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Lessons from allergic rhinitis versus asthma pathogenesis and treatment

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At least 20 years have passed since the pathogenesis of asthma and allergic rhinitis formally was attributed to immunoglobulin E (IgE)-dependent mechanisms. Since then, the concept that upper and lower airway inflammation leads to chronic airway disease widened the search for the types of cellular and molecular interactions that are responsible for linking the initial stimulus to the final abnormality in airway function. It has not been possible to integrate this information into a single model for the development of airway inflammation and remodeling, but a useful framework has been based on the behavior of the adaptive immune system. In that paradigm, an exaggeration of T helper type 2 (T_H2) over T_H1 responses to allergic and nonallergic stimuli leads to airway inflammatory disease, especially asthma. This article examines the role of antigen-presenting cells in the T_H2 bias in allergic rhinitis (an upper airway disease) and how this process differs in asthma (a lower airway disease). Alternative evidence is summarized that implicates a principal component of the innate immune response (ie, airway epithelial cells) in the pathogenesis of asthma. This new model highlights specific interactions between epithelial, viral, and allergic (Epi-Vir-All) components and better explains the basis for airway immunity, inflammation, and remodeling in response to viral infection. The development of long-term disease phenotypes that are typical of asthma and other hypersecretory airway diseases, which include allergic rhinitis, can be understood more clearly using this model.

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This article is divided into seven major sections. The next section summarizes the impact of allergic rhinitis and asthma in the population. The third section summarizes the pathogenic mechanisms underlying allergic rhinitis, focusing on the role of antigen-presenting cells. The development of the Epi-Vir-All paradigm for asthma is described, and this scheme may help explain the development of acute and chronic inflammatory disease in the upper airway. Two sections outline current and future treatment strategies for allergic rhinitis and asthma. A list of recommendations for future research and therapeutic investigations is included.

Scope of the clinical problem

Allergic rhinitis is the most common form of atopic disease and is one of the five most common of all chronic diseases [1]. The disorder affects an estimated 20 to 40 million people in the United States (10%–30% of adults and up to 40% of children), and the incidence is increasing in adult and pediatric age groups in countries of the Western world [2–5]. In accord with its high prevalence, the disorder extracts high societal costs. Annual expenditures for medications in the United States were estimated at US\$2.7 billion in 1995, with approximately 40% of expenditures for prescription items and 60% for nonprescription items [3,7,8].

Allergic rhinitis is categorized as seasonal or perennial. Seasonal allergic rhinitis is easier to identify because of the rapid and reproducible onset and offset of symptoms in association with pollen exposure. Perennial allergic rhinitis generally occurs during 9 months of the year and is more difficult to detect than the seasonal form because of the overlap with sinusitis, respiratory infections, and vasomotor rhinitis. An estimated 20% of all cases of allergic rhinitis are seasonal, 40% are perennial, and the remaining 40% are mixed (ie, perennial with seasonal exacerbation).

Although asthma is not as common in the population as allergic rhinitis, it affects nearly 15 million people in the United States, and almost a third of asthmatic individuals are younger than 18 years [9]. The prevalence of asthma [6] and expenditures for asthma care have been increasing. In 1994, direct expenditures for asthma care topped US\$6.1 billion, with over US\$2.4 billion spent on medications [10]. In contrast to allergic rhinitis, the indirect costs of asthma caused by missed work or school days are equally high. Total costs for asthma were estimated at US\$10.7 billion for the United States in 1994.

Epidemiologic data suggest significant overlap between allergic rhinitis and asthma, but the correlation is not precise. The prevalence of asthma in patients with allergic rhinitis ranges from 10% to 43%, whereas the prevalence of asthma in patients without allergic rhinitis is 5% or less [11–15]. These studies indicate that allergic rhinitis is a risk factor for asthma but that asthma may not necessarily predispose to rhinitis. One possible factor in the relationship of atopy to the development of asthma is the age of onset for the atopic phenotype. Children who were atopic at 8 to 10 years of age were more likely to have asthma than were those who developed atopy between the ages of 10 and 14 years [16]. These

differences in the occurrence of allergic rhinitis and asthma may be explained by the multifactorial nature of asthma and by the corollary that asthma is less likely than allergic rhinitis to be driven solely by an allergic mechanism.

Pathogenesis of allergic rhinitis

Allergic rhinitis symptoms are a result of early- and late-phase responses to inhaled allergen. Sneezing, congestion, and rhinorrhea characterize both responses, but congestion predominates in the late-phase response. The early- or immediate-phase response is caused by the release of mast cells and basophil mediators that is induced by an IgE-mediated immune reaction to specific allergens. The late-phase response is caused by the subsequent inflammatory response [1]. Ongoing research is directed at each of these components to define the critical inflammatory mediators and the cellular sources and molecular mechanisms that generate these mediators.

Common seasonal allergens responsible for rhinitis are tree, grass, and weed pollens and outdoor mold spores. The length of exposure to these allergens is dependent on geographic location, so familiarity with the pollinating season of the major trees, grasses, and weeds of the locale makes the syndrome easier to diagnose and treat [17,18]. In temperate regions of North America, tree pollen generally predominates in early to mid-spring, grasses predominate in late spring and early summer, and weeds are common from late summer until early fall [19]. Certain outdoor mold spores also display seasonal variation, with the highest levels in the summer and fall months [20]. In the case of perennial allergic rhinitis, year-round exposure to dust mites, cockroaches, indoor molds, and cat, dog and other danders leads to persistent tissue edema and inflammation.

Deposition and distribution of allergen along the airway may influence the subsequent allergic response (Fig. 1). Upper and lower airways differ markedly in the size of particles that deposit within them. Larger particles, equal to or greater than 10 μm in diameter, impact the nasal mucosa and are unable to penetrate further into the respiratory tract [21]. Smaller particles (0.1–10 μm in diameter) bypass the nasal mucosa and deposit in the intrapulmonary airways. Most pollen grains, which are larger than 10 μm , tend to deposit preferentially in the nasal airway [21]. A notable exception is cat allergen, for which a significant fraction (1/3) of the allergen can be found as particles less than 2.5 μm in diameter.

