

Use of mouse models of allergic rhinitis to study the upper and lower airway link

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Purpose of review

Allergic rhinitis and asthma are examples of a continuum of airway diseases with diverse clinical manifestations. This review examines the most recent work in mouse models studying upper and lower airway links and interactions.

Recent findings

The concept of united airways has been supported by investigative and epidemiological studies. Studies using mouse models of asthma and models of allergic rhinitis have demonstrated that analogous pathways lead to inflammation and airway hyperresponsiveness. Th2-type T cells and IL-13 play important immunopathologic roles. Recent studies have examined upper airway mucosal immune responses and development of both allergic and tolerant phenotypes. In a model of allergic airways disease, there is evidence of lower airway inflammation and airways hyperresponsiveness following application of allergen only to the nares, suggesting local stimulation can activate distal allergic responses.

Immunomodulatory properties of the airway mucosa have also been explored. Allergen-specific tolerance can be induced by appropriate stimulation of airway mucosa and is associated with activation of IL-10-producing T cells. This effect is mediated by antigen presenting cells, especially dendritic cells.

Summary

Immune stimulation of the airway mucosa, both in the upper and lower airways, results in active T-cell-mediated immune responses leading toward tolerance or asthma and allergic rhinitis. Regulation of these T-cell responses is currently under investigation. It is clear from these studies that antigenic stimulation of any part of the respiratory mucosa can have ripple effects along the entire airway and supports the concept of united airways.

Keywords

animal models, united airways, allergy, immune tolerance, asthma, rhinitis

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Introduction

Allergic rhinitis and asthma are atopic diseases affecting up to 20% of the general population with significant morbidity. They often coexist, such that 78% of asthma patients have nasal inflammation [1–3]. These diseases are associated with acute and chronic inflammatory processes resulting from protein particles in the environment, which elicit specific immune responses leading ultimately to production of IgE [3,4]. Cross-linking of IgE by these allergens is implicated as an initiator of, at least, acute allergic rhinitis and asthma exacerbations. However, despite significant overlap in the nature of allergic rhinitis and asthma, including anatomical location, function and local immunity, these diseases have been primarily investigated as distinct entities. Recently, focus has shifted toward the consideration of allergic rhinitis and asthma as a continuum of airway allergic disease, with common etiology and diverse end-organ manifestations [3,4].

Evidence of united airways in clinical and epidemiological studies

Allergic rhinitis and asthma are comorbid diseases and have shared immune pathways [5–7,8**]. Functionally the upper airways act to humidify air and filter particles before entry into the lower airways [3,6,9]. The large particle size of many aeroallergens suggests that the primary site of allergic sensitization is the nares and little allergen is deposited in the lungs [4]. Treatment of allergic rhinitis results in amelioration of some asthma symptoms [5,10–13]. While there are unique features, such as bronchial smooth muscle, playing a significant role in airways hyperresponsiveness of lungs, and nasal bronchial reflex, stimulating production of mucous in response to noxious stimuli in the upper airway, the underlying pathophysiologic mechanism remains the same [3,9,14–18]. In one study [4], patients with allergic rhinitis were subjected to segmental bronchial provocation and subsequently developed asthma and rhinitis symptoms. This occurred in the absence of allergen in the nares, suggesting that local allergic stimulation had significant regulatory effects on distal allergic responses.

Allergic rhinitis usually precedes the onset of asthma [5,8**,19]. In a nested case–control study of the Tucson Epidemiologic Study of Obstructive Lung Diseases, Guerra *et al.* [8**] found rhinitis was a significant, independent risk factor for asthma development conferring a threefold increased risk. They showed an

association between rhinitis severity and asthma diagnosis in a linear dose–response manner. Treatment of allergic rhinitis with inhaled corticosteroids decreases bronchial hyperresponsiveness [20]. This results in a reduction of emergency visits for asthma exacerbations [10,11]. As well, immunotherapy for pollen-induced allergic rhinitis appears to reduce the frequency of subsequent asthma development [12]. Thus control of lower airways disease is linked to control of upper airway inflammation.

