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# Food allergy: mechanisms and therapeutics

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The immunologic mechanisms responsible for the development of allergic sensitization rather than tolerance to foods are not well understood, although there have been a number of recent advances in our understanding of why some foods are inherently allergenic. In addition, the involvement of alternative routes of exposure that are not inherently tolerogenic may play a role in sensitization to foods. Although there are no currently accepted therapeutic approaches to food allergy, there are a number of approaches to treatment in preclinical or clinical trials. Here, we review selected findings published since 2009 that advance our understanding of mechanisms and new therapeutics for IgE-mediated food allergy.

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## Introduction

Food allergy is defined as an immunologically mediated adverse reaction to foods, and as such encompasses a range of disorders including IgE-mediated anaphylaxis, food protein-induced enterocolitis syndrome, and food-induced eosinophilic gastrointestinal disorders. For the purpose of this summary of recent advances in the field, we will focus on mechanisms and emerging treatments for IgE-mediated food allergies. Readers are referred to the recently published NIAID guidelines on food allergy for a discussion of topics not covered in this update [1].

### Oral tolerance

Prior exposure to a food antigen by the oral route generates a regulatory T cell response that can then suppress allergic sensitization to that food allergen. There is a lack of consensus about the phenotype of regulatory T cells that prevent food allergy. Hadis *et al.* [2•] recently showed that oral tolerance could suppress experimental food allergy through the development of antigen-specific Foxp3$^+$ T cells. This was shown definitively using 'DEREG' mice that express the diphtheria toxin (DT) receptor under the Foxp3 promoter. Specific ablation of Foxp3$^+$ T cells with DT after antigen feeding abolished oral tolerance. In humans, antigen-specific CD25$^+$ Foxp3$^+$ Tregs are associated with the onset of clinical tolerance to milk [3].

Tolerance is initiated by dendritic cells (DCs) residing in the gastrointestinal lamina propria. CD103$^+$ DCs capture antigen in the lamina propria, migrate, and initiate oral tolerance in the draining lymph node by activation of antigen-specific Tregs that then migrate back to the lamina propria. $CX_3CR1^+$ DCs/macrophages that are resident in the lamina propria expand the pool of antigen-specific Tregs that can then suppress food allergy [2•]. Modification of food antigens by adding sugar structures that allow binding to the receptor SIGNR1 on gastrointestinal DCs enhances tolerance through induction of IL-10-producing Tregs [4•], presenting a potential future approach for immunotherapy. It is not yet known if Tregs can be used therapeutically once sensitization has already been established.

### Mechanisms of allergic sensitization: bypassing oral tolerance

In order to generate allergic sensitization to foods experimentally, adjuvants are commonly used to break oral tolerance. Emerging data suggest that allergic sensitization may occur if the naturally tolerogenic oral route is not the primary route of exposure. Household exposure to peanut has been shown to be associated with allergic sensitization to peanut in children, independent of maternal ingestion [5]. One important route of sensitization may be the skin. Supporting this hypothesis, loss-of-function mutations within the filaggrin gene were found to be associated with peanut allergy independent of atopic dermatitis [6•]. The filaggrin gene encodes the skin epidermal protein profilaggrin that contributes to barrier function of the skin. Mice deficient in filaggrin are susceptible to allergic sensitization through the skin [7]. The allergenic potential of the skin as a route of exposure is highlighted by the ability to sensitize mice to food allergens via the skin in the absence of adjuvant [8]. However, against the conclusion that the skin is inherently allergenic is the finding that tolerance can also be induced via skin exposure [9]. Furthermore, other relevant allergens such as milk α-lactalbumin require exogenous adjuvant to generate productive sensitization through the skin by promoting antigen presentation by dermal DCs [10]. The different capacity of food allergens to induce adjuvant-independent sensitization via the skin

may be due to differences in activity on the innate immune system, as discussed below.

