

Advances in Cellular Immune Mechanisms of Atopic Dermatitis

Jianghui Li^{1,a}, Xiaoning Yan^{2,b,*}, Haoyuan Hu^{1,c}

¹*Shaanxi University of Chinese Medicine, Xiayang 712046, Shaanxi, China*

²*Shaanxi Provincial Hospital of Chinese Medicine, Xi'an 710003, Shaanxi, China*

^a*1106350563@qq.com*, ^b*yanxiaon2005@126.com*, ^c*hhy980527@126.com*

**corresponding author*

Keywords: Atopic Dermatitis, Immune Mechanism, Inflammation, Cytokines

Abstract: Atopic dermatitis is a common chronic inflammatory skin disease with severe itching as the most obvious clinical symptom. Its immunological mechanism is very complex, involving the participation of multiple immune cells and their cytokines, chemokines, pro-inflammatory molecules and other immune cascades. At the same time, it is related to skin barrier destruction, decreased expression of antimicrobial peptides, and immune-nervous system crosstalk. This article mainly reviews the various cells, cytokines and their cascades in the immune-related pathogenesis of atopic dermatitis, in order to provide corresponding theoretical basis for the treatment of atopic dermatitis.

1. Introduction

Atopic Dermatitis (AD) is a common chronic inflammatory skin disease. The initial onset of AD is usually in infancy and early childhood, which can continue to adulthood [1]. The basic clinical features of AD are recurrent attacks, pleomorphism of skin lesions, dry skin and severe itching [2]. Atopic means: (1) A familial predisposition to asthma, allergic rhinitis and eczema; (2) Allergy to heterologous proteins; (3) High level of immunoglobulin E (IgE) in serum; (4) Blood eosinophilia.

Immune abnormalities have been a hot research area in AD in recent years. Increasing evidence has shown that the disease involves a variety of immune pathways [3], such as IgE, T lymphocytes and their related cytokines [4], and the persistence of inflammatory factors and tissue damage is the fundamental cause of chronic inflammation. This article reviews the various cells and cytokines in the immune-related pathogenesis of AD, and elucidates their regulatory effects and clinical significance in AD.

2. Helper T cells and AD

2.1. Th2 cells

Th1/Th2 imbalance is the main immunological mechanism of AD disease. The obvious imbalance of Th2 cells leads to increased levels of type 2 cytokines, among which IL-4 and IL-13 can cause initial tissue inflammation, IgE synthesis, mast cell (MC) activation, and basophil and eosinophil (EOS) aggregation [5], and their combination with the proinflammatory factor TNF- α can induce an AD-like phenotype in human skin tissue equivalents. It is characterized by spongiform changes in the epidermis, changes in the differentiation of keratinocytes (KC) and changes in the lipid composition of the stratum corneum [6]. The level of IL-13 in the skin and serum of AD patients is increased, which can upregulate the transcription level of IL-13R α 2 in KC, bind to the IL-13R α 2 / YKL-40 receptor complex with high affinity, and down-regulate the expression of filagrin (FLG), entricin (IVL), and keratin in KC with IL-4. It promotes neurogenic inflammation, causes and aggravates AD epidermal barrier dysfunction, pruritus and transepithelial water loss, and induces long-term chronic mossy lesions [7-9]. In a positive feedback loop formed during the acute phase of AD, IL-4 - and IL-13-induced responses can be driven by signal transduction and STAT6 to promote the production of thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, among which TSLP is a key mediator in allergic inflammation. It can trigger Th2 polarization to produce IL-4 and IL-13 [10], promote the differentiation of Th2 cells and type II innate lymphocytes (ILC2) and stimulate the production of IL-13, aggravating Th2 immune response, thus causing a vicious cycle of atopic xeroderma [11]. Genetically, AD is associated with IL-4 and IL-13 diversity, and eczema-like features can develop in transgenic mice overexpressing these cytokines [12]. Both IL-4 and IL-13 reduce the production of antimicrobial peptides (AMPS) by KCS, which usually precede the development of AD lesions and play a role in skin dysbiosis. In the comprehensive analysis of genome-wide association studies, FLG, OVOL1 (an upstream transcription factor that regulates FLG expression), and IL13 were the three genes most significantly associated with AD among the 31 susceptibility gene loci [13]. The latest cascade studies have shown that IL-13 infiltrated by local lesions of AD can cause barrier dysfunction by down-regulating OVOL1-FLG axis and up-regulating periostin IL-24 axis [14].

As another cytokine of Th2 cells, IL-31 belongs to the IL-6 superfamily and is a pruritus mediator, which is mainly produced by Th2 cells and MC under the action of antimicrobial peptides (Amps) and is significantly increased in AD [15]. In the pathogenesis of AD pruritus, IL-31 can stimulate delayed pruritus compared to histamine-mediated pruritus [16]. Other studies have found that the expression of IL-31 in peripheral blood lymphocytes of AD patients is increased, and the expression level is linearly correlated with the severity of the disease [17]. Th2 cells release IL-31 in the acute phase, which, after binding to IL-31 receptor A and activating STAT3 in EOS, can delay the apoptosis of EOS and significantly increase the secretion of proinflammatory cytokines and chemokines, leading to the development of AD lesions with skin barrier breakdown and transeptocutaneous water loss [18,19]. The damage of skin barrier function in AD increases the number of environmental irritants and allergens penetrating into the skin, leading to the aggravation and recurrence of inflammation or allergic reactions.

