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Factors affecting the clinical picture of atopic dermatitis

Joanna Krzysiek, Aleksandra Lesiak, Joanna Narbutt

Department of Dermatology, Paediatric Dermatology and Oncology, Medical University of Lodz, Poland

ABSTRACT

Atopic dermatitis (AD) is a chronic and recurrent disease affecting both, children and adults. Over the last decades, its prevalence has been constantly growing, causing significant psychological and social issues. Risk factors have been associated with the development of AD such as genetic, environmental, and abnormal immune response, as well as disorders of the skin barrier and skin microbiome. The following review comprehensively discusses all aspects affecting the clinical picture of AD. It allows a better understanding of the mechanisms underlying disease and may initiate appropriate treatment.

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Key words: atopic dermatitis, etiopathogenesis, risk factors

INTRODUCTION

Atopic dermatitis (AD) is one of the most common inflammatory dermatoses, affecting 15–20% of children and 1–3% of adults [1]. The American Academy of Dermatology (AAD) reports the incidence of AD in children of up to 25% [2]. Although the peak incidence is at preschool age, this diagnosis is also made in adults. Sex does not appear to affect the risk of AD while ethnicity (race) may be relevant [3]. Studies show that AD is more common in Asians and African Americans compared to Caucasians. The characteristic clinical features of the disease is eczematous lesions with pruritus, which occur in 60% of patients within the first year of life, and approximately one-third of cases develop in adulthood [4]. The clinical picture in AD depends on the age and duration of the disease. Initially, erythematous and exudative eruptions appear on the skin of the face, trunk, and extensor surface of the limbs. After the second year of life, the disease pattern is dominated by erythematous lesions with lichenification, occurring on antecubital, popliteal fossa and feet. In adulthood, however, the eruptions show a predilection for upper half of the body. The chronic and recurrent nature of the disease with associated pruritus predisposes to lichenification and impetiginization. Persistent itching interferes with daily activities and causes insomnia, and in consequence significantly reduces the quality of life [5]. Pruritus is one of Hanifin and Rajka's primary criteria. Over many years, these criteria have established themselves as diagnostic tool that is useful in everyday clinical practice. These criteria are currently the most well-known. In addition to skin manifestations, AD patients may have several other comorbid atopic diseases such as food allergy, asthma, atopic rhinitis, or eosinophilic oesophagitis. This sequence of diseases is termed 'allergic march' [6]. Chronic pruritus, psychosocial stress, and inflammation often leads to anxiety, depression, or suicidal thoughts [7]. AD may predispose to an increased risk of infection and cardiovascular diseases. A positive correlation was found between the severity of AD and the incidence of these diseases. In these cases it places an economic burden on the patient and the whole family involved in the treatment. Moreover, there is a social problem — an increase in indirect costs that are necessary to combat the disease, which is caused by medical visits, absence from work and school, or hospitalization.

The pathogenesis of AD is multifactorial and composed of multiple synergistic factors that affect the disease. The most important include: genetic and epigenetic disorders, epidermal barrier defect, altered immune response, and disturbed microbial balance of the skin. These factors cause damage to the skin barrier and change in epidermal permeability, which as a result increases the contact of microorganisms and allergens with the skin's immune system. In response to the release of pro-inflammatory cytokines (IL-1β, TSLP, IL-25, MDC, TARC, IL-33) and chemokines, damaged keratinocytes activate dendritic cells (DCs) and inflammatory dendritic epidermal cells (IDECs). By inducing OX40L ligand expression on DCs, thymic stromal lymphopoietin (TSLP) stimulates IL-4 and IL-13 production. The initiation of Th2 and TH22 immune response also occurs through

Address for correspondence:
Joanna Krzysiek, Department of Dermatology, Paediatric Dermatology and Oncology Clinic, Medical University of Lodz, Kniaziewicza 1/5, 91–347 Lodz, Poland; e-mail: joanna.krzysiek@umed.lodz.pl

