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Paper Accepted[1]

ISSN Online 2406-0895

Review Article / Прегледни рад

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Atopic dermatitis – novel insights in the immunopathology of the disease

Атопијски дерматитис – нови увиди у имунопатологију болести

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Received: November 19, 2025
Revised:February 19, 2026
Accepted: April 19, 2026
Online First: May 28, 2026
DOI: https://doi.org/10.2298/SARH251119045J

[1]**Accepted papers** are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.
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Atopic dermatitis – novel insights in the immunopathology of the disease

Атопијски дерматитис – нови увиди у имунопатологију болести

SUMMARY

Atopic dermatitis is an inflammatory skin disease that is characterized by the chronic-relapsing course and a pronounced feeling of itching. Altered production of structural proteins, lipids and antimicrobial peptides result in the epidermal impairment leading to the early onset of disease, more severe lesions and a numerous comorbidities. Atopic dermatitis has been recently recognized as a systemic type 2 inflammation by which emerging novel therapeutic modalities reflect sophisticated molecular and immunopathological pathways. The aim of this article is to deliver thorough review of the existing knowledge regarding the most significant immunological aspects of the development and progression of atopic dermatitis.

Keywords: atopic eczema; epidermis; inflammation; Th2 cells

САЖЕТАК

Атопијски дерматитис је инфламаторна болест коже коју карактерише хронично-рецидивантни ток и изражен осећај свраба. Нарушена продукција структурних протеина, липида и антимикробних пептида доводи до оштећења епидермиса и последичног раног настанка болести, интензивнијих лезија и бројних коморбидитета. Атопијски дерматитис је недавно препознат као системска инфламација типа 2 што уз нове терапијске модалитете одражава софистициране молекуларне и имунопатолошке путеве. Циљ овог чланка је да пружи свеобихватни преглед досадашњих сазнања о најзначајнијим аспектима развоја и прогресије атопијског дерматитиса.

Кључне речи: атопијски екцем; епидермис; инфламација; *Th*2 ћелије

INTRODUCTION

Atopic dermatitis (AD) is a dermatosis characterized by pruritus and typical cutaneous lesions that vary through acute, subacute and chronic phases [1–6]. It affects approximately 20% of children and 2–10% of adults [1, 2, 4]. Additionally, 40–60% of patients with atopic dermatitis also have another form of atopy, such as asthma, allergic rhinitis or food allergy [1, 2, 4, 6]. The pathogenesis of AD reflects a multifactorial condition, with genetics underpinning epidermal barrier impairment as initial state, triggerred by environmental insults (allergens, irritans, pollutants) and microbiome alteration, contributing to the sustained type 2 inflammation [1, 5]. This article seeks to provide thorough review of the previous knowledge with regard to key mechanisms involved in the development and progression of atopic dermatitis.

EPIDERMAL BARRIER IN AD

A damaged skin barrier in some hereditary diseases is directly related to the disease phenotype, while in atopic dermatitis it represents an initial condition that triggers further inflammation and sensitization [5, 7–9]. Abnormalities in the production of structural proteins, lipids and antimicrobial peptides result in skin barrier dysfunction, early onset of disease, more extensive lesions and a greater number of comorbidities [1, 2, 5, 10]. Impaired barrier culminates in increased permeability of epidermis, heightened transepidermal water loss (TEWL), compromised natural moisturization of skin, dysregulated skin surface pH, and penetration of exogenous agents: irritants, aeroallergens, contact

sensitizers, and microbial products [5, 11–14]. Epidermal barrier deficiency manifests clinically as extremely dry skin, followed by intense pruritus, scratching and rubbing creating 'itch-scratch' cycle underlying secondary bacterial infections and contact sensitization [5, 14–17].