2.2. Th17 cells

Th17 cells and their related cytokines make up for the deficiency of Th1/Th2 pattern and play an important role in clearing pathogens in AD. IL-17, a pleiotropic pro-inflammatory cytokine mainly produced by Th17 cells, positively regulates IL-1, IL-6, TNF- α and chemokines CCL-7, CXCL1, etc., and acts to promote Th2 cell differentiation and release angiogenic factor (VEGF) [20], which

is linearly correlated with the severity of AD. One study showed that AD patch test sites are infiltrated with more IL-17 cytokine than healthy skin, and its expression in AD skin can induce relatively low AMP expression, which may account for the frequent bacterial infections in AD patients [21,22]. IL-17A and IL-17F promote the formation of eosinophils and increase the levels of IL-1 β and IL-23 [23], while eosinophils that reach the site of inflammation begin to produce IL-1 β . IL-23 and IL-17E affect the number of Th2 cells and release large amounts of cytokines. The interaction between forming eosinophils and Th17 cells in the pathogenesis of AD [24]. IL-17E is also known as IL-25, and its receptor IL-17RB needs to bind to IL-17RA to form a complex to mediate downstream signaling cascades in target cells. Including nuclear factor κ B (NF- κ B), mitogen-activated protein kinase (MAPK) and Janus kinase/signal transducer and activator of transcription (JAK/STAT) [25]. Hvid [26] found that IL-25 may be involved in the link between skin inflammation and skin barrier dysfunction in AD through downregulated FLG synthesis in KCS. In addition, IL-25 was found to be involved in the pathophysiology of AD pruritus by significantly increasing pruritogenic endothelin-1 expression in KCS via the extracellular regulated protein kinase (ERK1/2) and stress-activated protein kinase (JNK) pathways [27].

2.3. Th22 cells

Th22 is a new helper T cell subset that is different from Th2 and Th1. It can interfere with the normal differentiation of KC, enhance the expression of TSLP and IL-33, and increase the susceptibility to *Staphylococcus aureus* by down-regulating the levels of epidermal FLG, IVL and loricolin by secreting cytokines such as IL-22. It has a destructive effect on the skin barrier function, and its expression is linearly related to the severity of AD [28-30]. Recent studies have shown that Th22 cells play an important role in the initiation and maintenance of AD. In the acute stage of AD, β -defensin 2, 3 and Th22-related genes (S100A7, S100A8, S100A9, S100A12) show significantly up-regulated inflammatory expression [31]. There was an initial activation of Th1 cells and a sustained activation of Th2 and Th22 cells [32]. IL-22 induces a significant increase in the expression of the neuropeptide pruritogens gastrin-releasing peptide (GRP) and an increase in the number of sensory neurons innervating cutaneous nerves in the dorsal root ganglion (DRG), suggesting a complex bidirectional interaction between the peripheral nervous system and dermal inflammation, immune cells and cytokine stimulation. This causes a strong Th2/ Th22-biased inflammation in AD skin [33]. In addition, IL-22 primarily activates STAT3 in KCS and induces epithelial proliferation and expression of anti-apoptotic genes (e.g., Bcl-2 and Bcl-xl) through membrane-binding IL-22 receptor 1 (IL-22R1). Release chemokines that attract leukocytes (such as chemokine ligands CXCL1, CXCL2, CXCL5, and CXCL8), mediate epithelial integrity to control antimicrobial immunity at barrier surfaces, promote tissue active repair, and protect stem cells from injury [34-36]. (Figure 1)

