

Is localized immunoglobulin E synthesis the problem?

Cell-cell interactions controlling immunoglobulin E synthesis could be important components of the feedback loops that are initiated by exposure to allergens.

Allergic reactions have three required components: allergen, allergen-specific antibody and effector cells. Allergens are typically multivalent antigens, such as pollens. The antibody component is immunoglobulin E (IgE). The effector cells are mast cells or basophils, which constitutively express high-affinity IgE receptors (FcεRI) on their surface. The classic allergic reaction is set up when monomeric IgE (IgE that is not bound to antigen) binds to FcεRI on the surface of mast cells or basophils. This is not sufficient for receptor activation, which requires receptor aggregation. The latter occurs when FcεRI-bound IgE contacts allergens. The activated receptors transduce an intracellular signal, leading to cell degranulation and the release of various mediators of allergic reactions, such as histamine and leukotrienes. The allergen-activated mast cells and basophils also produce a panel of cytokines, including interleukin-4 (IL-4), which plays an important part in the development of allergic reactions (reviewed in [1,2]).

The first step in the pathogenesis of an allergic disease is the production of an IgE antibody response to an allergen. The B cells of allergic individuals produce IgE directed against environmental allergens, whereas those of non-allergic individuals do not. The reason for this difference is not yet clear, but both genetic and environmental factors have been shown to play a part. Significant progress has, however, been made in understanding how B cells are induced to produce IgE. It is now well established that naive B cells require at least two types of signal before they will produce IgE, one given by IL-4 and the other by CD4-bearing T cells. These two signals induce B cells to switch antibody classes, from making IgM to IgE (reviewed in [3-7]).

IL-4 first activates transcription in B cells from a promoter within the immunoglobulin locus, resulting in synthesis of mRNA comprising an upstream exon (the 'I exon') spliced to the exons encoding the IgE-specific constant regions [8-10]. This mRNA cannot be translated into protein, because it contains translational stop codons in all three reading frames, but its synthesis is necessary for the class switch to IgE production. The mechanism by which it facilitates class switching is not yet known.

The other signal required to induce B cells to switch to IgE production is provided by direct contact with CD4⁺ T cells, and significant progress has been made in understanding this interaction in recent years. At least two pairs of complementary cell-surface molecules are

known to participate in this cell-cell interaction: CD40/CD40L [11] and CD23/CD21 [12]. CD40 is expressed on the surface of B cells, and interacts with its ligand, CD40L, which is found on the surface of activated T cells. CD23 and CD21 can each be expressed on either T cells or B cells, and the precise consequences of their interaction are not yet clear. Flores-Romo *et al.* [13] have, however, recently shown that antibodies against CD23 can inhibit an antigen-specific IgE response *in vivo*.

Bonnefoy *et al.* [14] argue that, for the CD21/CD23 pair, the critical interaction is between CD21 on B cells and CD23 on T cells, based on the observation that treatment of B cells with anti-CD21 antibodies or recombinant soluble CD23 stimulates IgE production in the absence of T cells [12]. Epstein-Barr Virus (EBV) similarly stimulates IgE production by B cells, presumably by interacting with CD21, which is known to function as an EBV receptor [15]. Furthermore, CD23 is not expressed on non-activated T cells and its expression is strongly induced by IL-4 [16] — thereby potentially allowing enhanced CD23-CD21 interactions in allergic individuals. It should also be noted that CD23 is a low-affinity IgE-binding protein, hence its alternative name FcεRII [7,17]. This means that the CD21-CD23 interaction may be inhibited by the end product of the process that it promotes — IgE synthesis.

How could these interactions be coordinated *in vivo*? The current view of the events that constitute the development of an allergy goes broadly as follows (see [18]). When a specific allergen is first encountered by a predisposed individual, it is processed and presented to T cells in the usual manner by antigen-presenting cells, which include antigen-specific B cells. This process, thought to occur in lymph nodes, activates a subpopulation of T cells that are of a particular type — T helper cells, type 2 (Th2 cells) — and receptor specificity; these cells recognize the allergen (reviewed in [19]). Unlike Th1 cells, which secrete interferon γ , a strong inhibitor of IL-4-induced IgE synthesis, Th2 cells secrete high levels of IL-4. As a consequence, any B cell interacting with these Th2 cells would tend to be switched to IgE production by the combination of IL-4 and the cell-cell contact signals described above.

Because antigen-specific B cells interact with cognate T cells to present antigen, they would more frequently be induced to switch to IgE production than would non-cognate B cells, resulting in production of more allergen-specific than non-specific IgE. The secreted IgE