The cornerstone of skin barrier is the integrity of the stratum corneum. The main components of corneocytes are keratin filaments organized by filaggrin (FLG), which represent the ground of the extracellular lipid matrix [2]. Defective FLG or its reduction contributes to the reduced production of acidic metabolites and an increase in skin pH, lessened activity of enzymes involved in lipid metabolism (beta-glucocerebrosidase, acid sphingomyelinase), accumulation and impaired secretion of lamellar bodies, and disruption of the entire lipid organization of the stratum corneum [7, 18, 19]. Apart from FLG, other essential constituents are loricrin, involucrin, corneodesmosin, SPRR3/4 (small proline rich proteins) and claudin-1 and -3, which are vital for epidermal integrity [19]. Additionally, diminished ceramide levels in the stratum corneum contribute to increased TEWL and epidermal damage. Significant accumulation of very short ceramide chains and reduced ceramide/cholesterol ratio are present in AD patients [20].

Environmental agents contribute to impaired barrier permeability, affecting its structure and function, while simultaneously triggering keratinocyte activation and alarmin release – interleukin (IL)-25, IL-33 and thymic stromal lymphopoietin (TSLP), inducing innate lymphoid cells type 2 (ILC2) involvement with subsequent type 2 inflammation and IL-4, IL-5 and IL-13 secretion, reflecting the link between the epidermal barrier and inflammation [1, 9, 21, 22]. IL-4 and IL-13 in turn damage epidermal barrier through altered filaggrin and loricrin expression, with reduced levels of antibacterial peptide, resulting in permanent epidermal dysfunction (Figure 1) [1, 9, 21, 22].

IMMUNE DYSFUNCTION DRIVES DISEASE

Keratinocytes and alarmin release

Thymic stromal lymphopoietin (TSLP), secreted by keratinocytes, plays a paramount role in altered immune response observed in allergic diseases and AD [2, 18]. TSLP, as a interleukin-7 cytokine, acts on dendritic cells to stimulate the naïve CD4+T lymphocytes, inducing the production of IL-4, IL-5 and IL-13 [2, 21]. This induction of Th2 cytokines impacts other immune cells such as mast cells, basophils, innate lymphoid cells (ILCs), macrophages and epithelial cells [2]. Beyond TSLP, keratinocytes also release other alarmins such as IL-25 and IL-33 [2, 18]. IL-33, part of the IL-1 cytokine family, is produced mainly by epithelial cells in response to allergenic and microbial stimuli. It promotes a type 2 immune response through by activating ILC2 cells, leading to the secretion of IL-5 and IL-13 [22]. IL-33 reduces filaggrin expression in keratinocytes, generates the itch sensation, activates Th1 and Th2 cells. Elevated levels of IL-33 are observed in lesional skin of AD, while serum IL-33 levels correlate with disease severity [22].

Langerhans cells and innate lymphoid cells type 2 are highly positioned in the immune hierarchy

Langerhans cells (LC) are pivotal in AD pathogenesis, alongside keratinocytes [23, 24]. LC cells participate in the recruitment and polarization of various immune cells in AD [25]. GWAS studies linked CD207 gene mutations to a heightened risk of AD. LCs show increased activity and proliferation in an AD model [25]. LCs are basically antigen-presenting cells and are responsible for the activation of Th2 and B-lymphocytes. It has been experimentally shown that TSLP can induce AD precisely through the activation of LC. Activated LCs activated secrete CCL17 and CCL22 and thus further polarize the Th2 phenotype [25]. Additionally, LCs facilitate IgE production by mature B-cells and binding through low-affinity receptor FcεRII/CD23 and FcεRI, resulting in IL-16-mediated attraction of Th cells, inflammatory epidermal dendritic cell (IDEC) precursors, and eosinophils. IDECs in turn, bind IgE via FcεRI, polarizing naïve T-cells into Th1 characteristic of chronic AD [25]. LCs also secrete CCL5, enhancing eosinophil infiltration typical of AD [25].

