

Review Article

Mechanism of Lower Airway Hyperresponsiveness Induced by Allergic Rhinitis

Yiting Liu,¹ Jichao Sha,^{1,2} Cuida Meng ^{1,2} and Dongdong Zhu ^{1,2}

¹Department of Otolaryngology Head and Neck Surgery, China-Japan Union Hospital of Jilin University, Changchun, China

²Jilin Provincial Key Laboratory of Precise Diagnosis and Treatment of Upper Airway Allergic Diseases, China

Correspondence should be addressed to Dongdong Zhu; zhudd@jlu.edu.cn

Received 23 December 2021; Accepted 24 June 2022; Published 12 July 2022

Academic Editor: Carlo Cavaliere

Copyright © 2022 Yiting Liu et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Allergic rhinitis is a global illness that puzzles many researchers. Most patients with allergic rhinitis also have lower airway hyperresponsiveness, and an allergic rhinitis attack can increase lower airway hyperresponsiveness. However, the mechanism of the effect of allergic rhinitis on the lower airways is still unclear. In this paper, the effects of allergic rhinitis on the lower airways are studied in terms of epidemiology, anatomy, pathophysiology, nasal function loss, inflammation drainage, nasobronchial reflex, and whole-body circulatory flow to determine the mechanism involved and provide ideas for future diagnosis, treatment, and experiments.

1. Introduction

Upper and lower airways are considered a unified morphological and functional unit, and the connection existing between them has been observed for many years, both in health and disease [1, 2]. The relationship between the upper airways, which consist of the two nasal passages and the paranasal sinuses, and the lower airways, which consist of the bronchi and bronchioles, is of great interest from both clinical and physiological standpoints [3, 4]. To understand illnesses that appear on the surface to affect only one element of an integral organ system, one should be able to understand and visualize the function of the entire system. The concept of a unified airway disease was suggested [5]. However, there is no clear conclusion about the effect of allergic rhinitis (AR) on the lower airways, especially on the hyperresponsiveness of the lower airways. This article will review the previous researches in this field to provide direction for future research on AR.

2. Epidemiology

AR currently affects approximately 40% of adults and 25% of children worldwide [6–8]. Several recently published studies have illustrated the connection of AR with asthma. This sug-

gests that the evolution of asthma and rhinitis is bidirectional. Approximately 40% of AR patients have asthma symptoms, and approximately 80% of asthmatic patients have symptoms of AR [9–11]. In 1998, William et al. [12] reported a 23-year follow-up study that involved a total of 738 college students. The students' responses to the questionnaire revealed a frequent combination of asthma and AR. The results showed that 85.7% of patients with asthma had AR at the same time. Among patients with AR, asthma occurred in 21.3%. Another 23-year follow-up study conducted by Settupane et al. [13] included 1836 college students. The results demonstrated that two risk factors for developing new asthma were AR and positive allergy skin tests. Individuals with these two risk factors were approximately three times more likely to develop asthma than negative controls. Another 10-year follow-up study from Lombardi et al. [14] described a natural history of allergic disease evolution in 99 patients. One of their results showed that 31.8% of patients with AR developed concomitant asthma after 10 years.

3. Pathophysiology

The mucosa of the upper and lower airways is continuous, and they share many similar anatomical and histological

characteristics [15]. The two parts of the respiratory mucosa, which is made up of pseudostratified ciliated columnar epithelium and the supporting lamina propria, have common structures, such as glands, ciliary epithelium, lamina propria, basement membrane, and goblet cells [16]. The epithelium is located above the basement membrane, which is mainly made up of type V laminin and type IV collagen. The function of the basement membrane is to separate the epithelium from the underlying mesenchymal components and make it possible for epithelial and inflammatory cells to migrate [17]. The lamina propria is under the basement membrane. The lamina propria contains serous glands, which are composed of water, polysaccharide, and collagen, and their function is to secrete mucus and keep the airway moist [18]. The ratio of extracellular matrix to serous glands plays a key role in regulating cell function, serving as the matrix and scaffold of various cell activities [19]. The epithelial tissue acts as a barrier by forming a continuous layer with almost no intracellular gaps, and it protects the body from environmental stress and physical damage. Additionally, airway epithelial cells not only comprise a physical barrier but also produce antimicrobial peptides, several chemokines, and cytokines which play key roles in immune, inflammatory, repair, and remodelling responses upon encounters with triggers, including inhaled allergens and pathogens [20].

The nasal mucosa contains many vessels, whereas the bronchial mucosa contains many smooth muscle cells [4, 21]. Under healthy conditions, epithelial cells can quickly repair when suffering from inflammatory injury. However, chronic epithelial damage causes structural changes in the airways [22], including epithelial shedding, goblet cell metaplasia, basement membrane thickening, extracellular matrix deposition in the submucosa, smooth muscle hypertrophy, subepithelial angiogenesis, and myofibroblast hyperplasia [23]. Defects in the epithelial barrier, the so-called leaky epithelium, have been demonstrated in affected organs in asthma, chronic rhinosinusitis, and allergic rhinitis, leading to the development of the epithelial barrier hypothesis in the pathogenesis of these diseases [24, 25]. Related experiments [26, 27] have reported the defects in the epithelial barrier of the nasal epithelium in patients with both seasonal and perennial allergic rhinitis (PAR).

Allergen immunotherapy (AIT) is a curative treatment for allergic diseases, such as AR and asthma, that alters the underlying pathophysiology, alters the skewed Th2 response, and induces long-term clinical tolerance against allergens [28, 29]. AIT leads to a significant reduction in symptoms and medication use, improves quality of life, and prevents the development of new sensitizations [30]. Furthermore, AIT prevents the development of asthma in patients with allergic rhinitis and the progression of prevalent asthma [31].

4. The Effect of Nasal Dysfunction on the Lower Airways

The loss of nasal function due to mucosal congestion and retention in the nasal cavity has a significant effect on the lower airways. In allergic diseases, complete or partial obstruc-

tion of the nose prevents airflow through the nasal cavity, and oral respiration becomes obligatory. Shturman-Ellstein et al. have shown that oral breathing associated with nasal obstruction will increase the intensity of bronchospasms [32].

