

broad-based food producing economies. In each case, recipient populations made strategic decisions about the utility of incorporating introduced domesticates into existing subsistence practices that were encoded in systems of ecological knowledge about local environments and biotic resources and produced stable subsistence economies.

The study of Kistler *et al.* also reveals the value of domestication as a model for exploring evolution—both biological and cultural. A debate is currently roiling evolutionary biology over the need to revise and extend traditional evolutionary theory through the development of an extended evolutionary synthesis (EES) (10). As Kistler *et al.* demonstrate, the domestication of plants and animals touches on all the areas of contention in this debate (4). The expanded time frame for the manifestation and fixation of key domestication traits documented by Kistler *et al.* provides an opportunity to evaluate the role of constructive developmental processes (especially phenotypic plasticity and niche construction) that advocates of the EES believe lend directional bias to the variation on which evolution operates (11). It also provides a window into how traits that arise through these processes become fixed parts of the domesticated genome. The coevolutionary relationships between humans and target species responsible for the initial domestication of maize and its later evolution allow for an assessment of the evolutionary consequences of ecological inheritance and social learning that EES proponents see as additional inheritance systems guiding evolution (12). As such, the study of Kistler *et al.* joins other studies of initial domestication in providing a robust body of genetic, archaeological, and archaeological data within a well-constrained temporal framework to serve as models for evaluating core EES assumptions about evolution and the interface of human and natural systems that shape it (4). ■

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IMMUNOLOGY

Peanut allergen-specific antibodies go public

Characterizing peanut-specific antibodies may identify targets to treat food allergy

By **Hannah J. Gould** and **Faruk Ramadani**

Changes in the human environment and activities over the past few decades have caused an epidemic of food allergies (1). People suffering from allergies often feel that they live on a cliff edge, as the allergens to which they react are potentially fatal (2). For example, tiny amounts of peanut picked up on skin or contaminating other foods can be dangerous to peanut-sensitized individuals (2–4). Immunoglobulin E (IgE) antibodies mediate the allergic response. They bind to specific receptors on inflammatory immune cells: mast cells in mucosal tissues lining body surfaces and cavities, and basophils in the circulation. These cells mediate allergic responses triggered by specific antigens (allergens) that are recognized by IgE. B cells expressing IgG antibodies have long served as the paradigm for the development of B cells into antibody-secreting plasma cells in

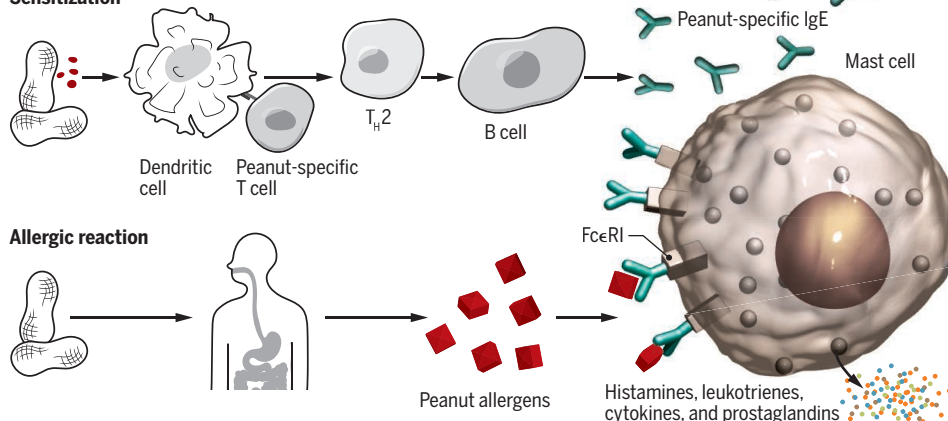
the immune response. Until recently, the far less abundant IgE-expressing B cells have proved to be elusive. On page 1306 of this issue, Croote *et al.* (5) have analyzed single B cells from six individuals with peanut allergy, which enabled the identification of the natural Ig heavy- and light-chain pairs from IgE-expressing B cells that are responsible for peanut allergy. With this information they produced recombinant antibodies, identified the peanut allergen-specific antibodies, and used site-directed mutagenesis to suppress their activity. The mutated antibodies could be used to treat peanut allergy.

Whole-exome sequencing of single B cells from peanut-allergic individuals yielded two principal components of gene expression, representing naïve or memory B cells and plasmablasts (the circulating precursors of plasma cells). The majority of IgE-expressing cells were plasmablasts, whereas the majority of cells expressing IgG or IgA (the more abundant antibody classes) were naïve or memory B cells. It has previously been observed that IgE-expressing B cells tend to develop into the plasma cell lineage as opposed to the memory cell lineage. The

From sensitization to peanut allergy

Dendritic cells in the skin pick up peanut allergens and present them to peanut allergen-specific T helper 2 (T_H2) cells, which in turn present them to B cells. Interaction between peanut allergen-specific T_H2 cells and B cells solicits help from T_H2 cells for B cell proliferation, somatic hypermutation and affinity maturation, class switching to IgE, and plasma cell differentiation. Allergen-specific IgE secreted by plasma cells binds to resident mast cells in the gut, so the ingestion of peanuts triggers an allergic reaction.