The activation of T-cells, eosinophils, basophils, macrophages, mast cells and innate lymphoid cells type 2 (ILC2), along with secretion of cytokines, culminates in localized inflammation in the atopic skin [23]. ILC2s are fundamental in shaping the immune response, maintaining tissue homeostasis, and driving inflammation [20]. Elevated levels of active ILC2s presented in AD lesions are associated with an increased level of type 2 cytokines and inflammation, whereas decreased NK cells was noted in blood of AD patients [20]. ILC2s secrete IL-4, IL-5, IL-9 and IL-13 upon activation by alarmins (TSLP, IL-25, IL-33) or eicosanoids, even in the absence of antigenic stimulation, fostering a Th2 response [22, 26]. Regarding the main immune pathways, the interaction of OX40L/OX40 between stimulated dendritic cells and T cells, may represent key mechanism in atopic inflammation [1, 9, 21, 22]. The OX40L-OX40 interaction between dendritic cells and T-cells also contributes to this response [22]. OX40 (CD134) expression is enhanced on T cells, following specific T cell receptor activation, OX40L-OX40 is mediates the antigen presentation process and plays a significant role in allergic diseases and tumor pathologies. Recent studies indicate that inhibiting OX40-OX40L interactions suppresses T cell-driven inflammation in AD [22, 26].

The persistent "vicious cycle" of immune activation

The inflammatory "vicious cycle" and epidermal barrier damage is initiated by activated keratinocytes and Langerhans cells, which secrete IL-10, IL-12, IL-18, IL-23, IL-17, IL-22, TSLP. This cascade further triggers Th2-mediated inflammation and the secretion of cytokines IL-4, IL-13, IL-31 and IL-22, compromising the epidermal barrier by reducing the expression of filaggrin, loricrin, claudin, and periplakin [20, 22, 27]. Concurrently, type 2 cytokines (IL-4, IL-5, IL-13) reactivate ILC2 and eosinophils [23, 27].

The increased production of IgE in AD stimulates mast cells and basophils [5, 26]. IgE can be non-specific (intrinsic AD - iAD) and allergen-specific (extrinsic AD - eAD). Elevated levels of specific IgE increase the risk of developing atopic march [23]. IgE-mediated stimulation of mast cells trigers degranulation and release of histamine, IL-6, IL-8, PGD2, αTNF, IL-23, and IL-31 [27]. Specific IgE binds to and activates dendritic epidermal cells and epidermal Langerhans cells that secrete proinflammatory cytokines TSLP, CCL17, CCL18, CCL22, and IL-33, initiating T-cell sensitization and subsequent inflammation [20].

Numerous studies underscore the importance of Th2-mediated inflammation in allergic diseases [28]. Th2-inflammation is a key phenomenon in the onset of immune dysfunction leading to the acute phase of atopic dermatitis characterized by the large amount of IL-4 and IL-13. These cytokines activate B lymphocytes to secrete IgE, adversely affecting filaggrin production in a feedback loop, while the release of IL-5 sustains eosinophilia in AD patients [19]. Type 2-inflammatory response is characteristic of antiparasitic, antitoxic effects, and allergic inflammation [28]. This type of immune response initially involves ILC2 and keratinocytes, along with dendritic cells, macrophages and Langerhans cells, extending to the activation of Th2, Tc, NK, B-cells, eosinophils, mast cells and basophilic granulocytes, leading to the secretion of IL-4, IL-5, IL-9, IL-13, IL-31 and IgE, the primary mediators of inflammation in AD (Figure 2) [28]. Clinical studies have already largely indicated the efficacy of monoclonal antibodies directed against IL-4, IL-13, and IL-31, or their receptors, in the treatment of AD [1, 5, 22].