After the allergic particle has impacted on the nasal mucosa, it is dismantled by proteases and other enzymes into smaller components that can be taken up into antigen-presenting cells (eg, dendritic cells) [21]. Dendritic cells that are located within the epithelium (intraepithelial dendritic cells) are similar to the Langerhans' cells of the skin. Both of these antigen-presenting cells contain Birbeck granules and the antigen CD1 [22]. In skin from atopic individuals, Langerhans' cells express the high-affinity receptor for IgE (ie, Fc ϵ RI), and 20% to 40% of the intraepithelial dendritic cells in the nasal mucosa also express this receptor [23]. As discussed later, this population of dendritic cells may be critical

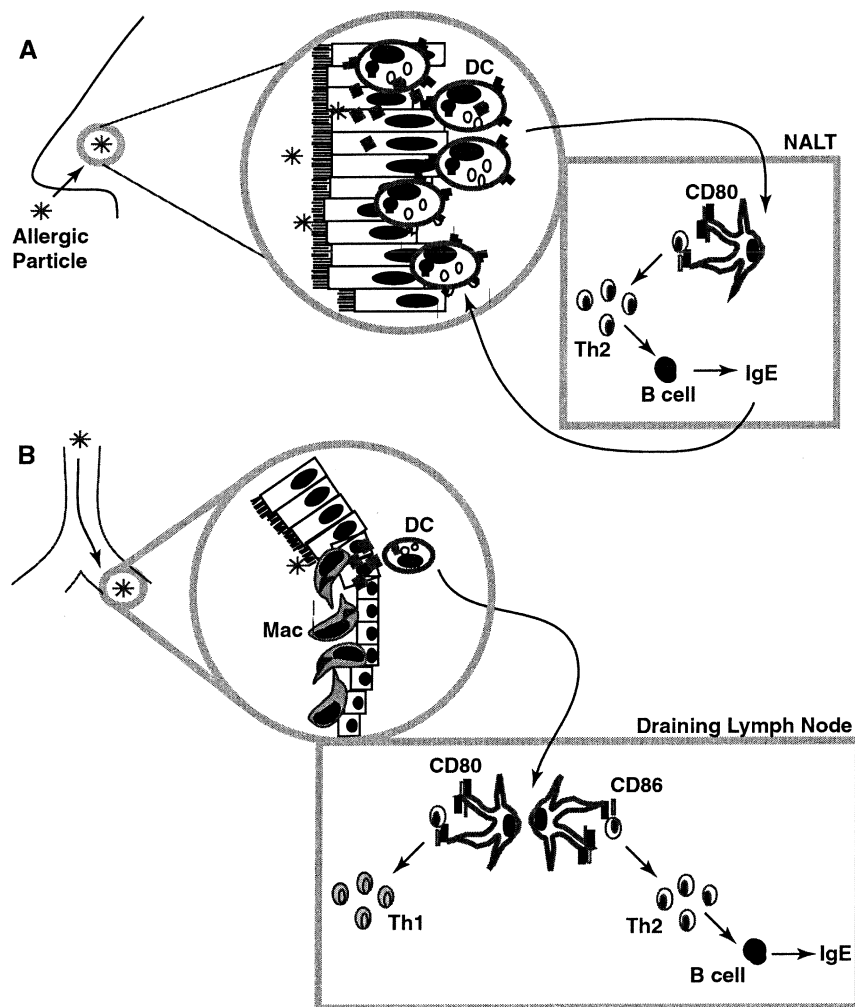


Fig. 1. Comparison of nasal and bronchial mechanisms for antigen processing and presentation. (A) The process in nasal airways begins with inhalation and deposition of large ($> 10 \mu\text{m}$) allergenic particles onto the nasal epithelium and subsequent breakdown into smaller particles. Dendritic cells (DCs) process these particles in the course of migrating to the NALT and maturing into active antigen-presenting cells. Using CD80–CD28 interaction, DCs activate and promote the development of $\text{T}_\text{H}2$ cells that in turn direct B cells toward IgE production. The resulting IgE binds to high-affinity IgE receptors present on DCs and on effector cells that cause airway dysfunction. (B) The same process in bronchial airways. Allergenic particles are smaller ($< 10 \mu\text{m}$) and may be taken up by airway macrophages (Mac) that may down-regulate the allergic response. The remaining particles are taken up by DCs that migrate back to the draining lymph nodes and use CD86 to promote antigen-dependent activation and differentiation of $\text{T}_\text{H}2$ cells.

for causing allergic rhinitis. Although dendritic cells that are similar in appearance can be found in the lower airways, the greatest density of these cells is

located in nasal tissue [24]. By contrast, the lower airways have higher numbers of alveolar macrophages than does the upper airway. Macrophages may mediate tolerance to allergens—macrophage elimination caused an increase in IgE responses to inhaled antigen in mice [25–27]. There does not seem to be a nasal equivalent to the alveolar macrophage, suggesting that no such dampening effect is present in the upper airway.

After the uptake of antigen, the dendritic cell processes the antigen into peptides that can be presented to T cells. During this process, the dendritic cell matures and migrates out of the epithelium to the draining lymphatic tissue. Cell maturation is associated with the expression of several chemokine receptors, including CCR7 [28]. These receptors mediate migration of dendritic cells to the T-cell region of draining lymph nodes, usually by way of the ligand for the CCR7 receptor (ie, CC chemokine CCL21 [secondary lymphoid-tissue chemokine]) [28]. In most epithelial tissues (including the lower airways), dendritic cells migrate to draining lymph nodes. In nasal tissue, however, dendritic cells seem to migrate to a local collection of lymphatic tissue that surrounds the nasal cavity. In mice, this tissue has been named the nasal-associated lymphoid tissue (NALT) [29]. In humans, Waldeyer's ring (the adenoids and palatine and lingual tonsils) likely represents the counterpart of this regional draining lymphoid tissue [30]. After intranasal instillation of antigen in mice, uptake was more rapid in the NALT than that in the draining cervical lymph nodes [31]. The accumulation of antigen in the NALT lasted longer than that in the lymph nodes, suggesting that this nasal-specific lymphoid tissue is positioned distinctly to handle intranasal antigens and may be important for the development of allergic rhinitis. Further support for this possibility comes from evidence of increased dendritic cells in the adenoids of atopic children compared with those of non-atopic children [32].

