Parteek Prasher · Mousmee Sharma · Sachin Kumar Singh · Ronan MacLoughlin · Kavita Pabreja · Kamal Dua *Editors*

Understanding Allergic Airway Diseases

Contemporary Treatment Paradigm

Springer

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Preface

In the realm of medical science, few domains have witnessed as profound a transformation as our understanding of allergic airway diseases. From the earliest observations of wheezing and breathlessness to the intricate molecular pathways that govern these conditions, the journey has been both enlightening and challenging. The landscape of allergic airway diseases, encompassing conditions such as asthma, allergic rhinitis, and sinusitis, has not only expanded in its scope but has also revealed layers of complexity that demand a nuanced approach.

Understanding Allergic Airway Diseases: Contemporary Treatment Paradigm emerges from a convergence of clinical experience, cutting-edge research, and patient narratives. This book is not merely a compilation of facts and figures but a comprehensive exploration into the multifaceted nature of allergic airway diseases. We delve deep into the aetiology, pathophysiology, clinical manifestations, and diagnostic modalities that characterize these conditions. Furthermore, in recognition of the dynamic nature of medical science, this text provides a thorough review of the contemporary treatment paradigms that are shaping patient care today.

One cannot overstate the significance of understanding allergic airway diseases in the context of modern healthcare. With an increasing prevalence globally, the socio-economic burden of these conditions is palpable. Yet, amidst the challenges lie opportunities to innovate, collaborate, and redefine the boundaries of therapeutic interventions. This book endeavours to bridge the gap between knowledge and practice, equipping clinicians, researchers, and students with the tools they need to navigate the complexities of allergic airway diseases with confidence and competence.

As you embark on this literary journey, you will encounter a blend of foundational principles, emerging trends, and expert insights. Each chapter is meticulously crafted to offer a balanced perspective, drawing upon evidence-based practices while fostering a spirit of inquiry. Whether you are a seasoned pulmonologist, an aspiring medical student, or a patient seeking clarity, *Understanding Allergic Airway Diseases: Contemporary Treatment Paradigm* promises to be a valuable resource.

In closing, I extend my heartfelt gratitude to all the contributors who have dedicated their expertise and passion to this endeavour. May this book serve as a beacon

of knowledge, fostering innovation, compassion, and excellence in the ever-evolving landscape of allergic airway diseases.

Dehradun, India — Parteek Prasher
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Phagwara, Punjab, India — Sachin Kumar Singh
Galway, Ireland — Ronan MacLoughlin
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reviewed more than 75 research papers upon invitation from publishers of high repute. He has graduated 8 PhD students and 30 M pharmacy students and currently graduating 3 masters and 6 PhD students. Currently, his h index is 27 with total citations > 2300. In January 2020, he received Dr. B.C. Deb Memorial Award for the popularization of science by the Indian Science Congress Association at 107th Indian Science Congress held at UAS Bengaluru. He is the first recipient from the field of pharmaceutical sciences to receive this award. He is also a recipient of the 2014 Bharat Shiksha Ratan Award given by the Global Society for Health and Education Growth, Delhi, India. His core area is improving the oral bioavailability of poorly water-soluble drugs using various formulation approaches, including nanotechnology, complexation, solid dispersion, liquisolid technology, etc.

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Kamal Dua, Senior Lecturer, Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney (UTS), has a research experience of over 12 years working in the field of drug delivery targeting inflammatory diseases. He is also a leader of Drug Delivery Research in the Centre for Inflammation at Centenary Institute/UTS, where the targets identified from the research projects are pursued to

develop novel formulations as the first step toward translation into clinics. His key research areas are drug delivery and immunology, specifically addressing how these disciplines can advance one another helping the community to live longer and healthier. This is evidenced by his extensive publication record in reputed journals. His research interests focus on harnessing the pharmaceutical potential of modulating critical regulators such as interleukins and microRNAs and developing new and effective drug delivery formulations for the management of inflammation in chronic airway diseases and cancer.