The main physiological function of the nose is to heat and humidify the air inhaled before airflow reaches the lower airways. Resistance to airflow is less in oral breathing than in nasal breathing, but the air will be cooler and drier. These changes in air may affect the degree of bronchoconstriction. Proctor [33] concluded that at an ambient temperature of 23°C, air temperature increases to approximately 30°C in the midnasal passage, approximately 33°C in the nasopharynx, and only slightly above that in the upper trachea. At each of these sites, the relative humidity is nearly 100%. The subepithelial capillary network of the nasal cavity and the venous sinus below it accumulate a large amount of blood, leading to submucosal tissue hyperaemia and increased contact of the surface with airflow [33, 34], which is conducive to the distribution of heat and water transport. Therefore, these structures contribute to the humidification and heating of nasal air. Griffin et al. [35] carried out an experiment in which asymptomatic asthmatic and healthy control subjects inhaled cold air at equal ventilation through their noses or mouths in a random fashion, and the temperature in the retrotracheal oesophagus and pulmonary mechanics were recorded before and after ventilation. A linear relationship between the degree of airway cooling and the severity of subsequent bronchoconstriction was found in asymptomatic asthmatic patients. The healthy control subjects showed similar changes in temperature, but their lung function did not change. Assanasen et al. [36] conducted a prospective, parallel experiment on healthy control subjects, patients with seasonal AR and perennial AR, and patients with asthma. The temperature and humidity of the air were measured when cold, dry air entered and left the nasal cavity. The results showed that the noses of patients with asthma had a reduced ability to condition cold, dry air compared with those of healthy control subjects but a similar ability to those of seasonal AR subjects out of season.

Immunological function is another important function of the nose and includes the activity of nonspecific and specific systems. Nonspecific systems filter the particles and gaseous materials in inhaled air before they reach the lower airways [37]. The nasal mucus and mucocilia play an essential role in this process. The nasal mucus carries surface secretions backward to the nasopharynx through the sweeping action of the nasal mucocilia, which are located from the anterior nasal cavity to the nasopharynx. These materials are dispatched to the stomach periodically through swallowing and destroyed by gastric enzymes [38]. At the most anterior portion of the inferior turbinates, the cilia propel the mucus anteriorly towards the nasal vestibule. This action enables the clearance of deposited foreign materials by nose blowing, wiping, and so on, limiting true access of these foreign particles to the body [39]. In addition, the presence of these foreign materials will lead to the release of several factors through the activation of inflammatory monocytes, and macrophages will be mobilized to eliminate viral and cellular debris. The submucosal glands release antifactors, such as

lysozyme and lactoferrin [40], or chemical defences, such as uric acid, in the epithelial lining fluid [41]. Specific immune functions facilitate the coupling of IgA with the secretory component-specific defence system, which consists of immunological humoral and cellular responses. This system is responsible for the complete elimination of pathogens and for the induction of immunological memory phenomena [41–43].

Another theory is that the blockade of the paranasal sinus and the loss of nasal epithelial function may reduce the release of nitric oxide (NO) in the airways. NO plays an important protective role in the upper airway. Lundberg et al. [44, 45] demonstrated that there is a large amount of NO in the upper airway, mainly from the nasal sinus. Other experiments have shown that NO has strong antiviral and antibacterial activities, improves oxygenation, plays a role in bronchodilation, and regulates the reactivity of the lower airways [46–48].

Complete or partial obstruction of the nose leads to air flowing directly into the lower airways without passing through the nasal cavity, and allergens or cold air is inhaled directly into the bronchus, causing hyperresponsiveness of the lower airways.

5. Upper Airway Drainage of Inflammatory Mediators

Upper airway drainage of inflammatory mediators is another mechanism by which AR leads to lower airway hyperresponsiveness. The nasopharynx, oropharynx, laryngopharynx, and lower airways are interconnected areas, and allergens that are inhaled into the upper airway may be discharged into the lower airways. Brugman et al. [49] performed animal experiments to measure bronchial reactivity when histamine was inhaled. The responsiveness to histamine increased with the presence of upper airway inflammation, and this responsiveness could be prevented when the draining of exudate out of the larynx was blocked. The results of this experiment demonstrated that nasal drainage can increase bronchial responsiveness. Huxley et al. [50] documented pulmonary aspiration among both healthy patients and patients with depressed consciousness with a radiolabelled marker that was released into the lower airways. Sato [51] used white-pepper-irritated nasal mucosa to examine airway resistance in laryngectomized patients and healthy adults, and they found that airway resistance increased after nasal mucosa irritation in healthy adults but that there was no such change in laryngectomized patients. The anatomical changes in laryngectomized patients may have led to the nose being unable to drain the increased secretions following white pepper stimulation into the lower airways. However, Bardin et al. [52] found that the drainage of secretions into the lower airways is unlikely to lead to coexistent pulmonary disease. They investigated pulmonary aspiration in a study by means of a technique in which a radionuclide was placed in a maxillary sinus. After 24 hours, no radionuclide was found in the lungs of any patient, but the radionuclide was found in the maxillary sinus, nasopharynx, oesophagus, and lower gastrointestinal tract. The authors pointed out that the association was probably related to generalized mucosal disease affecting both the upper and lower airways.

6. The Nasobronchial Reflex

In 1919, Sluder pointed out that asthma may be caused by neural reflexes of the nose. The nasobronchial reflex is a branch of the diving reflex, which leads to the suppression of respiration, laryngospasm, and bronchoconstriction when the head is immersed in water [53]. This reflex leads to an increase in airway resistance caused by bronchoconstriction [54]. The smooth muscle contraction of the bronchus is caused by the efferent pathway of the vagus nerve, which originates from the sensory nerve endings in the nose that enter the central nervous system through the trigeminal nerve [55]. Because of the changes mentioned above, mammals can remove water from their lungs when diving. However, when harmful substances are inhaled in the nose (or when allergic patients inhale allergens), this reflex may induce immediate bronchoconstriction with the cessation of respiration in the expiratory phase due to the relaxation of inspiratory muscles.