Commonly defined risk factors for both allergic rhinitis and asthma include family history of atopy, maternal smoking history, pollutant and other chemical exposures [4,19]. In contrast, early daycare attendance, late birth order, house pets, frequent early-life upper respiratory tract infections and early-life exposure to farms are protective for development of atopic diseases [4,21–25,26**].

Mechanisms of upper and lower airway association

Factors mechanistically linking upper and lower airway allergic inflammation include loss of nasal protection secondary to rhinitis-induced congestion and the nasal–bronchial reflex [3,4]. Allergen-specific IgE production is strongly correlated with both allergic rhinitis and asthma, suggesting allergic immune responses are important in their etiology and pathogenesis [1,2,4,8**,24]. The inflammatory processes arise from inappropriate immune responses to otherwise innocuous aeroallergens resulting in development of an allergic immune, instead of a tolerant phenotype. Several studies have emphasized the importance of Th2-type T cells in the development and propagation of this response [27,28*,29**,30*,31]. Animal models of asthma have been developed to study these T cells and their cytokines (IL-4, IL-5, IL-13 and IL-9) as well as the effector cells and other mediators [32**,33,34,35*]. The allergic response is a dynamic one, requiring interplay of cells, cytokines and chemical mediators and key pathways in this response have been elucidated using animal models.

Animal models to define pathways in the allergic cascade

In man, natural exposure to aeroallergens occurs via the nares and upper respiratory tract. Allergic sensitization is affected by a variety of host and antigenic factors [19,36]. Host factors include genetic predisposition, age and immune status at first exposure. The status of the mucosal site of exposure is likely of key importance for developing the immune response. Studies have indicated that presence of microbial antigens, such as endotoxins, is inversely correlated with allergic sensitization while aerosolized particles, such as those found in chemical pollutants, may be proallergenic [26**,37**].

Characteristics of the antigen also direct the nature of the immune response. Concentration of allergen, duration and frequency of exposure may all affect the clinical manifestations [38,39]. Prolonged sensitization to indoor allergens, such as dust mite and cockroach, generally leads toward both asthma and rhinitis, while intermittent exposures, such as those of pollens, generally, although not exclusively, localize as upper airway symptoms [2]. Once sensitization occurs, subsequent allergen exposures will lead to the allergic cascade, including mast cell degranulation recruitment of inflammatory cells, especially eosinophils, activation of T and B cells, elaboration of chemokines, cytokines and adhesion molecules, resulting in clinical allergic manifestations in the upper and lower airways [40].

To study components of this cascade, classical murine models of asthma and rhinitis have been generated using a method of systemic intraperitoneal sensitization. This method results in rapid elaboration of Th2-type T cells and cytokines and production of allergen-specific IgE. Following local challenge of the airways, using nebulized or intranasal allergen in anesthetized animals, allergen deposition is found in both the upper and lower airways. Studies with these models have shown that Th2 cells can induce airway eosinophilia and hyperresponsiveness and implicated IL-4 and IL-5 as important, although not essential, cytokines [32**,41–43]. IL-13 has recently been implicated as an essential cytokine in mediating allergic responses in the lower airways [32**,33,34,35*]. IL-13 is produced by a variety of cells including T cells, mast cells, basophils and eosinophils. In a recent review [35*], the authors have addressed the pleotropic effects of IL-13 release and proposed mechanisms by which this cytokine can induce not only the inflammatory manifestations of allergy, but also contribute to airway hyperresponsiveness via direct activity on airway epithelial and smooth muscle cells.

Mouse models of allergic rhinitis and those of asthma usually rely on the systemic sensitization and local challenge protocol. In general, the same pathways for allergic inflammation have been found in both the upper and lower airways [41,43,44,45**]. Very few studies, however, have examined upper and lower allergen responses in the same animals. In one study in particular, this was addressed [44]. These investigators found simultaneous eosinophilic inflammation of both upper and lower airways following aerosol challenge. Bronchial hyperreactivity of the lower airways was found in association with nasal mucosa thickening, suggesting common airway inflammation occurs after allergen inhalation. Recently, the role of the airway mucosal immune system in regulation of responses to allergens has become the focus of several independent investigations [46**,47–49,50*]. To study this system, antigen

sensitization via local intranasal application has been employed.

