



Mechanisms of oral immunotherapy

Suzanne M. Barshow^{1,2} | Michael D. Kulis¹ | A. Wesley Burks¹ | Edwin H. Kim¹

¹University of North Carolina-Chapel Hill, Chapel Hill, NC, USA

²Duke University School of Medicine, Durham, NC, USA

Correspondence

Suzanne M. Barshow, University of North Carolina at Chapel Hill, 116 Manning Dr., Room 3310, Chapel Hill, NC 27599, USA.
Email: suzannebarshow@unc.edu

Funding information

NIH; National Institute of Allergy and Infectious Diseases (NIH/NIAID); National Center for Complementary and Integrative Health (NIH/NCCIH); FARE; Wallace Research Foundation

Abstract

Food allergy presents a significant global health concern with up to 10% of the population affected in developed nations and a steadily increasing prevalence. In many cases, particularly with peanut, tree nut and shellfish, food allergy is a lifelong and potentially life-threatening diagnosis. While no 'cure' for IgE-mediated food allergy exists, oral immunotherapy (OIT) is a promising treatment modality with the peanut OIT drug Palforzia (Aimmune Therapeutics) the only treatment for food allergy that is currently approved by the United States Food and Drug Administration. OIT primarily induces a state of desensitization with only a minority of subjects achieving sustained unresponsiveness, a state of limited clinical remission that appears to be immunologically distinct from natural tolerance. Early humoral changes during OIT include an initial increase in allergen-specific IgE, which eventually decreases to below baseline levels as OIT progresses, and a gradual increase in allergen-specific IgA and IgG4 that continues throughout the course of OIT. Basophil hyporesponsiveness and decreased skin prick test wheal size are observed within the first year of OIT, and persistence after completion of therapy has been associated with sustained unresponsiveness. In the T-cell compartment, there is an initial expansion followed by a decline in the number and activity of T helper 2 (T_H2) cells, the latter of which may be dependent on an expansion of IL-10-producing cells, including regulatory T-cells. Our understanding of the immunomodulatory effects of OIT continues to evolve, with new technologies such as single-cell transcriptional profiling and antibody epitope analysis allowing for more detailed study of T-cell and B-cell responses to OIT. In this review, we present evidence to illustrate what is currently known about the immunologic changes induced by OIT, explore potential mechanisms and emphasize knowledge gaps where future research is needed.

1 | INTRODUCTION

Food allergy is a global health concern with a prevalence that has increased substantially over the past two decades. In developed nations, an estimated 5–10% of the population suffers from food allergy,^{1–5} a diagnosis which negatively impacts quality of life for patients and their caregivers and carries a significant economic burden.^{6–8} While allergy to certain foods such as egg, milk, wheat and soy often resolves, allergy to peanuts, tree nuts and seafood is usually lifelong. There is no cure for food allergy, and strict avoidance of

the culprit food(s) with prompt medical management in the event of an allergic reaction is the standard of care.⁹

Food allergen-specific immunotherapy, including oral immunotherapy (OIT), epicutaneous immunotherapy (EPIT) and sublingual immunotherapy (SLIT), has shown promise in the treatment of IgE-mediated food allergy with OIT the most thoroughly studied to date. The peanut OIT product Palforzia (Aimmune Therapeutics) is the only treatment for food allergy that has been approved by the United States Food and Drug Administration to date.¹⁰ The approach to food allergy immunotherapy is perhaps most analogous

to that of drug desensitization with continued exposure to an allergen achieved through an initial dose escalation (IDE) followed by a build-up and then longer maintenance phase. The majority of OIT trials have utilized single-allergen OIT, mainly peanut, milk and egg, but multi-allergen OIT is an area of ongoing investigation.¹¹⁻¹³ OIT primarily induces desensitization, which is a temporary increase in clinical reaction threshold that protects from accidental ingestion during ongoing daily subthreshold allergen exposure. Some patients achieve sustained unresponsiveness (SU), or an increased clinical reaction threshold that persists despite discontinuation of daily dosing.¹⁴⁻²⁰ Long-term trials suggest that SU may wane over time.^{21,22} It is unknown why some patients achieve SU, and the clinical and immunological phenotypes associated with SU are an area of active research.²³⁻²⁵

The development of natural oral tolerance involves a complex interplay between tissues and cells resident in the intestinal mucosa. In a TGF β and retinoic acid-dependent mechanism, CD103+ dendritic cells (DCs) carry food antigens from the lamina propria to mesenteric lymph nodes where they interact with T cells and promote the formation of forkhead box protein 3 (FOXP3) positive regulatory T (Treg) cells. These newly induced antigen-specific Tregs migrate to the lamina propria and undergo expansion, the latter of which is dependent on the production of IL-10 by CX3CR1+ macrophages.²⁶⁻²⁹ Additional Treg subsets have been implicated in oral tolerance, including Th3 and Tr1 cells, but the role of these specific cell types is not clear. Other factors, such as the intestinal microbiome and dose and timing of antigen exposure, likely also contribute to oral tolerance.²⁸ Although the pathways above are postulated to play a role in the mechanism of action of OIT, this remains poorly understood.

OIT, through daily ingestion of allergen, may exploit these same cells and tissues that are involved in the development of oral tolerance. OIT protocols vary but typically start with an IDE resembling a rush desensitization protocol, where increasing doses of allergenic protein are administered over several hours under observation in a clinical setting. Starting with the highest tolerated dose, a build-up period follows where the first dose is ingested under observation and then continued daily at home for one to two weeks until the next escalation. Each dose escalation ranges from 25% to 100% and is again administered under clinical observation before continuing the new dose at home.³⁰ During this period, patients commonly have dose-related adverse effects, typically mild to moderate in severity.³¹⁻³³ In some subjects, these allergic symptoms may necessitate holding or decreasing dosage and, in some cases, cessation of therapy. The build-up phase typically occurs over 6–12 months until the maintenance phase is reached. Dosing during the maintenance phase is variable and ranges from 300 mg to 4000 mg of protein, which continues for weeks, years or lifelong. Response to treatment is determined using double-blind placebo-controlled food challenges (DBPCFC), which are administered at specified intervals during and post-treatment.

Our goal in this review is to summarize what is known about the immunomodulatory effects of OIT while highlighting areas where

more research is needed. To increase clinical relevance, we will focus on literature primarily from human subjects with supplementation from animal models where warranted.