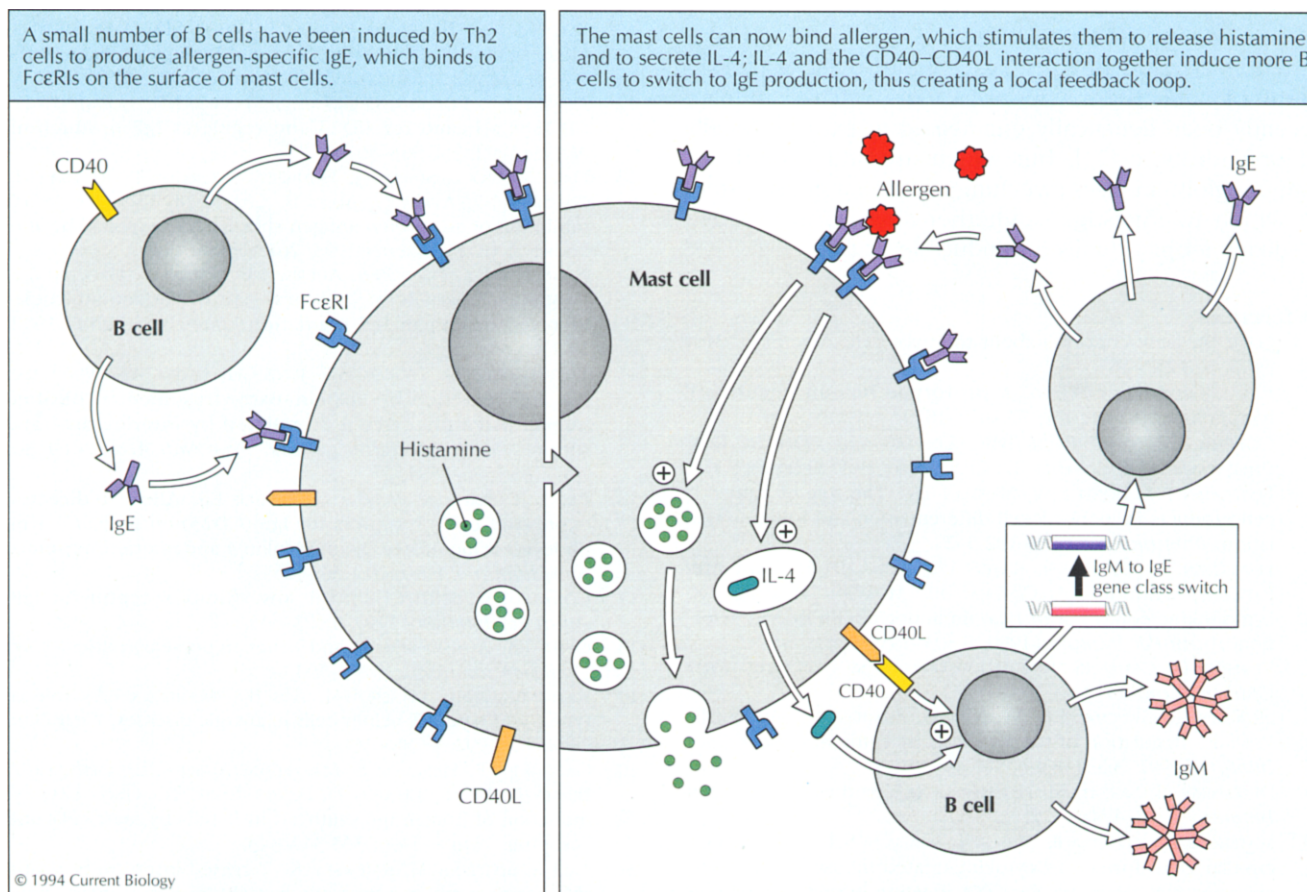


Fig. 1. The interactions between B cells and mast cells or basophils may constitute a feedback loop that allows IgE synthesis to be induced to high levels locally, without systemic levels of allergen-specific IgE being significantly increased.

would then bind to FcεRI on the surface of mast cells and basophils, allowing repeated contact with the same allergen to cause aggregation of FcεRI-bound specific IgE, leading to further IL-4 production by mast cells and basophils. In addition to stimulating B cells to switch to IgE production, IL-4 can also promote the development of antigen-specific T cells into Th2 cells. Exposure of a responsive individual to allergen could thus initiate a positive feedback loop: a Th2 predominant response to the allergen leads to IL-4 release, giving rise to overproduction of allergen-specific IgE and Th2 cells, which in turn provides the means for further production of IL-4, and so on.

A new twist in this tale has recently been reported by Gauchat *et al.* [20], who have found that B cells do not necessarily need to contact T cells to receive the co-stimulatory signal for immunoglobulin class switching — *in vitro*, at least, the signal can be provided by mast cells and basophils, both of which express CD40L. This raises the interesting possibility that a high local level of IgE synthesis could be induced by a feedback loop between B cells and mast cells or basophils (Fig. 1). The attraction of this hypothesis is its ability to explain why allergic individuals often have very localized symptoms, such as rhinitis and conjunctivitis, and why they frequently do not have systemically elevated levels of allergen-specific IgE.

In the scenario shown in Figure 1, when an allergic individual contacts an allergen expansion of allergen-specific B cells and production of a certain amount of allergen-specific IgE would be induced, thereby 'priming the immunological pump'. On repeated contact with the same allergen, local activation of mast cells, via their FcεRI-bound IgE, would induce IL-4 synthesis; the secreted IL-4 and direct contact with mast cells would together induce local B cells to switch to IgE synthesis. Increased local synthesis of allergen-specific IgE would prime more tissue mast cells to react to the allergen, thus creating a local positive feedback loop.

This hypothesis has an important testable implication. Both the allergen specificity and the potential for positive feedback depend on the distribution of antibody specificities (idiotypes) made by the local B cell population. If the set of idiotypes is too varied, the switched B cells would produce predominantly non-specific IgE, which would bind to mast cells but would not allow their activation by allergen. At some threshold level of allergen-specific B cells, however, the switched B cells would produce enough allergen-specific IgE for repeated contact with the allergen to establish and maintain the feedback loop. Therefore, this hypothesis would predict that allergic individuals would have B-cell idiomotype distributions in symptomatic areas which

are skewed towards being allergen specific. A corollary of this is that an individual with a limited idiotype repertoire should be very susceptible to the establishment of such feedback loops. The mice that have recently been genetically engineered to express B cells of one idiotype [21], but which are still capable of immunoglobulin class switching, may be a good system in which to investigate whether such local positive feedback loops actually are inducible *in vivo*.

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A.M. Scharenberg and J-P. Kinet, Molecular Allergy and Immunology Section, NIAID, National Institutes of Health, Twinbrook II Building, Room 108, 12441 Parklawn Drive, Rockville, Maryland 20852, USA.