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New treatment directions in food allergy

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Key Messages

- Desensitization with immunotherapy has shown promise in clinical trials, however, recurrence of allergenic sensitivity is common after discontinuation of therapy.
- Oral immunotherapy with adjunct omalizumab, an anti-IgE antibody, expedites time to desensitization and enables simultaneous treatment of multiple allergies.
- Other adjunctive therapies with oral immunotherapy that have shown promise are probiotics and Chinese herbal formula.
- Sublingual immunotherapy has a better safety profile than oral immunotherapy but oral immunotherapy is more effective than sublingual immunotherapy in inducing desensitization.
- Novel vaccines and biologics, such as lysosomal associated membrane protein (LAMP) DNA vaccine and anti-IL-33, respectively, are being evaluated in clinical trials for the treatment of food allergy.

INSTRUCTIONS

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- Review the target audience, learning objectives and all disclosures.
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Overall Purpose

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

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Learning Objectives
At the conclusion of this activity, participants should be able to:
- Recognize the differences between tolerance, sustained unresponsiveness, and desensitization with immunotherapy
- Determine the benefits and drawbacks of the different routes of immunotherapy and the adjunctive treatments that are being used with immunotherapy.

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Physicians involved in providing patient care in the field of allergy/asthma/immunology
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Introduction

There is general consensus that food allergies (FAs) are increasing in prevalence. However, because of the lack of a simple diagnostic test for FA and methodologic differences between studies to determine prevalence of FA, true FA prevalence in the past or present is difficult to determine.[1] Based on a number of studies, FA is estimated to affect approximately 5% of adults and 8% of children.[2] Increases in the rate of emergency department visits and hospital admissions for food-induced anaphylaxis in children have been reported.[3] These increases in rates of FA are worrisome and have intensified research into effective treatments for the disease. Currently, there is no treatment approved by the US Food and Drug Administration (FDA) for FA and the standard of care is individualized avoidance of the offending food allergens and treatment of symptoms at accidental ingestion.[2] Allergen avoidance is difficult to accomplish because many allergenic foods, such as milk, eggs, and peanuts, are common ingredients in many foods. Accidental ingestion is common and 1 study reported that during a 5- and 10-year follow-up period, 58% and 75% of individuals with peanut allergy, respectively, accidentally consumed peanuts.[4] Constant vigilance and monitoring of foods for potential allergens lead to stress and lower quality of life. Localized reactions at accidental ingestion are treated with antihistamines or glucocorticoids, whereas systemic reactions are treated with epinephrine.[5] These pharmaceutical agents are inadequate, offer only symptomatic relief, and do not address the underlying immune disorder.

Food allergies are classified as mediated by immunoglobulin E (IgE), not mediated by IgE, and mixed (mediated and not mediated by IgE). Although this classification is an oversimplification

of the various pathologies underlying FAs, it plays an essential part in diagnosis and treatment. IgE-mediated reactions are immediate (minutes to within 1–2 hours) and symptoms include urticaria, nausea, abdominal pain, respiratory symptoms, and potentially fatal systemic anaphylaxis. Non–IgE-mediated reactions are delayed and include food protein-induced allergic enterocolitis, food protein-induced allergic proctocolitis, and food protein-induced enteropathy. Eosinophilic gastrointestinal disorders constitute another group of FA disorders with chronic eosinophilic infiltration of the gastrointestinal wall.[6] These were initially considered mixed (IgE and non–IgE-mediated), but currently the role of IgE in these diseases is controversial.[6–8] This review focuses on current treatments that show promise in desensitizing individuals with IgE-mediated FA.

Immune Mechanism: Tolerance, IgE-Mediated Allergic Sensitization and Reaction, and Desensitization with Immunotherapy

A number of excellent reviews of the mechanisms underlying allergic tolerance, IgE-mediated allergic sensitization and reaction, and immunologic changes with immunotherapy have been published.[2,6,9–12] These mechanisms are briefly discussed in this article.