Animal models to study the united airways

In their laboratory the author and colleagues have developed a murine model of allergic rhinitis and asthma using exclusive local sensitization and challenge of the upper airways [48]. They were interested in developing a model which as closely as possible reflected the development of asthma and allergic rhinitis in humans. Studies have demonstrated that deposition of allergen occurs primarily in the upper airway in man with results varying from 85 to 100% upper airway deposition. They therefore developed a model that minimized lower airway deposition. Their model relies on daily intranasal sensitization of awake BALB/C mice for 10 days followed by a 3–5-day IN challenge protocol 2 weeks later. This allows adequate time for the development of ovalbumin-specific IgE in these animals. Unlike tolerance-inducing protocols described below, this model provides prolonged intranasal antigenic stimulation and results in allergic responses upon subsequent local exposure. Using this technique they have shown significant deposition of allergen occurs only in the upper airways of these mice. They have also been able to demonstrate evidence of both upper and lower airways inflammation characterized by mucous gland hyperplasia and eosinophilic infiltration, and generation of allergen-specific IgE. In a recently completed study they found significant increases in airway hyperresponsiveness following methacholine challenge in both exclusive local and systemically sensitized animals. As mucosal deposition of allergen was localized in the upper airway, these findings of not only lower airway inflammation but also hyperresponsiveness (consistent with the asthmatic phenotype) are strong evidence for global airways disease [51]. Currently, the author and colleagues are using this model to evaluate the effects of exclusive upper airway mucosal exposure to endotoxin, lipopolysaccharide, or allergen (ovalbumin) in the neonatal period, to assess the development of subsequent allergic rhinitis and asthma. Preliminary data suggest that stimulation of the upper airway of newborns using either lipopolysaccharide or specific antigen prevents development of asthma and rhinitis in adult mice. This supports the concept of a united airway and also provides evidence for the early-life immunomodulatory role of endotoxins (Wang and McCusker, unpublished data).

Steenberg *et al.* [37••] have used a similar model to examine the adjuvant effects of ambient particles (pollutants) on the development of airways inflammation. They demonstrated increases in allergen-specific IgE when animals were exposed to allergen in the presence of several different small ambient particles as

well as evidence for significant lower airway inflammation in these mice. While there were increases in inflammatory cells in general, eosinophils were not specifically increased in this model. This study emphasizes the utility of these models for the study of the upper and lower airway interactions, and effects of environmental stimuli on airway immune responses. Thus, there is enormous potential to exploit these models to test treatment regimens for asthma and allergic rhinitis [52–54].

Animal models to study the nature of airway tolerance to allergen

A central question in the study of asthma and allergic rhinitis remains: ‘Why do some individuals develop allergic disease while the majority develop tolerance?’ Aeroallergens, characterized as nonreplicating soluble protein antigens, usually induce specific hyporesponsiveness at mucosal sites [49,50•,55]. This tolerance is postulated to be mediated by IL-10-producing regulatory T cells. Thus induction of allergy and tolerance both require the activation of T cells, presumably by antigen presenting cells, in particular the dendritic cell. In a series of studies, a model of allergen-specific hyporesponsiveness was developed and examined [46••,56–58]. Investigators used an established animal model of asthma using systemic intraperitoneal sensitization, followed by local intranasal challenge to elicit classical airways inflammation and hyperresponsiveness. Using an inverse protocol, that is, local intranasal sensitization with allergen and subsequent systemic intraperitoneal challenge, they demonstrated antigen-specific tolerance and inhibition of airways hyperresponsiveness on subsequent local intranasal challenges [45••,56]. Induction of tolerance in these animals appears to be mediated by T cell–dendritic cell interactions at mucosal sites and in the bronchial lymph nodes. Intranasal allergen exposure resulted in migration of pulmonary dendritic cells to draining lymph nodes. These cells transiently produced IL-10 and stimulated regulatory CD4+ T cells producing IL-10 [57]. Tolerance could be adoptively transferred with these dendritic cells. Most recently, this model has been used to demonstrate that regulatory T cells producing IL-10 are able to specifically inhibit airway hyperresponsiveness in an animal model of asthma [46••]. B cells as antigen presenting cells also play an immunomodulatory role [59].

