

# Evolution of Immune Responses in Food Immunotherapy



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## KEYWORDS

• Food allergy • Immunotherapy • IgE • IgG4 • Th2 • Mast cells • Basophils

## KEY POINTS

- Immunotherapy for food allergy transiently modifies the established allergic immune response.
- Changes in T-cell phenotypes following food allergy immunotherapy include decreased T helper 2-type cytokine production, expansion of regulatory T cells, and emergence of anergic allergen-specific T cells.
- Allergen-specific immunoglobulin G1 (IgG1), IgG2, IgG3, IgG4, IgA1, and IgA2 are increased with repeated antigen exposure during immunotherapy, whereas IgE initially increases but after several months of therapy is decreased from baseline levels.
- Clinical desensitization, as demonstrated by double-blind, placebo-controlled food challenges, following immunotherapy is associated with decreased degranulation responses of both mast cells and basophils.
- Although immunologic correlates to food allergen immunotherapy have been described, the field still lacks biomarkers that definitively can confirm a subject has achieved desensitization or sustained unresponsiveness.

## INTRODUCTION

### *Epidemiology*

Food allergy is a growing public health concern that affects an estimated 10% of adults<sup>1</sup> and 8% of children.<sup>2,3</sup> The prevalence of food allergy has increased over the past 2 decades.<sup>4</sup> The most common foods that cause allergic reactions are peanuts, tree nuts, shellfish, fish, soy, milk, egg, and wheat. Management of food allergy depends on strict avoidance of the eliciting food, because even trace amounts can

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lead to severe anaphylaxis.<sup>5</sup> The hypervigilance causes decreased quality of life in allergic individuals and their families and caretakers.<sup>6</sup> Unfortunately, accidental reactions occur quite frequently,<sup>7</sup> and the only way to treat them is with antihistamines and/or epinephrine. In fact, an estimated 200,000 hospital emergency department visits are made each year as a result of food-induced anaphylaxis.<sup>8</sup>

### Immunotherapy Approaches

Currently, there are no Food and Drug Administration–approved therapies to treat food allergies. However, several antigen-specific therapies are in clinical trials, including oral immunotherapy (OIT), epicutaneous immunotherapy (EPIT), and sublingual immunotherapy (SLIT). Phase 3 trials have been completed for an OIT drug formulated by Aimmune Therapeutics, AR101,<sup>9</sup> and an EPIT drug formulated by DBV Technologies, Viaskin.<sup>10</sup> The routes of administration and duration differ between therapies, but the overall design involves administering small but increasing doses of the food antigen over several months until a maintenance dose is achieved. The maintenance dose is continued indefinitely to reach and maintain a desensitized state, which is assessed by double-blind placebo-controlled food challenges. To date, immunotherapy trials have been conducted using peanut,<sup>11–21</sup> egg,<sup>22–26</sup> milk,<sup>27–30</sup> wheat,<sup>31</sup> and tree nuts.<sup>32</sup> In general, results from these clinical trials indicate that OIT is the most efficacious, as indicated by the amount of food protein ingested without dose-limiting symptoms. OIT also has the most side effects, including urticaria, wheezing, and upper respiratory and gastrointestinal symptoms, whereas EPIT and SLIT have few, mainly local side effects, but lower efficacy.<sup>14,15,17,30</sup> There appears to be a tradeoff between efficacy and adverse effects, and this may be related to the amount of antigen administered through the different routes. As shown in **Fig. 1**, OIT uses milligram-gram quantities (300–4000 mg); SLIT uses milligram quantities (2–5 mg), and EPIT uses microgram quantities (50–250  $\mu$ g).

