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Allergic rhinitis: Pathophysiology

David H. Broide, M.B., Ch.B.

ABSTRACT

The inflammatory response in the nasal mucosa in subjects with allergic rhinitis challenged intranasally with an allergen includes an immediate IgE-mediated mast cell response as well as a late-phase response characterized by recruitment of eosinophils, basophils, and T cells expressing Th2 cytokines including IL-4, a switch factor for IgE synthesis, and IL-5, an eosinophil growth factor. Recent advances have suggested that additional pathways may contribute to the pathophysiology of allergic rhinitis including local synthesis of IgE in the nasal mucosa, the epithelial expression of cytokines that regulate Th2 cytokine responses (i.e., thymic stromal lymphopoietin, IL-25, and IL-33), and the activation of histamine receptors other than H_1 and H_2 such as H_4 -histamine receptors. This review focuses on briefly reviewing well-established pathways in the pathophysiology of allergic rhinitis and then updating knowledge on recent advances in the pathophysiology of allergic rhinitis. The review references information obtained from original articles published and available online on PubMed. In vitro and in vivo studies indicate that B cells in nasal mucosa can be induced to express IgE. Preclinical studies show an important role for epithelial-derived cytokines (thymic stromal lymphopoietin, IL-25, and IL-33) in regulating Th2 responses at mucosal surfaces, and for H_4 -histamine receptors in mediating itching. In addition, regulatory T cells may play an important role in mediating active tolerance to allergens. An improved understanding of the pathophysiology of allergic rhinitis may provide important insight into novel therapeutic targets.

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The inflammatory response in the nasal mucosa in patients with allergic rhinitis has been well characterized after exposure to an intranasally applied allergen in laboratory research settings.^{1,2} The immediate response to allergen exposure is characterized by typical symptoms of allergic rhinitis (i.e., sneezing, rhinorrhea, and nasal congestion) within 5–30 minutes. These initial symptoms are caused by an immediate IgE-mediated mast cell response that is followed in 60–70% of subjects by a late-phase inflammatory response characterized by influx into the nasal mucosa of eosinophils, basophils, and T cells expressing Th2 cytokines including IL-4, a switch factor for IgE synthesis, and IL-5, an eosinophil growth factor.^{3,4} Recent advances in mechanisms of allergic inflammation have suggested that additional pathways may contribute to the patho-

physiology of allergic rhinitis including (a) local synthesis of IgE in the nasal mucosa,^{5,6} (b) expression of epithelial-derived cytokines that up-regulate Th2 cytokine responses (i.e., thymic stromal lymphopoietin [TSLP], IL-25, and IL-33),^{7,8} (c) activation of H_4 -histamine receptors that promote allergic responses that are not inhibited with H_1 -antagonists,^{9,10} and (d) alteration in the number of regulatory T cell (Tregs) that down-regulate allergic responses.¹¹

GENES AND ALLERGIC RHINITIS

The development of allergic rhinitis involves both a genetic and an environmental contribution. Studies of identical monozygotic twins have revealed an approximate 45–60% concordance in the development of allergic rhinitis,¹² whereas studies of nonidentical dizygotic twins have shown concordance in the development of allergic rhinitis in ~25%,¹² a rate in the range of the general population prevalence of allergic rhinitis. Although there have been extensive studies of genes associated with asthma, there are much fewer studies of genes associated with allergic rhinitis. The studies of genes associated with allergic rhinitis include family genome-wide association studies,^{13–18} as well as studies of single nucleotide polymorphisms (SNPs).^{19–21} The results of the genetic studies in allergic rhinitis need to be interpreted with caution at present based on the

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small number of subjects studied, the inclusion of subjects with allergic rhinitis and associated conditions including asthma and atopic dermatitis, as well as the lack of a replication population in most studies. A Danish study¹³ found a principle candidate gene region in chromosome 4q24–q27, which was, however, not noted in four other studies.^{14,16–18} Additional studies have identified linkage of allergic rhinitis to regions in chromosome 3 in three studies (3q13, 3q13.31, and 3p24).^{16–18} Studies of SNPs in candidate genes have identified an association in polymorphisms of the transcription factor GATA3 as well as the Th2 cytokine IL-13 with the risk of developing allergic rhinitis in a cohort of children followed up until the age of 10 years.²¹ However, at present, the contribution of individual genes or chromosomal regions to the development of allergic rhinitis requires further study and replication of results in more than one study cohort.