Introduction to Allergic Airway Disease

1

Anurag Mishra, Mohit Agrawal, and Yogendra Singh

Abstract

The incidence of allergic airway illnesses has seen a notable escalation in recent decades, affecting around 30 percent of the population in affluent nations. The global prevalence of this condition is estimated to impact over 315 million individuals, with around 10% of asthma sufferers experiencing severe or uncontrolled symptoms. In the setting of airway allergies, immunological responses develop upon initial encounters with allergens in a manner associated with type 2 helper T-cell (Th2) functioning. The aforementioned procedure leads to the expression of interleukin (IL)-4, IL-5, and IL-13 inflammatory proteins, as well as the production of allergen-specific antibodies known as immunoglobulin E (IgE) at heightened levels. Efficient treatment techniques are required for the control and management of allergic disorders. Medicinal interventions for respiratory conditions include the use of bronchodilators and inhaled corticosteroids, which have demonstrated efficacy in mitigating inflammation and alleviating associated symptoms. However, it is important to note that these medications are unable to alter the inherent nature and course of the disease. Therefore, the need is crucial to clarify the shared major physiological variables and biological mechanisms driving AADs, because any therapy that targets these "master switches" is better than the standard approach.

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1.1 Introduction

The term "allergic airway disease (AADs)" refers to a range of chronic disorders that affect the airways and lungs and are typically induced by allergic responses to particular chemicals. Common forms of AAD include allergic asthma (AA), chronic rhinosinusitis (CRS), and allergic rhinitis (AR). The exponential rise in AA, AR and CRS incidence rates since the global advent of industrialization has been a major burden on both the economy and human society. While each AAD has its own unique set of symptoms and anatomical location where damage occurs, recent research reveals that these conditions may actually coexist in the same person and share some of the common pathophysiological pathways. In addition, inflammation and constriction of the airways are hallmarks of these illnesses, which can cause a wide variety of symptoms and greatly reduce an individual's quality of life.

The incidence of allergic airway illnesses has seen a notable escalation in recent decades, affecting around 30 percent of the population in affluent nations. AA is widely recognized as a very significant condition globally, mostly due to the substantial impact it has on individuals' functional limitations and the prolonged length of impairment it entails. The global prevalence of this condition is estimated to impact over 315 million individuals, with around 10% of asthma sufferers experiencing severe or uncontrolled symptoms. Several variables contribute to the heightened prevalence of asthma, encompassing genetic susceptibility and exposure to environmental pollutants and aeroallergens. The development of chronic airway inflammation starts with repetitive occurrences of wheezing, dyspnea, cough, and chest tightness. This process subsequently results in inflammatory structural alterations, such as increased sensitivity of the bronchial tubes to various stimuli, blockage of the airways, and remodeling of the airways caused by inflammation. AR refers to an allergic inflammation of the nasal mucosa, which manifests as symptoms such as sneezing, rhinorrhea, pruritus, and nasal congestion. Furthermore, CRS is defined by chronic inflammation of the nasal and sinus mucous membranes, which can cause a wide range of symptoms. Chronic rhinosinusitis is distinct from acute rhinosinusitis, which is an infection of the nasal and sinus cavities that clears itself quickly. According to reports, there is a global prevalence of allergic rhinitis among adults ranging from 10% to 40%. Moreover, there has been a significant surge in the number of cases observed in recent decades. Despite the recent publication of more articles on the role of AAD, such as AR and AA, in the severity and mortality of COVID-19, a meta-analysis found that having a history of AAD is not likely to worsen the course of COVID-19. In addition, individuals with COVID-19 who took AAD had a considerably lower probability of mortality. Data from 34 studies with 345,091 individuals with COVID-19 demonstrated that the frequency of concomitant AAD in patients with COVID-19 did not vary among nations or regions. AAD population size would also be a factor in the reliability of the findings.

There has to be more research done to determine the underlying pathogenic processes and potential therapeutic applications (Ming et al. 2022).

In the setting of airway allergies, immunological responses develop upon initial encounters with allergens in a manner associated with type 2 helper T-cell (Th2) functioning. The aforementioned procedure leads to the expression of interleukin (IL)-4, IL-5, and IL-13 inflammatory proteins, as well as the production of allergen-specific antibodies known as immunoglobulin E (IgE) at heightened levels. These substances then facilitate the recruitment and activation of effector cells, such as eosinophils, basophils, and mast cells. The majority of IgE antibodies have affinity for FcεR1 receptors found on mast cells, basophils, and eosinophils. Many mediators of inflammatory processes, including prostaglandins, leukotrienes, and histamine, are released into the bloodstream once allergens and IgE come into interaction. These mediators contribute to the manifestation of early-phase symptoms, including itching, swelling, and bronchoconstriction. The late-phase responses are facilitated by the infiltration of T cells and the release of their produced cytokines, which contribute to the exacerbation of tissue inflammation. Upon rechallenge, the durable specific memory B and T cells exhibit fast proliferation, therefore establishing an immunologic memory and serving as a prompt reservoir for further immune responses.

