

Local IgE Production

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ABSTRACT

Recent data from a number of groups have confirmed that IgE antibody may be produced, at least in part, locally within the nasal mucosa. Our data support the theory that B cell switching may also occur locally, although this remains to be confirmed. Local IgE may account for local disease expression in atopic subjects, although it is not clear which step is rate-limiting in this process. Our results highlight the importance of developing local strategies targeted against IgE for treatment of allergic diseases. (American Journal of Rhinology 14, 305–307, 2000)

Atopy refers to the tendency to develop an exaggerated IgE response as reflected by a positive skin-prick test to one or more common inhaled allergens, i.e., a *predisposition* to develop allergic diseases. Only a proportion of atopic subjects develop *allergy*, i.e., the clinical expression of atopic disease. Common IgE-mediated allergic diseases include rhinitis, asthma, eczema, and food allergy. Clinical symptoms occur following cross-linking of IgE on the surface of mast cells and/or basophils by multivalent allergen. However, it is not clear why some atopic individuals develop asthma, whereas others may have rhinitis, whereas others may have positive skin tests but no clinical manifestations. One explanation may be the regulation and production of IgE *locally* within the target organ. Huggins and Brostoff suspected local IgE synthesis on clinical grounds in patients with perennial symptoms of rhinitis but no positive skin test or detectable house dust mite-specific IgE in their serum.¹ House dust mite sensitivity was confirmed by nasal provocation with a mite extract and specific IgE was detectable in nasal fluid in amounts comparable to those in rhinitis sufferers who also showed positive skin tests and

elevated serum allergen-specific IgE. Platts-Mills demonstrated grass pollen-specific IgE in nasal but not salivary secretions of hay fever patients.² Further evidence for local IgE synthesis within the nasal mucosa has come from studies of cultured B cells derived from nasal secretions that express IgE at both messenger RNA and protein level.^{3,4} However, it is not clear whether these cells ever resided in the nasal mucosa. For example, Bachert was unable to demonstrate IgE positive B cells or plasma cells in the nasal mucosa, whereas they were detectable in cervical lymph nodes and tonsillar tissue from patients with allergic rhinitis.⁵

ISOTYPE SWITCHING BY B CELLS

The critical step in the commitment of B cells to the synthesis of IgE is referred to as heavy chain switching, and comprises somatic recombination within the immunoglobulin heavy chain gene cluster to transform the ϵ germ-line gene into the rearranged gene.^{6,7} This then gives rise to mRNA for the ϵ heavy chain of IgE. Two signals are required for heavy chain switching to IgE. IL-4 (and IL-13) target the ϵ gene for recombination, whereas cross-linking of CD40 on the B cell membrane initiates heavy chain gene rearrangement. Following allergen provocation in the nose IL-4 is released from both TH2-type lymphocytes and mast cells,^{8,9} both of which express CD40 ligand, thereby providing the necessary signals for IgE switching of B cells to occur locally (Fig. 1).

LOCAL IgE IN RHINITIS

We have studied the expression of ϵ germ-line gene transcripts and messenger RNA for the ϵ heavy chain gene of IgE in nasal B cells.¹⁰ We used techniques of immunohistochemistry and *in situ* hybridization using a gene probe that detects only sterile ϵ germ-line gene transcript (I ϵ) and a C ϵ probe, which detects both the ϵ germ-line gene transcript and messenger RNA for the ϵ heavy chain. When hay fever patients were administered allergen locally early (10–30 minutes) and late (1–24 hours), symptoms ensued. After 24 hours, coincident with an increase in the number of cells expressing messenger RNA for IL-4 in the nasal mucosa, ϵ germ-line