In chronic AD lesions, the Th1-mediated immune response predominates, featuring gamma-interferon and IL-12 [5, 26]. Over time, some patients also exhibit a Th17/Th22 response significantly affecting keratinocyte lipid metabolism and epidermal function [27, 29]. Dendritic cells and eosinophils produce IL-2 and IL-18 while activating Th1 lymphocytes and promoting secretion of αTNF, IL-2, IL-12, αINF, favoring chronic inflammation in AD. Th1-released γIFN induces keratinocyte apoptosis, whereas IL-17 and IL-22 induce epidermal acanthosis clinically manifested by lichenoid lesions of chronic AD [22, 27]. Chronic AD lesions show elevated levels of IL-5 and IL-12, and decreased levels of IL-4 and IL-13 [27]. Furthermore, increased expression of VEGF originating from keratinocytes and mast cells is detected in AD, mediating angiogenesis in chronic inflammation [27]. Research demonstrated that IL-17A induces Th2-inflammation, with IL-4 reversibly inhibiting IL-17A. Thus, the elevated level of IL-17A were detected in peripheral blood mononuclear cells in severe AD [30]. γδ T-cells, a primary source of IL17A, participate in inflammation, tissue repair, pathogen elimination, immune regulation and tumor suppression [19]. AD patients exhibit elevated levels of circulating Vγ9Vδ2+ T-cells, which also produce IL-4 and IL-13, crucial in the pathogenesis of AD. Beyond allergic cutaneous inflammation, γδ T-cells also contribute to airway allergic inflammation by promoting IgE reactivity and Th2 inflammation [30]. According to previous studies, a subpopulation of lymphocytes - Th9-cells and IL-9 – may also have great potential in the development of allergic inflammation [31]. Elevated IL-9 levels in skin and blood observed in AD patients correlate with the SCORAD index, and hypothesis suggest

that IL-9 involved in pathogenesis of AD originates from activated mast cells, not Th9 cells. However, studies found IL-9 levels correlate with Th9 cells and PU.1 transcript in peripheral blood mononuclear cells, as well as with VEGF expression in AD lesions [31].

Fibroblasts – the secret of the inflammation in AD

Recent studies highlighted the role of fibroblasts in pathogenesis of AD. Altered fibroblasts in AD affect the keratinocyte terminal differentiation markers, such as filaggrin and loricrin, and lack of LIF (leukemia inhibitory factor) impairing epidermal differentiation [32]. In AD, particularly at the epidermal-dermal border, COL6A5+ COL18A1+ fibroblasts show an inflammatory phenotype (CCL2, CCL19, CCL26, IL-32). Abnormal fibroblasts adhesion, disturbed synthesis and metabolism of collagen, and damaged epidermal barrier are observed [32]. Conversely, COL18A1 inhibits angiogenesis and disrupts dermal organization by binding to extracellular matrix components in AD. Furthermore, up-expressed CCL19 and CCL2, interacting with CCR7, CCR1 and CCR2 on T-lymphocytes and dendritic cells, contribute to the infiltration of type 2 inflammatory response cells [32]. In addition, fibroblasts interact with Th2/Th22 and TRM (tissue-resident memory T cells) cells via CXCL12, promoting allergic inflammation in AD [32]. Experimental evidence shown fibroblast-eosinophil interaction could play a significant role in the inflammatory cascade. In cell cultures, IL-37 b inhibits IL31/IL-33-induced expression of αTNF, IL-6, CXCL8, CCL2, and CCL5, promoting autophagic mechanisms through regulation of the AMPK-mTOR signaling pathway [32]. Namely, elevated levels of IL-33 and PRG4 inhibit NF-κB activation, a key regulatory inflammatory mechanism. Deletion of the Ikkb (inhibitor of nuclear factor kappa-B kinase subunit beta) gene leads to the development of AD manifestations, increased expression of CCL11, infiltration of eosinophils and Th2 inflammation [32].

The JAK/STAT signaling pathway as an integral part of AD inflammation

The JAK/STAT signaling pathway represents a central mechanism in modifying multiple immune processes in AD pathogenesis [26, 33, 34]. Previous research indicate that JAK-STAT pathway enables IL-4, -5, -13, -31, and TSLP exerting effects, epidermal barrier regulation, nerve modulation and pruritus etiopathogenesis [26, 33, 34]. The JAK family includes four kinases associated with receptors: JAK1, JAK2, JAK3 (janus kinase 1/2/3) and TYK2 (tyrosine kinase 2), while STAT (signal tranducer and activator of transcription) includes seven proteins: STAT1, STAT2, STAT3, STAT4, STAT5, STAT5a, STAT5b, STAT6 [26, 33, 34]. The proposed mechanism of JAK/STAT signaling pathway include phosphorylation of intracellular receptor's domain, subsequently recruiting and inducing phosphorylated STAT dimerization that culminates in translocation into the nucleus and regulation of gene transcription by binding to DNA [26, 33, 34]. TSLP binds to the heterodimeric receptor TSLPR, containing the IL-7Rα receptor, and interacts with JAK1 and JAK2, with further STAT5 activation [34]. IL-4 binds to the