In lymphatic tissue, dendritic cells present the processed antigen to T-helper cells and, in the case of allergic disease, presumably skew T-cell development toward a T_H2 profile for cytokine production. In a mouse model of nasal allergen challenge, this initial sensitization phase depends on the costimulatory molecule CD80 (B7-1) [33]. In the lung, however, CD80 has been associated with T_H1 responses, whereas CD86 (B7-2) may mediate T_H2 responses [34]. The production of cytokines, notably IL-4 and 13, by T_H2 cells induces B cells to produce antigen-specific IgE antibody. IgE binds to its receptor (FcεRI) on the surface of mast cells and basophils and on dendritic cells in the nasal mucosa. Subsequent exposure to allergens allows for cross-linking of adjacent IgE molecules that causes receptor activation and leads to the release of histamine and other pro-inflammatory mediators (eg, tryptase, kinins, heparin, platelet-activating factor, prostaglandins, leukotrienes) by mast cells and basophils [1,35]. Stimulation of autonomic neurons also may cause release of acetylcholine and neuropeptides. Together, these mediators cause the early response to allergen and the consequent symptoms of rhinorrhea, nasal pruritus, sneezing, and congestion. Antigen-presenting cells may be critical during the effector phase of allergen exposure. The blockade of CD80 and CD86 during allergen exposure causes a decrease

in the levels of IgE and IgG1 and reduces submucosal eosinophil infiltration in a mouse model of rhinitis [33].

Dendritic cells may have additional roles in the subsequent exposure to allergen based on their capacity to capture and process antigen. Because some dendritic cells express Fc ϵ RI and maintain antigen-specific IgE on their surface, they can capture small amounts of antigen. This process of IgE-mediated uptake, processing, and presentation of antigen has been shown to be more efficient during the subsequent exposure to antigen than during the primary response [36]. These activated dendritic cells were capable of stimulating antigen-specific T cells that were primed by the initial exposure to antigen, and this secondary response is more rapid and vigorous than is the primary response. Clusters of IgE-positive dendritic cells were found to be closely associated with activated T cells in the subepithelial layer of the nasal mucosa after allergen challenge. This finding suggests that dendritic cells are capable of presenting antigen within the nasal tissue without migrating back to the draining lymphatic tissue [37]. Accumulation of dendritic cells in the nasal mucosa during seasonal exacerbations of allergic rhinitis provides further evidence of this phenomenon [38].

These early events in response to allergen are followed by a late-phase response that is characterized by immune-cell infiltration into the nasal mucosa and nonspecific hyperreactivity to inhaled irritants. The principal cell type that enters the nasal secretions is the eosinophil, and the main cell type found in the mucosal tissue is the T_H2 cell. Recruitment of these immune cells from the circulation depends on up-regulation of cell adhesion molecules and chemokines that are released by immune and parenchymal (eg, epithelial, endothelial) cells [39]. The products of recruited and activated immune cells (eg, peroxidases, IL-4, IL-5, IL-13) cause further end-organ dysfunction. Successful immunotherapy and early-life infection may stimulate the T_H1 response. This action and related observations suggest that the increased incidence of allergic disease in Westernized countries is linked to diminished stimulation by infectious agents [40]. Studies of the lower airways indicate that T_H1 cells may be required for the allergic response and that increased activity of T_H1 pathways can be found in asthma [41–44]. The role of these mechanisms in allergic rhinitis needs to be determined to develop effective treatment strategies.

Pathogenesis of asthma

As in allergic rhinitis, evidence of immune abnormalities and excessive airway inflammation in asthma has driven an attempt to define the types of inflammatory cells and mediators that might be responsible for abnormal airway function. Cell types that have been implicated in the development of asthmatic airway inflammation include immune and parenchymal cells. Cell-to-cell interactions are attributed to classes of mediators, such as lipids, proteases, peptides, glycoproteins, and cytokines. As in allergic rhinitis, the leading scheme for integrating this information has been based on the classification of the adaptive immune system

and the responses of T-helper cells. In this scheme, CD4⁺ T-cell-dependent responses are classified as T_H1 or T_H2. T_H1 cells characteristically mediate delayed-type hypersensitivity reactions and selectively produce interleukin 2 (IL-2) and interferon γ (IFN- γ), whereas T_H2 cells promote B-cell-dependent humoral immunity and selectively produce IL-4. T_H2 reactions may underlie the airway hyperreactivity and inflammation characteristic of the late response to allergen inhalation and account for the overproduction of T_H2-derived cytokines, which is characteristic of allergic rhinitis and asthma [45,46].

The traditional proposal for asthma pathogenesis (often designated the T_H2 hypothesis) is similar to that for allergic rhinitis. Each scheme is based on a relative increase in T_H2 cellular responses in combination with a decrease in T_H1 responses (often linked to the so-called “hygiene hypothesis,” in which fewer infections lead to a less robust T_H1 system). The consequent alteration in cytokine milieu, with excess T_H2 products (eg, IL-4, IL-5, IL-13) and decreased T_H1 products (eg, IFN- γ , IL-12), is predicted to drive the asthma phenotype (Fig. 2A). Evidence for such a shift in the T_H1 and T_H2 balance derives from studies of asthma in cellular and murine models, in which the polarization of T-helper cells and the allergen-dependence of T_H2 responses are defined most clearly, and from human studies that profile cytokine production and immune-cell infiltrate. In the murine system, IL-4, IL-5, IL-9, and IL-13 promote T_H2-cell differentiation, B-cell-dependent production of IgE, tissue eosinophilia, mucous-cell hyperplasia, and airway hyperreactivity [47–50]. These responses are down-regulated by T_H1 cytokines, such as IFN- γ and IL-12 [51,52]. In humans, asthma is tied to this paradigm by association with atopy and increased production of IgE and T_H2-cell cytokines and by genetic linkage to polymorphisms in the IgE receptor, IL-4, IL-4 receptor, and IL-13 genes [1,46,53,54]. Similarly, eosinophils and mast cells are characteristic of upper and lower airway inflammation [45,55,56] and may act as critical effector cells under certain circumstances [57,58].

