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Research Advances on the Immunoregulatory Mechanisms and Targeted Therapy of the JAK-STAT Signaling Pathway in Allergic Rhinitis

Qiuye Wu [1], Jinjiang Xu [1], Man Zhang [2], Xiongbin Gui [2, *]

[1] Guangxi University of Chinese Medicine, Nanning, Guangxi, 530023, China
[2] The First Affiliated Hospital of Guangxi University of Chinese Medicine, Nanning, Guangxi, 530023, China

*** Corresponding author:** Xiongbin Gui (Email: GuiXB2008@163.com)

Abstract: Allergic rhinitis (AR) is a chronic airway disease characterized by immunoglobulin E (IgE)-mediated inflammation of the nasal mucosa, featuring complex pathogenesis where current therapeutic approaches remain insufficient to fully control symptoms and disease progression. The Janus kinase (JAK)/signal transduction and activator of transcription (STAT) pathway, a core signaling cascade ubiquitously expressed in cells, demonstrates multidimensional and multitargeted involvement in immunopathological processes of AR, including immune balance regulation, epithelial barrier impairment, and tissue remodeling. Recent advances reveal that JAK/STAT pathway-targeted inhibitors and herbal components exhibit therapeutic potential for AR by modulating Th1/Th2 immune imbalance, reducing mucus hypersecretion, and mitigating local inflammation. This review systematically summarizes the multidimensional regulatory network of the JAK/STAT pathway in AR and its targeted therapeutic strategies, aiming to provide theoretical foundations for elucidating AR pathogenesis, optimizing treatment approaches through immune microenvironment remodeling, and proposing novel insights for JAK/STAT-targeted therapeutic interventions.

Keywords: Allergic Rhinitis; JAK-STAT Signaling Pathway; Immunoregulatory.

1. Introduction

Allergic rhinitis (AR) is a chronic inflammatory airway disorder driven by a T helper 2 (Th2) cell-mediated immune response. It affects 10%-40% of the global population, with prevalence rates reaching up to 24% in certain regions of China, posing a significant public health burden [1]. The disease is characterized by immunoglobulin E (IgE)-mediated inflammation of the nasal mucosa. Its cardinal symptoms include nasal itching, sneezing, nasal congestion, and watery rhinorrhea. The characteristic seasonal recurrence of symptoms leads to a substantial decline in patients' quality of life and contributes to a "unified airway" vicious cycle with comorbidities such as asthma [2]. Although current therapeutic options (e.g., antihistamines, intranasal corticosteroids) can provide temporary symptomatic relief, they are ineffective for some patients and fail to halt tissue remodeling during disease progression[3]. Consequently, elucidating the key signaling pathways involved in AR pathogenesis and exploring more effective treatment strategies represent pressing clinical challenges.

In recent years, the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, a central hub for cytokine signaling, has achieved breakthrough progress in the treatment of autoimmune diseases [4]. This pathway also plays a significant role in the immunopathology of AR. A key mechanism involves the JAK-STAT6 signaling axis driving Th2 cell polarization [5]. Although the regulatory mechanisms of the JAK-STAT pathway have been extensively studied in other inflammatory diseases, its specific functions in AR—particularly concerning immune cell regulation, epithelial barrier integrity, and tissue remodeling—remain to be fully elucidated. Furthermore, the distinct roles of different JAK and STAT protein isoforms in the immune mechanisms underlying AR require further clarification.

This review will focus on elucidating the multifaceted regulatory roles of the JAK-STAT pathway in AR by integrating findings from emerging research areas, including pathway-targeted therapies. It aims to provide a theoretical foundation for clarifying the pathogenesis of AR and developing more effective treatments capable of remodeling its immune microenvironment. Furthermore, it seeks to offer novel perspectives for JAK/STAT signaling pathway-targeted therapeutic strategies.

2. Immunopathological Features of Allergic Rhinitis (AR)

2.1. Cascade of the Canonical Th2-Type Immune Response

The pathogenesis of AR initiates when allergens (e.g., dust mites, pollen) penetrate the nasal mucosal barrier, triggering epithelial cells to release alarmins such as thymic stromal lymphopoietin (TSLP), interleukin (IL)-25, and IL-33. These factors drive dendritic cells (DCs) toward Th2-polarized differentiation [6]. Activated DCs migrate to draining lymph nodes, where they present antigens to naïve T cells (Th0) via major histocompatibility complex (MHC) class II molecules; under IL-4 stimulation, Th0 cells differentiate into Th2 effector cells, thereby initiating AR [7]. This process culminates in a biphasic reaction: Th2-derived IL-4 and IL-13 promote B cell production of allergen-specific IgE, which binds to the high-affinity receptor FcεRI on mast cells to form IgE-FcεRI complexes, establishing host sensitization. Upon re-exposure to allergens, mast cell degranulation releases histamine and leukotrienes, provoking immediate symptoms (sneezing, nasal pruritus) in the IgE-mediated early phase[8]. Concurrently, Th2-secreted IL-5 recruits eosinophils, whose cytotoxic proteins (eosinophil cationic protein and major basic protein) drive persistent nasal congestion and airway inflammation during the eosinophil-dominated late phase [7, 8].

