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REVIEW

Common Allergens and Immune Responses Associated with Allergic Rhinitis in China

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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.[1,2] The pathophysiology of AR involves IgE-mediated inflammation of the nasal mucosa.[3] In recent years, the incidence and prevalence of AR in China have increased, negatively impacting the economy and people's quality of life.[4–6] 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.[3,7] Dust mites, animal furs, and mold spores are the primary triggers for perennial allergic reactions,[8] whereas pollen and weed powder are the primary causes of seasonal allergies.[9] 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.[10–12]

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.[13] The nasal mucosa is the primary site of allergen exposure, and inflammatory reactions lead to AR symptom development.[14] The symptoms are predominantly triggered by the interactions between specific mast cells, IgE antibodies, and airborne allergens.[15] Allergen exposure induces inflammatory mediator release, causing the specific symptoms and the inflammatory morphology seen in AR.[15,16]

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.[17,18] China is a large country with a vast geography and diverse climates and lifestyles, which leads

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to significant regional differences in AR distribution.[19] 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.[20] 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.[21] A cross-sectional survey was conducted in eight cities in China and revealed significant geographical differences in the prevalence of AR among Chinese children.[22] 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.[18] 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.[23,24] 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%).[25] 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%).[26] 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%).[27] 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%).[28]

China is a vast territory that spans approximately 50 latitudes. Therefore, a great diversity in vegetation is seen across the country.[29] 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.[30,31] 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.[32] 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.[33] 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.[34]

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*).[35] In Northern China, trees and weeds produce the main pollen types and are responsible for the two main allergic pollen seasons.[36] 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*.[36–38]

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 (Ambrosia, Artemisia),	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).[39] In Qingdao, China, children with AR are highly sensitive to ragweed and pollen.[18] 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.[40] 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.[41] 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.[42]

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).[43] 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.[44] *Neurospora crassa* is a saprophyte that exists vegetatively as an incompletely septate syncytium.[45] *Blattella germanica* normally resides in human habitats, in warm, moist, and dark hidden places.[46] As *B. germanica* contains several symbiotic microorganisms,[47] 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.[48] Certain foods, such as mussels, shrimp, carp, eggs, and milk, increase AR incidence.[18] Some drugs, such as aspirin and nonsteroidal