NASAL MUCOSA IgE PRODUCTION

Local nasal mucosa IgE production has been established in subjects with allergic rhinitis who have positive immediate hypersensitivity skin tests and specific IgE to relevant aeroallergens,⁵ as well as in subjects with idiopathic rhinitis and negative immediate hypersensitivity skin tests and undetectable serum-specific IgE to relevant aeroallergens.⁶ Studies of nasal mucosal explants from subjects with allergic rhinitis have indicated that *in vitro* allergen challenge of the explants induced increased levels of allergen-specific IgE in allergic subjects but no change in levels of IgE in nonallergic subjects.²² These observations support the notion that B cells in the nasal mucosa can be induced to express allergen-specific IgE. At present, the relative amount of allergen-specific IgE produced locally in the nasal mucosa when compared with regional lymph nodes and systemic sites is unknown. Estimates of local nasal mucosa IgE production based on the number of B cells expressing IgE have suggested that in allergic rhinitis ~3–4% of B cells in the nasal mucosa express IgE.²³ Although this supports the observation that more IgE may be produced locally in the nasal mucosa, the absolute number of IgE⁺ B cells in the blood and regional lymph nodes may be much greater than the absolute number of IgE⁺ B cells in nasal mucosa.

NASAL MUCOSA IgE PRODUCTION IN IDIOPATHIC RHINITIS

Idiopathic rhinitis is estimated to occur in 19 million individuals in the United States.²⁴ Local allergic rhinitis may be suspected in subjects with idiopathic rhinitis who have a history suggestive of either seasonal or perennial rhinitis but have negative immediate hyper-

sensitivity allergy skin tests and negative radioallergen sorbent tests (RASTs) to inhaled allergens.⁶ A subset of these idiopathic rhinitis subjects have evidence of a positive response to nasal allergen challenge, which may be associated with local nasal production of allergen-specific IgE.⁶ These subjects are classified as having local allergic rhinitis.

Perennial Allergens and Local Allergic Rhinitis

In 1975 Huggins and Brostoff in the United Kingdom showed that a subset of subjects with perennial allergic rhinitis and negative immediate hypersensitivity and negative RASTs to *Dermatophagoides pteronyssinus* may, indeed, have dust-mite allergy, which can only be confirmed by nasal challenge.²⁵ They studied 14 subjects with a history of perennial allergic rhinitis suggestive of dust-mite allergy, but negative immediate hypersensitivity skin tests and negative RASTs to *D. pteronyssinus*. In these subjects they could induce nasal symptoms with nasal challenge with *D. pteronyssinus* as well as detect *D. pteronyssinus* local IgE production in nasal secretions collected on filter strips. More recent studies in 2002 from an Ear, Nose, and Throat Clinic in the United Kingdom have also shown that idiopathic rhinitis may be caused by perennial allergens such as dust mites.²⁶ In this study, ~62% of the subjects with idiopathic rhinitis (immediate hypersensitivity skin test negative; RAST test negative) had positive nasal allergen challenge as assessed by rhinomanometry with 85% of the positive responses being caused by dust-mite allergen challenge.²⁶ In a third study of 50 subjects with idiopathic rhinitis and perennial symptoms, ~54% had a positive nasal allergen challenge with *D. pteronyssinus*, and 22% of these subjects had evidence of local nasal mucosa IgE production to *D. pteronyssinus*.²⁷