2.2. Epithelial Barrier Dysfunction

Recent studies reveal significantly reduced expression of tight junction proteins (including claudin-1, claudin-4, claudin-7, and occludin) in the nasal mucosa of AR patients. This barrier defect facilitates allergen penetration and amplifies local inflammation[9]. The core mechanism involves damaged epithelial cells releasing cytokines such as TSLP, IL-25, and IL-33. Specifically, TSLP activates dendritic cells (DCs) to upregulate the T-cell co-stimulatory receptor OX40 ligand (OX40L), thereby enhancing Th2 cell effector functions[10]; concurrently, TSLP induces STAT6 phosphorylation to promote expression of the pro-inflammatory chemokine CCL17, intensifying inflammatory responses[11]. Meanwhile, IL-25—a member of the IL-17 cytokine family—binds to IL-17A/IL-17B receptors, activating and upregulating the expression of transcription factors STAT6, GATA-3, and nuclear factor kappa-B (NF-κB) to stimulate memory Th2 cells [12]. Furthermore, IL-25 suppresses Th1/Th17-associated transcription factors (T-bet and STAT4), reducing secretion of IL-17A, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), which disrupts Th1/Th2 equilibrium and further aggravates Th2-polarized immunity [13]. Additionally, impaired epithelial cells release IL-33 to stimulate goblet cell metaplasia and mucus hypersecretion, further compromising mucosal integrity [14].

2.3. Neuroimmune Regulation

Research reveals that hallmark symptoms of AR—such as paroxysmal sneezing and nasal pruritus—represent a form of neurogenic inflammation. In humans, nasal nociceptors primarily consist of C-fibers, which typically respond to chemical and physical stimuli. These nerve endings express multiple receptors and ion channels, including the transient receptor potential vanilloid 1 (TRPV1) channel. Upon allergen exposure, TRPV1 activation triggers the release of substance P (SP) and calcitonin gene-related peptide (CGRP) [15]. Mechanistically, SP binds to neurokinin-1 receptors (NK-1R) on mast cells, inducing inflammatory mediator release and recruiting immune cells to provoke innate immune responses [16]. Concurrently, CGRP stimulates type 2 innate lymphoid cells (ILC2s) to secrete IL-5, thereby promoting eosinophil infiltration and amplifying allergic inflammation [17].

3. JAK-STAT Pathway and Immunoregulatory Mechanisms

3.1. Pathway Signaling and Immune Modulation

The JAK-STAT signaling cascade, activated by cytokine stimulation, comprises non-receptor tyrosine kinases of the JAK family (JAK1, JAK2, JAK3, TYK2) and transcription factors of the STAT family (STAT1-6) [18]. When cytokines—including interferons (IFNs), interleukins, or growth factors—bind to their receptors, they activate single or multiple JAKs. These kinases phosphorylate residues on the receptor's cytoplasmic tail, creating docking sites for STAT proteins [19]. Prior to activation, STATs exist as antiparallel dimers constantly shuttling between the cytoplasm and nucleus [18]. Following JAK-mediated receptor phosphorylation, cytoplasmic STATs are recruited to the receptor, undergo tyrosine phosphorylation, and undergo structural reorganization into active parallel dimers. These dimers dissociate from the receptor, translocate to the nucleus, bind specific DNA sequences, and initiate transcription of target genes. Subsequently, STATs are dephosphorylated in the nucleus and return to the cytoplasm. This cyclical process regulates diverse cellular functions—including immune modulation, inflammation, hematopoiesis, tissue repair, and apoptosis—notably driving the development of T/B cells, modulating inflammatory cytokine secretion, and shaping immune tolerance [18-20]. Critically, in AR-related immune dysregulation, the JAK-STAT pathway exerts two core effects: IL-4/IL-13-stimulated STAT6 nuclear translocation upregulates Th2 transcription factors to perpetuate IgE production, while IL-5-driven STAT5 activation promotes eosinophil maturation and chemotaxis, exacerbating nasal inflammation [21].

3.2. Negative Regulators

The JAK-STAT pathway exhibits rapid activation and inactivation dynamics, tightly controlled by inhibitory factors. Three primary classes of negative regulators modulate this signaling: suppressors of cytokine signaling (SOCS), protein inhibitors of activated STATs (PIAS), and protein tyrosine phosphatases (PTPs) [20]. Notably, the SOCS family—comprising SOCS1-SOCS7 and cytokine-inducible SH2-containing protein (CIS)—serves as the dominant inhibitory mechanism. SOCS proteins suppress JAK-STAT signaling through three strategies: (i) competing with STATs for phosphorylated tyrosine residues on cytokine receptors, (ii) directly binding JAKs to inhibit their kinase activity, or (iii) inducing ubiquitin-mediated degradation of JAKs/STATs [22-24]. Critically, SOCS3 inhibits IL-2 signaling to reduce Th2 cytokines (IL-4, IL-5, IL-10), positioning it as a potential therapeutic target for AR [22]. Conversely, the PIAS family (PIAS1, PIAS3, PIASx, PIASy) blocks STAT function by preventing dimerization or obstructing DNA binding of STAT dimers [25]. Additionally, PTPs dephosphorylate either receptor-bound JAKs or nuclear STAT dimers, terminating signal transduction [26].

