Clin Exp Allergy*, 2002; 32:205-209.
  47. Khan A, Adalsteinsson J, Whitaker-Worth DL. Atopic dermatitis and nutrition. *Clin Dermatol*, 2022, 40(2): 135-144. <https://doi.org/10.1016/j.clindermatol.2021.10.006>
  48. Zhao M, Shen C, Ma L. Treatment efficacy of probiotics on atopic dermatitis, zooming in on infants: a systematic review and meta-analysis. *Int J Dermatol*, 2018, 57:635-641.
  49. Pessi T, Sütas Y, Hurme M, et al. Interleukin-10 generation in atopic children following oral lactobacillus rhamnosus GG. *Clin Exp Allergy*, 2000, 30:1804-1808.