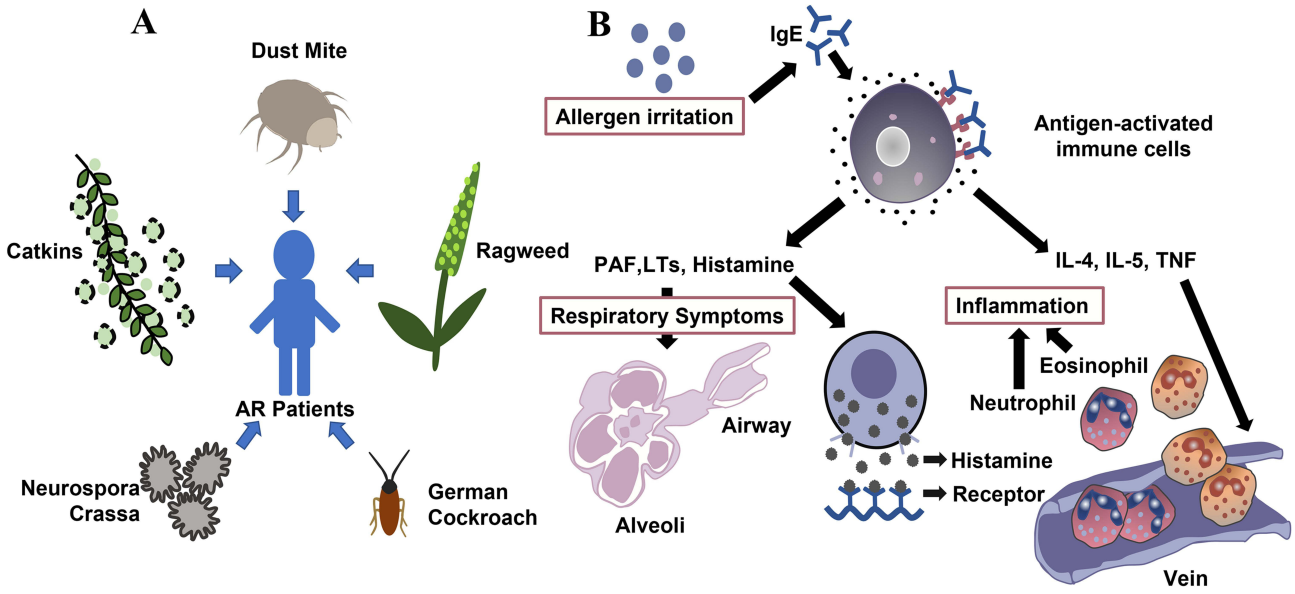

Figure 1 Common allergens and pathogenesis of AR. (**A**). The main allergens causing AR in northern China (dust mites, summer and autumn pollen, weed pollen, Neurospora crassa, and Blattella germanica). (**B**). Immune response to allergens. Specific IgE binds to the high-affinity IgE Fc receptor on 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,[49] while physical factors, such as morning hours, winter, and cold air, are common AR triggers.[24]

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,[50] thereby inducing the secretion of histamine, kininogenases, LTs, cytokines, and other mediators.[14] This causes the airway smooth muscles and telangiectasia to contract, increasing permeability and leading to excessive glandular secretion.[51] This process culminates in sneezing, runny nose, nasal itching, congestion, and other symptoms.[52] 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.[57–59] 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.[13,60] 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.[60] T cells from patients with AR are primarily transformed into allergen-specific Th2 cells.[61] These cells release cytokines, including interleukin (IL)-4, IL-5, and IL-13, to initiate the inflammatory immune response.[13] 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.[62] IL-4, IL-5, and IL-13 interact with B cell surface receptors, inducing ε germline transcription to produce immunoglobulins.[63] 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.[63,64] 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,[13] 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 (FcεRI) expressed on mast cells and basophils.[65] Upon subsequent exposure, IgE antibodies bound to FcεRI receptors recognize specific allergens,[66,67] resulting in the rapid degranulation of mast cells and basic granulocyte vesicles and the release of histamine, platelet-activating factor, and tryptase.[13,68] Activated mast cells release membrane-stored arachidonic acid and participate in the production of cysteinyl LTs (LTC4, LTD4, and LTE4) and prostaglandins (mainly PGD2).[69] 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, δ, and unmyelinated C fibers, and sympathetic and parasympathetic nerves.[14,70] 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.[50,71] The FcεRI receptor is a member of the polysubunit immunoreactive receptor (multisubunit immune response receptor [MIRR]) family.[72] FcεRI is mainly involved in type I hypersensitivity and mediates mast cell degranulation and the release of inflammatory mediators. FcεRI aggregation and crosslinking activate the Lyn PTK and src families; activated Lyn phosphorylates the β-chain, γ-chain, and adjacent tyrosine proteins. The latter process, in turn,

activates Lyn and Syk.[72] 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.[73] It has strong and diverse biological functions, including in AR pathophysiology.[74] Lung tissue contains four histamine receptors: H1, H2, H3, and H4.[75–78] The pulmonary artery has a biphasic response to histamine due to H1 receptor-mediated vasoconstriction and H2 receptor-mediated vasodilation.[79] 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.[80] 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).[79] The mast cells release other inflammatory mediators, such as 9 α, 11 β-prostaglandins F2-α 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[81] and upregulates proinflammatory cytokine expression, mediating the early immune response,[70] including allergic reactions and inflammation.[82–85] The release of histamine from mast cells promotes H1 receptor activation.[86,87] The activated sensory nerves transmit the signals to the central nervous system, which causes motor reflexes, such as itching and sneezing.[88,89] 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.[90–92]

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).[93,94] 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.[95,96] 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.[97–99] CAMP-dependent protein kinase signaling inhibits LT synthesis in neutrophils.[100] The histamine H3 receptor inhibits the release of substance P from nasal nociceptive sensory nerves[101–103] and promotes the IgE-mediated activation of mast cell degranulation.[104] 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.[63] 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.[57] These responses sustain inflammation and prolong allergic reactions.[57,105] Although nasal congestion and sneezing can last for a significant period, persistent nasal congestion indicates late-stage allergic reactions.[16]