### Immunobiology of Food Allergy

Food allergy is the result of an aberrant immunologic response involving mast cells, basophils, T cells, B cells, and immunoglobulin E (IgE).<sup>33</sup> Briefly, food antigens are taken up

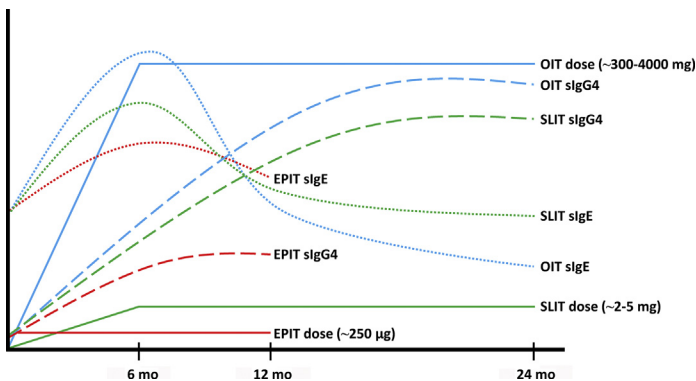


**Fig. 1.** Representative changes known to occur during allergen-specific OIT, SLIT, and EPIT. Relative allergen doses (solid lines) and the corresponding changes in allergen-specific IgE (sIgE; dotted lines) and IgG4 (sIgG4; dashed lines) in OIT (blue), SLIT (green), and EPIT (red) subjects.

by dendritic cells in the mucosa and presented to naïve T cells. T helper 2 (Th2) and T follicular helper cells then lead to B-cell production of antigen-specific IgE. IgE binds to FcεRI on basophils in circulation and mast cells in tissue, priming the immune system for an allergic reaction. Upon reexposure to the food, antigens are taken up and cross-link the FcεRI receptor on the surface of basophils and mast cells, which leads to degranulation and the release of mediators such as histamine.<sup>5</sup> The aim of this review is to give an overview of the immunologic changes that occur during immunotherapy. Specifically, the authors discuss T cells, B cells, and immunoglobulins, effector cells, and their evolution throughout OIT, SLIT, and EPIT.

## T-CELL MODULATION

Gastrointestinal exposure through oral feeding usually results in immunologic tolerance to food antigens, a phenomenon termed oral tolerance.<sup>34</sup> When oral tolerance to food antigens fails, IgE-mediated food allergy may result. Oral tolerance is an antigen-specific state of immunologic unresponsiveness and can be induced by multiple mechanisms. Animal models have demonstrated that low-dose antigen exposure results in immune suppression by regulatory T cells (Tregs), whereas high-dose antigen exposure results in antigen-specific clonal deletion or T-cell anergy. Tolerance induction occurs in the mesenteric lymph nodes by tolerogenic CD103<sup>+</sup> dendritic cells that induce differentiation of naïve T cells into Tregs, leading to active suppression of the antigen-specific immune response.<sup>35</sup>

Once a food allergy is established, there is a clear Th2-skewed response to the allergen. Allergen-specific T cells are very rare in circulation; a tetramer study found 10 Ara h 1-specific T cells per million CD4<sup>+</sup> cells.<sup>36</sup> The T-cell response is dominated by the secretion of Th2 cytokines, including interleukin-4 (IL-4), IL-5, and IL-13. In addition, IL-9 has also been shown to be upregulated in response to food allergens in allergic individuals.<sup>37</sup> Allergic individuals also produce Th1 cytokines, including interferon-γ and tumor necrosis factor-α, along with IL-10 and IL-17, in response to the food allergen. Tregs and their cytokines are also present in allergic individuals. More recently, a new Th2 subset, referred to as Th2A cells (CD4<sup>+</sup> CD45RO<sup>+</sup> CRT<sup>+</sup> CD49D<sup>+</sup> CD27<sup>−</sup> CD161<sup>+</sup> cells), were identified that are present at higher quantities in allergic subjects compared with nonatopic subjects.<sup>38</sup> One aim of immunotherapy is to reverse the proallergic T-cell response, which may lead to tolerance.

Although there is no definitive T-cell signature in individuals who have undergone food allergen immunotherapy, overall trends are seen in this population. Generally, Th2 cytokines are decreased after immunotherapy, and Tregs are increased. For example, peanut OIT and SLIT lead to decreased IL-5 and IL-13 expression from restimulated peripheral blood mononuclear cells,<sup>13,15,19,39</sup> and a decreased number of Th2A cells have been shown with OIT.<sup>38</sup> Interestingly, a 10-fold difference in dose of peanut OIT (300 vs 3000 mg) did not result in meaningful differences in cytokine suppression.<sup>39</sup> OIT also leads to increased CD4<sup>+</sup> Foxp3<sup>+</sup> Tregs.<sup>18,19</sup> One study demonstrated that individuals who completed OIT and were classified as immune tolerant had decreased methylated sites on the Foxp3 locus of antigen-induced Tregs compared with nontolerant individuals,<sup>18</sup> indicating that Foxp3 methylation could be used as a biomarker to distinguish desensitization and sustained unresponsiveness. A previously unidentified subset of anergic CD4<sup>+</sup> T cells was identified in subjects who completed OIT.<sup>40</sup> Although no human data exist for T-cell changes during EPIT, a mouse study indicates that EPIT induces LAP<sup>+</sup> Tregs in the intestine, providing a potential mechanism underlying the efficacy of EPIT.<sup>41</sup>