This hypothesis underwent rigorous testing through a variety of animal experiments. Whicker and Kern [56] found that pulmonary resistance increased in awake and anaesthetized dogs after stimulation of the nasal mucosa. Whicker et al. [57] found that nasal stimulation typically produced marked changes in breathing patterns and a large transient increase in pulmonary airflow resistance. This response to nasal stimulation could be abolished by interrupting either the trigeminal nerve or the vagus nerve. In 1969, Kaufman et al. [58] measured tracheobronchial airway resistance by unilateral nose irritation in 5 patients who had undergone complete resection of the second division of the trigeminal nerve. There was no increase in resistance after irritation of the nose and nasopharynx on the resected side but a significant increase in resistance following stimulation of the intact side. In another experiment [59], they also showed that significant elevations in airway resistance were prevented by prior subcutaneous injections of atropine. Therefore, it can be concluded that the nasobronchial reflex results in bronchoconstriction by vagal and trigeminal pathways and the presence of afferent receptor sites in the nose. Other experiments demonstrated that allergen antigen exposure in AR patients increased the level of hyperresponsiveness in the lower airways [60]. Therefore, it can be concluded that the nasobronchial reflex results in bronchoconstriction by vagal and trigeminal pathways and the presence of afferent receptor sites in the nose.

Despite being well documented in those experiments, the existence of this reflex is still controversial [4]. Nadel and Widdicombe [61] found that there was no significant change in lung resistance after irritation of the nasal mucosa in decerebrated cats and anaesthetized cats. Schumacher et al. [62] reported a clinical trial of nasal stimulation with saline, allergen, and histamine in patients with asthma and control subjects and found that nasal symptomatology occurred without increases in lower airway resistance. Small et al. [63] measured the pulmonary function of patients with PAR 30 minutes after nasal challenge and found no significant decrease in flow rates. In addition, other experiments [64–67] demonstrated that inflammation will cause some

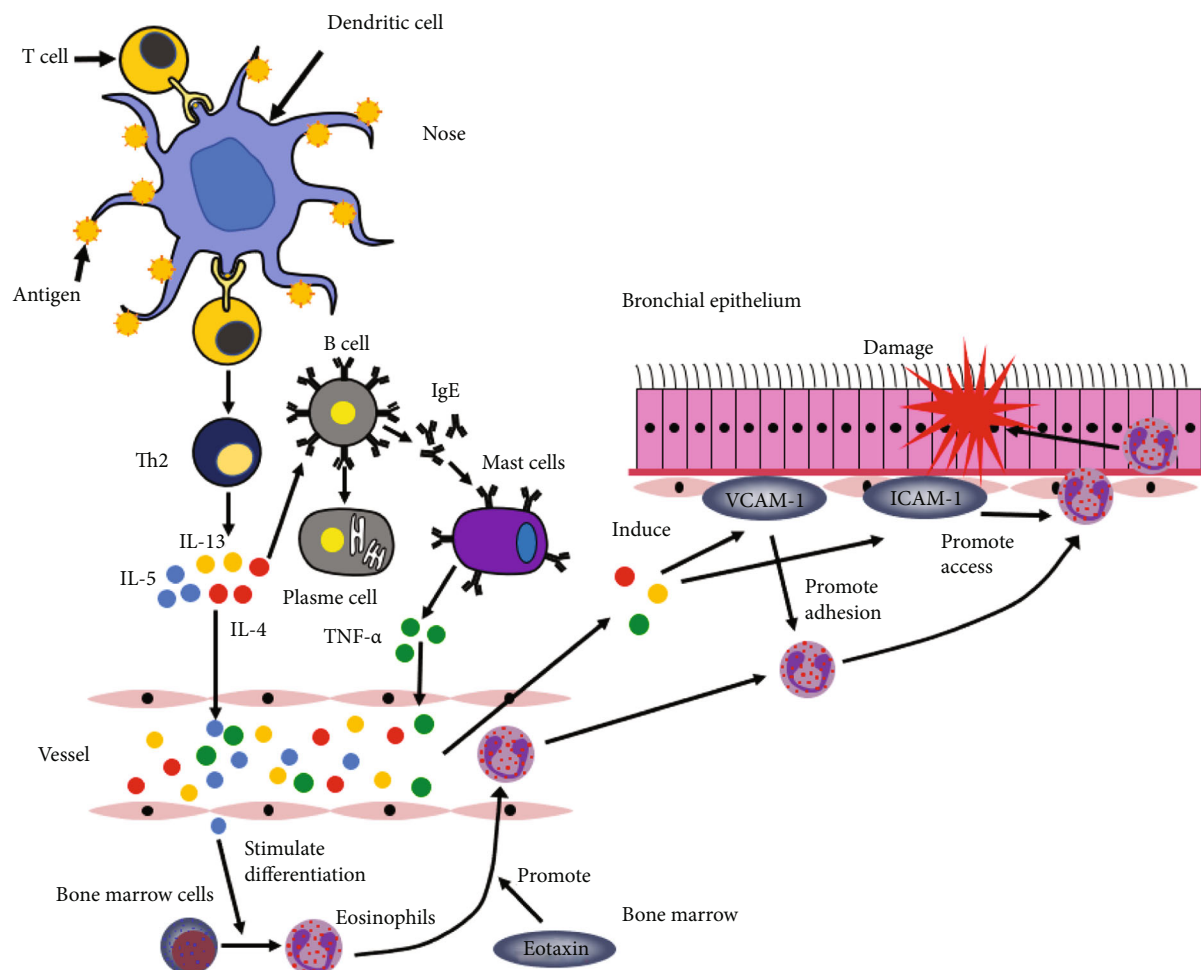


FIGURE 1: After the upper airway is stimulated by allergens, the inflammatory factors and cytokines produced by the upper airway cause the aggregation of eosinophils in the lower airway, which causes the hyperresponsiveness of the lower airway.

changes in airway nerves, including an increase in nerve density and the excitability of airway nerves. Furthermore, the sensory nerves innervating the tissue produce more neuropeptides after the stimulation of inflammation [68]. The nasobronchial reflex may be strengthened by neural hyperresponsiveness caused by exogenous stimulated factors or endogenous immune factors [69]. The interaction between the immune and nervous systems will make the neural mechanism more complicated.