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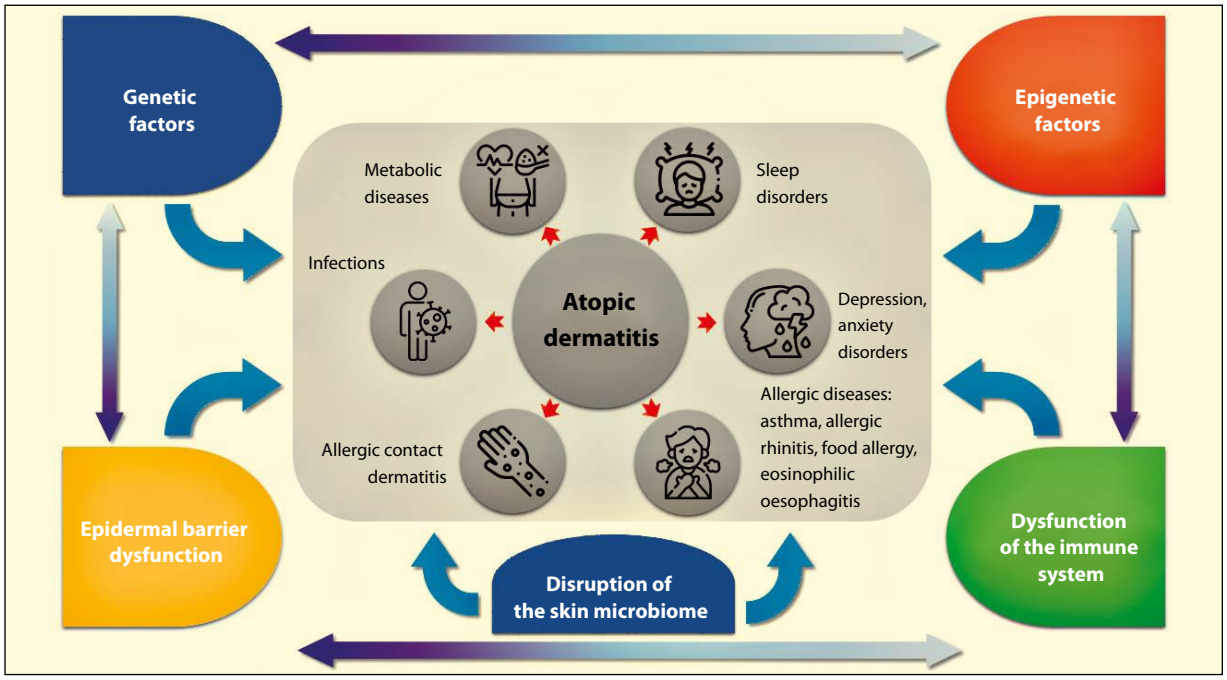

Figure 1. The role of genetic, epigenetic, immune, environmental factors, epidermal barrier dysfunction, and skin microbiome in the aetiopathogenesis of atopic dermatitis; authors' own elaboration

the presentation of exogenous antigens recognized by DCs and IDECs. Activated Th2 cells and CD8+ lymphocytes release IL-4 and IL-13 by inducing immunoglobulin IgE. Additionally, ILC2 cells — natural lymphoid cells activated by tissue-derived cytokines, i.e. IL-33, IL25, and TSLP — potentiate the Th2-dependent response by being a source of the cytokines IL-4, IL-13, and IL-5 (involved in the maturation of eosinophils). IL-33, TSLP, and Th2-dependent cytokines act directly on skin sensory neurons, thus contributing to pruritus. Th1/Th22/Th17 lymphocytes are involved in both the acute and chronic phases of the disease. T-lymphocyte infiltration maintains skin inflammation, hence contributing to skin remodeling (Fig. 1).

GENETIC FACTORS AND EPIDERMAL BARRIER DYSFUNCTION

A fundamental role in the pathogenesis of AD is played by epidermal barrier dysfunction. The results of the study proved that — previously affected areas with clinical inflammation have still impaired epidermal barrier structure and function [8]. Reasearchers made a breakthrough discovery in filaggrin loss-of-function mutation, which was observed in patients with early-onset AD with comorbid atopic conditions [3]. It is a protein that binds keratin fibers together in the stratum corneum. So far, 30–50% of AD patients are known to have a mutation in a gene encoding FLG. It is possible to have multiple FLG mutations that inactivate the protein to varying degrees. Most notably, these are R501X and 2282del4 FLG mutations that lead to a complete loss of FLG function [9, 10]. Genome-wide association studies (GWAS) identified multiple FLG mutation variants in Asian, African, and Caucasian populations [11–13]. At least one study reported that patients of African descent also have a gene mutation in FLG2 [14]. Many thousands of FLG variants have been identified so far, which can be searched in a population database such as gnomAD (genome aggregation database, https:://gnomad.broadinstitute.org/). This database includes continuously updated genetic data from whole exome or genome sequencing. It should be noted that AD sometimes develops independently of FLG mutations and not all of the carriers may have the disease manifested. This is due to the incomplete knowledge of the human genome, as well as the influence of the environment and the complex interaction between genetic and external factors.

