

Local IgE Production in the Nasal Mucosa: A Review

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ABSTRACT

IgE is one of the most important markers for allergy. The presence of specific IgE on skin mast cells (skin test) and/or the existence of specific IgE in serum (RAST) indicates sensitization, but not necessarily clinical allergy, in the target organ. Discrepancies between sensitization and disease could be explained by local IgE production. The nasal mucosa contains all the cell types necessary for a local IgE immune response. Moreover, it has been shown that this local IgE is specific for the specific allergen to which the patient is allergic. The availability of IL-4 and IL-13 produced in the nasal mucosa creates the possibility for isotype switching of B cells to IgE-positive B cells, and proliferation and maturation of B cells to IgE-producing plasma cells. The IgE positivity of B cells and plasma cells implies that IgE production occurs in the nasal mucosa. The observation of the presence of allergen-positive plasma cells and the finding that all allergen-positive cells were also IgE-positive indicates that this local IgE production is allergen-specific. Data discussed in this review provide strong evidence for the local production of specific IgE in the nasal mucosa. (American Journal of Rhinology 14, 299–303, 2000)

IgE is one of the most important markers for allergy. From birth, the nasal mucosa is continuously exposed to antigens, leading to a primary and a secondary immune response. When the immune response is directed against an allergen, sensitization occurs and this results in the formation of specific IgE against the allergen. Specific IgE can be detected using *in vivo* (skin prick test)^{1,2} and *in vitro* (serum

specific IgE, e.g., RAST or Alastat) diagnostic tests. The presence of specific IgE on skin mast cells (skin test) and/or the existence of specific IgE in serum (RAST) indicates sensitization, but not necessarily clinical allergy, in the target organs such as lungs, skin, eyes, or nose. Although positive skin tests or specific IgE for allergens in serum have been reported in 30–40% of the population, only 10–17% evince symptoms of allergic disease.^{3–5} However, considerable discrepancies between sensitization and symptomatic allergic disease have been observed, particularly in children.⁶ In earlier studies of atopic rhinitis in children, we found that only half the children with clinical signs of allergic rhinitis and eosinophilia in the nasal mucosa had specific IgE against allergens in serum.⁷ We therefore need other methods for diagnosing allergy in children, especially in rhinitis, because of the absence of clear-cut signs and symptoms of allergic disease. Moreover, data on the local phenomena of allergic disease will increase our knowledge of preventive and therapeutic options. One of the explanations of the difference between sensitization and clinical allergic disease might be the occurrence of local IgE and local IgE production. This manuscript discusses the available data, especially in children, which confirm local IgE production.

ALLERGIC RHINITIS AND IgE IN THE NASAL MUCOSA OF CHILDREN

Allergic children have significantly more IgE-positive cells in the nasal mucosa than non-allergic children.⁸ The same phenomenon has been described previously in adults.⁹ The IgE+ cell population in children consists mainly of mast cells and LC. The total number of IgE-positive cells in the epithelium and lamina propria of allergic children is strongly correlated with total serum IgE ($R_s \geq 0.82$; $P = 0.0001$). In animals also there is clear evidence for an equilibrium between circulating IgE and cell-bound IgE.¹⁰ Cells carrying an IgE receptor (FcεRI/RII) that are situated in an environment containing high levels of circulating IgE are more often found to be positive for IgE.

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Moreover, high serum IgE levels also induce IgE receptor display on basophils and mast cells, and therefore actually increase the potential number of IgE-positive cells.¹¹ However, this correlation cannot be found in a general population (unpublished results). For example, patients with high total IgE because of helmitic infections do not appear to have high numbers of IgE-positive cells in the nasal mucosa. In addition, this correlation cannot be found if the population of IgE+ cells is subdivided into different cell populations such as IgE+ mast cells and IgE+ Langerhans cells. In allergic children, no correlation could be found between the total serum IgE level and the percentage of IgE+ nasal mucosal mast cells. Furthermore, IgE-positive Langerhans cells were only found in children with specific serum IgE against aero-allergens, and not in allergic patients with a food allergy or patients with a high total IgE in which specific sensitization could not yet be proven.⁸ In children with specific IgE against aero-allergens, two-thirds of the nasal mucosal mast cells carried IgE. In allergic children without specific IgE against aero-allergens, only 11% (range 1%–30%) of the nasal mucosal mast cells carried IgE (unpublished data). These results suggest that the local IgE concentration, which seems to be responsible for the IgE receptors on mast cells and the IgE positivity, is not directly dependent on the serum concentration of IgE.