7. The Propagation of Inflammation via the Systemic Circulation

An allergic inflammatory response, such as increased eosinophil numbers deep in the nasal mucosa and then peripheral blood eosinophilia or other systemic inflammatory events, can be found in patients with AR after nasal allergen provocation. Eosinophils can selectively accumulate in the circulation and various tissues of patients with allergic diseases. Because eosinophils are potent proinflammatory effector cells, they have a role in defending parasites. However, the overaccumulation of eosinophils, which always occurs in an allergic inflammatory response, will cause severe host tissue damage

[70]. In the lower airways, when stimulated, eosinophils can release some toxic proteins, including eosinophil cationic protein (ECP), eosinophil peroxidase (EPO), and major basic protein (MBP), which will damage the integrity of the epithelium of the lower airways, leading to a decrease in ciliated and brush cells, mast cell secretion, and the exposure of underlying sensory nerve endings, which promote bronchial hyperresponsiveness and bronchoconstriction [71–76].

The allergic reaction of AR starts with the recognition of allergens by antigen-presenting cells, mainly dendritic cells, which drive type 2 T helper (Th2) cell polarization. Then, Th2 cells release various inflammatory cytokines, including IL-4, IL-5, and IL-13, leading to the recruitment of effector cells, such as eosinophils and mast cells [77, 78]. These inflammatory factors and eotaxin have an important function in the generation and recruitment of effector cells, such as eosinophils, in the lower airways. Experiments have reported higher concentrations of eotaxin in the epithelium of the nose and bronchus (mainly in macrophages) in patients with allergic inflammation [79, 80]. The absorption of IL-5 from the nose into the blood after allergen challenge can mediate the increase in the differentiation of progenitors into eosinophils in bone marrow [81]. Eotaxin is a

chemokine that accelerates the egress of eosinophils from bone marrow, which has a significant synergism with IL-5 mobilization of mature eosinophils from the femoral marrow [82]. Then, IL-4 and IL-13 upregulate vascular cell adhesion molecule-1 (VCAM-1) on the endothelium. Eosinophils become tethered to the endothelium through the effects of VCAM-1 and then transfer into the endothelium through leukocyte function-associated antigen-1 (LFA-1) and intercellular adhesion molecule-1 (ICAM-1) [81]. These inflammatory factors and adhesion molecules, including TNF- α , which is stored in mast cells and released upon IgE-dependent stimulation, are involved in this process [83–85] (Figure 1).

Palframan et al. [82] found that the injection of eotaxin into guinea pigs stimulated an increase in blood eosinophilia and a corresponding decrease in the number of eosinophils retained in the bone marrow. The preincubation of bone marrow cells with IL-5 produced considerably more eosinophils than preincubation with eotaxin. Braunstahl et al. [86] found that at 24 hours after nasal allergen provocation, an influx of eosinophils and increased expression of vessels positive for ICAM-1, VCAM-1, and e-selectin vessels were detected in the nasal epithelium and its lamina propria, as well as in the bronchial epithelium and its lamina propria. The number of mucosal eosinophils correlated with the expression of ICAM-1, e-selectin, and VCAM-1 in patients with AR. Sedgwick et al. [87] observed bronchoalveolar lavage fluid obtained from AR patients and found a significant increase in histamine and tryptase 12 minutes after challenge with antigen and another increase in IL-5 concentrations that correlated with the presence of eosinophils and eosinophil granular proteins 48 hours after challenge. Neither eosinophils nor soluble mediators of eosinophils were increased in healthy control subjects.

8. Summary

The influence of AR on the lower airways is very complex and cannot be explained by only one of the above mechanisms but may be the common result of the interaction of several mechanisms. Within a short time after AR, the hyperresponsiveness of the lower airways may be caused by the rhinopulmonary reflex, lower airway drainage of allergens, and nasal obstruction. From the verification experiments for various mechanisms, we noticed that in the rhinopulmonary reflex test, the time of AR-induced lower airway hyperresponsiveness was short because sensory nerves of the nose can quickly convert the stimulation into an electrical signal, which can be quickly transmitted to the lower airways through A-fibres and produce corresponding complications [68]. In addition, allergens directly drained from the nose or untreated air can quickly reach the lower airways through the normal anatomical structure. Therefore, the above three mechanisms may provide a reasonable explanation for the occurrence of lower airway hyperresponsiveness within a short time after AR. However, after prolonged nasal stimulation, lower airway hyperresponsiveness is more caused by circulating inflammatory factors because it takes a certain time for IL-5 to stimulate bone marrow

cells to differentiate into eosinophils and for IL-4 and IL-13 to upregulate adhesion- and chemotaxis-related proteins.

The evidence for these complex, multiple mechanisms also provides some inspiration for follow-up experiments. Until now, the mechanism of propagation of inflammation via the systemic circulation has been a common view, and evidence for several other mechanisms remains controversial. In addition to some defects in the experiments themselves, evidence for the existence of several mechanisms shows that experimental manipulation of these mechanisms individually can lead to interference with other mechanisms and thus incorrect results. Therefore, in future experiments, we can target these mechanisms individually in both animal and human experiments to avoid affecting several mechanisms. For example, in a mouse experiment, the trigeminal nerve of the mouse can be cut off in advance to block the influence of the nasobronchial reflex. When nasal irritation is administered, allergens can be administered in a way that avoids the inhalation of allergens into the lower airways. For example, cotton pledgets with allergens in inferior turbinates or head-down positions and tracheal cannulas have been used in animal experiments [49, 88]. These methods can reduce the impact of allergens directly drainage and inhalation into the lower airways.