Filaggrin gene (FLG) is a protein that binds the stratum corneum together with keratin fibers. The degradation products of FLG, namely urocainic acid and pyrrolidine carboxylic acid, contribute to the hydration of the stratum corneum as a result skin pH remains acidic [15]. The acidic pH in the stratum corneum has many protective functions, including limiting the growth of skin pathogenic bacteria and keeping serine proteases inactive on the surface of the skin. Activation of serine proteins leads to further barrier dysfunction through the degradation of corneodesmosomes and enzymes involved in the extracellular lipid metabolism [16, 17]. Consequently, the dysregulation of the skin's pH affects

the disturbance of fat metabolism in the lipid layer, further increasing skin permeability. A decrease in saturation of naturally occurring lipids, a reduction in the amount of the natural moisturizing factor, and excessive transepidermal water loss (TEWL) exacerbate the symptoms of dry skin, which is one of the main clinical characteristics of atopic skin [18–20]. FLG deficiency and its breakdown products lead to increased skin exposure to extrinsic agents such as bacteria, viruses, and food or inhalant allergens. The results of studies in murine fillagrin gene mutation showed increased penetration of allergens across the epidermal barrier compared to the control group [21]. This initiates inflammation through various mechanisms: production of specific IgE, basophil activation, production of pro-inflammatory cytokines, and penetration of bacterial toxins.

In addition to FLG mutations, there are other genetic pathways implicated in the pathogenesis of AD, namely genes encoding epidermal structural and functional proteins: genes encoding intercellular junction proteins (claudins, occludins), genes encoding epidermal proteases, caspase-activating factor genes (CARD4, CARD15), genes encoding serine protease inhibitors (cystatin A), the transcription factor OVOL1 in keratinocytes increasing FLG expression and the SPRR3 cross-linked protein in the cornified envelope [22]. An inherited loss-of-function mutation in the SPINK5 gene, which encodes the peptidase inhibitor LEKTI, causes Netherton syndrome. In this syndrome, there is a relatively severe course of AD, which important role of abnormalities in serine protease balance in the pathogenesis of this condition.

EPIGENETIC FACTORS

Genetic factors do not fully explain the reason for such a sudden increase in the incidence of AD. The patient's skin is affected by the rapid development of industry, chemicalization or urban lifestyle [23]. In the modern household, residents are constantly exposed to products such as cosmetics, tobacco, and processed foods, which can further interact through epigenetic changes. It means that external factors can modify gene expression without altering the nucleotide sequence in the DNA. In AD, epigenetic changes involve genes that regulate the primary immune response, secondary immune response, and response of genes encoding epidermal structural proteins [24]. Moreover, abnormalities in the epigenome can persist in subsequent generations.

ENVIRONMENTAL FACTORS

A risk factor contributing to the increased incidence of AD is the impact of the external environment. Exposure to air pollution and chemical agents negatively affect the epidermal barrier [25]. It appears that pollutants of all kinds may be responsible for causing or exacerbating AD. Studies revealed that eczematic symptoms were significantly associated with exposure to benzene, particulate matter PM10, nitrogen oxide compounds, and carbon monoxide [26, 27]. Short-term exposure to airborne formaldehyde causes increased TEWL, and toluene can directly reduce FLG synthesis [28, 29]. Not only the degree of pollution but also the change in temperature plays a role in the development of AD. Exposure to a cold dry climate also predisposes to the disease. This is explained by skin contact to low temperatures, as well as low ambient humidity due to indoor heating. This adversely affects the skin barrier [30]. Prolonged exposure to reduced ambient humidity accelerates TEWL, intensifying the disruption of the epidermal barrier. Bathing infants in hard water may increase the risk of AD, probably as a result of increased skin pH, which i.a. causes premature degradation of corneodesmosomes [31]. The use of alkaline soaps also contributes to increasing pH of the skin and thinning the lipid layer [32]. Such a process takes place both in eczematous lesions and normal-appearing lesional skin. Detergents are responsible for increasing the release of pro-inflammatory cytokines and proteolytic enzymes [33]. Overuse of detergents and soaps negatively affects the skin by disrupting the regulation of PAR-2 receptors that are closely involved in the pathomechanism of pruritus in AD [34].

