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## Introduction

Food allergies are adverse immune reactions to food proteins that can lead to a range of symptoms. A meta-analysis focusing on milk, egg, peanut, and seafood allergy determined that the prevalence of food allergies is approximately 3.5% (1). A recent US study that utilized several national health databases and health care surveys concluded that 3.9% of US children are reported as having food allergy, with an 18% increase in prevalence between 1997 and 2007 (2). Specifically, studies on peanut allergy in the US and United Kingdom indicate that the number of children affected has doubled in the past decade, with the prevalence now over 1% (3, 4).

This review will focus on the immunopathophysiology of food allergies as well as provide an overview of therapeutic strategies currently being investigated with the aim of long-term treatment and possible cures.

## Pathophysiology of food allergy

**Oral tolerance.** Food allergies may be IgE mediated (causing immediate symptoms and possible anaphylaxis), non-IgE mediated (cell-mediated reactions with more delayed symptoms), or a combination of both. Although these different forms of food allergy have varying clinical presentations, they likely share a common pathophysiology, with food antigen sensitization and Th2 skewing of the immune system. Recently, there has been increasing understanding of oral tolerance, the mechanisms by which ingested proteins are able to interact with unique populations of antigen-presenting cells leading to suppression of cellular and humoral immune responses. Advances in this area have primarily come from animal models. Food allergies are believed to be a result of either loss of oral tolerance or the failure to induce tolerance.

Oral tolerance results from complex interactions among DCs, T regulatory cells, and NKT cells as well as other immunologic components. These cells play different roles that may vary depending on their location and method of antigen presentation. For example, DCs are capable of inducing active T cell immunity via uptake, processing, and presentation of antigen to T cells, but may also induce tolerance by inducing T regulatory cells or deleting T cells (5). DCs may encounter antigen in the gastrointestinal tract by directly sampling luminal contents through dendrites extending

to paracellular spaces, by directly interacting with epithelial cells, or by taking up antigen via the Peyer patches. Various antigenic properties likely determine the route of exposure and will result in different immunologic responses. Although the exact mechanisms of oral tolerance are incompletely understood, migration of DCs to mesenteric lymph nodes appears to be a critical step, since oral tolerance cannot be induced in mice lacking these structures (6).

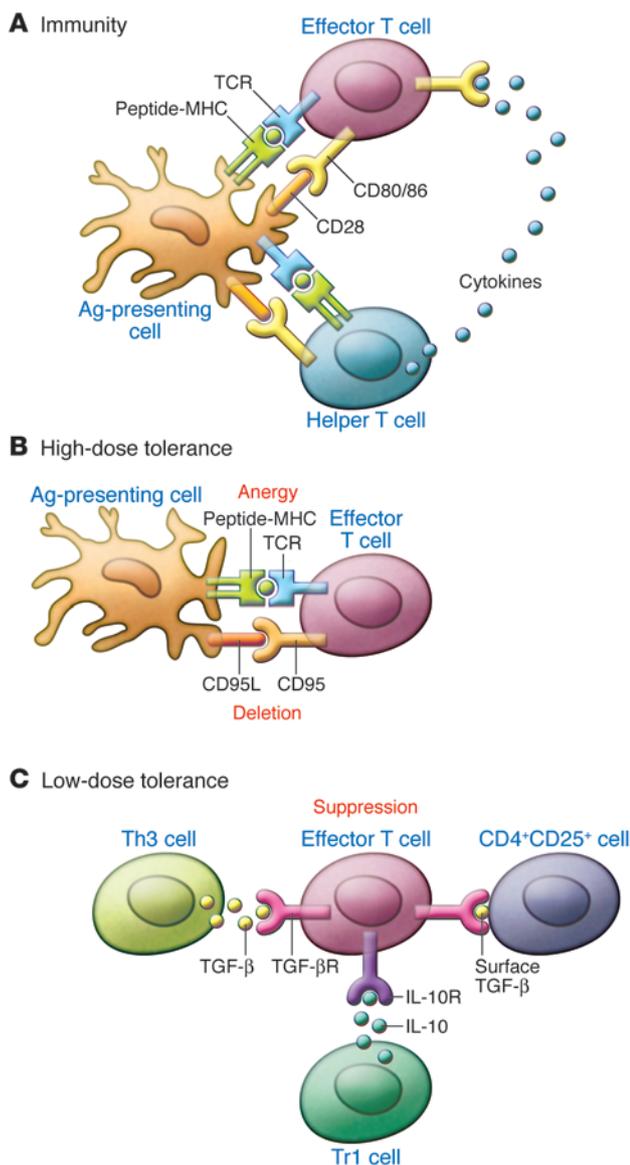
Oral tolerance can develop with repeated low-dose exposure to antigen, which is mediated by regulatory T cells (suppressor CD8<sup>+</sup> cells, Th3 cells, Tr1 cells, CD4<sup>+</sup>CD25<sup>+</sup> cells, and NK1.1<sup>+</sup> T cells) (7). These regulatory T cells migrate to lymphoid organs, where they suppress immune responses via cytokines such as IL-10 and TGF- $\beta$  (Figure 1). Oral tolerance can also be induced by high-dose exposure of allergen, which is mediated by lymphocyte anergy (absence of costimulation or interactions between CD28 on T cells and CD80/86 on APCs) (8) and deletion by FAS-mediated apoptosis (9). It is possible that a combination of these effects leads to oral tolerance.