These data have led to interest in the upper airway mucosa as an immunomodulatory site. Hall and colleagues [60•,61••] have pursued this concept in two recent studies. In the initial study [60•] they investigated the ability of nasal mucosal allergen stimulation to prevent the induction of Th2-mediated pulmonary inflammation. Using the immunodominant peptide from dust mite

allergen (Der p1) alone or adsorbed to chitosan, a mucopolysaccharide designed to enhance absorption, animals were exposed intranasally. Subsequently, these animals received intraperitoneal sensitization and aerosol challenge as per the usual protocols. They demonstrated reductions in airway eosinophilia and decreased recruitment of activated CD4+ T cells into the airways following challenge in animals receiving chitosan adsorbed peptide. They were also able to show localized production of IL-10 by antigen-specific T cells derived from bronchial lymph nodes in these animals. Interestingly, peptide alone had no inhibitory effect, suggesting that site and dose of antigen delivery during primary exposure have significant effects on the characteristics of subsequent immune responses. Additionally, this study shows the ability of the upper airway mucosal immune system to direct subsequent responses in the lower airways and in bronchial lymph nodes, supporting the upper and lower airways link.

The subsequent study [61**] further explored the effects of antigen delivery and sites of sensitization on development of the allergic immune response. Intranasal Der p1 peptide, alone or absorbed in delivery particles, designated MEA, was given to mice pre or post intraperitoneal antigen exposure. Animals were then challenged by intratracheal instillation of Der p1. Results showed reduction in airway inflammation only in animals treated with intranasal MEA-Der p1 prior to systemic challenge. Delivery of the immunodominant peptide alone or intranasal MEA-Der p1 following intraperitoneal exposure did not affect allergic inflammation. Thus developing immune responses are significantly affected by nature and timing of mucosal antigen delivery.

One common thread in all of these studies is the use of the nares as a site of primary immunization. In the latter models, upper airway sensitization led to upper and lower airway hyporesponsiveness following challenge [46**,56–59,60*,61**]. In human disease, however, nares are the first sites of allergen exposure and in our model, upper airway is an excellent site for allergen sensitization [48,62]. This apparent contradiction may be a consequence of changes in timing, frequency and dose of allergen exposure used, resulting in differential activation of T cells toward Th2-type allergic or T-regulatory phenotypes. The site of second exposure may also play a key role in subsequent response, as in the tolerance-inducing models intranasal sensitization was followed by systemic challenge. Changing the site of immune deposition may have caused the elaboration of regulatory T cells. Site-specific dendritic cells likely play important roles in regulating these responses [63]. Determining the interplay between local and systemic immunity as well as the upper and lower airways in induction of the allergic versus tolerant phenotype is essential to the

understanding of allergic rhinitis and asthma. Thus studies need to be conducted in models using the upper airway as the location of initial allergen deposition and aimed at understanding the regulatory nature of this immune site.

Conclusion

Allergic rhinitis and asthma clearly represent a continuum of airways allergy. Studies have suggested that nature of the antigen, age at first contact, duration and severity of exposure as well as immune status with respect to chemical pollutants and microbial products, may all affect clinical manifestations of the upper and lower airway immune responses. Using the mouse models of asthma, rhinitis and united airways, several essential pathways, responsible for allergic inflammation, airway hyperresponsiveness and allergen-specific tolerance, have been investigated. It is difficult to change the course of allergic disease once established. However, it may be possible, using these models, to determine the essential characteristics of the immune stimulation required to induce tolerance to allergens and devise and test treatment strategies aimed at abrogating and ultimately preventing asthma and allergic rhinitis.

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