Efficient treatment techniques are required for the control and management of allergic disorders. Medicinal interventions for respiratory conditions include the use of bronchodilators and inhaled corticosteroids, which have demonstrated efficacy in mitigating inflammation and alleviating associated symptoms. However, it is important to note that these medications are unable to alter the inherent nature and course of the disease. Therefore, the need is crucial to clarify the shared major physiological variables and biological mechanisms driving AADs, because any therapy that targets these "master switches" is better than the standard approach.

1.1.1 Immunopathology of AAD

As a way to highlight the common vulnerability and pathophysiology across allergic illnesses, the term "atopic disease" is frequently used. An individual with atopy has a genetic or inherited predisposition to develop environmental sensitization and an IgE antibody response (Johansson et al. 2004). Atopic diseases have a complicated and as-yet-ununderstood etiology. There is considerable evidence that both hereditary and environment-related elements contribute to AAD pathogenesis. Many cases of allergic illness begin in infancy or early childhood, and the onset of symptoms typically follows a predictable pattern known as the "atopic march" (Spergel and Paller 2003). Environmental allergen exposure in conjunction with adjuvant variables throughout infancy and early childhood influences the atopic status of genetically sensitive patients (Björkstén 1999; Peden 2000). Atopic dermatitis (AD) can be diagnosed in children as early as 1 year old, and it frequently occurs alongside an allergy to cow milk in children with a propensity for allergic illnesses. Diagnosis of AR and, subsequently, AA in these kids is possible as early as age 6–7.

Children that possess a predisposition for allergic illnesses are frequently identified as having atopic dermatitis (AD) at a tender age of 1 year, commonly accompanied by an allergic reaction to cow milk. These children frequently exhibit a pattern of advancement leading to the development of AR and subsequently AA, which may typically be identified by diagnosis at about 6–7 years of age (Čelakovská et al. 2020). Several children will carry their asthma attacks into adulthood, while others may see a remission of their symptoms or a total disappearance of their condition as they become grow older. Although hereditary variables influence vulnerability, environmental triggers can cause the onset of the illness, as shown by the greater prevalence of asthma in infants who suffered from virally (respiratory syncytial virus, RSV) produced bronchiolitis in infancy (Mackay 1985). There are extensive environmental and host-based biological networks involved in the pathophysiology of inflammatory airway disorders. The airways' epithelium serves as a main line of defense against aeroallergens inside the individual's respiratory system in the context of AR. Nonetheless, allergens' intrinsic proteolytic activity may lead the epithelium to lose its passive structural barrier role, enabling allergens to enter local tissues and set off ongoing chronic inflammatory processes (Bashir et al. 2013; Stamataki et al. 2021). The genesis of immune-mediated illness including AR, CRS, and AA has been further investigated, and it has been demonstrated that intrinsic barrier failure contributes to the disease (Steelant et al. 2016; Hellings and Steelant 2020). However, the relative contributions of basic (genetic) and secondary (inflammatory) pathways in causing barrier dysfunction remain unclear. Although epithelial cells certainly have a role in providing a barrier of tissue against inhaled allergens, they also participate in airway inflammation by sensing and reacting to external triggers. In response to allergens or infections, the airway epithelium induces toll-like receptors, which are proteins that recognize patterns (Radman et al. 2015; van Tongeren et al. 2015a), which then trigger the synthesis of various mediators. These mediators provide an environment that promotes local inflammation by altering the activity of immune cells and influencing the migration of inflammatory cells to affected tissues (Van Tongeren et al. 2015b). An inability to turn off the activation response may contribute to the persistent activation of the nasal epithelium seen in allergic illness (Golebski et al. 2015).