Additional components of the immune system are increasingly shown to play important roles in oral tolerance induction. Although much focus has been placed on Foxp3<sup>+</sup> T regulatory cells, recent data suggest that other types of T cells are important in tolerance development as well, including  $\gamma\delta$  T cells (10) and NKT cells (11). Data also suggest that the gut mucosal epithelium may not only serve as a physical barrier to foreign antigen, but plays additional roles in the induction of tolerance. An example is thymic stromal lymphopoietin (TSLP), which is expressed by epithelial cells as well as stromal cells and basophils (12). TSLP is a potent inducer of Th2 responses (13) and is involved in allergic inflammation of the skin and lung, resulting in asthma and atopic dermatitis (14). In the gastrointestinal tract, TSLP appears to have a regulatory role (15). Interestingly, its presence has been shown to enhance allergic Th2 responses in the gut, but is not required for primary sensitization or tolerance to food protein (16). Currently, little is known about the role of TSLP in human food allergy, but TSLP has been identified as a candidate gene for eosinophilic esophagitis (17).

**Breakdown of oral tolerance.** A breakdown in the development of oral tolerance or the loss of oral tolerance is believed to lead to food allergy; however, it is currently not clear where and when this breakdown occurs. Furthermore, it is unclear how differences in breakdown lead to the various types of IgE-mediated and non-IgE-mediated food allergies, but possibilities include increased intestinal permeability, decreased oral tolerance, and defects in regulating T cell activity.

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**Figure 1**

Mechanisms of oral tolerance. (A) Generation of an immune response requires ligation of the T cell receptor with peptide-MHC complexes in the presence of appropriate costimulatory molecules (CD80 and CD86) and cytokines. (B) With high doses of oral antigen, T cell receptor cross-linking can occur in the absence of costimulation or in the presence of inhibitory ligands (CD95 and CD95 ligand), leading to anergy or deletion, respectively. (C) Low doses of oral antigen lead to the activation of regulatory T cells, which suppress immune responses through soluble or cell surface-associated suppressive cytokines (IL-10 and TGF-β). Adapted from ref. 7 with permission from Elsevier.

Defects in regulatory T cell activity are exemplified by the disorder of immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX), which is due to a mutation in the *FOXP3* gene, a transcription factor expressed in CD4<sup>+</sup>CD25<sup>+</sup> regulatory T cells. Atopic dermatitis and food allergies are known manifestations of this disorder (24). The importance of regulatory T cells in the development of tolerance was also demonstrated in a study of non-IgE-mediated milk allergy in which the development of tolerance to milk was associated with higher numbers of circulating CD4<sup>+</sup>CD25<sup>+</sup> regulatory T cells (25).

**Host factors influencing food allergy**

A variety of host factors may influence the development of food allergies. One twin study (26) found a significantly higher concordance rate of peanut allergy among monozygotic twins (64%) as compared with dizygotic twins (7%), suggesting a strong genetic influence. The maturity of the gastrointestinal tract may also be a factor, as epidemiologic studies have shown a higher rate of food allergies in young children as compared with adults (1). In contrast, population-based studies suggest that early introduction of foods may be protective of food allergy. In Israel, where infants are fed a peanut snack (Bamba) starting at an early age, there is a 10-fold lower incidence of peanut allergy compared with Jewish children in Hebrew schools in London, where peanut products are not introduced until children are much older (27). The Learning Early About Peanut Allergies (LEAP) study is exploring the role of timing of peanut allergen exposure in the development of peanut allergy by randomly assigning high-risk infants to early or more delayed exposure to peanut (28). Two recent studies suggest that the role of timing of allergen exposure may vary for different foods (29, 30). Early egg exposure, by 4 to 6 months of age, appeared to be protective for egg allergy; in contrast, introduction of milk in the first 2 weeks of life was protective, while introduction between 4 and 6 months of age was associated with the highest risk of developing milk allergy. While these questionnaire-based studies are subject to recall bias and/or reverse causation, they point out that studies on one food allergen may not be applicable to other foods. Differences may also be due to variations in the form of foods being introduced (i.e., natural egg vs. baked egg) or the quantity of exposure at each age period.