In conclusion, the mechanisms of AR-induced lower airway hyperresponsiveness are complex. This review provides some exploration of the details. At the same time, this review also forward some noteworthy features for future experiments to avoid the interactions among several mechanisms and to conduct more accurate experiments.

Conflicts of Interest

All authors declare that they have no conflicts of interest relevant to this article.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (81870701 and 82071016); the Jilin Provincial Science and Technology Development Plan Outstanding Young Talent Fund Project (20190103097JH); the Natural Science Foundation of Jilin Province (20200201600JC, 20200201200JC, and 20200201411JC); and the Jilin Province Health Science and Technology Talent Project (2019scz004).

References

- [1] G. Ciprandi, D. Caimmi, M. M. del Giudice, M. La Rosa, C. Salpietro, and G. L. Marseglia, “Recent developments in united airways disease,” *Allergy, Asthma & Immunology Research*, vol. 4, no. 4, pp. 171–177, 2012.
- [2] J. Grossman, “One airway, one disease,” *Chest*, vol. 111, no. 2, pp. 11S–16S, 1997.
- [3] A. Licari, R. Castagnoli, C. F. Denicolò, L. Rossini, A. Marseglia, and G. L. Marseglia, “The nose and the lung: united airway disease?,” *Frontiers in Pediatrics*, vol. 5, p. 44, 2017.

- [4] P. Giavina-Bianchi, M. Aun, P. Takejima, J. Kalil, and R. Agondi, "United airway disease: current perspectives," *Journal of Asthma and Allergy*, vol. 9, pp. 93–100, 2016.
- [5] J. Bousquet, N. Khaltaev, A. A. Cruz et al., "Allergic rhinitis and its impact on asthma (ARIA) 2008*," *Allergy*, vol. 63, Suppl 86, pp. 8–160, 2008.
- [6] J. L. Brożek, J. Bousquet, I. Agache et al., "Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines–2016 revision," *The Journal of Allergy and Clinical Immunology*, vol. 140, no. 4, pp. 950–958, 2017.
- [7] M. I. Asher, S. Montefort, B. Björkstén et al., "Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys," *Lancet*, vol. 368, no. 9537, pp. 733–743, 2006.
- [8] C. H. Katelaris, B. W. Lee, P. C. Potter et al., "Prevalence and diversity of allergic rhinitis in regions of the world beyond Europe and North America," *Clinical and Experimental Allergy*, vol. 42, no. 2, pp. 186–207, 2012.
- [9] B. Leynaert, C. Neukirch, S. Kony et al., "Association between asthma and rhinitis according to atopic sensitization in a population-based study," *The Journal of Allergy and Clinical Immunology*, vol. 113, no. 1, pp. 86–93, 2004.
- [10] B. Leynaert, J. Bousquet, C. Neukirch, R. Liard, and F. Neukirch, "Perennial rhinitis: an independent risk factor for asthma in nonatopic subjects: results from the European Community Respiratory Health Survey," *The Journal of Allergy and Clinical Immunology*, vol. 104, no. 2, pp. 301–304, 1999.
- [11] S. Guerra, D. L. Sherrill, S. Baldacci et al., "Rhinitis is an independent risk factor for developing cough apart from colds among adults," *Allergy*, vol. 60, no. 3, pp. 343–349, 2005.
- [12] W. A. Greisner, R. J. Settipane, and G. A. Settipane, "Co-existence of asthma and allergic rhinitis: a 23-year follow-up study of college students," *Allergy and Asthma Proceedings*, vol. 19, no. 4, pp. 185–188, 1998.
- [13] R. J. Settipane, G. W. Hagy, and G. A. Settipane, "Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow-up study of college students," *Allergy Proceedings*, vol. 15, no. 1, pp. 21–25, 1994.
- [14] C. Lombardi, G. Passalacqua, S. Gargioni et al., "The natural history of respiratory allergy: a follow-up study of 99 patients up to 10 years," *Respiratory Medicine*, vol. 95, no. 1, pp. 9–12, 2001.
- [15] C. Cingi, N. B. Muluk, B. Cobanoglu, T. Çatli, and O. Dikici, "Nasobronchial interaction," *World Journal of Clinical Cases*, vol. 3, no. 6, pp. 499–503, 2015.
- [16] C. H. Feng, M. D. Miller, and R. A. Simon, "The united allergic airway: connections between allergic rhinitis, asthma, and chronic sinusitis," *American Journal of Rhinology & Allergy*, vol. 26, no. 3, pp. 187–190, 2012.
