

# Common Allergens and Immune Responses Associated with Allergic Rhinitis in China

Qirong Li<sup>1,2,\*</sup>, Xinyi Zhang<sup>2,\*</sup>, Qiang Feng<sup>2,\*</sup>, Hengzong Zhou<sup>2,\*</sup>, Chaoyang Ma<sup>3</sup>, Chao Lin<sup>4</sup>, Dongxu Wang<sup>2</sup>, Jianmei Yin<sup>1</sup>

<sup>1</sup>Department of Otolaryngology-Head and Neck Surgery, the First Hospital of Jilin University, Changchun, People's Republic of China; <sup>2</sup>Laboratory Animal Center, College of Animal Science, Jilin University, Changchun, People's Republic of China; <sup>3</sup>Hepatology Hospital of Jilin Province, Changchun, People's Republic of China; <sup>4</sup>School of Grain Science and Technology, Jilin Business and Technology College, Changchun, People's Republic of China

\*These authors contributed equally to this work

Correspondence: Dongxu Wang; Jianmei Yin, Email wang\_dong\_xu@jlu.edu.cn; yinjianmei1985@jlu.edu.cn

**Abstract:** Allergic rhinitis (AR) is a chronic allergic disease of the upper respiratory system that affects approximately 10–40% of the global population. Due to the large number of plant pollen allergens with obvious seasonal variations, AR is common in China. AR is primarily caused by the abnormal regulation of the immune system. Its pathophysiological mechanism involves a series of immune cells and immune mediators, including cytokines. The present review summarizes the common allergens in China and the complex pathophysiological mechanism of AR. Additionally, host allergen contact, signal transduction, immune cell activation, cytokine release, and a series of inflammatory reactions are described according to their sequence of occurrence.

**Keywords:** allergic rhinitis, host immune response, immunoglobulin E, histamine, inflammation

## Introduction

Allergic rhinitis (AR), a chronic upper respiratory tract disease, is one of the most common allergic diseases resulting from exposure to specific allergens.<sup>1,2</sup> The pathophysiology of AR involves IgE-mediated inflammation of the nasal mucosa.<sup>3</sup> In recent years, the incidence and prevalence of AR in China have increased, negatively impacting the economy and people's quality of life.<sup>4–6</sup> AR, also known as hay fever, is characterized by a blocked nose, runny nose, itching, sneezing, and postnasal drip syndrome (PND), which involves eye itching, redness, and tearing.<sup>3,7</sup> Dust mites, animal furs, and mold spores are the primary triggers for perennial allergic reactions,<sup>8</sup> whereas pollen and weed powder are the primary causes of seasonal allergies.<sup>9</sup> AR occurs when its corresponding allergen activates mast cells or basophils to release various immune mediators, including cytokines that mediate T helper 2 (Th2) cell maturation and mucosal inflammation.<sup>10–12</sup>

The pathophysiological mechanism of AR is complex and involves the activation of effector cells and the release of immune mediators, such as leukotrienes (LTs), prostaglandins (PGD), and platelet-activating factors.<sup>13</sup> The nasal mucosa is the primary site of allergen exposure, and inflammatory reactions lead to AR symptom development.<sup>14</sup> The symptoms are predominantly triggered by the interactions between specific mast cells, IgE antibodies, and airborne allergens.<sup>15</sup> Allergen exposure induces inflammatory mediator release, causing the specific symptoms and the inflammatory morphology seen in AR.<sup>15,16</sup>

This review highlights the common allergens responsible for AR in China. As the pathogenesis of AR is caused by an individual's immune response, this response and its underlying mechanisms are also comprehensively reviewed. It also summarizes the immune regulatory mechanisms that occur in host cells following allergen exposure.

## AR Allergens in China

### Regional Differences of Rhinitis Allergens in China

The prevalence of allergic diseases is closely related to various environmental allergens and direct contact, inhalation, or ingestion exposure levels.<sup>17,18</sup> China is a large country with a vast geography and diverse climates and lifestyles, which leads

to significant regional differences in AR distribution.<sup>19</sup> The most common pattern of sensitization in Southern and Eastern China is house dust mites sensitization, while the prevalence of low pollen sensitization in Western and Northern China is extremely high.<sup>20</sup> In China, over 38,000 adults have self-reported AR, and its prevalence varies widely across regions, ranging from 8.7% in Beijing in North China to 24.1% in Urumqi in Northwest China.<sup>21</sup> A cross-sectional survey was conducted in eight cities in China and revealed significant geographical differences in the prevalence of AR among Chinese children.<sup>22</sup> Therefore, identifying the specific allergens prevalent in particular regions that affect populations is important for the early diagnosis, treatment, and prevention of respiratory allergic diseases, including AR.<sup>18</sup> The incidence of allergic diseases has increased in China, particularly rhinitis caused by house dust mites and weed pollen (Table 1). Several environmental factors, such as cold air, fog, and tobacco smoke, play important roles in the etiology of AR and other respiratory allergic diseases.<sup>23,24</sup> However, the sensitivity to these allergens differs among populations and different regions of China. In one study, the three most common self-reported allergens among individuals with AR in Northern China were *Blattella germanica* (16.6%), *Dermatophagoides farinae* (14.6%), and *Dermatophagoides pteronyssinus* (13.9%).<sup>25</sup> A multicenter study reported the most common allergens in Eastern China to be *D. farinae* (74.9%) and *D. pteronyssinus* (74.3%), while in the West, they were mugwort (60.0%) and marguerite (56.6%).<sup>26</sup> The most common allergens in South China are house dust mites (28.1%), cockroaches (24.3%), shrimp (19.2%), crabs (15.5%), and egg whites (9.9%).<sup>27</sup> An analysis of allergen-specific IgE in serum samples from individuals based in Guangzhou, Southern China, revealed that *D. pteronyssinus* (85.0%) had the highest proportion of specific IgE, followed by *D. farinae* (83.5%), egg whites (19.3%), milk (14.6%), German cockroaches (14.2%) and ox-eye daisy (12.6%).<sup>28</sup>

China is a vast territory that spans approximately 50 latitudes. Therefore, a great diversity in vegetation is seen across the country.<sup>29</sup> The main difference in allergens between different regions lies in the species and richness of the sensitized pollen present. Understanding the aerobiological data regarding the atmospheric pollen linked to micrometeorological indices can help determine the correlation between air pollen concentration and AR, thereby establishing the appropriate etiological diagnosis and treatment plan.<sup>30,31</sup> In a study that was conducted over 2 years, the main air allergens in Guangxi were found to be *Artemisia* spores, providing basic information on seasonal allergies in Southern China and Southeast Asia.<sup>32</sup> During spring in Wuhan, airborne pollen primarily comes from *Artemisia*, willow, Acanthaceae, Lauraceae, and pine, while in autumn, it is primarily derived from *Artemisia* and Cucurbitaceae.<sup>33</sup> In Zhongshan City in Southern China, Gramineae is associated with the highest annual pollen levels, with other common pollen contributors being pine, alfalfa, water chestnut, and Casuarinaceae, which have peak seasons in February and March I.<sup>34</sup>

Northern China is dry and windy, with abundant pollen in the air during the spring and autumn. Studies have examined the aerobiological data similarity matrices of eight selected pollen monitoring stations at 45–50°N for four different air allergens: birch (*Betula platyphylla*), grass (Gramineae), *Artemisia* (*Artemisia*), and ragweed (*Ambrosia*).<sup>35</sup> In Northern China, trees and weeds produce the main pollen types and are responsible for the two main allergic pollen seasons.<sup>36</sup> One season occurs in spring and is caused by tree pollen, including *Fraxinus mandshurica*, *Betula platyphylla*, and poplar trees. The other occurs in late summer and autumn and is caused by weed pollens such as *Artemisia*, amaranth, gourd, tall bran, and *Chenopodium*.<sup>36–38</sup>