Disruption of normal gut barrier functions due to alterations in gastric pH or commensal bacteria is another factor to consider. In a study of 152 patients on antacid treatment for dyspepsia, increased food allergen sensitization was seen in 25% of patients after 3 months (31). Moreover, gastric digestion has been shown to reduce the allergenicity of food proteins, such as the egg allergen ovomucoid (32). The role of commensal bacteria has been

Increased intestinal permeability has been suggested as a potential cause for the breakdown in tolerance, since food-allergic infants have been found to have increased permeability compared with healthy children, as measured by urinary lactulose/mannitol ratio (18). In addition, there are several reports of food allergies developing after solid-organ transplantation, which is believed to be in part due to tacrolimus-induced increases in intestinal permeability (19, 20).

Loss of oral tolerance can occur or may be bypassed by antigen presentation via alternative routes, such as exposure through the skin or the respiratory tract. Using a mouse model, Wang et al. (21) demonstrated that exposure of protein antigen via the epicutaneous route can cause sensitization and induce a Th2 immune response. Furthermore, higher rates of peanut allergy have been found in children with atopic dermatitis who used topical creams containing peanut oil (odds ratio [OR] 6.8) (22). Respiratory exposures can also lead to food allergies, as seen in pollen-food syndrome (oral allergy syndrome) (23).

**Table 1**  
Major food allergens

Food allergen family	Food source	Allergen examples
<b>Animal food protein families</b>		
Caseins	Mammalian milk	$\alpha$ s1, $\alpha$ s2, $\beta$ , $\kappa$ -casein — cows' milk
EF-hand proteins (mainly parvalbumin)	Fish	Gad c 1 — cod
Tropomyosin	Crustaceans and mollusks	Pen a 1 — shrimp
<b>Plant food protein families</b>		
Bet v 1 superfamily	Fruits, vegetables, soy	Gly m 4 — soy; Mal d 1 — apple
Cupin superfamily		
7S globulin	Peanut, tree nuts, legumes, seeds	Ara h 1 — peanut; $\beta$ -conglycinin — soy
11S globulin	Peanut, tree nuts, legumes	Ara h 3 — peanut; glycinin — soy
Cysteine protease C1 family	Soy, kiwi	Gly m 1 — soy
Profilins	Fruits, vegetables, legumes	Ara h 5 — peanut Api g 4 — celery
Prolamin superfamily		
Prolamins	Cereals	$\alpha$ - and $\gamma$ -gliadin — wheat
Nonspecific lipid-transfer proteins	Fruits and vegetables	Mal d 3 — apple Pru p 3 — peach Cor a 8 — hazelnut
$\alpha$ -Amylase/trypsin inhibitors	Barley and rice	Hor v 1 — barley
2S albumins	Peanut, tree nuts, seeds	Ara h 2 — peanut

Information from refs. 44,45.

examined in several studies with conflicting results (33–35). These studies demonstrate that varying effects can be seen depending on the strain of organisms used, timing of treatment, and whether treatment is given to the mother and/or infant.

Additional host factors can modulate the clinical response of food allergy. In a study of fatal food allergic reactions, the majority of victims had underlying asthma (36, 37). Exercise, alcohol consumption, use of medication (i.e., beta blockers, angiotensin converting enzyme inhibitors, tricyclic antidepressants), and concurrent infection may increase the severity of anaphylactic reactions or diminish the efficacy of epinephrine (38–39). Recently, low serum activity of platelet-activating factor acetylhydrolase (PAF-AH) was reported to be associated with more severe food-induced anaphylaxis (40). However, low PAF-AH activity in patients with fatal anaphylaxis might also be a result of severe hypoxia followed by systemic necrosis rather than the cause of more severe reactions (41).