2 | BASELINE

Aberrant activation of the innate immune system with T helper 2 (T_H2) skewing leads to sensitization in food allergic subjects. This is characterized by the decreased development of Tregs in favour of allergen-specific T_H2 cells, which promote IgE class-switching and the expansion of downstream allergic effectors.²⁷ The mechanism by which detectable levels of allergen-specific IgE (sIgE) are maintained is not well understood, but memory B cells and/or long-lived IgE+plasma cells may be responsible. At baseline, food allergic subjects produce sIgE which binds to the high-affinity IgE receptor Fc ϵ RI on mast cells and basophils. Once primed with sIgE, mast cells and basophils rapidly degranulate upon subsequent exposure to supathreshold amounts of the specific food allergen, resulting in allergic symptoms ranging from mild to life-threatening (Figure 1). Prior to beginning OIT, subjects have variably elevated sIgE and skin prick testing (SPT) with clinical reactivity documented by failure to pass a DBPCFC, which establishes the baseline reactivity threshold.³⁴

3 | DURING OIT

3.1 | Basophils and mast cells

While the majority of data are on peanut OIT, what has been published for milk and egg OIT has overall been consistent with peanut. Immunologic evidence of desensitization is seen within the first year of OIT and includes decreased SPT wheal diameter and decreased basophil activation *in vitro*.^{14,17,18,35-39} These findings are associated with early clinical desensitization and are likely secondary to the constant low-dose allergen exposure provided by OIT. Decreased basophil reactivity does not appear to be restricted to the allergen used in OIT and was noted even when basophils from subjects undergoing peanut OIT were non-specifically stimulated with an anti-IgE antibody. A subset of these patients had concomitant sensitization to egg, and a lack of basophil activation as measured by upregulation of CD63 was also seen when basophils were stimulated with egg allergen. There was no suppression in basophil activation when stimulated by the fMLP receptor pathway, which is distinct from the IgE receptor pathway.⁴⁰ These findings suggest that OIT induces an overall state of basophil hyporesponsiveness or anergy in a pathway-specific manner.

The mechanism by which basophil hyporesponsiveness occurs does not appear to be dependent on sIgE levels. There is an early and rapid increase in sIgE upon initiation of OIT, and sIgE levels remain elevated for months until they drop to baseline levels or lower.^{35,36,41} Nevertheless, the monoclonal anti-IgE antibody omalizumab has shown benefit as adjunctive therapy in OIT trials, allowing

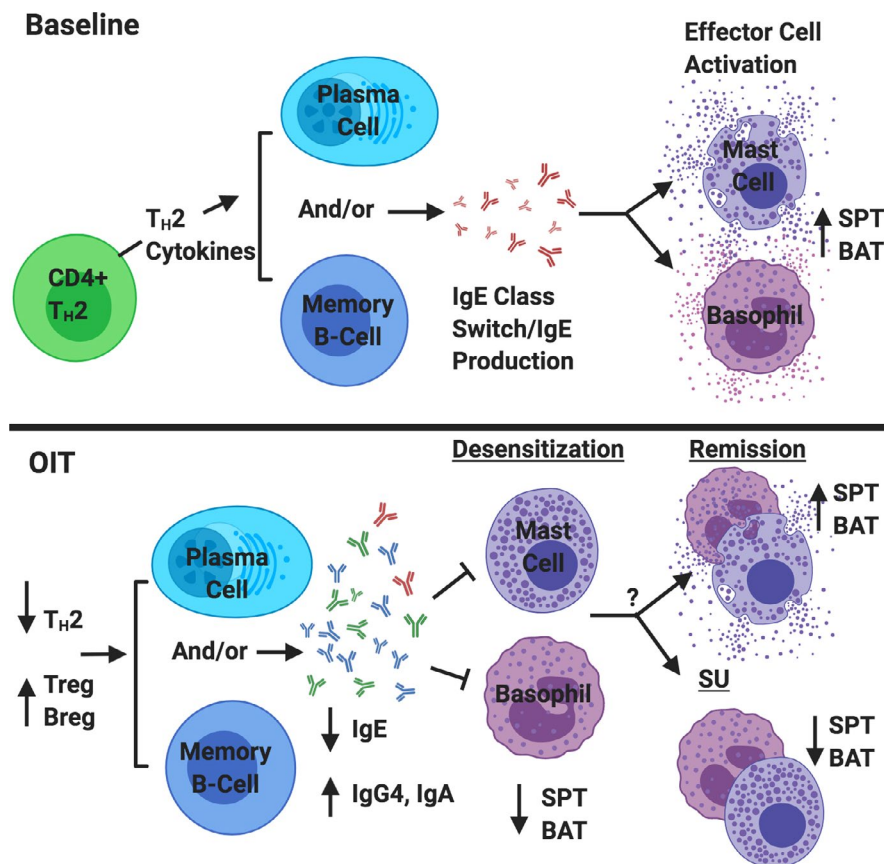


FIGURE 1 B-cell and effector cell responses in OIT. Baseline T_H2 skewing in food allergic subjects results in IgE class-switching and specific IgE (sIgE) production, which binds to the high-affinity IgE receptor FcεRI on mast cells and basophils. Once primed with sIgE, mast cells and basophils rapidly degranulate on subsequent exposure to suprathreshold amounts of allergen, leading to an allergic response. This allergic state is characterized by elevated skin prick (SPT) wheal diameter and basophil activation (BAT). Oral immunotherapy (OIT) leads to decreased T_H2 responses and increased regulatory responses, resulting in decreased production of sIgE and an increase in allergen-specific IgA (sIgA) and IgG4 (sIgG4). In desensitized subjects, sIgA and sIgG4 may function as blocking antibodies, preventing mast cell and basophil degranulation. It is unknown why some subjects experience loss of desensitization or remission, characterized by recurrence of clinical reactivity and loss of suppression of SPT and BAT, while some achieve sustained unresponsiveness (SU), characterized by the continued lack of clinical reactivity and suppression of SPT and BAT despite discontinuation of OIT.

participants to rapidly tolerate higher doses of OIT during dose escalation.^{42,43} In part, these beneficial effects of anti-IgE therapy may be due to a decrease in circulating IgE and downregulation of FcεRI on mast cells and basophils, but the full picture is probably more complex.⁴⁴ With regard to other antibodies, studies have shown that allergen-specific IgG and IgA may serve as blocking antibodies, likely explaining much of the clinical evidence of desensitization from OIT.^{45–47} Plasma from subjects post-peanut OIT was able to suppress basophil activation by pre-OIT sera, and this inhibition was blocked by antibodies targeting FcγRIIb,⁴⁸ the inhibitory receptor to which IgG4 binds with high affinity.⁴⁹ Similarly, depletion of peanut-specific IgG or IgG4 in plasma from subjects treated with peanut OIT failed to inhibit basophil and mast cell activation while the IgG-enriched fraction substantially blocked basophil activation.⁴⁸