**Table 1** Partial Data for Rhinitis Patients in China

Types of Allergens in AR Patients in China	Proportion of Patients	Symptoms of Onset	References
Dust mites	26.2%	Nasal congestion, rhinorrheas, sneezing	[18,53–56]
Tree pollen (catkins)	29.9%	Nasal congestion, itchy nose, sneezing	[53,54,56]
Summer and autumn weed pollen ( <i>Ambrosia</i> , <i>Artemisia</i> ),	35.2%	Nasal congestion, rhinorrhea, itchy nose, sneezing, itchy/red eyes	[44,53,55,56]
Fungi	2.7%	Nasal congestion, rhinorrhea, itchy nose	[18,44,53,56]
Food (eggs, soybeans, peanuts, milk, seafood, fruits)	3.5%	Nasal congestion, rhinorrhea, itchy nose	[18,53–56]
Other (formaldehyde and other decoration materials, animal fur, cockroaches)	2.5%	Nasal congestion, rhinorrhea, itchy nose, sneezing, itchy/red eyes	[18,53–55,56]

In Western Inner Mongolia, the typical peak pollen seasons occur in summer and autumn and involves primarily weeds and grass pollen, while in the east, there are two peak seasons in spring (involving mainly tree pollen) and summer and autumn (involving mainly weeds and grass pollen).<sup>39</sup> In Qingdao, China, children with AR are highly sensitive to ragweed and pollen.<sup>18</sup> Compared with South China, the main pollen allergens in North China are birch, *Artemisia*, poplar, and ragweed.

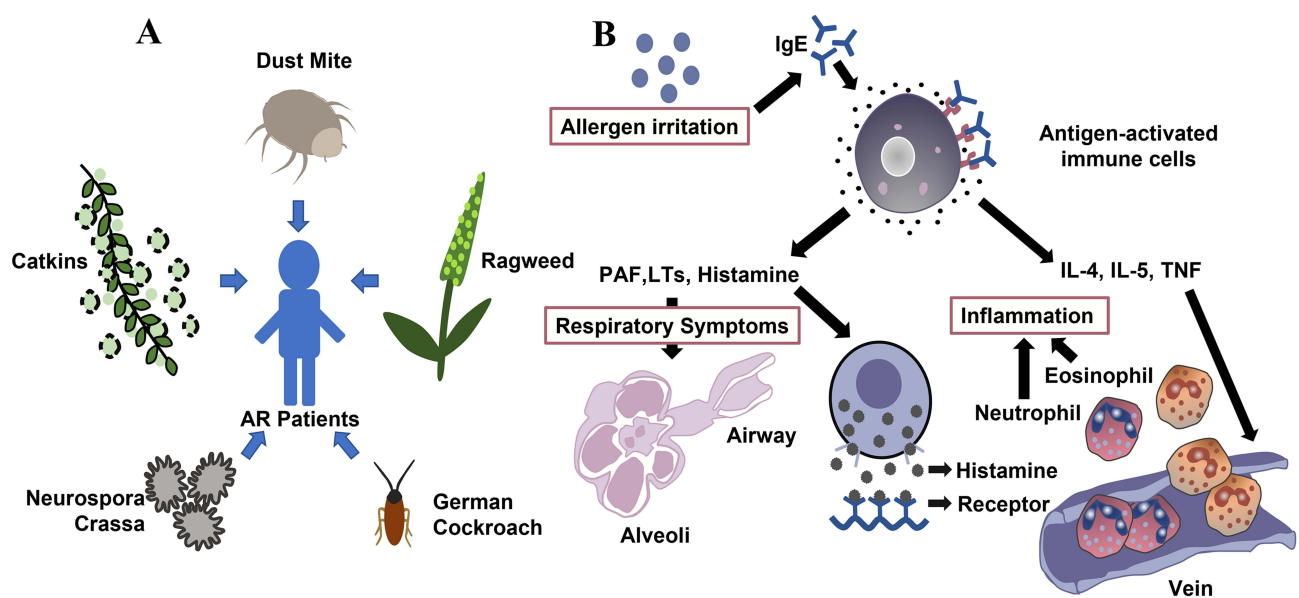
The prevalence of AR is higher in developed countries and currently affects 10–40% of adults and 2–25% of children worldwide. With the rapid economic development, the prevalence of AR has also increased in developing countries in recent decades.<sup>40</sup> Persistent AR prevalence is higher in Northern Europe and northern China compared to southern regions, while Western Europe has a higher prevalence of AR than Eastern Europe.<sup>41</sup> Different allergens exist in different regions, for example birch and grass pollen are the most common allergens in Denmark, while Japanese cedar pollen is the most common in Japan.<sup>42</sup>

Since AR is a chronic disease caused by a specific allergen, it is important for patients to try to identify allergens and environmental factors that may trigger AR. Avoiding or minimizing exposure to disease-causing allergens should be the first management step for AR. Therefore, exploring the differences of allergens in China can help to identify and avoid allergens in specific regions and prevent AR.

## Rhinitis Allergens

Dust mites, summer and autumn pollen, weed pollen, *Neurospora crassa*, and *Blattella germanica* are common allergens that cause AR in China (Figure 1A).<sup>43</sup> Dust mites mainly reside in mattresses, clothing, blankets, carpets, plush toys, and pets. Sensitization to house dust mites (HDM) is highest in South China, while the three most common seasonal airborne allergens in Northwest China are mugwort, ragweed, and dandelion pollen.<sup>44</sup> *Neurospora crassa* is a saprophyte that exists vegetatively as an incompletely septate syncytium.<sup>45</sup> *Blattella germanica* normally resides in human habitats, in warm, moist, and dark hidden places.<sup>46</sup> As *B. germanica* contains several symbiotic microorganisms,<sup>47</sup> insect excretions, and an exfoliated epidermis, it also carries allergens that may be transmitted to humans and result in AR.

Sensitivity to common allergens among hospitalized patients in different geographical areas and who belong to different age groups varies considerably. Many factors, such as climate and plants, affect AR incidence.<sup>48</sup> Certain foods, such as mussels, shrimp, carp, eggs, and milk, increase AR incidence.<sup>18</sup> Some drugs, such as aspirin and nonsteroidal



**Figure 1** Common allergens and pathogenesis of AR. (A). The main allergens causing AR in northern China (dust mites, summer and autumn pollen, weed pollen, *Neurospora crassa*, and *Blattella germanica*). (B). Immune response to allergens. Specific IgE binds to the high-affinity IgE Fc receptor on the surface of mast cells and induces the release of PAF, LTs, histamine, and other inflammatory mediators. Histamine binds its receptor, whereas IL-4, IL-5, TNF, and other cytokines stimulate eosinophils, and Neutrophils stimulate respiratory tract contraction, causing AR.

anti-inflammatory drugs, can also cause AR,<sup>49</sup> while physical factors, such as morning hours, winter, and cold air, are common AR triggers.<sup>24</sup>

Direct contact with specific allergens is the first step in AR occurrence. This causes the immune system to be sensitized and activated, and immune response signals are subsequently transmitted between cells. Allergen-specific IgE binds to high-affinity IgE Fc receptors on the surface of mast cells, or the allergen directly binds to the sensitized target cell's IgE,<sup>50</sup> thereby inducing the secretion of histamine, kininogenases, LTs, cytokines, and other mediators.<sup>14</sup> This causes the airway smooth muscles and telangiectasia to contract, increasing permeability and leading to excessive glandular secretion.<sup>51</sup> This process culminates in sneezing, runny nose, nasal itching, congestion, and other symptoms.<sup>52</sup> AR is an allergic disease caused by abnormal immune system regulation. As allergic reactions primarily involve immune cells, signaling molecules, and mediators, research on AR pathogenesis has focused on host immune responses to allergens. The following sections summarize the existing findings on the immune response to allergens.