It is questionable how a T_H2-polarized response can account for asthma that also is triggered by exposure to nonallergic stimuli (especially respiratory viruses) that ordinarily would trigger a T_H1 response. Based on the likelihood that T_H2-skewed responses may develop in this setting [59–61], it is possible that a T_H2-dominant response may mediate inflammation and hyperreactivity in response to nonallergic stimuli (see Fig. 2A). This dichotomous view of the immune response may not be completely accurate, however, because there is often ambiguity in the type of T-helper response triggered by most stimuli and significant cross-regulation between the two types of responses [43]. Studies in mice that used adoptive transfer with T_H1 and T_H2 cells have indicated that T_H1 cells may be required for allergic inflammation [41,44,62]. This T_H1 involvement presumably is based on the superior trafficking ability of these cells into (airway) tissue, compared with that of their T_H2 counterparts, and on the consequent establishment of an inflammatory milieu that is conducive to T_H2 recruitment during allergen exposure (Fig. 2B). Respiratory viruses might influence allergic inflammation by increasing T_H1 activity and thus increase subsequent allergic inflammation.

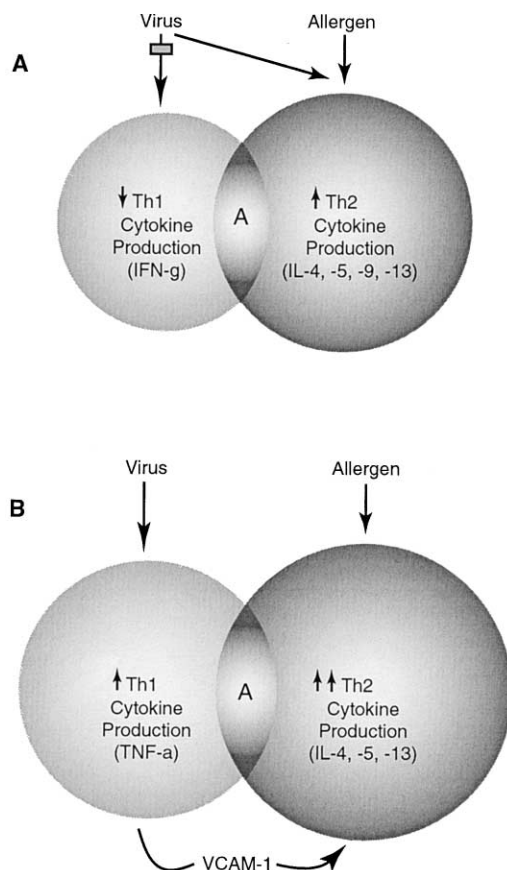


Fig. 2. The role of the airway immune response in the development of asthmatic airway inflammation. (A) Decreases in the virus-driven production of T_H1 cytokines (eg, IFN- γ) and increases in the allergen-dependent production of T_H2 cytokines (eg, IL-4, IL-5, IL-13) are characteristic of asthma (where spheres intersect [A]). This T_H2 -skewed setting enables flares of the disease that are driven by virus infection (with a functional blockade in the normal T_H1 response and a concomitant shift to an increase in the T_H2 response) or by allergen (with an increase in the T_H2 response). (B) A modified scheme based on the increased activity of T_H1 and T_H2 responses. Pathogen-activated T_H1 cells in the airway tissue generate factors (eg, TNF- α) that mediate subsequent recruitment of T_H2 cells (eg, by way of vascular cell adhesion molecule-1 [VCAM-1]) to provide a setting for enhanced allergen responsiveness. (Adapted from Castro M, Walter MJ, Chaplin DD, Holtzman MJ. Could asthma worsen by stimulating the T-helper type 1 (TH1) response? *Am J Respir Cell Mol Biol* 2000;22: 143–6.) ↑, increased; ↑↑, greatly increased; ↓, decreased.

Each of these proposals for asthma pathogenesis relies on the possibility that excessive production of T_H2 cytokines is responsible for driving the asthma phenotype. Several lines of evidence in model systems and in humans question whether the T_H2 hypothesis is the sole explanation for asthma. As noted earlier, asthma and allergy do not correlate completely in humans. Persons with allergy do

not always develop asthma, and persons with asthma do not have an absolute requirement for developing allergy. Endpoints of the asthmatic phenotype, such as airway hyperreactivity and mucus production, may develop without IgE production and eosinophil influx in experimental models and in asthmatic subjects [43,50,63,64]. In general, the T_H1 response and the antiviral response are characterized incompletely in human airways, and much of the commentary about these responses is extrapolated from experimental models or observations of tissues other than airway tissues. The possible primary role of viral infection in causing and triggering, asthma is characterized poorly. The relationship between respiratory syncytial virus (RSV) bronchiolitis to the subsequent development of childhood asthma needs to be defined. In model systems and in humans, the T_H2 hypothesis is confined to the adaptive immune response and does not account for components of the innate immune system (eg, airway epithelial cells) that may take an active and critical role in airway inflammation. Because of these uncertainties, the authors have questioned whether other aspects of immunity and inflammation might be critical for the pathogenesis of airway disease. The authors aimed to develop a model that better accounted for the dissociation between the development of allergy and asthma in many persons and that was based on a more precise appraisal of the T_H1 system and the innate immune response in the airway.

One particular deficiency of the T_H2 hypothesis is that it does not account for the possibility that the airway epithelial cells may act as active sentinels of innate immunity and, like other components of the innate immune system, may provide critical signals to the adaptive immune system. Studies of airway epithelial cells over the past 20 years indicate that these cells are programmed to mediate host defense and are programmed abnormally in airway disease [39]. In the case of host defense, studies proceeded from a relatively simple scheme for leukocyte recruitment (based on cell adhesion and chemoattraction) to a scheme that depends on the coordinated expression of a network of epithelial immune-response genes under distinct transcriptional and post-transcriptional controls. The transcriptional program depends primarily on IFN and Jak–signal transducer and activator of transcription (Stat) signaling, whereas post-transcriptional regulation uses a distinct RNA–protein interaction that is responsive directly to viral replication [65–71].

