

Local and Systemic IgE in the Evaluation and Treatment of Allergy

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- Immunoglobulin E • IgE • Allergy • Nasal polyp
- Chronic rhinosinusitis • Allergic fungal rhinosinusitis
- Allergic rhinitis • Asthma

Allergy is a clinical manifestation of an exaggerated immune response following repeated exposures in a genetically predisposed “atopic” patient. In allergic patients, the body responds to usually harmless substances as though they were pathogens. Allergy may present as a variety of systemic conditions, most commonly hay fever, allergic rhinitis, asthma, and eczema. The symptoms of allergy are predictable when considered in context of chemical mediators released by mast cells during a type I immunoglobulin E (IgE)-mediated hypersensitivity reaction. Mast cells are concentrated in the submucosal layer of the respiratory tract, gastrointestinal tract, conjunctiva of the eye, and subcutaneous layer of the skin, which correlates directly to the target organs that manifest symptoms during an allergic reaction. Histamine and other mediators released from mast cells and basophils during allergic reactions contribute to vasodilation, glandular secretion, and increased vascular permeability.

It is estimated that 20% to 25% of the general population manifests clinical symptoms of allergy.¹ A nationwide survey in 2006 showed that 54.6% of people in the United States tested positive to at least one allergen.² The profound economic impact of allergy is increasing. Between 2000 and 2005, the cost of treating allergic rhinitis

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almost doubled from \$6.1 to \$11.2 billion, with more than half of this money spent on prescription medications.^{3,4} Costs related to lost productivity, missed work, and health care costs incurred by exacerbation of coexisting medical conditions by allergy are more difficult to quantify.¹

IMMUNOLOGY

A discussion of allergy and its treatment would be incomplete without an understanding of the effector cells involved. An IgE-mediated allergic reaction consists of 2 phases: early humoral reaction and a late cellular reaction.⁵ An almost immediate response to an allergen occurs with a preformed specific IgE molecule presenting an antigen to an attached mast cell. This antigen presentation results in degranulation and release of histamine from mast cells in the submucosal layer, with subsequent vasodilatation and increased vascular permeability. In addition to histamine, mast cells release a cascade of other proinflammatory mediators (prostaglandins, leukotrienes, platelet-activating factor, bradykinin, and cytokines) within minutes of the antigen-antibody reaction. The presence of cytokines and leukotrienes up-regulate or induce de novo expression of adhesion molecules, selectins, and integrins. This release of mediators inspires an influx of other inflammatory cells, primarily eosinophils, but also basophils and neutrophils into the reaction site within several hours following the humoral reaction. This cellular influx comprises the late or cellular reaction, and may enhance the allergic symptom expression for up to several days.⁶

In a milieu of cytokines and other mediators, B lymphocytes proceed to generate further antigen-specific IgE that will be displayed on the B cells in preparation for subsequent exposures.⁷ The critical step in the commitment of B cells to synthesis of IgE is heavy chain class switching, which involves recombination within the immunoglobulin heavy chain gene cluster, thus changing the ϵ germ line gene into the rearranged gene. This gives rise to the ϵ mRNA for the ϵ heavy chain of IgE.⁸ Several signals are necessary for heavy chain switching, whether in vivo or in vitro. When provoked by allergen exposure, mast cells and Th2-type lymphocytes release interleukin (IL)-4 and IL-13.⁹ These signals target the ϵ gene for recombination by binding to CD40. CD40 ligand is constitutively expressed on mast cells and expressed after allergen activation on T cells. Cross-linking of CD40 on B-cell membrane induces the cell to undergo heavy chain switching.^{8,9} Immunoglobulin subclasses vary in abundance. The 4 IgG subclasses make up 75% of the immunoglobulins found in serum, with a concentration in healthy individuals of about 10 mg/mL.¹⁰ IgG responds to a wide range of antigens, including many bacterial proteins.¹⁰ In contrast, the least-abundant Ig in serum is IgE, with a normal concentration of approximately 150 ng/mL.¹¹

TRADITIONAL SYSTEMIC ALLERGY TESTING

Current diagnostic and treatment regimens for allergic patients revolve around systemic IgE. Diagnostic techniques are dependent on sufficiently detectable levels of systemic IgE, and treatment is administered for local and systemic symptom control with pharmaceutical agents or antigen-specific immunotherapy. Increased evidence for local IgE production and concomitant disease manifestations incurred by local inundation with IgE has abounded recently. Local IgE production and its effects have been hypothesized to explain the discrepancy between sensitization detected by systemic allergy testing and clinical expression of allergy. Despite research evidencing increased local tissue IgE levels, the development of routine testing for local IgE and treatment regimens centered on elevated local IgE have not been routinely used.