### Food allergen factors influencing food allergy

Although any food can trigger an allergic response, relatively few protein families account for the majority of allergic reactions. In the US, milk, egg, peanut, tree nuts, fish, shellfish, soy, and wheat are the major food allergens (42). Seeds, particularly sesame, also appear to be an increasingly recognized allergen in many countries (43). The majority of animal food allergens can be classified into 3 protein groups, and the majority of plant food allergens can be grouped into 4 families (refs. 44, 45, and Table 1). In general, proteins with more than 62% homology to human proteins are unlikely to be allergenic (44).

The presence of specific IgE to sequential or conformational epitopes appears to distinguish between different phenotypes of food allergy. Sequential epitopes comprise consecutive amino acids along the protein backbone that are recognized by IgE antibodies, whereas conformational epitopes consist of amino acids that are brought into close proximity by protein folding and thus depend

upon maintenance of the tertiary structure of the protein. Several studies have shown that IgE antibody binding predominantly to conformational epitopes is associated with transient allergy to milk and egg, whereas binding to sequential epitopes in these proteins is a marker for persistent allergy (46, 47). With maturation of gastrointestinal enzymes, decreasing intestinal permeability, and increases in antigen-specific IgA and IgG, it is hypothesized that proteins no longer penetrate the mucosal barrier and activate tissue mast cells. However, peptides of various lengths penetrate the GI tract of all individuals (48, 49), allowing peptides with intact sequential epitopes access to tissue mast cells and other cells involved in allergic reactions. Approximately 80% of milk- and egg-allergic children can tolerate extensively heated or baked forms of these foods (50, 51), which lack native conformational epitopes due to heat denaturation, implying that conformational epitopes are primarily recognized in these individuals. In addition, studies suggest that different patterns of epitope recognition and degrees of epitope diversity may correlate with clinical manifestations of allergic reactions to peanut and milk, including their natural history or severity of reactions (46, 47, 52–56). These assays are investigational and not commercially available, and the clinical utility of these tests requires confirmation.

Carbohydrates associated with these food proteins can also influence their allergenicity. For example, Maillard reaction products or advanced glycation end products that result from roasting peanuts at very high temperatures lead to increased stability and allergenicity of peanut allergens (57). This finding may in part explain the differences in prevalence of peanut allergy in the US, where peanuts are primarily consumed in the roasted form, compared with China, where boiled or fried peanuts are more common. Similar results have recently been reported for ovalbumin (58). The presence of sugar moieties naturally occurring in peanuts has also been shown to increase the allergenicity of this food. Glycosylated Ara h 1, a major peanut allergen, has been shown to act as a Th2 adjuvant by



**Table 2**  
Suggested predictive values of sIgE and SPT for selected food allergens

	~50% react (62)	~95% react (> 2 years of age) (61, 62)	~95% react (≤ 2 years of age) (63–65)
Milk	sIgE = 2 kU <sub>A</sub> /l	sIgE = 15 kU <sub>A</sub> /l SPT = 8-mm wheal <sup>A</sup>	sIgE = 5 kU <sub>A</sub> /l SPT = 6-mm wheal
Egg	sIgE = 2 kU <sub>A</sub> /l	sIgE = 7 kU <sub>A</sub> /l SPT = 7-mm wheal	sIgE = 2 kU <sub>A</sub> /l SPT = 5-mm wheal
Peanut	sIgE = 2 kU <sub>A</sub> /l (convincing history) sIgE = 5 kU <sub>A</sub> /l (unconvincing history)	sIgE = 14 kU <sub>A</sub> /l SPT = 8-mm wheal	– SPT = 4-mm wheal

<sup>A</sup>SPT, dependent upon extracts and technique utilized.

activating DCs to drive Th2 cell maturation (59). In contrast, deglycosylated Ara h 1, or the highly homologous soy vicilin, which does not contain the carbohydrate moiety, did not activate DCs (59).

Recently, there has been evidence that carbohydrates alone can trigger IgE-mediated food allergies. Commins et al. (60) published the first report of galactose- $\alpha$ -1,3-galactose ( $\alpha$ -gal) as a potential food allergen mediating adult-onset, delayed hypersensitivity reactions to red meats (beef, pork, lamb). Interestingly, these patients were from a distinct regional location in the southeastern US, raising the possibility of a sensitizing exposure that may be geographically isolated, e.g., deer tick bites. Additional studies will be needed to elucidate the mechanism for these delayed clinical symptoms as well as to establish the mode of sensitization to alpha in these patients.