Premature exposure to external environmental stimuli, even during the prenatal period, can contribute to the development of AD. Maternal exposure to environmental tobacco smoke is thought to induce a postnatal Th2 lymphocyte response [35]. Shifting the immune balance towards a Th2 profile in these youngest patients may contribute to the appearance of the first eczematous lesions. Exacerbation of AD may also be caused by contact allergens. Metals such as nickel, cobalt and chromium are most likely to cause hypersensitivity reactions that often mimic the symptoms of the disease [36]. Based on the analysis of the study results, elevated levels of IFN-γ and IL-5 were identified as playing an important role in the exacerbation of AD after metal exposure [37]. Cosmetics that contain irritants, fragrances or preservatives can show a similar effect [38]. Food allergens, which are commonly discussed, are the subject of much controversy and debate. Food allergy is most common in children under three years of age, and 15% of patients develop clinical manifestations of the disease [39]. Five allergens were identified as potentially involved in the pathogenesis of AD. These include milk, eggs, peanuts, soya, and wheat [40]. The indication for an elimination diet in patients is recommended on the basis of parents' history on potential allergen as a trigger to AD symptoms. Implementation of such a diet based on allergen-specific immunoglobulin E (IgE) test without performing an oral food provocation test is unjustified. When elimination diet is recommended, maintenance of a balanced should be followed.

IMBALANCE OF THE SKIN MICROBIOME

Disruption of the skin microbiome may play an integral role in the pathogenesis of AD. Loss of skin bacterial diversity and of natural antimicrobial peptides (AMPs) in the skin were extensively reported in the literature [41]. Reduced function of human β-defensins, cathelicidins, and AMPs inhibits the skin immune system, which allows the growth of unstable bacterial flora. Decrease in skin commensal bacteria, including *Staphylococcus epidermidis* (*S. epidermidis*) and other coagulase-negative staphylococci, leads to the proliferation of *Staphylococcus aureus* (*S. aureus*). *S. aureus* was found to colonise 30–100% of AD patients [42]. Studies found that early skin colonization by *S. aureus* may lead to atopic lesions in infancy [43]. *S. aureus* increases skin inflammation and allergic reactions by stimulating innate and secondary immune responses. This bacterium activates lymphocytes and macrophages through the secretion of superantigens, i.e., enterotoxin B, toxic shock syndrome toxin-1 (TTST1), exotoxin, alpha-toxin and δ-haemolysin [44-47]. Moreover, *S. aureus* increases levels of pro-inflammatory cytokines such as TSLP, IL-4, IL-13, IL-17, and IL-22 and stimulates mast cell degranulation, resulting in an increased Th2 lymphocyte response [48]. It was observed that Th2-skewing and inflammation enhancement are correlated with higher number of *S. aureus* on atopic skin in comparison to unlesional skin [49]. Increased colonization of this bacterium may also contribute to the activation of ligands for toll-like receptors type 2 (TLR2) [50]. Stimulation of TLR2 triggers further transduction of signals that activate nuclear transcription factor NF-κB and mitogen-activated protein kinase (MAPK) to produce AMP proteins.

Recent studies show that TLR2 polymorphisms can occur in AD patients and consequently impair TLR2 function, resulting in development of inflammation or its exacerbation [51, 52]. TLRs are an important link between primary and secondary responses of the immune system. The non-specific response also remains stimulated by components of the *S. aureus* cell wall that enhance the production of TSLP by keratinocytes [53]. This cytokine activates chemokines CCL17 and CCL20, increasing cytokine production by Th2 lymphocyte populations.

Another immunomodulatory role of *S. aureus* is production of IL-33 by keratinocytes [54]. Recent studies reported increased expression of IL-33 in the skin in AD. The role of IL-33 is to activate innate lymphoid cells (ILCs) expressing ST2, eosinophils, and macrophages to produce Th2 effector cells [55]. *S. aureus* stimulates IL-33 production in keratinocytes, most likely via IgG-binding proteins (Sbi, *Staphylococcal binding immunoglobulin protein*) [56]. Kindi et al. [56] found that IL-33 degrades corneodesmosin, which is a component of corneodesmosomes that form a intercellular binder in the stratum corneum. Consequently, the epidermal barrier function is disrupted.