3.3. Crosstalk with Other AR-Associated Pathways

JAKs activate non-canonical signaling beyond the classical JAK-STAT axis, forming multipathway crosstalk critically involving the MAPK and PI3K/Akt pathways—both essential for cell growth, differentiation, and immune homeostasis in AR [27, 28]. Mechanistically, JAK-phosphorylated receptors recruit SH2 domain-containing proteins (including STATs, SHP2, and PI3K). SHP2 then mobilizes GRB2 to activate Ras, thereby initiating the MAPK cascade; concurrently, upstream RTK/Ras signaling elevates MAPK activity, which enhances STAT transcriptional potency via C-terminal serine phosphorylation [28]. Meanwhile, PI3K binding activates the PI3K-Akt pathway, suppressing pro-apoptotic proteins to prolong eosinophil survival and tissue infiltration [29]. This intricate JAK-STAT-MAPK-PI3K network constitutes a complex signaling web that complicates AR pathogenesis, demanding further research for therapeutic interventions.

4. JAK-STAT Regulation of AR Immune Balance

4.1. Immune Cells

Cytokine-induced JAK-STAT activation critically drives AR inflammation by regulating the proliferation, differentiation, and inflammatory cytokine expression of multiple immune cells—including T-cell subsets, B cells, eosinophils, and mast cells. Furthermore, this pathway transduces signals for cytokines (e.g., IL-4, IL-6, IL-13) that disrupt Th1/Th2 balance and broader immune homeostasis, thereby serving as a central driver of AR inflammatory initiation, persistence, and tissue remodeling [30].

4.1.1. T Helper Cell Subsets

The Th1/Th2 immune imbalance and Th2-dominant response are pivotal in AR pathogenesis, with Th17 and regulatory T cells (Tregs) also playing critical roles. Specifically, Th1 cytokines (e.g., IFN-γ) bind receptors alongside IL-12 to activate JAK1/JAK2, phosphorylating STAT1/STAT4 and inducing the Th1-specific transcription factor T-bet—thereby forming a positive feedback loop that amplifies IFN-γ secretion and Th1 responses [31]. Conversely, Th2 cytokines IL-4 and IL-13 trigger STAT6 phosphorylation, upregulating GATA3 (the master Th2 transcription factor), which further enhances IL-4/IL-13 production and drives Th2 polarization [32]. Meanwhile, Th17 differentiation—primarily regulated by IL-6 and TGF-β—involves IL-6-induced STAT3 activation via gp130 receptors, boosting expression of the pro-inflammatory cytokine IL-17 and its key transcription factor RORγt; this cascade exacerbates AR by activating Th2 cells, recruiting neutrophils, stimulating macrophages, and increasing mucus secretion [33-35]. Notably, while TGF-β modulates both RORγt and the Treg-specific factor Foxp3, high TGF-β levels promote Th0-to-Treg differentiation. Additionally, IL-2 activates JAK1/JAK3-STAT5 signaling to directly induce Foxp3 transcription and Treg development. Critically, Tregs exert immunosuppressive effects in AR through anti-inflammatory cytokines like IL-10, which collaborates with IL-33 to sustain Treg-mediated immune inhibition [36, 37].

4.1.2. B Cells

B cells differentiate into plasma cells upon cytokine stimulation, producing allergen-specific IgE that binds mast cells to sensitize the host—a core mechanism in AR's immediate-phase reaction [8]. Critically, the JAK-STAT pathway regulates B-cell development and differentiation: IL-4 activates JAK1/JAK3 upon binding B-cell surface receptors, phosphorylating STAT6 to promote its nuclear translocation, thereby upregulating CD23 (low-affinity IgE receptor) and MHC class II molecules to enhance antigen presentation [38]. Furthermore, cytokines like IL-21 from follicular helper T cells (Tfh) are essential for B-cell maturation; IL-21 drives plasma cell differentiation via JAK1-STAT3 signaling, while IL-6 cooperates with IL-12 to modulate Tfh differentiation through STAT3 [39]. Notably, STAT3 deficiency—as demonstrated by Ma et al.—compromises Tfh differentiation and reduces B-cell activity [40].

4.1.3. Eosinophils

IL-5-driven eosinophil precursors differentiate and mature, subsequently infiltrating nasal mucosa alongside lymphocytes, monocytes, and plasma cells to amplify inflammation—constituting the core process of AR's late-phase reaction [8]. Specifically, IL-5 binding to eosinophil surface receptors activates the JAK2-STAT5 pathway, which upregulates anti-apoptotic proteins BCL-2 and MCL-1 to promote bone marrow differentiation/maturation while suppressing apoptosis via cyclin D and Pim-1 genes [41, 42]. Meanwhile, IL-4-induced STAT6 activation translocates to the nucleus and binds the CCL11 promoter, enhancing this chemokine's expression to recruit eosinophils to inflammatory sites [43]. Furthermore, STAT3 activation upregulates CCL8 and other chemokines, amplifying eosinophil infiltration into nasal mucosa and exacerbating local inflammation [44].

4.1.4. Mast Cells

Re-exposure to allergens binding the IgE-FcεRI complex on mast cells triggers degranulation, releasing TNF-α, leukotriene B4, IL-5, and IL-6 to activate inflammatory cells—a hallmark of allergic responses [45]. Critically, the JAK-STAT pathway regulates mast cell proliferation and survival: IL-3 activates STAT5 to induce nuclear translocation and upregulate anti-apoptotic proteins, while stem cell factor (SCF, mast cell growth factor) binding to its receptor c-Kit activates JAK2-STAT5 signaling, synergistically promoting mast cell proliferation/survival with IL-3 [46]. Moreover, STAT5 cooperates with NF-κB p65 to bind the TNF-α promoter, enhancing its transcriptional activity; dihydromyricetin (DHM) inhibits STAT5 phosphorylation, thereby significantly reducing TNF-α and IL-6 secretion in IgE-activated mast cells [47, 48].

