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Evolution of Immune Responses in Food Immunotherapy

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Keywords

Food allergy; Immunotherapy; IgE; IgG4; Th2; Mast Cells; Basophils

Introduction

Epidemiology

Food allergy is a growing public health concern that affects an estimated 10% of adults¹ and 8% of children.^{2–3} The prevalence of food allergy has increased over the past two decades.⁴ The most common foods that cause allergic reactions are peanuts, tree nuts, shellfish, fish, soy, milk, egg and wheat. Management of food allergy is dependent upon strict avoidance of the eliciting food, as even trace amounts can lead to severe anaphylaxis.⁵ The hypervigilance causes decreased quality of life in allergic individuals and their families and caretakers.⁶ Unfortunately, accidental reactions occur quite frequently,⁷ 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.⁸

Immunotherapy approaches

Currently, there are no FDA-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 III trials have been completed for an OIT drug formulated by Aimmune Therapeutics, AR101,⁹ and an EPIT drug formulated by DBV Technologies, Viaskin.¹⁰ 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 (DBPCFCs). To date, immunotherapy trials have been conducted using peanut,^{11–21} egg,^{22–26} milk,^{27–30} wheat³¹ and tree nuts.³² 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 GI symptoms, whereas EPIT and SLIT have few, mainly local

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side effects, but lower efficacy.^{14–15, 17, 30} 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 Figure 1, OIT uses milligram-gram quantities (300–4000 mg), SLIT uses milligram quantities (2–5 mg) and EPIT uses microgram quantities (50–250 µg).

Immunobiology of food allergy

Food allergy is the result of an aberrant immunologic response involving mast cells, basophils, T cells, B cells, and IgE.³³ Briefly, food antigens are taken up by dendritic cells in the mucosa and presented to naïve T cells. T helper 2 (Th2) and T follicular helper (Tfh) 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 re-exposure 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.⁵ The aim of this review is to give an overview of the immunologic changes that occur during immunotherapy. Specifically, we will 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.³⁴ 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+ dendritic cells (DCs) that induce differentiation of naïve T cells into Tregs, leading to active suppression of the antigen-specific immune response.³⁵

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+ cells.³⁶ The T cell response is dominated by the secretion of Th2 cytokines, including IL-4, IL-5 and IL-13. Additionally, IL-9 has also been shown to be up-regulated in response to food allergens in allergic individuals.³⁷ Allergic individuals also produce Th1 cytokines including IFN-γ and TNF-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+ CD45RO+ CRTh2+ CD49d+ CD27- CD161+ cells), were identified that are present at higher quantities in allergic subjects compared to non-atopic subjects.³⁸ One aim of immunotherapy is to reverse the pro-allergic T cell response, which may lead to tolerance.

While 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 PBMCs,^{13, 15, 19, 39} and a decreased number of Th2A cells have been shown with OIT.³⁸ Interestingly, a tenfold difference in dose of peanut OIT (300 vs. 3000 mg) did not have meaningful differences in cytokine suppression.³⁹ OIT also leads to increased CD4⁺ Foxp3⁺ Tregs.^{18–19} 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 to non-tolerant individuals,¹⁸ indicating that Foxp3 methylation could be used as biomarkers to distinguish desensitization and sustained unresponsiveness. A previously unidentified subset of anergic CD4⁺ T cells was identified in subjects who completed OIT.⁴⁰ While no human data exist for T cell changes during EPIT, a mouse study indicates that EPIT induces LAP⁺ Tregs in the intestine providing a potential mechanism underlying the efficacy of EPIT.⁴¹

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 utilized 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 were Ara h 2-specific.⁴² 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 three-fold during OIT.⁴³ 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.

Prior to 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.

9, 17, 20–21, 23, 26, 30, 39, 44–45^{Importantly, even if antigen-specific IgE does not significantly decrease over the course of therapy, desensitization may still be induced.^{15, 19}}

IgG and IgA subclasses in OIT and SLIT

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 one year of OIT.⁴⁶ 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 the majority of inhibition effects.⁴⁷ A more recent study found that IgG blocking effects are associated with sustained unresponsiveness in OIT subjects.⁴⁸ Many studies have shown increased IgG4 against whole antigen extract, purified allergens as well as specific epitopes in single antigen OIT.^{21, 43, 49–51} In a multi-allergen OIT study, IgG4 to all allergens increased after OIT.⁵² These trends in IgG4 occur in OIT, SLIT and EPIT, and appear to be universal regardless of allergen (Figure 1). Interestingly, salivary IgG4 to α-lactalbumin, β-lactoglobulin, and casein has also been shown to increase during milk OIT in a published abstract.⁵³ 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.⁴³ Increases in IgA have also been shown during egg OIT, including IgA1 and IgA2 specific for egg white and allergen components.⁵⁴ 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.⁵⁵ 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.¹⁷ Although the quantity of IgG4 induced as a result of OIT was approximately ten-fold higher compared to SLIT. In the same trial, peanut-specific IgE was increased from baseline on SLIT while it decreased for subjects on OIT. Other OIT and SLIT trials have demonstrated similar findings.³⁰ 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.^{21, 23} In the same trial comparing peanut OIT and SLIT as described above, SPT wheal size decreased by about three-fold in SLIT subjects, and by over six-fold in OIT subjects after 12 months of therapy.¹⁷ 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.⁵⁶ Another mechanism was discovered which indicates that actin rearrangement occurs during desensitization, which then inhibits calcium flux required for degranulation.⁵⁷

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 utilize 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 up-regulated upon activation. Both of these markers have been assessed during immunotherapy.⁵⁸ 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.⁵⁹ Therefore, once commercialized, BAT assays may be

employed 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.^{23, 30, 60} During peanut SLIT, similar trends towards less reactive basophils have been shown.¹⁵ 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

While the past decade has brought the field of 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 utilize omics based approaches, along with systems biology to identify important, yet currently unknown, changes that occur while undergoing immunotherapy.^{61–62}

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,⁶³ which leaves the field wondering whether immunotherapy can restore tolerance in food allergic patients.⁶⁴

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Key Points:

- Immunotherapy for food allergy transiently modifies the established allergic immune response.
- Changes in T cell phenotypes following food allergy immunotherapy include decreased Th2-type cytokine production, expansion of regulatory T cells, and emergence of anergic allergen-specific T cells.
- Allergen-specific 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.
- While 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.

Synopsis:

Food allergies are a growing public health concern now affecting an estimated 8% of children and 10% of adults in the United States. Several immunotherapy approaches are under active investigation, including oral immunotherapy (OIT), epicutaneous immunotherapy (EPIT), and sublingual immunotherapy (SLIT). Each of these approaches utilizes a similar strategy of administering small, increasing, amounts of allergen to the allergic subject. Immunologic studies have described changes in the T cell compartment, serum and salivary immunoglobulin profile, and mast cell and basophil degranulation status in response to allergens. In this review, we highlight the immunologic changes induced by allergen-specific immunotherapy for food allergy and discuss future needs in this field.

Figure 1.

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