Systemic Skin Testing for Allergy

The gold standard for allergy testing is in vivo antigen-specific skin testing, which is essentially a semiquantitative measurement of the early-phase type I hypersensitivity reaction. Antigens are selected by the tester according to their likelihood to induce a reaction based on the patient's medical history. These are applied to the skin by an epicutaneous screening method or an intracutaneous diluted fashion. If a sensitized mast cell to that specific antigen exists, a humoral reaction will ensue with development of a wheal and flare that reaches its maximum at about 20 minutes after exposure. The diameter of the early-phase wheal is measured and the exuberance of the allergy inferred. A late-phase cellular reaction may ensue, but this is not interpreted as part of standard testing. Therefore, despite manifestations of allergy typically occurring at local intranasal, ocular, or bronchial sites, gold standard allergy testing methods have traditionally been undertaken via systemic skin-testing protocols.

The most commonly used epicutaneous test is the prick or puncture method initially described by Lewis and Grant in 1924 and later modified by Pepys in 1975.⁷ A drop of purified antigen or control fluid is applied to the skin, and a needle or similar device is used to puncture the epidermis through the fluid without inciting bleeding. After allowing time for a humoral reaction to develop, based on presence or absence of antigen-specific IgE-sensitized mast cells in the skin, the resulting reaction is graded. More exuberant reactions develop in patients with higher levels of systemic antigen-specific IgE; however, negative prick tests do not preclude existence of allergen-specific IgE at lower levels that may still result in clinical allergy symptoms.

Intracutaneous or intradermal systemic allergy testing may complement prick testing, or be used alone to quantify systemic antigen-specific responses. Although the antigen concentration used in intradermal testing is far weaker than antigen concentration in prick testing, the volume of antigen to which the patient is exposed is much greater, increasing a risk of an anaphylactic reaction. The intradermal test was reported as an allergy skin testing method by Cooke in 1915.⁷ The 2 most common methods for intradermal testing are single-dilution and intradermal dilution testing, previously known as skin-endpoint titration. Intradermal dilution testing is more clinically relevant given the ability to accurately quantitate a patient's sensitivity and infer the starting concentration for immunotherapy. Single-dilution testing provides only a positive or negative result, and all immunotherapy is begun at an extremely low dose to ensure safety, prolonging overall time of escalation dosing.

Systemic In Vitro Testing for Allergy

Systemic in vivo skin testing, despite remaining the gold standard, inherently presents several drawbacks. The degree of reactivity is suppressed by antihistamines, which must be avoided for at least 72 hours before testing. Patients often experience an increase in symptoms with withdrawal of antihistamine medications. Skin-testing methods have been refined to encompass exposure to very low doses or diluted antigen to maximize the safety profile; however, a small risk of anaphylactic reaction persists with in vivo testing. Rates of untoward reactions during skin testing, both large local reactions and systemic reactions, are reported at a rate of 0.02% to 1.40%.^{12,13} Protocols to manage these life-threatening reactions are mandated for administering centers to maximize success for management of anaphylaxis.

An alternative to in vivo testing exists for patients who are advised against or unlikely to be able to tolerate skin testing. Radioallergosorbent testing, or RAST testing, involves a radioimmunoassay capable of detecting specific IgE antibodies in serum. A solid phase is manufactured in which allergens react with serum drawn from

a patient. Antigen-specific IgE binds to the solid phase antigens. This solid phase antigen-antibody complex is then incubated with radiolabeled rabbit antibodies to human IgE. The amount of antibody present is calculated by measurement of the radioactive marker.⁷ The modified RAST was introduced in 1979 by Fadal and Nalebuff¹⁴ to increase the sensitivity of the test while maintaining its specificity. Adjustments were made not only to the technical aspects of the testing procedure but also to the scoring and interpretation mechanisms. The modified RAST is more useful to the clinician as correlations to intradermal dilutional testing can be made to facilitate initiation of immunotherapy.¹⁵ Some advocate that total quantitative measurement of serum systemic IgE provides additional diagnostic value in addition to modified RAST. Even modified RAST, however, remains less sensitive than *in vivo* skin testing for allergy detection.^{12,16}

TREATMENT OF ALLERGY

Management options for allergy consist of avoidance measures and several classes of pharmacotherapeutic agents, but the only “cure” for this disorder requires immunotherapy. A tailored regimen, largely designed by trial and error, can be designed for the patient with the goal of symptom control, from antihistamines, decongestants, mast cell stabilizers, corticosteroids, anticholinergics, and leukotriene modifiers. Unsatisfactory relief with these mechanisms prompts consideration of immunotherapy.

Avoidance

The best and most effective management of allergy is avoidance of allergens when possible. Patient education can be provided by verbal counseling as well as administration of printed materials with specific control regimens for various antigens, such as dust mites, molds, and animal dander. Antigens are not always avoidable, and even when immunotherapy is instituted, overwhelming exposure to antigens both during treatment and following therapy may continue to provoke symptoms. As such, pharmacotherapeutic management of symptoms is a cornerstone in treating the allergic patient.

