

infants and their mothers. This information, together with characterizing the representation of genes involved in HMO acquisition and degradation in different bacterial strains cultured from these children, would allow an assessment of (i) whether and how the presence of these different organisms and their genome features correlate with maternal breastmilk composition and (ii) the degree to which products of breastmilk metabolism correlate with host features. The answers, from analyses of human biospecimens as well as animal models colonized with consortia of human gut microbes representing different stages of community assembly (10, 11), could have important therapeutic implications. These include the development of new probiotic, HMO-based prebiotic and/or synbiotic (prebiotic combined with probiotic) therapies (12).

NEC provides a different type of opportunity to characterize the mother-breastmilk-infant triad. One of the most common and fatal gastrointestinal disorders in preterm infants, NEC develops within the first few weeks of delivery. It is characterized by destruction of the integrity of the intestinal wall, invasion of luminal bacteria, marked inflammation, and sepsis. Maternal and infant physiology are immature after preterm delivery in terms of producing and digesting breastmilk. Moreover, the use of antibiotics and other medications and interventions, when both mother and infant face serious and often life-threatening crises, further disrupts the mother-breastmilk-infant triad, including initial colonization of the infant intestine. Although breastmilk composition is not fully adapted to the physiological needs of the premature infant, breastmilk feeding, compared to enteral feeding with specialized breastmilk substitutes, reduces NEC incidence by 6- to 10-fold (13). The mechanisms underlying these protective effects remain largely uncharacterized.

HMOs significantly improve survival and reduce pathology in a neonatal rat model of NEC, leading to the identification of the HMO, disialyllacto-*N*-tetraose (DSLNT), as a protective factor (14), likely through its direct interactions with gut epithelial and immune cells. A multicenter study of mothers and their very-low-birthweight infants found that infants who developed NEC received breastmilk containing less DSLNT than infants who did not develop NEC (15). Proof of a causal relationship requires a randomized controlled clinical trial, which raises several challenges, including the availability of DSLNT and ethical considerations if control groups of high-risk infants were to be treated with

formula alone. More generally, NEC illustrates the need to comprehensively define states of “triad immaturity.” This would entail longitudinal studies of the set of features that define breastmilk given to prematurely born neonates who do and do not develop this devastating disease. It would also require a simultaneous effort to obtain comprehensive definitions of the biological characteristics of chronologically age-matched preterm infants with and without NEC, as well as of their mothers.

Mothers face a “balancing-act” between various socioeconomic, cultural, and even marketing pressures to maintain or forego breastfeeding and their motivation to provide their infants with what is best for their health and development. This balancing act is perpetuated in part by confusion surrounding the respective attributes of breastmilk versus breastmilk substitutes, with consumer understanding being heavily influenced by commercial interests. Aspirational goals include new parameters for defining health status and deeper understanding of how health outcomes are related to breastfeeding and breastmilk components. Within a risk-stratified continuum of care, knowledge of the latter has potential therapeutic implications and opportunities, personalized to the circumstances of an individual mother and her infant (1). Such efforts will not only provide new appreciation of the remarkable properties of nature’s first food, but also serve to further develop analytic approaches that yield insights into the dynamic systems that direct infant development. ■

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#### IMMUNOLOGY

# Origins of peanut allergy-causing antibodies

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

By Duane R. Wesemann<sup>1</sup> and Cathryn R. Nagler<sup>2,3</sup>

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

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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., C $\mu$ , C $\gamma$ , C $\epsilon$ , and C $\alpha$ ), which define the different antibody isotypes (2).

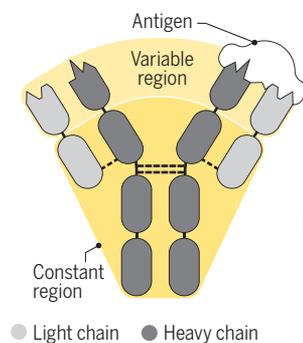
Newly assembled Ig is produced as IgM. However, during an immune response, the same V region of IgH (VH) can be expressed in the context of another C-region isotype through a process called class switch recombination (CSR). This positions an alternative CH region next to the VH exon by permanent excision 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 can switch to IgG1, and then that same IgG1<sup>+</sup> B cell can switch to IgE because C $\epsilon$  is 3' (downstream) to C $\gamma$ 1 in the *IGH* locus. However, IgE-expressing B cells cannot switch to IgG1 (or any other isotype whose CH is positioned 5' to C $\epsilon$ ). 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

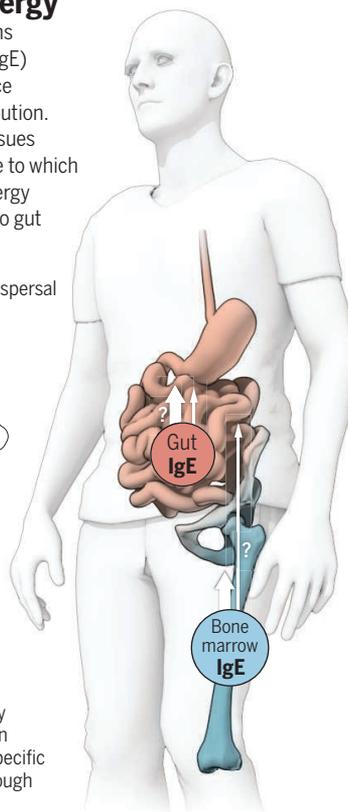
## Sources of peanut allergy

Allergic reactions to peanut proteins are caused by immunoglobulin E (IgE) antibodies. Bone marrow is a source of IgE antibody for systemic distribution. Hoh *et al.* demonstrate that gut tissues are also a source of IgE. The degree to which gut IgE contributes to systemic allergy and bone marrow IgE contributes to gut sensitization is unknown.

⇨ Systemic dispersal ⇨⇨ Local dispersal



● Light chain ● Heavy chain  
IgE antibodies are composed of heavy and light chains, with a variable region that recognizes antigen and an IgE-specific constant region, which is derived through class switch recombination.



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<sup>+</sup> 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.

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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## Origins of peanut allergy-causing antibodies

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