Both allergen-specific and non-specific basophil hypo-responsiveness persists through dose escalation and to some degree through maintenance but may not be long lasting. Several studies in human subjects undergoing peanut OIT have found a reduction from

baseline in both peanut-specific and non-specific CD63 expression and histamine release during dose escalation and maintenance. However, this initial suppression appears to be temporary in many subjects. Non-specific suppression of basophil expression of the T_H2 cytokine IL-4 was similarly observed during peanut OIT but began increasing once maintenance therapy was discontinued, providing further evidence that OIT-induced basophil suppression is temporary.⁵⁰ More recently, there is mounting evidence that persistent suppression of basophil activity is necessary to maintain remission after discontinuation of OIT.^{21,48,51}

While tissue-resident mast cells are also critical effector cells in food allergy, there is a paucity of data on their role in OIT, largely due to the difficulty in routinely sampling these cells in human subjects. There are a number of intrinsic differences between mast cells and basophils, and they should not be considered equivalent. While basophils live for several days, mast cells live for months to years, raising important questions about the contribution of each cell type to the kinetics of desensitization. Additionally, the inhibitory receptor

FcγRIIb is present on mast cells that reside in the gastrointestinal (GI) tract but absent on dermal mast cells, and it is possible that these cells are differentially impacted by OIT.⁵² This is an area of ongoing interest but methods to sample and track GI-resident mast cells are lacking. In a mouse model of passive anaphylaxis, *in vitro* rapid desensitization of peritoneal mast cells (PMCs) inhibited degranulation and led to decreased surface levels of IgE and increased IgE receptor internalization.⁵³ In contrast, a second study did not find a reduction in surface IgE or in the signal transduction ability of the high-affinity IgE receptor (FcεRI), but instead found that reorganization of the actin cytoskeleton in desensitized mast cells led to impaired Ca²⁺ signalling and prevention of mast cell degranulation.⁵⁴ A recent study using a cutaneous model of local anaphylaxis in dual-sensitized mice showed that desensitization to one allergen conferred protection when challenged to the second allergen.⁵⁵ This suggests that early subclinical degranulation of mast cells plays an important role in desensitization and, like basophils, probably provides bystander protection upon exposure to other allergens. Although the murine studies discussed above are compelling, there remains no consensus on the role of mast cells in OIT and more research is needed before these findings can be generalized to humans. It is feasible that rapid suppression of mast cells and basophils due to continued low-dose allergen exposure accounts for the clinical desensitization seen during early OIT, and that waning of this suppression correlates with the gradual recurrence of clinical reactivity that is seen in some subjects on discontinuation of OIT.

3.2 | T cells

Aberrant T-cell activation with T_H2 skewing drives downstream effector responses in patients with food allergy (Figure 2); however, it is not well understood what causative events or processes lead to this breakdown of oral tolerance. Epithelial cytokines, including thymic stromal lymphopoietin, IL-33 and IL-25, may be produced during an innate immune response to tissue inflammation or damage and can drive T_H2 responses.^{56,57} Mouse models of food allergy differ from humans in that oral sensitization typically requires the addition of adjuvants such as cholera toxin (CT), although several adjuvant-free models have been described.^{58,59} Notably, the development of food allergy in a CT-induced mouse model of peanut allergy was found to be dependent on IL-33. In fact, both IL-33 and CT cause the upregulation of OX40 ligand (OX40L) on dendritic cells, which potently signals naïve T cells through ligation of OX40-OX40L to develop into T_H2 cells.^{60,61}

While T_H2 responses characterize the allergic state, Tregs are essential to the development of oral tolerance. In mice, the production of IL-4 by group 2 innate lymphoid cells (ILC2s) stimulated by IL-33 suppresses the development of allergen-specific Tregs and promotes food allergy.⁶² Under normal conditions, it is thought that repeat exposure to low doses of antigen promote the development of Tregs.⁶³ In contrast, exposure to large amounts of antigen leads to T-cell anergy or FAS-mediated clonal deletion,⁶⁴ both of which result in the secretion of TGF-β.⁶⁵ In mouse models of oral tolerance,

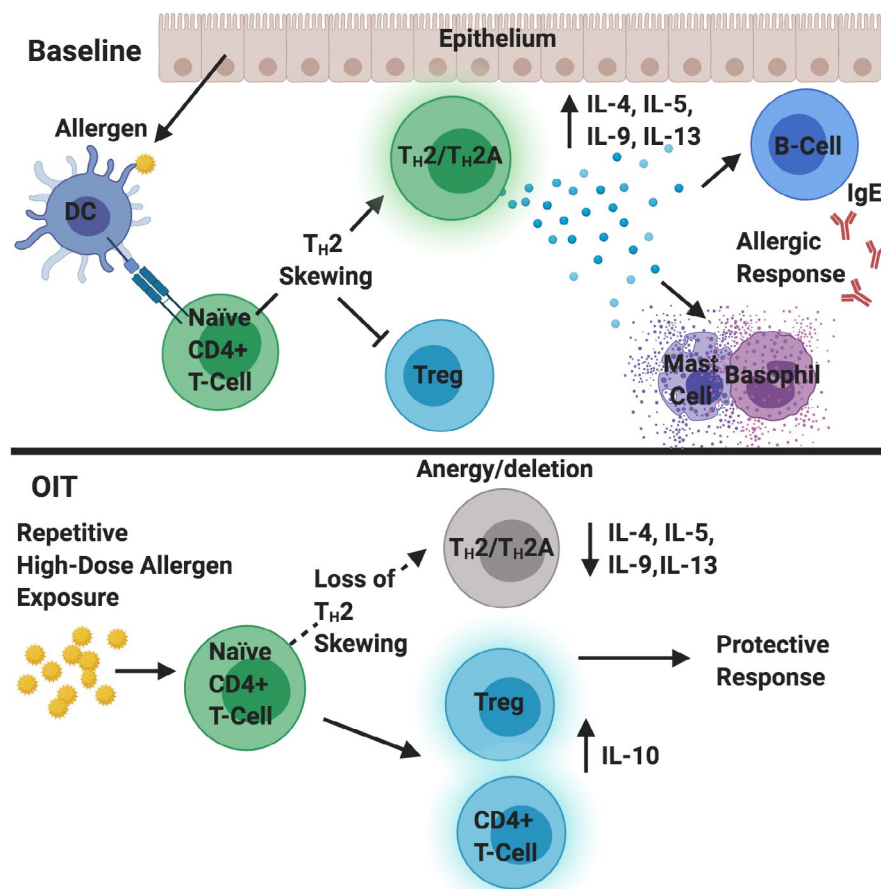


FIGURE 2 T-cell responses in OIT. In food allergic subjects, a breakdown in natural oral tolerance leads to decreased development of regulatory T (Treg) cells in favour of allergen-specific T_H2 cells, including the allergen-specific T_H2 (T_H2A) subset. T_H2 and T_H2A cells produce the T_H2 cytokines IL-4, IL-5, IL-9 and IL-13, which promote IgE class-switching in addition to the activation and expansion of downstream allergic effectors, including mast cells, basophils and eosinophils. During oral immunotherapy (OIT), continuous high-dose allergen exposure leads to T_H2 and T_H2A anergy and/or deletion and an increase in regulatory cells, including Tregs and IL-10-producing CD4+ T cells. Together, these changes result in the suppression of downstream allergic responses as shown in Figure 1.

