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IgE producers in the gut expand the gut's role in food allergy

Onyinye I. Iweala^{†,1,2}, A. Wesley Burks²

¹Department of Medicine, Thurston Arthritis Research Center, Division of Rheumatology, Allergy, and Immunology, University of North Carolina at Chapel Hill, USA

²Department of Pediatrics, University of North Carolina Food Allergy Initiative, Division of Allergy, Immunology and Rheumatology, University of North Carolina at Chapel Hill, USA.

Abstract

Details about IgE-producing B cells in the gut in the context of food allergy are scarce, despite the frequent exposure of the gut and its associated lymphoid tissues to dietary antigens. A new study finds that IgE-producing B cells are enriched in gut tissues and are probably generated from local antibody isotype switching.

Food allergies are an emerging public health concern. The prevalence of food allergies has increased markedly over the past decade worldwide, ranging from 6–10% depending on the study population ^{1,2}. Food allergen-specific IgE complexed with high-affinity IgE receptors expressed by mast cells and basophils drive effector responses in food allergy, generating adverse symptoms in individuals with food allergy who ingest allergenic foods ³.

Circulating IgE concentrations are low and IgE-producing B cells rare in individuals without food allergy⁷. The signals that increase both IgE production and frequency of allergen-specific, IgE-producing B cells in individuals with food allergy remain unclear. Where IgE⁺ B cells develop and how IgE antibody repertoires compare between individuals with and without food allergy are not well established. These questions are challenging to address as IgE-producing cells are rare and can be difficult to distinguish from cells that bind IgE via high or low affinity IgE receptors. Moreover, IgE-producing B cells (plasma cells and plasmablasts, FIGURE 1A) express low levels of cell surface IgE. Flow cytometry can misidentify circulating cells as IgE⁺ B cells. In one study, only 30% of cells identified as IgE⁺ B cells with flow cytometric techniques were actually 'true' IgE⁺ B cells by analysis of their immunoglobulin heavy chain (IgH) gene sequences ⁴. Despite these challenges, a few studies have characterized circulating IgE-producing B cells in the blood from individuals with peanut allergy receiving experimental peanut oral immunotherapy ^{5,6} and those practicing strict avoidance ⁴.

[†] onyinye.iweala@med.unc.edu .

Competing interests

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Food allergens, peanut included, frequently make first contact with the host through the upper gastrointestinal tract and gut-associated lymphoid tissues (GALT). Yet, few studies have scrutinized IgE-producing B cells in these tissues. Moreover, the relationship of circulating IgE-producing B cells to IgE-producers in the gut is poorly understood. Hoh et al.⁷ sought to address this knowledge gap. To understand their approach, it helps to review how the immune system generates antibody, including IgE. During B cell development, somatic rearrangements of the germline B cell DNA encoding the antigen-binding “variable” (V) regions of B cell-generated antibodies result in our diverse antibody repertoire. Somatic hypermutation in mature, activated B cells enhances this diversity while isotype or class switch recombination (CSR) later in the immune response results in the same rearranged V region associating with different antibody isotypes aside from the initial IgM response, including IgA, IgE, and IgG (Supplementary BOX 1).

These investigators hypothesized that IgE-producing plasma cells were located in the gut because IgE antibodies are detectable in the stool and intestinal secretions from patients with food allergy, and unlike IgG, or polymeric IgM or IgA, IgE antibodies are not among those actively transported across epithelial barriers. The researchers used high-throughput DNA sequencing techniques to evaluate IgH variable region transcripts in mucosal upper gastrointestinal tract biopsy samples and peripheral blood of 19 individuals with peanut allergy. They identified an abundance of IgE-expressing B cell clones in the stomach, duodenum, and peripheral blood when compared with individuals who did not have food allergy. Through immunohistochemistry, they demonstrated that IgE⁺CD138⁺ plasma cells formed small foci in the lamina propria of stomach and duodenum and were morphologically distinct from brightly-staining IgE⁺CD138⁻ mast cells. They found substantial overlap in expanded IgE⁺ clonal lineages among stomach, duodenum and peripheral blood of individuals with peanut allergy⁷.

To determine whether IgE class switching was occurring locally in the gut, the investigators reasoned that if IgE⁺ B cells were generated from local class switch recombination (CSR), then potential precursor B cells expressing isotypes upstream of human IgE (IgM, IgD, IgG, and IgA1) would be enriched in the same tissue biopsy sample rather than in samples from other noncontiguous biopsy sites. By contrast, if IgE⁺ B cells that had undergone CSR in distant lymph nodes were trafficking to the gut, then IgE, IgM, IgD, IgG and IgA1 expressing clone members should be evenly dispersed across biopsy sites. They found that 90% of B-cell clones in individuals with peanut allergy were identified in only a single tissue site with shared somatic mutation patterns between IgE⁺ and IgA⁺ clone members in the upper gastrointestinal tract. IgA was the most common non-IgE isotype B-cell clone in the gastrointestinal mucosa and peripheral blood of individuals with peanut allergy. Moreover, there was a positive correlation between the clone counts from the stomachs and duodenums of these individuals and peanut-specific serum IgE levels, suggesting disease relevance for these clones⁷.