Seasonal Allergens and Local Allergic Rhinitis

Seasonal allergens such as grass pollen have also been identified as a cause of idiopathic rhinitis.⁶ In a Spanish study 38 asymptomatic subjects with local allergic rhinitis were challenged intranasally with grass pollen or diluent out of the grass pollen season.²⁸ All of the local allergic rhinitis subjects had previously reported a history of seasonal rhinitis symptoms during the grass pollen season but were negative by immediate hypersensitivity skin test (prick puncture and intradermal) and RAST to grass pollen. Despite this initial negative allergy evaluation, nasal allergen challenge with grass pollen was positive for symptoms (e.g., rhinorrhea, sneezing, itching, and nasal congestion) in all of the local allergic rhinitis subjects, but not in any of the healthy controls. A late-phase nasal response was present in 70% of the

local allergic rhinitis subjects. The response to nasal allergen challenge was associated with a significant decrease in volume on acoustic rhinometry, suggesting that nasal allergen challenge was associated with physiological changes (*i.e.*, nasal airflow obstruction). There was a significant increase in levels of mast cell-derived mediators (*i.e.*, tryptase) in nasal secretions in the immediate response, as well as a significant increase during the late-phase response in levels of tryptase and the eosinophil-derived mediator eosinophil cationic protein (ECP) in the nasal secretions. Surprisingly levels of ECP increased as early as 15 minutes after nasal allergen challenge (a very early time point for eosinophil recruitment) and continued to further increase for up to 24 hours.

Nasal IgE to grass pollen was detected in only 30% of local allergic rhinitis subjects (*i.e.*, nasal IgE to grass pollen was not detectable in 70% of local allergic rhinitis subjects).²⁸ Nasal allergen challenge in local allergic rhinitis subjects with nasal IgE to grass pollen resulted in an increase in nasal IgE to grass pollen at 1 hour, which persisted for 24 hours. Levels of nasal lavage tryptase and ECP were significantly increased in 100% of local allergic rhinitis subjects with nasal IgE. In contrast, levels of nasal lavage tryptase and ECP were only elevated in <20% of local allergic rhinitis subjects who did not have increased nasal IgE.²⁸ Overall, these studies suggest that local IgE production may explain symptoms in a subset of subjects with idiopathic rhinitis, negative immediate hypersensitivity skin tests, and negative RASTs, although the frequency of this occurrence requires further study.²⁹

Evolution of Local Allergic Rhinitis to Allergic Rhinitis

A cohort of 180 subjects with local allergic rhinitis were reevaluated 3–7 years later to determine whether any of these nasal allergen challenge-positive but immediate hypersensitivity skin test-negative and RAST-negative subjects had become skin test or RAST positive.³⁰ Approximately 24% of the local allergic rhinitis subjects became either skin test positive or RAST test positive over the 3- to 7-year follow-up period.

CYTOKINES THAT REGULATE TH2 CYTOKINE RESPONSES

IL-4 is a cytokine that has long been recognized as playing an important role in the differentiation of Th2 cells.³ More recently, three additional cytokines (*i.e.*, TSLP, IL-25, and IL-33)⁷ have been recognized to play an important role in initiating, amplifying, and maintaining Th2 responses important to allergic inflammation (Table 1).

Thymic Stromal Lymphopoietin

Increased levels of TSLP have been noted in skin biopsies from subjects with atopic dermatitis as well as in the airways of subjects with asthma.^{31,32} The increased levels of TSLP in the airway in asthma correlated with disease severity.³² Increased levels of TSLP have also been observed in the nasal epithelium in a mouse model of allergic rhinitis, and a monoclonal antibody to TSLP significantly reduced the development of rhinitis in these mice.³³ TSLP is derived from epithelial cell and nonepithelial cell sources and acts on dendritic cells to up-regulate the costimulatory molecule OX40 ligand and hence favors Th2 responses.⁶

Interleukin-25

IL-25 (also known as IL-17E) is a member of the IL-17 cytokine family. Increased levels of IL-25 have been detected in asthma and atopic dermatitis.³⁴ Studies in mouse models of asthma suggest that IL-25 may play an important role in promoting or sustaining an ongoing Th2 immune response.³⁴ IL-25 is produced by multiple cell types including epithelial cells, mast cells, eosinophils, and basophils.