## Host Immune Responses to Allergens

### Antigen Presentation and Sensitization

Antigen-presenting cells (APCs) are immune cells that uptake, process, and present antigens to the T and B lymphocytes.<sup>57–59</sup> Upon binding to antigens, water-soluble proteins are engulfed and processed by APCs (dendritic cells [DCs] and macrophages) and then processed by naïve CD4+ T lymphocytes (Th0) in the lymph nodes via major histocompatibility complex II molecules (MHCII) expressed on APC surfaces.<sup>13,60</sup> The activation of CD4+ lymphocytes involves direct contact with MHCII molecules on APCs via specific T cell surface receptors and costimulatory receptors CD80 and CD86 on APCs, which connect to the CD28 receptors on T cells.<sup>60</sup> T cells from patients with AR are primarily transformed into allergen-specific Th2 cells.<sup>61</sup> These cells release cytokines, including interleukin (IL)-4, IL-5, and IL-13, to initiate the inflammatory immune response.<sup>13</sup> IL-4 stimulates the differentiation of specific B cells into antibody-producing plasma cells. IL-4 and IL-13 send the first signal from T cells.<sup>62</sup> IL-4, IL-5, and IL-13 interact with B cell surface receptors, inducing  $\epsilon$  germline transcription to produce immunoglobulins.<sup>63</sup> The second signal is produced by the costimulatory interaction between CD154 (CD40 ligand) on the surface of activated T cells and CD40 molecules on the surface of B cells; this interaction activates B cells and stimulates class-switch recombination, inducing IgE production.<sup>63,64</sup> This, in turn, stimulates cytokine secretion and triggers the inflammatory response.

Although IgE antibodies only account for a small proportion of the entire antibody family,<sup>13</sup> they induce strong inflammation by binding to specific cell surface receptors and crosslinking with antigens. Allergen-specific IgE antibodies bind strongly to high-affinity receptors (Fc $\epsilon$ RI) expressed on mast cells and basophils.<sup>65</sup> Upon subsequent exposure, IgE antibodies bound to Fc $\epsilon$ RI receptors recognize specific allergens,<sup>66,67</sup> resulting in the rapid degranulation of mast cells and basic granulocyte vesicles and the release of histamine, platelet-activating factor, and tryptase.<sup>13,68</sup> Activated mast cells release membrane-stored arachidonic acid and participate in the production of cysteinyl LTs (LTC4, LTD4, and LTE4) and prostaglandins (mainly PGD2).<sup>69</sup> These reactions induce the contraction of the smooth muscle in the respiratory tract and vasodilation and enhance permeability and excessive glandular secretion (Figure 1B).

## Prophase Immune Response

### Nasal Mucosal Receptor Signal Transduction

The surface of the nasal mucosa is covered with receptors and is innervated by a group of sensory nerve fibers, including A,  $\delta$ , and unmyelinated C fibers, and sympathetic and parasympathetic nerves.<sup>14,70</sup> When the temperature difference is high during the turn of seasons in China, catkins and ragweed pollen allergens are blown into the air. For patients with rhinitis that occurs following exposure to specific allergens, direct contact with the respective antigens activates the immune system and increases its sensitivity. In this process, the specific IgE binds to high-affinity IgE Fc receptors on mast cell surfaces.<sup>50,71</sup> The Fc $\epsilon$ RI receptor is a member of the polysubunit immunoreactive receptor (multisubunit immune response receptor [MIRR]) family.<sup>72</sup> Fc $\epsilon$ RI is mainly involved in type I hypersensitivity and mediates mast cell degranulation and the release of inflammatory mediators. Fc $\epsilon$ RI aggregation and crosslinking activate the Lyn PTK and src families; activated Lyn phosphorylates the  $\beta$ -chain,  $\gamma$ -chain, and adjacent tyrosine proteins. The latter process, in turn,

activates Lyn and Syk.<sup>72</sup> The activated (ie, depolarized) sensory nerves transmit signals to the central nervous system, resulting in motor reflexes, such as sneezing, watery nose, nasal itching, and nasal congestion.

### Histamine Release

Histamine is a biogenic amine secreted by mast cells during allergic reactions.<sup>73</sup> It has strong and diverse biological functions, including in AR pathophysiology.<sup>74</sup> Lung tissue contains four histamine receptors: H1, H2, H3, and H4.<sup>75–78</sup> The pulmonary artery has a biphasic response to histamine due to H1 receptor-mediated vasoconstriction and H2 receptor-mediated vasodilation.<sup>79</sup> Histamine causes plasma leakage from the microcapillary venules by affecting the bronchial microcirculatory system. Additionally, histamine accelerates chloride ion transport in the respiratory epithelial cells, which is closely related to the water transfer process within the respiratory tract.<sup>80</sup> When an inhaled allergen comes into contact with the bronchi of patients with northern rhinitis, it triggers the release of histamine to the surface of the respiratory tract, which can then be identified in the bronchoalveolar lavage fluid (BALF).<sup>79</sup> The mast cells release other inflammatory mediators, such as 9  $\alpha$ , 11  $\beta$ -prostaglandins F2- $\alpha$  and trypsin.

The early allergen response can be attributed to the allergen-induced degranulation of nasal mast cells. This phenomenon causes IgE-mediated histamine release into the nasal mucosa<sup>81</sup> and upregulates proinflammatory cytokine expression, mediating the early immune response,<sup>70</sup> including allergic reactions and inflammation.<sup>82–85</sup> The release of histamine from mast cells promotes H1 receptor activation.<sup>86,87</sup> The activated sensory nerves transmit the signals to the central nervous system, which causes motor reflexes, such as itching and sneezing.<sup>88,89</sup> Histamine stimulates watery secretions in the mucosa, leading to rhinorrhea and the expression of H1 and H2 receptors in the nasal vessels, increasing vascular permeability and vasodilation, which causes nasal mucosal congestion.<sup>90–92</sup>

Sensory nerve stimulation induces the release of acetylcholine from the parasympathetic nerves. Cytokines are increased on both sides of the central reflex, which upregulates nasal mucus secretion. H1R binds to the G protein GQ/11, activating phospholipase C and stimulating the production of 5-inositol triphosphate; this induces calcium and diacylglycerol mobilization and activates protein kinase C (PKC).<sup>93,94</sup> PKC activates the transcription factor NF-kappa B, which enhances the transcription of proinflammatory genes, while calcium promotes nasal vasodilation. These processes augment the pericellular permeability and the antigen capture and processing ability of APCs.<sup>95,96</sup> The histamine H2 receptor causes nasal congestion by binding to the GS protein. Hypo 2R activates adenylyl cyclase (AC) by binding to the GS protein. In turn, AC stimulates cyclic adenosine monophosphate (cAMP) and induces the secretion of the cAMP response element-binding protein.<sup>97–99</sup> CAMP-dependent protein kinase signaling inhibits LT synthesis in neutrophils.<sup>100</sup> The histamine H3 receptor inhibits the release of substance P from nasal nociceptive sensory nerves<sup>101–103</sup> and promotes the IgE-mediated activation of mast cell degranulation.<sup>104</sup> Numerous antihistamine drugs, such as loratadine, and methods are currently available to treat AR. Effective AR prevention and treatment strongly relies on the regulation of histamine release.