### Adjuvant activity of food allergens

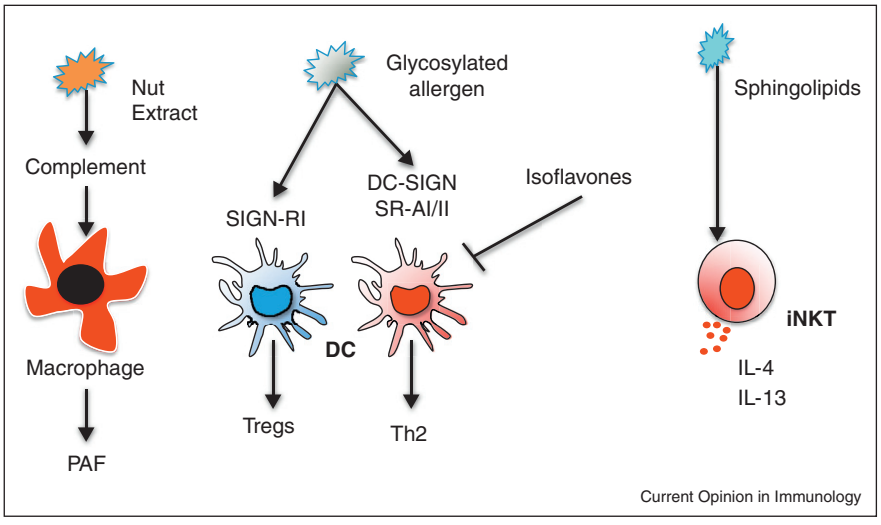
The majority of food allergic reactions are induced by a limited number of food allergens. Accumulating data suggest that activation of the innate immune system is a property of common food allergens. Confirming earlier findings with human DCs, peanut was shown to alter the phenotype of mouse DCs independent of TLR signaling [11]. Peanut and cashew extract, but not milk or egg allergens, can induce anaphylaxis in naïve mice primed for anaphylaxis through pretreatment with propranolol and IL-4 [12•]. This was triggered by activation of the complement pathways and downstream activation of macrophages. These data show direct innate effects of nut extracts. Milk contains sphingolipids that have recently been shown to activate invariant NKT cells and induce production of Th2 cytokines from the responder cells [13]. Food processing can also enhance innate activity of food allergens. Generation of advanced glycation endproducts during processing of a model food allergen (ovalbumin) resulted in enhanced uptake and presentation by human and mouse DCs by enhanced binding to scavenger receptors [14,15]. In addition to innate factors that promote sensitization, foods can also contain factors that suppress sensitization. Isoflavones found in soy are directly suppressive on gastrointestinal DCs [16], which may explain why soy is a weak food allergen despite homology to peanut allergens. Innate immune modulatory actions of food allergens are summarized in Figure 1.

### Host factors promoting sensitization to foods

Innate activity of allergens does not explain why only some individuals become sensitized to foods. Gastrointestinal epithelial cells at the interface between the gastrointestinal contents and the mucosal immune system are host factors that likely determine the immune response to foods. Epithelial cells from food allergic subjects express higher levels of galectin-9 that can act on DCs to promote allergic sensitization [17]. The epithelial cytokine thymic stromal lymphopoietin (TSLP) is critical for gastrointestinal but not systemic manifestations of food allergy in mice [18]. Mutations resulting in enhanced expression of TSLP are associated with eosinophilic esophagitis [19], but the relationship to IgE-mediated food allergy has not yet been addressed in humans.

Central to the pathophysiology of food allergy is the generation of food-specific IgE. Class-switching to IgE is supported by T cell production of IL-4 and IL-13. Short-term (six hours) stimulation of human peripheral blood mononuclear cells (PBMCs) with peanut or tetramer staining of freshly isolated human PBMCs has been used to phenotype the allergen-specific T cell response [20,21•]. Both studies emphasized that the frequency of allergen-specific T cells was a magnitude higher in peanut-allergic individuals than healthy controls. Interestingly, peanut-specific T cells expressed CCR4 (consistent with skin