### Diagnostic tests for food allergy

Conventional diagnostic tests for IgE-mediated food allergy include skin prick testing (SPT) and serum-specific IgE testing (sIgE). Although higher levels of allergen-specific IgE and larger SPT wheal sizes are associated with increased likelihood of allergic reactions, they still lack precision and do not predict severity of allergic reactions. Predictive values for sIgE levels (using the UniCAP [Phadia]) and SPT have been published for the major food allergens, and levels above the 95% positive predicative value are highly indicative of clinical reactivity (Table 2) (61–65). Currently in the US, there are 3 commercial assays that measure sIgE levels. Each meets the WHO IgE standard for analytical sensitivity, precision, and reproducibility; however, multiple studies have demonstrated that these assays are not interchangeable or equivalent, and therefore, comparison of results using different assays may not be reliable (66–68).

The gold standard for the diagnosis of food allergy is a double-blind, placebo-controlled oral food challenge, in which the potential allergen is gradually fed in increasing doses under supervision. Open challenges (in which the food is fed in the natural form in an unblinded manner) are more practical and less time and resource intensive than the double-blind challenge and are useful when the concern for bias is low (69). Open challenges are generally used in clinical practices, and if results are equivocal, blinded challenges can be performed. Single-blind challenges are also an option when the potential for subjective symptoms and patient anxiety are high. SPT and sIgE levels are used in conjunction with the patient history to assess the risks and benefits of undergoing a food challenge, with most using at least a 50% likelihood of reaction before considering challenges (69). Food challenges should be performed in settings where medical staff and equipment are available to treat anaphylactic reactions.

Unfortunately, no standardized tests are currently available for the detection of non-IgE-mediated food allergies. Atopy patch

testing has been investigated as a possible diagnostic tool to identify foods that may cause delayed symptoms (70, 71), but this test is limited by the lack of standardized reagents and methods, and there is inconsistency in interpretation of results.

*Novel diagnostic tests.* One limitation of current tests (SPT and sIgE) is that positive results may not be diagnostic of food allergy since cross-reactivity between proteins can give false-positive test results (e.g., wheat and grass, birch and peanut/hazelnut) (72). Component-resolved diagnostics has the potential to address these obstacles. A recent study reported the use of component resolved diagnosis to distinguish between peanut-allergic subjects and peanut-sensitized but tolerant subjects (73). By assessing IgE binding to individual recombinant proteins of peanut, grass, and potentially cross-reactive components, peanut-allergic individuals were found to have high responses to Ara h 1–3; in contrast, peanut-sensitized, but clinically tolerant subjects had high responses to grass allergens and cross-reactive carbohydrate determinants. Further analysis indicated that Ara h 2–specific IgE was the best discriminant between clinical reactivity and simple sensitivity to peanut. Similar results have been seen in studies for hazelnut and kiwi (74, 75), but further studies are necessary to establish the value of this approach.

Standard allergy tests are unable to provide an assessment of allergy severity or prognosis. Peptide microarray immunoassays, as noted above, and basophil activation tests appear to provide some of this information. Preliminary studies showed that basophil activation, as determined by antigen-induced CD63 upregulation on basophils, correlated with different phenotypes of milk allergy. In a study evaluating the effects of ingesting heat-denatured milk proteins in milk-allergic individuals, basophil reactivity was strikingly distinct between heated milk-tolerant and heated milk-reactive subjects (76).

Although further studies are needed to validate these tests, they may one day improve physicians' ability to confidently diagnose food allergies, preventing unnecessary avoidance diets that can have nutritional as well as social consequences. In addition, they may decrease the need for costly, time-consuming, and potentially life-threatening reactions with oral food challenges.

### Therapies for food allergy

The standard of care for treating food allergies consists of identifying the responsible food allergen and educating patients on how to avoid ingesting the food unknowingly and how to recognize and treat early signs of an allergic reaction in case of accidental ingestion. Given the increasing prevalence of food allergy and associated hospitalizations (77), this approach is clearly not optimal and there is a strong need to develop effective therapies. Several allergen-specific and allergen-nonspecific strategies are currently being investigated (Table 3).