Pharmacotherapy

Antihistamines help to control symptoms of sneezing and rhinorrhea, symptoms induced by vasodilation, increased vascular permeability, and increased glandular production that occurs with direct effects of histamine. First-generation antihistamines, or “sedating” antihistamines, compete with histamine for H1 receptor sites on target organs (Table 1). Second-generation, or “nonsedating,” antihistamines do not cross the blood-brain barrier, and as such, have a better tolerated side-effect profile. Topical, intranasal antihistamines are now available and offer benefits of antihistamine and anti-inflammatory actions. Third-generation antihistamines seek to offer equal or superior potency with further-enhanced safety profile and longer duration of action.⁷

Decongestants are alpha-adrenergic agonists that oppose vasodilation and decrease symptoms of nasal congestion.⁷ Systemic administration carries a risk profile characterized by the vasopressive actions, mainly exacerbation of hypertension. They readily cross the blood-brain barrier, and can cause central nervous system stimulation. When applied topically to the nose, systemic effects are minimized, but risk of rebound rhinitis and cycles of addiction can ensue.

Mast cell stabilizers have multiple actions, but retain their original description in name. They are used topically intranasally, and are most effective when administered

Table 1 Summary of pharmacotherapeutic agents used to treat allergic and related disease			
Drug Class	Example	Mechanism of Action	Current Indication
Oral antihistamine	1st generation	Blocks H1 receptor sites on target organs	Allergic rhinitis
	2nd		
	3rd		
Topical antihistamine	Azelastine	Blocks H1 receptor site	Allergic rhinitis
Topical decongestant	Neosynephrine	Alpha-adrenergic agonist	Acute nasal congestion
Oral decongestant	Phenylephrine	Alpha-adrenergic agonist	Nasal congestion
Oral steroid	Prednisone	Decreases capillary permeability, stabilizes lysosomal membranes, blocks action of migratory inhibitory factor, inhibits phospholipase	Late-phase allergic reactions
Intranasal steroid	Mometasone	See above	Chronic allergic rhinitis
Leukotriene modifier	Montelukast	Inhibits formation of leukotrienes	Asthma, nasal polyposis, allergic rhinitis
Chromones	Sodium cromoglycate	Mast cell stabilizer	Before allergen exposure
Topical anticholinergic	Ipratropium bromide	Blocks muscarinic receptors (M2 and M3)	Allergic rhinitis with prominent rhinorrhea, Asthma
Sympathomimetic	Epinephrine	α and β adrenergic receptor activation	Anaphylaxis
Inhaled short-acting selective beta2-adrenergic agonists	Albuterol	Directly activates β 2-receptors	Bronchospasm
Inhaled long-acting selective β 2 agonist	Salmeterol	Directly activates β 2-receptors	Asthma, COPD
Methylxanthine	Theophylline	Nonselective phosphodiesterase inhibitor, $\uparrow$ apoptosis of inflammatory cells, $\uparrow$ histone deacetylase activity	Asthma
Anti-IgE antibodies	Omalizumab	Prevents IgE binding to mast cells	Asthma

Abbreviations: COPD, chronic obstructive pulmonary disease; IgE, immunoglobulin E.
Data from Bousquet J, Khaltaev N, Cruz AA, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;63(Suppl 86):8–160; and Bousquet J, van Cauwenberge P, Ait Khaled N, et al. Pharmacologic and anti-IgE treatment of allergic rhinitis ARIA update (in collaboration with GA2LEN). *Allergy* 2006;61:1086–96.

before allergen exposure to prevent an allergic reaction. They have a short half-life and must be redosed multiple times daily. Advantages include a very limited side-effect profile.

Corticosteroids are anti-inflammatory agents that are primarily effective for the late-phase allergic reaction.⁷ They do not prevent allergic reaction, but diminish the effects by mitigating effector cells and enzymes. Systemically administered, this class of medication has a side-effect profile list that is quite lengthy, often increased as dose and duration of treatment are increased. They can result in suppression of endogenous steroid production, central nervous system stimulation, gastrointestinal upset, exacerbation of hypertension and diabetes, and skeletal and tendon injury. Topical nasal or inhaled corticosteroids are a heavily relied upon class of agents for allergy and asthma symptom management, as they are the most potent nasal therapy and they diminish the need for systemic administration.¹⁷ Topical administration results in very low systemic absorption, and has usually few side effects locally, including nasal crusting, epistaxis, hoarseness, oral candidiasis, and drying of the mucous membranes.

Anticholinergics were originally used systemically to counteract rhinorrhea present in allergy. They were poorly tolerated given the excessive mucosal drying effects, with nasal crusting and thickened mucous. Intranasal anticholinergics are effective at controlling rhinorrhea with very little systemic absorption and, therefore, limited side effects.⁷

Leukotriene modifiers were designed to modulate development of allergic reaction by inhibiting development of leukotrienes or barring their effects.⁷ They were originally solely used for asthma and nasal polyposis, but have recently gained approval from the Food and Drug Administration for a role in treatment of allergic rhinitis as well.⁷