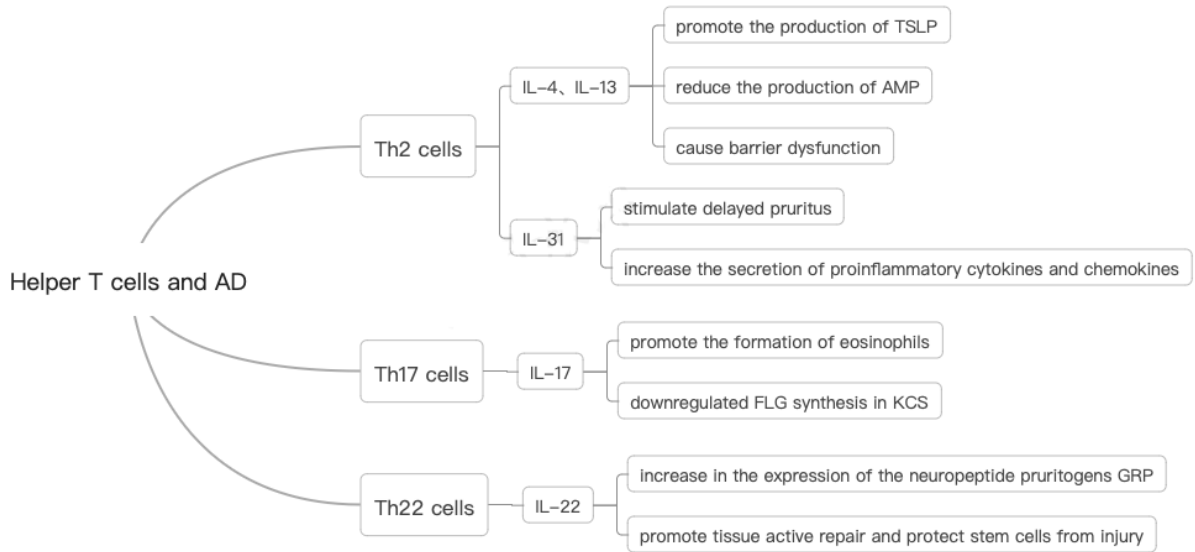


Figure 1. Helper T cells and AD

3. Neutrophils and AD

Neutrophils are the host's first line of defense against microbial invasion [37], and when inflammation occurs, they are attracted to the site of inflammation by chemotactic substances, which are mainly present in the dermis in AD lesions [38] and are associated with pruritus and pain mechanisms. It has long been thought that Th2 immunity causes pruritus by directly activating itch sensory neurons and secretory mediators such as IL-31 [39]. However, recent experiments have shown that neutrophils can release known pruritogens, including proteases, reactive oxygen species and/or histamine, inflammatory lipids, and cytokines that sensitizes or activates itch receptors [40]. At the same time, neutrophils are the first to infiltrate AD skin and are essential for the induction of CXCL10, a ligand of the C-X-C chemokine receptor (CXCR3) produced by neutrophils, which promotes pruritus by activating sensory neurons [41]. Neutrophils can be induced by CXCL1 and KC to accumulate in the inflammatory site of AD through CXCR1 and 2 [42]. Arachidonic acid (ARA) released from their cell membrane further produces prostaglandin (PG), which has a synergistic effect on the production of pruritus. It can reduce the threshold of pruritus and improve the sensitivity to histamine and papanase. At the same time, it regulates inflammatory pain [43]. In addition, IL-4 in neutrophils directly acts on neutrophils through type 2 IL-4R to inhibit the aggregation and migration of neutrophils through activation of p38 α MAPK and inhibition of CXCR2, forming an IL-4R-p38 MAPK-CXCR2 axis. The skin of AD patients is known to express high levels of IL-4 and low neutrophil counts and is generally more susceptible to bacterial infections that are accumulated by neutrophils, as shown in Figure 2. Therefore, therapeutic approaches targeting IL-4R or p38 MAPK may reduce the risk of recurrent bacterial infections and reduce inflammatory responses [44,45].



Figure 2. IL-4R-p38 MAPK-CXCR2 axis

4. Eosinophils and AD

AD patients have increased peripheral blood eosinophil (EOS), and the higher the relative eosinophil count in the blood, the higher the pruritus level in AD patients, which is positively correlated with disease activity [46]. As the main effector cells of AD, eosinophils are mediated by the specific eosinophil chemokine CCL11, vascular cell adhesion molecule-1, intercellular adhesion molecule-1 and E-selectin, which accumulate and infiltrate in the inflammatory sites [47]. Some studies have shown that degranulation EOS and substance P accumulate near nerve fibers, which may activate EOS, and then EOS directly interact with nerves, leading to pruritus and the release of IL-31, a key cytokine for nerve growth [48-50]. Leonie et al. [51] found that histamine receptor type 4 (H4R) is strongly expressed in eosinophils and can selectively activate and regulate specific genes, among which the most obvious up-regulation is IL-18R α , which binds to pro-inflammatory cytokine IL-18, promotes Th1 and Th2 immune responses, and is involved in the pathogenesis of AD. At the same time, considering that mast cells can also express IL-18R, the association between eosinophils and mast cells worsens allergic inflammation to a certain extent, and histamine may enhance this association through the IL-18/IL-18R axis [52].

In addition, EOS can form eosinophil extracellular traps (EETs), the formation of which is associated with IL-5, TSLP and Staphylococcus aureus infection, and is present in mitochondrial DNA (mtDNA) and granule proteins released by activated cells [53][54]. As part of the innate immune response, EETs are mainly concentrated at the site of epithelial defects, which can capture and kill Staphylococcus aureus, maintain skin barrier function after inflammation-related epithelial cell damage, and protect the skin of AD patients from infection [55]. (Figure 3)

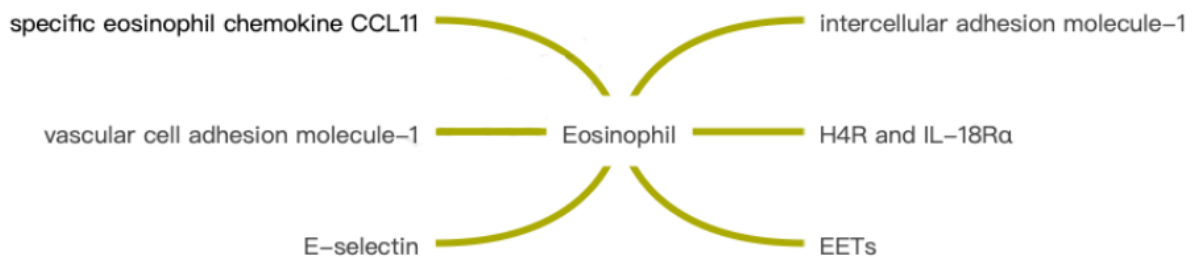


Figure 3. Eosinophils and AD

5. Basophils and AD

Basophils are the major source of type 2 inflammatory cytokines in the skin. It plays both pro-inflammatory and anti-inflammatory roles in different skin states of AD [56]. In the active AD region, type 2 inflammation leads to the aggregation of basophils and the release of histamine, major basic proteins, lipid mediators and type 2 inflammatory cytokines, which not only aggravate inflammation, but also aggravate skin barrier damage by down-regulating cuticle (SC) structural proteins and destroying tight junctions (TJ) [57], further amplifying the pathogenesis of AD. However, during the regression phase, basophils induce a decrease in proinflammatory cells, differentiation of M2-like macrophages, and support a pro-regression macrophage phenotype [58], which is associated with skin repair and tissue remodeling [59]. A recent study found that basophils are highly reactive to sweat antigens. In AD patients, type I hypersensitivity to sweat can be manifested by the release of histamine by patient basophil in response to semi-purified sweat antigen (QR) and the binding of IgE to MGL-1304 (a component of QR), suggesting that sweat may aggravate AD[60]. Basophils play a role in the mechanism of AD pruritus and are required for acute

