Вестник РУДН. Серия: МЕДИЦИНА
RUDN Journal of MEDICINE. ISSN 2313-0245 (Print). ISSN 2313-0261 (Online)
2025;29(3)
http://journals.rudn.ru/medicine

ИММУНОЛОГИЯ
IMMUNOLOGY

DOI 10.22363/2313-0245-2025-29-3-365-384
EDN QSMOXR

REVIEW
ОБЗОР

The role of type 2 inflammation in the pathogenesis of atopic dermatitis

Olga G. Elisyutina[1, 2] ✉, Evgenii V. Smolnikov[1, 2], Daria D. Chernushevich[1, 2], Alla O. Litovkina[1, 2], Maria G. Byazrova[1, 2], Elena A. Levkova[2], Elena S. Fedenko[1]

[1] National Research Center — Institute of Immunology FMBA of Russia, *Moscow, Russian Federation*
[2] RUDN University, *Moscow, Russian Federation*
✉ el-olga@yandex.ru

Abstract. *Relevance.* Atopic dermatitis (AD) is classified as a chronic immune-mediated disease, with its pathogenesis rooted in genetic predisposition and immune response dysregulation, predominantly driven by T2-inflammatory reactions. This review highlights key aspects of the immunopathogenesis of AD, emphasizing its systemic inflammatory nature linked to T2-immune dysregulation. This leads to the activation of cytokines such as IL-4, IL-5, IL-13, and IL-31. The article analyzes modern treatment approaches, including targeted therapy aimed at blocking T2 cytokines, stressing the importance of early intervention to prevent complications and the development of the atopic march. Understanding T2-inflammation mechanisms opens new opportunities for developing effective personalized therapies for AD. *Conclusion.* Type 2 inflammation plays a pivotal role in the pathogenesis of AD, driving chronic inflammation, skin barrier dysfunction, and the clinical manifestations of the disease. Key mediators of T2 inflammation-including IL-4, IL-5, IL-13, and IL-31-regulate the activation of various immune-competent cells, not only amplifying inflammation but also contributing to the development of pruritus. This, in turn, establishes the self-perpetuating "itch-scratch" cycle, which exacerbates skin damage and further stimulates inflammatory processes. Impaired skin barrier function also facilitates the penetration of allergens and microbial agents, further activating the immune response and worsening disease severity. Studying type 2 inflammation as a central mechanism in AD pathogenesis not only advances our understanding of the disease but also facilitates the development of new therapeutic strategies to control AD and improve patients' quality of life, which remains a priority in contemporary immunology, allergology, and dermatology.

Keywords: atopic dermatitis, T2-inflammation, cytokines, biomarkers, target therapy

Funding. The research and publication were supported by the Russian Science Foundation grant No. 23–15–00432, https://rscf.ru/project/23-15-00432

Author contribution. O.G. Elisyutina — collection and analysis of literary sources, preparation and writing of the article; E.V. Smolnikov — collection and analysis of literary sources, writing the article; D.D. Chernushevich — collection and analysis of literary sources; A.O. Litovkina — collection and analysis of literary sources; M.G. Byazrova — collection and analysis of literary sources; E.A. Levkova — collection and analysis of literary sources, writing the article; E.S. Fedenko — writing the text and editing the article. All authors have made significant contributions to the development concepts, research, and manuscript preparation, read, and approved final version before publication.

Conflict of interest statement. The authors declare no conflict of interest.

Ethics approval — not applicable.

Acknowledgements — not applicable.

Consent for publication — not applicable.

Received 08.12.2024. Accepted 13.01.2025.

For citation: Elisyutina OG, Smolnikov EV, Chernushevich DD, Litovkina AO, Byazrova MG, Levkova EA, Fedenko ES. The role of type 2 inflammation in the pathogenesis of atopic dermatitis. *RUDN Journal of Medicine.* 2025;29(3):365—384. doi: 10.22363/2313-0245-2025-29-3-365-384. EDN QSMOXR

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by genetic predisposition, epidermal barrier dysfunction, and dysregulated type 2 immune responses [1, 2]. Immune-mediated inflammatory diseases are classified into three main types based on the predominant immune response driving their pathogenesis.

Type 1 inflammatory diseases are associated with excessive activation of Th1 lymphocytes and innate immune cells, leading to increased production of cytokines such as interferon-γ (IFN-γ), interleukin (IL)-12, and tumor necrosis factor (TNF). These cytokines provide protection against intracellular pathogens, but their overproduction triggers chronic inflammation and tissue damage. Examples of such diseases include rheumatoid arthritis, sarcoidosis, and Crohn's disease.

Type 2 inflammatory diseases are characterized by the predominance of Th2 lymphocytes, type 2 innate lymphoid cells (ILC2s), and cytokines such as IL-4, IL-5, and IL-13, which are associated with allergic inflammation, eosinophil activation, IgE production, and impaired skin and mucosal barrier function. Examples include AD, asthma, allergic rhinitis (AR), and related conditions.

Type 3 inflammatory diseases are driven by Th17 cell activation and the production of IL-17 and IL-22, which promote neutrophilic inflammation. This immune response targets extracellular bacteria and fungi, but when dysregulated, it contributes to tissue damage and chronic inflammation in diseases such as psoriasis, ankylosing spondylitis, and ulcerative colitis [3, 4]. This classification of chronic immune-mediated inflammatory diseases has become particularly relevant with the advent of targeted therapies directed at specific biological pathways.

According to global epidemiological studies, the prevalence of AD is 15–20% in children and up to 10% in adults [5]. One in five children with AD shows no detectable allergen-specific IgE to food or airborne allergens [6]. In 20–40% of patients, AD manifests as moderate-to-severe disease and is considered a systemic disorder with multi-organ involvement [7–9]. The pathogenesis of AD involves genetic predisposition, impaired

epidermal barrier function, predominant type 2 immune responses, skin microbiome alterations, IgE-mediated sensitization to allergens, and autoimmune mechanisms, which collectively determine the disease phenotype and endotype [10].

The immune response in AD involves various immune cells, including T lymphocytes, dendritic cells, ILC2s, keratinocytes, monocytes, and eosinophils. These cells are activated by allergens and microbial agents penetrating the compromised skin barrier and produce pro-inflammatory cytokines such as IL-4, IL-5, IL-13, IL-31, and others.

Investigation of the immunological mechanisms underlying AD has become particularly crucial with the emergence of novel targeted biologic therapies. This review synthesizes current understanding of type 2 inflammation in AD pathogenesis and evaluates contemporary therapeutic approaches for disease management.

Key characteristics of type 2 inflammation

The type 2 immune response normally provides protection against parasitic and helminthic invasions and supports the barrier functions of the skin and mucous membranes. However, its dysregulation can lead to the development of type 2 inflammation. This type of immune response is characterized by the activation of Th2 cells, ILC2s, and an increased production of cytokines such as IL-4, IL-5, IL-9, IL-10, IL-13, IL-31, certain chemokines, as well as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), which are mainly secreted by non-immune cells. The main biological functions of these cytokines are presented in Table 1 [3, 11].

Table 1

The main biological functions of T2 cytokines

Cytokine/ References	Main biological functions
IL-4/ [11–13]	Stimulation of Th2 cell differentiation.Maintenance of survival, long-term persistence, and activity of Th2 cells under inflammatory conditions.Regulation of antibody production: stimulation of B cell isotype switching from IgM to IgE; enhancement of IgG4 production.Stimulation of eosinophils via activation of IL-5 and other mediators.Epidermal barrier dysfunction: downregulation of structural barrier proteins (filaggrin, involucrin, loricrin).Impaired antimicrobial defense: reduced synthesis of skin lipids and antimicrobial peptides.Modulation of inflammation through activation of other immune cells, including mast cells, basophils, and macrophages, and maintenance of pro-inflammatory cytokine production (IL-13).Tissue remodeling via stimulation AAMs, which participate in tissue repair and remodeling.
IL-13/ [11–13]	Stimulation of the production of other Th2 cytokines: IL-4 and IL-5.Maintenance of eosinophilic inflammation through interactions with other cytokines, including IL-5.Activation of AAMs, supporting chronic inflammation.Epidermal barrier dysfunction: downregulation of structural barrier proteins (filaggrin, involucrin, loricrin).Impaired antimicrobial defense: reduced synthesis of skin lipids and antimicrobial peptides (cathelicidins and beta-defensins).Enhancement of collagen and polyamine synthesis, contributing to tissue remodeling and repair.Goblet cell hyperplasia and increased mucus production, especially in the airways.Activation of sensory neurons, amplifying itch perception and pruritogenic responses.Stimulation of B cells isotype switching to IgE, thereby intensifying allergic reactions.
IL-5/ [11,14]	Regulation of eosinophils: stimulation of proliferation, maturation, and survival of eosinophils in the bone marrow; enhancement of eosinophil migration from the bloodstream to inflamed tissues.Activation of eosinophils: increased capacity of eosinophils to secrete granule contents (major basic protein, peroxidase, etc.) for the destruction of parasites and pathogens.Increased accumulation of eosinophils at sites of inflammation, contributing to the chronicity of inflammatory processes, especially in allergic diseases.Interaction with other Th2 cytokines (IL-4, IL-13), supporting allergic inflammation.Participation in the elimination of large extracellular pathogens, such as helminths, through activation of eosinophils and basophils.Maintenance of basophil survival, their activation, and migration into tissues.Induction of angiogenesis: stimulation of new blood vessel growth, which is associated with the maintenance of inflammatory processes
IL-31/ [15,16]	Pruritogenic function: activation of sensory neurons via IL-31 receptor alpha (IL-31RA) and oncostatin M-specific receptor beta (OSMRβ); IL-31 is a key mediator of itch in AD, chronic nodular prurigo, and other inflammatory skin diseases.Epidermal barrier dysfunction: downregulation of structural barrier proteins (filaggrin, involucrin, loricrin). Stimulation of keratinocytes to produce pro-inflammatory cytokines and chemokines CCL17 and CCL22.Amplification of skin inflammation by recruiting additional immune cells, including eosinophils and Th2 cells.Tissue remodeling: stimulation of cell proliferation and growth factor production.Interaction with other type 2 inflammation mediators IL-4 and IL-13.Involvement in itch mechanisms in systemic diseases such as Hodgkin lymphoma.Influence on the skin microbiome, creating conditions favorable for the growth of pathogenic microorganisms like *Staphylococcus aureus*.Interaction of IL-31 with skin and immune cells contributes to the transition from acute to chronic inflammation.

