

The IgE memory reservoir in food allergy



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IgE is a central effector component of T_H2 immune responses toward helminths and allergens. With regard to food allergens, the clinical manifestations of food allergy are primarily mediated by IgE. Certain food allergies, such as those to peanut, tree nuts, fish, and shellfish, are lifelong in the majority of patients, and their persistence has been attributed to long-lived, IgE-secreting plasma cells (PCs). This led to the proposition that these cells are potential therapeutic targets in patients with food allergy.¹ However, several lines of evidence have disputed this concept and have compelled researchers to search for alternative explanations for allergic persistence.

The half-life of allergen-specific IgE^+ PCs was calculated to be only 60 days in a mouse model of food allergy and anaphylaxis,¹ which is consistent with the evidence that IgE^+ B cells are predisposed to differentiate into short-lived PCs.² Accordingly, allergen-specific IgE titers became undetectable between 3 and 6 months after sensitization in mice that were not re-exposed to the allergen.¹

In patients with food allergy, whether allergen-specific IgE levels are maintained in the absence of allergen restimulation is exceedingly difficult to investigate because of the high rate of accidental and subclinical exposures.¹ Evidence from helminth infections in which allergen (parasite) exposure and clearance can be ascertained is informative. For example, subjects infected with *Anisakis* species, common contaminants of raw fish, show a continuous and substantial decrease in serum levels of allergen-specific IgE after parasite clearance.³ Together, these findings suggest that in the absence of repeated exposure to the IgE-eliciting antigen, allergen-specific IgE levels are not persistent

in accordance with the limited survival of IgE^+ PCs that has been demonstrated in mice.¹

Although allergen-specific IgE levels in allergic mice are not sustained over time, the capacity to regenerate allergen-specific IgE and develop anaphylaxis is virtually lifelong. This suggests the existence of long-lived, allergen-specific memory cells established at the time of sensitization, which replenish the transient IgE^+ PC compartment on allergen re-exposure.¹ Given the current understanding that memory IgE^+ cells are extremely rare or absent in mice,² identifying the reservoir of IgE memory responses has been the subject of intense research. In mice orally sensitized to food allergens, a population of allergen-specific IgG_1^- but not IgE^- expressing memory B cells was identified at least 9 months after sensitization.⁴ In a model of epicutaneous sensitization to foods, a population of immature allergen-specific IgG_1^+ memory B cells ($PDL2^-CD80^-CD73^+CD35^+$) predated IgE responses; on allergen re-exposure, a population of cells with more mature markers emerged ($PDL2^+CD73^+CD80^+$).⁴ This mature phenotype of IgG_1^+ memory B cells was identified as a reservoir of high-affinity IgE in a model of *Nippostrongylus brasiliensis* infection.⁵ In a similar model IgE production was aborted when the extracellular domain of IgG_1 was replaced with IgE sequences,⁶ thus establishing that high-affinity IgE originated from the IgG_1^+ memory compartment.⁵

In human subjects Scott Boyd's group sequenced almost 16 million immunoglobulin heavy regions from the peripheral blood of healthy and allergic subjects. This analysis provided indirect evidence that IgE cells primarily originated from antigen-experienced, somatically hypermutated, IgG_1 -expressing cells, with lesser contributions from precursors expressing IgG_2 and IgA .⁷ In human tissues it has been shown that most IgE^+ PCs formed in tonsillar B-cell cultures stimulated with IL-4 and anti-CD40 developed through sequential class-switching from IgG .⁸ However, a few studies have reported IgE^+ memory B cells in PBMCs from allergic patients by using flow cytometry.⁹ Although neither the allergen specificity nor their contribution to the recall response was determined, it is possible that sequentially class-switched IgE^+ B cells acquire a memory-like phenotype before committing to a PC fate. Nonetheless, the body of evidence from both murine and human studies suggests that the memory B-cell compartment generated in T_H2 responses is largely populated by non- IgE -expressing cells (Fig 1).

It follows from this evidence that deciphering the cellular and molecular mechanisms that regenerate IgE might have substantive therapeutic implications. Using a model of adoptive transfer of T and memory B cells, IL-4, IL-13, or both derived from T cells were sufficient to induce IgE class-switching from IgG_1^+ memory B cells and subsequent IgE secretion.⁶ In a recent study, Wambre et al¹⁰ characterized a subset of T_H2 memory cells ($CD27^-CD45RB^-CRTH2^+CD49d^+CD161^+$) that produced multiple