Tolerance

Healthy immune tolerance to foods is an active process, with T-regulatory cells (Tregs) playing a central role in inhibiting mast cell degranulation and sustaining tolerance. Much of our understanding of responses to allergens in the gut is based on animal studies. It is believed that tolerogenic responses primarily begin with the uptake of potential allergens at the gastrointestinal mucosa of the small intestine, which contains most of the gut-associated lymphoid tissue. Uptake can occur through transcytosis, paracytosis, or endocytosis (through specialized micro-fold cells)[13] or through capture by dendritic cells ($CD103^+$) or macrophages ($CX3CR1^+$), which are located in the lamina propria. $CX3CR1^+$ cells can sample antigens present in the lumen of the gut by extending processes between intestinal epithelial cells. These cells do not migrate but are believed to transfer the antigens to $CD103^+$ dendritic cells through a gap junction and promote tolerance through interleukin (IL)-10 production.[14] $CD103^+$ dendritic cells might capture antigens directly from the lumen by extending a process through a tight junction or through a transcellular pore in a micro-fold cell or might sample those antigens already translocated to the lamina propria. Then, these dendritic cells migrate to the draining lymph nodes, where they induce differentiation of naïve T cells into Tregs and facilitate their homing to the gut by (1) production of transforming growth factor-β and retinoic acid, (2) expression of indoleamine 2,3-dioxygenase, and (3) expression of C-C chemokine receptor type 9 and α4β7 on Tregs. Although it is clear that $Foxp3^+$ and $Foxp3^-$ IL-10 and transforming growth factor-β producing Tregs are present in the gut, the role of the individual Tregs in promoting tolerance is poorly understood. Tregs that have honed to the gut also might promote B-cell production of noninflammatory IgA[11,12] (Fig 1).

Allergic Sensitization and Allergic Response

IgE-mediated reactions include a sensitization phase, an activation phase, and an effector phase. Antigens are initially encountered at barrier surfaces, such as the skin, gastrointestinal tract, or respiratory tract, and sensitization is believed to occur through at least 1 of these routes. Increased allergen permeability caused by disruption of the epithelial barrier is believed to play an essential role in allergic sensitization. Loss of epithelial barrier integrity can be caused by injury or the presence of a loss-of-function mutation of the filaggrin gene, a key gene involved in skin barrier function. Studies have shown that infants who develop atopic dermatitis are significantly more likely to develop FA. Filaggrin mutations represent a significant risk factor for IgE-mediated peanut allergy[15]; however, not all children with a filaggrin mutation develop atopic dermatitis or FA and not all children with FA have atopic dermatitis. Increased allergen permeability leads to the production of proinflammatory epithelial-derived cytokines (IL-25, IL-33, and thymic stromal lymphopoietin).[16] Some potential ways that these cytokines might drive T-helper cell type 2 (T_H2) responses and production of type 2 cytokines (IL-4, IL-5, IL-9, and IL-13) are by stimulation of type 2 innate lymphoid cells, upregulation of IL-9–producing mucosal mast cells,[17,18] and upregulation of OX40 ligand on dendritic cells and driving differentiation of naïve $CD4^+$ T cells to T_H2 cells.[6] Together, these type 2 cytokines promote tissue mast cells, basophils, and eosinophil accumulation, IgE class switching by B cells, and binding of allergen-specific IgE antibodies to FcεRI receptors on mast cells or basophils (Fig 2). At this stage, the individual is sensitized to the allergen. During the activation phase, further exposure to the specific allergens leads to crosslinking of FcεRI-bound IgE antibodies and subsequent degranulation of mast cells or basophils leading to the release of histamine and other inflammatory chemical mediators such as cytokines, interleukins, leukotrienes, and prostaglandins into the surrounding tissue. During the final effector phase, these proinflammatory mediators mediate allergic reactions through the production of mucous, infiltration of eosinophils, vasodilation, smooth muscle contraction, and other effects.[11]

Desensitization with Immunotherapy

The mechanisms of desensitization with immunotherapy and the differences between desensitization and natural tolerance are not well understood. Immunotherapy has been shown to decrease specific IgE levels and diversity[19] and basophil activation[20] and increase IgA[21] and IgG4[19] levels. IgG4 antibodies are believed to act as blocking antibodies by competing with IgE. Decreases in the number and function of T_H2 cells through apoptosis and anergy and increases in Treg number and function (through hypomethylation of Foxp3)[22–25] have been demonstrated by a few studies. Increases in allergen-specific memory B cells have been observed, suggesting a potential role of these cells in tolerance.[26] Allergen-specific memory B cells have been implicated in the production of IgG4 and IL-10.[27] Further research into the mechanism underlying oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT) are needed that can guide protocols toward safer and more efficacious treatments (Fig 3).