Airborne allergens such dust mite feces, cockroach dander, pet dander, mold spores, and pollens trigger AR by invading the nasal cavity lining with inflammatory cells like macrophages, mast cells, B lymphocytes, CD4+ T lymphocytes, and eosinophils. IgE is generated by plasma cells, while IL-3, IL-4, IL-5, and IL-13 are induced in the circulation by Th2 cells. However, the mechanism that generates IgE remains a mystery to many. It has been discovered in recent years that follicular helper T (Tfh) cells, a subgroup of CD4+ T-effector cells, rather than Th2 cells, are the key regulators of IgE production. The interaction between allergen cross-linked IgE and mast cells results in the release of a number of mediators (such as leukotrienes and histamine) which promote vascular permeability and arteriole dilatation, the contraction of pulmonary smooth muscle, an accumulation of mucus, chronic runny nose, and itchy skin (Small et al. 2007; Dykewicz and Hamilos 2010). Cellular late inflammatory responses are triggered by the released mediators and cytokines

4–8 h later, causing a return of symptoms, most often nasal congestion, that typically lasts for days. Both AR and AA have comparable immunopathological characteristics, including the invasion of eosinophils, mast cells, and Th2 cells. Airway remodeling structural alterations are most understood in AA, although they may also occur in AR. AR and AA also differ on a pathophysiological level. Epithelial hyperplasia, increased mucus production, and goblet cell metaplasia are all examples of mucosal pathological abnormalities seen with AA illness (Fahy 2015). Airway constriction and increased mucus formation characterize an asthma episode, accompanied by symptoms including breathlessness, wheezing, chest discomfort, and coughing, all of which originate in the submucosal layer, where significant mucus glands, collagen adhesion, and smooth muscle hypertrophy predominate (Mims 2015) (Fig. 1.1).

The imbalance of Th cells has been hypothesized to be at the root of AA, an adaptive immune illness (Busse and Rosenwasser 2003). The Th hypothesis has been called into question due to the lack of a consistent response to Th2-directed therapies for AA, the presence of innate signatures in subtypes of asthmatics, and the association between respiratory viral infections and the onset and exacerbation of disease (Holtzman 2012; Brasier 2013). There is mounting evidence that antigen-independent mucosal responses, known as "innate" responses, play crucial roles in both the onset and development of the illness. Both viral infections and exposure to common aeroallergens can set off innate immune responses (IIRs) in the normal and asthmatic airway. In addition, atopy modifies the IIR to viral pathogens, and viral

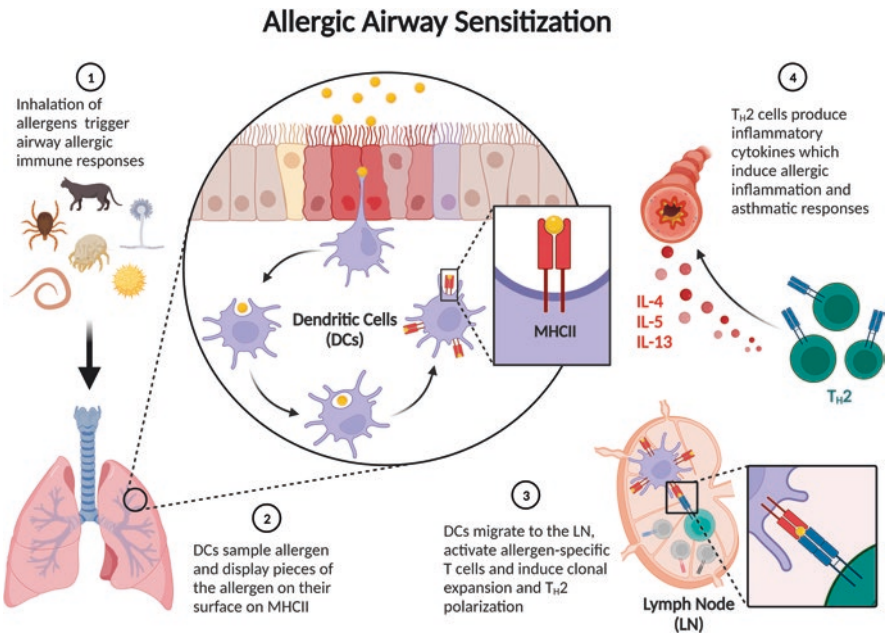

Fig. 1.1 Exhibits aeroallergens-mediated allergic immune response in AAD

infections themselves predispose to the development of atopy (Message et al. 2008; Sigurs et al. 2010). This suggests a more holistic understanding of mucosal innate immune dysregulation in AA. New evidence supports the treatment development route by showing that the NFB/RelA-BRD4 complex facilitates epithelial barrier breakdown and remodeling in response to viruses and allergens (Brasier 2019). Emerging scientific investigations suggest that modifications to the epigenome have a role in changes to the morphology of epithelial cells (Seaton et al. 1994; Hewitt and Lloyd 2021; Wang et al. 2023). Epigenomic moderators may also be a way to restore normalcy to the epithelium injury-repair process by inhibiting the antiviral IFN signal and modification of innate communication pathway. Reversing structural remodeling and restoring normal IIR in AA may be possible with the use of therapies that target epigenetic alterations in the mucosa (Brasier 2019).