Sensitization



IgE plasma cells inherit their antigen specificity from B cells of other antibody classes, which have undergone affinity maturation. This is advantageous for their biological function in immediate hypersensitivity to antigens as it cuts out the time that would be required for affinity maturation of IgE memory B cells (6, 7).

In immune responses, antigens bind to specific B cells expressing a membrane-bound form of the antibody [the B cell receptor (BCR)], which stimulates B cell maturation through the processes of somatic hypermutation (mutations affecting the antibody affinity for antigen) and affinity maturation (the selection of cells expressing BCRs with the highest affinity for antigen). The cells may also undergo class switching (from IgM to IgG, IgA, or IgE) to the most effective antibody class for a particular location in the body. IgE expression is needed for protection from parasites at barriers to the environment (airways, gut, skin). The cost of this elaborate immune mechanism is frequently the lack of normal tolerance to harmless allergens, causing allergy.

There is compelling clinical and experimental evidence that both IgE class switching and somatic hypermutation in humans occur transiently in the respiratory tract upon allergen stimulation (8–10). Whether primary contact with peanuts through the skin (3, 4) is followed by local class switching to IgE in the aerodigestive tract in food allergy remains to be investigated. Immediate hypersensitivity that is characteristic of allergic reactions mediated by IgE occurs in the gut as it does in the airways (see the figure). The IgE-expressing B cells isolated from blood by Croote *et al.* may represent peanut-specific cells that have migrated out of the tissue to other sites in the body where they continue to function (10, 11).

The authors focused on B cells that were of interest because the variable region sequences in six B cells from two of the six individuals studied were similar. Such similarity between individuals is highly improbable (one in 10^{14} potential sequences in the far fewer number of B cells that occur in each individual). The similarities suggest that the antigen-binding sequences are convergent or “public” sequences (inherited sequences that are conserved in evolution). Convergent sequences have been observed in infectious disease and in vaccination studies. A rationale is to hand: The relatively small germline gene repertoire encoding the Ig variable region sequences, compared to the repertoire resulting from somatic hypermutation and affinity maturation of the B cells, may have evolved in our ancestors to protect them

against commonly encountered pathogens. Whether the conserved sequences serve the same purpose now or allergens are mistaken for the pathogens that affected our ancestors is unclear (12).

The six convergent clones were expressed as recombinant antibodies. This revealed high levels of somatic hypermutation, reflecting affinity maturation in the B cells specific for the three most common and clinically relevant peanut allergens, Ara h 1, Ara h 2, and Ara h 3. The coincidence of convergence and peanut specificity here is remarkable. Genetic mutagenesis gave insight into the crucial residues for activity, and this could be further understood through high-resolution crystal structure determination of the allergen-antibody complexes (13). One other B cell was shown to express an Ara h 3-specific IgE antibody. This cell was especially interesting because the IgE was related to an IgG4 (an IgG subclass) in the same cell. This confirms previous reports of related IgG4 and IgEs in allergy (10). IgG4 is an antibody class that confers tolerance to allergens by competing with IgE for specific antigens (14, 15) and is dramatically increased in specific allergen immunotherapy. It is reassuring that the immune system itself can operate a mechanism to prevent or ameliorate allergy, which can be exploited in the clinic.

Further research on these antibodies could lead to modified antibodies or antibody fragments that compete with IgE for allergen binding and prevent the allergic response. Future use of whole-exome sequencing, perhaps comparing the development of IgE-expressing plasma cells with those expressing other antibody classes, may identify genes that regulate IgE plasma cell development and survival that could be counteracted. The work of Croote *et al.* exemplifies a concerted approach to understanding and potentially intervening in allergic disease. ■

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AGRICULTURE

Can witchweed be wiped out?

A potent stimulant induces parasitic plant germination that causes it to die

By Harro Bouwmeester

Root parasitic weeds of the *Orobanchaceae* such as broomrapes and witchweeds form a serious threat to agriculture in many countries around the world (1). They cause large yield losses in crops such as sorghum, millet, maize, rapeseed, tomato, sunflower, and legumes (1). These obligate parasitic plants are dependent on a host for survival, using them to grow and reproduce on. Therefore, they only germinate in the presence of a germination stimulant exuded by the host root (2). On page 1301 of this issue, Uruguchi *et al.* (3) reveal the discovery of a potent synthetic germination stimulant. Their discovery provides the basis for the development of an agrochemical that may be used to germinate parasitic

“...SPL7 can induce suicidal germination of *Striga* in soil and thus reduces *Striga* infection of maize...”

weeds in the absence of a host (so that they will die, called suicide germination) and gives insight into what may be determining host specificity of these parasites.

The tight control of germination of these root parasitic plants is caused by their ability to respond to germination stimulants (4). These are secreted by the roots of host plants and induce seed germination. Although several compounds, from different chemical classes, in the root exudate have been identified as germination stimulants, the most important class is the strigolactones (5) (see the figure). The first discovered strigolactone, strigol, was isolated from the root exudate of cotton and induced germination of the root parasitic plant *Striga*

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Peanut allergen-specific antibodies go public

Hannah J. Gould and Faruk Ramadani

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