The same pathways that seem to be appropriate for antiviral immunity also are activated in asthma, even in the apparent absence of viral infection. Selective activation of Stat1 in the airway epithelium is an invariant feature of asthma [72]. Because Stat1 activation is not dependent on cytokine (ie, IFN- γ) production in this setting, the findings point to a signaling abnormality that likely occurs in the upstream kinases or downstream phosphatases that regulate Stat1 phosphorylation and activation. Other epithelial behavior that is typical of the antiparamyxoviral response also is found in asthmatic subjects. Epithelial IL-12 p40 is expressed in a pattern that resembles the response to experimental paramyxoviral infection [73]. These epithelial programs are activated in subjects with asthma despite symptomatic control with glucocorticoid treatment. Other programs are activated in asthmatic subjects with exacerbations after withdrawal of glucocorticoid treatment. Increased expression of epithelial RANTES (regulated on

activation normal T-cell expressed and secreted) may be found in these subjects and correlates with increases in symptoms, inflammation, and airway obstruction and hyperreactivity (M. Castro, M.J. Holtzman, unpublished data, 2002) [74].

To integrate these concepts and better explain the pathogenesis of airway inflammatory disease, the authors have revised the model for the role of the airway immune response in asthma. The revised model accounts for how an alternative T_H1 -oriented epithelial network may act in combination with an enhanced T_H2 response, and the combination of epithelial, viral, and allergic components led to its designation as an Epi-Vir-All paradigm (Fig. 3). In this scheme, increases in epithelial antiviral signals (eg, Stat1 activation, IL-12 p40 expression) and allergen-driven production of T_H2 cytokines (eg, IL-4, IL-5, IL-9, IL-13) are characteristic of stable patients with asthma during treatment with inhaled glucocorticoids. Further increases in epithelial signaling (driven by viral infection) or T_H2 cytokine production (driven by further allergen exposure) would develop in patients with asthma during a flare of the disease. Increased levels of Stat1 activity may mediate a hypersensitive T_H1 -type response in the airway. In vitro, persistent Stat1 activation leads to exaggerated Stat1-dependent gene expression in response to normal levels of stimulation (Y. Zhang, M.J. Holtzman,

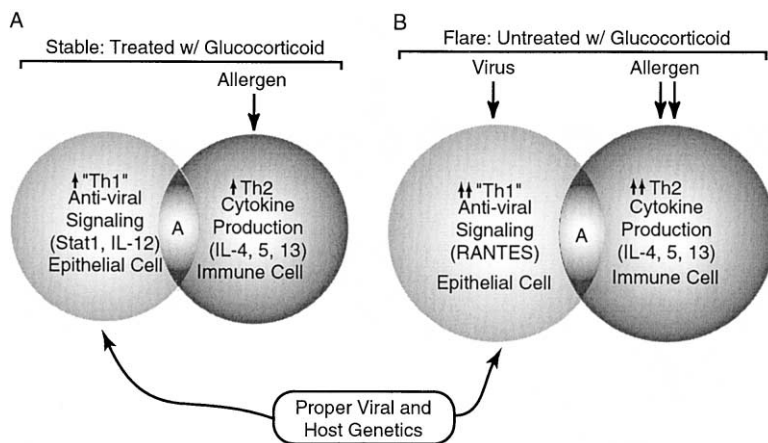


Fig. 3. The role of the airway immune response in the development of airway inflammation and remodeling. (A) Increases in epithelial antiviral signals (eg, Stat1 activation, expression of IL-12 p40 expression) and allergen-driven production of T_H2 cytokines (eg, IL-4, IL-5, IL-13) are characteristic of patients with asthma (where spheres intersect [A]) who are studied under stable conditions during treatment with inhaled glucocorticoids. (B) Further increases in epithelial signaling (driven by viral infection) or T_H2 cytokine production (driven by further allergen exposure) may develop in patients with asthma who are studied during a flare without glucocorticoid treatment. The abnormality in epithelial-cell behavior may depend on persistence of virus at low copy number and proper genetic background. The combination of epithelial, viral, and allergic components led to designation of this pathogenesis model as an Epi-Vir-All paradigm. (Adapted from Holtzman MJ, Morton JD, Shornick LP, Tyner JW, O'Sullivan MP, Antao A, Lo M, Castro M, Walter MJ. Immunity, inflammation, and remodeling in the airway epithelial barrier: the epithelial-viral-allergic (epi-vir-all) paradigm. *Physiol Rev* 2002;82:19–47; with permission.)

unpublished data, 2002). Flares of the disease are associated closely with induction of the expression of the RANTES gene. This system, which seems to be regulated at the post-transcriptional level during viral infection, may rely on a similar regulatory mechanism in asthmatic flares.

These possibilities question how the abnormality in the behavior of epithelial cells originally develops in asthma. The authors questioned whether the antiviral response could persist, and if so, how it would persist. A relationship between viral infection and the development of chronic inflammatory disease has been proposed for diverse clinical syndromes, but the basis for this relationship is often uncertain. In asthma, paramyxoviral infections are the leading cause of lower respiratory tract illness in infants and young children [75,76]. Children with clinically significant viral bronchiolitis seem to be marked for the subsequent development of a chronic wheezing illness that is independent of allergy [77–79]. Paramyxoviral infection presumably triggers a switch to an abnormal host response, because paramyxoviruses (or other respiratory RNA viruses) are not believed to persist in airway tissue as a cause of chronic respiratory disease [80]. With or without viral persistence, however, the role of specific host factors in the development of chronic wheezing or lifelong asthma has not been determined. In ongoing work, the authors have observed that transient paramyxoviral infection causes acute and chronic manifestations of the asthma phenotype in some genetic backgrounds [135]. Initial observations were obtained in a mouse model of viral bronchiolitis, but the same phenotypic markers appear in human subjects with asthma (J. Morton, et al, unpublished data, 2002). These findings raise the possibility that asthma may be characterized and caused by a persistent antiviral response. Further studies of this system using inbred mice will allow for molecular definition of genetic susceptibility to enable extension to human studies.