4.2. Epithelial-Immune Regulation

Nasal epithelial cells (NECs), comprising basal, ciliated, and functional goblet cells, constitute the first-line physical barrier of the nasal cavity. Notably, Th2 cytokines dominate goblet cell metaplasia: IL-4 and IL-13 activate STAT6 to promote goblet cell hyperplasia and mucus hypersecretion—both elevated in AR, driving pathological overproliferation [49]. Concurrently, IL-6 activates JAK1/JAK2-STAT3 signaling to further stimulate goblet cell proliferation and differentiation [50]. Mechanistically, loratadine alleviates AR symptoms partly by inhibiting IL-6 transcription, thereby downregulating this signaling axis to suppress goblet cell hyperplasia and mucus production [51]. Additionally, IL-1β—a potent proinflammatory cytokine secreted by lymphocytes, macrophages, and monocytes—exacerbates inflammation via the STAT1 pathway, inducing NECs to release mediators (e.g., IL-6, IL-8, GM-CSF) [52]. In contrast, IL-22 activates JAK1/JAK2-STAT3 to promote NEC repair/regeneration, attenuate goblet cell hyperplasia, and restore normal mucosal function [50].

4.3. Tissue Remodeling Mechanisms

Chronic and seasonally recurrent AR drives structural airway changes through repeated inflammation-repair cycles, with the JAK-STAT6 pathway critically implicated in airway remodeling—primarily via hyperplasia and activation of airway fibroblasts [53]. Specifically, IL-13 activates STAT6 to induce platelet-derived growth factor AA (PDGF-AA) production by fibroblasts, which via autocrine/paracrine mechanisms activates the ERK signaling pathway in fibroblasts, promoting their pathological activation [53-55]. Meanwhile, IL-4 upregulates mucin genes MUC5AC and MUC4 (mediating mucus hypersecretion) through JAK3-dependent signaling; notably, MUC4 acts as a ligand for human epidermal growth factor receptor 2 (HER2), regulating epithelial proliferation during airway injury [56, 57].

Furthermore, STAT6 activated by IL-13 binds to promoter sequences of collagen genes COL1A1 and COL1A2, inducing their transcription [58], while blocking IL-13-STAT6 signaling suppresses fibroblast proliferation, activation, and collagen production [59].

5. Clinical Prospects of JAK-STAT Pathway-Targeted Therapy

JAK inhibitors are clinically approved for autoimmune diseases including rheumatoid arthritis, psoriasis, and atopic dermatitis [4], with emerging applications in Th2-driven airway inflammation. The selective JAK1 inhibitor GDC-0214 significantly reduced IL-4/IL-13 secretion and decreased fractional exhaled nitric oxide (FeNO) levels in mild asthma patients, demonstrating targeted Th2 immunomodulation [60]. Although not yet clinically implemented for allergic rhinitis (AR), preclinical evidence reveals that CYT387 suppresses JAK-STAT signaling in AR murine models, reducing MHC II expression and impairing Th0-to-Th2 differentiation, thereby attenuating eosinophil infiltration [10]. Concurrently, JAK-STAT6 inhibitors SOCS1 and AS1517499 downregulate goblet cell-derived MUC5AC expression and ameliorate airway mucus hypersecretion [61, 62], while ruxolitinib inhibits JAK2-STAT5 phosphorylation to diminish mast cell accumulation and mediator release [63]. Beyond synthetic agents, traditional Chinese medicine (TCM) compounds exhibit regulatory effects: Astragaloside IV—the primary bioactive component of Astragalus in Buzhong Yiqi Decoction—inhibits STAT6 phosphorylation in AR mice, reducing eosinophils, mast cells, IL-4/IL-13, and p-JAK2 while elevating IFN-γ, thereby restoring Th1/Th2 balance [64]; α-linolenic acid suppresses serum IgE and rectifies Th1/Th2 imbalance by upregulating T-bet/STAT1 and downregulating GATA3/STAT6 [65]; and the formula Chuanxiong Chatiao Powder alleviates nasal inflammation and mucus hypersecretion via T-bet induction and STAT6 suppression [66]. Collectively, the JAK-STAT pathway represents a promising therapeutic target for AR by modulating immune dysregulation, particularly Th1/Th2 polarization in inflammatory responses.