**Table 3**  
Treatments for food allergy that are currently under investigation

	Mechanism	Effects	Concerns	References
<b>Allergen-specific therapies</b>				
OIT	Gradual exposure to allergens to induce desensitization or tolerance	Improved clinical tolerance; clinical trials for egg, milk, and peanut currently underway	Unclear whether the effects are desensitization or induction of tolerance; side effects are common and unpredictable	80–83
SLIT	Gradual exposure to allergens to induce desensitization or tolerance	Improved clinical tolerance	Unclear whether the effects are desensitization or induction of tolerance; side effects are common	84–86
Recombinant vaccines	Mutate IgE-binding sites; proteins stimulate T cells to proliferate, but have greatly reduced IgE-binding capacity	Protection against peanut anaphylaxis in mice; clinical trials currently underway	Improved safety profile compared with conventional IT; requires identification of IgE-binding sites for each allergen	89–92
Peptide immunotherapy	Peptide fragments contain T cell epitopes, but are not of sufficient length to cross-link IgE and therefore cannot trigger mast cell or basophil activation	Protection against peanut anaphylaxis in mice	Improved safety profile compared with conventional IT, requires identification of T cell epitopes for each allergen	93, 94
ISS-conjugated protein immunotherapy	ISS bound to proteins can act as adjuvants to promote switching to a Th1 response	Protection against peanut sensitization in mice	Concern for excessive Th1 stimulation and potential for autoimmunity	95, 96
Plasmid DNA immunotherapy	Allergen gene immunization to promote endogenous allergen production resulting in possible induction of tolerance	Less severe and delayed peanut-induced anaphylaxis in a murine model	Serious concerns regarding safety in view of strain-dependent effects in mice	97, 98
<b>Allergen-nonspecific therapies</b>				
Anti-IgE	Decreases circulating free IgE, inhibits the early- and late-phase allergic response, suppresses inflammation and provides improved control for allergic diseases	Provides an improved threshold against peanut-induced reactions in 80% of treated patients	May be useful in combination with immunotherapy	99–101
Chinese herbal medicine	Inhibit Th2 immune response	Long-term protection from peanut anaphylaxis in a murine model. Also effective in murine model of multiple food allergies.	Oral, generally safe and well tolerated; phase I study completed	102–107
Cytokine/anti-cytokine	Block proallergic cytokines	Anti-IL-5 causes reduction in tissue eosinophils, but does not induce resolution of histologic or clinical features of eosinophilic esophagitis (EoE).	Concerns for systemic side effects	108
TLR-9	Induction of Th1-type immune responses	Protect from peanut anaphylaxis in a murine model	Concern for excessive Th1 stimulation and potential for autoimmunity	109

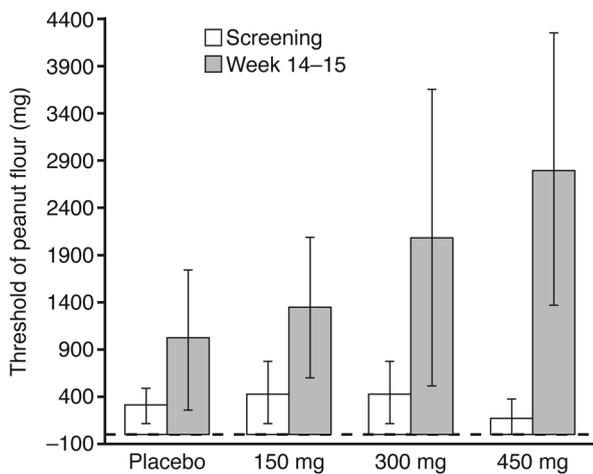
IT, immunotherapy; ISS, immunostimulatory sequence.

### Allergen-specific therapies

*Allergen immunotherapy.* Immunotherapy entails gradual increasing exposure to allergens in the hopes of desensitization (temporary loss of responsiveness due to continuous exposure) and/or promoting tolerance (permanent immunologic nonresponse). Immunotherapy is widely used to treat respiratory allergies, and with the success of subcutaneous immunotherapy (SCIT)

for asthma and allergic rhinitis, food-specific immunotherapy has been investigated as a potential treatment for food allergy.