ALLERGIC RHINITIS AND IgE IN THE NASAL MUCOSA OF ADULTS

The number of IgE-positive cells in the epithelium and lamina propria is significantly higher in allergic rhinitis patients than non-allergic controls or patients with non-allergic rhinitis.^{9,12,13} The nasal mucosal population of IgE positive cells in grass pollen allergic rhinitis patients consists of mast cells (confirmed by total of chymase-tryptase staining) 80% (20–95); Langerhans cells 10% (1–30); B cells 4% (0–14); and plasma cells 2% (0–29) in season. Contrary to past findings, numbers of mast cells in the nasal mucosa do not appear to increase significantly during allergen provocation or clinical disease, although most studies describe a redistribution from the lamina propria to the epithelium.^{13–17} Other factors, such as degranulation and cytokine production, are probably more important. Mast cells are capable of producing cytokines such as IL-3, IL-4, IL-5, GM-CSF, and TNF α .^{18–21}

In ongoing allergic inflammation, as has been shown by repeated allergen provocation, an increasing number of mast cells are extensively degranulated.^{13,15} Recently, the role of mast cells and basophils has been thoroughly reviewed by Peebles and Togias.²² Apart from mast cells, other cells can be positive for IgE. Langerhans cells are able to bind allergens to IgE via the high-affinity receptor for IgE.^{23–27} This has been shown to be specific.²⁵ Immunodouble staining methods using CD1 and anti-IgE-FITC on sections of the nasal mucosa of patients with allergic rhinitis revealed IgE on 20–40% of the CD1+ cells in the epithelium and occasionally on CD1+ cells in the lamina pro-

pria.²⁸ Although the absolute number of IgE+/CD1+ cells increases during the grass pollen season, no difference was observed in the percentage of IgE+/CD1+ cells during, before or after the grass pollen season. IgE+/CD1+ cells are not present in the nasal mucosa of non-allergic polyposis patients or non-allergic controls.

LOCAL PRODUCTION OF IgE IN THE NASAL MUCOSA: CIRCUMSTANTIAL EVIDENCE

For more than 20 years now, studies have suggested that the nasal mucosa itself is able to produce at least a large proportion of IgE.^{29–33} Huggins and Brostoff report patients who have specific IgE in nasal secretion and who had no detectable levels of specific IgE in serum.³⁴ In addition, Small et al. detected specific IgE in nasal polyps.³⁵ However, the final proof has been long in coming. Apart from the production of IgE in the nasal mucosa itself, the lymphoid tissues of Waldeyer's ring or the cervical lymph nodes have been posited as the primary source of locally produced IgE.^{32,36–39} The nasal mucosa contains all the cell types (dendritic cells, T cell and B cells in clusters) required for an IgE immune response.⁹ In the subepithelial layer of the nasal mucosa of patients with allergic rhinitis, clusters of (IgE+) Langerhans cells and activated (HLA-DR+) T cells are regularly found, suggesting a role for Langerhans cells in the secondary response to inhaled allergen and the subsequent development of chronic airway inflammation leading to chronic eosinophilic airway inflammation.⁴⁰

The availability of IL-4 and IL-13 produced in the nasal mucosa^{19,41,42} creates the possibility for isotype switching of B cells to IgE-positive B cells and proliferation and maturation of B cells to IgE-producing plasma cells.⁴³ The IgE positivity of B cells and plasma cells implies that IgE production occurs in the nasal mucosa. Durham et al. observed that epsilon germline transcripts were formed after local allergen provocation in the nasal mucosa of allergic rhinitis patients.⁴⁴

LOCAL PRODUCTION OF IgE IN THE NASAL MUCOSA

Zurcher et al. demonstrated the possibility of IgE synthesis by nasal epithelial B cells *in vitro*; functional B cells can be isolated from the nose and after stimulation with IL-4 and antibodies against CD40, it was possible to induce IgE protein synthesis.⁴⁵ Diaz-Sanchez et al. also found IgE-producing B cells in nasal lavages and mRNA for IgE in allergic rhinitis patients.⁴⁶ In the nasal mucosa of allergic patients and controls, we found IgE+ B cells and IgE+ plasma cells. The numbers of IgE+ plasma cells and the numbers of IgE B cells were significantly higher in allergic patients compared to controls.⁴⁷

LOCAL PRODUCTION OF SPECIFIC IgE

Recently, it has become possible to detect specific IgE in nasal mucosal biopsies.²⁵ This method is based on the measurement of cell-bound specific IgE. Specific IgE-bear-