Mast cells release cytokines, such as IL-4, IL-13, and tumor necrosis factor-α. 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.[105–107] 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 α on the eosinophil surfaces, which leads to increased IL-5 levels.[108] It transmits signals via the IL-5 receptor α-chain

and β-chain complexes.[109] 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.[110] 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.[110] The mediators released by mast cells, such as LTs, prostaglandins, and platelet-activating factors, lead to the observed reactions and immune chemotaxis,[13] 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.[111–113] 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.[114] Late mucosal inflammation in patients with HDM-specific AR activates neutrophil circulation and increases neutrophil migration into the nasal mucosa.[112] T cells play a major role in allergic respiratory inflammation. Th1 cell differentiation from CD_4 T cells (TH0) is mediated by IL-12 and interferon-γ. The number of Th1 cells and the level of Th1-derived interferon-γ are relatively lower in the nasal lavage fluid of patients with AR than in individuals without AR.[115] 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.[116] 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.[117,118] In pollen-sensitized AR patients, nasal mucosal eosinophils increase within a few days of an allergen challenge.[119] 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.[120] Eosinophils secrete IL-5, which promotes the activation and survival of eosinophils in an autocrine manner.[121] 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.[122,123] 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

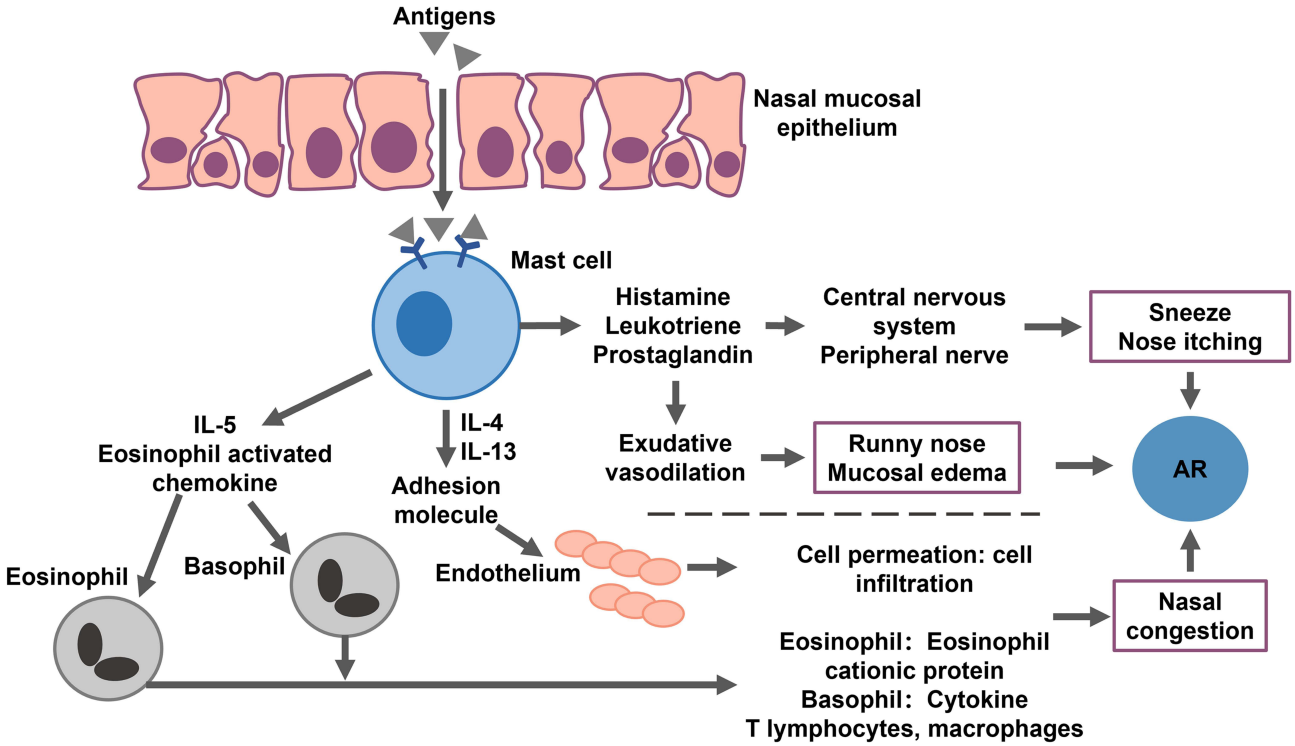

Figure 2 Allergens trigger the body's AR immune response process.

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.

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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.

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Disclosure

The authors report no conflicts of interest in this work.

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