pruritus episodes in AD-related inflammation. Basophils can directly interact with sensory nerve fibers in the skin, and their derived leukotrienes (LTs) are key inducers of acute pruritus episodes in AD. Leukotriene C4-cysteine LT receptor 2 (LTC4-CysLTR2) neuroimmune axis is the basis of its attack [61]. In addition, in the immune cascade, KCS will produce inflammatory mediators (such as TSLP) when the skin is stimulated by antigens, which will accumulate and activate basophils. Its activation can release IL-4, induce naive T cells to differentiate into Th2 cells for Th2 immune response, and the depletion of basophils can improve the symptoms of AD and reduce the immune response. This suggests that basophils have a potential role in the initiation of Th2 immunity and are partially responsible for Th2 immunity [62]. (Figure 4)

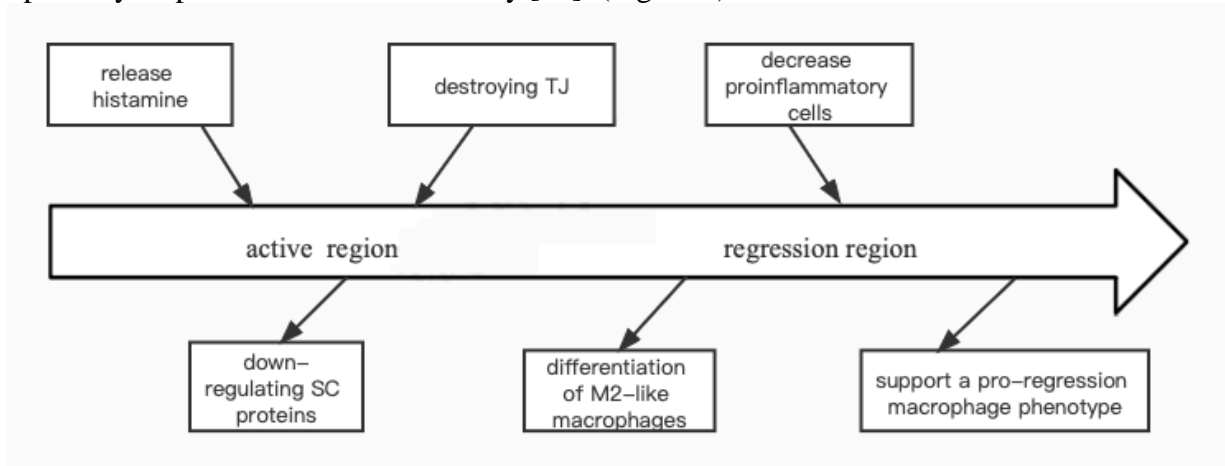


Figure 4. Basophils and AD

6. Monocyte-macrophages and AD

Monocytes are the largest blood cells in the blood [63]. Monocytes fixed in the skin tissue are called macrophages, which can play an important role in the coordination of adaptive immune response, inflammation resolution and repair as antigen presenting cells (apcs) [64]. According to the differences and similarities of the microenvironment at the inflammatory site, macrophages produce different polarization with different functions, which are divided into classic M1 macrophages and alternative M2 macrophages. M1 macrophages are mainly involved in the extension of inflammation and high antigen presentation, producing proinflammatory cytokines (such as TNF- α , IL-6 and IL-12) and triggering Th1 polarization [65]. M2 macrophages are alternately activated by IL-4 and IL-13. This macrophage population is associated with allergic inflammation and has anti-inflammatory and immunomodulatory functions. Mononuclear-macrophages can produce TSLP [66], and TSLP/TSLPR signaling is an important enhancer in the polarization and expansion of M2 macrophages and the production of chemokines, which plays a significant role in promoting type 2 immune response locally and systemically [67]. CCL18 secreted by M2 macrophages is the most abundant chemokine in the skin of AD patients [68]. Histamine can stimulate the histamine receptor (H2R) in M2 macrophages, leading to the up-regulation of CCL18 expression induced by IL-4, IL-13 and IL-10 [69]. This suggests that the blockade of the IL-4, IL-13 pathway or the administration of histamine receptor antagonists may lead to a transition from inflammation to a more stable state by modulating CCL18 expression. In addition, monocytes and macrophages can produce potent pro-inflammatory cytokine IL-18, which participating in host defense against infection and regulating innate and acquired immune responses [70,71]. (Figure 5)