Immunotherapy

Immunotherapy can increase the threshold of reactivity (desensitize) to specific allergens in most individuals with allergy. However, the definition of successful desensitization can vary. It can indicate a high level of desensitization as that required to enable individuals to consume normal amounts of the offending allergens or a lower level of desensitization as that required to prevent allergic reaction at accidental ingestion of allergenic foods.

One of the major drawbacks of immunotherapy is that, in most individuals, desensitization is a temporary state and recurrence of allergenic sensitivity often occurs after discontinuation of therapy. To maintain desensitization, regular exposure to the offending allergen appears to be necessary for most individuals. Desensitization differs from true tolerance, which is defined as a permanent immunologic change, and can occur naturally in some individuals and perhaps with immunotherapy. Currently, because biomarkers to

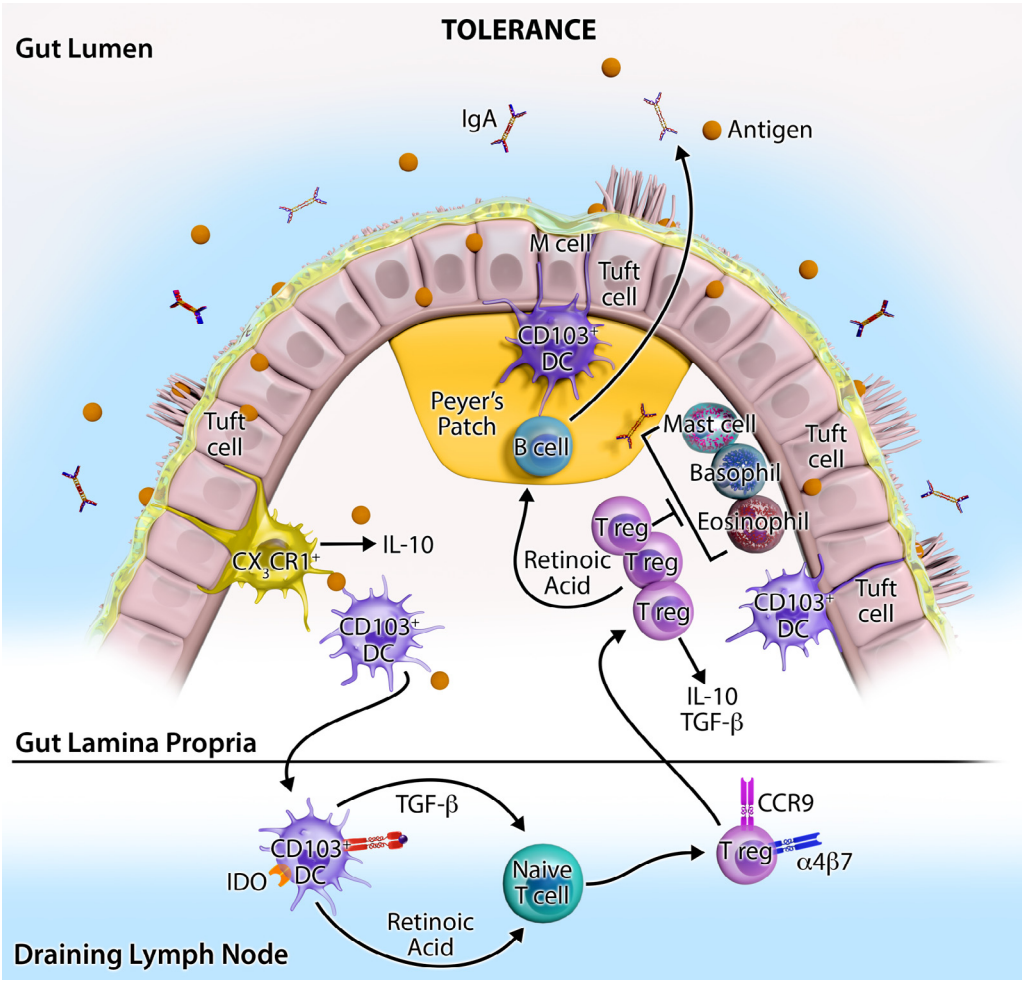

Figure 1. Healthy immune tolerance to foods is an active process. Upregulation of T-regulatory cells and inhibition of mast cell degranulation are key to maintaining tolerance. CCR9, C-C chemokine receptor type 9; DC, dendritic cell; IDO, indoleamine 2,3-dioxygenase; IgA, immunoglobulin A; IL-10, interleukin-10; M cell, micro-fold cell; TGF-β, transforming growth factor-β.

determine tolerance are unavailable, focus has shifted to evaluating sustained unresponsiveness (SU), which is defined as the ability to successfully pass a food challenge after a period of allergen avoidance after cessation of active therapy. Long-term data are currently inadequate to determine whether SU (of a few years and beyond) can be achieved and the immunologic differences among SU, tolerance, and desensitization.

Other barriers against acceptance of immunotherapy into regular clinical practice include extended length of treatment (generally months to years), frequent clinic visits, and risk of adverse reactions during treatment. A recent systematic review and meta-analysis of immunotherapy trials concluded that although immunotherapy is effective in increasing the threshold of reactivity to specific allergens, it is associated