Recent studies show that *S. aureus* also induces expression of IL-36α in epidermis, which induces pro-inflammatory production of IL-17A by T cells through the IL-36R/MyD88 pathway [57]. The response from T-lymphocytes was observed in epidermis which indicates that the immune response depends largely on cells in direct contact with *S. aureus*. This bacterium damages keratinocytes through phenol-soluble modulins (PSMs) by inducing the secretion of IL-1α and IL-36 and thus skin inflammation [58].

S. aureus colonization not only affects the polarisation of activated Th lymphocytes towards Th2 but also the allergic response. It is postulated that *S. aureus* contributes to the development of atopic march by increasing skin inflammation and allergen sensitization [59]. In a mouse model, *S. aureus* was indeed found to cause allergen-induced airway hyperresponsiveness. The effect of *S. aureus* on food allergy was also investigated in a group of AD patients aged 4 to 11 months [60]. The analysis of the results showed a correlation between food allergy and *S. aureus* colonization, regardless of the severity of the lesions. In contrast, no such result was observed in other studies [61]. Serum IgE levels against specific food allergens were accurately determined in AD children. In the aforementioned study, there was a correlation between *S. aureus* colonization and food allergy to peanuts, egg whites, and cow's milk [62]. There were also significantly higher levels of specific IgE for peanut allergens in patients with methicillin-resistant *S. aureus* (MRSA) colonization compared to those with methicillin-sensitive *S. aureus* (MSSA) strains.

The reduction of *S. aureus* and its negative effects on the skin may be provoked by other species of the *Staphylococcus spp.* [63]. *Staphylococcus lugdunensis* and *S. hominis* inhibit the growth of *S. aureus* by secreting antibiotics and lantibiotics. Another example is *S. epidermidis* which stimulates keratinocytes to produce AMP and glutamyl endopeptidases (Esp) that inhibit biofilm formation from *S. aureus*.

In recent years, numerous scientific papers have provided numerous evidence of the key role of the skin microbiota in the pathogenesis of AD [41]. Nevertheless, there is still a lack of full understanding of the skin microbiom and its impact on AD's development in the host.

IMMUNE DISORDERS

It is not yet clear whether epidermal dysfunction precedes immune dysregulation in the etiopathogenesis of AD or vice versa. It was initially hypothesized that epidermal barrier dysfunction, environmental stress, and mechanical factors led to skin barrier damage and increased epidermal permeability, which in turn increased microbial and allergen contact with the immune system [64]. On the other hand, another hypothesis emerged that an immune response occurs as a result of the activation of Th2-type responses in the skin leading to the AD phenotype. Current