## Late Immune Response

### Primary Effector Cells Release Cytokines and Chemokines

Mast cells are the primary effector cells in the early allergen response. Mast cells release cytokines and attract eosinophils, Th2 cells, and neutrophils to the nasal mucosa.<sup>63</sup> The late response in AR involves the release of newly secreted cytokines, such as LTs, and the recruitment of numerous effector cells from the lymphoid tissue and general circulation.<sup>57</sup> These responses sustain inflammation and prolong allergic reactions.<sup>57,105</sup> Although nasal congestion and sneezing can last for a significant period, persistent nasal congestion indicates late-stage allergic reactions.<sup>16</sup>

Mast cells release cytokines, such as IL-4, IL-13, and tumor necrosis factor- $\alpha$ . In turn, the cytokines activate the endothelial cells and upregulate the expression of adhesion molecules, such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, inducing the migration of eosinophils, T cells, basophils, and neutrophils.<sup>105–107</sup> IL-5 participates in the early activation, terminal differentiation, growth, and survival of eosinophils and inflammation. In AR, IL-5 signal transduction involves JAK-STAT-p38MAPK-NFkB activation, extracellular matrix remodeling, epithelial-mesenchymal transition, and immune response mediation. Allergens increase the expression of IL-5 receptor  $\alpha$  on the eosinophil surfaces, which leads to increased IL-5 levels.<sup>108</sup> It transmits signals via the IL-5 receptor  $\alpha$ -chain



and  $\beta$ -chain complexes.<sup>109</sup> IL-18 participates in the immune response and plays a vital role in the inflammatory pathway, being involved in the production, transformation, and maturation of pathogenic eosinophils (CD101+ and CD274+). In a previous study, mice models showed that IL-18 promotes ovalbumin immunity and the migration of eosinophils to the respiratory tract following ragweed pollen exposure.<sup>110</sup> Additionally, IL-18 stimulates human invariant natural killer T cells and endothelial cells in vitro and induces the eosinophil-active cytokines IL-5 and IL-13.<sup>110</sup> The mediators released by mast cells, such as LTs, prostaglandins, and platelet-activating factors, lead to the observed reactions and immune chemotaxis,<sup>13</sup> which further helps maintain inflammation. After the release of histamine, various cytokines and chemokines released by different cell types interact with each other and mediate AR pathogenesis.

## Inflammatory Reaction

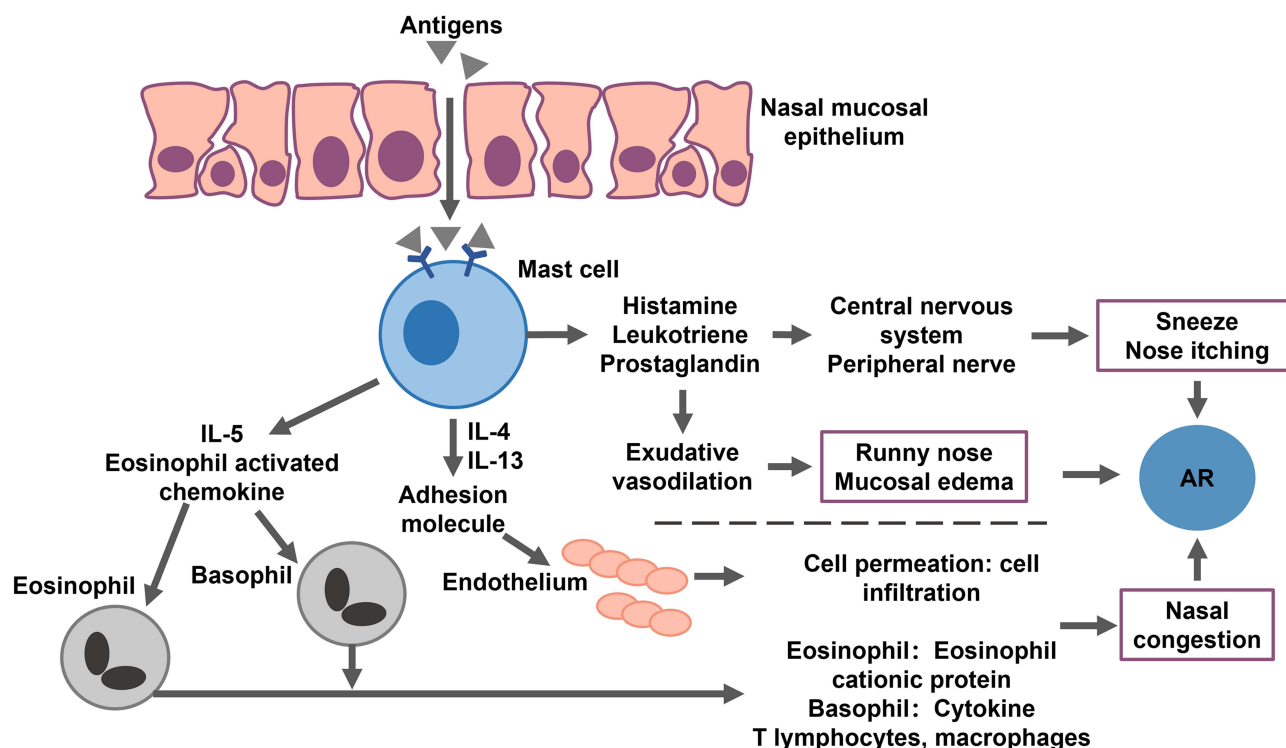
Eosinophils and neutrophils migrate to the respiratory tract of patients with AR, maintaining the inflammatory state and prolonging its related reactions by releasing corresponding cytokines and inflammatory mediators.<sup>111–113</sup> A recent nasal cytological study on 468 patients with AR indicated that neutrophils mediated major inflammatory cell responses in 14.32% of patients, whereas a mixture of eosinophils and neutrophils was observed in 23.93% of patients.<sup>114</sup> Late mucosal inflammation in patients with HDM-specific AR activates neutrophil circulation and increases neutrophil migration into the nasal mucosa.<sup>112</sup> T cells play a major role in allergic respiratory inflammation. Th1 cell differentiation from CD<sub>4</sub> T cells (TH0) is mediated by IL-12 and interferon- $\gamma$ . The number of Th1 cells and the level of Th1-derived interferon- $\gamma$  are relatively lower in the nasal lavage fluid of patients with AR than in individuals without AR.<sup>115</sup> Activated T cells promote allergic inflammation by releasing IL-5. Eosinophils are granulated inflammatory cells involved in the innate immune system which possess multiple inflammatory functions.<sup>116</sup> In allergic inflammation, these cells promote Th2 polarization by releasing IL-4, IL-25, and indole-2,3 dioxygenase. Eosinophils promote B cell proliferation and antibody induction and stimulate the secretion of several chemokines, including CCL17/CCL22, which in turn recruits Th2 cells to interact with DCs.<sup>117,118</sup> In pollen-sensitized AR patients, nasal mucosal eosinophils increase within a few days of an allergen challenge.<sup>119</sup> Immune cells mediate allergic inflammatory reactions in the respiratory tract by inducing the release of the corresponding cytokines.

Inflammation persists in patients with rhinitis, during which activated eosinophils flow into the nasal mucosa. Nasal epithelium injury exposes the nerve fibers, and overactivity in the nasal cavity triggers AR reactions. Epithelial damage is caused by the toxic effect of superoxide anions, the production of hydrogen peroxide, and the release of granule products, such as eosinophil cationic proteins, eosinophil-derived neurotoxins, and the basic protein released by eosinophils.<sup>120</sup> Eosinophils secrete IL-5, which promotes the activation and survival of eosinophils in an autocrine manner.<sup>121</sup> Additionally, T cells and mast cells promote the survival of eosinophils in the nasal mucosa by releasing granulocyte-macrophage colony-stimulating factor and IL-5.<sup>122,123</sup> These proinflammatory molecules are chemoattractants that enhance the Th2 response and participate in the recruitment of eosinophils, basophils, and T cells to the nasal mucosa (Figure 2). Cytokines and other mediators induce immune cells to continuously increase and maintain the number of proinflammatory molecules in the nasal mucosa, thereby sustaining the inflammatory response and mediating AR pathogenesis.

Understanding the mechanisms that trigger AR is crucial for the treatment of AR. At present, the identification of novel biomarkers of AR phenotype or endotype patients is an important research direction, which can be used to predict the therapeutic effect and develop treatment strategies. Further elucidating the novel molecular mechanisms involved in the allergen specific reaction in the nasal mucosa, as well as the transformation and integration of biochemical methods such as genomics in the treatment of AR are also relatively frontier research areas.

