Food allergy: mechanisms and therapeutics
M Cecilia Berin and Scott Sicherer

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.

Address
Elliott and Roslyn Jaffe Food Allergy Institute, Division of Allergy and Immunology, Department of Pediatrics, Mount Sinai School of Medicine, New York, NY, USA

Corresponding author: Sicherer, Scott (Scott.Sicherer@mssm.edu)

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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. CX3CR1+ 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
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.

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

<sup>a</sup> 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 allergens 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 with baseline 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 1 phase 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 IgG2a 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.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest


A milestone randomized controlled trial of OIT for peanut allergy showing efficacy for desensitization and failure in immune responses from therapy.


An important observation that treatment effects may wane once daily therapy is discontinued.


Although an uncontrolled small study, the results suggest that prolonged therapy may increase the chance to achieve tolerance (cure).


A randomized controlled trial of sublingual immunotherapy for peanut showing efficacy and safety but less robust response than OIT.


An important observation that extensively heated milk, often tolerated among those with milk allergy, may speed tolerance.


A pilot study suggests that chronic epicutaneous exposure may be a safe means of immunotherapy.


Building upon promising preclinical studies, this formula was shown safe and is now undergoing clinical trials.


Although a pilot, this proof of concept study indicates that anti-IgE may be a useful adjunct to OIT.