TGF- β is necessary for inducible Treg (iTreg) cell differentiation.⁶⁶ It is likely that both low- and high-dose responses play a role in the development of tolerance.²⁸ Natural Tregs (CD4+CD25+FOXP3+) develop in the thymus and are important in maintaining tolerance to self-antigens. In contrast, iTregs develop from naïve CD4+ T cells in the periphery after exposure to antigen and are thought to govern response to exogenous antigens, including allergens. Experiments in mice have shown that FOXP3+ iTregs are necessary to develop mucosal tolerance on exposure to inhaled allergen.⁶⁶ There are at least two types of iTregs: T_H1 cells produce IL-10 while T_H3 cells produce TGF- β . Continued exposure to allergen leads to the development of T_R1 cells in humans, which is linked with clinical tolerance.⁶⁷ Additional IL-10-producing cells, including CD4+ T cells and regulatory B cells,⁶⁸ may also influence the development and maintenance of peripheral tolerance.

Within the first weeks and months of OIT, there is a rapid increase in sIgE.^{17,35,36,38,41,69,70} Clinically, this time period is associated with the highest rate of adverse reactions. Atopic features and presumably worse T_H2 skewing at baseline appear to predict the likelihood of allergic adverse events (AEs) during OIT. In a cohort of patients receiving peanut OIT, baseline allergic rhinitis and peanut SPT size were significantly associated with an increased risk of AEs.³² During the build-up phase, this rapid increase in sIgE is likely driven by an expansion in allergen-specific T_H2 cells.⁷¹ Single-cell transcriptional analysis of Ara h 2-specific CD4+ T cells in human subjects undergoing peanut OIT has shown an increase in a cluster of cells expressing a T_H2 phenotype (IL4+ IL13+ CD27_{low}) within the first 3 months of OIT. Interestingly, during this same time period, there is a decrease in a cluster expressing a Treg phenotype (FOXP3+, IL-10+, CD25+) and a gradual increase in an anergic cluster (CD28_{low} K_i-67_{low}), the latter of which increases throughout OIT.⁷² These observations suggest that constant exposure to low doses of allergen during the first few months of OIT may enhance pathogenic T_H2 responses and inhibit formation of Tregs.

In contrast, when omalizumab is used as adjunctive therapy, there is evidence of early suppression of T-effector (Teff) responses. In a cohort of children undergoing high-dose cow's milk OIT with omalizumab, an almost absent CD4+ T-cell response to milk was found within a week of starting therapy.⁴³ More recently, it was shown that treatment with omalizumab prior to starting high-dose peanut OIT led to markedly decreased proliferation of allergen-specific CD4+ Teff and Treg cells. Interestingly, these Tregs had a T_H2-like phenotype at baseline and lacked the ability to suppress peanut-specific Teff cells. The *in vitro* addition of IL-2 or anti-IL-10 monoclonal antibodies failed to rescue proliferation of either peanut-specific Teff or Treg cells, providing evidence that omalizumab-mediated suppression may not be due to anergy or suppression via IL-10, although deletion is possible.⁷³

As OIT progresses, subjects are continually exposed to larger doses of allergen, which has been associated with a decline in the activity and expansion of T_H2 cells.⁷² Notably, suppression of the T_H2 cytokines IL-13, IL-5 and IL-9 in subjects undergoing peanut

OIT was recently found to be dose-independent, with no significant difference found between 300 and 3000 mg maintenance dosing.⁷⁴ In support of these observations, a recent phase III clinical trial demonstrated tolerability and efficacy with a maintenance dose of just 300 mg of peanut protein.¹⁰ Although a shift from T_H2 to T_H1 responses has been proposed to occur during OIT, there was no increase in T_H1 or Tr1 cytokines during peanut OIT, suggesting that OIT does not skew away from T_H2 responses and restore natural tolerance.⁷⁴ A recently described allergic-specific T_H2 subset, termed T_H2A cells, is specifically upregulated in atopic patients including patients with food allergy.⁷⁵ These terminally differentiated CD4+ T cells express CRT_H2, CD49d and CD161 and, unlike canonical T_H2 cells, express multiple T_H2 cytokines simultaneously. Compared to T_H2 cells, T_H2A cells more highly express the epithelium-derived cytokine receptors for IL-25 (IL-17RB), IL-33 (IL1RL1), and thymic stromal lymphopoietin (CLRF2), providing evidence that T_H2A cells may be involved in the pathogenesis of allergic disorders. In subjects undergoing peanut OIT, the majority of peanut-reactive CD4+ T cells at baseline were T_H2A cells, which decreased throughout the course of OIT. Importantly, the decrease in T_H2A cells after completion of OIT directly correlated with successful desensitization.⁷⁵ Recently, others have identified T_H2 cells with cell-surface marker expression and cytokine profiling similar to T_H2A cells.⁷⁶

How T_H2 responses are downregulated during OIT is unknown. This may be orchestrated by an expansion of IL-10-producing cells, whether these are T_H2,⁷⁷ Treg³⁹ or Breg cells.⁶⁸ Tregs are critical in the successful response to immunotherapy in mice, but the role of Tregs in the human response to OIT is less clear. Nevertheless, several studies have observed an increase in FOXP3+ Tregs with OIT and Syed et al recently demonstrated an association with sustained unresponsiveness.³⁹ Furthermore, there is evidence that different subsets of Tregs are induced depending on the type of immunotherapy used, including OIT, SLIT and EPIT.⁷⁸ Additional cell types such as T follicular helper (Tfh) cells may be involved in the response to OIT, but this is largely unexplored. A unique cell subset of Tfh, termed Tfh13, was recently described that co-expresses BCL6 and GATA3 and has the cytokine profile IL-13^{hi} IL-4^{hi} IL-5^{hi} IL-21^{lo}. Tfh13 cells are present in mice and humans during allergic conditions and were found to be essential for the production of high-affinity IgE during anaphylaxis.⁷⁹ More research is needed to better characterize the T-cell changes associated with successful oral immunotherapy.