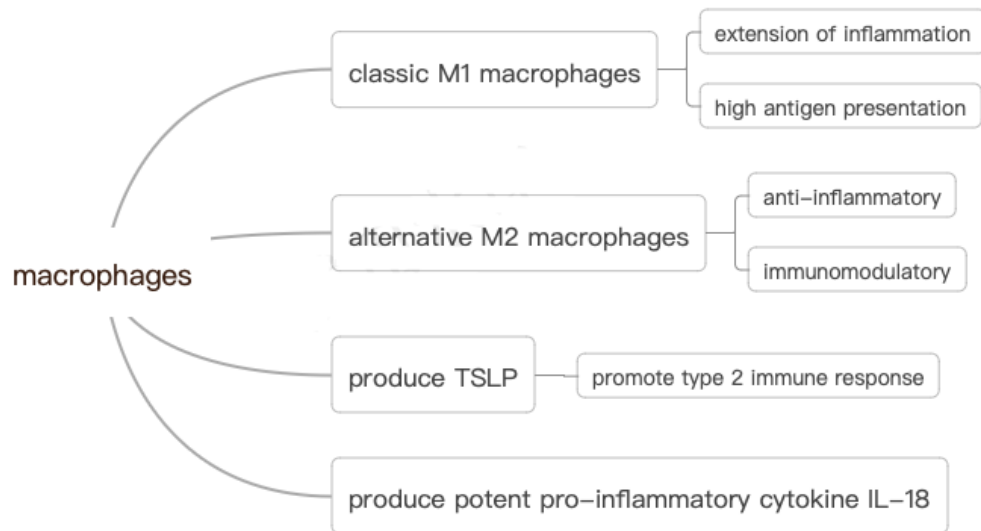


Figure 5. Monocyte-macrophages and AD

7. Mast cells and AD

Mast cells (MCS) are tissue-resident immune cells derived from the hematopoietic lineage and are located close to peripheral nerve endings and subepithelial vessels. In contrast to histamine-mediated or histaminergic pruritus, the IgE-mast cell-histamine axis, which has previously been the classic pruritus mechanism [72], Activation of Mrgprb2 (a mouse homologue of MRGPRX2), a recently discovered novel itch mediating molecule in the Mas-related G-protein-coupled receptor (Mrgpr) family, is independent of the IgE-FcεRI histamine axis and causes divergent, nonhistaminergic, and differential pruritus, activating distinct populations of itch sensory neurons. Deficiency of Mrgprb2 reduces pruritus in multiple preclinical models of AD. MRGPRX2 is a recently discovered multiligand receptor that responds to a variety of exogenous and endogenous stimuli. MRGPRX2 is highly expressed in skin MC, leading to MC degranulation and the release of proinflammatory mediators through a cascade initiated by Gαi, Gαq, ERK1/2, PI3K, etc. [73], and promoting multicellular signaling cascades, such as pruritus induction and transmission in sensory neurons [74]. Substance P and many other MRGPRX2 agonists, including corticostatin, somatostatin, vasoactive intestinal peptide (VIP) and proadrenomedullin N-terminal peptide (PAMP) PAMP-20 and PAMP-12, are increased in AD itch skin. This suggests that activation of MC via MRGPRX2 may lead to neurogenic inflammation, pain, and pruritus, which could be used as a novel therapeutic target for the treatment of associated pruritus disorders unresponsive to antihistamines [75-77].

8. Conclusion

In summary, AD is a skin disease with complex mechanisms and is regulated by multi-cellular and cytokine immune factors. In recent years, a number of studies on related immune cells and cytokines at home and abroad have proved their importance in the symptoms or causes of AD such as pruritus, pain, skin barrier destruction, and *Staphylococcus aureus* colonization. Studies on immune cells and cytokines are essential for the future development of effective biological targeting agents for AD and the exploration of more detailed pathogenesis of AD.

Funding

This article is not supported by any foundation.

Data Availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Conflict of Interest

The author states that this article has no conflict of interest.

References

- [1] Yun Yang. *Clinical manifestations and characteristics of atopic dermatitis in children. Journal of Medicine Forum*, 2022, 43(07):16-19+23.
- [2] Lu Huang, Caiyun Li, Yan Zhao. *Association of atopic dermatitis with related autoimmune diseases. Journal of Clinical and Pathology*, 2022, 42(6):1466-1471.
- [3] Sin áid M Langan, Alan Owen, Stephen Weittinger. *Atopic Dermatitis. Lancet*, 2020, 396:345-360.
- [4] Yuan Li, Lei Zheng, Dong Chen. *To investigate the correlation between the levels of serum IgE, IFN- γ and Th17 cytokines and the severity of adult atopic dermatitis[J/OL]. Journal of Wuhan University (Medical Edition)*, 2022-12-02/2022-12-20.
- [5] Stefano Piazza, Marco Fumagalli, Giulia Martinelli, et al. *Hydrolyzable Tannins in the Management of Th1, Th2 and Th17 Inflammatory-Related Diseases. Molecules*, 2022, 27(21):7593.
- [6] Danso M O, van Drongelen V, Mulder A, et al. *TNF- α and Th2 cytokines induce atopic dermatitis-like features on epidermal differentiation proteins and stratum corneum lipids in human skin equivalents. Investig Dermatol*, 2014, 134(7), 1941-1950.
- [7] Tsuji G, Hashimoto-Hachiya A, Kiyomatsu-Oda M, et al. *Aryl hydrocarbon receptor activation restores filaggrin expression via OVOL1 in atopic dermatitis[J/OL]. Cell Death Dis*, 2017-07-13/2022-12-20.
- [8] Thomas Bieber. *Interleukin - 13: Targeting an underestimated cytokine in atopic Dermatitis. Allergy*, 2020, 75(1):54-62.
- [9] Xiao S, Lu Z, Steinhoff M, et al. *Innate immune regulates cutaneous sensory IL-13 receptor alpha 2 to promote atopic dermatitis. Brain Behav Immun*, 2021, 98:28-39.
- [10] Furue M, Chiba T, Tsuji G, et al. *Atopic dermatitis: immune deviation, barrier dysfunction, IgE autoreactivity and new therapies. Allergol Int*. 2017, 66(3):398-403.
- [11] Lee E, Min K, Ahn H, et al. *Potential Therapeutic Skin Microbiomes Suppressing Staphylococcus aureus-Derived Immune Responses and Upregulating Skin Barrier Function-Related Genes via the AhR Signaling Pathway. Int J Mol Sci*, 2022, 23(17):9551.
- [12] Patrick M Brunner, Emma Guttman-Yassky, Donald Y M Leung. *The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. J Allergy Clin Immunol*, 2017, 139(4):65-76.
- [13] Tsuji G, Hashimoto-Hachiya A, Kiyomatsu-Oda M, et al. *Aryl hydrocarbon receptor activation restores filaggrin expression via OVOL1 in atopic dermatitis. Cell Death Dis*, 2017, 8:e2931.
- [14] Kazuhisa Furue, Takamichi Ito, Gaku Tsuji, et al. *The IL-13-OVOL1-FLG axis in atopic dermatitis. Immunology*, 2019, 158(4):281-286.
- [15] Michael J Cork, Simon G Danby, Graham S Ogg. *Atopic dermatitis epidemiology and unmet need in the United Kingdom. Journal of Dermatological Treatment*, 2020, 31(8):801-809.