1.2 Biomarkers of AAD

New "biomarkers" for illness existence, vulnerability, and even varied response to therapy have emerged as the direct outcome of the fast expansion and utilization of molecular methods in the area of AAD. These biomarkers are helping to pave the way for "personalized" medicine, in which patients receive care that is more precisely customized to their unique needs and preferences and less in accordance with the current "one-size-fits-all" clinical management recommendations. Existing and new biomarkers are expected to influence daily clinical decision-making by physicians; this will allow them to focus medicines to patients who will benefit while sparing expense and possible negative consequences for individuals who will not.

Although there is no such thing as a perfect biomarker, an ideal biomarker for AA and other AAD would have the following features: (1) the ability to reliably differentiate among health conditions and diseases with high positive and negative anticipatory values; (2) the ability to convey data regarding disease prognosis and clinical efficacy conclusions; (3) flexibility to adapt to illness development and return to "normal" after effective therapy; and (4) being able to be replicated successfully in a healthcare setting. AA and AAD biomarkers may potentially have several potential points of genesis, each with its own set of benefits and drawbacks.

Notable and potentially relevant biomarkers are outside the focus of this chapter but include CRP, TNF-α, pendrin, IL-2, and osteopontin.

1.2.1 Products of the Arachidonic Acid Metabolic Pathway

Inflammatory signaling involves the release of arachidonic acid, an unsaturated fatty acid normally found in cell membrane phospholipids. Prostaglandins, leukotrienes, and lipoxins are all byproducts of arachidonic acid metabolism (Fig. 1.2). Lipoxins and leukotriene E4 (LTE4), a cysteinyl leukotriene, are the primary targets of ongoing biomarker research.

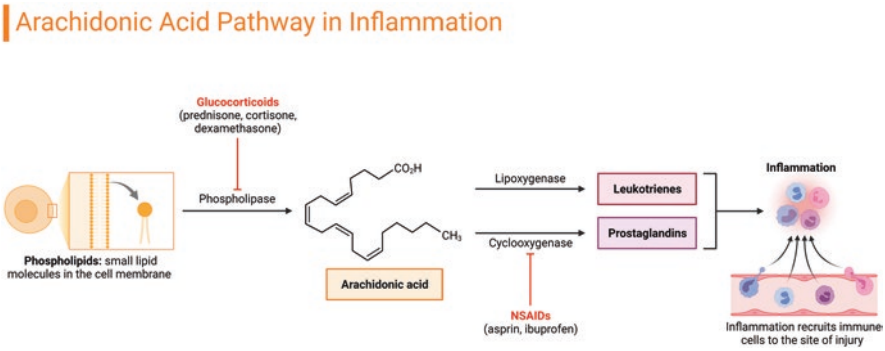

Fig. 1.2 Illustrates the role of arachidonic acid pathway in inflammatory consequences of AAD

1.2.1.1 Lipoxins

Furthermore, to their role in chemotaxis and the transduction of signals that goes along with it, lipoxins also suppress inflammation in a number of different ways. Lipoxin A4 values are lesser in critically sufferers of AA than in individuals with milder forms of the disease (Planagumà et al. 2008), and this is accompanied by extended innate lymphoid cell activity and eosinophilia, in addition to missing of activity in essential enzymes and receptors necessary for lipoxin synthesis (Barnig et al. 2013). In serious asthmatics, decreased airway macrophage lipopolysaccharide-stimulated lipoxin A4 synthesis is strongly linked with airflow limitation (Bhavsar et al. 2010). Lipoxin A4 production has been shown to be increased in airway specimens from individuals with AA, suggesting that blockers of soluble epoxide hydrolase ability may be useful for the therapeutic management of life-threatening asthma.