Though not as thoroughly studied as the lower airway, existing reports indicate that airway epithelial abnormalities are not a prominent feature of allergic inflammation in the upper airway. The upper airway problem is often attributed more completely to the allergic response. Further definition of upper and lower airway inflammation is required to make definitive comments about the role of the epithelium and the antiviral response. It is possible that the differences in the occurrence of allergic rhinitis versus asthma may be driven in part by the degree of involvement of the airway epithelial barrier. Existing evidence suggests that greater degrees of epithelial reprogramming may drive the host toward the asthma phenotype.

Treatment of allergic rhinitis

The treatment of allergic rhinitis consists of allergen avoidance, antiallergic medication, and immunotherapy for specific allergens. Treatment protocols for allergic rhinitis have been summarized by task force parameters [3,81,82] and review articles [83–85]. Drugs that commonly are used for treatment include antihistamines, cromolyn, and anticholinergic agents for relief of symptoms and

leukotriene antagonists and glucocorticoids to suppress allergic inflammation. Immunotherapy with allergen extracts generally is reserved for patients who do not respond to or cannot tolerate these treatments.

Antihistamines

Histamine H₁-receptor antagonists generally are considered first-line therapy for allergic rhinitis by most physicians and have been used effectively for managing symptoms of allergic rhinitis for more than 50 years. Oral antihistamines are generally effective in reducing symptoms of itching, sneezing, and rhinorrhea, but have little objective impact on nasal congestion. Antihistamine use in allergic rhinitis has been the subject of several reviews of the pharmacology and mode of action of antihistamines [3,86,87]. Second-generation H₁-receptor antagonists, such as loratadine (Claritin), cetirizine (Zyrtec), and fexofenadine (Allegra), are less sedating and more pharmacologically selective than are earlier antihistamines. However, some nonsedating agents may still cause sedation or dysfunction of the central nervous system even at recommended doses in certain individuals [88]. Although second-generation antihistamines possess an improved safety profile, most evaluations show that this new class is no more effective than is the first-generation H₁-receptor antagonists [89]. Azelastine is the only second-generation, single-agent, H₁-receptor antagonist that is marketed in the United States as a nasal spray, and in several controlled trials, it was efficacious in the treatment of seasonal allergic rhinitis [90]. Oral antihistamines reduce symptoms of the allergic conjunctivitis that often is associated with allergic rhinitis and offer an advantage over topical preparations. Over-the-counter status for second-generation antihistamines is being considered.

Although there are many antihistamines from which to choose, none is ideal. When comparing antihistamine therapy with intranasal glucocorticoids, first- and second-generation oral antihistamines are less potent in improving symptoms of allergic rhinitis, although they provide more relief of ocular symptoms. A major drawback to this class of drugs is their relatively small effect on nasal congestion. A concomitant decongestant often is needed, and some preparations are available as combination drugs (discussed later). Some H₁-receptor antagonists, such as cetirizine, may inhibit allergen-induced infiltration of tissue by eosinophils, but the added benefit is uncertain [91]. A new, selective H₁-receptor antagonist, desloratadine, may exhibit anti-inflammatory activity and seemed to decrease nasal congestion, concomitant asthma symptoms, and use of β_2 -adrenergic agonists [87].

Decongestants

Because first- and second-generation antihistamines are not effective in relieving nasal blockage, a decongestant agent (eg, pseudoephedrine) or a topical nasal glucocorticoid may need to be added to oral antihistamine therapy. Several studies have demonstrated that the efficacy of these drugs in combination with

antihistamines in the management of allergic rhinitis is superior to the efficacy of either drug alone. Many combination antihistamine–decongestant formulations are available in a fixed-dose preparation, which allows the patient the convenience of taking a single tablet. These combination agents, however, do not allow adjustment of each ingredient to maximize efficacy and decrease side effects.

Anticholinergics

Intranasal anticholinergics effectively may reduce rhinorrhea but have no effect on other nasal symptoms of allergic rhinitis. Ipratropium bromide, oxitropium bromide, tiotropium bromide, and glycopyrrolate are quaternary-structured, ammonium-muscarinic receptor antagonists that are absorbed poorly across biologic membranes. Ipratropium bromide (Atrovent) is the most extensively studied agent in patients with allergic rhinitis and is absorbed poorly from the nasal mucosa into the systemic circulation. Atrovent nasal spray is marketed in the United States and is an effective agent for the symptomatic relief of rhinorrhea that is associated primarily with gustatory or viral rhinitis and less often with allergic rhinitis.

Cromolyn

Intranasal cromolyn sodium is effective in some patients in controlling symptoms of allergic rhinitis and is associated with minimal side effects [92]. Patients who are given nasal cromolyn sodium must be instructed to use it before an anticipated allergen exposure and to use it on a regular basis during the season or during a period of exposure that is associated with allergic symptoms. In controlled studies, cromolyn is significantly less effective than intranasal glucocorticoids in treating allergic rhinitis. Given this fact and the requirement to use the intranasal medication four times a day for maximum efficacy, it often is not a practical choice for patients—although it is available over the counter for intranasal and ocular use.

Leukotriene antagonists

Three agents of this class are available in the United States: montelukast (Singulair) and zafirlukast (Accolate), which act by blocking the cysteinyl leukotriene receptor 1, and zileuton (Zyflo), which inhibits the 5-lipoxygenase that is responsible for one of the early steps in leukotriene generation. Studies indicate that these oral antileukotriene agents may be of value in the treatment of allergic rhinitis [93,94]. Whether these agents provide partial or complete relief of symptoms in this condition needs to be determined, but they are likely to receive approval from the Food and Drug Administration for this indication. These agents have adjunctive efficacy in treating asthma and most likely act on the allergic component of asthma; they can treat both asthma and allergic rhinitis at the same time [95]. The concomitant use of loratadine and zafirlukast is more effective than either drug alone in blocking the response to inhaled allergen

challenge in asthmatic subjects and in blocking symptoms in patients with allergic rhinitis [96,97]. These initial results suggest that this combination may be useful in treating these conditions.

Glucocorticoids

Since their introduction more than 20 years ago, intranasal glucocorticoids have been established as first-line treatment for allergic rhinitis. With proper use, topical glucocorticoids provide symptomatic relief in over 90% of correctly diagnosed patients with allergic rhinitis [98]. Nasal steroids account for about 25% of the prescriptions for seasonal allergic rhinitis [99]. As with other intranasal topical medications, these agents have minimal effect on the associated eye symptoms.