To assess the antigen specificity of the IgE⁺ sequences extracted from the gastrointestinal tract, they used a single-chain variable phage display library created from IgE heavy and light chains isolated and pooled from the stomach and duodenal biopsy samples of 10 individuals with peanut allergy and measured the ability of the IgE in these libraries to bind

purified Ara h 2 peanut protein. There is considerable opportunity for substantial antibody diversity within an individual's antibody repertoire, as VDJ recombination and somatic hypermutation can generate an expansive array of antibodies against a single antigen, each with a unique affinity and specificity. Amazingly, Hoh et al. found that Ara h 2 specific-antibodies from individuals with peanut allergy showed clonal convergence; in other words, substantial similarities in the antibody repertoires against Ara h 2 allergen amongst unrelated individuals⁷. This finding suggests that a restricted antibody repertoire could serve as a marker of peanut allergy or might even predispose to the development and persistence of peanut allergy. In this regard, Hoh and colleagues recapitulate and expand upon earlier studies that also demonstrated antibody repertoire restriction in Ara h 2 recognition, but using peripheral blood samples⁴⁻⁶.

These findings place the spotlight on the upper gastrointestinal tract as a clinically relevant cache for food allergen-specific IgE⁺ plasma cells. Moreover, IgE⁺ plasma cells resulting from localized CSR, rather than migrating IgE⁺ plasma cells from distant sites, could be primarily responsible for producing the allergen-specific IgE that sensitizes gut mast cells. This work also expands our understanding of the sequential isotype switching pathways required to generate high-affinity IgE. In addition to the well-accepted sequential switches from IgG1 and IgG4 to IgE⁸, there might be CSR from IgA1 to IgE and from IgE to IgA2, as the investigators identified a high frequency of clones comprised of both IgE and IgA subtypes in those with peanut allergy. A range of diverse IgA clonotypes with distinct functions are critical for modulating the composition of the gut microbiota⁹. This study provides evidence for the existence of food-specific IgA in the gastrointestinal tract in individuals with and without food allergy, though the interactions between food-specific IgA-producing and microbial IgA-producing clones remain to be explored⁹.

Even as this study widens our understanding of the origins and clonality of gastrointestinal IgE⁺ cells, it opens the door for future investigation. The location in the gut where non-IgE to IgE⁺ B cell CSR takes place is still unknown. This location could be within primary foci in the lamina propria or within the GALT followed by preferential migration of B-cell clones to distinct anatomical niches in the gut. The investigators do not address the role of T-cell help in the generation of these gut-resident IgE-producing plasma cells. Future studies might reveal a T follicular helper (T_{FH}) cell subset analogous to the T_{FH13} cells described in mice¹⁰, critical for CSR of non-IgE to IgE⁺ clones producing the high-affinity IgE that drives anaphylaxis.

A role for the elusive and controversial IgE⁺ memory B cell⁸ in generating these IgE-producing plasma cells also remains in question. A popular model to explain how human allergic responses are sustained hinges on circulating IgE⁺ plasma cells or plasmablasts replenished by IgG⁺ memory B-cell precursors⁸. Hoh et al. do not identify any IgE⁺ memory B cells in their study; their findings seem to support reservoirs of not only IgG⁺, but also IgA1⁺ B-cell clones in the gut undergoing CSR in the right conditions to produce IgE-producing B-cell clones⁷. Future studies should address the longevity of these IgE-producing B-cell clones in the gut and whether this aspect correlates with prognosis of patients with peanut allergy.

Hoh et al. have added another piece to the puzzle of where IgE-producing cells reside, placing the upper gastrointestinal tract front and centre as a critical environmental reservoir for IgE-producing cells. Their study opens a new frontier, with potential to enhance our current diagnostic and prognostic markers for food allergy and to develop targeted tissue-specific therapies for conventional food allergies and beyond.