with a modest increase in serious systemic adverse reactions and a substantial increase in minor local adverse effects. In addition, most immunotherapy protocols aim to desensitize individuals to only 1 offending allergen at a time, making it impractical for those with multiple FAs. Optimization of immunotherapy protocols (route of delivery, dose, treatment frequency and duration, or use of allergen epitopes and adjunctive therapies) to address these shortcomings of immunotherapy is an active area of research.

Clinical trials of OIT, SLIT, and EPIT for FA are currently being evaluated. Subcutaneous immunotherapy for FAs was attempted in the 1990s and was shown to be efficacious; however, it was associated with high rates of adverse reactions,[28] and studies on FA immunotherapy mostly have been limited to OIT, SLIT, or EPIT. However, there have been recent attempts to develop safer, chemically modified aluminum hydroxide adsorbed peanut extracts for subcutaneous immunotherapy administration and 1 formulation is currently being tested in clinical trials (clinicaltrials.gov identifier NCT02991885).

Oral Immunotherapy

Oral immunotherapy has been conducted mainly for milk, peanut, and egg allergy. Simultaneous OIT for multiple allergens (up to 5) also has been attempted and shown to be feasible.[29] Although protocols vary widely, in general, OIT consists of the following 4 phases: (1) an initial dose escalation day (micrograms to milligrams) at which the highest tolerated dose of allergen that can be safely consumed is determined, (2) a buildup phase of varying length when the allergen dose is gradually increased over time until a predetermined maintenance dose is reached, and (3) a dose maintenance phase of variable length at the end of which an oral food challenge (OFC) is conducted to determine desensitization success or failure. To determine SU, many clinical trials incorporate a fourth phase (allergen elimination phase), which includes varying periods of allergen withdrawal at the end of which SU is determined through OFCs. For peanut allergies, maintenance doses generally have varied from 300 to 4,000 mg (equivalent to ~17 peanuts). High maintenance doses are associated with low compliance. A recent study by Vickery et