6. Conclusion and Future Directions

Allergic rhinitis (AR) is a chronic airway inflammatory disease dominated by Th2-type immune responses, characterized pathologically by IgE-mediated inflammation, nasal mucosal barrier dysfunction, neurogenic hyperreactivity, and airway remodeling. As a central hub for cytokine signal transduction, the JAK-STAT signaling pathway critically contributes to AR immunopathology by regulating Th2 polarization, eosinophil differentiation/survival, and epithelial barrier integrity. This review systematically delineates the multidimensional regulatory roles of JAK-STAT signaling in AR, encompassing STAT6-mediated Th2 polarization and IgE production, STAT5-driven eosinophil infiltration, and STAT3-associated mucus hypersecretion, while highlighting the therapeutic potential of pathway inhibition for symptom alleviation and immune microenvironment modulation. However, current research exhibits significant limitations: the crosstalk between JAK-STAT and other pathways (e.g., MAPK, PI3K/Akt) remains incompletely elucidated, rendering single-target approaches inadequate for deciphering complex regulatory networks; moreover, most evidence derives from animal or cellular models, lacking clinical validation and large-scale cohort studies. Future investigations should prioritize clinical trials—employing rigorous methodologies (large-scale, multicenter, randomized controlled trials) and advanced techniques (bioinformatics, multi-omics integration)—to elucidate AR pathogenesis and enhance real-world translatability. Additionally, the multicomponent, multitarget nature of traditional Chinese medicine (TCM) and its interactions with JAK-STAT signaling require systematic exploration. Integrative strategies (e.g., gene editing, combined agonist/inhibitor applications) are warranted to dissect how TCM formulas modulate JAK-STAT pathways to ameliorate AR, with parallel clinical validation of efficacy. In conclusion, targeting JAK-STAT signaling offers novel avenues for immune modulation and precision therapy in AR, wherein the multitarget properties of TCM may overcome current therapeutic bottlenecks, though mechanistic and clinical substantiation demands further refinement.

References

[1] Li Q, Zhang X, Feng Q, Zhou H, Ma C, Lin C, Wang D, Yin J. Common Allergens and Immune Responses Associated with Allergic Rhinitis in China. Journal of Asthma and Allergy 2023; Volume 16: 851-861.

[2] Bousquet J, Anto JM, Bachert C, Baiardini I, Bosnic-Anticevich S, Walter Canonica G, Melén E, Palomares O, Scadding GK, Togias A, Toppila-Salmi S. Allergic rhinitis. Nature Reviews Disease Primers 2020; 6(1).

[3] Wise SK, Damask C, Roland LT, Ebert C, Levy JM, Lin S, Luong A, Rodriguez K, Sedaghat AR, Toskala E, Villwock J, Abdullah B, Akdis C, Alt JA, Ansotegui IJ, Azar A, Baroody F, Benninger MS, Bernstein J, Brook C, Campbell R, Casale T, Chaaban MR, Chew FT, Chambliss J, Cianferoni A, Custovic A, Davis EM, DelGaudio JM, Ellis AK, Flanagan C, Fokkens WJ, Franzese C, Greenhawt M, Gill A, Halderman A, Hohlfeld JM, Incorvaia C, Joe SA, Joshi S, Kuruvilla ME, Kim J, Klein AM, Krouse HJ, Kuan EC, Lang D, Larenas-Linnemann D, Laury AM, Lechner M, Lee SE, Lee VS, Loftus P, Marcus S, Marzouk H, Mattos J, McCoul E, Melen E, Mims JW, Mullol J, Nayak JV, Oppenheimer J, Orlandi RR, Phillips K, Platt M, Ramanathan M, Jr., Raymond M, Rhee CS, Reitsma S, Ryan M, Sastre J, Schlosser RJ, Schuman TA, Shaker MS, Sheikh A, Smith KA, Soyka MB, Takashima M, Tang M, Tantilipikorn P, Taw MB, Tversky J, Tyler MA, Veling MC, Wallace D, Wang Y, White A, Zhang L. International consensus statement on allergy and rhinology: Allergic rhinitis - 2023. Int Forum Allergy Rhinol 2023; 13(4): 293-859.

[4] Jinesh S, Radhakrishnan R. Pharmaceutical aspects of JAK inhibitors: a comparative review. Inflammopharmacology 2025; 33(1): 91-104.

[5] Pelaia C, Crimi C, Vatrella A, Tinello C, Terracciano R, Pelaia G. Molecular Targets for Biological Therapies of Severe Asthma. Front Immunol 2020; 11: 603312.

[6] Cayrol C, Girard JP. IL-33: an alarmin cytokine with crucial roles in innate immunity, inflammation and allergy. Curr Opin Immunol 2014; 31: 31-37.

[7] Shamji MH, Sharif H, Layhadi JA, Zhu R, Kishore U, Renz H. Diverse immune mechanisms of allergen immunotherapy for allergic rhinitis with and without asthma. J Allergy Clin Immunol 2022; 149(3): 791-801.

[8] Banafea GH, Bakhashab S, Alshaibi HF, Natesan Pushparaj P, Rasool M. The role of human mast cells in allergy and asthma. Bioengineered 2022; 13(3): 7049-7064.

[9] Duan S,Han XL,Li Y,Zhang L. Research on the expression of tight junctions on allergic rhinitis. Chinese Archives of

Otolaryngology-Head and Neck Surgery 2021; 28(05): 293-296 (in Chinese).

[10] Shi Z, Jiang W, Wang M, Wang X, Li X, Chen X, Qiao L. Inhibition of JAK/STAT pathway restrains TSLP-activated dendritic cells mediated inflammatory T helper type 2 cell response in allergic rhinitis. Mol Cell Biochem 2017; 430(1-2): 161-169.

[11] Williams TC, Jackson DJ, Maltby S, Walton RP, Ching YM, Glanville N, Singanayagam A, Brewins JJ, Clarke D, Hirsman AG, Loo SL, Wei L, Beale JE, Casolari P, Caramori G, Papi A, Belvisi M, Wark PAB, Johnston SL, Edwards MR, Bartlett NW. Rhinovirus-induced CCL17 and CCL22 in Asthma Exacerbations and Differential Regulation by STAT6. Am J Respir Cell Mol Biol 2021; 64(3): 344-356.