1.2.1.2 The E4 Leukotriene

Leukotriene (LT) E4, a stable consequence of cysteinyl leukotriene breakdown, is readily identifiable in specimens of urine and does not need any invasive method for detection. Multiple studies have shown that both teens suffering from AA and adults suffering aspirin-induced airway disease had increased amounts of LTE4 in their urine (Rabinovitch et al. 2006; Bochenek et al. 2014). Urinary LTE4 concentrations have also been linked to asthma exacerbations and airflow restriction severity, albeit this biomarker may be muddled by other factors (Lang et al. 2013). However, in children with AA who have been impacted by passive smoking, elevated LTE4 levels are no longer a good predictor of future exacerbations. Other prospective clinical studies using urine LTE4 as a biomarker have shown promising findings (Rabinovitch et al. 2011; Kolmert et al. 2021). In research, a leukotriene receptor antagonist outperformed inhaled corticosteroids in improving pulmonary function and asthma management in children having a greater baseline ratio of urine LTE4 to FeNO. Add-on treatment with the combination of an inhaled corticosteroid and an antagonist of the LT receptor was shown to be more effective than long-acting agonists, regardless of baseline urine LTE4 concentrations, according to a more recent

investigation (Rabinovitch et al. 2010; Hu et al. 2023). This correlation was small and may have been underpowered, but the results nonetheless support future investigation into the use of LTE4 as a biomarker in the selection of asthma medication.

1.2.1.3 3-Bromotyrosine in the Urine

During the respiratory burst process, activated eosinophils produce hypobromous acid, which may be used to posttranslationally modify tyrosine protein residues, resulting in 3-bromotyrosine. 3-Bromotyrosine's potential biomarker benefits from its stability and the ease with which it may be detected in the urine. In addition to being linked to airway limitation, asthma management, and future exacerbations, recent investigations have revealed that 3-bromotyrosine concentrations are greater in individuals with AA (Wedes et al. 2009; Wang et al. 2022). Other research has indicated that the use of inhaled corticosteroids leads to a reduction in urine 3-bromotyrosine concentrations.

1.2.1.4 Chitinase Homologous Proteins

Extracellular matrix remodeling and control are processes that may include chitinases, a class of hydrolases distinguished by their capacity to split chitin. Airflow restriction and other clinical markers of illness severity are linked to the chitinase-like protein YKL-40 (also known as human cartilage glycoprotein-39), which is present in the blood and airways of individuals with AA (Chupp et al. 2007). Additionally, YKL-40 expression is elevated during acute asthma exacerbations, suggesting that it may be used as a predictor of the progressive loss of lung function that occurs in response to cigarette smoking. In children, researchers have shown that thicker bronchial walls are linked to higher levels of YKL-40 expression in both bronchoalveolar lavage fluid and serum (Tang et al. 2010). Further research is required; however, YKL-40 shows promise as a tool for predicting asthma outcomes and risks in the future.

1.2.1.5 Periostin

Periostin is secreted by airway epithelial cells in anticipation of IL-13, a cytokine associated with inflammatory responses that activates the TGF-beta regulatory pathway and affects epithelial-mesenchymal communications (Corren et al. 2011; Lopez-Guisa et al. 2012). Serum testing is a noninvasive technique to check for elevated periostin levels, which have been proven to be present in the airways of people with AA. However, there is little evidence that these two measures correspond (Wagener et al. 2015). Serum periostin values have been demonstrated to have no or little correlation with bronchial eosinophils according to recent studies (Kim et al. 2014). However, higher blood periostin concentrations in people with asthma have been linked to more severe airflow restriction, a steeper loss in lung function, and other markers of asthma severity (Kanemitsu et al. 2013).

1.3 Treatment Approaches for AAD

1.3.1 Mast Cell-Specific Therapy

Histamine, produced mostly by mast cells, stimulates the H1 receptor to generate a cascade of reactions that manifest as allergy and inflammatory illness symptoms (such as urticaria) in susceptible individuals (Thangam et al. 2018). Treatment for numerous mast cell-driven disorders has relied heavily on H1 antihistamines since their discovery.

There has been mixed success treating AAD with leukotriene inhibitors including montelukast, zafirlukast, pranluton, and zileuton. For the management of AA and AR, the US FDA has approved the therapeutic application of montelukast. It is believed to be less effective than inhaled or intranasal corticosteroids in treating both diseases. The Food and Medicine Administration warned of significant neuropsychiatric events in 2020 among montelukast users and that the medicine be used only as a last resort in the treatment of AR.

