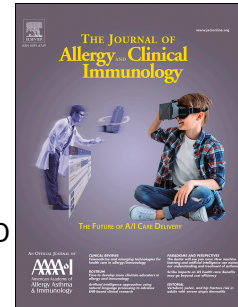


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B cells in food allergy

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Approximatively 10% of the world population suffers from food allergies, which usually develop from allergic sensitization early in infancy to milk, egg and peanut. In fact, some allergic individuals with milk and egg allergies seem to outgrow their allergic symptoms in a few years, while peanut allergic individuals do not seem to outgrow their peanut allergy. Knowledge on the immune tolerance mechanisms to food allergens is essential for establishing precise prevention and treatments in food allergies.¹ A particularly important research focus is the accurate quantification and qualitative characterization of allergen-specific memory B cells in food allergic patients and tolerant individuals. Monitoring the changes that occur in allergen-specific B cells in response to food allergen immunotherapy may provide valuable clues about the mechanisms that drive unresponsiveness to food allergens. Currently, the role of B cells in the development of food allergy and tolerance to food allergens remains poorly understood. Here, we highlight the current understanding on the role of B cells in food allergies in this “Paradigms and perspectives” article.

Infants with egg allergy tend to develop natural tolerance in the first year of life. Neeland *et al.*² purified B cells to phenotype and quantify circulating B cell subsets from infants with persistent, transient egg allergy and healthy controls. Following the toll-like receptor 9 (CpG-2006) stimulation, their circulating B cell population produced a high level of interleukin (IL)-8 from persistent egg allergy group. Hence, they suggest that an increase in proinflammatory cytokine production

of B cells may lead to the persistent egg allergy. Similarly, children with milk allergy seem to outgrow their allergic symptoms in an early age. Noh *et al.*³ examined the role of IL-10-producing regulatory B cell (Br1) prior to allergen stimulation in milk allergic and milk tolerant subjects. IL-10 has a potent immunosuppressive capacity and plays a major role in the induction of IgG4 and suppression of IgE in allergen immunotherapy. They observed that Br1 cells was decreased in milk allergy group but not in milk tolerant group. For this reason, the result suggests the development of immune tolerance is regulated by anti-inflammatory IL-10 producing Br1 cells.

Long term *in vivo* follow up of antigen/allergen-specific B cells is an exciting research area to gather information about clonal existence and expansion of memory B cells specific to a given antigen/allergen in the circulation or tissues. A recent study by Hoh *et al.* focusing on B cell responses in peanut allergy has demonstrated that in humans, local class switch recombination (CSR) to IgE in gastrointestinal sites may contribute significantly to the development of food allergen-specific IgE antibodies.⁴ Using high-throughput BCR repertoire analysis, IgE-expressing B cell and/or plasma cell clones were detected in blood, stomach, duodenum, and esophagus of peanut-allergic patients in addition to circulation. IgE clones in peanut-allergic individuals were enriched in stomach and duodenum tissue, and many individuals shared similar peanut-specific IgE sequences. It was demonstrated in the same study that a high frequency of clonal lineages containing IgE and IgA1 or IgA2 members were present in the GI tract. These data suggest that IgA1 CSR to IgE and possibly IgE CSR to IgA2 are common events in peanut allergic patients. This was never reported in mouse models, because mice cannot switch from IgA to IgE due to the order of immunoglobulin constant heavy gene segments in their IgH locus. Previously, the data from peripheral blood B cells of patients with respiratory allergies demonstrated

that IgE clone members were most closely related to IgG1 members that might show sequential switch from IgG1 to IgE. These data, therefore, suggest that B cell differentiation pathways in patients, who develop food allergy differ from patients with respiratory allergies. In addition, this study identified the gastrointestinal tract as a reservoir of IgE⁺ and peanut allergen-specific B cells in food allergy, representing an exciting area to study the changes during food allergy oral immunotherapy in allergen-specific IgE⁺ and other isotype-expressing B lineage cells in the GI tract in comparison to respiratory tissue, lymphatic organs and bone marrow (Fig 1).

The biological pathways that lead to the production of antigen-specific IgE antibodies remain incompletely understood. Croote *et al.* isolated IgE⁺ B cells from individuals with food allergies and used single-cell RNA sequencing to elucidate the gene expression and splicing patterns unique to these cells.⁵ They found that circulating IgE⁺ B cells were mostly immature plasmablasts. Interestingly, these IgE antibodies showed high affinity and unexpected cross-reactivity to different peanut allergens. This study provides insight into IgE B cell transcriptomics and enables biochemical dissection of this antibody class.