3.3 | B cells and antibodies

In patients with IgE-mediated food allergy, serum levels of sIgE and the ratio of specific to total IgE positively correlate with the likelihood of an allergic reaction during oral food challenge.⁸⁰ sIgE is critical to the pathogenesis of food allergy. In mice, sIgE is required for both humoral and T_H2 responses to ingestion of peanut and leads to the impairment of Treg induction. Furthermore, deletion of the FC ϵ RI kinase Syk or Syk blockade prevents sensitization and, in mice with established peanut allergy, Syk blockade

facilitates desensitization and Treg induction.⁸¹ In addition to food-specific IgE, component-resolved diagnostics is commonly used both in clinical practice and research settings, and in many cases is more predictive than food-specific IgE alone.²⁴ In the case of peanut allergy, elevated sIgE to Ara h 1, Ara h 2, Ara h 3 and Ara h 6 is associated with clinical reactivity⁸² with elevated sIgE to Ara h 2 having greater predictive value than sIgE to peanut alone.^{83,84} Epitope analysis, which assays IgE binding to individual regions on an allergen, is a newer diagnostic tool that provides further resolution. Linear epitope analysis in subjects undergoing peanut OIT showed associations with OFC outcomes, including eliciting dose at baseline OFC, and likelihood of attaining SU.⁸⁵ Recent publications using multiplex bead-based assays have demonstrated efficacy as a predictor of clinical peanut allergy when combined with peanut sIgE⁸⁶ and in distinguishing clinical phenotype in children with cow's milk allergy.⁸⁷ Future studies are needed to better characterize the clinical utility of epitope sIgE in patients undergoing OIT for food allergy.

It is well established that there is an early increase in sIgE after initiation of OIT. Patil et al used fluorescent Ara h 2 multimers to demonstrate that peanut OIT induced a greater than 3-fold transient expansion of circulating oligoclonal Ara h 2-specific memory B cells that peaked at week 7. This temporally aligned with an increase in Ara h 2 sIgE that peaked at almost twice baseline at 7 weeks and remained above baseline until after week 35. Ara h 2 sIgA, sIgG and sIgG4 all increased significantly above baseline by 7 weeks and continued to increase throughout the duration of peanut OIT.⁴¹ Interestingly, analysis of these oligoclonal Ara h 2-specific memory B cells in 3 unrelated patients showed significant sequence homology among immunoglobulin heavy chain sequences, which may represent shared or 'public' clonotypes as recently described.⁸⁸ Providing further support for this notion, next generation sequencing of BCR repertoires similarly revealed an oligoclonal enrichment of specific immunoglobulin alpha and gamma heavy chain clones after peanut OIT.⁸⁹

Allergen-specific IgG and IgA increase throughout the course of OIT, and their appearance coincides with the formation of allergen-specific memory B cells and plasmablasts.⁴¹ IgG4 levels may increase by more than 10-fold throughout the course of OIT and remain elevated years after therapy is completed.^{14,17,35-37} The processes that lead to an increase in IgG4-producing B cells are not known, but this could be explained by an expansion of IL-10-producing cells such as Tregs and Bregs.⁷¹ sIgA levels correlate with food challenge outcome in subjects undergoing peanut SLIT,⁹⁰ and elevated IgA and IgA2 are associated with response to egg OIT.⁹¹ It is important to note that although sIgE eventually decreases below baseline during OIT, it is not eliminated, and sIgE retains its functional abilities to induce mast cell activation despite OIT.⁴⁶

4 | SUSTAINED UNRESPONSIVENESS

A significant limitation of OIT is that, while the majority of subjects can be effectively desensitized, many will experience loss of

desensitization after stopping daily dosing, with a higher risk of loss of desensitization over time.^{17,50} A minority of subjects remain clinically unreactive, which has been termed sustained unresponsiveness (SU) to distinguish it from natural tolerance. It is not presently clear whether SU is simply a state of prolonged desensitization or if it is a state of induced tolerance that lies somewhere between desensitization and natural tolerance.

In support of the former hypothesis, basophil activation and SPT rarely completely normalize in patients who have achieved SU and may remain positive for years after OIT. Persistence of decreased SPT and basophil activation tests is associated with SU.^{17,50,51} In contrast, loss of suppression of these tests is seen in patients who regain allergic reactivity, which has been reported as early as one week after completion of OIT.³⁷ Longer duration of maintenance therapy in addition to younger age¹⁸ appears to be associated with an increased chance of achieving SU.¹⁵ Studies have identified biomarkers that are predictive of SU, including lower baseline and end of maintenance SPT and sIgE in addition to an early and persistent decrease in basophil reactivity.^{21,24,51} Interestingly, IgG4 levels alone do not appear to be predictive of SU. OIT may induce qualitative changes in antibodies themselves, such as epitope specificity and avidity,^{85,92} and there is evidence that OIT modifies the B-cell repertoire itself through oligoclonal expansion of allergen-specific memory B cells.⁸⁹

As described above, OIT also modulates the T-cell compartment through anergy or deletion of pathogenic CD4+ T cells such as T_H2A cells. Epigenetic modification has been linked to SU, with hypomethylation of *FOXP3* CpG sites in peanut-specific Tregs associated with SU and increased methylation found in subjects who later lost tolerance.³⁹ An expansion of IL-10-producing cells may be necessary for the downregulation of T_H2 responses as has been shown in other forms of immunotherapy.^{68,93} Recently, Yoneyama et al determined that the Notch-dependent expansion of IL-10-producing CD4+ T cells and myeloid-derived suppressor cells (MDSCs) was critical to the development of SU in a mouse model of ovalbumin OIT. Importantly, depletion of Gr1+ monocytic MDSCs in this model abrogated SU.⁹⁴ MDSCs inhibit T-cell function and are involved in the pathogenesis of a wide variety of conditions, including malignancy and autoimmunity, but their role in food allergy immunotherapy has not previously been reported.^{95,96}

5 | CONCLUSIONS AND FUTURE DIRECTIONS

Our understanding of the immunologic mechanisms underlying OIT continues to evolve. It is clear that OIT impacts multiple cell compartments, which together orchestrate an adaptive immune response that culminates in desensitization or SU. It is still unclear why some subjects achieve SU while others experience loss of desensitization, and there is a need for biomarkers that are highly predictive of SU. Going forward, it will be important to clarify the role of suppressor cells and more fully characterize the adaptive and humoral changes

that are associated with successful OIT. Additional cell types such as dendritic cells, ILCs, Tfh cells and MDSCs should be explored in the context of food allergy and immunotherapy. The microbiome⁹⁷ and other local factors in the gut may also impact the response to OIT. Future studies are needed to better elucidate the complex immunologic changes that occur during OIT, particularly those that are associated with SU.

ACKNOWLEDGEMENTS

Figures were created with BioRender.com.

CONFLICT OF INTEREST

SM Barshow has received research funding from the NIH as part of a shared institutional T32 grant through Duke University and the University of North Carolina at Chapel Hill. MD Kulis has received research funding from the NIH and the United States Department of Defense. EH Kim reports clinical medical advisory board membership with DBV Technologies; consultancy with Aimmune Therapeutics, DBV Technologies, Duke Clinical Research Institute, ALK-Abello, AllerGenis, Kenota Health, Ukko Inc, and Vibrant America, Belhaven Biopharma; and receives grant support to his institution from the National Institute of Allergy and Infectious Diseases (NIH/NIAID), National Center for Complementary and Integrative Health (NIH/NCCIH), FARE and the Wallace Research Foundation. AW Burks has no conflicts to declare.