1.3.2 Target Lipid Messenger: PGs and LTs

PGD2, a lipid messenger produced mostly by mast cells, has been linked to urticaria and allergies through its impact on chemoattractant receptor homologue substance presented on T helper 2 cells (TH2 cells). AZD1981 (a selective CRTh2 antagonist) was well tolerated, lowered weekly itch ratings more than wheals, and blocked PGD2-mediated eosinophil morphology change in individuals with antihistamine-resistant chronic sclerodactylic urticaria (CSU) (Oliver et al. 2019). In the treatment of people with AA and AR, various studies have found little or poor clinical success for many CRTh2 antagonists, such as setipiprant, AZD1981, timapiprant (OC-459), fevipiprant, and BI671800 (Brightling et al. 2021). In individuals with severe asthma, for instance, fevipiprant did not demonstrate substantial improvement in phase III studies, but another CRTh2 antagonist, GB001, did show modest efficacy in reducing asthma symptoms (Asano et al. 2020).

1.3.3 Immunotherapy

Allergen immunotherapy is an alternative to pharmacological treatment that modifies the immune system's response to allergens by means of prolonged, carefully monitored exposure. Treatment with this method usually takes between 3 and 5 years. Subcutaneous (SCIT) and sublingual (SLIT) immunotherapy are two forms of this treatment. While anaphylaxis is a worry with SCIT, it is considerably less likely to occur with SLIT (Solelhac and Charpin 2014).

Currently, the treatment of AADs with the biologic agents omalizumab, benralizumab, mepolizumab, reslizumab, and dupilumab is approved. Other anti-inflammatory medicines used to treat asthma include bronchodilating agents,

chromones, and theophylline, and in recent years, researchers have developed antibodies against IL-4/IL-13 receptors and IL-5/IL-5 receptors.

1.4 Conclusion

Over the course of many decades of study, scientists have come to a much better knowledge of the immunological and environmental underpinnings of AAD. Unfortunately, the state-of-the-art treatments for these disorders have yet to catch up. Allergies are immunologically complicated, and they might entail many different types of hypersensitivity that all work together. The immunological response of the airways to particles and allergens in the air is complex and multifaceted, as shown by recent investigations. Asthma and rhinosinusitis have been associated to infections that are of the airway tract caused by viruses, particularly HRV and fungi, according to recent research. Therefore, it is anticipated that future therapies will aim to both reduce environmental factors that promote the development of allergic responses and reduce endogenous chemicals (such as cytokines) that coordinate allergic inflammation in AAD.

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Pathophysiology of Allergic Airways Disease

2

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Abstract

Allergic airways disease, encompassing conditions such as asthma and allergic rhinitis, presents a significant global health burden. This chapter provides a comprehensive exploration of its pathophysiology, including immune responses, inflammatory mediators, airway remodeling, and the role of allergens. Current diagnostic methodologies and biomarkers crucial for accurate diagnosis and monitoring are discussed, emphasizing the need for a multidimensional diagnostic approach. Furthermore, this chapter sheds light on the implications of these findings for clinical practice and research, advocating for personalized therapeutic strategies and further interdisciplinary studies to propel advancements in the field, ultimately enhancing patient care and outcomes.

Keywords

Allergens · Airway · Pathophysiology · Cytokines · Inflammatory mediators

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2.1 Introduction

Allergic airways disease, also known as allergic respiratory disease or allergic airway inflammation, encompasses a group of chronic respiratory disorders characterized by hypersensitive airways and immune system responses to specific allergens. This condition primarily involves the respiratory tract, including the nasal passages, throat, bronchi, and lungs. It significantly affects the quality of life for those afflicted and represents a substantial global health concern. Allergic airways diseases can manifest in various forms, including allergic rhinitis (hay fever), allergic asthma, allergic bronchitis, and allergic sinusitis (Ackerman et al. 2016; Adams et al. 2019). The common thread among these conditions is an exaggerated immune response triggered by exposure to allergens. Allergens are substances from the environment that, for most individuals, are harmless but induce an immune response in allergic individuals. The pathophysiology of allergic airways disease centers on an abnormal immune response, primarily involving two key immune components: immunoglobulin E (IgE) and various immune cells, such as mast cells, eosinophils, and T lymphocytes (Agresta et al. 2014; Ahmad et al. 2023).