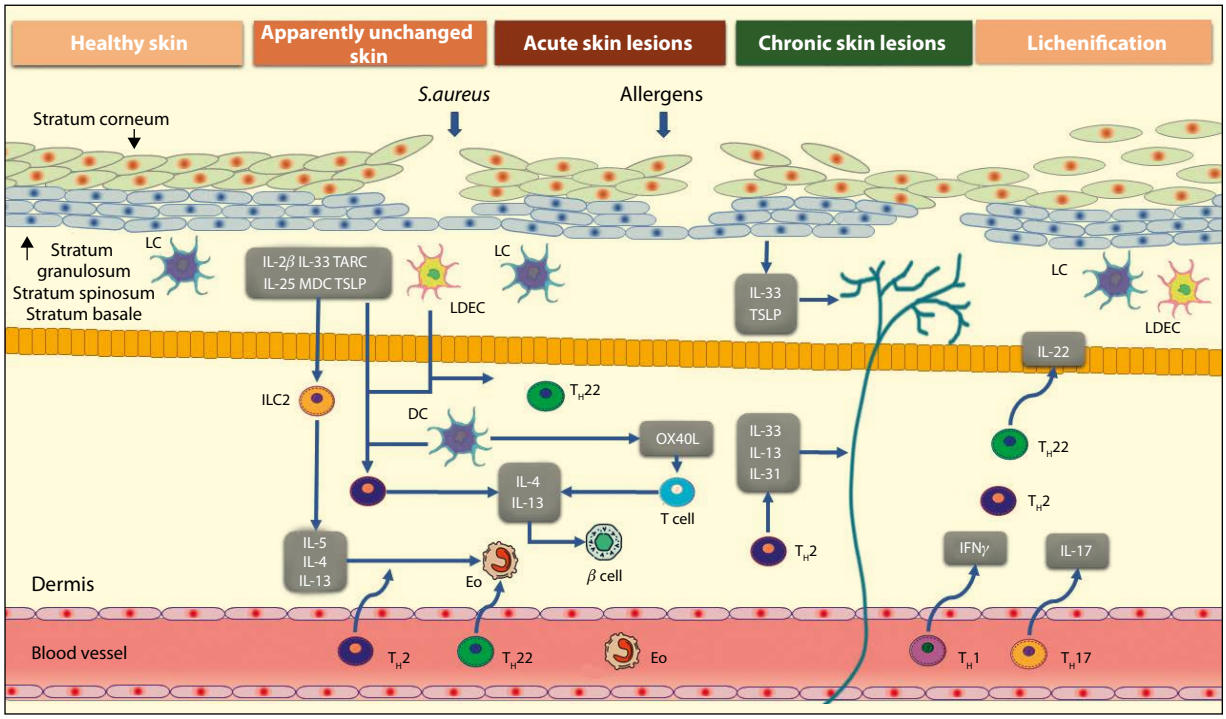

Figure 2. Etiopathogenesis of atopic dermatitis; authors' own elaboration

scientific papers consider the immune response in AD to be biphasic. The acute phase is dominated by Th2 cells while the subsequent shift from Th2 to Th1 signaling dominates in chronic disease [65]. However, there is no complete "immune switching" towards Th1.

Chronic lesions are maintained by an intense infiltration of Th22 cells that secrete IL-22 and simultaneously stimulate dendritic cells [66]. Both Th2 and Th22 cytokines also play an important role in the inhibition of genes encoding proteins that form the cornified envelope, including FLG. They also take part in limiting production of antimicrobial proteins and enhancing epidermal barrier destruction [67].

The origins of the immune pathway for the development of AD lesions can be traced to, the activation of the primary immune response. Pro-inflammatory cytokines (IL-25, TSLP and IL-33) and chemokines are realesed by keratinocytes and antigen presented by Langerhans cells (Fig. 2). Simutaneously Th2-dependent response is being promoted. TSLP and IL-33 enhance the itching sensation while all of the pro--inflammatory cytokines enrich the inflammatory infiltrate with IL-4, IL-5, IL-13, eosinophils, and IgE [68]. Recent studies have revealed an important function of the TSLP signaling pathway that affects the induction of the cytokines IL-4, IL-5, and IL-13.TSLP stimulates mouse dendritic cells to express OX40L while OX40L-positive dendritic cells stimulates differentiation of Th2 cells to the aforementioned cytokines [69].

Natural ILC2 cells are an important link between the response of tissue-derived cytokines (IL-25, TSLP, and IL-33) released by damaged keratinocytes and Th2-dependent effector cells [70]. They secrete IL-5 which is involved in the activation of eosinophils as well as IL-4 and IL-13. The released cytokines IL-4, IL-5, IL-13, and IL31 enhance the re-secretion of the chemokines CCL-17, CCL-22, CCL-24. Moreover, cytokines (especially IL-4 and IL-13) inhibit the synthesis of FLG and other cornified envelope proteins, as well as lipids within the epidermis, thus contributing to barrier dysfunction in AD [71]. For many years, the most important role in the pathogenesis of AD has been attributed to IL-4 and IL-13 which are involved in chemokine production, skin barrier dysfunction, and suppression of AMP peptides and allergic response. IL-4 and IL-13 gene polymorphisms were proved to be associated with the development of AD in children and adults, as well as in individuals from different ethnic groups [72, 73]. The IL-4 cytokine was found to be crucial in the initiation of the Th2 response while IL-13 plays a greater role in its maintenance [74]. Interestingly, IL-13 has a unique function in acting on skin fibroblasts to increase collagen production. This leads to skin remodeling and lichenification [75]. This is one of the main features that differentiate the role of IL-13 from IL-4 in the pathogenesis of AD. The direct effect of these cytokines on neurogenic pruritus through interaction with IL-31 is one of their common features [76]. In AD patients, much attention was paid to IL-31 in terms of its role in the development of pruritus and inflammation. Many gene variants and polymorphisms of IL-31 are important in the development of atopic and

non-atopic eczema, as well as asthma [77] This explains its important role in both Th2-dependent allergy and non--allergic reactions. The progression of inflammation is dominantly influenced by the activation of IL-31 receptors on eosinophils resulting in the secretion of pro-inflammatory cytokines and chemokines including IL-6, IL-8, IL-16, IL-32, CXCL1, CXCL8, CCL18, and metalloproteinases. Consequently, IL-31 contributes to extensive inflammation and remodeling of the skin surface [78, 79].