Immunotherapy

Systemic immunotherapy is offered to patients whose symptoms are not well controlled by simple pharmacotherapeutic measures, symptoms that are severe and prolonged, allergies to antigens that are not readily avoidable, and to patients who are capable of complying with the prolonged treatment time. Standard antigen-specific immunotherapy was developed in 1911 by Leonard Noon.¹⁸ It entails injecting escalating doses of antigen until a maintenance dose is achieved, and then continuing injection treatments until the patient has been completely asymptomatic for perennial allergens for 1 to 5 years and seasonal allergens for 2 to 3 seasons. Injections are usually administered once weekly with increasing dose and potency of antigen until desired effects are noted, continued for a total of 1 year, and then maintenance doses are continued every 2 to 3 weeks for a total duration of 3 to 5 years. Patients are monitored in the treatment environment following each injection in the unlikely event that systemic reaction ensues. Multiple studies have been performed detailing efficacy of this regimen for treatment of multiple allergens in curing the patient of allergic symptoms with lasting efficacy after treatment has ceased.¹⁹

Alternative routes for administering immunotherapy have been explored and developed with the goal of creating a system of treatment that can be safely administered by the patient at home, decreasing cost and increasing convenience, while maintaining comparable results. Additional benefits that have been hypothesized are directly treating the reactive sites, namely airway mucosa. Oral administration of antigen concentrates was originally investigated in the 1920s; however, further pursuit was abandoned because of the perception of suboptimal efficacy.¹⁹ An adaptation of oral immunotherapy is sublingual immunotherapy (SLIT), where the allergen extract is held under the tongue for 2 to 3 minutes before swallowing. Major investigations

for this regimen have been pursued in Europe, and results from several studies demonstrate similar long-term results of symptom improvement with treatment for both seasonal and perennial allergens when compared with subcutaneous immunotherapy.^{19–25}

The concept of intranasal and intrabronchial immunotherapy has been suggested for many years. Initial trials from Europe revealed efficacy in local symptom control without development of a systemic effect, measured by a total decrease in serum IgE.^{19,26–30} Further investigation has been abandoned given the superior efficacy and better tolerated side-effect profile of SLIT.

LOCAL IgE: INTRANASAL *Elevated IgE in Nasal Tissues*

Local production of IgE was suspected as early as the 1950s when a higher concentration of IgE was detected in nasal secretions than in serum.³¹ In 1970, Tse and colleagues demonstrated ragweed-specific IgE in nasal washings of ragweed-allergic patients with allergic rhinitis, providing additional evidence for local antigen-specific IgE in nasal mucosa.^{31–33} In a 1974 study by Huggins and Brostoff,³⁴ patients with typical allergic rhinitis symptoms with both positive and negative systemic allergy tests, as well as patients free from any allergic symptoms, were exposed to grass-pollen extract intranasally. Subsequent nasal washings revealed elevated grass pollen-specific IgE in all patients with allergic rhinitis regardless of systemic allergy test status, when compared with nonallergic controls, suggesting local intranasal IgE production.^{31,35} In a similar study by Merrett and colleagues,³⁶ nasal washings revealed specific IgE to grass, house-dust mite, animal dander, and mold without allergen provocation in patients with allergic rhinitis with both positive and negative systemic allergy tests.¹⁹

The role of local IgE has also been investigated in allergic fungal rhinosinusitis (AFRS). This disease process is classically defined by 5 criteria: type I hypersensitivity, nasal polypsis, characteristic radiologic findings, eosinophilic mucin without fungal invasion, and positive fungal stain.³⁵ Traditionally, systemic allergy testing is administered as an adjunct to diagnosis and treatment of this patient population. Patients with AFRS frequently exhibit positive reactions to multiple fungal and nonfungal antigens, guiding subsequent allergen-specific immunotherapy.^{32,37–41} There is a subset of patients, however, who demonstrate the classic features of AFRS, but do not exhibit elevated systemic levels of total IgE.^{32,42}

In a 2004 study, Collins and colleagues⁴³ investigated a phenomenon termed “entopy,” or increased local IgE in the absence of systemic disease in AFRS.³² These investigators identified fungus-specific IgE in paranasal sinus allergic mucin of patients with AFRS undergoing endoscopic sinus surgery in the absence of fungus-specific serum IgE. A study by Carney and colleagues⁴⁴ provided further support for local IgE in AFRS with the discovery of the highest concentrations of IgE-positive cells in sinus tissue biopsies from patients with AFRS when compared with samples from those with chronic rhinosinusitis (CRS) and with control subjects.³² Wise and colleagues⁴⁵ further defined the role of local IgE production in paranasal sinus tissue of patients with AFRS by demonstrating profound elevation of IgE-secreting cells in the epithelium and subepithelium of tissue obtained from the osteomeatal complex from patients with AFRS as compared with samples evaluated at both levels from those with nonpolypoid CRS and controls. Specific IgE to both fungal and nonfungal antigens were also demonstrated in higher concentrations from patients with AFRS as opposed to controls.⁴⁵ A follow-up study by Ahn and colleagues⁴⁶ in 2009 affirmed

previous findings of elevated levels of total and specific IgE in sinonasal tissue obtained from patients with AFRS relative to those with CRS and healthy controls. This group also demonstrated that elevated local tissue IgE appears to be a diffuse process throughout nose and paranasal sinuses, with similar amounts of IgE detectable in tissue from the paranasal sinuses as the inferior turbinate samples, despite the predisposition for polyps to form in the sinus cavity rather than on the inferior turbinates (**Figs. 1 and 2**).