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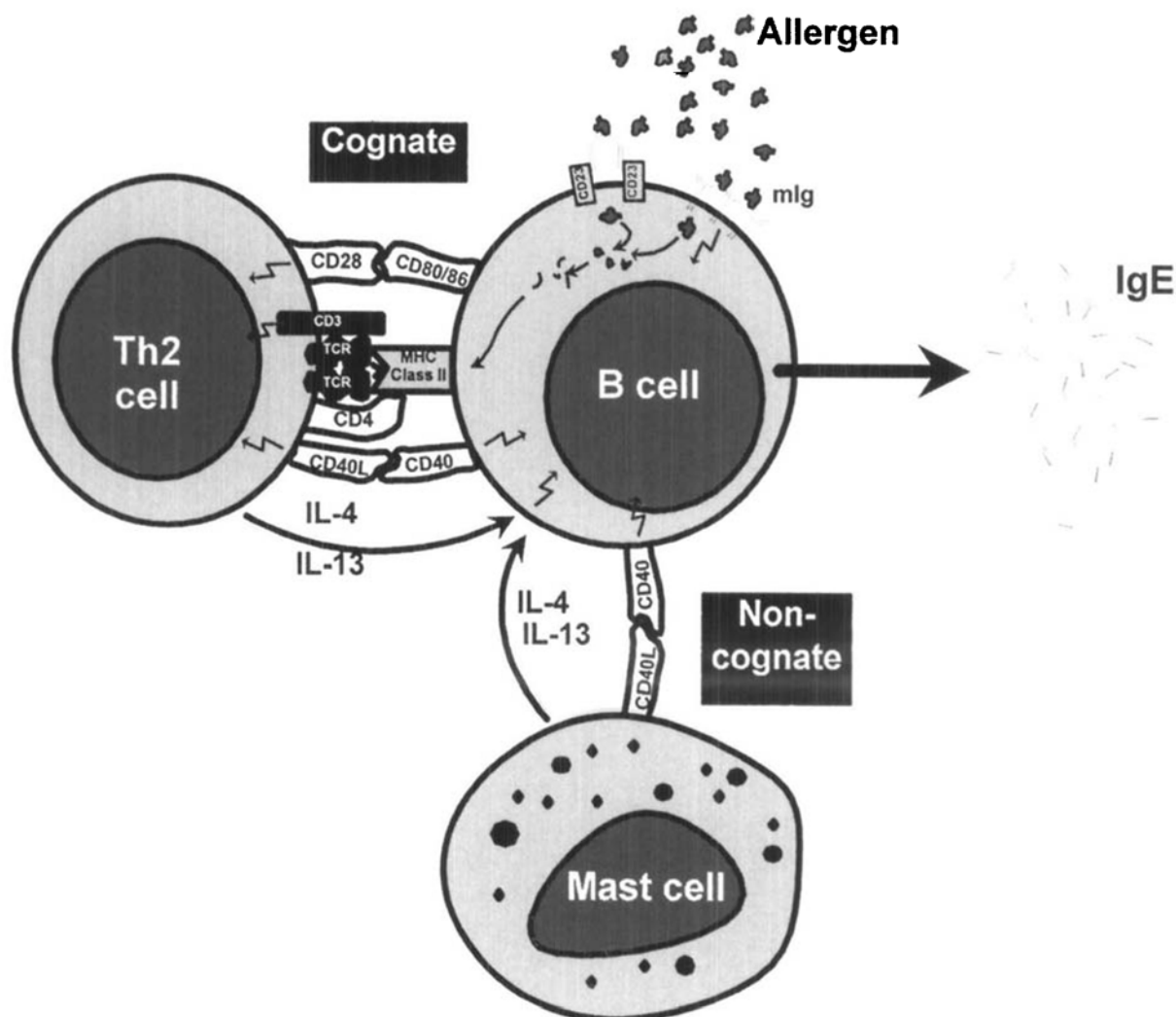


Figure 1. Cognate and non-cognate B cell interactions.

gene transcripts appeared in the nasal B cells. The induction by allergen of IL-4 mRNA and ϵ germ-line gene transcripts was inhibited by topical corticosteroid (fluticasone propionate). This effect of allergen was isotype-specific since no increase in C γ transcripts was detected after allergen. We have confirmed the results after allergen challenge by detecting seasonal increases in IL-4, C ϵ , and I ϵ expression by nasal mucosal B cells, which are also inhibitable by topical corticosteroids.¹¹ In these experiments we could not detect IgE protein by nasal B cells or plasma cells, possibly due to the sensitivity of the technique of immunohistochemistry used. However, more recent data¹² and personal communication (from Dr. Wytse Fokkens, Erasmus University, Rotterdam) have shown that a proportion of both CD19+ B cells and CD138+ plasma cells may indeed express IgE protein within the nasal mucosa. Taken together, these studies provide strong evidence that B cells within the nasal mucosa do indeed synthesize and produce IgE, and that local switching by B cells to IgE may possibly occur.

LOCAL IgE IN ASTHMA

We have also studied bronchial mucosal biopsies from patients with atopic and non-atopic asthma.¹³ Our hypothesis was that local IgE expression may also occur in asthma and may possibly explain why some atopic individuals develop asthma, whereas others do not. Similarly, local IgE expression may possibly account for so-called "non-atopic" asthma in the absence of raised serum IgE or positive skin tests. We therefore studied the presence of B cells and expression of IL-4, C ϵ , and I ϵ using immunohistochemistry and *in situ* hybridization. CD20+ B cells were detected in the bronchial mucosa in both asthmatics and normal subjects, with no differences between the groups. We demonstrated increases in IL-4 in both atopic and non-atopic asthma using parallel techniques of semi-quantitative PCR, *in situ* hybridization, and immunohistochemistry. There were increases in both C ϵ and I ϵ RNA that colocalized to bronchial mucosal B cells. We also identified a significant correlation between IL-4 message expression and the ex-

pression of Iε transcripts. We concluded that local expression of IgE at the RNA level is increased in both atopic and non-atopic asthma.