Ending tabl. 1

IL-9/[17]	Proliferation, survival, and activation of mast cells, promoting the release of histamine and other mediators. Maintenance of type 2 inflammation: stimulation of IL-4 and IL-13 production.Participation in the immune response against helminths by stimulating mast cells, mucus secretion, and recruitment of immune cells to affected tissues. Stimulation of eosinophils.Enhancement of mucus secretion in the airways, contributing to parasite clearance but also causing hypersecretion in bronchial asthma.Stimulation of fibroblasts to produce collagen, potentially contributing to tissue fibrosis in chronic inflammation.Activation of ILC2s, which produce type 2 cytokines.Stimulation of B cells isotype switching to IgE, thereby intensifying allergic reactions.
IL-10/[18–20]	Suppression of inflammation: inhibition of the production of pro-inflammatory cytokines IL-1, IL-6, IL-12, IFN-γ, and TNF-α.Reduction of macrophage and dendritic cell activation by suppressing their antigen-presenting capacity and release of pro-inflammatory mediators.Inhibition of activation and proliferation of Th1 cells, thereby limiting inflammation.Maintenance of survival and function of Tregs, which play a critical role in preventing autoimmune diseases.Stimulation of antibody production by B cells, especially IgG4 and Ig A.Decreased production of autoantibodies, which is important for preventing the development of autoimmune reactions.Limitation of the inflammatory activity of neutrophils and macrophages.Reduction in the production of reactive oxygen species and enzymes capable of causing oxidative stress.Stimulation of growth factor production that supports tissue repair.Maintenance of immune tolerance: prevents hyperactivation of the immune system, ensuring tolerance to self-antigens and promoting tolerance to commensal microbes in the gut and other barrier tissues.Regulation of the microbiome.Limitation of tissue damage during infections by reducing the intensity of the inflammatory response; however, excessive IL-10 production may weaken immune defense and contribute to infection chronicity.
IL-33/[16,21]	Activation of ILC2: IL-33 stimulates ILC2 to produce key type 2 cytokines IL-5 and IL-13.Enhancement of Th2 cells differentiation and increased production of IL-4, IL-5, and IL-13, contributing to the development of allergic reactions. Activation of mast cells, basophils, and eosinophils, and recruitment of immune cells to sites of inflammation. Maintenance of skin itch through activation of keratinocytes and impairment of barrier function, facilitating allergen penetration.Stimulation of macrophage and fibroblast activation, promoting tissue remodeling and repair after injury.Support of immune responses against helminths by enhancing mucus secretion and recruiting immune cells. Alarmin function: released upon tissue damage to trigger inflammatory responses.Increased vascular permeability. Influence on the microbiome composition, promoting growth of pathogenic microorganisms and thereby exacerbating inflammation.
IL-25/ [21,22]	Stimulation of differentiation and activation of Th2 lymphocytes and activation of ILC2s, which enhances the production of cytokines IL-4, IL-5, and IL-13.Enhancement of eosinophil migration and activation.Participation in immune defense against helminths by stimulating mucus production, recruiting immune cells to affected tissues, and promoting intestinal smooth muscle contraction, thereby facilitating parasite expulsion.Activation of dendritic cells and macrophages, which sustain the inflammatory response.Increased production of chemokines that attract additional immune cells to the site of inflammation, further amplifying the immune response.Supports epithelial repair after injury.Maintains a type 2 immune response while suppressing Th1 and Th17 responses, thus limiting inflammation associated with other immune pathways.Interacts synergistically with other alarmins such as IL-33 and TSLP, creating a potent signal for the activation of type 2 inflammation.
TSLP/ [23,24]	Activation of dendritic cells, promoting their migration and enhancing their antigen-presenting capacity; programs dendritic cells to stimulate Th2 lymphocyte differentiation, thereby amplifying the type 2 immune response.Stimulation of Th2 cells to produce IL-4, IL-5, and IL-13, which intensify the inflammatory process.Activation of ILC2.Induction of itch and skin inflammation through activation of sensory neurons, contributing to increased pruritus, especially in AD.Enhancement and maintenance of chronic skin inflammation.Regulation of barrier functions of the skin and mucous membranes.Stimulation of migration and activation of eosinophils, mast cells, and basophils.Maintenance of survival and activation of Th2 lymphocytes.Interaction with other alarmins such as IL-33 and IL-25, enhancing their effects and promoting robust activation of type 2 inflammation.Modulation of interactions between immune and nervous system cells, strengthening the link between inflammation and itch.

The functions of IL-4 and IL-13 are largely similar but not identical: IL-4 and, to a lesser extent, IL-13 regulates immune response switching and IgE synthesis by plasma cells. IL-4, but not IL-13, promotes differentiation of T-helper cells from Th0 to Th2 cells. They also recruit inflammatory effector cells, reduce expression of filaggrin and other skin structural proteins; in mouse models these cytokines increased *S. aureus* skin colonization. IL-4 and IL-13 play a key role in macrophage activation through interaction with the IL-4Rα receptor, which is a common receptor chain for both cytokines. This process leads to the formation of alternatively activated macrophages (AAMs), which differ from classically activated macrophages by their role in inflammation regulation, tissue repair, and parasite defense [13, 25]. Several studies have shown that IL-4 and IL-13 stimulate macrophages to produce mediators such as arginase-1 (Arg1) and Resistin-like

molecule α (RELMα) [26, 27]. Arg1 competes with nitric oxide synthase (iNOS) for the common substrate arginine and suppresses NO-mediated antimicrobial pathways in classically activated macrophages. A key function of Arg1 is inflammation suppression, achieved not only through iNOS inhibition but also via direct effects on T-cell function. T-cells are sensitive to arginine concentration, and its depletion through arginase activation impairs their function. Ornithine, in turn, is used for polyamine and proline synthesis, which support cell proliferation and collagen production. These processes may underlie fibrosis development and pathological tissue remodeling in asthma [28]. Furthermore, studies demonstrate Arg1's ability to participate in tissue repair via L-ornithine and exert effector activity against nematodes by limiting parasite mobility and promoting macrophage uptake [29]. Macrophages also secrete RELMα, which can disrupt parasite metabolism and reduce their motility [30]. Macrophage activation through the IL-4Rα receptor, shared by IL-4 and IL-13 cytokines, leads to their alternative activation, significantly enhancing their ability to interact with antibody-coated parasites. This process involves several key mechanisms: increased Fc receptor expression, improved adhesion and interaction, and secretion of Arg1 and polyamines. Through IL-4Rα activation, macrophages alter their metabolism, switching to aerobic glycolysis, which enhances their capacity for active uptake and processing of opsonized particles. Thus, IL-4Rα-mediated macrophage activation makes them more efficient at recognizing antibody-coated parasites, enhancing their phagocytic capacity and providing significant immune defense against parasitic infections. AAMs also participate in recruiting other immune cells, such as eosinophils, which contribute to parasite destruction through toxic granule proteins. A key biological function of IL-4 is stimulating naive T-lymphocytes (Th0) and their differentiation into Th2 cells [3]. IL-4 and IL-13 promote immunoglobulin class switching in B-lymphocytes [31] and enhance IgE production [11]. One of the most important functions of IL-4 and IL-13 is their ability to activate sensory neurons (itch receptors) in the skin and participate in the pathological "itch-scratch" cycle, which on one hand aims to eliminate pathogens from the skin surface, but on the other exacerbates skin damage and inflammation [32, 33].

IL-5 plays a key role in eosinophil activation, mobilization, and parasite-killing capacity. This process involves several stages ensuring effective parasite elimination and inflammatory response regulation. IL-5 stimulates eosinophil differentiation and maturation in bone marrow, acting on eosinophil precursors through the IL-5 receptor (IL-5R), enhancing their proliferation, and after cell maturation, promotes eosinophil release from bone marrow into bloodstream and migration to inflammation sites [11, 14, 34, 35]. IL-5 increases adhesion molecule expression on eosinophils, enabling their interaction with endothelial cells and tissue migration through vascular walls [34]. IL-5 activates eosinophils, enhancing their ability to release toxic granules upon parasite contact.

IL-9 is an important cytokine in Th2 response, supporting mast cell, basophil and eosinophil activation. It enhances IL-4, IL-5 and IL-13 production, promoting development and maintenance of allergic inflammation. IL-9 plays a key role in parasite defense by stimulating mucus secretion and recruiting immune cells to affected tissues [36]. IL-9 participates in both protective mechanisms and pathological processes associated with allergic diseases and chronic inflammation [37].

IL-10 plays a crucial role in immune response regulation and homeostasis maintenance. On one hand, IL-10 suppresses proinflammatory cytokine production (IL-1, IL-6, IL-12, TNF-α, IFN-γ) by acting on macrophages, dendritic cells and other innate immune effector cells [19, 38, 39]. IL-10 reduces antigen presentation and inflammatory mediator release by macrophages and dendritic cells, limiting excessive inflammation and protecting tissues from damage [40]. On the other hand, IL-10 supports regulatory T-cells (Tregs), enhancing their role in suppressing inflammatory responses and preventing autoimmune reactions [41]. IL-10 stimulates antibody production by B-cells, particularly IgA, important for maintaining mucosal barrier function in gut and airways [42]. Moreover, IL-10 plays a key role in establishing immune tolerance to commensal microbiota, preventing excessive inflammation in

barrier tissues [43]. Thus, IL-10 has multifunctional roles, restraining inflammation and protecting against autoimmune reactions, but under certain conditions may weaken pathogen defense.

IL-31 is a key mediator of skin itching, inflammation and tissue remodeling. It activates sensory neurons causing itch, enhances skin inflammation through keratinocyte activation and proinflammatory cytokine production [44], and impairs skin barrier function by reducing expression of key structural proteins including filaggrin [45].

Alarmins (IL-25, IL-33 and TSLP)

Damaged epithelial cells release alarmins that play an important role in activating innate immunity and signaling threats to the body. Their function is to rapidly recruit immune cells to sites of injury and infection.

IL-25 plays a key role in activating type 2 inflammation by stimulating production of IL-4, IL-5 and IL-13 by Th2 cells and ILC2s [46]. Studies show elevated levels of this cytokine in patients with AD and asthma [47]. IL-25 also enhances protection against parasites and amplifies allergic inflammation by increasing migration and activation of immune cells [48]. IL-33 is a key mediator of type 2 inflammation that activates ILC2s, basophils and mast cells, boosting production of IL-5 and IL-13. It plays an important role in development of asthma and AD, where its levels are elevated in affected tissues [49]. IL-33 receptors are found on memory Th2 cells, suggesting its role in activating adaptive immune responses [50]. IL-33 is also involved in tissue remodeling processes and exacerbates chronic inflammation, particularly in allergic and inflammatory diseases. TSLP plays a crucial role in initiating and maintaining type 2 inflammation. It activates dendritic cells which stimulate Th2 cell differentiation and production of IL-4, IL-5 and IL-13 [51,52]. TSLP also enhances inflammatory responses through OX40 ligand expression, increasing activity of Th2 cells and ILC2s [53]. Its elevated expression in skin correlates with severity of AD and induces itching by acting on sensory neurons [54].

Thus, type 2 inflammation plays an important biological role in protecting against infections including parasitic infections and maintaining skin and mucosal barrier functions. Type 2 inflammation is characterized by activation of Th2 lymphocytes, ILCs and production of key cytokines including IL-4, IL-5, IL-13 and IL-31. These cytokines regulate eosinophils, mast cells and basophils which secrete inflammatory mediators and toxic proteins to eliminate parasites. Type 2 inflammation also activates IgE production. However, beyond its protective role, type 2 inflammation contributes to pathogenesis of chronic inflammatory and allergic diseases. It disrupts skin and mucosal barriers by suppressing structural protein synthesis and increasing permeability to allergens, pathogens and nonspecific irritants. Simultaneously, type 2 inflammation maintains chronic inflammation by recruiting immune cells to affected tissues, stimulating mucus secretion and provoking itch through activation of sensory neurons by alarmins IL-31 and TSLP. Interaction with microbiome further exacerbates inflammation, creating favorable conditions for growth of pathogenic microorganisms like *S. aureus.* Mechanisms of type 2 inflammation are involved in pathophysiology of multiple diseases: AD, prurigo nodularis, chronic spontaneous urticaria, bullous pemphigoid, eosinophilic esophagitis, chronic rhinosinusitis with nasal polyps, asthma, and eosinophilic chronic obstructive pulmonary disease [11, 55–57].

Pathogenetic mechanisms of atopic dermatitis

AD is a common chronic type 2 inflammatory systemic disease characterized by a chronic relapsing course, based on genetic predisposition to allergy, immune dysregulation, and skin barrier dysfunction [1, 10, 58].

Impairment of skin barrier function

Disruption of the epidermal barrier is a key link in AD pathogenesis, determining both predisposition to the disease and clinical features. These changes lead to increased skin permeability to various antigens and

nonspecific irritants and elevated transepidermal water loss. The main aspects of epidermal barrier dysfunction involve defects in epidermal structural proteins (filaggrin, involucrin, loricrin) [59, 60], changes in skin lipid layer composition (reduced ceramides, free fatty acids, and cholesterol) [61], increased transepidermal water loss, and decreased synthesis of antimicrobial peptides [62].

Filaggrin, the most important structural skin protein responsible for keratinization, hydration, and antimicrobial defense, is the main component of keratohyalin granules [63, 64]. Filaggrin deficiency caused by genetic disorders can lead to development of AD in early childhood, severe disease course, higher likelihood of concomitant respiratory allergic diseases, and predisposition to recurrent microbial and viral skin infections [65]. However, approximately 40% of filaggrin gene mutation carriers do not develop AD, and filaggrin mutations are found in only 15–50% of AD patients [64]. In a recently published study by Sahlén P. et al., the influence of single nucleotide polymorphisms (SNPs) identified through genome-wide association studies (GWAS) on epidermal barrier dysfunction was investigated using chromosome conformation capture [66]. It was shown that many GWAS-identified SNPs can affect distant genes, with only 35% of target genes being closest to known GWAS variants. In a GWAS-based study by DeVore et al., caspase recruitment domain family member 14 (CARD14) was shown to regulate filaggrin expression in the skin of children with AD [67], with CARD14 regulating filaggrin homeostasis depending on the rs11652075 variant in the CARD14 gene, which is also associated with psoriasis. Genetic filaggrin abnormalities do not explain all skin barrier dysfunctions in AD, but patients without such genetic defects may later show secondarily reduced filaggrin levels [68]. AD also features decreased levels of other terminal differentiation proteins of keratinocytes, such as loricrin and involucrin [69], as well as tight junction proteins [70].