**Figure 1**



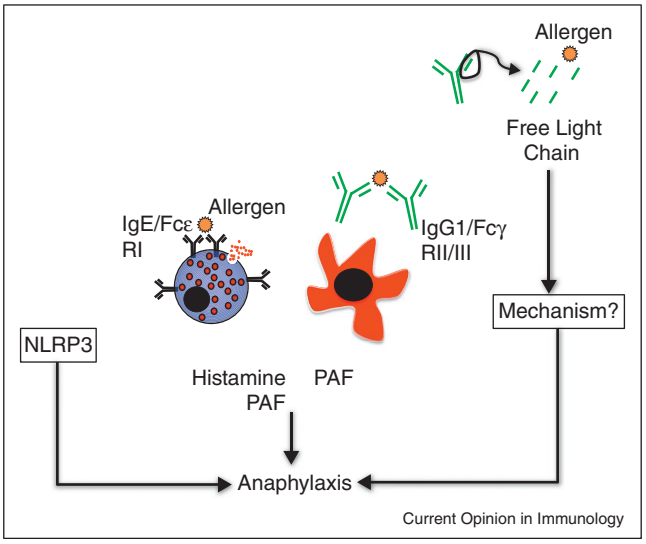

Activation of innate immunity by food allergens. Food allergens can directly activate various components of the innate immune system that may provide self-adjuvant activity. Nut extracts activate complement, leading to macrophage activation and release of platelet activating factor (PAF). Allergens with different glycosylation patterns can bind to innate receptors. Binding to SIGNR1 on dendritic cells (DCs) promotes the generation of regulatory T cells. Binding to DC-SIGN or the scavenger receptor-alpha type I or II (SR-AI/II) alters the phenotype of the DC to promote the generation of Th2 cells. Isoflavones from soy prevent sensitization by suppressing DC activation. Sphingolipids found in milk can directly act on invariant NKT cells, leading to preferential release of the Th2 cytokines IL-4 and IL-13. This modulation of innate immunity would be predicted to influence the adaptive immune response to food allergens, and thereby promote or inhibit allergic sensitization.

homing) but not β7 (associated with gut homing) [21•]. Changes in production or responsiveness to Th2 cytokines may underlie individual susceptibility to food allergy. A gain-of-function mutation in the IL-4 receptor was shown to result in increased susceptibility to allergic sensitization to foods in mice [22]. In addition to IL-4, IL-9 and IL-13 are critical for gastrointestinal manifestations of food allergy [23,24], potentially through direct action on gastrointestinal epithelial cells [25].

### Mechanisms of food-induced anaphylaxis

IgE-mediated food allergy is believed to result from triggering of mast cells to release histamine that acts on target cells including endothelial cells, epithelial cells, and smooth muscle. Studies in mouse models have identified mast cell-derived platelet activating factor as another important mediator of anaphylaxis [26]. Alternative pathways of anaphylaxis, involving IgG and macrophages, can also participate in peanut-induced anaphylaxis in mice [27]. Immunoglobulin free light-chains have also been shown to participate in casein-triggered hypersensitivity reactions in the skin, by an as-yet-unidentified effector mechanism [28]. The contributions of these alternative mechanisms to food-induced anaphylaxis in humans have not yet been determined. Human studies have shown that mutations in the NLRP3 gene that result in either enhanced transcription or stability are associated with food and aspirin-induced anaphylaxis, but not food sensitization [29]. Mechanistic studies explaining the contribution of NLRP3 or inflammasome signaling to anaphylaxis have not yet been performed, but may reveal the existence of novel mechanisms of anaphylaxis to food. Figure 2 summarizes the findings to date on the mechanisms of food-induced anaphylaxis.

**Figure 2**




Immune mechanisms of food-induced anaphylaxis. Mouse models of food-induced anaphylaxis have confirmed the central role of mast cells activated by IgE crosslinking of FcεRI. Mediators released by mast cells that induce symptoms include histamine and platelet activating factor (PAF). In addition, peanut-induced anaphylaxis in mice is also mediated by IgG1-induced activation of macrophages. In a mouse model of sensitization to casein, immunoglobulin free light-chains mediate local hypersensitivity reactions. The mechanism of effector cell activation has not yet been identified. Mutations in NLRP3 are associated with food-induced anaphylaxis in humans, but the effector mechanisms utilizing NLRP3 signaling remain unknown.

## Therapeutics

There are no currently accepted therapeutic approaches to food allergy [1]. This lags behind treatment of venom or respiratory allergy, where subcutaneous immunotherapy (SCIT) is available. SCIT with peanut allergen resulted in adverse reactions that stalled food immunotherapy for decades [30•]. However, there are now numerous treatments under study, as recently reviewed [30•,31], and summarized in Table 1. Here we focus upon treatments reported in human trials in the past two years.

### Allergen specific therapies

*Oral immunotherapy (OIT)*

The immune system is poised toward tolerance of ingested allergens [32]; therefore, oral delivery of proteins would presumably be effective. Studies have reported success for desensitization, increasing the threshold of reactivity during treatment. Jones *et al.* [33] described peanut OIT in an open study of 39 children. There was an initial escalation toward 50 mg of peanut protein, buildup to 300 mg and eventually, for some, to 1800 mg, followed by maintenance phases. Of 29 subjects completing the protocol, 27 ingested 3.9 g peanut protein during an oral food challenge (OFC). Peanut-specific IgE decreased by 18 months and peanut-specific IgG4 increased significantly. Safety data [34] were favorable, although reactions to treatment occurred, especially with concurrent illness, suboptimally controlled asthma, and physical exertion after dosing [35]. This initial study was followed by a randomized controlled trial [36•]. All of the treated OIT subjects tolerated a cumulative dose of 5000 mg while placebo subjects tolerated a median dose of 280 mg ($P < 0.001$).