- [17] M. Paulsson, "Basement membrane proteins: structure, assembly, and cellular interactions," *Critical Reviews in Biochemistry and Molecular Biology*, vol. 27, no. 1-2, pp. 93–127, 1992.
- [18] W. J. Howat, J. A. Holmes, S. T. Holgate, and P. M. Lackie, "Basement membrane pores in human bronchial epithelium: a conduit for infiltrating cells?," *The American Journal of Pathology*, vol. 158, no. 2, pp. 673–680, 2001.
- [19] D. E. Ingber, L. Dike, L. Hansen et al., "Cellular tensegrity: exploring how mechanical changes in the cytoskeleton regulate cell growth, migration, and tissue pattern during morphogenesis," *International Review of Cytology*, vol. 150, pp. 173–224, 1994.
- [20] Z. C. Sozener, B. O. Ozturk, P. Cerci et al., "Epithelial barrier hypothesis: effect of the external exposome on the microbiome and epithelial barriers in allergic disease," *Allergy*, vol. 77, no. 5, pp. 1418–1449, 2022.
- [21] M. Okano, S. Kariya, N. Ohta, Y. Imoto, S. Fujieda, and K. Nishizaki, "Association and management of eosinophilic inflammation in upper and lower airways," *Allergology International*, vol. 64, no. 2, pp. 131–138, 2015.
- [22] P. Demoly, J. Simony-Lafontaine, P. Chanez et al., "Cell proliferation in the bronchial mucosa of asthmatics and chronic bronchitics," *American Journal of Respiratory and Critical Care Medicine*, vol. 150, no. 1, pp. 214–217, 1994.
- [23] P. K. Jeffery, A. J. Wardlaw, F. C. Nelson, J. V. Collins, and A. B. Kay, "Bronchial biopsies in asthma. An ultrastructural, quantitative study and correlation with hyperreactivity," *The American Review of Respiratory Disease*, vol. 140, no. 6, pp. 1745–1753, 1989.
- [24] Z. C. Sözen, L. Cevhertas, K. Nadeau, M. Akdis, and C. A. Akdis, "Environmental factors in epithelial barrier dysfunction," *The Journal of Allergy and Clinical Immunology*, vol. 145, no. 6, pp. 1517–1528, 2020.
- [25] K. Samitas, A. Carter, H. H. Kariyawasam, and G. Xanthou, "Upper and lower airway remodelling mechanisms in asthma, allergic rhinitis and chronic rhinosinusitis: the one airway concept revisited," *Allergy*, vol. 73, no. 5, pp. 993–1002, 2018.
- [26] M. A. Calderón, S. Lozewicz, A. Prior, S. Jordan, C. J. Trigg, R. J. Davies et al., "Lymphocyte infiltration and thickness of the nasal mucous membrane in perennial and seasonal allergic rhinitis," *The Journal of Allergy and Clinical Immunology*, vol. 93, no. 3, pp. 635–643, 1994.
- [27] M. C. Lim, R. M. Taylor, and R. M. Naclerio, "The histology of allergic rhinitis and its comparison to cellular changes in nasal lavage," *American Journal of Respiratory and Critical Care Medicine*, vol. 151, no. 1, pp. 136–144, 1995.
- [28] S. R. Durham, "The allergen specificity of allergen immunotherapy-doubt no more," *Allergy*, vol. 74, no. 11, pp. 2054–2056, 2019.
- [29] M. C. Zelm, C. I. McKenzie, N. Varese, J. M. Rolland, and R. E. O'Hehir, "Recent developments and highlights in immune monitoring of allergen immunotherapy," *Allergy*, vol. 74, no. 12, pp. 2342–2354, 2019.
- [30] S. Zielen, P. Devillier, J. Heinrich, H. Richter, and U. Wahn, "Sublingual immunotherapy provides long-term relief in allergic rhinitis and reduces the risk of asthma: a retrospective, real-world database analysis," *Allergy*, vol. 73, no. 1, pp. 165–177, 2018.
- [31] J. Schmitt, E. Wüstenberg, D. Küster, V. Mücke, N. Serup-Hansen, and F. Tesch, "The moderating role of allergy immunotherapy in asthma progression: results of a population-based cohort study," *Allergy*, vol. 75, no. 3, pp. 596–602, 2020.
- [32] R. Shturman-Ellstein, R. J. Zeballos, J. M. Buckley, and J. F. Souhrada, "The beneficial effect of nasal breathing on exercise-induced bronchoconstriction," *The American Review of Respiratory Disease*, vol. 118, no. 1, pp. 65–73, 1978.
- [33] D. F. Proctor, "The upper airways. I. Nasal physiology and defense of the lungs," *The American Review of Respiratory Disease*, vol. 115, no. 1, pp. 97–129, 1977.
- [34] V. Negus, "Further observations on the air conditioning mechanism of the nose," *Annals of the Royal College of Surgeons of England*, vol. 27, pp. 171–204, 1960.