AD patients also show reduced ceramide levels in both affected and unaffected skin, as well as disturbances in ceramide-to-cholesterol ratios [71]. The stratum corneum of AD patients shows elevated pH levels, leading to increased serine protease activity and contributing to inactivation and degradation of acid sphingomyelinase and glucocerebrosidase enzymes necessary for ceramide synthesis. Increased serine protease activity reduces lamellar body secretion through the protease-activated receptor 2 (PAR2) signaling pathway, leading to decreased stratum corneum thickness in AD patients.

Activation of type 2 inflammation

AD features dysregulation of type 2 immune response, leading to development of local and systemic inflammation characterized by activation and proliferation of Th2 lymphocytes, ILCs) and involvement of proinflammatory type 2 cytokines — IL-4, IL-5, IL-13 in response to allergens penetrating the impaired epidermal barrier [3, 4] (Figure). Although many immune signaling pathways involved in AD pathogenesis may underlie different disease subtypes, activation of type 2-mediated immune mechanisms is the dominant mechanism in disease pathogenesis [1, 72, 73].

Type 2 inflammation activation is a multi-stage process beginning with epidermal barrier damage, which can be caused by genetic defects such as filaggrin gene mutations [60, 71, 74], or external factors such as allergens [75], environmental pollution [76], and microbial toxins [77]. In response, skin epithelial cells release alarmins, including TSLP, IL-25 and IL-33, which activate innate and adaptive immune mechanisms. A recently published systematic review and meta-analysis included original articles examining TSLP levels in serum of AD patients [52]. The meta-analysis included 14 studies with 1032 AD patients and 416 controls. It showed that TSLP levels were significantly higher in AD patients compared to controls, with stratification by region, age, disease severity, TSLP detection method, sample size and study quality revealing significantly increased TSLP levels in adult AD patients living in Europe. TSLP elevation was found at all severity levels compared to controls, with higher levels in adults than children, and increasing with disease severity. The biological role of alarmins is described in Table 1, importantly, they play a key role in initiating type 2 inflammation

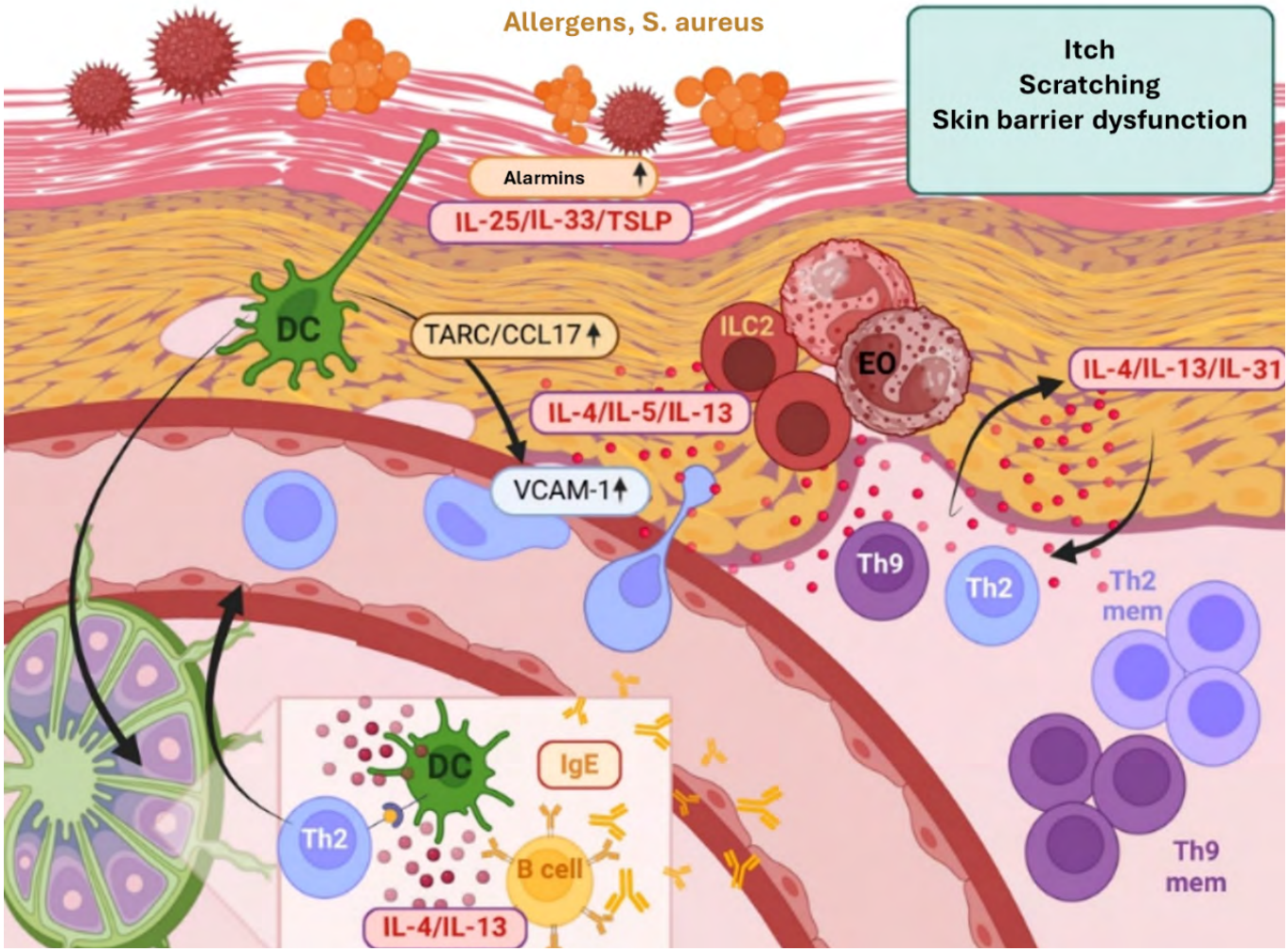

Fig. The main pathogenetic mechanisms of T2 inflammation in AD

by activating ILC2, mast cells, basophils and dendritic cells. TSLP-stimulated dendritic cells migrate to lymph nodes where they activate naive T cells and stimulate their differentiation into Th2 cells. These Th2 cells secrete key type 2 inflammation cytokines such as IL-4, IL-5, IL-13 and IL-31. IL-4 and IL-13 stimulate antibody isotype switching to IgE by plasma cells, maintaining allergic sensitization. Additionally, IL-4 plays a key role in differentiation of Th0 cells into Th2 cells, enhancing type 2 immune response (Figure).

IL-4 and IL-13 suppress synthesis of epidermal structural proteins such as filaggrin, involucrin and loricrin, which impairs skin barrier function and promotes colonization by pathogenic microorganisms such as *S. aureus*. IL-5 stimulates recruitment and activation of eosinophils, which release cytotoxic granules that damage tissues and enhance inflammation. IL-31 acts on sensory neurons, causing itch that contributes to the “itch-scratch” cycle [44]. This cycle exacerbates mechanical skin damage, worsens inflammation and maintains the chronic nature of the disease. Subsequently, inflammation may transition to a chronic phase when Th1- and Th17-mediated immune responses join type 2 inflammation. These mechanisms contribute to tissue remodeling, epidermal thickening and increased inflammation, making AD course more severe.

Relationship between inflammation and skin microbiome disruption

Microbial factors such as *S. aureus* toxins and superantigens further stimulate immune response by increasing proinflammatory cytokine production and exacerbating barrier dysfunction. The skin microbiome state depends on severity of epidermal barrier impairment, climatic factors, hygiene product use, and topical therapy. In AD patients, *S. aureus* colonization is particularly significant as it not only triggers exacerbations but also maintains pathological immune response. *S. aureus* attaches to corneocytes by binding to the N-terminal region of corneodesmosin [78], and also forms biofilms closely associated with AD severity [79]. *S. aureus* has been shown to not only be an exacerbation factor and cause of secondary bacterial infections, but also to initiate immediate hypersensitivity-type immune responses [80–82]. Moreover, *S. aureus* exacerbates epidermal barrier dysfunction in AD and stimulates expression of proinflammatory cytokines [83, 84]. AD features reduced skin microbiome diversity due to staphylococcal dominance, with *S. aureus* contamination being significantly higher in affected versus unaffected skin areas [84,85]. A prospective skin microbiome study assessing relationship between skin microbiota and disease progression in children aged 2–15 years with AD at different disease stages showed decreased microbiome diversity during exacerbations [86]. With impaired epidermal barrier, *S. aureus* can penetrate deep skin layers where it may interact with immune cells and stimulate production of type 2 cytokines: IL-4, IL-13 and IL-22 and TSLP.

Not only skin microbiome but also respiratory and gastrointestinal microbiomes may play roles in AD pathogenesis. In a prospective cohort study by Lehtimäki J. et al. [87] involving 700 children from urban and rural areas, respiratory and gut microbiota were studied for potential associations with asthma and AD development. Risk of asthma and IgE sensitization to respiratory allergens was higher in urban-reared children, with respiratory and gut microbiota composition differing between urban and rural infants.

AD patients also show increased susceptibility to fungal infections caused by *Candida* and *spp*. TLR2 receptors play an important role in this process by mediating interaction between immunogenic proteins and keratinocytes, stimulating production of antimicrobial peptides α- and β-defensins and chemokine CXCL8. Additionally, *Malassezia* antigens can induce specific IgE production through T cell-mediated B cell activation [88].

Thus, type 2 inflammation activation in AD represents a complex interaction between innate and adaptive immune mechanisms, epithelial cells, nervous system and microbial factors. This interaction underlies AD clinical manifestations including itch, chronic inflammation, skin barrier dysfunction and increased allergen sensitivity. Understanding these processes opens possibilities for targeted therapy aimed at blocking key type 2 inflammation cytokines such as IL-4, IL-13 and IL-31, as well as restoring skin barrier function.

Therapeutic approaches to control type 2 inflammation

Early intervention aimed at reducing the impact of systemic type 2 inflammation in AD may not only achieve disease control or remission but also reduce the likelihood of developing atopic march, i.e., the addition of comorbid allergic diseases such as asthma, allergic rhinitis, food allergies, as well as normalize skin structural changes and alter disease course [89]. The main goals of AD therapy are inflammation control, prevention of exacerbations, and improvement of patient quality of life. AD treatment depends on disease severity but always includes the use of emollients, identification and elimination of allergens and triggers. For mild cases, low-potency topical corticosteroids or calcineurin inhibitors are used, along with antihistamines to reduce itching. For moderate cases, moderate or high-potency corticosteroids are applied, with antibacterial agents prescribed when necessary to treat secondary infection. For severe AD, systemic therapy is prescribed: cyclosporine, methotrexate or targeted biologics, such as dupilumab, which blocks key type 2 inflammation cytokines IL-4 and IL-13, or selective JAK inhibitors (abrocitinib, baricitinib, upadacitinib) [2, 57].

Anti-cytokine targeted therapy for AD

Targeted immunotherapy for AD is aimed at specifically affecting key molecules and signaling pathways involved in inflammation development and pathological immune response in this disease. Unlike traditional systemic therapy using systemic corticosteroids or immunosuppressants, targeted therapy selectively acts on cytokines, receptors or other molecules, reducing side effect risks and increasing treatment effectiveness. The first approved targeted drug for moderate-to-severe AD was dupilumab, which inhibits IL-4 and IL-13, key mediators of type 2 inflammation [90–92]. In some countries, various biologics targeting type 2 cytokines are already registered or undergoing clinical trials for efficacy and safety in AD treatment: anti-IL-13 (lebrikizumab and tralokinumab), anti-IL-5 (mepolizumab and reslizumab); drugs blocking type 2 cytokine receptors (benralizumab (IL-5Rα), nemolizumab (IL-31RAα); anti-IgE (omalizumab and ligelizumab). The efficacy and safety of other drugs targeting other type 2 inflammation mediators such as alarmins IL-33 (astegolimab, etokimab, itepekimab, MEDI-3506), IL-33 receptor (melrilimab) and TSLP (tezepelumab) are also being studied. Table 2 presents the main targeted biologics acting on key type 2 inflammation cytokines, their biological targets and indications.