The phenomenon of local IgE production has been used to speculate further on the etiology of nasal polyposis in disease processes other than classic AFRS. Since the 1930s, nasal polyps were presumed to have an allergic etiology because of the high concentration of eosinophils detectable in the polyp tissue,⁴⁷ but later evidence has disputed this hypothesis.^{48–50} Early studies of nasal polyp tissue contributed to evidence for local production of IgE by revealing high concentrations of specific IgE in polyp tissue in subsets of patients both with and without systemic atopy.^{51–55} Investigations to define the role of local IgE in nasal polyp tissue have described the significant contribution of *Staphylococcus aureus* superantigens.³² *S aureus* is commonly found colonizing the upper respiratory tract; however, certain conditions can predispose the host to infection by the organism. These bacteria can cause infection via a variety of mechanisms, including coagulase enzymes, direct invasion, and enterotoxins with superantigenic properties. Superantigens differ from conventional antigens in that they are presented directly on antigen-presenting cells in an unprocessed state and are capable of activating up to 30% of circulating T cells, eliciting an extremely strong primary response.⁵⁶ To fully evaluate the role of *S aureus* superantigens in polyp formation, Bachert's⁵⁶ group used specific IgE antibodies to the *S aureus* enterotoxin (SAE) as a marker for current or former immune reaction to this entity. They described several different patterns of IgE antibodies in polyp samples. In 30% there is no evidence for the role of SAEs in nonallergic subjects, as there is no IgE to SAEs or to specific inhalant allergens and low total IgE. Approximately 50% demonstrate the situation of superantigen activity in an allergic patient with the presence of specific IgE to SAEs, high total IgE, and IgE to specific inhalant allergens. About 10% of subjects with nasal polyposis represent superantigen activity in a nonallergic subject with the presence of IgE to SAEs, moderate to high total IgE, and no

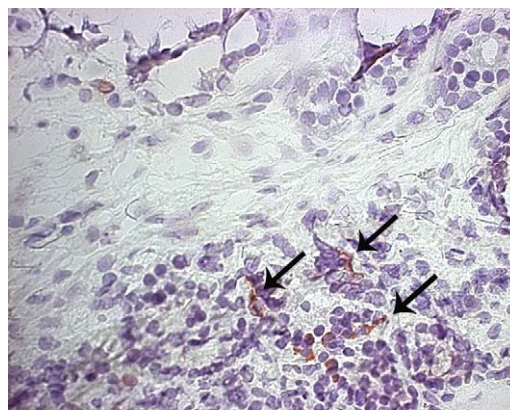


Fig. 1. Representative histologic section demonstrating IgE-positive staining (red-stained cells, arrows) in a biopsy from the osteomeatal complex of a patient with chronic rhinosinusitis.

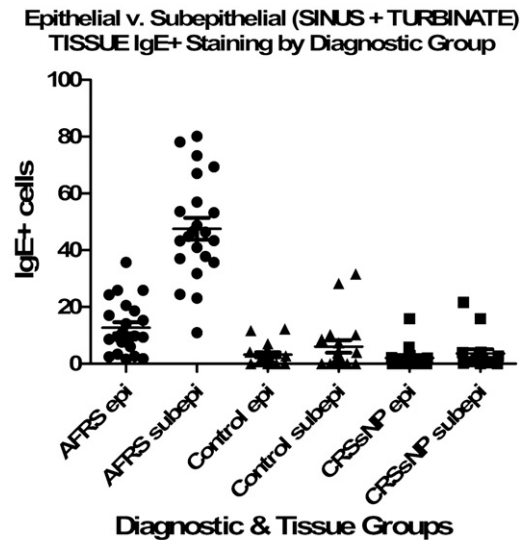


Fig. 2. Graph of local IgE staining by immunohistochemistry in AFRS, chronic rhinosinusitis without nasal polyps (CRSsNP), and control patients. Positive staining in osteomeatal complex sinus tissue and inferior turbinate (turb) tissue is compared between the epithelial (epi) and subepithelial (subepi) compartments. The largest number of IgE-positive cells was found in the subepithelium of AFRS patients. (Data from Wise S, Ahn C, Lathers D, et al. Antigen-specific IgE in sinus mucosa of allergic fungal rhinosinusitis patients. *Am J Rhinol* 2008;22:451–6; and Ahn CN, Wise SK, Lathers DMR, et al. Local production of antigen-specific IgE in different anatomic subsites of allergic fungal rhinosinusitis patients. *Otolaryngol Head Neck Surg* 2009;141:97–103.)