IL-4R type I receptor, resulting in JAK1 and JAK3 phosphorylation, which activate and phosphorylate the IL-4Rα chain (common to IL-13Rα1 in type II IL-4 receptor) and STAT6. IL-4 and IL-13 bind to IL-4R type II leading to JAK1 and TYK2 phosphorylation, STAT3 and STAT6 activation, inducing reduced filaggrin expression, epidermal barrier dysfunction, and increased TSLP, IL-25, IL-33 production in keratinocytes [26, 33, 34]. IL-5 binding to the α subunit of its receptor, and IL-3 and granulocyte-macrophage-colony stimulating growth factor (GM-CSF) binding to the β subunit, activate and phosphorylate JAK1 and JAK2, as well as STAT, STAT3 and STAT5 [26, 33, 34]. IL-31 binds to its receptor complex's α subunit, containing oncostatin-M-receptor-β (OSMRβ). The IL-31Rα-OSMRβ complex activates JAK1 and JAK2, STAT3 and STAT5, and to a lesser extent, STAT1 [26, 33, 34].

During AD's chronic phase, Th1, Th17 and Th22 subpopulations and cytokines sustain local inflammation, presence of proinflammatory cytokines, and epidermal hyperplasia [26, 33, 34]. The JAK-STAT signaling pathway indirectly influences differentiation and function of Th17 cells through the activation of STAT3, affecting the release of pro-Th17 cytokines: IL-6, IL-21, and IL23, and the final production of IL-17. On the other hand, IL-22 after binding to its receptor leads to the phosphorylation of JAK1 and TYK2, and STAT3, STAT1 and STAT5 [26, 33, 34]. Elevated Th1 cytokines levels include: γIFN, IL-12, and granulocyte colony-stimulating factor (G-SCF). IL-12 primarily stimulates naïve T cells differentiation into the Th1 subpopulation. IL-12 receptor beta subunits binding activates JAK2 and TYK2, and STAT4, as well as STAT1, STAT3, and STAT5, to a lesser extent [26, 33, 34]. γIFN, playing its pathophysiological role in epidermal dysfunction by reducing ceramide and long-chain fatty acids expression, upon its receptor binding, activates JAK1 and JAK2, and STAT1 [26, 33, 34]. JAK1's implication in epidermal barrier dysfunction is linked to JAK1-dependant exertion of IL-4, IL-5, IL-13, IL-22, TSLP, and γIFN [26, 33, 34]. JAK1 abundant activation is associated with cutaneous serine proteases overexpression and epidermal degradation, whereas STAT3, as a key transcription factor, impacts keratinocytes differentiation and thus skin integrity maintenance. Inhibition of JAK1/JAK2/JAK3/STAT3 axis, benefits epidermal barrier functionality by enhancing filaggrin, loricrin and other factors responsible for epidermal homeostasis [26, 33, 34].