## Conclusions

AR is one of the common allergic diseases associated with the immune response and is mediated by IgE. AR is closely related to host immunity. Dominant allergens vary across the different vegetation environments in China. Compared with traditional allergens, AR caused by specific allergens places a higher burden on the immune system. Upon exposure, the allergens are engulfed, processed, and presented by APCs to the T cells. The T cells then differentiate and proliferate into



**Figure 2** Allergens trigger the body's AR immune response process.

Th2 cells, which then secrete cytokines and induce IgE on B cells and stimulate B cell differentiation into specific antibody-producing plasma cells. The IgE secreted by the plasma cells binds to the receptor on mast cell surfaces. Degranulated mast cells secrete more chemical mediators, including histamine, which induce AR. Understanding the China-specific allergens of AR and the host regulatory mechanisms that cause AR are important for the development of therapeutic methods for AR.

## Data Sharing Statement

The data presented in this study are available in the article.

## Acknowledgments

Appreciate all participants for their contributions.

## Author Contributions

Qirong Li, Xinyi Zhang and Dongxu Wang wrote the manuscript. Qirong Li, Xinyi Zhang, Qiang Feng, Hengzong Zhou, Chaoyang Ma, Chao Lin, Dongxu Wang, Jianmei Yin searched PubMed and Web of Science for citations and prepared figures. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This work was supported by the Jilin Province University Key Laboratory Scientific Research Program under Grant [2019] No. 004, the Jilin Education Department Program under Grant JJKH20230259KJ, the Jilin Province Development and Reform Commission Program under Grant 2023C028-6, and the Jilin Scientific and Technological Development Program under Grant 20210101010JC and 20220505033ZP.

## Disclosure

The authors report no conflicts of interest in this work.

## References

- Tohidinik HR, Mallah N, Takkouche B. History of allergic rhinitis and risk of asthma; a systematic review and meta-analysis. *World Allergy Organ J.* 2019;12(10):100069. doi:10.1016/j.waojou.2019.100069
- Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy.* 2008;63(Suppl 86):8–160. doi:10.1111/j.1398-9995.2007.01620.x
- Rahim NA, Jantan I, Said MM, Jalil J, Abd Razak AF, Husain K. Anti-allergic rhinitis effects of medicinal plants and their bioactive metabolites via suppression of the immune system: a mechanistic review. *Front Pharmacol.* 2021;12:660083. doi:10.3389/fphar.2021.660083
- Wang XD, Zheng M, Lou HF, et al. An increased prevalence of self-reported allergic rhinitis in major Chinese cities from 2005 to 2011. *Allergy.* 2016;71(8):1170–1180. doi:10.1111/all.12874
- Meltzer EO. Allergic rhinitis: burden of illness, quality of life, comorbidities, and control. *Immunol Allergy Clin North Am.* 2016;36(2):235–248. doi:10.1016/j.iac.2015.12.002
- Leynaert B, Neukirch C, Liard R, Bousquet J, Neukirch F. Quality of life in allergic rhinitis and asthma. A population-based study of young adults. *Am J Respir Crit Care Med.* 2000;162(4 Pt 1):1391–1396. doi:10.1164/ajrccm.162.4.9912033
- Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol.* 2001;108(1 Suppl):S2–S8. doi:10.1067/mai.2001.115569
- Pomes A, Chapman MD, Wunschmann S. Indoor allergens and allergic respiratory disease. *Curr Allergy Asthma Rep.* 2016;16(6):43. doi:10.1007/s11882-016-0622-9
- Wakamiya S, Matsune S, Okubo K, Aramaki E. Causal relationships among pollen counts, tweet numbers, and patient numbers for seasonal allergic rhinitis surveillance: retrospective analysis. *J Med Internet Res.* 2019;21(2):10450.
- Wheatley LM, Togias A, Solomon CG. Clinical practice. Allergic rhinitis. *N Engl J Med.* 2015;372(5):456–463. doi:10.1056/NEJMcpl412282
- Barnes PJ. Pathophysiology of allergic inflammation. *Immunol Rev.* 2011;242(1):31–50. doi:10.1111/j.1600-065X.2011.01020.x
- Georas SN, Guo J, De Fanis U, Casolaro V. T-helper cell type-2 regulation in allergic disease. *Eur Respir J.* 2005;26(6):1119–1137. doi:10.1183/09031936.05.00006005
- Bernstein DI, Schwartz G, Bernstein JA. Allergic Rhinitis: mechanisms and Treatment. *Immunol Allergy Clin North Am.* 2016;36(2):261–278. doi:10.1016/j.iac.2015.12.004
- Watts AM, Cripps AW, West NP, Cox AJ. Modulation of allergic inflammation in the nasal mucosa of allergic rhinitis sufferers with topical pharmaceutical agents. *Front Pharmacol.* 2019;10:294. doi:10.3389/fphar.2019.00294
- Galli SJ, Tsai M. IgE and mast cells in allergic disease. *Nat Med.* 2012;18(5):693–704. doi:10.1038/nm.2755
- Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol.* 2001;108(5 Suppl):S147–S334. doi:10.1067/mai.2001.118891
- Sun BQ, Chen DH, Zheng PY, et al. Allergy-related evidences in relation to serum IgE: data from the China state key laboratory of respiratory disease, 2008–2013. *Biomed Environ Sci.* 2014;27(7):495–505. doi:10.3967/bes2014.081
- Lin H, Lin R, Li N. Sensitization rates for various allergens in children with allergic rhinitis in Qingdao, China. *Int J Environ Res Public Health.* 2015;12(9):10984–10994. doi:10.3390/ijerph120910984
- Luo WT, Wang DD, Zhang T, et al. Prevalence patterns of allergen sensitization by region, gender, age, and season among patients with allergic symptoms in Mainland China: a Four-year Multicenter Study. *Allergy.* 2021;76(2):589–593. doi:10.1111/all.14597
- Hou XQ, Luo WT, Wu LT, et al. Associations of Four sensitization patterns revealed by Latent Class Analysis with Clinical symptoms: a multi-center study of China. *Eclinicalmedicine.* 2022;46. doi:10.1016/j.eclinm.2022.101349
- Zhang L, Han D, Huang D, et al. Prevalence of self-reported allergic rhinitis in eleven major cities in China. *Int Arch Allergy Immunol.* 2009;149(1):47–57. doi:10.1159/000176306
- Li F, Zhou Y, Li S, et al. Prevalence and risk factors of childhood allergic diseases in eight metropolitan cities in China: a multicenter study. *BMC Public Health.* 2011;11:437. doi:10.1186/1471-2458-11-437
- Feleszko W, Ruszczyński M, Jaworska J, Strzelak A, Zalewski BM, Kulus M. Environmental tobacco smoke exposure and risk of allergic sensitisation in children: a systematic review and meta-analysis. *Arch Dis Child.* 2014;99(11):985–992. doi:10.1136/archdischild-2013-305444
- Li CW, Chen DD, Zhong JT, et al. Epidemiological characterization and risk factors of allergic rhinitis in the general population in Guangzhou City in China. *PLoS One.* 2014;9(12):e114950. doi:10.1371/journal.pone.0114950
- Huang Y, Zhang Y, Zhang L. Prevalence of allergic and nonallergic rhinitis in a rural area of northern China based on sensitization to specific aeroallergens. *Allergy Asthma Clin Immunol.* 2018;14:77. doi:10.1186/s13223-018-0299-9
- Wu L, Luo W, Hu H, et al. A multicenter study assessing risk factors and aeroallergens sensitization characteristics in children with self-reported allergic rhinitis in China. *J Asthma Allergy.* 2021;14:1453–1462. doi:10.2147/jaa.S342495
- Luo WT, Hu HS, Tang WB, et al. Allergen sensitization pattern of allergic adults and children in southern China: a survey based on real life data. *Allergy Asthma Clin Immunol.* 2019;15. doi:10.1186/s13223-019-0357-y
- Liao CX, Huang DM, Hu HS, et al. 广东地区儿童呼吸过敏性疾病患者过敏原特异性IgE抗体检测的研究 [Analysis of serum allergen-specific IgE in children with respiratory allergic disease in Guangdong]. *Zhonghua Yu Fang Yi Xue Za Zhi.* 2021;55(5):613–619. Chinese. doi:10.3760/cma.j.cn112150-20201217-01467
- Cheng YY, Ruan B. Species and distribution of airborne pollen plants in major cities of China. *Chin J Allergy Clin Immunol.* 2015;2015:136–141.
- Pfaar O, Karatzas K, Bastl K, et al. Pollen season is reflected on symptom load for grass and birch pollen-induced allergic rhinitis in different geographic areas-an EAACI Task Force Report. *Allergy.* 2020;75(5):1099–1106. doi:10.1111/all.14111
- Geller-Bernstein C, Portnoy JM. The clinical utility of pollen counts. *Clin Rev Allergy Immunol.* 2019;57(3):340–349. doi:10.1007/s12016-018-8698-8