Interleukin-33

IL-33 (a member of the IL-1 cytokine family) increases cytokine production from polarized Th2 cells.⁷ Cellular sources of IL-33 include epithelial cells, macrophages, and dendritic cells. Increased levels of IL-33 have been detected in the airway of subjects with severe asthma.³⁵

Epithelial Cells and Th2 Responses

Because TSLP, IL-25, and IL-33 are all produced by epithelial cells,⁷ the potential for these three cytokines to enhance Th2-mediated allergic inflammation at mucosal surfaces is evident. In addition, both IL-25 and IL-33 induce TSLP production from epithelial cells, suggesting a potential mechanism by which these three cytokines interact and potentiate their function at mucosal surfaces.

HISTAMINE H₄-RECEPTORS

H₄-receptors are expressed by immune and inflammatory cells (*i.e.*, T cells, mast cells, and eosinophils) as well as nerve endings.^{9,10} The H₄-receptor may play a role in chemotaxis and calcium mobilization. In mouse models administration of an oral H₄-antagonist decreased scratching induced by histamine,³⁶ whereas in a mouse model of allergic rhinitis intranasal administration of the H₄-antagonist decreased symptoms of sneezing and nasal rubbing.⁹ Because the H₄-receptor does not regulate IgE-mediated mast cell degranulation, the decreased symptoms of allergic rhinitis may be caused by effects on H₄-receptors expressed by na-

Table 1 Cytokines that regulate Th2 response: TSLP, IL-25, and IL-33

	Cellular Sources	Inducing Stimuli	Target Cell Populations
TSLP	Epithelium	TLR ligands	T cells
		Viruses	CD4 ⁺ T cells
	Nonepithelium	Bacteria	Non-T cells
		Helminth parasites	Monocytes
		IL-1, TNF- α	Dendritic cells
		IL-4, IL-13	Mast cells
		IL-25	B cells
IL-25	Epithelium	IL-33	
		Tissue damage	
	Nonepithelium	Allergens	T cells
		Helminth parasites	Th2 T cells
		FcE cross-linking	Non-T cells
			Epithelial cells
			Macrophages
IL-33	Epithelium		Eosinophils
			Smooth muscle cells
	Nonepithelium		T cells
			Non-T cells
			Mast cells
			Basophils
			Eosinophils

Source: Adapted from Ref. 7.

TLR = Toll-like receptor; TNF- α = tumor necrosis factor α ; TSLP = thymic stromal lymphopoietin.

sal sensory nerves.⁹ At present, there are no reported results of studies of H₄-receptor antagonists in human allergic rhinitis to determine their relative efficacy and safety profile compared with traditional H₁-antagonists.

REGULATORY T CELLS

An improved understanding of what induces tolerance to inhaled allergens in nonallergic individuals may provide important insight into potential novel therapies for allergic rhinitis. Recent advances have identified an important role for Tregs in maintaining tolerance through active suppression of responses to environmental antigens.¹¹ There is evidence that in allergic diseases, suppression of Th2 responses by Tregs is deficient.^{37,38} For example, reduced Treg number and function have been noted in bronchoalveolar lavage and blood in asthmatic patients.^{39,40} Allergen immunotherapy in allergic rhinitis has been noted to induce Tregs, suggesting that Tregs may be mediating some of the beneficial effect of immunotherapy.¹¹ However, further study is needed to determine how important Tregs are in mediating tolerance in allergic rhinitis as current studies in humans show evidence of a correlation of Tregs with tolerance but have not

shown a cause and effect relationship between Tregs and tolerance in subjects with allergic rhinitis or asthma.

SUMMARY

An increased understanding of the pathophysiology of allergic rhinitis has revealed insight into potential novel therapeutic targets in allergic rhinitis (TSLP, IL-25, IL-33, and H₄-receptors) as well as identified the importance of Tregs in maintaining tolerance to inhaled allergens. In addition, local nasal mucosal IgE production may explain why a subset of patients with apparent idiopathic rhinitis based on negative immediate hypersensitivity skin test and negative RAST have clinical responses when challenged intranasally with specific allergens. Additional studies are needed to determine how these cells, mediators, and receptors influence the pathophysiology of allergic rhinitis and whether any will serve as safe and effective novel therapeutic targets in allergic rhinitis.

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