Although early attempts at using SCIT for food allergies resulted in unacceptably high rates of severe adverse reactions (78), oral immunotherapy (OIT) appears to be a more promising option. Although the first report of OIT was published in 1908 (79), the first double-blind, placebo-controlled OIT study

**Figure 2**

Mean threshold dose of peanut flour eliciting symptoms in patients receiving Hu-901 or placebo. The mean increase in the threshold of sensitivity, as compared with that in the placebo group, reached significance only in the 450-mg group ( $P < 0.001$ ); however, results of the test for trend with increasing doses were significant ( $P < 0.001$ ). Data show 95% confidence intervals. Adapted from ref. 99 with permission from the Publishing Division of the Massachusetts Medical Society.

for food allergy was performed 100 years later by Skripak et al. (80). Twenty children were randomized to receive daily milk OIT in 3 phases. Double-blind, placebo-controlled oral food challenges were performed before and after 13 weeks of OIT to establish thresholds of reactivity to milk. Following treatment, the threshold dose for reactions to milk increased more than 50- to 100-fold for all children on active OIT but remained unchanged in the placebo group. All children in the active OIT group experienced multiple adverse reactions; most were mild, but four children received epinephrine for treatment of more severe symptoms. Although there was no significant change in milk-specific IgE levels or SPT results, there was a significant increase in milk-specific IgG and IgG<sub>4</sub> in the active treatment group. Importantly, the majority of participants experienced reactions during the post-OIT food challenge, indicating that complete protection from allergic reactions was not achieved. Furthermore, all successfully desensitized participants continued daily consumption of milk; therefore, it is unclear whether any OIT participants developed tolerance rather than desensitization. Jones et al. (81) reported an uncontrolled open-label peanut OIT study in which desensitization appeared successful in 93% of patients after 4–22 months of maintenance therapy. The increased tolerance was accompanied by decreased IgE levels at 12–18 months and significantly increased IgG<sub>4</sub>.

It is important to note that adverse reactions during OIT are fairly common. Nearly half of the active doses are associated with symptoms that ranged from mild localized reactions to systemic reactions requiring epinephrine (80, 81). A follow-up report from a peanut OIT trial reported that 3.5% of home doses were associated with adverse reactions, and epinephrine was required for three of the seven reactions described (82). A similar report of 15 subjects on milk OIT indicated that six reactions (in four subjects) with the home doses required treatment with epinephrine (83). Adverse reactions from OIT are common, variable, and unpredictable.

Sublingual immunotherapy (SLIT) is another potential route of administration and has been investigated for hazelnut (84, 85) and peach allergy (86). Both studies demonstrated increased tolerance after 5–6 months of treatment. Patients receiving SLIT frequently experience mild, localized adverse symptoms, but systemic symptoms sometimes occur. Like OIT, SLIT appears to desensitize patients, but whether it will lead to permanent tolerance remains to be established.

Clinical studies investigating tolerance to extensively heated (baked) milk and egg in allergic children demonstrated that 80% of milk- or egg-allergic children could tolerate baked products. Subsequent ingestion of these baked products on a regular basis in tolerant children resulted in virtually no adverse symptoms and was associated with decreased milk- and egg-specific SPT sizes and increased IgG<sub>4</sub> levels (51). Furthermore, heated milk-tolerant children had a higher frequency of milk allergen-specific Treg cells (87), suppressed IgE-mediated basophil responses to milk allergen stimulation (76), and decreased IgE epitope diversity and lower affinity binding on peptide microarray immunoassays (56) as compared with milk-allergic children who could not tolerate baked products. These immunologic changes are similar to many of the changes seen with OIT, suggesting that ingestion of heat-denatured milk or egg may present a more natural and safer form of immunotherapy. A prospective study is underway to confirm the efficacy of this approach as a form of immunotherapy (88).

Overall, immunotherapy appears to be a promising option for the treatment of food allergy, although high rates of adverse reactions with OIT are problematic. Additional randomized, placebo-controlled trials are necessary to determine the true efficacy and safety of these methods, to standardize extracts, protocols, and durations of treatment, and to determine whether these forms of therapy can induce lasting oral tolerance, rather than simply desensitization, which necessitates continuous, almost daily treatment.

**Modified recombinant vaccines.** In order to decrease adverse effects of immunotherapy due to allergen activation of mast cells and basophils, modified recombinant food proteins have been engineered to decrease IgE-binding capacity while retaining the protein's ability to stimulate T cells. Modified peanut allergens (Ara h 1, 2, 3), altered using site-directed mutagenesis, can stimulate T cells from peanut-allergic individuals to proliferate, but have greatly reduced IgE-binding capacity as compared with wild-type peanut protein (89). Heat-killed *E. coli* producing recombinant peanut proteins have demonstrated protective effects in a murine model of peanut anaphylaxis (90). The mechanisms hypothesized to induce this effect include activation of T regulatory cells and downregulation of Th2 cells and reduction of mast cell mediator release on reexposure to antigen (91). Human clinical trials are currently underway (92).