Although the precise cellular and molecular mechanism of action is uncertain, glucocorticoids are the most effective medication class in controlling symptoms of allergic rhinitis. Except for intranasal dexamethasone, these agents generally are not associated with significant systemic side effects in adults. Local side effects are minimal if the patient is instructed carefully in the use of these drugs, although nasal irritation and bleeding can occur, and nasal septal perforation rarely is reported. Despite the efficacy of these medications, some physicians are reluctant to prescribe them because of concerns about potential local and systemic adverse effects. Pharmacologically, newer drugs, such as mometasone furoate and fluticasone propionate, seem to have substantially higher topical potencies and lipid solubilities and lower systemic bioavailabilities than do older drugs. In clinical use, however, all of the available drugs seem to be equally effective in controlling symptoms of seasonal and perennial allergic rhinitis. With respect to adverse effects, data suggest that mometasone and fluticasone may have less potential for systemic effects during prolonged use, particularly in children in whom bone growth is a concern [100]. Mometasone may have the least systemic availability and consequently is expected to have the fewest systemic side effects [101].

Immunotherapy

Allergen immunotherapy may be highly effective in controlling symptoms of allergic rhinitis. In general, most patients experience significant improvement in their symptoms with properly administered immunotherapy [102]. Consideration for this treatment is based on severity of symptoms, failure of other treatment modalities because of a lack of efficacy, presence of comorbid conditions, and presence of IgE that is specific for the allergen causing the symptoms. Immunotherapy often is used when patients will not or cannot tolerate other therapies (eg, because of real or perceived side effects of medications). Because of the relative risk and high cost of immunotherapy, the treatment is reserved for patients that meet these criteria. Because of the risk for exacerbation, asthma should be well controlled when immunotherapy is administered. A shortcoming is the lack of available standardized allergenic extracts for all clinically important allergens.

Future therapy

There is no single satisfactory treatment for all patients with allergic rhinitis. There is, however, a step-wise progression of over-the-counter and prescribed medications that must be tailored to each patient [85]. Even under optimal conditions, available treatments do not always lead to satisfactory resolution of symptoms in the absence of patient and physician anxieties about perceived and actual side effects. There are continued efforts to develop new and more improved forms of treatment for this condition and to assess these treatments objectively through quality of life and economic measures [103,104]. In this research and development area, there is also significant overlap with and consideration for the associated condition of allergic asthma.

Immunotherapy

Unlike antiallergic drugs, allergen-specific immunotherapy attenuates symptoms for several years after it is discontinued. The potential for adverse effects, particularly anaphylaxis, and the relatively crude allergen extracts that are available serve to limit the usefulness of immunotherapy. To overcome these problems, newer approaches have been assessed in animals or are undergoing clinical evaluation. Naturally occurring isoforms of allergens from plants and trees have been shown to have a reduced capacity for being bound by IgE as a result of the substitution or deletion of amino acids [105]. The use of hypoallergenic isoforms in immunotherapy may minimize the risk for anaphylaxis. The use of recombinant allergens should circumvent the problem of standardization of crude extracts by allowing production and purification of many major allergens in ways that eliminate variation between batches [106].

Immunotherapy that involves T-cell peptide epitopes entails the administration of short, synthetic, allergen-derived peptides that induce T-cell anergy or tolerance but, because of their short length, are unable to cross-link IgE and induce anaphylaxis. Early clinical trials in patients with allergy to cat dander showed that treatment with T-cell peptides afforded limited protection against allergic symptoms that are induced by exposure to cats [107]. The use of mixtures of allergen-derived peptides that are selected on the basis of their ability to bind to common major histocompatibility complex (MHC) class II molecules may have greater efficacy, because they are recognized by T cells from most persons within a population [108,109].

DNA vaccines

DNA vaccines are promising in the treatment of allergic diseases [110,111]. Plasmid vectors containing genes that encode allergens have been injected into animals, either before or after allergen challenge, and markedly can decrease T_H2 -mediated responses, enhance T_H1 -mediated responses, and suppress the allergic response. Virus-like particles can induce IFN- γ that produces CD8⁺ T cells, rather than a T_H2 -mediated response, in a vector that expresses a Der p 1

peptide [112]. Given the concerns raised in the Epi-Vir-All paradigm, it is unclear how successful this approach will be. Another consideration is the induction of tolerance using mucosal DNA vaccination. The main peanut allergen, which was cloned into an expression vector and administered orally, increased fecal IgA and serum IgG_{2a} titers, decreased serum IgE titers, and resulted in a decreased anaphylactic response [113]. Whether this approach or an approach directed at the airway mucosa would be efficacious for inhaled allergens needs to be determined.

An additional approach is the administration of unmethylated CpG dinucleotide motifs (optimally GACGTC or GACGTT) that induce strong T_H1-mediated responses, either alone or in combination with allergen [114–116]. These motifs seem to function as T_H1-promoting adjuvants that are capable of switching the usual T_H2 response toward a T_H1 response [117,118]. Trials of this approach have been proposed for allergic rhinitis. As noted earlier, at least some aspects of the vaccine approach must be tempered by studies of the lower airways, indicating that the T_H1 response may augment the allergic and inflammatory response.

IgE inhibitors

Another therapeutic approach under consideration is the blockage of IgE or its synthesis to interrupt the T_H2-dependent allergic cascade. Treatment with a recombinant humanized monoclonal antibody (mAb) against IgE (rhuMAB-E25 [omalizumab]) virtually eliminated IgE and markedly decreased the expression of FcεRI on basophils [119]. Although the mAb neutralized IgE in blood and inhibited the production of IgE by B cells, it did not activate mast cells, basophils, or monocytes and was not prone to cause anaphylaxis. The agent reduced symptoms of allergic rhinitis [120] and glucocorticoid usage in patients with asthma [121]. It also inhibited the allergen-induced, early-phase and late-phase asthmatic reactions [122,123]. The degree of functional improvement and the safety of the treatment are being defined.