- [16] Borgia F, Custurone P, Li Pomi F, et al. IL-31: State of the Art for an Inflammation-Oriented Interleukin. *Int J Mol Sci*, 2022, 23(12):6507.
- [17] Liyuan Liu, Xinsuo Duan. Research progress on immune-related pathogenesis of atopic dermatitis. *Journal of Chengde Medical College*, 2022, 39(3):247-251.
- [18] Swindell W R, Bojanowski K, Chaudhuri R K. Isosorbide Fatty Acid Diesters Have Synergistic Anti-Inflammatory Effects in Cytokine-Induced Tissue Culture Models of Atopic Dermatitis. *Int J Mol Sci*, 2022, 23(22): 14307.
- [19] Tsiogka A, Kyriazopoulou M, Kontochristopoulos G, et al. The JAK/STAT Pathway and Its Selective Inhibition in the Treatment of Atopic Dermatitis: A Systematic Review. *J Clin Med*, 2022, 11(15):4431.
- [20] Lee H J, Hong Y J, Kim M. Angiogenesis in Chronic Inflammatory Skin Disorders. *Int J Mol Sci*, 2021, 22(21):12035.
- [21] Eyerich K, Pennino D, Scarponi C, et al. IL-17 in atopic eczema: Linking allergen-specific adaptive and microbial-triggered innate immune response. *J Allergy Clin Immunol*, 2009, 123(1):59–66.
- [22] Sugaya M. The Role of Th17-Related Cytokines in Atopic Dermatitis. *Int J Mol Sci*, 2020, 21(4):1314.
- [23] Sahiner U M, Layhadi J A, Golebski K, et al. Innate lymphoid cells: The missing part of a puzzle in food allergy. *Allergy*, 2021, 76(7):2002-2016.
- [24] Packi K, Matysiak J, Klimczak S, et al. Analysis of the Serum Profile of Cytokines Involved in the T-Helper Cell Type 17 Immune Response Pathway in Atopic Children with Food Allergy. *Int J Environ Res Public Health*, 2022, 19(13):7877.
- [25] Julia Borowczyk, Maria Shutova, Nicolo Costantino Brembilla, et al. IL-25 (IL-17E) in epithelial immunology and pathophysiology. *J Allergy Clin Immunol*, 2021, 148(1):40-52.
- [26] Hvid M, Vestergaard C, Kemp K, et al. IL-25 in atopic dermatitis: a possible link between inflammation and skin barrier dysfunction?. *J Invest Dermatol*, 2011, 131(1): 150-157.
- [27] Aktar M K, Kido-Nakahara M, Furue M, et al. Mutual upregulation of endothelin-1 and IL-25 in atopic dermatitis. *Allergy*, 2015, 70(7): 846-854
- [28] SiHang Wang, YaGang Zuo. Mechanism and clinical application of thymic stromal lymphopoietin in atopic dermatitis. *Chinese Journal of Allergy and Clinical Immunology*, 2022, 16(1):66-71.
- [29] Zhi Li, Tingting Yang, WenZhe Li. Expression of Th22, Treg cells and their cytokines in peripheral blood of patients with atopic dermatitis. *Chinese Journal of Laboratory Diagnosis*, 2019, 23(5):788-791.
- [30] Zhang D J, Hao F, Qian T, et al. Expression of Helper and Regulatory T Cells in Atopic Dermatitis: A Meta-Analysis. *Front Pediatr*, 2022, 10:777992.
- [31] Masutaka Furue, Takahito Chiba, Gaku Tsuji, et al. Atopic dermatitis: immune deviation, barrier dysfunction, IgE autoreactivity and new therapies. *Allergology International*, 2017, 66(3):398-403.
- [32] Gittler J K, Shemer A, M Suarez-Farinas, et al. Progressive activation of T2/T22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. *J Allergy Clin Immunol*, 2012, 130, 1344.
- [33] Hongfei Lou, Jingning Lu, Eun Byul Choi, et al. Expression of IL-22 in the Skin Causes Th2-Biased Immunity, Epidermal Barrier Dysfunction, and Pruritus via Stimulating Epithelial Th2 Cytokines and the GRP Pathway. *J Immunol*, 2017, 198 (7): 2543-2555.
- [34] Fukaya T, Fukui T, Uto T, et al. Pivotal role of il-22 Binding Protein in the epithelial autoregulation of interleukin-22 signaling in the control of skin inflammation. *Front Immunol*, 2018, 9:1418.