IL-5 plays an important role in the production and survival of eosinophils in AD. Studies in AD infants revealed a positive correlation between synthesized IL-5 from peripheral blood mononuclear cells (PBMCs) and the severity of AD [80]. These findings imply that IL-5 plays an important role in the pathogenesis of eczema. Mepolizumab (anti-IL5) did not show sufficiency in AD treatment [81].

During the acute phase of the disease, in addition to an increase in the Th2 response, there is activation of Th22 lymphocytes that produce IL-22 cytokines and S100A proteins [82, 83]. Enhanced expression of S100A genes induces increased development of the epidermal response. The protein itself is subject to cytokine regulation via IL-22 and IL-17. In addition to an increased Th22 lymphocyte response, Th17-lineage cells are activated in the acute phase of the disease. AD patients have an imbalance in Th17/Treg cells, and the percentage of Th17 cells in the peripheral blood of the patients is significantly increased [84]. Th17 cells promote the inflammatory response while Treg cells inhibit it.

IL17 is the main interleukin produced by the Th17 lymphocyte population, which is involved in the inflammatory process. With regard to different stages of AD, it was reported that the percentage of IL-17-positive lymphocytes in the blood of AD patients was significantly higher in acute lesions compared to chronic lesions [85, 86]. IL17 remains an extremely pleiotropic cytokine that affects many cell types, including epithelial cells, fibroblasts, and macrophages. Its role depends on the function of its subunits. One of them is IL-17A which induces Th2-cell differentiation. IL-17A causes B-lymphocyte-mediated stimulation of IgE by increasing B lymphocyte survival, proliferation, and differentiation towards plasma cells. However, such an effect is not shown by IL-17F [87]. Moreover, both IL-17A/F subunits may promote the production of CXCL1, IL-8, and CCL4 by eosinophils.

IL17 was found to be a key stimulator of neutrophil chemoattractants and AMP peptides, which may be involved in the chronic phase of AD [88]. It is postulated that disruption of the skin microbiome is associated with increased levels of IL-17. Niebuhr et al. [89] found that α-toxins from *S. aureus* induce IL-17 production in Th17 cells in AD patients. Other studies showed significant importance of this interleukin in neutrophil stimulation also beyond AD. IL-17A as well as IL-17F and its polymorphisms are also associated with neutrophilic infiltration in the bronchial tree in patients with asthma [90]. A meta-analysis showed a statistically significant effect of the IL-17A rs2275913 polymorphism on the risk of asthma [91]. In Polish population, one study found a relationship between the A/A IL-17A genotype with comorbid asthma and AD. However, another research showed a negative correlation between these variables [92]. Other studies analyzed the importance of polymorphisms for IL17F [93, 94]. The results indicated a positive correlation between rs763780 IL17F genotype and the incidence of AD. The experiments differed in the study population. The IL17F rs763780 genotype variant increased the risk of AD at 11–13 years of age but not in adult patients. An analysis of a larger population is needed to determine the impact of IL-17A and IL-17F AD polymorphisms.

Another protein belonging to the IL-17 family of cytokines is IL-17C. It was hypothesized that IL-17C topically increased skin inflammation, not only in psoriasis but also in AD [95]. Studies in mice showed that neutralization of IL-17C led to a reduction in IL-4, mast cells, and IgE levels. It can be concluded that IL-17C contributes to the atopic inflammatory process in both the initiation and maintenance of lesions.

In the phenotype of chronic AD, cooperation between dendritic cells and Th22 is of great importance. In some cases, Th1 lymphocytes that stimulate IL-10 production are also involved in maintaining inflammation. Th1 cytokines, i.e. IL-18 and IL-12, in turn, support the process of dendritic cell differentiation [96]. They further stimulate the inflammatory process. Th22 cells, which produce IL-22, are involved in the activation of these cells. Based on the results of *in vitro* keratinocyte culture, IL-22 was found to decrease the expression of FLG, loricrin and involucrin levels in keratinocytes [97]. This supports the hypothesis that an imbalance in the Th22 response leads to impaired epidermal barrier function, independently of the inhibition of epidermal protein expression by Th2-dependent cytokines, namely IL-13 and IL-4. In contrast, activation of both Th2 and Th22 cytokines induces epidermal hyperplasia, and apoptosis of keratinocytes of AMP protein production [98–100].