32. Chen K, Liao YF, Zhang JT. The major aeroallergens in Guangxi, China. *Clin Allergy*. 1988;18(6):589–596. doi:10.1111/j.1365-2222.1988.tb02910.x
33. Wang Y, Gao Z, Lv H, Xu Y. Online public attention toward allergic rhinitis in Wuhan, China: infodemiology study using Baidu index and meteorological data. *Front Public Health*. 2022;10:971525. doi:10.3389/fpubh.2022.971525
34. Wang Y, Zhan Z. Airborne pollens in Zhongshan city. *Chin J Allergy Clin Immunol*. 2012;6:261–265.
35. Bastl K, Bastl M, Bergmann KC, Berger U. How to do a clinical trial? Recommendations from the aerobiological point of view. *World Allergy Organ J*. 2019;12(4):100020. doi:10.1016/j.waojou.2019.100020
36. Xu Y, Guan K, Sha L, et al. Sensitization Profiles of Timothy Grass Pollen in Northern China. *J Asthma Allergy*. 2021;14:1431–1439. doi:10.2147/jaa.S334183
37. Ouyang YH, Zhang DS, Fan EZ, Li Y, Zhang L. 夏秋季花粉症症状与花粉播散的相关性分析 [Correlation between symptoms of pollen allergic rhinitis and pollen grain spreading in summer and autumn]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2012;47(8):623–627. Chinese.
38. Hu WN, Zhu L, Xie LF, et al. 北京市三年内每日花粉浓度与变应性鼻炎患者就诊比例的关联分析 [Correlation between the visiting rate of patients with allergic rhinitis and airborne pollen concentrations in Beijing in recent 3 years]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2017;52(1):31–36. Chinese. doi:10.3760/cma.j.issn.1673-0860.2017.01.006
39. Wang XY, Ma TT, Wang XY, et al. Prevalence of pollen-induced allergic rhinitis with high pollen exposure in grasslands of northern China. *Allergy*. 2018;73(6):1232–1243. doi:10.1111/all.13388
40. Zhang Y, Zhang L. Increasing prevalence of allergic rhinitis in China. *Allergy Asthma Immun*. 2019;11(2):156–169. doi:10.4168/aair.2019.11.2.156
41. Wise SK, Damask C, Roland LT, et al. International consensus statement on allergy and rhinology: allergic rhinitis-2023. *Int Forum Allergy Rh*. 2023;13(4):293–859. doi:10.1002/alr.23090
42. Meng YF, Wang CS, Zhang L. Advances and novel developments in allergic rhinitis. *Allergy*. 2020;75(12):3069–3076. doi:10.1111/all.14586
43. Yang Y, Zhao Y, Wang CS, Wang XD, Zhang L. 变应性鼻炎患者10030例吸入性变应原谱分析 [Prevalence of sensitization to aeroallergens in 10 030 patients with allergic rhinitis]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2011;46(11):914–920. Chinese.
44. Lou H, Ma S, Zhao Y, et al. Sensitization patterns and minimum screening panels for aeroallergens in self-reported allergic rhinitis in China. *Sci Rep*. 2017;7(1):9286. doi:10.1038/s41598-017-10111-9
45. Dunlap JC, Borkovich KA, Henn MR, et al. Enabling a community to dissect an organism: overview of the Neurospora functional genomics project. *Adv Genet*. 2007;57:49–96. doi:10.1016/s0065-2660(06)57002-6
46. Nazari M, Motlagh BA, Nasirian H. Toxicity of cypermethrin and chlorpyrifos against German cockroach [Blattella germanica (Blattaria: blattellidae)] strains from Hamadan, Iran. *Pak J Biol Sci*. 2016;19(6):259–264. doi:10.3923/pjbs.2016.259.264
47. Pan X, Wang X, Zhang F. New insights into cockroach control: using functional diversity of blattella germanica symbionts. *Insects*. 2020;11(10):696.
48. Heinzerling LM, Burbach GJ, Edenharter G, et al. GA(2)LEN skin test study I: GA(2)LEN harmonization of skin prick testing: novel sensitization patterns for inhalant allergens in Europe. *Allergy*. 2009;64(10):1498–1506. doi:10.1111/j.1398-9995.2009.02093.x
49. Liva GA, Karatzanis AD, Prokopakis EP. Review of rhinitis: classification, types, pathophysiology. *J Clin Med*. 2021;10(14):3183.
50. Gould HJ, Sutton BJ. IgE in allergy and asthma today. *Nat Rev Immunol*. 2008;8(3):205–217. doi:10.1038/nri2273
51. Togias A. Rhinitis and asthma: evidence for respiratory system integration. *J Allergy Clin Immunol*. 2003;111(6):1171–83; quiz 1184. doi:10.1067/mai.2003.1592
52. Rondón C, Fernández J, López S, et al. Nasal inflammatory mediators and specific IgE production after nasal challenge with grass pollen in local allergic rhinitis. *J Allergy Clin Immunol*. 2009;124(5):1005–11.e1. doi:10.1016/j.jaci.2009.07.018
53. Wang X, Guo M, Wang H, Wang X. Pollen allergen sensitization feature of seasonal allergic rhinitis in children and adolescents in northern China. *J Clin Otorhinolaryngol Head Neck Surg*. 2020;34(11):2096–7993. doi:10.13201/j.issn
54. Cheng L, Chen J, Fu Q, et al. Chinese Society of Allergy Guidelines for diagnosis and treatment of allergic rhinitis. *Allergy Asthma Immunol Res*. 2018;10(4):300–353. doi:10.4168/aair.2018.10.4.300
55. Yang L, Zhang Q, Zhang P. Analysis of HLA-DRB1 allele polymorphism for patients with allergic rhinitis. *Chin J Otorhinolaryngol*. 1999;34(3):0412–3948.
56. Li L, Guan K. Quality of life in 164 allergic rhinitis patients caused by different aeroallergens. *J Clin Otorhinolaryngol Head Neck Surg*. 2015;29(3):1101–1781. doi:10.13201/j.issn
57. Mandhane SN, Shah JH, Thennati R. Allergic rhinitis: an update on disease, present treatments and future prospects. *Int Immunopharmacol*. 2011;11(11):1646–1662. doi:10.1016/j.intimp.2011.07.005
58. Takhar P, Smurthwaite L, Coker HA, et al. Allergen drives class switching to IgE in the nasal mucosa in allergic rhinitis. *J Immunol*. 2005;174(8):5024–5032. doi:10.4049/jimmunol.174.8.5024
59. Lambrecht BN. Allergen uptake and presentation by dendritic cells. *Curr Opin Allergy Clin Immunol*. 2001;1(1):51–59. doi:10.1097/01.all.0000010985.57414.74
60. KleinJan A, Willart M, van Rijt LS, et al. An essential role for dendritic cells in human and experimental allergic rhinitis. *J Allergy Clin Immunol*. 2006;118(5):1117–1125. doi:10.1016/j.jaci.2006.05.030
61. Van Overtvelt L, Wambre E, Maillere B, et al. Assessment of Bet v 1-specific CD4+ T cell responses in allergic and nonallergic individuals using MHC class II peptide tetramers. *J Immunol*. 2008;180(7):4514–4522. doi:10.4049/jimmunol.180.7.4514
62. Stone KD, Prussin C, Metcalfe DD. IgE, mast cells, basophils, and eosinophils. *J Allergy Clin Immunol*. 2010;125(2 Suppl 2):S73–S80. doi:10.1016/j.jaci.2009.11.017
63. Sin B, Togias A. Pathophysiology of allergic and nonallergic rhinitis. *Proc Am Thorac Soc*. 2011;8(1):106–114. doi:10.1513/pats.201008-057RN
64. Janeway CATP, Walport M, Shlomchik M. *The Immune System in Health and Disease Immunobiology*. NY: Gerald Publishing. 2001:41.
65. Kraft S, Kinet JP. New developments in FcεpsilonRI regulation, function and inhibition. *Nat Rev Immunol*. 2007;7(5):365–378. doi:10.1038/nri2072