- [35] M. Griffin, E. Mcfaddenjr, and R. Ingramjr, "Airway cooling in asthmatic and nonasthmatic subjects during nasal and oral breathing," *The Journal of Allergy and Clinical Immunology*, vol. 69, no. 4, pp. 354–359, 1982.
- [36] P. Assanasen, F. M. Baroody, E. Naureckas, J. Solway, and R. M. Naclerio, "The nasal passage of subjects with asthma has a decreased ability to warm and humidify inspired air," *American Journal of Respiratory and Critical Care Medicine*, vol. 164, no. 9, pp. 1640–1646, 2001.
- [37] P. Van Cauwenberge, L. Sys, T. De Belder, and J.-B. Watelet, "Anatomy and physiology of the nose and the paranasal sinuses," *Immunology and Allergy Clinics of North America*, vol. 24, no. 1, pp. 1–17, 2004.
- [38] M. F. Quinlan, S. D. Salman, D. L. Swift, J. H. N. Wagner, and D. F. Proctor, "Measurement of mucociliary function in man," *The American Review of Respiratory Disease*, vol. 99, no. 1, pp. 13–23, 1969.
- [39] R. F. Hounam, "The removal of particles from the nasopharyngeal (NP) compartment of the respiratory tract by nose blowing and swabbing," *Health Physics*, vol. 28, no. 6, pp. 743–750, 1975.
- [40] G. D. Raphael, E. V. Jeney, J. N. Baraniuk, I. Kim, S. D. Meredith, and M. A. Kaliner, "Pathophysiology of rhinitis. Lactoferrin and lysozyme in nasal secretions," *The Journal of Clinical Investigation*, vol. 84, no. 5, pp. 1528–1535, 1989.
- [41] D. B. Peden, M. Swiersz, K. Ohkubo, B. Hahn, B. Emery, and M. A. Kaliner, "Nasal secretion of the ozone scavenger uric acid," *The American Review of Respiratory Disease*, vol. 148, no. 2, pp. 455–461, 1993.
- [42] N. G. Toremalm, "The pathophysiology of tracheotomy," *Laryngoscope*, vol. 82, no. 2, pp. 265–270, 1972.
- [43] P. Brandtzaeg, "Immunocompetent cells of the upper airway: functions in normal and diseased mucosa," *European Archives of Oto-Rhino-Laryngology*, vol. 252, Suppl 1, pp. S8–21, 1995.
- [44] J. O. Lundberg, E. Weitzberg, S. L. Nordvall, R. Kuylenstierna, J. M. Lundberg, and K. Alving, "Primarily nasal origin of exhaled nitric oxide and absence in Kartagener's syndrome," *The European Respiratory Journal*, vol. 7, no. 8, pp. 1501–1504, 1994.
- [45] J. O. Lundberg, T. Farkas-Szallasi, E. Weitzberg et al., "High nitric oxide production in human paranasal sinuses," *Nature Medicine*, vol. 1, no. 4, pp. 370–373, 1995.
- [46] S. P. Sanders, J. Kim, K. Ryan Connolly, J. D. Porter, E. S. Siekierski, and D. Proud, "Nitric oxide inhibits rhinovirus-induced granulocyte macrophage colony-stimulating factor production in bronchial epithelial cells," *American Journal of Respiratory Cell and Molecular Biology*, vol. 24, no. 3, pp. 317–325, 2001.
- [47] J. O. N. Lundberg, J. M. Lundberg, G. Settergren, K. Alving, and E. Weitzberg, "Nitric oxide, produced in the upper airways, may act in an 'aerocrine' fashion to enhance pulmonary oxygen uptake in humans," *Acta Physiologica Scandinavica*, vol. 155, no. 4, pp. 467–468, 1995.
- [48] R. M. Kacmarek, R. Ripple, B. A. Cockrill, K. J. Bloch, W. M. Zapol, and D. C. Johnson, "Inhaled nitric oxide. A bronchodilator in mild asthmatics with methacholine-induced bronchospasm," *American Journal of Respiratory and Critical Care Medicine*, vol. 153, no. 1, pp. 128–135, 1996.
- [49] S. M. Brugman, G. L. Larsen, P. M. Henson, J. Honor, and C. G. Irvin, "Increased lower airways responsiveness associated with sinusitis in a rabbit model," *The American Review of Respiratory Disease*, vol. 147, no. 2, pp. 314–320, 1993.
- [50] E. J. Huxley, J. Viroslav, W. R. Gray, and A. K. Pierce, "Pharyngeal aspiration in normal adults and patients with depressed consciousness," *The American Journal of Medicine*, vol. 64, no. 4, pp. 564–568, 1978.
- [51] T. Sato, "Effect of nasal mucosa irritation on airway resistance," *Auris Nasus Larynx*, vol. 7, no. 1, pp. 39–50, 1980.
- [52] P. G. Bardin, B. B. Van Heerden, and J. R. Joubert, "Absence of pulmonary aspiration of sinus contents in patients with asthma and sinusitis," *The Journal of Allergy and Clinical Immunology*, vol. 86, no. 1, pp. 82–88, 1990.
- [53] T. B. Casale, D. Wood, H. B. Richerson et al., "Elevated bronchoalveolar lavage fluid histamine levels in allergic asthmatics are associated with methacholine bronchial hyperresponsiveness," *The Journal of Clinical Investigation*, vol. 79, no. 4, pp. 1197–1203, 1987.
- [54] A. Taytard, D. Beaumont, J. C. Pujet, M. Sapene, and P. J. Lewis, "Treatment of bronchial asthma with terfenadine; a randomized controlled trial," *British Journal of Clinical Pharmacology*, vol. 24, no. 6, pp. 743–746, 1987.
- [55] A. Kanda, Y. Kobayashi, M. Asako, K. Tomoda, H. Kawachi, and H. Iwai, "Regulation of interaction between the upper and lower Airways in united airway disease," *Medical Science*, vol. 7, no. 2, p. 27, 2019.
- [56] J. H. Whicker and E. B. Kern, "The nasopulmonary reflex in the awake animal," *The Annals of Otolaryngology, Rhinology, and Laryngology*, vol. 82, no. 3, pp. 355–358, 1973.
- [57] J. H. Whicker, E. B. Kern, and R. E. Hyatt, "Nasopulmonary reflex: evaluation in the nonparalyzed and paralyzed anesthetized dog," *The Annals of Otolaryngology, Rhinology, and Laryngology*, vol. 87, no. 1, pp. 91–98, 1978.
- [58] J. Kaufman, J. C. Chen, and G. W. Wright, "The effect of trigeminal resection on reflex bronchoconstriction after nasal and nasopharyngeal irritation in man," *The American Review of Respiratory Disease*, vol. 101, no. 5, pp. 768–769, 1970.
- [59] J. Kaufman and G. W. Wright, "The effect of nasal and nasopharyngeal irritation on airway resistance in man," *The American Review of Respiratory Disease*, vol. 100, no. 5, pp. 626–630, 1969.
- [60] J. Corren, A. D. Adinoff, and C. G. Irvin, "Changes in bronchial responsiveness following nasal provocation with allergen," *The Journal of Allergy and Clinical Immunology*, vol. 89, no. 2, pp. 611–618, 1992.
- [61] J. A. Nadel and J. G. Widdicombe, "Reflex effects of upper airway irritation on total lung resistance and blood pressure," *Journal of Applied Physiology*, vol. 17, no. 6, pp. 861–865, 1962.
- [62] M. J. Schumacher, K. A. Cota, and L. M. Taussig, "Pulmonary response to nasal-challenge testing of atopic subjects with stable asthma," *The Journal of Allergy and Clinical Immunology*, vol. 78, no. 1, pp. 30–35, 1986.
- [63] P. Small and N. Biskin, "The effects of allergen-induced nasal provocation on pulmonary function in patients with perennial allergic rhinitis," *American Journal of Rhinology*, vol. 3, no. 1, pp. 17–20, 1989.
- [64] S. Bonini, A. Lambiase, S. Bonini et al., "Circulating nerve growth factor levels are increased in humans with allergic diseases and asthma," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 93, no. 20, pp. 10955–10960, 1996.
- [65] D. D. Hunter and R. D. Dey, "Identification and neuropeptide content of trigeminal neurons innervating the rat nasal epithelium," *Neuroscience*, vol. 83, no. 2, pp. 591–599, 1998.