[12] Rossi GA, Ballarini S, Salvati P, Sacco O, Colin AA. Alarmins and innate lymphoid cells 2 activation: A common pathogenetic link connecting respiratory syncytial virus bronchiolitis and later wheezing/asthma? Pediatr Allergy Immunol 2022; 33(6): e13803.

[13] Ji T, Li H. T-helper cells and their cytokines in pathogenesis and treatment of asthma. Front Immunol 2023; 14: 1149203.

[14] Ishinaga H, Kitano M, Toda M, D'Alessandro-Gabazza CN, Gabazza EC, Shah SA, Takeuchi K. Interleukin-33 induces mucin gene expression and goblet cell hyperplasia in human nasal epithelial cells. Cytokine 2017; 90: 60-65.

[15] Zhou Y, Chen R, Kong L, Sun Y, Deng J. Neuroimmune communication in allergic rhinitis. Front Neurol 2023; 14: 1282130.

[16] Larsson O, Tengroth L, Xu Y, Uddman R, Kumlien Georén S, Cardell LO. Substance P represents a novel first-line defense mechanism in the nose. J Allergy Clin Immunol 2018; 141(1): 128-136.e123.

[17] Sui P, Wiesner DL, Xu J, Zhang Y, Lee J, Van Dyken S, Lashua A, Yu C, Klein BS, Locksley RM, Deutsch G, Sun X. Pulmonary neuroendocrine cells amplify allergic asthma responses. Science 2018; 360(6393).

[18] Hu X, Li J, Fu M, Zhao X, Wang W. The JAK/STAT signaling pathway: from bench to clinic. Signal Transduct Target Ther 2021; 6(1): 402.

[19] Xue C, Yao Q, Gu X, Shi Q, Yuan X, Chu Q, Bao Z, Lu J, Li L. Evolving cognition of the JAK-STAT signaling pathway: autoimmune disorders and cancer. Signal Transduct Target Ther 2023; 8(1): 204.

[20] Xin P, Xu X, Deng C, Liu S, Wang Y, Zhou X, Ma H, Wei D, Sun S. The role of JAK/STAT signaling pathway and its inhibitors in diseases. Int Immunopharmacol 2020; 80: 106210.

[21] Zhang S, Wu W, Gu M, Zhao Y, Wang L, Liu K, Yu Z. House dust mite induced mucosal barrier dysfunction and type 2 inflammatory responses via the MAPK/AP-1/IL-24 Signaling pathway in allergic rhinitis. Int Immunopharmacol 2025; 148: 113972.

[22] Bachus H, McLaughlin E, Lewis C, Papillion AM, Benveniste EN, Hill DD, Rosenberg AF, Ballesteros-Tato A, León B. IL-6 prevents Th2 cell polarization by promoting SOCS3-dependent suppression of IL-2 signaling. Cell Mol Immunol 2023; 20(6): 651-665.

[23] Kausar S, Gul I, Liu R, Ke XX, Dong Z, Abbas MN, Cui H. Antheraea pernyi Suppressor of Cytokine Signaling 2 Negatively Modulates the JAK/STAT Pathway to Attenuate Microbial Infection. Int J Mol Sci 2022; 23(18).

[24] Klopfenstein N, Brandt SL, Castellanos S, Gunzer M, Blackman A, Serezani CH. SOCS-1 inhibition of type I interferon restrains Staphylococcus aureus skin host defense. PLoS Pathog 2021; 17(3): e1009387.

[25] Wu CS, Zou L. The SUMO (Small Ubiquitin-like Modifier) Ligase PIAS3 Primes ATR for Checkpoint Activation. J Biol Chem 2016; 291(1): 279-290.

[26] Pike KA, Tremblay ML. Protein Tyrosine Phosphatases: Regulators of CD4 T Cells in Inflammatory Bowel Disease. Front Immunol 2018; 9: 2504.

[27] Novosad J, Krčmová I, Souček O, Drahošová M, Sedlák V, Kulířová M, Králíčková P. Subsets of Eosinophils in Asthma, a Challenge for Precise Treatment. Int J Mol Sci 2023; 24(6).

[28] Xu Z, Chu M. Advances in Immunosuppressive Agents Based on Signal Pathway. Front Pharmacol 2022; 13: 917162.

[29] Luo M, Jin T, Fang Y, Chen F, Zhu L, Bai J, Ding J. Signaling Pathways Involved in Acute Pancreatitis. J Inflamm Res 2025; 18: 2287-2303.

[30] Howell MD, Kuo FI, Smith PA. Targeting the Janus Kinase Family in Autoimmune Skin Diseases. Front Immunol 2019; 10: 2342.

[31] Zhang H, Li X, Liu YL, Liu WJ, Wang Y, Bai HT, Zhang JX, Su FY, Yuan FL, Li L, Meng GY, Zheng RX, Zhang Y. miR-148a-3p inhibits Th1 cell polarization via down-regulating IL-12/IL-12Rβ1/IL-12Rβ2/IFN-γ pathway. Chinese Journal of Pharmacology and Toxicology 2021; 35(11): 816-823 (in Chinese).

[32] Wang L, Deng Z, Sun Y, Zhao Y, Li Y, Yang M, Yuan R, Liu Y, Qian Z, Zhou F, Kang H. The Study on the Regulation of Th Cells by Mesenchymal Stem Cells Through the JAK-STAT Signaling Pathway to Protect Naturally Aged Sepsis Model Rats. Front Immunol 2022; 13: 820685.