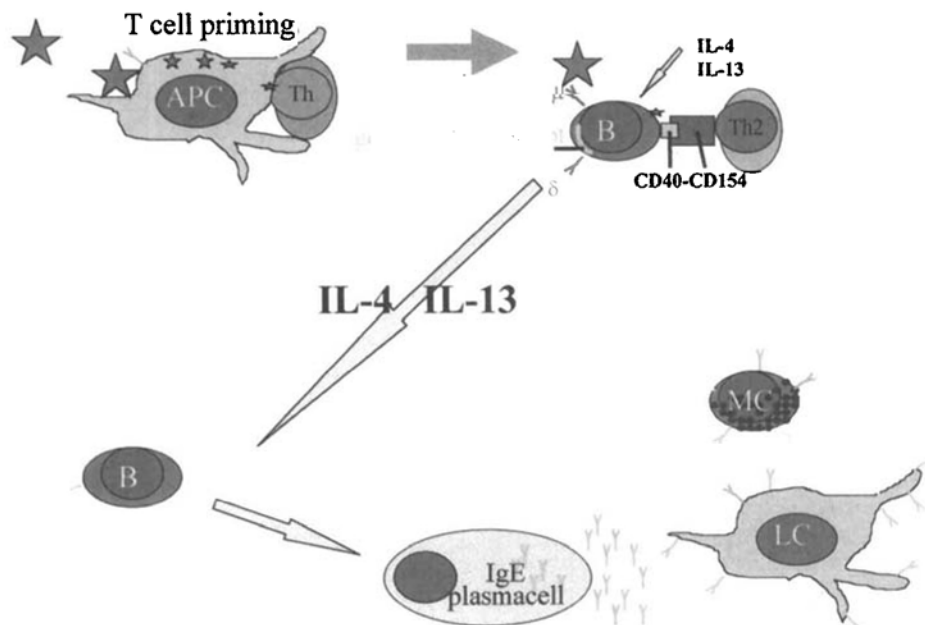


Figure 1. The nasal mucosa of allergic patients produces specific IgE locally. B-cell stimulation with IL-4 and CD40 can induce IgE production via B-cell isotype switch from sterile I germline transcripts to mature C germline transcripts. Locally produced specific IgE can bind on mast cells and Langerhans cells.

ing cells in the section can bind these biotinylated allergens (Alastat), which can then be visualized. Nasal mucosal biopsies were taken from 11 symptomatic patients with an isolated grass-pollen allergy, 10 symptomatic patients with a perennial allergic rhinitis for house dust mite allergen, and 10 non-allergic controls. Staining with biotinylated grass-pollen (GP1) demonstrated positive cells only in patients with a grass-pollen allergy. Biotinylated *Dermatophagoides pteronyssinus* (D1) only stained cells in patients with a perennial allergy. Specific binding of allergen to allergic patients and the blocking experiments proved the method to be highly specific. Allergen-positive cells stained double with IgE, and the high-affinity receptor for immunoglobulin E (FcεRI), CD1, HLA-DR, tryptase, chymase, and plasma cells (CD38).²⁵

The observation of the presence of allergen-positive plasma cells and the finding that all allergen-positive cells were also IgE-positive indicates that the local production of allergen-specific IgE takes place in the nasal mucosa. Blocking experiments showed that the binding was specific for IgE and not for IgG, A or M, meaning that specific IgE is the critical factor for allergen binding to cells and that this binding was not based on a binding between IgG, IgA, or IgM with the allergen²⁵ (see Fig. 1).

THERAPIES DIRECTED AGAINST THE LOCAL PRODUCTION OF IgE

Therapies directed toward decreasing local IgE production might be effective in allergic disease. Many cells and cytokines that play an active role in allergic inflammation in the nose are influenced by local corticosteroid treat-

ment.⁴⁸⁻⁵⁰ However, the extent to which cells—and probably cytokines as well—are reduced differs. Some cells, such as antigen-presenting (Langerhans) cells and eosinophils, are highly sensitive, while others, such as T cells, are only significantly reduced in exaggerated situations. Some cells, such as macrophages and neutrophils, are not affected at all.⁴⁸ Intranasal steroids have been shown to inhibit the seasonal increase in serum ragweed-specific IgE in ragweed-sensitive allergic rhinitis patients⁵¹ and recently it has been shown that local corticosteroid treatment resulted in a significant reduction of circulating total and specific IgE in the serum of atopic asthmatic patients.⁵² Local corticosteroid treatment had also been shown to suppress the induction by allergen of IL-4 mRNA and epsilon germline gene transcripts,⁴⁴ so local corticosteroid therapy has the potential to reduce local IgE production, but definitive proof has not yet been obtained. It is not clear whether a reduction of local IgE is correlated to the reduction in symptomatology after local corticosteroid treatment.

CONCLUSION

The data discussed in this review provide strong evidence for the local production of specific IgE in the nasal mucosa. This could be an explanation for the discrepancies between sensitization and clinical manifestation of disease. Moreover, the production of local IgE could explain why local corticosteroid treatment is so effective compared to systemic treatment.

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