AUTHOR CONTRIBUTIONS

SMB drafted the manuscript with guidance and input from MDK. MDK, EHK and AWB reviewed and provided feedback. All authors approved the final version of the manuscript.

ORCID

Suzanne M. Barshow  <https://orcid.org/0000-0002-6744-1834>

Michael D. Kulis  <https://orcid.org/0000-0001-8092-7444>

A. Wesley Burks  <https://orcid.org/0000-0003-1873-5702>

Edwin H. Kim  <https://orcid.org/0000-0001-6418-1785>

REFERENCES

- Gupta RS, Warren CM, Smith BM, et al. Prevalence and severity of food allergies among US adults. *JAMA Netw Open*. 2019;2(1):e185630.
- Sicherer SH, Sampson HA. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. *J Allergy Clin Immunol*. 2018;141(1):41-58.
- Loke P, Koplin J, Beck C, et al. Statewide prevalence of school children at risk of anaphylaxis and rate of adrenaline autoinjector activation in Victorian government schools, Australia. *J Allergy Clin Immunol*. 2016;138(2):529-535.
- Nwaru BI, Hickstein L, Panesar SS, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy*. 2014;69(8):992-1007.
- Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997-2011. *NCHS Data Brief*. 2013;121:1-8.
- Gupta RS, Warren CM, Smith BM, et al. The public health impact of parent-reported childhood food allergies in the United States. *Pediatrics*. 2018;142(6).
- Oria MP, Stallings VA, eds. Finding a path to safety in food allergy: assessment of the global burden, causes, prevention, management, and public policy. *Finding a Path to Safety in Food Allergy: Assessment of the Global Burden, Causes, Prevention, Management, and Public Policy*. Washington, DC; 2016.
- Flokstra-de Blok BM, Dubois AE, Vlieg-Boerstra BJ, et al. Health-related quality of life of food allergic patients: comparison with the general population and other diseases. *Allergy*. 2010;65(2):238-244.
- Savage J, Sicherer S, Wood R. The natural history of food allergy. *J Allergy Clin Immunol Pract*. 2016;4(2):196-203; quiz 4.
- Invest PG, Vickery BP, Vereda A, et al. AR101 oral immunotherapy for peanut allergy. *N Engl J Med*. 2018;379(21):1991-2001.
- Eapen AA, Lavery WJ, Siddiqui JS, Lierl MB. Oral immunotherapy for multiple foods in a pediatric allergy clinic setting. *Ann Allergy Asthma Immunol*. 2019;123(6):573-581.e3.
- Andorf S, Purington N, Block WM, et al. Anti-IgE treatment with oral immunotherapy in multifoed allergic participants: a double-blind, randomised, controlled trial. *Lancet Gastroenterol Hepatol*. 2018;3(2):85-94.
- Begin P, Winterroth LC, Dominguez T, et al. Safety and feasibility of oral immunotherapy to multiple allergens for food allergy. *Allergy Asthma Clin Immunol*. 2014;10(1):1.
- Burks AW, Jones SM, Wood RA, et al. Oral immunotherapy for treatment of egg allergy in children. *N Engl J Med*. 2012;367(3):233-243.
- Jones SM, Burks AW, Keet C, et al. Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy. *J Allergy Clin Immunol*. 2016;137(4):1117-1127.e10.
- Kim EH, Perry TT, Wood RA, et al. Induction of sustained unresponsiveness after egg oral immunotherapy compared to baked egg therapy in children with egg allergy. *J Allergy Clin Immunol*. 2020.
- Vickery BP, Scurlock AM, Kulis M, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. *J Allergy Clin Immunol*. 2014;133(2):468-475.
- Vickery BP, Berglund JP, Burk CM, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol*. 2017;139(1):173-81 e8.
- Chinthrajah RS, Purington N, Andorf S, et al. Sustained outcomes in oral immunotherapy for peanut allergy (POISED study): a large, randomised, double-blind, placebo-controlled, phase 2 study. *Lancet*. 2019;394(10207):1437-1449.
- Vickery BP, Ebisawa M, Shreffler WG, Wood RA. Current and future treatment of peanut allergy. *J Allergy Clin Immunol Pract*. 2019;7(2):357-365.
- Patil SU, Steinbrecher J, Calatroni A, et al. Early decrease in basophil sensitivity to Ara h 2 precedes sustained unresponsiveness after peanut oral immunotherapy. *J Allergy Clin Immunol*. 2019;144(5):1310-1319.
- Parrish CP, Har D, Andrew BJ. Current status of potential therapies for IgE-mediated food allergy. *Curr Allergy Asthma Rep*. 2018;18(3):18.
- Hardy LC, Smeekens JM, Kulis MD. Biomarkers in food allergy immunotherapy. *Curr Allergy Asthma Rep*. 2019;19(12):61.
- Patil SU, Bunyavanich S, Berin MC. Emerging food allergy biomarkers. *J Allergy Clin Immunol Pract*. 2020;8(8):2516-2524.
- Smeekens JM, Kulis MD. Evolution of immune responses in food immunotherapy. *Immunol Allergy Clin North Am*. 2020;40(1):87-95.
- Tordesillas L, Berin MC, Sampson HA. Immunology of food allergy. *Immunity*. 2017;47(1):32-50.
- Chinthrajah RS, Hernandez JD, Boyd SD, Galli SJ, Nadeau KC. Molecular and cellular mechanisms of food allergy and food tolerance. *J Allergy Clin Immunol*. 2016;137(4):984-997.
- Vickery BP, Scurlock AM, Jones SM, Burks AW. Mechanisms of immune tolerance relevant to food allergy. *J Allergy Clin Immunol*. 2011;127(3):576-584; quiz 85-6.