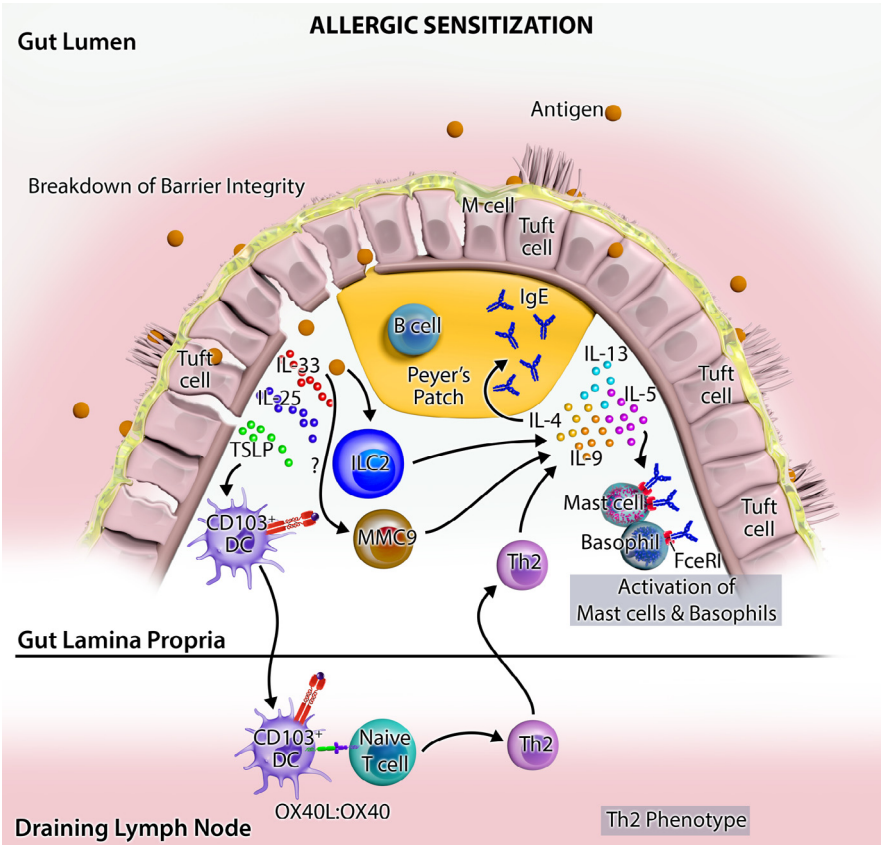

Figure 2. Upregulation of T_H2 cytokines and IgE antibodies lead to mast cell degranulation and allergic response. DC, dendritic cell; IgE, immunoglobulin E; IL, interleukin; ILC2, innate lymphoid cell type 2; MMC9, multifunctional interleukin-9–producing mucosal mast cell; OX40L, OX40 ligand; T_H2, T-helper cell type 2; TSLP, thymic stromal lymphopoietin.

al[30] in infants 9 to 36 months old indicated that a low 300-mg maintenance dose with peanut protein had similar efficacy and improved safety profile as a high 3,000-mg dose. Adverse reactions are the primary concern with OIT and can occur during OFC, initial day 1 escalation, buildup phase, or maintenance phase. Serious anaphylaxis reactions are rare but have been reported. Mild reactions (mainly abdominal) have been reported in 2% to 5% of doses, with epinephrine being used in less than 1% of doses (but up to 24% of patients).[31] A systematic review and meta-analysis showed that approximately 2.7% of patients undergoing OIT for FA developed new-onset eosinophilic esophagitis.[32]

Novel methods of introducing allergens are being evaluated, such as the use of heated allergens (mainly eggs and milk) or standardized commercial oral formulations. Use of heated milk might lower the rates of adverse effects with immunotherapy.[33] Some studies have indicated that regular use of baked egg or milk in the diet can increase tolerance to similar non-baked foods in certain individuals. These individuals are believed to be sensitized to conformational epitopes that are denatured with heating and bind to IgE bound to mast cells or basophils less strongly that unheated epitopes.[34] However, a recent systematic review did not support this hypothesis.[35] To facilitate a convenient and accurate way of delivering allergens, AR101, a peanut-derived pharmaceutical capsule, has been developed by Aimmune Therapeutics (Brisbane, California). It is currently in phase 3 immunotherapy trials and capsules are formulated to deliver 0.5 up to 300 mg of peanut protein.[36]