- [35] Masutaka Furue. Regulation of Filaggrin, Loricrin, and Involucrin by IL-4, IL-13, IL-17A, IL-22, AHR, and NRF2: Pathogenic Implications in Atopic Dermatitis. *Int J Mol Sci*, 2020, 21(15): 5382.
- [36] Lopez, DV, Kongsbak-Wismann M. Role of IL-22 in homeostasis and diseases of the skin. *APMIS*, 2022, 130(6): 314-322.
- [37] Yuting Xu, Qun Hu. Research progress of neutrophil dysfunction. *Journal of China Pediatric Blood and Cancer*, 2021, 26(1): 51-55.
- [38] David F Choy, Daniel K Hsu, Dhaya Seshasayee, et al. Comparative transcriptomic analyses of atopic dermatitis and psoriasis reveal shared neutrophilic inflammation. *J Allergy Clin Immunol*, 2012, 130(6): 1335-1343.
- [39] A Schabitz, K Eyerich, N Garzorz-Stark. So close, and yet so far away: The dichotomy of the specific immune response and inflammation in psoriasis and atopic dermatitis. *Journal of Internal Medicine*, 2021, 290: 27-39.
- [40] Hashimoto, T Rosen, J D Sanders, et al. Possible role of neutrophils in itch. *J Itch*, 2018, 3: e17.
- [41] Carolyn M Walsh, Rose Z Hill, Jamie Schwendinger-Schreck, et al. Neutrophils promote CXCR3-dependent itch in the development of atopic dermatitis [J/OL]. *eLife*, 2019-10-21/2022-12-20.
- [42] Cunha T M, Waldiceu A Verri, Ieda R Schivo, et al. Crucial role of neutrophils in the development of mechanical inflammatory hypernociception. *J Leukoc Biol*, 2008, 83(4): 824-832.
- [43] Wagner K M, Gomes A, McReynolds C B. Soluble epoxide hydrolase regulation of lipid mediators limits pain. *Neurotherapeutics*, 2020, 17(3): 900-916.
- [44] Sadik C D, Kim N D, Luster A D. Neutrophils cascading their way to inflammation. *Trends Immunol*, 2011, 32(10): 452-460.
- [45] Janine Woytschak, Nadia Keller, Carsten Krieg, et al. Type 2 Interleukin-4 Receptor Signaling in Neutrophils Antagonizes Their Expansion and Migration during Infection and Inflammation. *Immunity*, 2016, 45(1): 172-184.
- [46] D Simon, L R Braathen, H U Simon. Eosinophils and atopic dermatitis. *Allergy*, 2004, 59(6): 561-570.
- [47] Weller P F, Spencer L A. Functions of tissue-resident eosinophils. *Nat Rev Immunol*, 2017, 17(12): 746-760.
- [48] Inokuchi-Sakata S, Ishiuiji Y, Katsuta M, et al. Role of Eosinophil Relative Count and Neutrophil-to-Lymphocyte Ratio in the Assessment of Severity of Atopic Dermatitis [J/OL]. *Acta Dermatovenereologica*, 2021-07-07/2022-12-20.
- [49] Raap U, Goltz C, Deneka N, et al. Brain-derived neurotrophic factor is increased in atopic dermatitis and modulates eosinophil functions compared with that seen in nonatopic subjects. *J Allergy Clin Immunol*, 2005, 115(6): 1268-1275.
- [50] Kunsleben N, Rudrich U, Gehring M, et al. IL-31 Induces chemotaxis, calcium mobilization, release of reactive oxygen species, and CCL26 in eosinophils, which are capable to release IL-31. *J Invest Dermatol*, 2015, 135(7): 1908-1911.
- [51] Beyer L, Kabatas A S, Mommert S, et al. Histamine Activates Human Eosinophils via H2R and H4R Predominantly in Atopic Dermatitis Patients. *Int J Mol Sci*, 2022, 23(18): 10294.
- [52] Sandersa N L, Venkateshaiah S U, Manohar M. Interleukin-18 has an Important Role in Differentiation and Maturation of Mucosal Mast Cells. *J Mucosal Immunol Res*, 2018, 2(1): 109.
- [53] Yousefi S, Gold J A, Andina N, et al. Catapult-like release of mitochondrial DNA by eosinophils contributes to antibacterial defense. *Nat Med*, 2008, 14: 949-953.
- [54] Morshed M, Yousefi S, Stockle C, et al. Thymic stromal lymphopoietin stimulates the formation of eosinophil extracellular traps. *Allergy* 2012, 67: 1127-1137.