Several approaches to the inhibition of IgE biosynthesis and signaling are under investigation. Based in part on the role of IL-4 in IgE generation, several approaches to inhibiting IL-4 are being attempted. Treatment with soluble recombinant IL-4 receptor moderately improved severe atopic asthma in a placebo-controlled trial [124]. Other approaches for blocking the IL-4 receptor include administration of antibodies against the receptor and mutant IL-4 proteins [125]. Interrupting downstream signaling of the IL-4 receptor is also possible by targeting the signal transducer and activator of transcription 6 or c-maf. Similarly, interruption of FcεRI signals by blocking its interaction with ligand or downstream signaling molecules, such as Syk, is also a possibility.

Late-phase allergic reactions can be induced in patients with atopic asthma in the absence of immediate hypersensitivity involving mast cells. Such reactions were induced in patients with asthma and allergy to cats by an intradermal

injection of peptides that were derived from a cat allergen [108]. These late-phase reactions were independent of IgE and were MHC-restricted, indicating that the activation of T cells alone is sufficient to initiate airway narrowing in patients with allergic asthma. Similarly, immunotherapy has shown limited efficacy in treatment of asthma [126–128]. The extent of this IgE-independent mechanism in allergic rhinitis needs to be defined.

Anti-inflammatory strategies

Based on the hypothesis for allergic inflammation, allergic rhinitis and asthma might best be controlled by targeting specific inflammatory components. IL-5 has been proposed as a key target. In monkeys with ascaris-induced asthma, a mAb against IL-5 almost completely eliminated eosinophilia and airway hyperresponsiveness [129]. A study of patients with mild asthma showed that a high-affinity, humanized IgG₁ mAb against IL-5 abolished eosinophils in blood and reduced the number of eosinophils in sputum, but had no apparent effect on the allergen-induced, late-phase asthmatic reaction or on nonspecific airway hyperreactivity [130]. Long-term studies that eliminate tissue eosinophils are required to establish conclusively the role of eosinophils and IL-5 in chronic atopic allergic disease and asthma. Other strategies for reducing the number of eosinophils include inhibition of $\alpha_4\beta_1$ -integrin (very late antigen-4 [VLA-4]) or CCR3, the CC chemokine receptor on eosinophils that binds eotaxin, and other CC chemokines (e.g., RANTES) that attract eosinophils. Unpublished reports have indicated little efficacy of anti-VLA-4 approaches in asthma, and a trial using this approach has been halted. Although improved delivery of this agent may increase its efficacy, it is possible that the poor outcome reflects a lack of attention to the added nonallergic component that is critical for asthma. It is possible that these types of treatments are effective in cases of allergic rhinitis in which IgE-dependent allergic responses seem to be dominant.

Definition of molecular targets

The development of experimental models of the asthma phenotype and new tools for defining signaling pathways and genetic susceptibility have created the likelihood that additional targets will be identified for further drug development. Allergen-challenge and viral bronchiolitis models, in combination with new technology for generating gene-altered mice and for monitoring gene expression, indicate the capacity to define distinct signaling pathways for mucous-cell hyperplasia and airway hyperreactivity (J. Morton, et al, unpublished data, 2002) [131,132]. These same experimental models can be used to define genetic susceptibility using more rapid strategies for gene mapping in inbred mice and other species [133]. In each case, previously unsuspected gene products are being identified that may contribute to the asthma phenotype. Comparative analysis of

gene expression is being performed using airway samples from human subjects [134], and if these results validate the findings of experimental models, these new targets can be pursued for further drug development.

Summary

Allergy is an extremely common manifestation in humans, but the precise mechanism underlying allergic disease is uncertain. The traditional models for allergic rhinitis and asthma pathogenesis are similar, and both are based on the process of antigen processing and presentation and the subsequent development of a predominant T_H2 response in the airway tissues. There are several differences in this process for nasal versus bronchial airways, but one of the most striking new developments is the contribution of the innate immune system and the special programming of airway epithelial cells for antiviral defense and reprogramming of this system in asthma. Airway epithelial cells may be programmed abnormally for permanent proliferation and skewed mucus-cell differentiation by asthmagenic paramyxoviruses. This alteration in the process of epithelial repair exhibits genetic susceptibility and seems to be analogous to abnormal mucosal phenotypes in asthma and other hypersecretory diseases. These concepts can be integrated into a scheme that incorporates epithelial, viral, and allergic components (called an Epi-Vir-All paradigm) for a more complete explanation of the pathogenesis of airway disease. By extension, the same epithelial network is a target for therapy in airway disease and for improving host defense against respiratory viruses. Smart strategies have already been defined for reversing viral mimicry and engineering dominant-negative mutations that alter epithelial behavior, but full use of these approaches depends on the achievement of selective and high-level gene expression in the epithelium. This goal is dependent on determining the critical biology of the airway epithelium in antiviral defense and airway disease and on defining the contributions of specific viral and host genetic components.

The extent to which the paradigm shift in asthma may extend to the pathogenesis of nasal airway disease needs to be defined. There are a number of systemic and topical drugs with significant efficacy in the treatment of allergic rhinitis, including the seasonal variety. Perhaps the greatest efficacy and safety has been shown with intranasal glucocorticoids, but patient and physician acceptance of these drugs is not solid. These agents are not effective for associated conjunctivitis and raise some concern for use in children. Recommendations for improvement for existing therapies include: (1) conversion of second-generation antihistamines to over-the-counter status; (2) development of antihistamines with greater anti-inflammatory and decongestant activities; (3) further evaluation of leukotriene antagonists alone and in combination with other agents, especially antihistamines; and (4) evaluation of the efficacy and safety of anti-IgE alone and in combination with other agents. Recommendations for research and development of new therapies include: (1) improving immunotherapy with recombinant or synthetic peptide allergens; (2) testing DNA

vaccines with T_H1-stimulating capacity in models of allergic rhinitis and patients with allergic rhinitis; and (3) testing the efficacy of specific anti-inflammatory agents (eg, drugs directed against IL-4, IL-5, chemokines, chemokine receptors) in models of allergic rhinitis and asthma. Further definition of pathogenesis and drug action in models of allergic rhinitis is warranted. Comparison of these data with information on lower airway function would be useful, because an agent that affects both conditions would be valued highly.

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