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Origins of peanut allergy-causing antibodies:

Analysis of gut-produced antibodies raises questions about how food allergy arises

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Some people produce immunoglobulin E (IgE) antibodies to proteins in common foods. As a result, these foods can trigger severe allergic inflammation (anaphylaxis). There are several structurally and functionally distinct antibody isotypes (IgM, IgD, IgG, IgA, and IgE), and which isotype binds to a target molecule (antigen) influences what happens next. For example, IgG that binds peanut proteins is harmless, but IgE bound to the same proteins can induce anaphylaxis and death. Therefore, how, where, and why allergen-reactive IgE is made are decades-old questions. Hoh *et al.* (1) found that gut tissue is a likely place for IgE development in peanut-allergic individuals. In addition, despite vast sequence possibilities, they found that many individuals share similar peanut-reactive IgE DNA sequences. This suggests that IgE antibodies in different individuals recognize peanut proteins in a similar manner, which could inform strategies for pharmacological interventions.

Antibodies are produced by cells of the B lymphocyte lineage and consist of four Ig polypeptide chains—two identical heavy (H) chains and two identical light (L) chains—and each chain has a variable (V) region and a constant (C) region. The V region forms the surface that physically binds to antigens such as peanut proteins. The C region of IgH (CH) dictates antibody function largely by triggering processes that lead to neutralization, elimination, or induction of inflammation. Assembly of multiple *IGH* gene segments through the process of V(D)J recombination results in enormous sequence diversity, particularly in the exon encoding the V region, which comprises much of the antigen binding surface. Next to the V exon are a variety of C-region exons arranged in tandem (e.g., Cμ, Cγ, Cε, and Cα), which define the different antibody isotypes (2).

Newly assembled Ig is produced as IgM. However, during an immune response, the same V region of IgH (VH) can be expressed in the context of another C-region isotype through a process called class switch recombination (CSR). This positions an alternative CH region next to the VH exon by permanent excision of the intervening DNA and associated CH-encoding exons. The position of CH exons relative to each other thus determines which IgH isotypes are available for secondary switch events. For example, an IgM-expressing B cell

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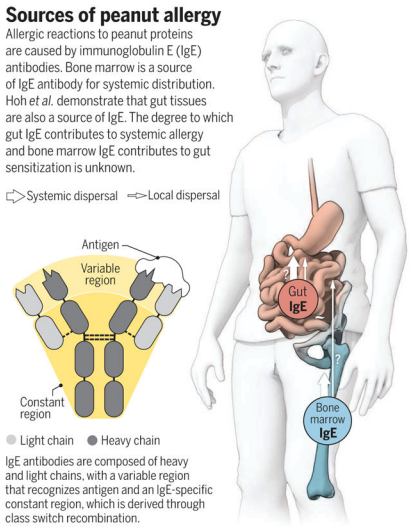
can switch to IgG1, and then that same IgG1$^+$ B cell can switch to IgE because Cϵ is 3' (downstream) to Cγ1 in the *IGH* locus. However, IgE-expressing B cells cannot switch to IgG1 (or any other isotype whose CH is positioned 5' to Cϵ). Somatic hypermutation (SHM) further diversifies V regions by introducing mutations that can enhance affinity to antigen (3).

The V(D)J recombination–, CSR-, and SHM-mediated processing of *IGH* enable phylogenetic mapping of how B-lineage cells and the antibodies they produce are related to one another. To gain insights into the origins of IgE production and the relationships between antibody-producing cells, Hoh *et al.* sequenced the *IGH* genes from B-lineage plasma cells in upper digestive tract tissues of 19 peanut-allergic individuals and compared them with those of nonallergic controls. They found more IgE-expressing cells in gut tissue in food-allergic individuals, confirming previous findings (4). Multiple clonally related VH-encoding sequences in IgE antibodies were also shared with other IgH isotypes. These findings suggest that B cells undergo CSR to IgE in the gut tissue as opposed to undergoing CSR to IgE elsewhere before migrating to the gut. This is different to the case of bone marrow, which is a major destination for antibody-producing cells after CSR elsewhere. This raises an important question: What features of the gut environment favor CSR to IgE? Moreover, because the bone marrow is a major location of antibody production, including IgE in allergic disease (5), the degree to which gut-derived versus bone marrow–derived IgE affects clinical disease, prognosis, and treatment approaches remains to be determined (see the figure).



Hoh *et al.* identified antibody sequences that are reactive to the peanut protein Ara h 2 (*Arachis hypogaea* allergen 2) and found groups of similar sequences among multiple individuals. Similar sequences were also found in analyses of IgE$^+$ B cells from peripheral blood in individuals with peanut allergy (6), further validating the concept of convergent IgE development to peanut proteins. Nonallergic individuals also had Ara h 2–reactive sequences, but only in non-IgE isotypes such as IgM, IgG, and IgA.

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These findings highlight how antibodies that induce a food-allergic response are generated. The production of antibodies that bind peanut proteins does not seem to be the problem per se; instead, the switching of that antibody to the IgE isotype appears to be key. This is consistent with observations that humans make IgG to a variety of dietary proteins without correlation to food allergy (7). In addition, it is possible that IgG to food antigens may be protective from food allergy by either blocking IgE binding or otherwise interfering with IgE function (8, 9). Perhaps an intervention that discourages gut IgE CSR could prevent food allergy.

The convergence of IgE sequences in multiple peanut-allergic individuals suggests that immune recognition may occur through antibody binding to a few finite regions on key proteins. In this regard, drugs that block IgE binding to these regions holds promise as a therapy in allergic disease. There is proof of principle: Two therapeutic monoclonal IgG antibodies against a cat allergen inhibited IgE binding, and treatment with the combination of these two antibodies alone was sufficient to reduce allergic symptoms in 34 cat-allergic individuals in a clinical trial (10). Blocking IgE to peanut antigens may be similarly efficacious.

Although seemingly innocuous, food allergens may influence the gut environment to generate conditions that induce CSR to IgE. In this regard, allergenic foods may have properties that induce allergic inflammation, as has been proposed (11, 12). Understanding the influences of the gut microbiota, age of exposure, and environment on the regulation of allergic responses to food (13, 14) promises to provide clues to elucidating how IgE CSR is regulated.

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