specific IgE to inhalant allergens. The final 10% of patients likely are allergic patients affected by superantigens other than classic SAE; nasal samples from this group show high total IgE and presence of IgE to specific inhalant allergens, but no IgE to SAEs.⁵⁷ Because asthma is frequently associated with nasal polyposis and because patients who have SAE-IgE-positive polyps more frequently have asthma compared with patients who have SAE-IgE-negative polyps, SAE investigation has delved into the lower airways as well.⁵⁶ Studies in mice provoked with SAE demonstrate recruitment of proinflammatory cells, including TCR V β (+) T cells, and release of cytokines associated with an increased airway responsiveness similar to asthma.⁵⁶ Bronchoalveolar lavage washings from humans demonstrate increased expression of TCR V β (+) T cells in human patients with poorly controlled asthma but not from those with well-controlled asthma or control subjects, potentiating the hypothesis that SAEs trigger T-cell activation in asthma.⁵⁶

Local Production of Intranasal IgE

Some theorized that elevated intranasal IgE was attributable to immunoglobulin production by B cells in regional lymph nodes, binding to high-affinity receptors on cells such as mast cells, and subsequent migration to intranasal tissues. However, further research aspired to demonstrate that this concentrated intranasal IgE was indeed locally synthesized, rather than transported to nasal tissues.

The nasal mucosa has been shown to contain all of the elements necessary for synthesis of immunoglobulins, immunoglobulin heavy chain class switching, and for

these elements to be inducible in response to allergen exposure.⁵⁸ Secondary lymphoid organization within nasal polyps was reported in a study by Gevaert and colleagues.^{19,55} IgE was demonstrated in association with both follicular structures containing B and T cells as well as with plasma cells. Zurcher and colleagues⁵⁹ demonstrated that functional B cells from the nose cultured in an IL-4-rich medium with blocking antibodies of CD40 were capable of producing IgE. Kleinjan and colleagues⁶⁰ found the nasal mucosa of patients with allergic rhinitis to be a rich repository of IgE-positive B cells and IgE-positive plasma cells. Further, this group observed that specific IgE-positive plasma cells were detected only in patients with allergic rhinitis and not found in healthy controls, and that specific IgE is the critical factor for a plasma cell to bind an allergen. No other immunoglobulin isotypes perform this function.

The necessary elements to promote synthesis of IgE and immunoglobulin heavy chain class switching, IL-4, IL-13, and CD40, were detected in sinonasal tissue, disputing previous theory that immunoglobulin class switching solely occurred within the large germinal centers comprising lymph nodes and splenic tissue.^{31,32,55} Activation of these mediators following provocation by allergen was suggested in studies by Wise and colleagues³² and Durham and colleagues.⁶¹ Following exposure to grass pollen, inferior turbinate tissue in patients with known sensitivity were found to contain an increase in IL-4 RNA and germ-line ϵ gene exons, which are spliced out during immunoglobulin class-switching gene recombination. Further evidence that immunoglobulin class switching indeed occurs within sinonasal tissue was provided by the ex vivo study by Cameron and colleagues⁶² in which similar findings were discovered after incubation of inferior turbinate biopsies from patients with ragweed allergy with the allergen.³² Takhar and colleagues⁶³ demonstrated that both in vivo and in vitro exposure to grass pollen allergen in allergic patients stimulates production of circle transcripts, a marker of ongoing class switch recombination, and that class switch recombination to IgE from multiple other isotypes occurs in the nasal mucosa.

Marcucci and colleagues⁶⁴ demonstrated the increased sensitivity of nasal mucosa compared with serum in response to allergen provocation, suggesting that the production of IgE occurs first in the target organ induced by allergen exposure, and is later followed by a systemic response. After in situ incubation of timothy grass, serum and nasal mucosa IgE measurements detected a significant immediate increase in the nasal mucosal levels, most profound in patients with known allergy during the peak of the pollen season.

Future attention to local IgE production within the nose will likely be directed toward the clinical relevance of this important finding, including diagnostic and therapeutic options for allergy testing and local immunotherapy. This may include development of an ideal test that is sensitive to allergen-specific IgE within nasal mucosa, which can aid in diagnosis of allergy when traditional systemic testing fails. Therapeutic options may ultimately modify local production of IgE with the long-term goal of decreasing local tissue disease severity and improving quality of life.

LOCAL IgE: PULMONARY

Studies of elevated IgE in pulmonary tissues aimed to describe the patterns of expression and the relationship to asthma severity, with goals of improving asthma control by means of anti-IgE therapy. Balzar and colleagues⁶⁵ studied more than 90 lung specimens, including healthy controls and those from patients with a range of asthma severity with and without atopy, and described a pattern of IgE distribution limited to the submucosa and excluded from the lung parenchyma. Mast cells bound to IgE were found primarily in the proximal airways. The amount of mucosal IgE more

directly correlated with eosinophilic and lymphocytic tissue inflammation, pulmonary function, and severity of asthma disease than did degree of systemic IgE. They proposed that an increase in serum IgE likely represents mucosal processes promoting an induction of the systemic IgE production mechanisms, and a high level of serum IgE occurs as a result of failure of immunologic process at the mucosal level.⁶⁵