Table 2

Targeted biologic therapies for type 2 inflammation

Targeted biologic drug / References	Biological targets and effects	Therapeutic indications
Dupilumab / [91–96]	IL-4 (IL-4Rα, IL-13Rα)	AD, asthma, CRSwNP, EoE, prurigo nodularis, COPD (approved) Bullous pemphigoid, CSU, CIU, allergic fungal rhinosinusitis, ABPA (phase 3) Food allergy, pollen allergy (phase 2)
Tralokinumab / [97, 98]	IL-13(IL-13Rα2)	AD (approved in EU)
Cendakimab /[99, 100]	IL-13 (IL-13Rα2)	AD (phase 2)EoE (phase 3)
Lebrikizumab /[101–103]	IL-13 (IL-13Rα1)	AD (phase 3)
Nemolizumab /[104–106]	IL-31 (IL-31Rα)	AD (phase 3)Prurigo nodularis (phase 3)Chronic itch (phase 2)
Mepolizumab /[14, 35,107–110]	IL-5	Asthma, EGPA, HES (approved)COPD, nasal polyposis (phase 3) EoE (phase 3)
Reslizumab /[14, 111–113]	IL-5	Asthma (approved)Sinusitis (phase 3)EGPA
Depemokimab / [114]	IL-5	Asthma (phase 3)
Benralizumab /[112, 115–119]	IL-5 (IL-5Rα)	Asthma (approved)Bullous pemphigoid, COPD, EoE, EGPA, HES, Nasal polyposis (phase 3)AD, CSU, Rhinosinusitis, Eosinophilic gastroenteritis (phase 2)
Tezepelumab /[120–122]	TSLP	Asthma (approved), CRSwNP (phase 3)CSU, COPD (phase 2)
Astegolimab / [123,124]	IL-33 (IL-33R)	Asthma, COPD (phase 2)
Itepekimab /[125]	IL-33	COPD (phase 3)
Tozorakimab /[126]	IL-33	Asthma, AD, COPD, COVID-19 (phase 2)
Omalizumab /[127–132]	IgE	Asthma, CSU, nasal polyposis, seasonal AR (approved)Food allergy (phase 3)
Ligelizumab /[133,134]	IgE	CSU, Food allergy (phase 3)
Fezakinumab /[135]	IL-22	AD (phase 2)

Note: CRSwNP — Chronic rhinosinusitis with nasal polyps; EoE — Eosinophilic esophagitis; COPD — Chronic obstructive pulmonary disease; ABPA — Allergic bronchopulmonary aspergillosis; CSU — Chronic spontaneous urticaria; CIU — Chronic inducible urticaria; EGPA — Eosinophilic granulomatosis with polyangiitis; HES — Hypereosinophilic syndrome; AR — Allergic rhinitis.

Interestingly, the clinical efficacy of targeted drugs against type 2 cytokines has provided deeper insights into their role not only in AD but also in other diseases such as asthma, chronic rhinosinusitis with nasal polyps, and eosinophilic esophagitis. The lack of efficacy of some targeted drugs in clinical trials has proven highly valuable for understanding the precise mechanisms underlying type 2 inflammatory diseases and their treatment. For instance, the limited effectiveness of mepolizumab [107], omalizumab [130], and ligelizumab [136] in AD suggested that IL-5-mediated peripheral blood eosinophilia is not the primary source of the inflammatory cascade in AD, and that extremely high IgE levels do not play a dominant role in disease symptom development. On the other hand, the use of certain biologic targeted drugs, such as anti-TNF [137], anti-IL-17 [138], and anti-IL-12/23 [139], demonstrated moderate clinical efficacy but was associated with an increased risk of opportunistic and/or serious bacterial, fungal, or viral infections.

JAK inhibitors

The JAK-STAT signaling system (Janus Kinases — signal transducer and activator of transcription) is a pathway consisting of Janus kinase (JAK) and signal transducer and activator of transcription (STAT) proteins, which transmits information from extracellular polypeptide signals through transmembrane receptors directly to target gene promoters in the nucleus. In AD, this signaling system plays a critical role in activating type 2 immune responses via IL-4, eosinophil activation, and B-cell differentiation. JAK inhibitors were initially approved for rheumatoid arthritis, psoriasis, and alopecia. The JAK1/JAK3 inhibitor tofacitinib is approved for rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis; pilot studies have also explored its efficacy in AD. Results from oral tofacitinib use in a small group (six AD patients) for 8–29 weeks showed a 66.6% reduction in SCORAD index, with no adverse events reported [140]. A study of topical 2% tofacitinib ointment in 69 adult AD patients confirmed its clinical efficacy compared to placebo [141]. Another JAK inhibitor, delgocitinib, has broad-spectrum activity, suppressing Th1, Th2, and Th17 responses by inhibiting JAK1, JAK2, JAK3, and TYK2. Its topical form is approved in Japan for AD treatment [142], with efficacy demonstrated over 28 and 52 weeks [143, 144]. A study in 22 children aged 6–24 months applied 0.25% or 0.5% delgocitinib ointment twice daily for 52 weeks, showing a –73.5% reduction in modified Eczema Area and Severity Index (mEASI) by week 4, –81.7% by week 28, and –81.9% by week 52, with no treatment-related adverse events [145].

The JAK1/JAK2 inhibitor ruxolitinib carries high immunosuppression and infection risks when administered orally. Its topical form is approved in the U.S. for short-term, intermittent treatment of mild-to-moderate AD in patients ≥12 years without immunosuppression, when other topical therapies are inadequate or contraindicated. Two Phase III trials (TRuE-AD1 and TRuE-AD2) demonstrated the efficacy and safety of 0.75% and 1.5% ruxolitinib cream in adolescents/adults with mild-to-moderate AD [146].

Baricitinib, a selective JAK1/JAK2 inhibitor, is approved in the EU and Russia for moderate-to-severe AD in adults. Short- and long-term studies showed improved skin condition, reduced itch, better sleep, and enhanced quality of life with 4 mg/day over 16 weeks [147], sustained efficacy at 68 weeks [148].

Next-generation JAK1-selective inhibitors upadacitinib and abrocitinib are approved in Russia, the EU, U.S., and Japan for AD. Upadacitinib is also approved for six other indications in Russia (rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, non-radiographic axial spondyloarthritis, ulcerative colitis, Crohn's disease). Its AD profile was evaluated in five trials involving >4,000 patients [149–152]. Abrocitinib is approved for moderate-to-severe AD in adults/adolescents, showing rapid symptom reduction by week 12 versus placebo [153, 154].

A recent network meta-analysis compared abrocitinib, baricitinib, and upadacitinib in moderate-to-severe AD [155]. Analysis of 10 trials revealed all three significantly improved Investigator's Global Assessment (IGA) and EASI scores. Upadacitinib 30 mg outperformed other doses/drugs in efficacy but had higher adverse event rates; upadacitinib 15 mg and abrocitinib 200 mg showed comparable high efficacy. However,

upadacitinib 30 mg may be optimal for short-term use due to its superior efficacy despite higher side effects. JAK inhibitors rapidly reduce itch and AD symptoms by targeting cytokine pathways, but their selectivity *in vivo* is dose-dependent. Rare adverse effects (cytopenia, gastrointestinal perforation, malignancies) occur more frequently than with biologics, underscoring the need for further optimization in type 2 inflammatory diseases.

Conclusion

Type 2 inflammation plays a pivotal role in the pathogenesis of AD, driving chronic inflammation, skin barrier dysfunction, and the clinical manifestations of the disease. Key mediators of T2 inflammation-including IL-4, IL-5, IL-13, and IL-31-regulate the activation of various immune-competent cells, not only amplifying inflammation but also contributing to the development of pruritus. This, in turn, establishes the self-perpetuating "itch-scratch" cycle, which exacerbates skin damage and further stimulates inflammatory processes. Impaired skin barrier function also facilitates the penetration of allergens and microbial agents, further activating the immune response and worsening disease severity. The advent of targeted biologic therapies, such as dupilumab, lebrikizumab, and tralokinumab, has opened new avenues for AD treatment by specifically blocking key type 2 cytokines. These targeted approaches have already demonstrated efficacy in reducing inflammation, alleviating pruritus, and restoring skin barrier function. However, not all biologics have proven equally effective, highlighting the need for further research into disease mechanisms. For example, the lack of significant clinical benefit from IL-5 inhibition underscores the complexity of the inflammatory cascade and points to the importance of other mechanisms, including microbiome disturbances and autoimmune processes. Future research should focus on deepening our understanding of the interactions between the immune system, epidermal barrier, and environmental, genetic, and epigenetic factors that may influence disease severity and treatment response. Additionally, it is important to consider ethnic and geographic differences in the clinical presentation and pathogenesis of AD to enable the development of personalized treatment approaches.

In summary, studying type 2 inflammation as a central mechanism in AD pathogenesis not only advances our understanding of the disease but also facilitates the development of new therapeutic strategies to control AD and improve patients' quality of life, which remains a priority in contemporary immunology, allergology, and dermatology.

Refereences / Список литературы

1. Weidinger S, Novak N. Atopic dermatitis. *The Lancet*. 2016;387(10023):1109–1122. doi:10.1016/S0140-6736(15)00149-X

2. Kubanov AA, Namazova-Baranova LS, Khaitov RM, Ilyina NI, Alekseeva AA, Ambarchian ET, Artemyeva S, Arshinskiy MI, Astafyeva NG, Vishneva EA, Volnukhin VA, Danilycheva IV, Elisyutina OG, Epishev RV, Zhestkov AV, Zhilova MB, Zhukova OV, Zaslavsky DV, Znamenskaya LF, Karamova AE, Korotky NG, Kokhan MM, Kruglova LS, Kungurov NV, Levina JG, Lvov AN, Materikin AI, Mishina OS, Monakhov KN, Murashkin NN, Nenasheva NM, Pampura AN, Plakhova XI, Potekaev NN, Prytulo OA, Raznatovskiy KI, Sapuntsova SG, Selimzianova LR, Skorokhodkina OV, Fedenko ES, Fomina DS, Frigo NV, Frolova ZV, Khaitov MR, Chikin VV. *Atopic dermatitis. Russian Journal of Allergy.* 2021;18(3):44–92. (In Russian). doi:10.36691/RJA1474 [Кубанов А.А., Намазова-Баранова Л.С., Хаитов Р.М., и др. Атопический дерматит // Российский аллергологический журнал. 2021. Т. 18, № 3. С. 44–92. doi: 10.36691/RJA1474].

3. Haddad EB, Cyr SL, Arima K, McDonald RA, Levit NA, Nestle FO. Current and Emerging Strategies to Inhibit Type 2 Inflammation in Atopic Dermatitis. *Dermatology and Therapy.* 2022;12(7): 1501–1533. doi:10.1007/s13555–022–00737–7

4. Beck LA, Cork MJ, Amagai M, De Benedetto A, Kabashima K, Hamilton JD. Type 2 Inflammation Contributes to Skin Barrier Dysfunction in Atopic Dermatitis. *JID Innovations.* 2022;2(5):100131. doi:10.1016/j.xjidi.2022.100131

5. Laughter MR, Maymone MBC, Mashayekhi S, Arents BWM, Karimkhani C, Langan SM, Dellavalle RP, Flohr C. The global burden of atopic dermatitis: lessons from the Global Burden of Disease Study 1990–2017. *The British Journal of Dermatology*. 2021;184(2):304–309. doi:10.1111/bjd.19580

6. Nemer AA, Zhukova OV, Tereshchenko GP. Clinical features and risk factors of IgE-independent atopic dermatitis in children. *RUDN Journal of Medicine*. 2023;27(1):90–100. (In Russian). doi: 10.22363/2313-0245-2023-27-1-90-100 [Немер *А.А., Жукова О.В., Терещенко Г.П.* Клинические особенности и факторы риска IgE-независимого атопического дерматита у детей // Вестник Российского университета дружбы народов. Серия: Медицина. 2023. Т. 27. № 1. С. 90–100. doi: 10.22363/2313-0245-2023-27-1-90-100].