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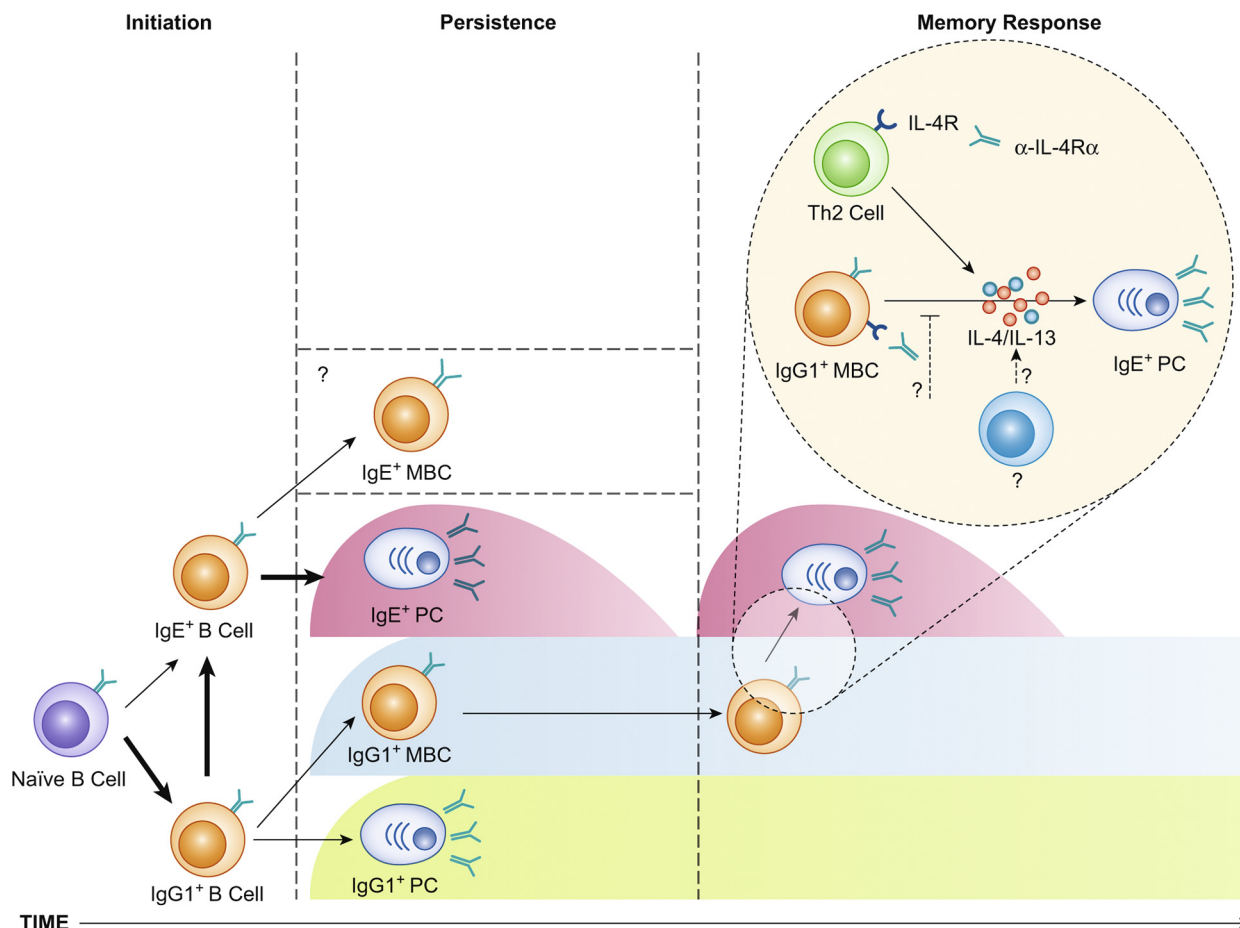


FIG 1. Cellular and molecular mechanisms facilitating memory IgE responses. On primary sensitization under $\text{T}_\text{H}2$ conditions, IgE^+ B cells primarily arise through sequential class-switching, with IgG1^+ as an intermediate. IgG1^+ B cells differentiate into both IgG1^+ PCs and IgG1^+ memory B cells (MBCs), both of which persist for a lifetime. IgE^+ B cells are predisposed to become PCs, which exist transiently. It is possible that IgE^+ B cells also acquire a memory-like phenotype; however, the longevity of these cells is not known. On a recall response, IgG1^+ MBCs can replenish the IgE^+ PC compartment in an IL-4- and/or IL-13-dependent manner. In a recall response these cytokines are produced by $\text{T}_\text{H}2$ cells and perhaps other cell types (ie, natural killer T cells). Therefore blockade of IL-4 receptor (IL-4R) α might inhibit replenishment of the IgE^+ PC compartment during a recall response.

$\text{T}_\text{H}2$ cytokines, including IL-4 and IL-13, in the circulation of atopic subjects. The frequency of these cells significantly increased during seasonal allergy and decreased but did not vanish in patients who had undergone successful desensitization with peanut oral immunotherapy.¹⁰ These findings suggest that this subset is a candidate for the production of IL-4/IL-13 to stimulate IgE switching and secretion and, ultimately, clinical reactivity. A caveat for studies using adoptive transfer strategies and of correlative but not causal human studies using PBMCs is that they might neglect relevant sources of IL-4 and IL-13 from tissue-resident cells, which have been reported in murine models of food allergy¹ and parasitic infections.⁵ This remains a challenge because of the limitations of accessing tissue-resident cells from relevant sites, especially in patients with food allergy.

Confinement of the IgE memory reservoir largely to the IgG1 compartment might serve as a regulatory mechanism. The IgG1 memory response produces IgG1 , which is not subclass equivalent between mice and human subjects but is less likely to induce anaphylaxis compared with IgE. Yet it has the potential to evolve into IgE under the influence of IL-4- and IL-13-mediated

signaling. As a consequence, IL-4 receptor α is positioned as a central molecule in the perpetuation of IgE-mediated allergic diseases, including allergic asthma, allergic rhinitis, atopic dermatitis and food allergy, and therefore it is a suitable target for therapeutic interventions.¹ Hypothetically, IL-4 receptor α blockade during allergen immunotherapy would prevent the generation of IgE-producing PCs and perhaps facilitate class-switching toward a protective isotype (IgG4); this intervention might also prevent CD4^+ $\text{T}_\text{H}2$ cell expansion. It stands to reason that these mechanisms might facilitate the development of tolerance rather than desensitization, thus potentially transforming the current therapeutic value of immunotherapy for food allergy and other allergic diseases.

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