NOVEL DISCOVERIES AND EMERGING THERAPEUTIC TARGETS

Recent studies highlight the role of small molecules, receptors, ion channels, transcription factors and signaling pathways in AD development and treatment. Among these, phosphodiesterase-4 (PDE4) plays a crucial role in AD pathogenesis, with four subtypes, of which particularly PDE4B impact the inflammatory response [26]. PDE4 is present in various cells, basophils, mast cells, neutrophils, eosinophils, monocytes, macrophages, B and T lymphocytes, endothelial cells, and dermal fibroblasts [26, 35]. PDE4 primarily hydrolyzes cyclic adenosine monophosphate - cAMP, or cyclic guanosine monophosphate - cGMP [26, 36]. cAMP affects the regulation of the inflammatory and immune response, with elevated levels of cAMP supressing lymphocytes and monocytes [26, 36]. AD patients

exhibit increased adenylate cyclase levels, leading to accumulation of cAMP and compensatory PDE4 activation [35]. This stimulation of PDE4 results in inadequate cAMP metabolism, with elevated levels of prostaglandin E2, IL-6 and IL-10 in monocytes of AD patients, contributing to Th1/Th2 imbalance and Th2 cytokines prevalence [35, 36]. Inhibiting PDE4 prevents intracellular cAMP degradation, activation of PKA (protein kinase A) and Epac 1/Epac 2 (exchange factor directly activated by cAMP 1/2), which lead to the inhibition of NF-κB mediation, promoting anti-inflammatory cytokines production via CREB (cAMP-responsive element binding) protein interaction [26, 36]. PDE4 inhibition influences immune functions by regulating inflammatory cytokines, T cell activation, neutrophil degranulation, antigen presentation, epidermal integrity, and oxidative stress suppression [26].

AHR (aryl hydrocarbon receptor) and NRF2 (nuclear factor erythroid 2-related factor 2) are transcription factors of cytoprotective genes involved in detoxification mechanisms and antioxidant activity of enzymes [37]. AHR, located in cytosol, forms complexes with several proteins [22, 26]. Upon ligand binding, AHR dissociates from other proteins, translocates to nucleus, and binds to the DNA molecule, regulating target genes expression. These receptors exhibit pro-inflammatory and anti-inflammatory activity after exposure to various exogenous and endogenous factors. AHR is found in Treg, Th17, Th22, Tc, γδ T and ILC cells [26]. AHR is involved in keratinocyte differentiation and proliferation mechanisms, inflammatory cytokines production, and T-cell immune regulation [22]. Studies confirmed AHR's critical role in FLG expression in human keratinocytes. Activated AHR binds to the EDC (epidermal differentiation complex) locus, regulates transcription factor OVOL1 and stimulates FLG, loricrin and involucrin expression [22]. Additionally, AHR regulates NRF2 activation, inducing cytoprotective genes expression encoding detox and antioxidant enzymes [22, 38]. NRF2 activation interferes with Th2 cytokines via STAT6 dephosphorylation. NRF2 also suppresses proinflammatory cytokines (IL-6 and IL-1β) production by impairing NF-κB transcriptional [22]. Modulating AHR and NRF2 inducers achives significant epidermal barrier regeneration and inflammation suppression in experimental AD models [22, 38, 39].

TLRs, as part of innate immunity, exhibit polymorphism in AD and pathological functions, affecting epidermal barrier repair delay, antimicrobial defense impairment, Th2 inflammation stimulation, Th1 response transition in AD chronicity, pruritus and UV radiation effects [40]. TLR activation is vital in microbial defense. Staphylococcal enterotoxin B increases TLR6 expression on monocytes in AD, while TLR2 stimulation on dendritic cells and monocytes leads to dysfunctional maturation and increased IL-17A production in AD [40]. Additionally, TLR2 activation interferes with IFNGR/JAK/STAT1 signaling pathway, reducing Th1 chemokines expression, while St. aureus ligands stimulate TLR2-mediated IL-10 secretion, directing Th1/Th17 response towards Th2 inflammation [40]. TLR agonists proved ameliorating effects on AD symptoms, barrier function and inflammation, while several experimental models underlined the need for careful modulation instead, considering diverse TLRs' functions in AD and inconsistent expression levels in various stages of disease [40].