These peanut OIT studies did not determine whether patients developed true tolerance, an ability to ingest the allergen without daily treatment. A German study of peanut OIT [37•] included a two-week period without treatment before a final OFC and IgG4 levels declined and several children lost their clinical benefit.

Different dosing regimens are being evaluated to improve efficacy and safety. Anagnostou *et al.* [38] utilized more gradual dosing and a higher maintenance dose than Blumchen *et al.* [37•] with good efficacy and safety. In a single blind study, Pajno *et al.* [39] gave milk OIT doses only once per week, rather than daily, with success.

**Table 1**

**Examples of therapies in preclinical and clinical studies [30•,31].**

| Therapy | Immune strategy | Comments | Status |
|---|---|---|---|
| **Allergen specific** | | | |
| Standard subcutaneous immunotherapy (native allergens) | Antigen presentation in nonmucosal site results in Th1 skewing | Proven efficacy in venom and respiratory allergy, some studies show benefit for oral allergy syndrome. Pilot studies reveal anaphylaxis as side effect (peanut). | No active development |
| Sublingual/oral immunotherapy[a] | Antigen presentation to mucosal site provides 'desensitization' and may induce 'tolerance' | Natural and convenient, reduced risk compared to injection immunotherapy. However, not universally effective, may not induce tolerance (see text). | Numerous active protocols including randomized controlled trials |
| Epicutaneous immunotherapy[a] | Alternative site of activation. | Preliminary study of milk shows potential efficacy (see text). | Trials underway |
| Modified protein vaccine | Avoid activation of IgE by mutation of binding sites but maintain T cell responses | A potentially safer form of immunotherapy compared to native protein. Tedious production of relevant proteins. | Effective in murine model, human studies underway |
| Peptide vaccine (overlapping peptides) | Avoid activation of IgE by lack of peptides large enough to crosslink IgE but maintain T cell responses | No requirement for IgE epitope mapping/mutation. Hard to characterize large number of peptides | Preclinical stages |
| Conjugation of immune stimulatory sequences to allergen | Enhance Th2 response by activating innate immune receptors, possibly hinder IgE binding | Increased efficacy, possibly improved safety. | Some promise based upon human studies using environmental allergens. |
| Plasmid DNA encoded vaccines | Endogenous production of allergen may result in tolerance | Possible one dose treatment Murine models reveal strain-specific response | No active development |
| 'Designer' therapies | Examples: mannosidase conjugation to allergen to activate SIGNR-1 positive dendritic cells; Fc-Fc fusion proteins stimulate Fc-gammaRIIb to reduce degranulation. | Some effective preclinical studies using murine models. | Preclinical |
| **Allergen nonspecific** | | | |
| Anti-IgE antibodies[a] | Bind and inactivate IgE while it is not bound to high affinity IgE receptors | Preliminary studies with 2 slightly different molecules did not show uniform protection, some improved threshold. Not a curative treatment. May be useful adjunct to allergen immunotherapy. | Clinical studies primarily underway for adjunct to allergen immunotherapy |
| Chinese herbal medicine[a] | Mechanism unknown, not generalized immune suppression, not steroid effect. | A safety study of FAHF-2 was completed and a randomized controlled trial commenced. | Preclinical studies promising, human safety and efficacy studies underway |
| Cytokine/anticytokine, TLR agonists | To interrupt inflammatory signals or stimulate Th1 responses | May allow directed interruption of inflammatory processes, prevention of sensitization, or redirection of immune response. | Mostly preclinical but efficacy studies underway for anti-IL-5 in eosinophilic esophagitis |
| Probiotics | Presumed to stimulate regulatory T cell or Th1 responses/ | Efficacy thus far more suggestive for prevention. | Clinical trials ongoing |
| Transfected bacteria | For example with IL-10, IL-12 and or allergen to stimulate regulatory and Th1 responses | May also allow for an allergen-specific approach. | Preclinical |
| Trichuris suis ova | Nonpathogenic (to human) to stimulate regulatory responses. | Appears to increase IL-10 responses. | Clinical study for allergic rhinitis not effective, clinical study in food allergy underway |

[a] Approaches highlighted in this review.