66. Fewtrell C, Metzger H. Larger oligomers of IgE are more effective than dimers in stimulating rat basophilic leukemia cells. *J Immunol.* 1980;125(2):701–710.
67. Knol EF. Requirements for effective IgE cross-linking on mast cells and basophils. *Mol Nutr Food Res.* 2006;50(7):620–624. doi:10.1002/mnfr.200500272
68. Norman PS, Naclerio RM, Creticos PS, Togias A, Lichtenstein LM. Mediator release after allergic and physical nasal challenges. *Int Arch Allergy Appl Immunol.* 1985;77(1–2):57–63. doi:10.1159/000233753
69. Peters-Golden M, Gleason MM, Togias A. Cysteinyl leukotrienes: multi-functional mediators in allergic rhinitis. *Clin Exp Allergy.* 2006;36(6):689–703. doi:10.1111/j.1365-2222.2006.02498.x
70. Wang D, Smitz J, Waterschoot S, Clement P. An approach to the understanding of the nasal early-phase reaction induced by nasal allergen challenge. *Allergy.* 1997;52(2):162–167. doi:10.1111/j.1398-9995.1997.tb00970.x
71. Kalesnikoff J, Galli SJ. Anaphylaxis: mechanisms of mast cell activation. *Chem Immunol Allergy.* 2010;95:45–66. doi:10.1159/000315937
72. Johnson SA, Pleiman CM, Pao L, Schneringer J, Hippen K, Cambier JC. Phosphorylated immunoreceptor signaling motifs (ITAMs) exhibit unique abilities to bind and activate Lyn and Syk tyrosine kinases. *J Immunol.* 1995;155(10):4596–4603.
73. Dale HH, Laidlaw PP. Histamine shock. *J Physiol.* 1919;52(5):355–390. doi:10.1113/jphysiol.1919.sp001837
74. White MV. The role of histamine in allergic diseases. *J Allergy Clin Immunol.* 1990;86(4 Pt 2):599–605. doi:10.1016/s0091-6749(05)80223-4
75. Jones JV. The nature of the pulmonary receptors excited by antihistamines. *Br J Pharmacol Chemother.* 1952;7(3):450–454. doi:10.1111/j.1476-5381.1952.tb00712.x
76. Tucker A, Weir EK, Reeves JT, Grover RF. Histamine H1- and H2-receptors in pulmonary and systemic vasculature of the dog. *Am J Physiol.* 1975;229(4):1008–1013. doi:10.1152/ajplegacy.1975.229.4.1008
77. Ichinose M, Barnes PJ. Inhibitory histamine H3-receptors on cholinergic nerves in human airways. *Eur J Pharmacol.* 1989;163(2–3):383–386. doi:10.1016/0014-2999(89)90212-4
78. Kay LJ, Suvama SK, Peachell PT. Histamine H4 receptor mediates chemotaxis of human lung mast cells. *Eur J Pharmacol.* 2018;837:38–44. doi:10.1016/j.ejphar.2018.08.028
79. Ahmed T, Mirbahar KB, Oliver W, Eyre P, Wanner A. Characterization of H1- and H2-receptor function in pulmonary and systemic circulations of sheep. *J Appl Physiol Respir Environ Exerc Physiol.* 1982;53(1):175–184. doi:10.1152/jappl.1982.53.1.175
80. Nadel JA, Davis B, Phipps RJ. Control of mucus secretion and ion transport in airways. *Annu Rev Physiol.* 1979;41:369–381. doi:10.1146/annurev.ph.41.030179.002101
81. Taylor-Clark T. Histamine in allergic rhinitis. *Adv Exp Med Biol.* 2010;709:33–41. doi:10.1007/978-1-4419-8056-4\_4
82. Huang H, Li Y, Liang J, Finkelman FD. Molecular regulation of histamine synthesis. *Front Immunol.* 2018;9:1392. doi:10.3389/fimmu.2018.01392
83. Schwartz JC, Arrang JM, Garbarg M, Pollard H, Ruat M. Histaminergic transmission in the mammalian brain. *Physiol Rev.* 1991;71(1):1–51. doi:10.1152/physrev.1991.71.1.1
84. Hill SJ. Distribution, properties, and functional characteristics of three classes of histamine receptor. *Pharmacol Rev.* 1990;42(1):45–83.
85. Hill SJ, Ganellin CR, Timmerman H, et al. International union of pharmacology. XIII. Classification of histamine receptors. *Pharmacol Rev.* 1997;49(3):253–278.
86. Doyle WJ, Boehm S, Skoner DP. Physiologic responses to intranasal dose-response challenges with histamine, methacholine, bradykinin, and prostaglandin in adult volunteers with and without nasal allergy. *J Allergy Clin Immunol.* 1990;86(6 Pt 1):924–935. doi:10.1016/s0091-6749(05)80156-3
87. Bachert C. The role of histamine in allergic disease: re-appraisal of its inflammatory potential. *Allergy.* 2002;57(4):287–296. doi:10.1034/j.1398-9995.2002.1r3542.x
88. Schmelz M, Schmidt R, Bickel A, Handwerker HO, Torebjork HE. Specific C-receptors for itch in human skin. *J Neurosci.* 1997;17(20):8003–8008.
89. Andrew D, Craig AD. Spinothalamic lamina I neurons selectively sensitive to histamine: a central neural pathway for itch. *Nat Neurosci.* 2001;4(1):72–77. doi:10.1038/82924
90. Secher C, Kirkegaard J, Borum P, Maansson A, Osterhammel P, Mygind N. Significance of H1 and H2 receptors in the human nose: rationale for topical use of combined antihistamine preparations. *J Allergy Clin Immunol.* 1982;70(3):211–218. doi:10.1016/0091-6749(82)90044-6
91. Wood-Baker R, Lau L, Howarth PH. Histamine and the nasal vasculature: the influence of H1 and H2-histamine receptor antagonism. *Clin Otolaryngol Allied Sci.* 1996;21(4):348–352. doi:10.1111/j.1365-2273.1996.tb01085.x
92. Togias A. H1-receptors: localization and role in airway physiology and in immune functions. *J Allergy Clin Immunol.* 2003;112(4 Suppl):S60–S68. doi:10.1016/s0091-6749(03)01878-5
93. De Backer MD, Gommeren W, Moereels H, et al. Genomic cloning, heterologous expression and pharmacological characterization of a human histamine H1 receptor. *Biochem Biophys Res Commun.* 1993;197(3):1601–1608. doi:10.1006/bbrc.1993.2662
94. Umemori H, Inoue T, Kume S, et al. Activation of the G protein Gq/11 through tyrosine phosphorylation of the alpha subunit. *Science.* 1997;276(5320):1878–1881. doi:10.1126/science.276.5320.1878
95. Flynn AN, Itani OA, Moninger TO, Welsh MJ. Acute regulation of tight junction ion selectivity in human airway epithelia. *Proc Natl Acad Sci U S A.* 2009;106(9):3591–3596. doi:10.1073/pnas.0813393106
96. Georas SN, Rezaee F. Epithelial barrier function: at the front line of asthma immunology and allergic airway inflammation. *J Allergy Clin Immunol.* 2014;134(3):509–520. doi:10.1016/j.jaci.2014.05.049
97. Houston C, Wenzel-Seifert K, Burckstummer T, Seifert R. The human histamine H2-receptor couples more efficiently to Sf9 insect cell Gs-proteins than to insect cell Gq-proteins: limitations of Sf9 cells for the analysis of receptor/Gq-protein coupling. *J Neurochem.* 2002;80(4):678–696. doi:10.1046/j.0022-3042.2001.00746.x
98. Hegyi K, Falus A, Toth S. Elevated CREB activity in embryonic fibroblasts of gene-targeted histamine deficient mice. *Inflamm Res.* 2007;56(8):339–344. doi:10.1007/s00011-007-7049-7
99. Shayo C, Davio C, Brodsky A, et al. Histamine modulates the expression of c-fos through cyclic AMP production via the H2 receptor in the human promonocytic cell line U937. *Mol Pharmacol.* 1997;51(6):983–990. doi:10.1124/mol.51.6.983