Research focused on discovering new activation mechanisms for mast cells, crucial in allergic and atopic diseases, which could represent potential targets for novel therapies. MRGPRX2 (Mas-related G protein-coupled receptor-X2) has gained importance in AD pathogenesis research in recent years [41]. MRGPRX2 involves non-IgE-mediated mast cell degranulation [41]. Elevated levels of MRGPRX2 agonists, such as neuropeptide SP, human β-defensin, cortistatin 14, and TSLP, are present in AD [39]. MRGPRX2 is expressed by basophils and eosinophils, in addition to mast cells and sensory neurons. MRGPRX2 facilitates effector cell degranulation, leading to inflammation [41]. Antagonizing MRGPRX2 demonstrated significant improvement of AD phenotypic changes, preservation of involucrin expression and periostin downregulation, suggesting MRGPRX2 be a novel therapeutic target in AD [41].

In type 2 allergic diseases, including AD, there is an abnormally increased NLRP3 (NLR family pyrin domain containing 3) inflammasome activation [42]. NLRP3, a protein complex, consists of NLRP3 protein, ASC and caspase-1. It can be activated via the NF-κB pathway, ion channels, and lysosome damage [42]. House mite allergens stimulate keratinocytes to form the NLRP3 inflammasome, secreting IL-1β and IL-18 and initiating inflammation [42]. NLRP3 inflammasome activation in keratinocytes increases ROS particles production and NF-κB signaling pathway activation. Phosphorylation of p38, ERK and JNK in keratinocytes triggers the MAPK (mitogen-activated protein kinase) signaling pathway and in turn activates the inflammasome via MAPK/AP-1/NF-κB [42]. NLRP3/IPF4/IL-33 axis activation in keratinocytes is also identified in AD, contributing to disease pathogenesis [42]. Suppressing NLRP3 expression effectively reduces inflammation, underlying NLRP3 inhibitors' therapeutic potential [42].

CONCLUSION

Considering an accelerated implementation of new therapeutic options in clinical practice, such as biologics and small molecule therapies, we believe that an in-depth review of current knowledge in the field of immunopathogenesis of atopic dermatitis provides an essential exposition of the basic principles that modern therapies are grounded in, while broadening horizons for future research. The coming years are expected to bring an expansion of the field of application of translational research in treatment and diagnostics, contributing to a more precise individual approach and stratification of patients with atopic dermatitis as well.

Ethics: The authors declare that the article was written in accordance with ethical standards of the Serbian Archives of Medicine as well as ethical standards of medical facilities for each author involved.

ACKNOWLEDGMENT

This paper is a part of a doctoral thesis.

Conflict of interest: None declared.

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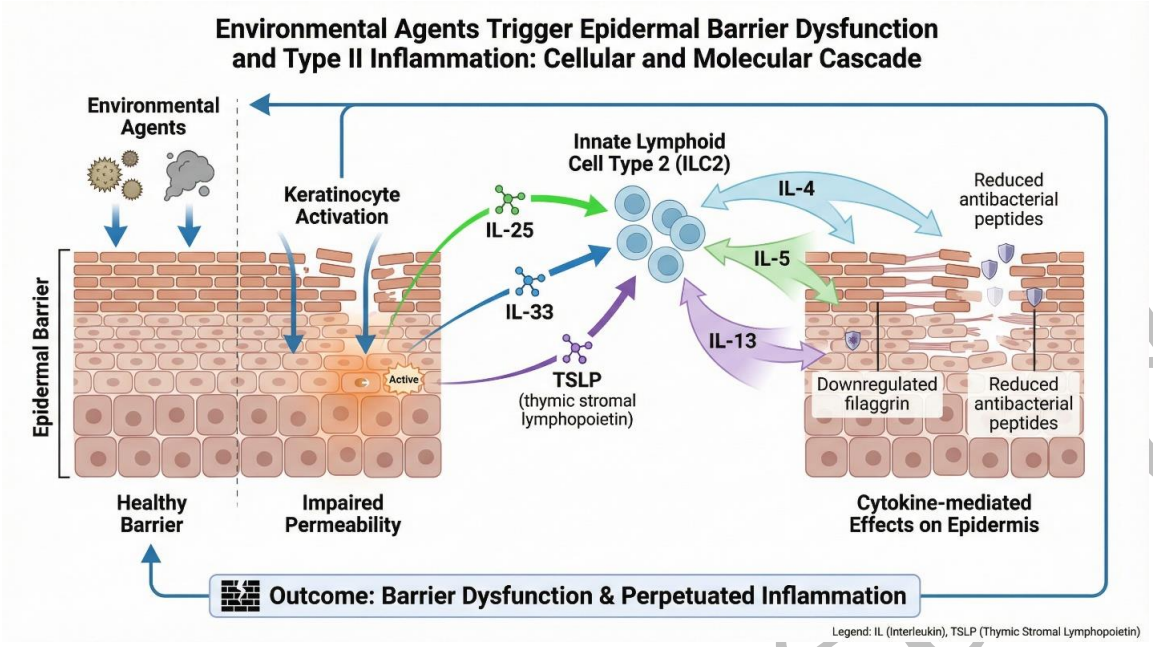