[33] Lindén A, Dahlén B. Interleukin-17 cytokine signalling in patients with asthma. Eur Respir J 2014; 44(5): 1319-1331.

[34] Raza A, Yousaf W, Giannella R, Shata MT. Th17 cells: interactions with predisposing factors in the immunopathogenesis of inflammatory bowel disease. Expert Rev Clin Immunol 2012; 8(2): 161-168.

[35] Xu W, Shu JH, Gan Y, Tu DN. Research advances in the regulatory mechanism of immune balance between Th17 and Treg cells. China Journal of Modern Medicine 2023; 33(24): 48-54 (in Chinese).

[36] Alvarez F, Istomine R, Shourian M, Pavey N, Al-Aubodah TA, Qureshi S, Fritz JH, Piccirillo CA. The alarmins IL-1 and IL-33 differentially regulate the functional specialisation of Foxp3(+) regulatory T cells during mucosal inflammation. Mucosal Immunol 2019; 12(3): 746-760.

[37] Dikiy S, Li J, Bai L, Jiang M, Janke L, Zong X, Hao X, Hoyos B, Wang ZM, Xu B, Fan Y, Rudensky AY, Feng Y. A distal Foxp3 enhancer enables interleukin-2 dependent thymic Treg cell lineage commitment for robust immune tolerance. Immunity 2021; 54(5): 931-946.e911.

[38] Moura RA, Fonseca JE. JAK Inhibitors and Modulation of B Cell Immune Responses in Rheumatoid Arthritis. Front Med (Lausanne) 2020; 7: 607725.

[39] Saadatdoust Z, Pandurangan AK, Ananda Sadagopan SK, Mohd Esa N, Ismail A, Mustafa MR. Dietary cocoa inhibits colitis associated cancer: a crucial involvement of the IL-6/STAT3 pathway. J Nutr Biochem 2015; 26(12): 1547-1558.

[40] Ma CS, Avery DT, Chan A, Batten M, Bustamante J, Boisson-Dupuis S, Arkwright PD, Kreins AY, Averbuch D, Engelhard D, Magdorf K, Kilic SS, Minegishi Y, Nonoyama S, French MA, Choo S, Smart JM, Peake J, Wong M, Gray P, Cook MC, Fulcher DA, Casanova JL, Deenick EK, Tangye SG. Functional STAT3 deficiency compromises the generation of human T follicular helper cells. Blood 2012; 119(17): 3997-4008.

[41] Banerjee S, Biehl A, Gadina M, Hasni S, Schwartz DM. Erratum to: JAK-STAT Signaling as a Target for Inflammatory and Autoimmune Diseases: Current and Future Prospects. Drugs 2017; 77(11): 1261.

[42] Sohrabi S, Alipour S, Ghahramanipour Z, Masoumi J, Baradaran B. STAT signaling pathways in immune cells and their associated mechanisms in cancer pathogenesis. Bioimpacts 2025; 15: 30030.

[43] Yamasaki A, Saleh A, Koussih L, Muro S, Halayko AJ, Gounni AS. IL-9 induces CCL11 expression via STAT3 signalling in human airway smooth muscle cells. PLoS One 2010; 5(2): e9178.

[44] Wang HY, Huang HY, Liu XL. The relationship between CCL8 related pathways and allergic diseases. Chemistry of Life 2021; 41(10): 2119-2124 (in Chinese).

[45] Cheng L, Chen J, Fu Q, He S, Li H, Liu Z, Tan G, Tao Z, Wang D, Wen W, Xu R, Xu Y, Yang Q, Zhang C, Zhang G, Zhang R, Zhang Y, Zhou B, Zhu D, Chen L, Cui X, Deng Y, Guo Z, Huang Z, Huang Z, Li H, Li J, Li W, Li Y, Xi L, Lou H, Lu M, Ouyang Y, Shi W, Tao X, Tian H, Wang C, Wang M, Wang N, Wang X, Xie H, Yu S, Zhao R, Zheng M, Zhou H, Zhu L, Zhang L. Chinese Society of Allergy Guidelines for Diagnosis and Treatment of Allergic Rhinitis. Allergy Asthma Immunol Res 2018; 10(4): 300-353.

[46] Morales JK, Falanga YT, Depcrynski A, Fernando J, Ryan JJ. Mast cell homeostasis and the JAK-STAT pathway. Genes Immun 2010; 11(8): 599-608.

[47] Chang TM, Hsiao TC, Yang TY, Huang HC. IgE-Induced Mast Cell Activation Is Suppressed by Dihydromyricetin through the Inhibition of NF-κB Signaling Pathway. Molecules 2021; 26(13).

[48] Denson LA, Held MA, Menon RK, Frank SJ, Parlow AF, Arnold DL. Interleukin-6 inhibits hepatic growth hormone signaling via upregulation of Cis and Socs-3. Am J Physiol Gastrointest Liver Physiol 2003; 284(4): G646-654.

[49] Zhang XX, Wu GP. Advances in the structure and effect mechanism study of nasal mucosal barrier. International Journal of Otolaryngology-Head and Neck Surgery 2023; 47(02): 82-86 (in Chinese).

[50] Lin YT, Chen WC, Tsai MH, Chen JY, Chien CY, Huang SC. JAK2 Phosphorylation Signals and Their Associated Cytokines Involved in Chronic Rhinosinusitis with Nasal Polyps and Correlated with Disease Severity. Biomolecules 2021; 11(7).