7. Barbarot S, Auziere S, Gadkari A, Girolomoni G, Puig L, Simpson EL. Epidemiology of atopic dermatitis in adults: Results from

an international survey. *Allergy.* 2018;73(6):1284–1293. doi:10.1111/all.13401

8. Italian Adult Atopic Dermatitis Study Group, Megna M, Patruno C, Balato A, Rongioletti F, Stingeni L. An Italian multicentre study on adult atopic dermatitis: persistent versus adult-onset disease. *Archives of Dermatological Research*. 2017;309(6):443–452. doi:10.1007/s00403-017-1739-y

9. Oliveira C, Torres T. More than skin deep: the systemic nature of atopic dermatitis. *European Journal of Dermatology.* 2019;29(3):250–258. doi:10.1684/ejd.2019.3557

10. Schuler CF, Billi AC, Maverakis E, Tsoi LC, Gudjonsson JE. Novel insights into atopic dermatitis. *Journal of Allergy and Clinical Immunology.* 2023;151(5):1145–1154. doi:10.1016/j.jaci.2022.10.023

11. Gandhi NA, Bennett BL, Graham NMH, Pirozzi G, Stahl N, Yancopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease. *Nature Reviews. Drug Discovery.* 2016;15(1):35–50. doi:10.1038/nrd4624

12. Junttila IS, Mizukami K, Dickensheets H, Meier-Schellersheim M, Yamane H, Donnelly RP. Tuning sensitivity to IL-4 and IL-13: differential expression of IL-4Rα, IL-13Rα1, and γc regulates relative cytokine sensitivity. *The Journal of Experimental Medicine.* 2008;205(11):2595–2608. doi:10.1084/jem.20080452

13. Licona-Limón P, Kim LK, Palm NW, Flavell RA. TH2, allergy and group 2 innate lymphoid cells. *Nature. Immunology.* 2013;14(6):536–542. doi:10.1038/ni.2617

14. Roufosse F. Targeting the Interleukin-5 Pathway for Treatment of Eosinophilic Conditions Other than Asthma. *Frontiers in Medicine.* 2018;5:49. doi:10.3389/fmed.2018.00049

15. Bağci IS, Ruzicka T. IL-31: A new key player in dermatology and beyond. *The Journal of Allergy and Clinical Immunology.* 2018;141(3):858–866. doi:10.1016/j.jaci.2017.10.045

16. Murdaca G, Greco M, Tonacci A, Negrini S, Borro M, Puppo F, Gangemi S. IL-33/IL-31 Axis in Immune-Mediated and Allergic Diseases. *Int J Mol Sci.* 2019;20(23):5856. doi: 10.3390/ijms20235856

17. Chakraborty S, Kubatzky KF, Mitra DK. An Update on Interleukin-9: From Its Cellular Source and Signal Transduction to Its Role in Immunopathogenesis. *International Journal of Molecular Sciences.* 2019;20(9):2113. doi:10.3390/ijms20092113

18. Chung F. Anti-inflammatory cytokines in asthma and allergy: interleukin-10, interleukin-12, interferon-gamma. *Mediators of Inflammation.* 2001;10(2):51–59. doi:10.1080/09629350120054518

19. Kuang PP, Liu XQ, Li CG, He BX, Xie YC, Wu ZC. Mesenchymal stem cells overexpressing interleukin-10 prevent allergic airway inflammation. *Stem Cell Research & Therapy*. 2023;14(1):369. doi:10.1186/s13287-023-03602-2

20. Hawrylowicz CM, O'Garra A. Potential role of interleukin-10-secreting regulatory T cells in allergy and asthma. *Nature Reviews. Immunology.* 2005;5(4):271–283. doi:10.1038/nri1589

21. Salter BM, Oliveria JP, Nusca G, Smith SG, Tworek D, Mitchell PD. IL-25 and IL-33 induce Type 2 inflammation in basophils from subjects with allergic asthma. *Respiratory Research.* 2016;17:5. doi:10.1186/s12931-016-0321-z

22. Saenz SA, Siracusa MC, Perrigoue JG, Spencer SP, Urban JF Jr, Tocker JE, Budelsky AL, Kleinschek MA, Kastelein RA, Kambayashi T, Bhandoola A, Artis D. IL25 elicits a multipotent progenitor cell population that promotes T(H)2 cytokine responses. *Nature*. 2010;464(7293):1362–6. doi: 10.1038/nature08901

23. Noda S, Krueger JG, Guttman-Yassky E. The translational revolution and use of biologics in patients with inflammatory skin diseases. *Journal of Allergy and Clinical Immunology.* 2015;135(2):324–336. doi:10.1016/j.jaci.2014.11.015

24. Luo J, Zhu Z, Zhai Y, Zeng J, Li L, Wang D. The Role of TSLP in Atopic Dermatitis: From Pathogenetic Molecule to Therapeutical Target. *Mediators of Inflammation.* 2023;2023:1–8. doi:10.1155/2023/7697699.

25. Gordon S, Martinez FO. Alternative Activation of Macrophages: Mechanism and Functions. *Immunity.* 2010;32(5):593–604. doi:10.1016/j.immuni.2010.05.007

26. Munder M, Eichmann K, Modolell M. Alternative metabolic states in murine macrophages reflected by the nitric oxide synthase/arginase balance: competitive regulation by CD4+ T cells correlates with Th1/Th2 phenotype. *Journal of Immunology. Baltimore*. 1998;160(11):5347–5354.

27. Zhu X, Pribis JP, Rodriguez PC, Morris SM, Vodovotz Y, Billiar TR. The Central Role of Arginine Catabolism in T-Cell Dysfunction and Increased Susceptibility to Infection After Physical Injury. *Annals of Surgery.* 2014;259(1):171–178. doi:10.1097/SLA.0b013e31828611f8

28. Maarsingh H, Zaagsma J, Meurs H. Arginase: a key enzyme in the pathophysiology of allergic asthma opening novel therapeutic perspectives. *British Journal of Pharmacology.* 2009;158(3):652–664. doi:10.1111/j.1476-5381.2009.00374.x

29. Esser-von Bieren J, Mosconi I, Guiet R, Piersgilli A, Volpe B, Chen F. Antibodies Trap Tissue Migrating Helminth Larvae and Prevent Tissue Damage by Driving IL-4Rα-Independent Alternative Differentiation of Macrophages. Wynn TA (ed.) *PLoS Pathogens.* 2013;9(11): e1003771. doi:10.1371/journal.ppat.1003771.

30. Nair MG, Du Y, Perrigoue JG, Zaph C, Taylor JJ, Goldschmidt M. Alternatively activated macrophage-derived RELM-α is a negative regulator of type 2 inflammation in the lung. *Journal of Experimental Medicine*. 2009;206(4):937–952. doi:10.1084/jem.20082048.

31. Granato A, Hayashi EA, Baptista BJA, Bellio M, Nobrega A. IL-4 regulates Bim expression and promotes B cell maturation in synergy with BAFF conferring resistance to cell death at negative selection checkpoints. *Journal of Immunology. Baltimore*. 2014;192(12):5761–5775. doi:10.4049/jimmunol.1300749

32. Garcovich S, Maurelli M, Gisondi P, Peris K, Yosipovitch G, Girolomoni G. Pruritus as a Distinctive Feature of Type 2 Inflammation. *Vaccines.* 2021;9(3):303. doi:10.3390/vaccines9030303

33. Murashkin NN, Opryatin LA, Epishev RV, Materikin AI, Ambarchian ET, Ivanov RA, et al. Pruritus and Atopic Dermatitis: from Etiological Features to Management. *Current Pediatrics*. 2020;19(6):468–476. doi:10.15690/vsp.v19i6.2151

34. Yuan Q, Campanella GS, Colvin RA, Hamilos DL, Jones KJ, Mathew A. Membrane-bound eotaxin-3 mediates eosinophil transepithelial migration in IL-4-stimulated epithelial cells. *European Journal of Immunology.* 2006;36(10):2700–2714. doi:10.1002/eji.200636112

35. Nagase H, Ueki S, Fujieda S. The roles of IL-5 and anti-IL-5 treatment in eosinophilic diseases: Asthma, eosinophilic granulomatosis

with polyangiitis, and eosinophilic chronic rhinosinusitis. Allergology International: Official Journal of the *Japanese Society of Allergology.* 2020;69(2):178–186. doi:10.1016/j.alit.2020.02.002

36. Licona-Limón P, Henao-Mejia J, Temann AU, Gagliani N, Licona-Limón I, Ishigame H. Th9 Cells Drive Host Immunity against Gastrointestinal Worm Infection. *Immunity.* 2013;39(4):744–757. doi:10.1016/j.immuni.2013.07.020

37. Goswami R, Kaplan MH. A brief history of IL-9. *Journal of Immunology. Baltimore.* 2011;186(6):3283–3288. doi:10.4049/jimmunol.1003049

38. Bazzoni F, Tamassia N, Rossato M, Cassatella MA. Understanding the molecular mechanisms of the multifaceted IL-10-mediated anti-inflammatory response: lessons from neutrophils. *European Journal of Immunology.* 2010;40(9):2360–2368. doi:10.1002/eji.200940294

39. Fang D, Zhu J. Molecular switches for regulating the differentiation of inflammatory and IL-10-producing anti-inflammatory T-helper cells. *Cellular and molecular life sciences: CMLS.* 2020;77(2):289–303. doi:10.1007/s00018-019-03277-0

40. Haben I, Hartmann W, Specht S, Hoerauf A, Roers A, Müller W, Breloer M. T-cell-derived, but not B-cell-derived, IL-10 suppresses antigen-specific T-cell responses in Litomosoides sigmodontis-infected mice. *Eur J Immunol.* 2013;43(7):1799–805. doi: 10.1002/eji.201242929

41. Matsuoka T, Shamji MH, Durham SR. Allergen immunotherapy and tolerance. *Allergology International: Official Journal of the Japanese Society of Allergology.* 2013;62(4):403–413. doi:10.2332/allergolint.13-RAI-0650

42. Rojas OL, Pröbstel AK, Porfilio EA, Wang AA, Charabati M, Sun T. Recirculating Intestinal IgA-Producing Cells Regulate Neuroinflammation via IL-10. *Cell.* 2019;176(3):610–624.e18. doi:10.1016/j.cell.2018.11.035

43. Sun H, Chen N, Yang X, Xia Y, Wu D. Effects induced by polyethylene microplastics oral exposure on colon mucin release, inflammation, gut microflora composition and metabolism in mice. *Ecotoxicology and Environmental Safety.* 2021;220:112340. doi:10.1016/j.ecoenv.2021.112340

44. Furue M, Yamamura K, Kido-Nakahara M, Nakahara T, Fukui Y. Emerging role of interleukin-31 and interleukin-31 receptor in pruritus in atopic dermatitis. *Allergy.* 2018;73(1):29–36. doi:10.1111/all.13239

45. Cornelissen C, Marquardt Y, Czaja K, Wenzel J, Frank J, Lüscher-Firzlaff J. IL-31 regulates differentiation and filaggrin expression in human organotypic skin models. The Journal of Allergy and Clinical Immunology. 2012;129(2):426–433. doi:10.1016/j.jaci.2011.10.042

46. Valizadeh A, Khosravi A, Zadeh LJ, Parizad EG. Role of IL-25 in Immunity. *Journal of clinical and diagnostic research: JCDR.* 2015;9(4): OE01–04. doi:10.7860/JCDR/2015/12235.5814

47. Wang YH, Angkasekwinai P, Lu N, Voo KS, Arima K, Hanabuchi S. IL-25 augments type 2 immune responses by enhancing the expansion and functions of TSLP-DC-activated Th2 memory cells. *The Journal of Experimental Medicine.* 2007;204(8):1837–1847. doi:10.1084/jem.20070406

48. Fallon PG, Ballantyne SJ, Mangan NE, Barlow JL, Dasvarma A, Hewett DR, McIlgorm A, Jolin HE, McKenzie AN. Identification of an interleukin (IL)-25-dependent cell population that provides IL-4, IL-5, and IL-13 at the onset of helminth expulsion. *J Exp Med.* 2006;203(4):1105–16. doi: 10.1084/jem.20051615

49. Drake LY, Kita H. IL-33: biological properties, functions, and roles in airway disease. *Immunological Reviews.* 2017;278(1):173–184. doi:10.1111/imr.12552

50. Endo Y, Hirahara K, Iinuma T, Shinoda K, Tumes DJ, Asou HK. The interleukin-33-p38 kinase axis confers memory T helper 2 cell pathogenicity in the airway. *Immunity.* 2015;42(2):294–308. doi:10.1016/j.immuni.2015.01.016

51. Shikotra A, Choy DF, Ohri CM, Doran E, Butler C, Hargadon B. Increased expression of immunoreactive thymic stromal lymphopoietin in patients with severe asthma. *The Journal of Allergy and Clinical Immunology.* 2012;129(1):104–111.e1–9. doi:10.1016/j.jaci.2011.08.031

52. Tatsuno K, Fujiyama T, Yamaguchi H, Waki M, Tokura Y. TSLP Directly Interacts with Skin-Homing Th2 Cells Highly Expressing its Receptor to Enhance IL-4 Production in Atopic Dermatitis. *J Invest Dermatol.* 2015;135(12):3017–3024. doi: 10.1038/jid.2015.318

53. Ito T, Wang YH, Duramad O, Hori T, Delespesse GJ, Watanabe N. TSLP-activated dendritic cells induce an inflammatory T helper type 2 cell response through OX40 ligand. *The Journal of Experimental Medicine.* 2005;202(9):1213–1223. doi:10.1084/jem.20051135