Murine models have been studied to delineate the cellular infiltrate present in asthma. Mice were sensitized using intratracheal instillation of ovalbumin, which has been shown to result in eosinophilia, mononuclear cell infiltration, and airway epithelial changes analogous to what is seen in asthma.⁶⁶ In the mice that had been sensitized, germinal centers were detected with the parenchyma of the inflamed lungs associated with follicular dendritic cells bearing ovalbumin on their plasma membranes and ovalbumin-specific IgE-producing plasma cells.⁶⁷ Germinal centers, or bronchial-associated lymphoid tissue, are constitutive structures in certain species such as rats and rabbits; however, are inducible in humans and mice via antigenic exposure.⁶⁷⁻⁷¹ These germinal centers are the likely local source of IgE-secreting plasma cells that contribute to release of inflammatory mediators in the lung during an allergic asthma exacerbation.

Given the correlation of local pulmonary IgE with degree of pathologic inflammation, degree of asthma severity, and pulmonary function, Soler and colleagues⁷² tested the hypothesis that anti-IgE therapy would indeed improve asthma severity. Omalizumab is a recombinant humanized monoclonal antibody that binds free circulating IgE and thereby prevents its binding to mast cells, preemptively avoiding degranulation. Given to patients with moderate to severe asthma, it improved symptoms, improved quality of life, and permitted decrease in dosages of oral and inhaled corticosteroids.⁷² Improving control of asthma and decreasing the number of exacerbations in patients with severe asthma will likely greatly decrease individual financial burden in addition to decreasing burden on the health care system.⁷³ A similar study undertaken in patients with allergic rhinitis revealed a less exuberant effect as an actual disease-modifying effector.⁷⁴ Although patients had improvement in nasal allergy symptoms while receiving the therapy, there was no correlating decrease in specific IgE or in ϵ mRNA, suggesting that therapy does not modulate synthesis of nasal IgE. Omalizumab therapy, therefore, is founded on local expression of IgE, but appears to be unrelated to local synthesis of IgE. Further, observations made by Corris and Dark⁷⁵ regarding transmission of asthma through lung transplantation from donors with mild asthma to recipients not previously afflicted, and cure of asthma by transplantation of healthy lungs into patients suffering with asthma gave strong support to the hypothesis that asthma was a local disease mediated by local production of chemical signals.

Much of the investigation into the matter of local production of IgE in the lungs parallels the steps that were addressed in the same phenomenon in nasal tissue. Durham and colleagues⁸ and Ying and colleagues⁹ showed that in asthmatic patients, irrespective of atopy, total number of CD20 + B cells present in bronchial mucosa was similar to the number found in healthy controls, however the number expressing ϵ germline gene transcript and mature mRNA for the ϵ heavy chain gene were elevated in asthmatic patients. It has been suggested that prior work evidencing local IgE synthesis in nasal tissue is applicable to the pulmonary system as well.^{8,76,77}

ANTIGEN SPECIFICITY OR DISORDERED PRODUCTION?

Traditionally it has been assumed that the selective pressures shaping the immune repertoire through repeated cycles of finely tuned somatic mutation are the same for all immunoglobulin isotypes. Emerging evidence from studies focusing on the

mutation rates and patterns observed in the variable region of the IgE gene suggest that IgE may develop along a distinct pathway. Recent studies have identified unusual mutation patterns in IgE from blood samples taken from individuals with allergic asthma, but few have investigated whether these patterns are also seen in IgE isolated from tissue.

Early B-cell development is a finely tuned process with multiple “check points” to eliminate self-reactive cells while ensuring the formation of functional immunoglobulin. Formation of the functional immunoglobulin gene requires a series of specialized tightly regulated somatic recombination events, known collectively as VDJ recombination, to occur early in B-cell development. Later, as mature naive B cells recirculate through the lymphatic system, they can be activated by encounters with antigen. During an immune challenge, the antigen specificity of activated cells is fine tuned within the germinal centers. Competition for antigen binding in the germinal centers results in selection of those B cells with the best existing binding affinity. Once selected, clonal expansion of these cells is initiated.⁷⁸ As the selected cells proliferate, they accumulate mutations with high frequency: approximately 1 mutation per generation.

These mutations are preferentially focused on hypervariable hotspots within the V region. Many of these hotspots fall within the complementarity-determining regions (CDRs) of the V gene, which correspond to the antigen-binding sites of an antibody.⁷⁹ The rate of mutations in the V region is a million times higher than the genome-wide rate, and negative selection eliminates cells with mutations that cause reduced antigen-binding affinity or loss of function.^{78,80} Cells that accumulate mutations improving the antigen-binding affinity of the expressed immunoglobulin are selected to give a subset of highly antigen-specific B cells.