Sublingual Immunotherapy

In SLIT, allergens are applied under the tongue in the form of a tablet or drops on a daily basis for a period of years. Maintenance doses with SLIT are in the range of micrograms to milligrams and much lower than with OIT, which are in milligrams to grams.[37] Another important difference between OIT and SLIT is that in SLIT allergens are delivered to the oral mucosa intact and in OIT digested antigens are delivered to the gastric mucosa. Several SLIT clinical trials (kiwi, hazelnut, milk, peach, and peanut allergies) have shown promising results. Results from randomized controlled studies for milk and peanut allergy comparing the safety and efficacy of SLIT and OIT showed that SLIT had a better safety profile than OIT but OIT was more effective than SLIT in inducing desensitization. Side effects with SLIT are minimal and typically limited to oropharyngeal itching in less than 2% of doses.[31] No severe anaphylactic reactions have been reported. SLIT efficacy is limited by the concentration of the allergen and the volume of liquid that can be administered sublingually. Currently, it remains investigation therapy and there are no standardized SLIT formulations available.

A randomized study by Keet et al[38] evaluated the use of SLIT alone or SLIT followed by OIT in children. The protocol consisted of an initial SLIT escalation phase followed by continuation of SLIT escalation or initiation of OIT (high or low dose). An OFC to 8 g of milk protein was conducted after 12 and 60 weeks of maintenance therapy. The study found that although the rates of reaction were the same, systemic reactions were more common during OIT than during SLIT and that SLIT followed by OIT was more effective than SLIT alone in achieving desensitization.

Epicutaneous Immunotherapy

In EPIT, allergens are introduced in an epicutaneous fashion through a patch applied to the back or upper arm.[39] Allergens applied to the patch are lower than those found in OIT and SLIT and are in