29. Tordesillas L, Berin MC. Mechanisms of Oral Tolerance. *Clin Rev Allergy Immunol*. 2018;55(2):107-117.
30. Kim EH, Burks AW. Food allergy immunotherapy: Oral immunotherapy and epicutaneous immunotherapy. *Allergy*. 2020;75(6):1337-1346.
31. Vazquez-Ortiz M, Turner PJ. Improving the safety of oral immunotherapy for food allergy. *Pediatr Allergy Immunol*. 2016;27(2):117-125.
32. Virkud YV, Burks AWW, Steele PH, et al. Novel baseline predictors of adverse events during oral immunotherapy in children with peanut allergy. *J Allergy Clin Immunol*. 2017;139(3):882-888.e5.
33. Nurmatov U, Dhami S, Arasi S, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy*. 2017;72(8):1133-1147.
34. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol*. 2012;130(6):1260-1274.
35. Varshney P, Jones SM, Scurlock AM, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. *J Allergy Clin Immunol*. 2011;127(3):654-660.
36. Jones SM, Pons L, Roberts JL, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. *J Allergy Clin Immunol*. 2009;124(2):292-300.e1-97.
37. Keet CA, Frischmeyer-Guerrero PA, Thyagarajan A, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. *J Allergy Clin Immunol*. 2012;129(2):448-455, 55 e1-5.
38. Narisety SD, Frischmeyer-Guerrero PA, Keet CA, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. *J Allergy Clin Immunol*. 2015;135(5):1275-1282.e1-6.
39. Syed A, Garcia MA, Lyu SC, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). *J Allergy Clin Immunol*. 2014;133(2):500-510.
40. Thyagarajan A, Jones SM, Calatroni A, et al. Evidence of pathway-specific basophil anergy induced by peanut oral immunotherapy in peanut-allergic children. *Clin Exp Allergy*. 2012;42(8):1197-1205.
41. Patil SU, Ogunniyi AO, Calatroni A, et al. Peanut oral immunotherapy transiently expands circulating Ara h 2-specific B cells with a homologous repertoire in unrelated subjects. *J Allergy Clin Immunol*. 2015;136(1):125-134 e12.
42. MacGinnitie AJ, Rachid R, Gragg H, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. *J Allergy Clin Immunol*. 2017;139(3):873-881 e8.
43. Nadeau KC, Schneider LC, Hoyte L, Borrás I, Umetsu DT. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. *J Allergy Clin Immunol*. 2011;127(6):1622-1624.
44. Stranks AJ, Minnicozzi SC, Miller SJ, et al. Immunoglobulin E blockade during food allergen ingestion enhances the induction of inhibitory immunoglobulin G antibodies. *Ann Allergy Asthma Immunol*. 2019;122(2):213-215.
45. Santos AF, James LK, Bahnson HT, et al. IgG4 inhibits peanut-induced basophil and mast cell activation in peanut-tolerant children sensitized to peanut major allergens. *J Allergy Clin Immunol*. 2015;135(5):1249-1256.
46. Santos AF, James LK, Kwok M, et al. Peanut oral immunotherapy induces blocking antibodies but does not change the functional characteristics of peanut-specific IgE. *J Allergy Clin Immunol*. 2020;145(1):440-443 e5.
47. Burton OT, Tamayo JM, Stranks AJ, Koleoglou KJ, Oettgen HC. Allergen-specific IgG antibody signaling through FcγRIIb promotes food tolerance. *J Allergy Clin Immunol*. 2018;141(1):189-201 e3.
48. Orgel K, Burk C, Smeekens J, et al. Blocking antibodies induced by peanut oral and sublingual immunotherapy suppress basophil activation and are associated with sustained unresponsiveness. *Clin Exp Allergy*. 2019;49(4):461-470.
49. Bianchini R, Karagiannis SN, Jordakieva G, Jensen-Jarolim E. The role of IgG4 in the fine tuning of tolerance in IgE-mediated allergy and cancer. *Int J Mol Sci*. 2020;21(14).
50. Gorelik M, Narisety SD, Guerrero AL, et al. Suppression of the immunologic response to peanut during immunotherapy is often transient. *J Allergy Clin Immunol*. 2015;135(5):1283-1292.
51. Tsai M, Mukai K, Chinthrajah RS, Nadeau KC, Galli SJ. Sustained successful peanut oral immunotherapy associated with low basophil activation and peanut-specific IgE. *J Allergy Clin Immunol*. 2020;145(3):885-896 e6.
52. Burton OT, Epp A, Fanny ME, et al. Tissue-specific expression of the low-affinity IgG receptor, FcγRIIb, on human mast cells. *Front Immunol*. 2018;9:1244.
53. Oka T, Rios EJ, Tsai M, Kalesnikoff J, Galli SJ. Rapid desensitization induces internalization of antigen-specific IgE on mouse mast cells. *J Allergy Clin Immunol*. 2013;132(4):922-932 e1-16.
54. Ang WX, Church AM, Kulis M, Choi HW, Burks AW, Abraham SN. Mast cell desensitization inhibits calcium flux and aberrantly remodels actin. *J Clin Invest*. 2016;126(11):4103-4118.
55. Killoran KE, Kropp LE, Lindrose AR, Curtis HE, Cook D, Mitre E. Rush desensitization with a single antigen induces subclinical activation of mast cells and protects against bystander challenge in dually sensitized mice. *Clin Exp Allergy*. 2019;49(4):484-494.
56. Hammad H, Lambrecht BN. Barrier epithelial cells and the control of type 2 immunity. *Immunity*. 2015;43(1):29-40.
57. Han H, Roan F, Ziegler SF. The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines. *Immunol Rev*. 2017;278(1):116-130.
58. Orgel K, Smeekens JM, Ye P, et al. Genetic diversity between mouse strains allows identification of the CC027/GeniUnc strain as an orally reactive model of peanut allergy. *J Allergy Clin Immunol*. 2019;143(3):1027-1037 e7.
59. Mathias CB, Hobson SA, Garcia-Lloret M, et al. IgE-mediated systemic anaphylaxis and impaired tolerance to food antigens in mice with enhanced IL-4 receptor signaling. *J Allergy Clin Immunol*. 2011;127(3):795-805 e1-6.
60. Chu DK, Llop-Guevara A, Walker TD, et al. IL-33, but not thymic stromal lymphopoietin or IL-25, is central to mite and peanut allergic sensitization. *J Allergy Clin Immunol*. 2013;131(1):187-200 e1-8.
61. Blazquez AB, Berin MC. Gastrointestinal dendritic cells promote Th2 skewing via OX40L. *J Immunol*. 2008;180(7):4441-4450.
62. Noval Rivas M, Burton OT, Oettgen HC, Chatila T. IL-4 production by group 2 innate lymphoid cells promotes food allergy by blocking regulatory T-cell function. *J Allergy Clin Immunol*. 2016;138(3):801-811 e9.
63. Chehade M, Mayer L. Oral tolerance and its relation to food hypersensitivities. *J Allergy Clin Immunol*. 2005;115(1):3-12; quiz 3.
64. Chen Y, Inobe J, Marks R, Gonnella P, Kuchroo VK, Weiner HL. Peripheral deletion of antigen-reactive T cells in oral tolerance. *Nature*. 1995;376(6536):177-180.
65. Burks AW, Laubach S, Jones SM. Oral tolerance, food allergy, and immunotherapy: implications for future treatment. *J Allergy Clin Immunol*. 2008;121(6):1344-1350.
66. Curotto de Lafaille MA, Kutchukhidze N, Shen S, Ding Y, Yee H, Lafaille JJ. Adaptive Foxp3+ regulatory T cell-dependent and -independent control of allergic inflammation. *Immunity*. 2008;29(1):114-126.
67. Akdis M, Verhagen J, Taylor A, et al. Immune responses in healthy and allergic individuals are characterized by a fine balance between allergen-specific T regulatory 1 and T helper 2 cells. *J Exp Med*. 2004;199(11):1567-1575.