Figure 1. The ILC2s link between epidermal barrier damage and type 2 inflammation, following the environmental insults; figure designed by figurelabs.ai

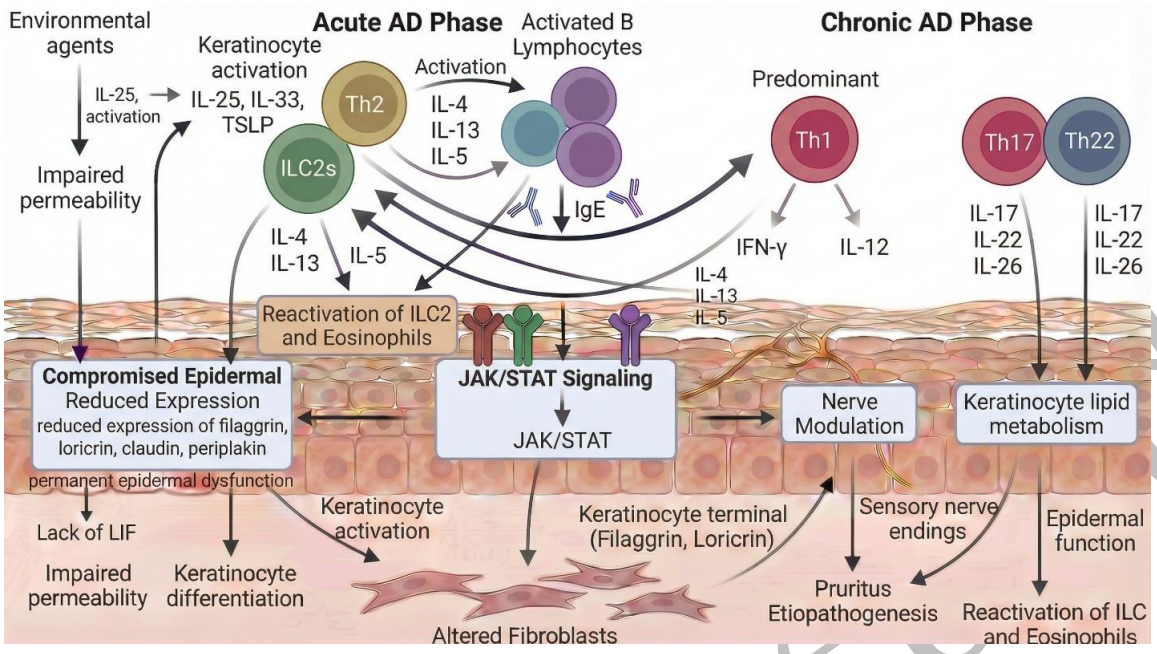

Figure 2. The immunopathogenesis of atopic dermatitis reflects the initial phase of keratinocyte activation, alarmin-stimulated ILC2s and secretion of IL-4, IL-5 and IL-13, which further promote Th2-driven inflammation in acute atopic dermatitis; Th1 cells with gamma interferon and IL-12 release, predominate in chronic phase; activation of B cells is responsible for IgE secretion; figure designed by figurelabs.ai