## B-CELL AND IMMUNOGLOBULIN CHANGES

B cells play a critical role in IgE production and maintaining IgE levels. B cells specific to any antigen are rare. Previous studies have used fluorescently labeled peanut allergens to show that there are very few peanut-specific B cells in the periphery of peanut-allergic individuals. One study showed that approximately 0.02% of B cells was Ara h 2 specific.<sup>42</sup> Another study showed that 0.0097% of B cells were Ara h 1 specific and 0.029% were Ara h 2 specific in peanut-allergic subjects; these quantities in both studies increased 3-fold during OIT.<sup>43</sup> In addition to changes in the number of B cells after immunotherapy, B-cell products, including IgE, IgG (IgG1, IgG2, IgG3 and IgG4) and IgA (IgA1 and IgA2), are also modulated in response to therapy.

Before immunotherapy, individuals generally have high levels of antigen-specific IgE and low levels of antigen-specific IgG and IgA. After immunotherapy is completed, antigen-specific IgG4 significantly increases, thereby increasing the ratio of IgG4 to IgE. These trends have been shown in immunotherapy to peanut, milk, and egg.<sup>9,17,20,21,23,26,30,39,44,45</sup> Importantly, even if antigen-specific IgE does not significantly decrease over the course of therapy, desensitization may still be induced.<sup>15,19</sup>

### *Immunoglobulin G and Immunoglobulin A Subclasses in Oral Immunotherapy and Sublingual Immunotherapy*

Food immunotherapy involves chronic exposure to the antigen, which leads to increased serum antigen-specific IgG. These trends have been shown in OIT for peanut, milk, and egg. A previous study demonstrated that all peanut-specific IgG subtypes, including IgG1, IgG2, IgG3, and IgG4, increased after 1 year of OIT.<sup>46</sup> Importantly, the IgG fraction was shown to inhibit basophil activation by binding to the FcγRIIb receptor, indicating IgG may have protective effects as a result of OIT. Specifically, IgG4 accounts for most inhibition effects.<sup>47</sup> A more recent study found that IgG blocking effects are associated with sustained unresponsiveness in OIT subjects.<sup>48</sup> Many studies have shown increased IgG4 against whole antigen extract, purified allergens as well as specific epitopes in single antigen OIT.<sup>21,43,49–51</sup> In a multiallergen OIT study, IgG4 to all allergens increased after OIT.<sup>52</sup> These trends in IgG4 occur in OIT, SLIT, and EPIT and appear to be universal regardless of allergen (see Fig. 1). Interestingly, salivary IgG4 to α-lactalbumin, β-lactoglobulin, and casein has also been shown to increase during milk OIT in a published abstract.<sup>53</sup> These results indicate that IgG4 in the saliva and serum may be contributing to the protective effects seen during OIT.

Antigen-specific IgA in the serum also increases as a result of food immunotherapy. During a peanut OIT trial, Ara h 2–specific IgA increased.<sup>43</sup> Increases in IgA have also been shown during egg OIT, including IgA1 and IgA2 specific for egg white and allergen components.<sup>54</sup> Specifically, IgA and IgA2 to egg white significantly increased in individuals who achieved sustained unresponsiveness to egg, indicating that IgA may contribute to the protective effects. In addition to serum, IgA levels in the local mucosa have also been quantified during SLIT. Salivary peanut-specific IgA and secretory IgA were found to be increased during peanut SLIT, and these correlated with desensitization challenge outcomes.<sup>55</sup> All of these results indicate that IgA is another important factor in immunotherapy.