When an allergic individual is exposed to an allergen, the immune system perceives it as a threat, leading to the production of allergen-specific IgE antibodies. These antibodies bind to specific receptors on mast cells and basophils, priming these cells for subsequent allergen encounters. Upon re-exposure to the allergen, it cross-links with the IgE antibodies on these cells, triggering the release of inflammatory mediators like histamine, leukotrienes, and cytokines. Histamine and other mediators induce a cascade of reactions, resulting in typical allergic symptoms. In the upper respiratory tract, this can manifest as sneezing, nasal congestion, and itching, while in the lower respiratory tract, it may lead to coughing, wheezing, shortness of breath, and chest tightness, which are characteristics of asthma. The inflammatory response in allergic airways disease involves the recruitment and activation of eosinophils, which release pro-inflammatory substances, contributing to airway inflammation and tissue damage (Al Heialy et al. 2011; Allen et al. 2009). This chronic inflammation leads to airway remodeling, characterized by structural changes in the airways, such as increased smooth muscle mass, collagen deposition, and mucus gland hyperplasia. These alterations further exacerbate the symptoms and complicate the management of the disease.

Environmental factors play a significant role in the development and exacerbation of allergic airways disease. Common allergens include pollen, pet dander, mold spores, dust mites, cockroach droppings, and certain foods. Additionally, respiratory infections, cigarette smoke, air pollution, and occupational exposures can worsen the condition. Management of allergic airways disease typically involves allergen avoidance, pharmacotherapy (e.g., antihistamines, corticosteroids, bronchodilators), allergen immunotherapy (desensitization), and lifestyle modifications. However, there is ongoing research and development of new treatment modalities to improve outcomes and provide more targeted and personalized approaches (Arm and Lee 1992; Asano et al. 2020; Athari 2019; Athari et al. 2017).

Understanding the pathophysiology of allergic airways disease is crucial for tailoring effective treatments and interventions. It provides insights into the mechanisms underlying the disease, aiding in the development of targeted therapies. Furthermore, comprehension of the disease's molecular and cellular pathways enables early diagnosis, accurate prognosis, and informed patient education. It forms the foundation for ongoing research, fostering innovation and advancements in medical approaches, ultimately striving for improved management and, potentially, prevention of this prevalent and burdensome respiratory condition (Audrit et al. 2017; Bachert et al. 2006, 2004; Backaert et al. 2021).

The primary objectives of this chapter on the pathophysiology of allergic airways disease are to consolidate existing knowledge and research, offering a comprehensive understanding of the disease's mechanisms. It aims to synthesize diverse findings, highlighting key immune processes, allergens, and triggers. Additionally, the chapter seeks to identify gaps in current knowledge, providing a basis for future research directions. Ultimately, by presenting a structured and informed overview, this chapter aspires to enhance clinical management and therapeutic strategies, ultimately improving the quality of life for individuals afflicted by allergic airways disease (Baraniuk 1998; Bates 2016; Bates et al. 2009; Blanchet et al. 2012; Bochner et al. 1994).

The scope of this chapter encompasses an in-depth analysis of the pathophysiology of allergic airways disease, focusing on immune mechanisms, airway inflammation, allergens, clinical manifestations, diagnostics, and therapeutic approaches (Bonay and Aubier 2007; Bonekat and Hardin 2003; Bonini and Silvers 2018). The chapter integrates historical perspectives, current research, and future prospects to provide a comprehensive understanding. Structurally, it follows a logical flow, commencing with an introduction and historical context, followed by sections delving into specific aspects of the disease. The chapter culminates in a conclusion summarizing key findings and implications, ensuring a thorough and organized presentation of the complex pathophysiology of allergic airways disease.

2.2 Historical Perspective

2.2.1 Early Discoveries and Descriptions of Allergic Airways Disease

Early discoveries and descriptions of allergic airways disease trace back to antiquity, although a comprehensive understanding has evolved significantly over time. Historically, the first recorded observations can be attributed to ancient civilizations like the Egyptians, Greeks, and Chinese, who documented symptoms resembling those of modern allergic airways disease. In ancient Egypt, writings dating back to 1500 BCE mention symptoms akin to hay fever, describing nasal congestion, sneezing, and eye irritation in response to certain plant exposures. Similarly, ancient Greek texts, such as those by Hippocrates (460–370 BCE), documented respiratory symptoms related to environmental exposures, emphasizing the influence of climate