The presented data demonstrate the important role of immune dysregulation. Over the past few years, many new therapies for AD were consequently developed that inhibit individual cytokines and agonists or antagonists of small molecules that play an important role in signal transduction in the cell. Dupilumab was the first biologic drug to be approved by the USA (FDA) and European (EMA) agencies for the treatment of moderate to severe AD [101]. It is a recombinant human monoclonal antibody of the IgG4 class that inhibits signaling by IL-4 and IL-13 through the IL-4Rα receptor. Next, in June 2021, the European Commission authorized tralokinumab for AD therapy. It is a pro-

tein that binds specifically to cytokine interleukin 13 (IL-13) and inhibits its interaction with IL-13 receptors. Promising results also came from clinical trials evaluating the efficacy and safety of the following drugs: lebrikizumab, [targeting interleukin-13 (IL-13)], nemolizumab (anti-IL-31R), mepolizumab (anti-IL-5) or MOR106 (anti-IL-17c), tezepelumab (TSLP inhibitor), etokimab (anti-IL-33), spesolimab (anti-IL-36R), fezakinumab (anti-IL-22), and GBR 830 (anti-OX4).

Subsequent studies suggested a possible blockade of the Th17 lymphocyte signaling pathway as a new option for the treatment of AD; however, secukinumab (IL-17A inhibitor), which was used in monotherapy, did not result in a clear clinical improvement in studied. Other studies evaluate the efficacy of new biologics in AD, namely risankizumab (anti--IL-23p19), bermekimab (anti-IL1-alpha), or FB825 (anti-IgE). It is worth mentioning phase 2 and phase 3 clinical trials on small molecules. A distinction is made between preparations against Janus kinases (baricitinib, abrocytinib, upadacitinib, ruxolitinib, tofacitinib, delgocitinib, cerdulatinib and gusacitinib), drugs that block H4 or NK1 receptors (e.g. serlopitant or tradipitant). Preliminary results from clinical trials on the said particles are very promising with regard to the efficacy and safety profile of AD treatment.

ENDOTYPES OF ATOPIC DERMATITIS

Several endotypes of AD can be listed based on immune profile and severity of the disease. The structures that link them are barrier damage and epidermal dysfunction. The AD endotype can reflect the disease phenotype [102]. In acute lesions, there is an activation of Th2 and Th22 axes and, to a lesser extent, Th17. As the disease progresses, there is enhancement in Th1 and Th2/Th22 response. However, there is an increasing number of discussions regarding the response of Th1, Th2, Th22, and Th17 lymphocytes according to ethnicity. In AD, there is a large variability in endotypes (Th1/Th2/Th22/Th17) that affects clinical features, i.e. the phenotype of the patients. In European and American populations, the Th2 and Th22 response predominates with lower Th1 and Th17 activity. Further research implies that Asian race and African American show a different endotype compared to the white race. In the Asian population, there was an increased activity of the Th2 and Th17/Th22 axes with decreased expression of Th1 lymphocytes. Likewise, peadiatric population with AD also show a predominant Th2/Th17 immune profile, including an increase in IL-19 expression. In contrast, the African American race shows a weakening of Th1/Th17 axis along with enhanced Th2/Th22 pathway. Increased Th22 levels in this race may represent a slightly different phenotypic pattern. This is due to the enhanced effect of IL-22, which causes hyperplasia and hyperkeratosis, thus contributing to lichenification of the skin. Determining the endotype in each patient, irrespective of race, may help to choose appropriate biological treatment. Although Th2-axis appears to be a universal immune response in AD, other signaling pathways might be more relevant to a specific subgroup of patients who present a distinct endotype.

CONCLUSIONS

The pathogenesis of AD is complex, with genetic, epigenetic, immune, and microbiological factors affecting both pheno- and endotypes of AD. With a better insight understanding of the nature of the disease, specialists will be able to plan a comprehensive treatment regimen in a rational way and search for new therapeutic options. Early intervention may prevent disease progression and maintain a long period of remission. Appropriate restoration of the skin barrier and microbiome as well as targeting treatment to a suitable endo(pheno-)type will contribute to monitoring and maintaining AD remission for as long as possible.

Conflict of interest

The authors declare no conflict of interest.

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