Sensitization via skin is an important aspect of food allergy. In a murine model of epicutaneous sensitization to food allergens, IgG1⁺ memory B cells preceded the generation of IgE responses, suggesting that the determination of humoral IgG1 immunity could be used to identify patients at the risk of developing IgE-mediated food allergy.⁶ Natural tolerance to food allergens is allergen-specific and long-lasting, and its specific allergen. Santos *et al.* demonstrated that most children with detectable peanut-specific IgE were not clinically allergic to peanut.⁷ Their data demonstrated that differences in allergen-specific IgE levels could not justify the clinical phenotype in allergic children compared to natural tolerance. However, the

authors proposed that blocking IgG4 antibodies could provide more explanation for the absence of clinical reactivity in allergic and natural tolerance subjects. Following this, a study of clonal diversity of allergen-specific B cells in patients with peanut allergy showed that there is increasing somatic mutation of IgG4 members of a B cell clone in oral immunotherapy, whereas IgE mutation levels in the clones did not increase.⁸ Most of the peanut allergen-binding B cells isolated by flow cytometry were mutated and expressed isotype-switched antibodies. The results of this study also suggest that oral immunotherapy can stimulate somatic mutation of allergen-specific IgG4.

Additionally, cross-reactivity between common food allergens and aeroallergens in allergic subjects could induce food allergy. Schwarz *et al.*⁹ examined IgG, IgG4 and IgE sensitization to 91 allergens from animal foodborne, vegetable foodborne and airborne in children from the Multicentre Allergy Study. The authors observed that IgG responses to each allergen is higher in IgE-sensitized compared to non-sensitized children at age 2 and 7. This prevalence of allergen-specific IgG is relying upon the routes of allergen exposure. Comparatively, there is only a minor contribution of IgG4 antibodies to the IgG responses in natural exposure children. To identify the circulating immune cell signatures associated with peanut allergy in the first year of life, high-dimensional mass cytometry-based single-cell profiling of resting and stimulated PBMCs was performed in peanut sensitization with tolerance versus clinical peanut-allergic patients.¹⁰ Interestingly, the major findings associated with clinical peanut-allergy showed increased frequencies of activated B cells (CD19^{hi}HLA-DR^{hi}), increased production of TNF- α by several cell types including NK cell, CD4 T cell, monocyte, DC, and B-cell populations, and increased frequencies of peanut-specific memory CD4 T cells. Moreover, infants with sensitized tolerance

displayed a reduced frequency, but hyper-responsive naive CD4 T cells and an increased frequency of plasmacytoid dendritic cells. This study successfully validates the utility and power of high-dimensional mass cytometry analysis to interrogate the cellular interactions that are associated with allergic sensitization and clinical food allergy in the first year of life.

In conclusion, IgE-mediated food allergy is common, often serious, and usually lifelong, if not outgrown in the first years of life. Early age induction and maintenance of oral tolerance to food antigens are crucial to clinical management of food allergy. Human IgE-expressing memory B cells and plasma cells play an important role in the development of food allergy and their counter regulation by Breg cells, IgG4, and development of oral tolerance. Nevertheless, the natural tolerance is developed differently to its specific allergens and those cellular parameters may differ. The uncertainty of threshold of reactivity to egg, milk or peanut allergens and persistency in food allergic individual remain unclear. Why egg and milk-allergic subjects could resolve their food allergies easier than peanut or shrimp-allergic individuals? What are the common features and distinctions in egg, milk and peanut-allergic subjects that are shared? From our perspective, B cells will be key players in answering those remaining questions. Accordingly, further studies on the role of B cells and food allergy are needed for the improvement of novel and precise medical treatments for food allergy and also other allergic patients in the future.

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Figure legend:

Fig 1. The development of IgE-mediated food allergy in human.