Pitfalls of OIT include reactions during dosing, inability to achieve desensitization for about 20%, and lack of tolerance. Indeed, in a follow-up open study of milk OIT [40], continued treatment revealed success, but also allergic reactions to doses and recurrence of allergy after brief cessation of dosing. However, Vickery *et al.* [41•] reported the results of an open label egg OIT study where some achieved tolerance after a median of 33 months of treatment.

### *Sublingual immunotherapy (SLIT)*

SLIT involves doses of allergen that are smaller than OIT that may be less prone to induce allergic reactions. Kim *et al.* [42•] performed a randomized controlled trial of peanut SLIT in children that included a maintenance therapy of 2 mg. There were fewer side effects than OIT. The treated group tolerated a median of 1710 mg of peanut protein compared 85 mg in the placebo group ($P = 0.011$). The clinical and mechanistic studies were similar but less robust than OIT [36•].

### *Ingestion of extensively heated milk proteins*

Approximately 70–80% of children with cow's milk allergy can tolerate extensively heated forms, for example, milk in muffins. The role of regulatory T cells in this phenomenon was evaluated by Shreffler *et al.* [3] who noted a higher percentage of proliferating allergen-specific $CD25^+CD27^+$ T cells from cultures of the heated milk tolerant subjects compared to those who react to heated milk (16% versus 5%; $P < 0.01$). Wanich *et al.* [43] found that basophils of those tolerating heated milk were significantly less responsive to milk allergen stimulation than those from reactive children. Autologous serum inhibited IL-3-induced and anti-IgE-induced, but not N-formyl-methionyl-leucyl-phenylalanine-induced responses, indicating that they were extrinsically suppressed.

In a follow-up study over three years, 60% of 65 children eating these foods became tolerant of regular unheated milk compared to only 9% of 23 who reacted to baked milk products initially ($P < 0.001$) [44•]. Subjects incorporating baked milk were 16 times more likely to achieve tolerance to regular milk compared to those who did not. Similar to OIT, milk specific IgG4 levels increased significantly.

### *Epicutaneous immunotherapy (EPIT)*

In an attempt to find safer routes of allergen administration for immunotherapy, a preclinical study of epicutaneous immunotherapy was performed in mice [45]. Ovalbumin and peanut were used, showing similar treatment success between EPIT and SCIT. A transient increase in peanut-specific IgE was noted but returned to baseline with treatment [9]. Dupont *et al.* [46•] studied a 90-day epicutaneous application of milk protein in a small pilot study of children. There was a trend toward improvement with thresholds increasing from 1.77 to 23 ml of milk ($P = 0.18$) in treated subjects compared to the placebo group (prepost of 4.4 ml and 5.4 ml respectively).

## Allergen nonspecific therapies

### *Anti-IgE*

A monoclonal humanized anti-IgE antibody (omalizumab) might improve the threshold of reactivity to any food allergen by inactivating specific IgE. A study of this strategy was initiated using peanut [47]. Unfortunately, the study was stopped prematurely due to significant reactions during the OFCs. Among 14 participants completing the study, 4 (44%) of the treated subjects and only 1 (20%) of the placebo subjects could tolerate $\geq$ 1000 mg of peanut flour.

### *Traditional Chinese medicine*

Food Allergy Herbal Formula-2 (FAHF-2), comprised according to traditional Chinese medicine, was tested in a phase 1 study with good results [48•]. PBMCs cultured with FAHF-2 demonstrated a significant decrease in IL-5 and an increase in culture supernatant interferon $\gamma$ and IL-10 levels. The treatment is now undergoing a phase 2 trial. A murine model testing FAHF-2 showed prolonged protection from peanut anaphylaxis after cessation of therapy [49]. Peanut-specific IgE levels were reduced, whereas $IgG_{2a}$ levels were increased. There was also suppression of IgE-mediated mast cell activation [50].

## Combined approach

In a pilot study, Nadeau *et al.* [51•] treated children with cow's milk allergy using omalizumab and OIT together, intending to improve safety and efficacy. Nine of 10 reached the top dose, but participants did experience reactions to therapy. The omalizumab was stopped at week 16 and a food challenge was performed at week 24. The nine subjects who had reached 2000 mg tolerated an equivalent of 220 ml of milk or more.

## Conclusions

Progress is being made in identifying why some foods are inherently allergenic, and identifying factors responsible for individual susceptibility to sensitization to foods. Understanding the basis of innate activity of food allergens will provide the opportunity to generate modified tolerogenic antigens for immunotherapy. Understanding mechanisms of immune tolerance will lead to the recognition of biomarkers to predict success of particular therapies, and potentially identifying those who may benefit most from a specific approach.

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