**Other allergen-specific therapies.** Several other strategies currently under investigation include immunotherapy with peptides representing T cell epitopes of major food allergens (93, 94), immunostimulatory sequence-conjugated protein immunotherapy (95, 96), and plasmid DNA immunotherapy (97, 98). Preliminary results in murine models of food allergy have shown promise, but questions remain as to whether these approaches will be equally effective in humans. For example, plasmid DNA was found to have beneficial effects in one mouse strain but worsened symptoms in another strain (98), raising concerns regarding the utility of this technique in humans.



## Allergen-nonspecific therapies

**Anti-IgE.** Recombinant monoclonal humanized anti-IgE treatment is currently used for the treatment of allergic asthma and has been investigated as a possible treatment for food allergy. In 2003, a double-blind, randomized, dose-ranging trial was carried-out in 84 peanut-allergic patients (99). Patients received either Hu-901 (humanized IgG1 monoclonal antibody against IgE) or placebo for four months (Figure 2). Patients receiving the highest dose experienced significant decreases in symptoms with peanut challenge as compared with the placebo group. The median threshold of sensitivity to peanut increased from 178 mg peanut protein (equivalent to one-half of a peanut kernel) to almost nine peanut kernels (2.8 grams). Although 25% of patients had markedly improved tolerance after treatment, another 25% had no change in their threshold of reactivity, indicating that the treatment response can be variable. Investigation of another anti-IgE preparation, omalizumab (Xolair; Genentech), for the treatment of peanut allergy was initiated, but discontinued for safety concerns related to the pretreatment oral peanut challenge (100).

Combination therapy of anti-IgE and allergen immunotherapy is being investigated as a method to decrease adverse reactions to immunotherapy and decrease antigen-facilitated presentation by IgE-bearing antigen-presenting cells, which promotes Th2 responsiveness, in order to increase the safety and efficacy of this method (101). No data from controlled clinical trials are currently available regarding the effectiveness of this strategy.

**Chinese herbal medicine and other allergen-nonspecific strategies.** A nine-herb formula based on traditional Chinese medicine, named the food allergy herbal formula (FAHF-2), has been shown to be effective in preventing anaphylaxis in a murine model of peanut allergy (102). Peanut-allergic mice treated with FAHF-2 had no signs of anaphylaxis following oral peanut challenge, but all sham-treated mice had severe symptoms, decreased rectal temperatures, elevated plasma histamine, and marked vascular leakage. Decreases in peanut-specific IgE levels and Th2 cytokine production by peanut-stimulated splenocytes *in vitro* (IL-4, IL-5, IL-13) was seen as well as enhanced production of IFN- $\gamma$ . Neutralization of IFN- $\gamma$  and depletion of CD8<sup>+</sup> T cells markedly attenuated the response to FAHF-2 (103). These protective effects lasted up to 6 months after therapy, which represents about 25% of the life span of the mouse (104). Furthermore, these effects are not peanut specific; treatment has been shown to modulate the allergic response in a murine model of multiple food allergies (105).

FAHF-2 has been shown to have multiple immunomodulatory effects, including a dose-dependent decrease in Th2 cytokine production, but increase in IFN- $\gamma$  (106), indicating that it is not a general immunosuppressive. In addition, human peripheral blood mononuclear cells from peanut-allergic individuals that were stimulated with crude peanut extract in the presence of FAHF-2 had a decrease in antigen-dependent T cell proliferation. The US FDA approved a botanical drug investigational new drug (IND) for FAHF-2, and a phase I trial demonstrated that it is safe and well tolerated. A phase II trial is under way (107).

Allergic diseases are believed to develop in part because of imbalances in Th1 and Th2 cytokines. Strategies targeting cytokines (108) or TLR-9 (109) have been investigated to promote Th1-type immune responses as a potential therapeutic approach, and applications in the field of food allergies are emerging.

## Conclusions

Food allergy continues to be a growing health concern. As we gain more insight into the immune mechanisms of oral tolerance and the complex interactions between host factors and food allergen properties, we can develop novel diagnostic tools to more accurately identify food allergies. Currently, several potential therapies are in clinical trials. The question of whether these treatments will induce only short-term desensitization or lead to long-term tolerance is under investigation. In addition to developing treatments, these studies will advance our understanding of the mechanisms of tolerance. These strategies, either alone or in combination, will hopefully provide long-term treatment options and potentially a cure for food allergy. Taken together, these next 5 years should provide several exciting advances in the field of food allergy.

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