The exposure of B cells to food allergen proteins occurs in the human stomach, duodenum, secondary and tertiary lymphoid organs. IgE class switch recombination in B cells, plasma cell differentiation and allergen-specific IgE production occurs locally in the stomach and duodenum. In secondary and tertiary lymphoid organs, food allergens are taken up by DCs, which then migrate to draining lymph nodes, and present allergen-derived peptides on MHC class II molecules to naïve T cells. These T cells can differentiate to Th2 and TFH cells, which produce type II cytokines such as IL-4, IL-5, IL-9, IL-13, and IL-6, IL-12 respectively, and induce IgE CSR. TFH cells interact with naïve B cell and induce direct and sequential CSR to IgE in B cells, plasma cell differentiation and allergen-specific IgE production.

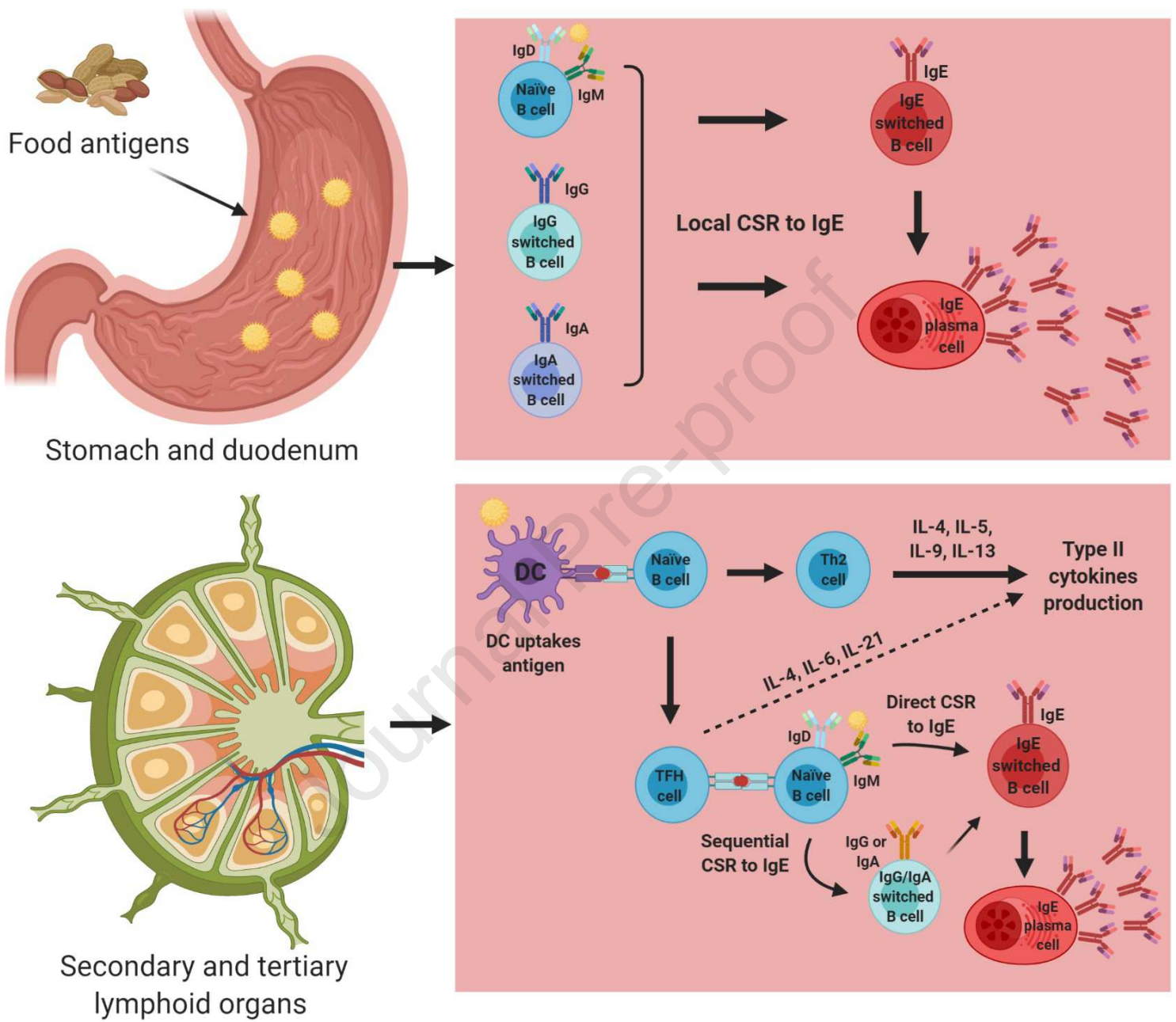


Fig 1.