Immunoglobulin levels, specifically IgG4, vary significantly between therapies. In a direct comparison of peanut OIT and SLIT, peanut-specific IgG4 significantly increased after 12 months of therapy.<sup>17</sup> Although the quantity of IgG4 induced as a result of OIT was approximately 10-fold higher compared with SLIT, in the same trial, peanut-specific IgE was increased from baseline on SLIT, whereas it decreased for

subjects on OIT. Other OIT and SLIT trials have demonstrated similar findings.<sup>30</sup> EPIT changes in IgG4 appear to be smaller in magnitude than SLIT, although no direct comparisons have been made between the therapies.

### MAST CELL AND BASOPHIL ACTIVATION

The effector cells involved in anaphylaxis, namely mast cells and basophils, are also affected as a result of immunotherapy. Mast cells in the skin become less reactive during immunotherapy, as demonstrated by skin prick test (SPT) data.<sup>21,23</sup> In the same trial comparing peanut OIT and SLIT as described above, SPT wheal size decreased by about 3-fold in SLIT subjects, and by over 6-fold in OIT subjects after 12 months of therapy.<sup>17</sup> Mast cells in other mucosal surfaces, including the gastrointestinal tract, are more difficult to analyze; therefore, studies in humans have yet to be performed. As a result, animal models of desensitization have been developed to gain insight into underlying mechanisms. One study demonstrated that low-dose antigen exposure, below the threshold of an allergic reaction, leads to internalization of IgE on sensitized mast cells, thus preventing allergic reactions.<sup>56</sup> Another mechanism was discovered that indicates that actin rearrangement occurs during desensitization, which then inhibits calcium flux required for degranulation.<sup>57</sup>

Basophils are circulating effector cells that have similar properties to mast cells and can be readily studied. Basophil activation tests (BATs) are *ex vivo* assays that use whole blood to assess degranulation in response to allergens. Activation is typically monitored by CD63 or CD203c, which are quantified by flow cytometry. CD63 is present on granules and upon degranulation becomes fused with the cell membrane, whereas CD203c is constitutively expressed on the cell membrane and becomes upregulated upon activation. Both of these markers have been assessed during immunotherapy.<sup>58</sup> Researchers have theorized that BAT assays could be useful to monitor subjects on allergen immunotherapy. Notably, BAT assays have been shown to differentiate peanut-sensitized but tolerant individuals from peanut-sensitized and allergic individuals.<sup>59</sup> Therefore, once commercialized, BAT assays may be used to distinguish subjects who are desensitized from subjects who achieved sustained unresponsiveness during immunotherapy.

Similar to decreases in mast cell activation, basophil activation also decreases during immunotherapy. For subjects on OIT, basophils become hyporesponsive during the first few months. These results have been shown for peanut, milk, and egg.<sup>23,30,60</sup> During peanut SLIT, similar trends toward less reactive basophils have been shown.<sup>15</sup> BAT assays have yet to be reported for EPIT. Notably, decreases in basophil activation seem to be independent from immunoglobulin changes during the initial dose escalation and early buildup. Sustained basophil hyporesponsiveness has been associated with blocking effects of IgG.

### FUTURE CONSIDERATIONS

Although the past decade has brought food allergy immunotherapy a wealth of clinical and immunologic knowledge, there is still much to be learned. The immunologic changes associated with food allergy immunotherapy are broadly applicable to many subjects, although biomarkers are lacking that (1) indicate who is a good candidate for OIT, SLIT, or EPIT and (2) can track subjects during immunotherapy to indicate when desensitization has occurred. Future studies may use omics-based approaches, along with systems biology to identify important, yet currently unknown, changes that occur while undergoing immunotherapy.<sup>61,62</sup>

## SUMMARY

Food allergen immunotherapy definitively induces changes in T cells, B cells, and allergic effector cells. Many studies have demonstrated increases in allergen-specific IgG4 and subsequent decreases in allergen-specific IgE, with apparent underlying changes in T cells driving these responses. Ultimately, effector cells become less responsive to allergen encounters such that mast cell and basophil reactivity sharply decreases during long-term immunotherapy. Unfortunately, many of these immunologic changes are transient,<sup>63</sup> which leaves the field wondering whether immunotherapy can restore tolerance in food allergic patients.<sup>64</sup>

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