[51] Song L, Zhu ZJ, Xu QR, Lu XJ, Dong JJ. Study on the protective effect of loratadine on allergic rhinitis rats based on IL-6/JAK2/STAT3 signaling pathway. Journal of Tropical Medicine 2020; 20(06): 735-740+716 (in Chinese).

[52] Xie X, Wang P, Jin M, Wang Y, Qi L, Wu C, Guo S, Li C, Zhang X, Yuan Y, Ma X, Liu F, Liu W, Liu H, Duan C, Ye P, Li X, Borish L, Zhao W, Feng X. IL-1β-induced epithelial cell and fibroblast transdifferentiation promotes neutrophil recruitment in chronic rhinosinusitis with nasal polyps. Nat Commun 2024; 15(1): 9101.

[53] Ingram JL, Antao-Menezes A, Mangum JB, Lyght O, Lee PJ, Elias JA, Bonner JC. Opposing actions of Stat1 and Stat6 on IL-13-induced up-regulation of early growth response-1 and platelet-derived growth factor ligands in pulmonary fibroblasts. J Immunol 2006; 177(6): 4141-4148.

[54] Liu S, Chen L, Shang Y. CEACAM5 exacerbates asthma by inducing ferroptosis and autophagy in airway epithelial cells through the JAK/STAT6-dependent pathway. Redox Rep 2025; 30(1): 2444755.

[55] Lu J, Zhu Y, Feng W, Pan Y, Li S, Han D, Liu L, Xie X, Wang G, Li M. Platelet-derived growth factor mediates interleukin-13-induced collagen I production in mouse airway fibroblasts. J Biosci 2014; 39(4): 693-700.

[56] Sahnoon L, Bajbouj K, Mahboub B, Hamoudi R, Hamid Q. Targeting IL-13 and IL-4 in Asthma: Therapeutic Implications on Airway Remodeling in Severe Asthma. Clin Rev Allergy Immunol 2025; 68(1): 44.

[57] Wawrzyniak P, Wawrzyniak M, Wanke K, Sokolowska M, Bendelja K, Rückert B, Globinska A, Jakiela B, Kast JI, Idzko M, Akdis M, Sanak M, Akdis CA. Regulation of bronchial epithelial barrier integrity by type 2 cytokines and histone deacetylases in asthmatic patients. J Allergy Clin Immunol 2017; 139(1): 93-103.

[58] Büttner C, Skupin A, Rieber EP. Transcriptional activation of the type I collagen genes COL1A1 and COL1A2 in fibroblasts by interleukin-4: analysis of the functional collagen promoter sequences. J Cell Physiol 2004; 198(2): 248-258.

[59] Du MZ, Shen JL, Wu Q, Hu XY, Chu DY. Inhibitory Effect of Paeoniflorin on the Collagen Production by Fibroblasts through IL-13/STAT6 Signaling Pathway. Chinese Journal of Parasitology and Parasitic Diseases 2011; 29(02): 93-98 (in Chinese).

[60] Braithwaite IE, Cai F, Tom JA, Galanter JM, Owen RP, Zhu R, Williams M, McGregor AG, Eliahu A, Durk MR, Dengler HS, Zak M, Kenny JR, Wilson ME, Beasley R, Chen H. Inhaled JAK inhibitor GDC-0214 reduces exhaled nitric oxide in patients with mild asthma: A randomized, controlled, proof-of-activity trial. J Allergy Clin Immunol 2021; 148(3): 783-789.

[61] Yan F, Li W, Zhou H, Wu Y, Ying S, Chen Z, Shen H. Interleukin-13-induced MUC5AC expression is regulated by a PI3K-NFAT3 pathway in mouse tracheal epithelial cells. Biochem Biophys Res Commun 2014; 446(1): 49-53.

[62] Zimmer J, Weitnauer M, Boutin S, Küblbeck G, Thiele S, Walker P, Lasitschka F, Lunding L, Orinska Z, Vock C, Arnold B, Wegmann M, Dalpke A. Nuclear Localization of Suppressor of Cytokine Signaling-1 Regulates Local Immunity in the Lung. Front Immunol 2016; 7: 514.

[63] Metz M, Kolkhir P, Altrichter S, Siebenhaar F, Levi-Schaffer F, Youngblood BA, Church MK, Maurer M. Mast cell silencing: A novel therapeutic approach for urticaria and other mast cell-mediated diseases. Allergy 2024; 79(1): 37-51.

[64] Chen XQ, Ma HA, Zhou LY, Yan DN, Liu SF, Wu JY. Preliminary Study on the Improvement Effects of Astragaloside IV on Allergic Rhinitis Model Mice. China Pharmacy 2021; 32(10): 1187-1195 (in Chinese).

[65] Ren M, Wang Y, Lin L, Li S, Ma Q. α-Linolenic Acid Screened by Molecular Docking Attenuates Inflammation by Regulating Th1/Th2 Imbalance in Ovalbumin-Induced Mice of Allergic Rhinitis. Molecules 2022; 27(18).

[66] Ren MY, Xiao Y, Tang MW, Wang M. Effects and Immunomodulatory Mechanisms of Chuanxiong Chatiao San on Allergic Rhinitis Model Mice. Chinese Traditional Patent Medicine 2022; 44(12): 4014-4018 (in Chinese).