54. Sano Y, Masuda K, Tamagawa-Mineoka R, Matsunaka H, Murakami Y, Yamashita R, Morita E, Katoh N. Thymic stromal lymphopoietin expression is increased in the horny layer of patients with atopic dermatitis. *Clin Exp Immunol.* 2013;171(3):330–7. doi: 10.1111/cei.12021

55. Carr S, Watson W. Eosinophilic esophagitis. *Allergy, Asthma, and Clinical Immunology: Official Journal of the Canadian Society of Allergy and Clinical Immunology.* 2011;7(Suppl 1): S8. doi:10.1186/1710-1492-7-S1-S8

56. Garudadri S, Woodruff PG. Targeting Chronic Obstructive Pulmonary Disease Phenotypes, Endotypes, and Biomarkers. *Annals of the American Thoracic Society.* 2018;15(Suppl 4): S234–S238. doi:10.1513/AnnalsATS.201808-533MG

57. Kulthanan K, Tuchinda P, Nitiyarom R, Chunharas A, Chantaphakul H, Aunhachoke K, Chularojanamontri L, Rajatanavin N, Jirapongsananuruk O, Vichyanond P, Chatchatee P, Sangsupawanich P, Wananukul S, Singalavanija S, Trakanwittayarak S, Rerkpattanapipat T, Thongngarm T, Wisuthsarewong W, Limpongsanurak W, Kamchaisatian W, Noppakun N. Clinical practice guidelines for the diagnosis and management of atopic dermatitis. *Asian Pac J Allergy Immunol.* 2021;39(3):145–155. doi: 10.12932/AP-010221–1050

58. Torres T, Ferreira EO, Gonçalo M, Mendes-Bastos P, Selores M, Filipe P. Update on Atopic Dermatitis. *Acta Médica Portuguesa.* 2019;32(9):606–613. doi:10.20344/amp.11963

59. Moosbrugger-Martinz V, Leprince C, Méchin MC, Simon M, Blunder S, Gruber R. Revisiting the Roles of Filaggrin in Atopic Dermatitis. *International Journal of Molecular Sciences.* 2022;23(10): 5318. doi:10.3390/ijms23105318

60. Furue M. Regulation of Filaggrin, Loricrin, and Involucrin by IL-4, IL-13, IL-17A, IL-22, AHR, and NRF2: Pathogenic Implications in Atopic Dermatitis. *International Journal of Molecular Sciences.* 2020;21(15):5382. doi:10.3390/ijms21155382

61. van Smeden J, Bouwstra JA. Stratum Corneum Lipids: Their Role for the Skin Barrier Function in Healthy Subjects and Atopic Dermatitis Patients. *Current Problems in Dermatology.* 2016;49:8–26. doi:10.1159/000441540

62. Suwanchote S, Waitayangkoon P, Chancheewa B, Inthanachai T, Niwetbowornchai N, Edwards SW, Virakul S, Thammahong A, Kiatsurayanon C, Rerknimitr P, Chiewchengchol D. Role of antimicrobial peptides in atopic dermatitis. *Int J Dermatol*. 2022;61(5):532–540. doi: 10.1111/ijd.15814

63. Yang G, Seok JK, Kang HC, Cho YY, Lee HS, Lee JY. Skin Barrier Abnormalities and Immune Dysfunction in Atopic Dermatitis. *International Journal of Molecular Sciences*. 2020;21(8): 2867. doi:10.3390/ijms21082867.

64. Palmer CNA, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nature Genetics.* 2006;38(4):441–446. doi:10.1038/ng1767

65. Szegedi A. Filaggrin mutations in early- and late-onset atopic dermatitis. *Br J Dermatol.* 2015;172(2):320–1. doi: 10.1111/bjd.13534

66. Sahlén P, Spalinskas R, Asad S, Mahapatra KD, Höjer P, Anil A. Chromatin interactions in differentiating keratinocytes reveal novel atopic dermatitis- and psoriasis-associated genes. *The Journal of Allergy and Clinical Immunology.* 2021;147(5):1742–1752. doi:10.1016/j.jaci.2020.09.035

67. DeVore SB, Stevens ML, He H, Biagini JM, Kroner JW, Martin LJ. Novel role for caspase recruitment domain family member 14 and its genetic variant rs11652075 in skin filaggrin homeostasis. *The Journal of Allergy and Clinical Immunology*. 2022;149(2):708–717. doi:10.1016/j.jaci.2021.07.003

68. Thyssen JP, Kezic S. Causes of epidermal filaggrin reduction and their role in the pathogenesis of atopic dermatitis. *J Allergy Clin Immunol.* 2014;134(4):792–9. doi:10.1016/j.jaci.2014.06.014

69. Suárez-Fariñas M, Tintle SJ, Shemer A, Chiricozzi A, Nograles K, Cardinale I, Duan S, Bowcock AM, Krueger JG, Guttman-Yassky E. Non-lesional atopic dermatitis (AD) skin is characterized by broad terminal differentiation defects and variable immune abnormalities. *The Journal of allergy and clinical immunology*. 2011;127(4):954–64.e1–4. doi:10.1016/j.jaci.2010.12.1124

70. De Benedetto A, Rafaels NM, McGirt LY, Ivanov AI, Georas SN, Cheadle C. Tight Junction Defects in Atopic Dermatitis. *The Journal of allergy and clinical immunology.* 2011;127(3):773–786.e7. doi:10.1016/j.jaci.2010.10.018

71. Elias PM, Wakefield J. Mechanisms of abnormal lamellar body secretion and the dysfunctional skin barrier in atopic dermatitis. *The Journal of allergy and clinical immunology.* 2014;134(4):781–791.e1. doi:10.1016/j.jaci.2014.05.048

72. Leung DY, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches. *The Journal of allergy and clinical immunology.* 2014;134(4):769–79. doi:10.1016/j.jaci.2014.08.008

73. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. *Lancet*. 2020;396(10247):345–360. doi:10.1016/S0140-6736 (20) 31286-1

74. Elhaji Y, Sasseville D, Pratt M, Asai Y, Matheson K, McLean WHI. Filaggrin gene loss-of-function mutations constitute a factor in patients with multiple contact allergies. *Contact Dermatitis.* 2019;80(6):354–358. doi:10.1111/cod.13268

75. Campana R, Dzoro S, Mittermann I, Fedenko E, Elisyutina O, Khaitov M. Molecular aspects of allergens in atopic dermatitis. *Current Opinion in Allergy & Clinical Immunology.* 2017;17(4):269–277. doi:10.1097/ACI.0000000000000378

76. Silverberg JI, Hanifin J, Simpson EL. Climatic factors are associated with childhood eczema prevalence in US. *The Journal of investigative dermatology.* 2013;133(7):1752–1759. doi:10.1038/jid.2013.19.

77. Sargen MR, Hoffstad O, Margolis DJ. Warm, humid, and high sun exposure climates are associated with poorly controlled eczema: PEER (Pediatric Eczema Elective Registry) cohort, 2004–2012. *J Invest Dermatol.* 2014;134(1):51–57. doi: 10.1038/jid.2013.274

78. Towell AM, Feuillie C, Vitry P, Da Costa TM, Mathelié-Guinlet M, Kezic S. Staphylococcus aureus binds to the N-terminal region of corneodesmosin to adhere to the stratum corneum in atopic dermatitis. *Proceedings of the National Academy of Sciences of the United States of America*. 2021;118(1): e2014444118. doi:10.1073/pnas.2014444118

79. Gonzalez T, Stevens ML, Baatyrbek Kyzy A, Alarcon R, He H, Kroner JW. Biofilm propensity of Staphylococcus aureus skin isolates is associated with increased atopic dermatitis severity and barrier dysfunction in the MPAACH pediatric cohort. *Allergy.* 2021;76(1):302–313. doi:10.1111/all.14489

80. Reginald K, Westritschnig K, Werfel T, Heratizadeh A, Novak N, Focke-Tejkl M. IgE antibody reactivity to bacterial antigens in atopic dermatitis patients. *Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology.* 2010;41(3):357. doi:10.1111/j.1365–2222.2010.03655.x

81. Tomczak H, Wróbel J, Jenerowicz D, Sadowska-Przytocka A, Wachal M, Adamski Z. The role of Staphylococcus aureus in atopic dermatitis: microbiological and immunological implications. *Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii.* 2019;36(4):485–491. doi:10.5114/ada.2018.77056

82. Nakamura Y, Oscherwitz J, Cease KB, Chan SM, Muñoz-Planillo R, Hasegawa M, Villaruz AE, Cheung GY, McGavin MJ, Travers JB, Otto M, Inohara N, Núñez G. Staphylococcus δ-toxin induces allergic skin disease by activating mast cells. *Nature*. 2013;503(7476):397–401. doi:10.1038/nature12655

83. Nakatsuji T, Chen TH, Two AM, Chun KA, Narala S, Geha RS. Staphylococcus aureus exploits epidermal barrier defects in atopic dermatitis to trigger cytokine expression. *The Journal of investigative dermatology.* 2016;136(11):2192–2200. doi:10.1016/j.jid.2016.05.127

84. Miajlovic H, Fallon PG, Irvine AD, Foster TJ. Effect of filaggrin breakdown products on growth of and protein expression by Staphylococcus aureus. *The Journal of Allergy and Clinical Immunology.* 2010;126(6):1184–1190.e3. doi:10.1016/j.jaci.2010.09.015

85. Totté JEE, van der Feltz WT, Hennekam M, van Belkum A, van Zuuren EJ, Pasmans SGMA. Prevalence and odds of Staphylococcus aureus carriage in atopic dermatitis: a systematic review and meta-analysis. *The British Journal of Dermatology.* 2016;175(4):687–695. doi:10.1111/bjd.14566

86. Kong HH, Oh J, Deming C, Conlan S, Grice EA, Beatson MA. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Research.* 2012;22(5):850–859. doi:10.1101/gr.131029.111

87. Lehtimäki J, Thorsen J, Rasmussen MA, Hjelmsø M, Shah S, Mortensen MS. Urbanized microbiota in infants, immune constitution, and later risk of atopic diseases. *The Journal of Allergy and Clinical Immunology.* 2021;148(1):234–243. doi:10.1016/j.jaci.2020.12.621

88. Glatz M, Bosshard PP, Hoetzenecker W, Schmid-Grendelmeier P. The Role of Malassezia spp. in Atopic Dermatitis. *Journal of Clinical Medicine.* 2015;4(6):1217–1228. doi:10.3390/jcm4061217

89. Bieber T. Disease modification in inflammatory skin disorders: opportunities and challenges. *Nature Reviews. Drug Discovery.* 2023;22(8):662–680. doi:10.1038/s41573-023-00735-0

90. Blauvelt A, Bruin-Weller M de, Gooderham M, Cather JC, Weisman J, Pariser D. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *The Lancet.* 2017;389(10086):2287–2303. doi:10.1016/S0140-6736 (17) 31191-1

91. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, Silverberg JI, Deleuran M, Kataoka Y, Lacour JP, Kingo K, Worm M, Poulin Y, Wollenberg A, Soo Y, Graham NM, Pirozzi G, Akinlade B, Staudinger H, Mastey V, Eckert L, Gadkari A, Stahl N, Yancopoulos GD, Ardeleanu M; SOLO 1 and SOLO 2 Investigators. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *N Engl J Med.* 2016;375(24):2335–2348. doi: 10.1056/NEJMoa1610020

92. Bruin-Weller M de, Thaçi D, Smith CH, Reich K, Cork MJ, Radin A. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical t. *British Journal of Dermatology.* 2018;178(5):1083–1101. doi:10.1111/bjd.16156

93. Thaçi D, Simpson EL, Deleuran M, Kataoka Y, Chen Z, Gadkari A. Efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe atopic dermatitis: a pooled analysis of two phase 3 randomized trials (LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2*). Journal of Dermatological Science.* 2019;94(2):266–275. doi:10.1016/j.jdermsci.2019.02.002

94. Wang FP, Tang XJ, Wei CQ, Xu LR, Mao H, Luo FM. Dupilumab treatment in moderate-to-severe atopic dermatitis: A systematic review and meta-analysis. *Journal of Dermatological Science.* 2018;90(2):190–198. doi:10.1016/j.jdermsci.2018.01.016

95. Busse WW, Maspero JF, Rabe KF, Papi A, Wenzel SE, Ford LB. Liberty Asthma QUEST: Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate Dupilumab Efficacy/Safety in Patients with Uncontrolled, Moderate-to-Severe Asthma. *Advances in Therapy.* 2018;35(5):737–748. doi:10.1007/s12325-018-0702-4

96. Rial MJ, Barroso B, Sastre J. Dupilumab for treatment of food allergy. The *Journal of Allergy and Clinical Immunology. In Practice.* 2019;7(2):673–674. doi:10.1016/j.jaip.2018.07.027

97. Panettieri RA, Sjöbring U, Péterffy A, Wessman P, Bowen K, Piper E. Tralokinumab for severe, uncontrolled asthma (STRATOS 1 and STRATOS 2): two randomised, double-blind, placebo-controlled, phase 3 clinical trials. *The Lancet. Respiratory Medicine.* 2018;6(7):511–525. doi:10.1016/S2213-2600(18)30184-X

98. Wollenberg A, Howell MD, Guttman-Yassky E, Silverberg JI, Kell C, Ranade K. Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb. *The Journal of Allergy and Clinical Immunology.* 2019;143(1):135–141. doi:10.1016/j.jaci.2018.05.029

99. Blauvelt A, Guttman-Yassky E, Lynde C, Khattri S, Schlessinger J, Imafuku S. Cendakimab in Patients With Moderate to Severe Atopic Dermatitis: A Randomized Clinical Trial. *JAMA dermatology.* 2024;160(8):856–864. doi:10.1001/jamadermatol.2024.2131.