LOCAL IgE SYNTHESIS *IN VITRO*

We have recently developed an explant model of IgE synthesis (unpublished), whereby nasal biopsies from atopic subjects were cultured *in vitro* for 0–14 days and compared with biopsies from non-atopic normal volunteers. We have confirmed IgE synthesis by use of ELISA of culture supernatants in atopic, but not normal, subjects. *De novo* synthesis was confirmed by observing (1) the effect of temperature on IgE synthesis, (2) detection of IgE in supernatants after acid-stripping of cell membrane-associated IgE, and (3) the incorporation of radio-labeled amino acids into explants and detecting IgE from culture supernatants by immunoprecipitation using anti-IgE followed by SDS-page electrophoresis and autoradiography. This model should enable studies of the mechanism of local switching and the influence of therapeutic agents directed against IgE.

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EASTERN ALLERGY CONFERENCE/SOUTHWEST ALLERGY FORUM COMBINED MEETING

Acapulco (Acapulco Princess), MEXICO

January 10 - 14, 2001

Wednesday, January 10

5:00 - 5:30 Mechanisms of Allergic Inflammation in Rhinitis and Urticaria
5:30 - 6:00 The Evolution of Pharmacotherapy for Rhinitis and Urticaria
6:00 - 6:30 Hidden Effects of Allergic Inflammation and Implications for Treatment
6:30 - 7:00 Panel Discussion

Pre-Conference Symposium: "Treating Allergic Inflammation in Rhinitis and Urticaria"
Lawrence DuBuske, MD
Bruce Prenner, MD
Gary Kay, MD

Thursday, January 11

8:30 - 9:10 Herbs 101. Or, What Every Allergist Should Know About Herbs
9:10 - 9:50 Herbal Medicine and Alternative Therapies in Allergy, Asthma & Immunology
9:50 - 10:00 Panel Discussion
10:00 - 10:30 Coffee Break, Visit Exhibitors
10:30 - 11:10 House Dust Endotoxin - New and Hot Stuff About an Old Allergen
11:10 - 11:50 Present and Future Advances in Immunotherapy
11:50 - 12:00 Panel Discussion
12:00 - 12:30 Case Presentations: Drs. Fournier and Charlesworth

Southwest Allergy Forum Section
Marianne Frieri, MD, PhD
Renata Engler, MD

Andrew H. Liu, MD
Harold Nelson, MD

Friday, January 12

8:30 - 9:10 Can Allergy Be Prevented? It's a Possibility
9:10 - 9:50 Hidden Factors in Allergy and Asthma
9:50 - 10:00 Panel Discussion
10:00 - 10:30 Coffee Break, Visit Exhibitors
10:30 - 11:10 Combination Therapies in Asthma
11:10 - 11:50 Theophylline (An Old Timer's Asthma Cure) Revisited
11:50 - 12:00 Panel Discussion
12:00 - 1:00 Lunch Program: Avoiding Implications of Fraud and Abuse Complying with 2001 Federal Guidelines (a 1 Hour Ethics CME program)

Southwest Allergy Forum Continued
Andrew H. Liu, MD
Laura L. Somerville, MD, PhD

Harold Nelson, MD
Laura L. Somerville, MD, PhD

Richard Honsinger, MD

Saturday, January 13

8:30 - 9:10 Inflammation of Viral Infections
9:10 - 9:50 Viral Infection and Allergy: The Upper Airway
9:50 - 10:00 Panel Discussion
10:00 - 10:30 Coffee Break, Visit Exhibitors
10:30 - 11:10 Viral Infection and Allergy: The Lower Airway
11:10 - 11:50 Vaccines: Present and Future
11:50 - 12:00 Panel Discussion

Eastern Allergy Conference Section: Sponsored by:
Allergy Societies of Pittsburgh and Pennsylvania
Deborah Gentile, MD
Philip Fireman, MD

David Skoner, MD
David Greenberg, MD

Sunday, January 14

8:30 - 9:00 Demographics and Epidemiology of Allergic and Nonallergic Rhinitis
9:00 - 9:30 Treatment Update: Allergic Rhinitis
9:30 - 10:00 Treatment Update: Nonallergic Rhinitis
10:00 - 10:30 Panel Discussion

Post-Conference Symposium:
"Advances in the Treatment of Allergic and Nonallergic Rhinitis"
Russell A. Settipane, MD
William Berger, MD
Phillip Lieberman, MD

CME's are pending

MEETING REGISTRATION FORM

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