100. Flamand N, Plante H, Picard S, Laviolette M, Borgeat P. Histamine-induced inhibition of leukotriene biosynthesis in human neutrophils: involvement of the H2 receptor and cAMP. *Br J Pharmacol*. 2004;141(4):552–561. doi:10.1038/sj.bjp.0705654
101. Bongers G, Bakker RA, Leurs R. Molecular aspects of the histamine H3 receptor. *Biochem Pharmacol*. 2007;73(8):1195–1204. doi:10.1016/j.bcp.2007.01.008
102. Nieto-Alamilla G, Marquez-Gomez R, Garcia-Galvez A-M, Morales-Figueroa G-E, Arias-Montano J-A. The histamine H3 receptor: structure, pharmacology, and function. *Mol Pharmacol*. 2016;90(5):649–673. doi:10.1124/mol.116.104752
103. Wijtmans M, Leurs R, de Esch I. Histamine H3 receptor ligands break ground in a remarkable plethora of therapeutic areas. *Expert Opin Investig Drugs*. 2007;16(7):967–985. doi:10.1517/13543784.16.7.967
104. Xu H, Gu L-N, Yang Q-Y, Zhao D-Y, Liu F. MiR-221 promotes IgE-mediated activation of mast cells degranulation by PI3K/Akt/PLC $\gamma$ /Ca $^{2+}$  pathway. *J Bioenerg Biomembr*. 2016;48(3):293–299. doi:10.1007/s10863-016-9659-7
105. Pawankar R, Mori S, Ozu C, Kimura S. Overview on the pathomechanisms of allergic rhinitis. *Asia Pac Allergy*. 2011;1(3):157–167. doi:10.5415/apallergy.2011.1.3.157
106. Amin K. The role of mast cells in allergic inflammation. *Respir Med*. 2012;106(1):9–14. doi:10.1016/j.rmed.2011.09.007
107. Okano M. Mechanisms and clinical implications of glucocorticosteroids in the treatment of allergic rhinitis. *Clin Exp Immunol*. 2009;158(2):164–173. doi:10.1111/j.1365-2249.2009.04010.x
108. Varricchi G, Bagnasco D, Borriello F, Heffler E, Canonica GW. Interleukin-5 pathway inhibition in the treatment of eosinophilic respiratory disorders: evidence and unmet needs. *Curr Opin Allergy Clin Immunol*. 2016;16(2):186–200. doi:10.1097/ACI.0000000000000251
109. Adachi T, Alam R. The mechanism of IL-5 signal transduction. *Am J Physiol*. 1998;275(3):C623–C633. doi:10.1152/ajpcell.1998.275.3.C623
110. Niranjana R, Rajavelu P, Ventateshaiah SU, et al. Involvement of interleukin-18 in the pathogenesis of human eosinophilic esophagitis. *Clin Immunol*. 2015;157(2):103–113. doi:10.1016/j.clim.2015.01.007
111. Arebro J, Ekstedt S, Hjalmarsen E, Winqvist O, Kumlien Georen S, Cardell LO. A possible role for neutrophils in allergic rhinitis revealed after cellular subclassification. *Sci Rep*. 2017;7:43568. doi:10.1038/srep43568
112. Fransson M, Benson M, Wennergren G, Cardell LO. A role for neutrophils in intermittent allergic rhinitis. *Acta Otolaryngol*. 2004;124(5):616–620. doi:10.1080/00016480310015173
113. Hosoki K, Itazawa T, Boldogh I, Sur S. Neutrophil recruitment by allergens contribute to allergic sensitization and allergic inflammation. *Curr Opin Allergy Clin Immunol*. 2016;16(1):45–50. doi:10.1097/ACI.0000000000000231
114. Chen J, Zhou Y, Zhang L, et al. Individualized treatment of allergic rhinitis according to nasal cytology. *Allergy Asthma Immunol Res*. 2017;9(5):403–409. doi:10.4168/aa.2017.9.5.403
115. Kirmaz C, Ozenturk Kirgiz O, Bayrak P, et al. Effects of allergen-specific immunotherapy on functions of helper and regulatory T cells in patients with seasonal allergic rhinitis. *Eur Cytokine Netw*. 2011;22(1):15–23. doi:10.1684/ec.2011.0277
116. Jordakieva G, Jensen-Jarolim E. The impact of allergen exposure and specific immunotherapy on circulating blood cells in allergic rhinitis. *World Allergy Organ J*. 2018;11(1):19. doi:10.1186/s40413-018-0197-0
117. Ho J, Bailey M, Zaunders J, et al. Group 2 innate lymphoid cells (ILC2s) are increased in chronic rhinosinusitis with nasal polyps or eosinophilia. *Clin Exp Allergy*. 2015;45(2):394–403. doi:10.1111/cea.12462
118. Nussbaum JC, Van Dyken SJ, von Moltke J, et al. Type 2 innate lymphoid cells control eosinophil homeostasis. *Nature*. 2013;502(7470):245–248. doi:10.1038/nature12526
119. Skrindo I, Scheel C, Johansen FE, Jahnsen FL. Experimentally induced accumulation of Foxp3(+) T cells in upper airway allergy. *Clin Exp Allergy*. 2011;41(7):954–962. doi:10.1111/j.1365-2222.2011.03710.x
120. Ayars GH, Altman LC, McManus MM, et al. Injurious effect of the eosinophil peroxidase-hydrogen peroxide-halide system and major basic protein on human nasal epithelium in vitro. *Am Rev Respir Dis*. 1989;140(1):125–131. doi:10.1164/ajrccm/140.1.125
121. Akuthota P, Weller PF. Eosinophils and disease pathogenesis. *Semin Hematol*. 2012;49(2):113–119. doi:10.1053/j.seminhematol.2012.01.005
122. Park CS, Choi YS, Ki SY, et al. Granulocyte macrophage colony-stimulating factor is the main cytokine enhancing survival of eosinophils in asthmatic airways. *Eur Respir J*. 1998;12(4):872–878. doi:10.1183/09031936.98.12040872
123. Yamaguchi Y, Suda T, Ohta S, Tominaga K, Miura Y, Kasahara T. Analysis of the survival of mature human eosinophils: interleukin-5 prevents apoptosis in mature human eosinophils. *Blood*. 1991;78(10):2542–2547.

## Publish your work in this journal

The Journal of Asthma and Allergy is an international, peer-reviewed open-access journal publishing original research, reports, editorials and commentaries on the following topics: Asthma; Pulmonary physiology; Asthma related clinical health; Clinical immunology and the immunological basis of disease; Pharmacological interventions and new therapies. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/journal-of-asthma-and-allergy-journal>