100. Hirano I, Collins MH, Assouline-Dayan Y, Evans L, Gupta S, Schoepfer AM. RPC4046, a Monoclonal Antibody Against IL13, Reduces Histologic and Endoscopic Activity in Patients With Eosinophilic Esophagitis. *Gastroenterology.* 2019;156(3):592–603.e10. doi:10.1053/j.gastro.2018.10.051

101. Bernardo D, Bieber T, Torres T. Lebrikizumab for the Treatment of Moderate-to-Severe Atopic Dermatitis. *American Journal of Clinical Dermatology.* 2023;24(5):753–764. doi:10.1007/s40257–023–00793–5

102. Blauvelt A, Thyssen JP, Guttman-Yassky E, Bieber T, Serra-Baldrich E, Simpson E. Efficacy and safety of lebrikizumab in moderate-to-severe atopic dermatitis: 52-week results of two randomized double-blinded placebo-controlled phase III trials. *The British Journal of Dermatology.* 2023;188(6):740–748. doi:10.1093/bjd/ljad022

103. Silverberg JI, Guttman-Yassky E, Thaçi D, Irvine AD, Stein Gold L, Blauvelt A. Two Phase 3 Trials of Lebrikizumab for Moderate-to-Severe Atopic Dermatitis. *The New England Journal of Medicine.* 2023;388(12):1080–1091. doi:10.1056/NEJMoa2206714

104. Kabashima K, Matsumura T, Komazaki H, Kawashima M, Nemolizumab-JP01 Study Group. Trial of Nemolizumab and Topical Agents for Atopic Dermatitis with Pruritus. *The New England Journal of Medicine.* 2020;383(2):141–150. doi:10.1056/NEJMoa1917006

105. Silverberg JI, Pinter A, Pulka G, Poulin Y, Bouaziz JD, Wollenberg A. Phase 2B randomized study of nemolizumab in adults with moderate-to-severe atopic dermatitis and severe pruritus. *The Journal of Allergy and Clinical Immunology.* 2020;145(1):173–182. doi:10.1016/j.jaci.2019.08.013

106. Kabashima K, Matsumura T, Komazaki H, Kawashima M; Nemolizumab-JP01 Study Group. Trial of Nemolizumab and Topical Agents for Atopic Dermatitis with Pruritus. *N Engl J Med.* 2020;383(2):141–150. doi: 10.1056/NEJMoa1917006

107. Kang EG, Narayana PK, Pouliquen IJ, Lopez MC, Ferreira-Cornwell MC, Getsy JA. Efficacy and safety of mepolizumab administered subcutaneously for moderate to severe atopic dermatitis. *Allergy.* 2020;75(4):950–953. doi:10.1111/all.14050

108. Roufosse F, Kahn JE, Rothenberg ME, Wardlaw AJ, Klion AD, Kirby SY. Efficacy and safety of mepolizumab in hypereosinophilic syndrome: A phase III, randomized, placebo-controlled trial. *The Journal of Allergy and Clinical Immunology.* 2020;146(6):1397–1405. doi:10.1016/j.jaci.2020.08.037

109. Wechsler ME, Akuthota P, Jayne D, Khoury P, Klion A, Langford CA. Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. The New England Journal of Medicine. 2017;376(20):1921–1932. doi:10.1056/NEJMoa1702079

110. Chupp GL, Bradford ES, Albers FC, Bratton DJ, Wang-Jairaj J, Nelsen LM, Trevor JL, Magnan A, Ten Brinke A. Efficacy of mepolizumab add-on therapy on health-related quality of life and

markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med.* 2017;5(5):390–400. doi: 10.1016/S2213-2600(17)30125-X

111. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 Study of Reslizumab in Patients With Poorly Controlled Asthma: Effects Across a Broad Range of Eosinophil Counts. *Chest.* 2016;150(4):799–810. doi:10.1016/j.chest.2016.03.018

112. Manka LA, Guntur VP, Denson JL, Dunn RM, Dollin YT, Strand MJ. Efficacy and safety of reslizumab in the treatment of eosinophilic granulomatosis with polyangiitis. *Annals of Allergy, Asthma & Immunology: Official Publication of the American College of Allergy, Asthma, & Immunology.* 2021;126(6):696–701.e1. doi:10.1016/j.anai.2021.01.035

113. Weinstein SF, Katial RK, Bardin P, Korn S, McDonald M, Garin M. Effects of Reslizumab on Asthma Outcomes in a Subgroup of Eosinophilic Asthma Patients with Self-Reported Chronic Rhinosinusitis with Nasal Polyps. The Journal of Allergy and Clinical Immunology. In Practice. 2019;7(2):589–596.e3. doi:10.1016/j.jaip.2018.08.021

114. Jackson DJ, Wechsler ME, Jackson DJ, Bernstein D, Korn S, Pfeffer PE, Chen R, Saito J, de Luíz Martinez G, Dymek L, Jacques L, Bird N, Schalkwijk S, Smith D, Howarth P, Pavord ID; SWIFT-1 and SWIFT-2 Investigators; SWIFT-1 Investigators; SWIFT-2 Investigators. Twice-Yearly Depemokimab in Severe Asthma with an Eosinophilic Phenotype. *N Engl J Med.* 2024;391(24):2337–2349. doi: 10.1056/NEJMoa2406673

115. Bachert C, Han JK, Desrosiers MY, Gevaert P, Heffler E, Hopkins C. Efficacy and safety of benralizumab in chronic rhinosinusitis with nasal polyps: A randomized, placebo-controlled trial. *The Journal of Allergy and Clinical Immunology.* 2022;149(4):1309–1317.e12. doi:10.1016/j.jaci.2021.08.030

116. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet (London, England).* 2016;388(10056):2115–2127. doi:10.1016/S0140–6736 (16) 31324–1

117. Cottu A, Groh M, Desaintjean C, Marchand-Adam S, Guillevin L, Puechal X. Benralizumab for eosinophilic granulomatosis with polyangiitis. Annals of the Rheumatic Diseases. 2023;82(12): 1580–1586. doi:10.1136/ard-2023-224624.

118. Criner GJ, Celli BR, Brightling CE, Agusti A, Papi A, Singh D. Benralizumab for the Prevention of COPD Exacerbations. *The New England Journal of Medicine.* 2019;381(11): 1023–1034. doi:10.1056/NEJMoa1905248

119. Guttman-Yassky E, Bahadori L, Brooks L, Clark KL, Grindebacke H, Ho CN. Treating moderate-to-severe atopic dermatitis with benralizumab: results from the HILLIER study, a plain language summary. *Immunotherapy.* 2024;16(10):641–648. doi:10.2217/imt-2023-0319

120. Amgen. A Dose-Ranging, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Tezepelumab Alone or Combined With Topical Corticosteroids in Moderate-to-Severe Atopic Dermatitis. Report number: NCT03809663, 2022 Mar [Accessed 8th December 2024]. https://clinicaltrials.gov/study/NCT03809663 [Accessed 8th December 2024].

121. Corren J, Menzies-Gow A, Chupp G, Israel E, Korn S, Cook B. Efficacy of Tezepelumab in Severe, Uncontrolled Asthma: Pooled Analysis of the PATHWAY and NAVIGATOR Clinical Trials. *American Journal of Respiratory and Critical Care Medicine.* 2023;208(1):13–24. doi:10.1164/rccm.202210–2005OC

122. Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME.Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma. *The New England Journal of Medicine.* 2021;384(19):1800–1809. doi:10.1056/NEJMoa2034975

123. Kelsen SG, Agache IO, Soong W, Israel E, Chupp GL, Cheung DS. Astegolimab (anti-ST2) efficacy and safety in adults with severe asthma: A randomized clinical trial. *The Journal of Allergy and Clinical Immunology.* 2021;148(3):790–798. doi:10.1016/j.jaci.2021.03.044.

124. Waters M, McKinnell JA, Kalil AC, Martin GS, Buchman TG, Theess W. Astegolimab or Efmarodocokin Alfa in Patients With Severe COVID-19 Pneumonia: A Randomized, Phase 2 Trial. *Critical Care Medicine.* 2023;51(1):103–116. doi:10.1097/CCM.0000000000005716

125. Wechsler ME, Ruddy MK, Pavord ID, Israel E, Rabe KF, Ford LB, Maspero JF, Abdulai RM, Hu CC, Martincova R, Jessel A, Nivens MC, Amin N, Weinreich DM, Yancopoulos GD, Goulaouic H. Efficacy and Safety of Itepekimab in Patients with Moderate-to-Severe Asthma. *N Engl J Med.* 2021;385(18):1656–1668. doi: 10.1056/NEJMoa2024257

126. England E, Rees DG, Scott IC, Carmen S, Chan DTY, Chaillan Huntington CE. Tozorakimab (MEDI3506): an anti-IL-33 antibody that inhibits IL-33 signalling via ST2 and RAGE/EGFR to reduce inflammation and epithelial dysfunction. *Scientific Reports.* 2023;13(1):9825. doi:10.1038/s41598–023–36642-y

127. Cao P, Xu W, Zhang L. Rituximab, Omalizumab, and Dupilumab Treatment Outcomes in Bullous Pemphigoid: A Systematic Review. *Frontiers in Immunology.* 2022;13:928621. doi:10.3389/fimmu.2022.928621

128. Chan SMH, Cro S, Cornelius V, Jahan R, Radulovic S, Lack G. Omalizumab for severe atopic dermatitis in 4- to 19-year-olds: the ADAPT RCT. Southampton (UK): National Institute for Health and Care Research; 2022 May. [Accessed 8th December 2024].

129. Gevaert P, Omachi TA, Corren J, Mullol J, Han J, Lee SE. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *The Journal of Allergy and Clinical Immunology.* 2020;146(3):595–605. doi:10.1016/j.jaci.2020.05.032.

130. Holm JG, Agner T, Sand C, Thomsen SF. Omalizumab for atopic dermatitis: case series and a systematic review of the literature. *International Journal of Dermatology.* 2017;56(1):18–26. doi:10.1111/ijd.13353

131. Tharp MD, Bernstein JA, Kavati A, Ortiz B, MacDonald K, Denhaerynck K. Benefits and Harms of Omalizumab Treatment in Adolescent and Adult Patients With Chronic Idiopathic (Spontaneous) Urticaria: A Meta-analysis of 'Real-world' Evidence. *JAMA dermatology.* 2019;155(1):29–38. doi:10.1001/jamadermatol.2018.3447

132. Omalizumab in IgE-Mediated Food Allergy: A Systematic Review and Meta-Analysis — PubMed. https://pubmed.ncbi.nlm.nih.gov/36529441/ [Accessed 8th December 2024].

133. Wedi B. Ligelizumab for the treatment of chronic spontaneous urticaria. *Expert Opinion on Biological Therapy.* 2020;20(8):853–861. doi:10.1080/14712598.2020.1767061.