Supplementary Material

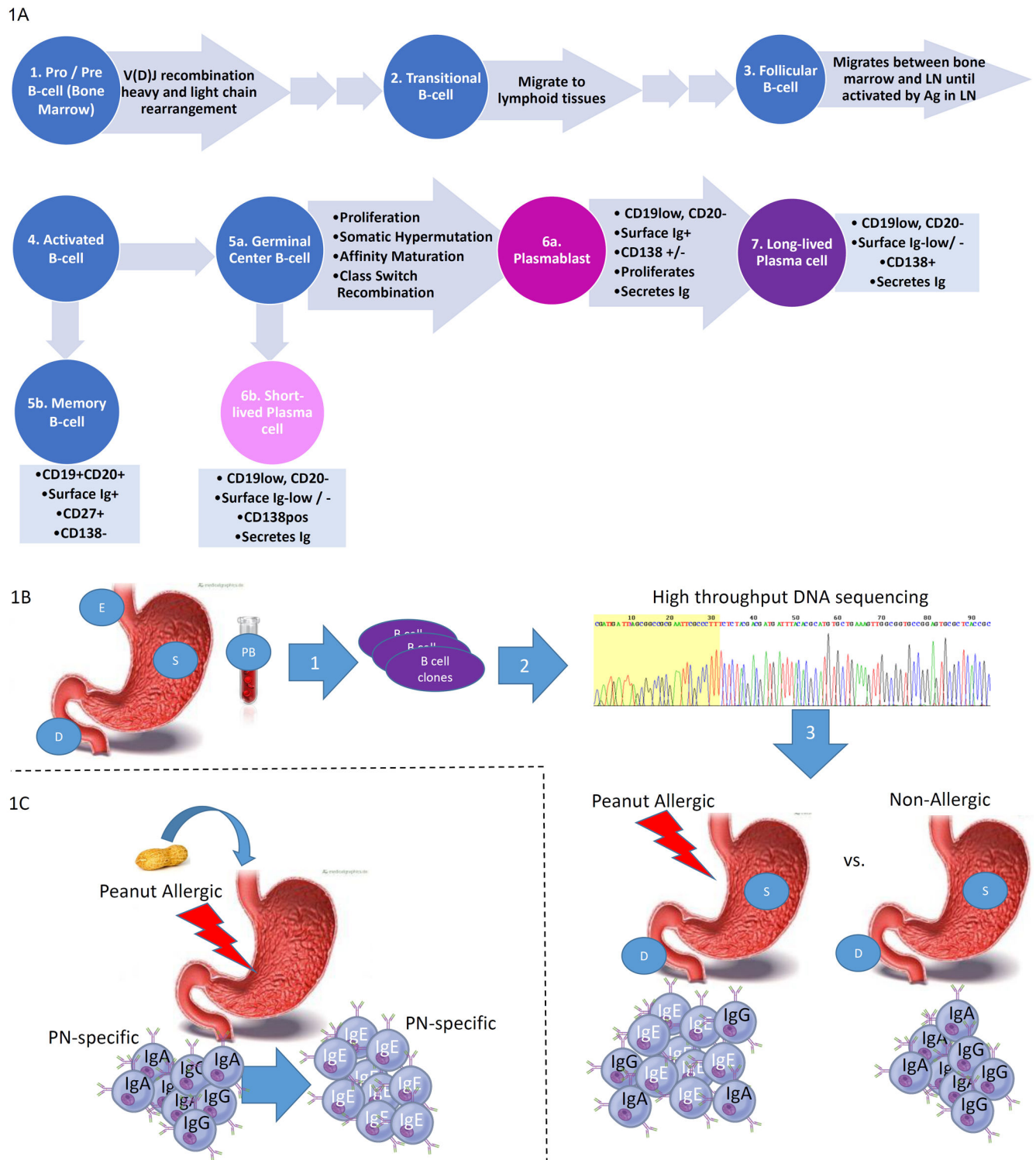
Refer to Web version on PubMed Central for supplementary material.

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lymphoid tissues. Immunoglobulin-secreting progeny (plasmablasts, long, and short-lived plasma cells) are delineated in shades of purple. Developmental stages between Pro / Pre B-cell and Transitional B-cell and between Transitional B-cell and Follicular B-cell have been omitted for space and clarity. LN = lymph node; Ag = antigen; Ig = immunoglobulin.

B. IgE+ B cell clones are enriched in gastrointestinal tract of allergic subjects. Hoh et al. characterized B cell clones from esophagus (E), stomach (S), duodenum (D), and peripheral blood (PB) of peanut-allergic and non-allergic individuals. They found that IgE+ cells are enriched in the stomach and duodenum of allergic patients and have a plasma cell phenotype. PN = peanut. **C. Local isotype switching in gastrointestinal tract.** In peanut allergic individuals, the frequency of clonally-related IgE+ cells and non-IgE cells support the possibility of local isotype switching in the upper gastrointestinal tract.