68. van de Veen W, Stanic B, Yaman G, et al. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. *J Allergy Clin Immunol*. 2013;131(4):1204-1212.
69. Blumchen K, Ulbricht H, Staden U, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. *J Allergy Clin Immunol*. 2010;126(1):83-91 e1.
70. Obh J, Beyer K, Abbas A, et al. Efficacy and safety of oral immunotherapy with AR101 in European children with a peanut allergy (ARTEMIS): a multicentre, double-blind, randomised, placebo-controlled phase 3 trial. *Lancet Child Adolesc. Health*. 2020;4(10):728-739.
71. Kulis MD, Patil SU, Wambre E, Vickery BP. Immune mechanisms of oral immunotherapy. *J Allergy Clin Immunol*. 2018;141(2):491-498.
72. Ryan JF, Hovde R, Glanville J, et al. Successful immunotherapy induces previously unidentified allergen-specific CD4⁺ T-cell subsets. *Proc Natl Acad Sci USA*. 2016;113(9):E1286-E1295.
73. Abdel-Gadir A, Schneider L, Casini A, et al. Oral immunotherapy with omalizumab reverses the Th2 cell-like programme of regulatory T cells and restores their function. *Clin Exp Allergy*. 2018;48(7):825-836.
74. Kulis M, Yue X, Guo R, et al. High- and low-dose oral immunotherapy similarly suppress pro-allergic cytokines and basophil activation in young children. *Clin Exp Allergy*. 2019;49(2):180-189.
75. Wambre E, Bajzik V, DeLong JH, et al. A phenotypically and functionally distinct human TH2 cell subpopulation is associated with allergic disorders. *Sci Transl Med*. 2017;9(401).
76. Chiang D, Chen X, Jones SM, et al. Single-cell profiling of peanut-responsive T cells in patients with peanut allergy reveals heterogeneous effector TH2 subsets. *J Allergy Clin Immunol*. 2018;141(6):2107-2120.
77. Altin JA, Goodnow CC, Cook MC. IL-10+ CTLA-4⁺ Th2 inhibitory cells form in a Foxp3-independent, IL-2-dependent manner from Th2 effectors during chronic inflammation. *J Immunol*. 2012;188(11):5478-5488.
78. Dioszeghy V, Mondoulet L, Puteaux E, et al. Differences in phenotype, homing properties and suppressive activities of regulatory T cells induced by epicutaneous, oral or sublingual immunotherapy in mice sensitized to peanut. *Cell Mol Immunol*. 2017;14(9):770-782.
79. Gowthaman U, Chen JS, Zhang B, et al. Identification of a T follicular helper cell subset that drives anaphylactic IgE. *Science*. 2019;365(6456).
80. Ballmer-Weber BK, Lidholm J, Fernandez-Rivas M, et al. IgE recognition patterns in peanut allergy are age dependent: perspectives of the EuroPrevall study. *Allergy*. 2015;70(4):391-407.
81. Burton OT, Noval Rivas M, Zhou JS, et al. Immunoglobulin E signal inhibition during allergen ingestion leads to reversal of established food allergy and induction of regulatory T cells. *Immunity*. 2014;41(1):141-151.
82. Nicolaou N, Poorafshar M, Murray C, et al. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. *J Allergy Clin Immunol*. 2010;125(1):191-197 e1-13.
83. Dang TD, Tang M, Choo S, et al. Increasing the accuracy of peanut allergy diagnosis by using Ara h 2. *J Allergy Clin Immunol*. 2012;129(4):1056-1063.
84. Klemans RJ, Broekman HC, Knol EF, et al. Ara h 2 is the best predictor for peanut allergy in adults. *J Allergy Clin Immunol Pract*. 2013;1(6):632-638 e1.
85. Dreskin SC, Germinaro M, Reinhold D, et al. IgE binding to linear epitopes of Ara h 2 in peanut allergic preschool children undergoing oral Immunotherapy. *Pediatr Allergy Immunol*. 2019;30(8):817-823.
86. Suprun M, Sicherer SH, Wood RA, et al. Early epitope-specific IgE antibodies are predictive of childhood peanut allergy. *J Allergy Clin Immunol*. 2020.
87. Sackesen C, Suarez-Farinas M, Silva R, et al. A new Luminex-based peptide assay to identify reactivity to baked, fermented, and whole milk. *Allergy*. 2019;74(2):327-336.
88. Soto C, Bombardi RG, Branchizio A, et al. High frequency of shared clonotypes in human B cell receptor repertoires. *Nature*. 2019;566(7744):398-402.
89. Kiyotani K, Mai TH, Yamaguchi R, et al. Characterization of the B-cell receptor repertoires in peanut allergic subjects undergoing oral immunotherapy. *J Hum Genet*. 2018;63(2):239-248.
90. Kulis M, Saba K, Kim EH, et al. Increased peanut-specific IgA levels in saliva correlate with food challenge outcomes after peanut sublingual immunotherapy. *J Allergy Clin Immunol*. 2012;129(4):1159-1162.
91. Wright BL, Kulis M, Orgel KA, et al. Component-resolved analysis of IgA, IgE, and IgG4 during egg OIT identifies markers associated with sustained unresponsiveness. *Allergy*. 2016;71(11):1552-1560.
92. Suarez-Farinas M, Suprun M, Chang HL, et al. Predicting development of sustained unresponsiveness to milk oral immunotherapy using epitope-specific antibody binding profiles. *J Allergy Clin Immunol*. 2019;143(3):1038-1046.
93. Piconi S, Trabattini D, Rainone V, et al. Immunological effects of sublingual immunotherapy: clinical efficacy is associated with modulation of programmed cell death ligand 1, IL-10, and IgG4. *J Immunol*. 2010;185(12):7723-7730.
94. Yoneyama T, Nakano N, Hara M, et al. Notch signaling contributes to the establishment of sustained unresponsiveness to food allergens by oral immunotherapy. *J Allergy Clin Immunol*. 2020.
95. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. *Nat Rev Immunol*. 2009;9(3):162-174.
96. Veglia F, Perego M, Gabrilovich D. Myeloid-derived suppressor cells coming of age. *Nat Immunol*. 2018;19(2):108-119.
97. He Z, Vadali VG, Szabady RL, et al. Increased diversity of gut microbiota during active oral immunotherapy in peanut-allergic adults. *Allergy*. 2020.

How to cite this article: Barshow SM, Kulis MD, Burks AW, Kim EH. Mechanisms of oral immunotherapy. *Clin Exp Allergy*. 2021;00:1-9. <https://doi.org/10.1111/cea.13824>