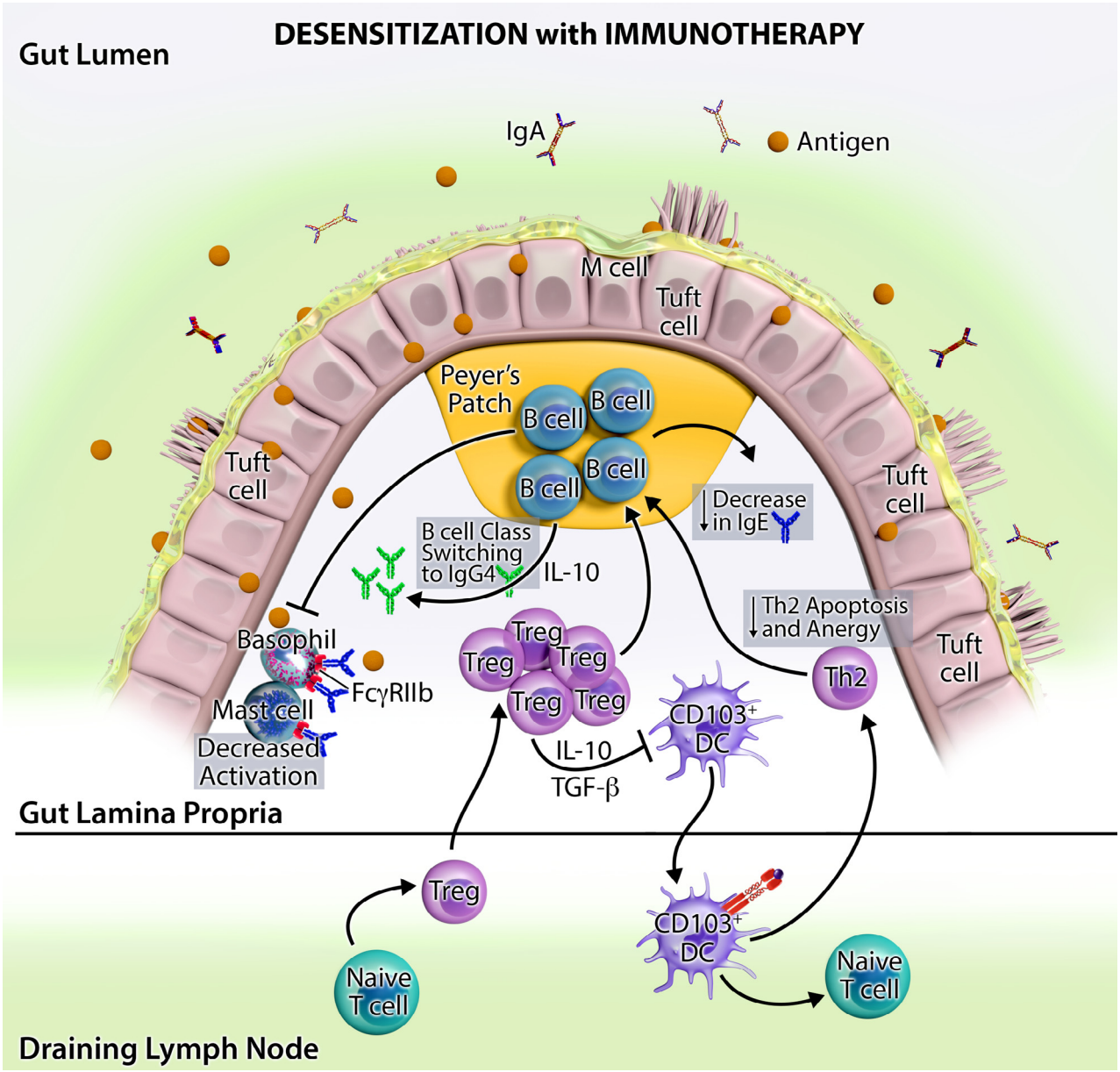

Figure 3. The mechanism of desensitization with immunotherapy is still being investigated. IgE levels and basophil activation decrease while IgG4 levels and Foxp3 Treg function increase with immunotherapy. DC, dendritic cell; Ig, immunoglobulin; M cell, micro-fold cell; TGF-β, transforming growth factor-β; T_H2, T-helper cell type 2; Treg, T-regulatory cell.

the microgram range (~100–500 μg of protein). Results of a recent multicenter, double-blinded, randomized, placebo-controlled study of EPIT using a proprietary peanut patch (Viaskin; DBV Technologies, Montrouge, France) indicated increases in specific IgG4 levels and IgG4/IgE ratios and a trend toward decreased basophil activation and specific T_H2 cytokines. Side effects were minimal and mainly consisted of mild skin irritation in the area of the skin where the patch was applied. No systemic reactions were reported. At 52 weeks, a 10-fold increase in the successfully consumed baseline dose, the primary end point, was significantly greater in the group treated with the 250-μg Viaskin peanut patch (48.0%) than in the placebo group (12%). However, the differences between these 2 groups were not significant when the additional criterion of a successfully consumed baseline dose of at least 1,044 mg of protein was used. Furthermore, when the results were stratified by age, no treatment success was observed for those older than 11 years.[39,40] Phase 3 studies using the Viaskin peanut patch are currently underway. EPIT for milk allergy using Viaskin milk and for egg allergy using Viaskin egg are currently in phase 2 and preclinical trials, respectively.

Adjunctive Therapies with OIT

Anti-IgE Therapy

Omalizumab is an anti-IgE antibody that decreases circulating IgE concentrations.[41] Importantly, it does not bind to FcεRI-bound IgE on mast cells or basophils and cannot induce IgE crosslinking or trigger anaphylactic reactions.[42] It has been approved by the FDA for treatment of allergic asthma and chronic urticaria. Omalizumab was first used by Nadeau et al[43] as adjuvant therapy to OIT in 2011 in a pilot study of 11 individuals with milk allergy. The protocol consisted of 9 weeks of pretreatment with omalizumab, 7 weeks of omalizumab plus OIT therapy, followed by 8 weeks of maintenance OIT without omalizumab. An OFC was conducted at the end

of the maintenance period. The results of the study demonstrated that adjunctive omalizumab with OIT was efficacious and might allow for faster desensitization. The frequency of adverse reactions was 1.6% of doses, and most symptoms were defined as mild. One subject dropped out of the study because of gastrointestinal symptoms and 1 subject developed rhinitis and generalized urticaria and responded to epinephrine at the time of OFC.[43]