- [55] Elieen Gevaert, Nan Zhang, Olga Krysko, et al. Extracellular eosinophilic traps in association with *Staphylococcus aureus* at the site of epithelial barrier defects in patients with severe airway inflammation. *J Allergy Clin Immunol* 2017, 139:1849-1860.
- [56] Kim B S, Wang K, Siracusa M C, et al. Basophils promote innate lymphoid cell responses in inflamed skin. *J Immunol*, 2014, 193(7):3717-3725.
- [57] Lisa A Beck, Michael J Cork, Masayuki Amagai, et al. Type 2 Inflammation Contributes to Skin Barrier Dysfunction in Atopic Dermatitis. *JID Innovations*, 2022, 2(5):100131.
- [58] Mayumi Egawa, Kaori Mukai, Soichiro Yoshikawa, et al. Inflammatory Monocytes Recruited to Allergic Skin Acquire an Anti-inflammatory M2 Phenotype via Basophil-Derived Interleukin-4. *Immunity*, 2013, 38(3):570-580.
- [59] Christophe Pellefigues, Karmella Naidoo, Palak Mehta, et al. Basophils promote barrier dysfunction and resolution in the atopic skin. *J Allergy Clin Immunol*, 2021, 148(3):799-812.
- [60] Numata T, Takahagi S, Ishii K, et al. Immunological Changes of Basophil Hyperreactivity to Sweat in Patients With Well-Controlled Atopic Dermatitis. *Front Immunol*, 2022, 13:883605.
- [61] Fang Wang, Anna M Trier, Fengxian Li, et al. A basophil-neuronal axis promotes itch. *Cell*, 2021, 184(2):422-440.
- [62] Tianheng Hou, Miranda Sin-Man Tsang, Lea Ling-Yu Kan, et al. IL-37 Targets TSLP-Primed Basophils to Alleviate Atopic Dermatitis. *Int J Mol Sci*, 2021, 22(14):7393.
- [63] Xujun Zheng, Huaicun Liu, Jun Wang. Research progress on the mechanism of monocyte-macrophage system involved in chemotherapy-induced peripheral neuropathic pain. *Chinese Journal of Pain Medicine*, 2022, 28(2):89-97.
- [64] Martinez F O, Helming L, Gordon S. Alternative activation of macrophages: an immunologic functional perspective. *Annu Rev Immunol*, 2009, 27:451-483.
- [65] Luting Zeng, Yingqin Liu, Congcong Xing, et al. Saponin from *Periploca forrestii* Schltr Mitigates Oxazolone-Induced Atopic Dermatitis via Modulating Macrophage Activation [J/OL]. *Hindawi*, 2020-10-15/2022-12-20.
- [66] Varricchi G, Pecoraro A, Marone G, et al. Thymic Stromal Lymphopoietin Isoforms, Inflammatory Disorders, and Cancer. *Front Immunol*, 2018, 9:1595.
- [67] Hongwei Han, Mark B Headley, Whitney Xu, et al. Thymic Stromal Lymphopoietin Amplifies the Differentiation of Alternatively Activated Macrophages. *J Immunol*, 2013, 190(3):904-912.
- [68] Kim H O, Cho S I, Chung B Y, et al. Expression of CCL1 and CCL18 in Atopic Dermatitis and Psoriasis. *Clin Exp Dermatol*, 2012, 37(5):521-526.
- [69] Mommert S, Schaper J T, Schaper-Gerhardt K, et al. Histamine Increases Th2 Cytokine-Induced CCL18 Expression in Human M2 Macrophages. *Int J Mol Sci*, 2021, 22(21):11648.
- [70] Charles A Dinarello, Daniela Novick, Soohyun Kim, et al. Interleukin-18 and IL-18 binding protein. *Frontiers in Immunology*, 2013, 4:289.
- [71] Stella Amarachi Ihim, Sharafudeen Dahiru Abubakar, Zeineb Zian, et al. Interleukin-18 cytokine in immunity, inflammation, and autoimmunity: Biological role in induction, regulation, and treatment. *Front Immunol*, 2022, 13:919973.
- [72] Ting-Lin B Yang, Brian S Kim. Pruritus in allergy and immunology. *J Allergy Clin Immunol*, 2019, 144(2):353-360.
- [73] Wang Z, Franke K, Bal G, et al. MRGPRX2-Mediated Degranulation of Human Skin Mast Cells Requires the Operation of Gai, Gaq, Ca⁺⁺ Channels, ERK1/2 and PI3K—Interconnection between Early and Late Signaling. *Cells*, 2022, 11(6):953.
- [74] Helen Kuhn, Pavel Kolkhir, Magda Babina, et al. Mas-related G protein-coupled receptor X2 and its activators in dermatologic allergies. *J Allergy Clin Immunol*, 2021, 147(2):456-469.

- [75] Zhao Wang, Magda Babina. *MRGPRX2 signals its importance in cutaneous mast cell biology: Does MRGPRX2 connect mast cells and atopic dermatitis?*. *Exp Dermatol*, 2020, 29(11):1104-1111.
- [76] James Meixiong, Michael Anderson, Nathachit Limjunyawong, et al. *Activation of Mast-Cell-Expressed Mas-Related G-Protein-Coupled Receptors Drives Non-histaminergic Itch*. *Immunity*, 2019, 50(5):1163-1171.
- [77] Helen Kuhn, Pavel Kolkhir, Magda Babina, et al. *Mas-related G protein-coupled receptor X2 and its activators in dermatologic allergies*. *J Allergy Clin Immunol*, 2021, 147(2):456-469.