134. Wood RA, Chinthrajah RS, Eggel A, Bottoli I, Gautier A, Woisetschlaeger M. The rationale for development of ligelizumab in food allergy. *The World Allergy Organization Journal.* 2022;15(9):100690. doi:10.1016/j.waojou.2022.100690

135. Guttman-Yassky E, Brunner PM, Neumann AU, Khattri S, Pavel AB, Malik K. Efficacy and safety of fezakinumab (an IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by conventional treatments: A randomized, double-blind, phase 2a trial. *Journal of the American Academy of Dermatology.* 2018;78(5):872–881.e6. doi:10.1016/j.jaad.2018.01.016

136. Bangert C, Loesche C, Skvara H, Fölster-Holst R, Lacour JP, Jones J. IgE Depletion with Ligelizumab Does Not Significantly Improve Clinical Symptoms in Patients with Moderate-to-Severe Atopic Dermatitis. *The Journal of Investigative Dermatology.* 2023;143(10):1896–1905.e8. doi:10.1016/j.jid.2023.01.040

137. Jacobi A, Antoni C, Manger B, Schuler G, Hertl M. Infliximab in the treatment of moderate to severe atopic dermatitis. *Journal of the American Academy of Dermatology.* 2005;52(3 Pt 1):522–526. doi:10.1016/j.jaad.2004.11.022

138. Ungar B, Pavel AB, Li R, Kimmel G, Nia J, Hashim P. Phase 2 randomized, double-blind study of IL-17 targeting with secukinumab in atopic dermatitis. *The Journal of Allergy and Clinical Immunology.* 2021;147(1):394–397. doi:10.1016/j.jaci.2020.04.055

139. Husein-ElAhmed H, Steinhoff M. Effectiveness of ustekinumab in patients with atopic dermatitis: analysis of real-world evidence. *The Journal of Dermatological Treatment.* 2022;33(4):1838–1843. doi:10.1080/09546634.2021.1914315

140. Levy LL, Urban J, King BA. Treatment of recalcitrant atopic dermatitis with the oral Janus kinase inhibitor tofacitinib citrate. *Journal of the American Academy of Dermatology.* 2015;73(3):395–399. doi:10.1016/j.jaad.2015.06.045

141. Bissonnette R, Papp KA, Poulin Y, Gooderham M, Raman M, Mallbris L. Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. *The British Journal of Dermatology.* 2016;175(5):902–911. doi:10.1111/bjd.14871

142. Tanimoto A, Shinozaki Y, Yamamoto Y, Katsuda Y, Taniai-Riya E, Toyoda K. A novel JAK inhibitor JTE-052 reduces skin inflammation and ameliorates chronic dermatitis in rodent models: Comparison with conventional therapeutic agents. *Experimental Dermatology.* 2018;27(1):22–29. doi:10.1111/exd.13370

143. Nakagawa H, Nemoto O, Igarashi A, Saeki H, Murata R, Kaino H. Long-term safety and efficacy of delgocitinib ointment, a topical Janus kinase inhibitor, in adult patients with atopic dermatitis. *The Journal of Dermatology.* 2020;47(2):114–120. doi:10.1111/1346–8138.15173

144. Nakagawa H, Nemoto O, Igarashi A, Saeki H, Kaino H, Nagata T. Delgocitinib ointment, a topical Janus kinase inhibitor, in adult patients with moderate to severe atopic dermatitis: A phase 3, randomized, double-blind, vehicle-controlled study and an open-label, long-term extension study. *Journal of the American Academy of Dermatology.* 2020;82(4):823–831. doi:10.1016/j.jaad.2019.12.015

145. Nakagawa H, Igarashi A, Saeki H, Kabashima K, Tamaki T, Kaino H. Safety, efficacy, and pharmacokinetics of delgocitinib ointment in infants with atopic dermatitis: A phase 3, open-label, and long-term study. Allergology International*: Official Journal of the Japanese Society of Allergology.* 2024;73(1):137–142. doi:10.1016/j.alit.2023.04.003

146. Papp K, Szepietowski JC, Kircik L, Toth D, Eichenfield LF, Leung DYM. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: Results from 2 phase 3, randomized, double-blind studies. *Journal of the American Academy of Dermatology.* 2021;85(4):863–872. doi:10.1016/j.jaad.2021.04.085

147. Reich K, Kabashima K, Peris K, Silverberg JI, Eichenfield LF, Bieber T. Efficacy and Safety of Baricitinib Combined With Topical Corticosteroids for Treatment of Moderate to Severe Atopic Dermatitis: A Randomized Clinical Trial. *JAMA dermatology.* 2020;156(12):1333–1343. doi:10.1001/jamadermatol.2020.3260

148. Silverberg JI, Simpson EL, Wollenberg A, Bissonnette R, Kabashima K, DeLozier AM. Long-term Efficacy of Baricitinib in Adults With Moderate to Severe Atopic Dermatitis Who Were Treatment Responders or Partial Responders: An Extension Study of 2 Randomized Clinical Trials. *JAMA dermatology.* 2021;157(6):691–699. doi:10.1001/jamadermatol.2021.1273

149. Blauvelt A, Ladizinski B, Prajapati VH, Laquer V, Fischer A, Eisman S. Efficacy and safety of switching from dupilumab to upadacitinib versus continuous upadacitinib in moderate-to-severe atopic dermatitis: Results from an open-label extension of the phase 3, randomized, controlled trial (Heads Up). *Journal of the American Academy of Dermatology.* 2023;89(3):478–485. doi:10.1016/j.jaad.2023.05.033

150. Guttman-Yassky E, Thaçi D, Pangan AL, Hong HCH, Papp KA, Reich K. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. *The Journal of Allergy and Clinical Immunology.* 2020;145(3):877–884. doi:10.1016/j.jaci.2019.11.025

151. Simpson EL, Papp KA, Blauvelt A, Chu CY, Hong HCH, Katoh N. Efficacy and Safety of Upadacitinib in Patients With Moderate to Severe Atopic Dermatitis: Analysis of Follow-up Data From the Measure Up 1 and Measure Up 2 Randomized Clinical Trials. *JAMA dermatology.* 2022;158(4):404–413. doi:10.1001/jamadermatol.2022.0029

152. Guttman-Yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL, Blauvelt A, Thaçi D, Chu CY, Hong HC, Katoh N, Paller AS, Calimlim B, Gu Y, Hu X, Liu M, Yang Y, Liu J, Tenorio AR, Chu AD, Irvine AD. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. *Lancet.* 2021;397(10290):2151–2168. doi: 10.1016/S0140–6736 (21) 00588–2

153. Gooderham MJ, Forman SB, Bissonnette R, Beebe JS, Zhang W, Banfield C. Efficacy and Safety of Oral Janus Kinase 1 Inhibitor Abrocitinib for Patients With Atopic Dermatitis: A Phase 2 Randomized Clinical Trial. *JAMA dermatology.* 2019;155(12):1371–1379. doi:10.1001/jamadermatol.2019.2855

154. Silverberg JI, Simpson EL, Thyssen JP, Gooderham M, Chan G, Feeney C. Efficacy and Safety of Abrocitinib in Patients

With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. *JAMA dermatology.* 2020;156(8):863–873. doi:10.1001/jamadermatol.2020.1406

155. Wan H, Jia H, Xia T, Zhang D. Comparative efficacy and safety of abrocitinib, baricitinib, and upadacitinib for moderate-to-severe atopic dermatitis: A network meta-analysis. *Dermatologic Therapy.* 2022;35(9): e15636. doi:10.1111/dth.15636

Роль Т2-воспаления в патогенезе атопического дерматита

О.Г. Елисютина[1, 2] ✉, Е.В. Смольников[1, 2], Д.Д. Чернушевич[1, 2], А.О. Литовкина[1, 2], М.Г. Бязрова[1, 2], Е.А. Левкова[2], Е.С. Феденко[1]

✉ el-olga@yandex.ru

[1] Институт иммунологии, *г. Москва, Российская Федерация*

[2] Российский университет дружбы народов, *г. Москва, Российская Федерация*

Аннотация. *Актуальность.* Атопический дерматит (АтД) относится к иммуноопосредованным хроническим заболеваниям, в основе патогенеза которого лежат генетические факторы и нарушения иммунного ответа, с преобладанием Т2-воспалительных реакций. В обзоре рассмотрены ключевые аспекты иммунопатогенеза заболевания, АтД рассматривается как системное воспалительное заболевание, связанное с дисрегуляцией Т2-иммунного ответа, который активируется при нарушении барьерной функции кожи и приводит к активации ряда цитокинов, таких как ИЛ-4, ИЛ-5, ИЛ-13, ИЛ-31 и др. В статье представлен анализ современных подходов к лечению АтД, включая таргетную терапию, направленную на блокировку Т2-цитокинов, с учетом важности раннего терапевтического вмешательства для предотвращения осложнений и развития атопического марша. Понимание механизмов Т2-воспаления открывает новые перспективы в разработке эффективных методов персонифицированной терапии Ат Д. *Выводы.* Т2-воспаление играет ключевую роль в патогенезе АтД, определяя хроническое воспаление, нарушения барьерной функции кожи и клинические проявления заболевания. Основные медиаторы Т2-воспаления, включая ИЛ-4, ИЛ-5, ИЛ-13 и ИЛ-31, регулируют активацию различных иммунокомпетентных клеток, не только усиливая воспаление, но и способствуя развитию зуда, который формирует порочный цикл «зуд-расчесывание», усугубляющий повреждение кожи и стимулирующий дальнейшую активацию воспалительных процессов. Нарушение барьерной функции кожи также облегчает проникновение аллергенов и микробных агентов, что дополнительно активирует иммунный ответ и усугубляет течение заболевания. Изучение Т2-воспаления как ключевого механизма патогенеза АтД не только углубляет наше понимание заболевания, но и открывает перспективы для разработки новых терапевтических стратегий, которые позволят контролировать течение АтД и улучшить качество жизни пациентов, что является приоритетной задачей современной иммунологии, аллергологии и дерматологии.

Ключевые слова: атопический дерматит, Т2-воспаление, цитокины, биомаркеры, таргетная терапия

Информация о финансировании. Исследование и публикация осуществлены при поддержке гранта Российского научного фонда № 23-15-00432, https://rscf.ru/project/23-15-00432.

Вклад авторов: О.Г. Елисютина — сбор и анализ литературных источников, подготовка и написание статьи, редактирование статьи; Е.В. Смольников — сбор и анализ литературных источников, написание статьи, Д.Д. Чернушевич — сбор и анализ литературных источников; А.О. Литовкина — сбор и анализ литературных источников, М.Г. Бязрова — сбор и анализ литературных источников, Е.А. Левкова — сбор и анализ литературных источников, написание статьи, Е.С. Феденко — написание текста и редактирование статьи. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Информация о конфликте интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с проведенным исследованием и публикацией настоящей статьи.

Этическое утверждение — неприменимо.

Благодарности — неприменимо.

Информированное согласие на публикацию — неприменимо.
Поступила 08.12.2024. Принята 13.01.2025.

Для цитирования: *Elisyutina O.G., Smolnikov E.V., Chernushevich D.D., Litovkina A.O., Byazrova M.G., Levkova E.A., Fedenko E.S.* The role of type 2 inflammation in the pathogenesis of atopic dermatitis // Вестник Российского университета дружбы народов. Серия: Медицина. 2025. Т. 29. № 3. С. 365—384. doi: 10.22363/2313-0245-2025-29-3-365-384. EDN QSMOXR

Corresponding author: Olga G. Elisyutina — MD, PhD, Leading Researcher of the NRC Institute of Immunology, FMBA of Russia; Head of the Immunology Department of the Medical Institute of the RUDN University named after Patrice Lumumba; Russian Federation, 117198, Moscow, Miklukho-Maklaya st, 6. E-mail: el-olga@yandex.ru
Elisyutina O.G. ORCID 0000-0002-4609-2591
Smolnikov E.V. ORCID 0000-0003-1302-4178
Chernushevich D.D. ORCID 0000-0003-0006-2773
Litovkina A.O. ORCID 0000-0002-5021-9276
Byazrova M.G. ORCID 0000-0002-9858-7596
Fedenko E.S. ORCID 0000-0003-3358-5087

Ответственный за переписку: Елисютина Ольга Гурьевна — доктор медицинских наук, ведущий научный сотрудник ФГБУ “ГНЦ “Институт иммунологии” ФМБА России; заведующий кафедрой иммунологии Медицинского института ФГАОУ ВО РУДН им. П. Лумумбы Минобрнауки России, г. Москва, Российская Федерация, 117198, г. Москва, ул. Миклухо-Маклая, д. 6; E-mail: el-olga@yandex.ru
Елисютина О.Г. SPIN 9567-1894, ORCID 0000-0002-4609-2591
Смольников Е.В. SPIN 4874-8100, ORCID 0000-0003-1302-4178
Чернушевич Д.Д. SPIN 2497-5608, ORCID 0000-0003-0006-2773
Литовкина А.О. SPIN 2337-7930, ORCID 0000-0002-5021-9276
Бязрова М.Г. SPIN 4317-9042, ORCID 0000-0002-9858-7596
Левкова Е.А. SPIN 6407-9880
Феденко Е.С. SPIN 5012-7242, ORCID 0000-0003-3358-5087