- [66] M. Tomaki, M. Ichinose, M. Miura et al., "Elevated substance P content in induced sputum from patients with asthma and patients with chronic bronchitis," *American Journal of Respiratory and Critical Care Medicine*, vol. 151, no. 3_part_1, pp. 613–617, 1995.
- [67] B. J. Undem, W. Hubbard, and D. Weinreich, "Immunologically induced neuromodulation of Guinea pig nodose ganglion neurons," *Journal of the Autonomic Nervous System*, vol. 44, no. 1, pp. 35–44, 1993.
- [68] B. J. Undem, M. McAlexander, and D. D. Hunter, "Neurobiology of the upper and lower airways," *Allergy*, vol. 54, Suppl 57, pp. 81–93, 1999.
- [69] A. Togias, "Mechanisms of nose-lung interaction," *Allergy*, vol. 54, Suppl 57, pp. 94–105, 1999.
- [70] G. J. Gleich and C. R. Adolphson, "The eosinophilic leukocyte: structure and function," *Advances in Immunology*, vol. 39, pp. 177–253, 1986.
- [71] J. C. Hogg, "The pathology of asthma," *APMIS*, vol. 105, no. 7-12, pp. 735–745, 1997.
- [72] E. Frigas, D. A. Loegering, and G. J. Gleich, "Cytotoxic effects of the Guinea pig eosinophil major basic protein on tracheal epithelium," *Laboratory Investigation*, vol. 42, no. 1, pp. 35–43, 1980.
- [73] G. J. Gleich, "The eosinophil and bronchial asthma: current understanding," *The Journal of Allergy and Clinical Immunology*, vol. 85, no. 2, pp. 422–436, 1990.
- [74] L. A. Laitinen, M. Heino, A. Laitinen, T. Kava, and T. Haahtela, "Damage of the airway epithelium and bronchial reactivity in patients with asthma," *The American Review of Respiratory Disease*, vol. 131, no. 4, pp. 599–606, 1985.
- [75] N. A. Flavahan, N. R. Slifman, G. J. Gleich, and P. M. Vanhoutte, "Human eosinophil major basic protein causes hyper-reactivity of respiratory smooth muscle. Role of the epithelium," *The American Review of Respiratory Disease*, vol. 138, no. 3, pp. 685–688, 1988.
- [76] E. Frigas and G. J. Gleich, "The eosinophil and the pathophysiology of asthma," *The Journal of Allergy and Clinical Immunology*, vol. 77, no. 4, pp. 527–537, 1986.
- [77] C. Cuppari, S. Leonardi, S. Manti et al., "Allergen immunotherapy, routes of administration and cytokine networks: an update," *Immunotherapy*, vol. 6, no. 6, pp. 775–786, 2014.
- [78] S. J. Galli, M. Tsai, and A. M. Piliponsky, "The development of allergic inflammation," *Nature*, vol. 454, no. 7203, pp. 445–454, 2008.
- [79] B. Lamkhioed, P. M. Renzi, S. Abi-Younes et al., "Increased expression of eotaxin in bronchoalveolar lavage and airways of asthmatics contributes to the chemotaxis of eosinophils to the site of inflammation," *Journal of Immunology*, vol. 159, no. 9, pp. 4593–4601, 1997.
- [80] E. M. Minshall, L. Cameron, F. Lavigne et al., "Eotaxin mRNA and protein expression in chronic sinusitis and allergen-induced nasal responses in seasonal allergic rhinitis," *American Journal of Respiratory Cell and Molecular Biology*, vol. 17, no. 6, pp. 683–690, 1997.
- [81] A. J. Wardlaw, "Molecular basis for selective eosinophil trafficking in asthma: a multistep paradigm," *The Journal of Allergy and Clinical Immunology*, vol. 104, no. 5, pp. 917–926, 1999.
- [82] R. T. Palframan, P. D. Collins, T. J. Williams, and S. M. Rankin, "Eotaxin induces a rapid release of eosinophils and their progenitors from the bone marrow," *Blood*, vol. 91, no. 7, pp. 2240–2248, 1998.
- [83] W. W. Busse, W. F. Calhoun, and J. D. Sedgwick, "Mechanism of airway inflammation in asthma," *The American Review of Respiratory Disease*, vol. 147, no. 6_part_2, pp. S20–S24, 1993.
- [84] M. D. Inman, R. Ellis, J. Wattie, J. A. Denburg, and P. M. O'Byrne, "Allergen-induced increase in airway responsiveness, airway eosinophilia, and bone-marrow eosinophil progenitors in mice," *American Journal of Respiratory Cell and Molecular Biology*, vol. 21, no. 4, pp. 473–479, 1999.
- [85] J. R. Gordon and S. J. Galli, "Release of both preformed and newly synthesized tumor necrosis factor alpha (TNF-alpha)/cachectin by mouse mast cells stimulated via the fc epsilon RI. A mechanism for the sustained action of mast cell-derived TNF-alpha during IgE-dependent biological responses," *The Journal of Experimental Medicine*, vol. 174, no. 1, pp. 103–107, 1991.
- [86] G.-J. Braunstahl, S. E. Overbeek, A. KleinJan, J.-B. Prins, H. C. Hoogsteden, and W. J. Fokkens, "Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways," *The Journal of Allergy and Clinical Immunology*, vol. 107, no. 3, pp. 469–476, 2001.
- [87] J. B. Sedgwick, W. J. Calhoun, G. J. Gleich et al., "Immediate and late airway response of allergic rhinitis patients to segmental antigen challenge. Characterization of eosinophil and mast cell mediators," *The American Review of Respiratory Disease*, vol. 144, no. 6, pp. 1274–1281, 1991.
- [88] N. T. Littell, C. C. Carlisle, R. P. Millman, and S. S. Braman, "Changes in airway resistance following nasal provocation," *The American Review of Respiratory Disease*, vol. 141, no. 3, pp. 580–583, 1990.