When a B cell has developed under the influence of pressure from antigen selection, a characteristic pattern of replacement mutations is seen in V region sequences. Antigen selection results in the accumulation of replacement mutations in the CDR of the V region (R_{CDR}) with higher frequency than in the surrounding framework regions (FR).⁸¹ In our laboratory, seminested polymerase chain reaction (PCR) was used to amplify the entire V region of IgE sequences from individuals with CRS with nasal polyps (CRSwNP). IgE sequences were analyzed for evidence of antigen selection to see if the mutation pattern reported in other allergic and inflammatory disorders is reflected in sequences from CRS sufferers. IgE sequences were successfully amplified from 4 individuals. In total, 217 IgE sequences were amplified, of which 38 were unique, and VDJ gene usage and mutation rates were analyzed for these sequences.

Dahlke and colleagues⁸² reported that there is a statistically significant difference in mutation frequency distribution among nonallergic IgE, allergic IgE, and IgG sequences. Although polyclonal IgE has been detected in nasal polyps, and it has been hypothesized that this is the result of stimulation by super-antigens.⁸³ Our studies have shown that there was no significant difference between the mean V region mutations of IgE sequences from individuals with CRSwNP and previously described nonallergic IgE sequences nor was there a difference with database-derived IgG (Richard J. Harvey, MD, unpublished data, 2009). Mutation analysis of 38 unique IgE sequences showed that only 6 were likely the product of IgE-expressing B cells that had developed under the influence of antigen selection (Fig. 3). Given that such IgE may have limited binding affinity for the proposed antigen and are unlikely to have undergone strong antigen selection, such findings have significant implications for the role of immunotherapy in chronic rhinosinusitis and the relevance of SAE or fungal IgE. Whether these IgE products and their production are tightly related to pathogenesis in chronic rhinosinusitis, merely a by-product of colonizing organisms

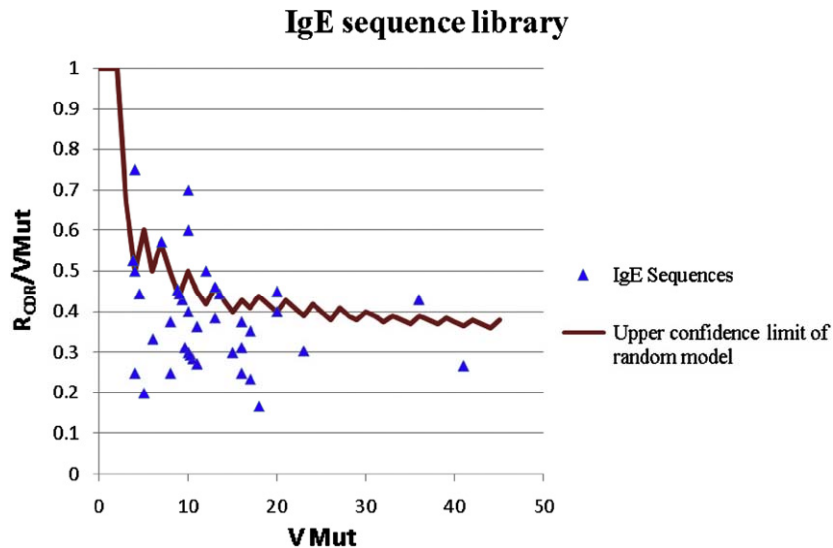


Fig. 3. Antigen selection in mucosal IgE sequences using $R_{\text{CDR}}/\text{VMut}$: VMut . Antigen selection results in the accumulation of replacement mutations in the CDR of the V region (R_{CDR}). VMut is the total mutations in the V region. Points falling on top of each other have been offset. Individual IgE sequences are represented by blue triangles. The red line shows the upper confidence limit of a random somatic mutation model. The lower confidence limit is not shown. Sequences above the red line suggest production under antigen selection.

(epiphenomenon), or part or a broader antigen-presenting cell disorder remains unresolved.

Implications for Research

Further research into the mechanisms that drive antigen presentation and then the subsequent immunologic response are more likely to procure future therapeutic targets. IgE production is likely to occur locally and under conditions of less antigen selectivity than previously believed. This significantly affects our current disease classifications and nomenclature, in particular for chronic rhinosinusitis. The concept of “AFRS-like” patient classification exemplifies this inability to match systemic markers with clinical findings. Likewise, research into SAE and fungal IgE may place too much assumption on the degree to which these antigens have influenced subsequent IgE production.

Implications for Clinical Practice

The blunt use of systemic IgE diagnostic testing may provide limited clinical insight to IgE-mediated disease in patients with sinonasal pathology. Immunotherapy, although effective for well-proven allergic IgE-mediated disease, is likely to have little role in chronic rhinosinusitis with polyps if highly selected antigen-specific IgE is not demonstrated in local mucosa.

SUMMARY

This is a review of local and systemic IgE as it relates to inflammatory conditions of the upper and lower airways. The potential exists for local IgE to enhance our identification

and treatment of patients with airway inflammatory conditions in the absence of elevated systemic IgE. Development of disease-modifying agents capable of inhibiting local IgE production may ultimately decrease the symptomatic manifestations and socioeconomic burden of allergy.

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