In addition to milk, clinical trials using adjunctive omalizumab with OIT have been conducted for egg,[44] peanut,[45] and multiple FAs.[46] Three recent randomized double-blinded, placebo-controlled trials of adjunctive omalizumab with OIT have been published and results from these studies are promising. A study by Wood et al[47] showed significant improvements in safety and time in achieving the maintenance dose in patients with milk allergy who received omalizumab during OIT but did not find increased success in desensitization or SU in patients. In patients treated with omalizumab, percentages of doses per subject provoking symptoms, dose-related reactions requiring treatment, and doses required to achieve maintenance were decreased compared with the placebo-controlled group during OIT escalation. A multicenter trial for peanut allergy found a significant difference in efficacy between the active and placebo arms. Twelve weeks after stopping omalizumab, 76% of patients in the omalizumab arm passed the 4,000-mg food challenge compared with 12.5% of patient in the placebo arm. Although the overall reaction rates were not significantly different in the omalizumab vs placebo arm, there was a trend toward lower rates. In addition, the omalizumab-treated subjects were exposed to much higher doses of peanut than the placebo group.[48] A phase 2 study of patients with multiple FAs who were simultaneously treated with up to 5 allergens demonstrated that adjunctive omalizumab with OIT enables safe and rapid desensitization.[46]

These studies indicate that adjunctive omalizumab with OIT expedites time to desensitization by allowing patients to start at a higher initial dose than OIT alone, decreasing the number of doses required to reach maintenance dose, and that desensitization is maintained even after discontinuation of omalizumab. It also indicates that it is safe and feasible for use in patients with multiple allergies.

Probiotics

There is significant evidence implicating the role of the microbiome in allergic disease.[49,50] The introduction of fruits and vegetables containing fermentable fiber in early infancy has been shown to increase microbial diversity and short-chain fatty acid levels, promote epithelial integrity, and decrease penetration of intact food allergens.[51,52] A few OIT trials that have used adjunctive probiotics have shown promise for FA desensitization. In 1 study, children with peanut allergy were randomly given a combination of the probiotic *Lactobacillus rhamnosus* with peanut protein or a placebo once daily for 18 months. Two to 5 weeks after the end of the trial, 82.1% of children who received OIT plus probiotics were deemed tolerant to peanuts compared with just 3.6% in the placebo group.[53] At 4-year follow-up, 70% of children who gained initial tolerance passed another challenge test, suggesting that is effective at inducing SU.[54]

Chinese Herbal Formula

The FA Herbal Formula-2 (FAHF-2) is a Chinese 9-herb formula. In a murine model of multiple FAs (peanut, egg, and codfish), FAHF-2 was efficacious and prevented anaphylactic reactions.[55] A double-blinded, randomized, placebo-controlled phase 1 study of FAHF-2 found it safe and well tolerated, with favorable in vitro immunomodulatory effects; however, no improvements in efficacy were observed.[56] The use of other Chinese herbal formulas in conjunction with multi-food OIT and anti-IgE are being tested in clinical trials (clinicaltrials.gov identifier NCT02879006).

Other Therapies

Vaccines

A novel immunotherapeutic approach is to provide exposure to allergens through DNA vaccines. Lysosomal associated membrane protein (LAMP) DNA plasmid vaccines are novel vaccines constructed to encode LAMP-1 and allergenic sequences. In a murine model, CryJ1-and CryJ2-LAMP, which encode the major allergens found in Japanese red cedar, induced robust T_H1-type immune responses.[57] A phase 1 study of CryJ2-LAMP DNA vaccine indicated that the vaccine is safe and could be immunologically effective in treating allergy induced by Japanese red cedar.[58] A DNA-LAMP vaccine, ASP0892, for treating peanut allergy has recently been developed by Astellas Pharma, Inc (Tokyo, Japan). Unlike conventional DNA vaccines that primarily elicit a cytotoxic T-cell immune response, ASP0892 is designed to desensitize individuals with peanut allergy to the 3 major peanut allergens (Ara h 1, Ara h 2, Ara h 3) and generate a T_H1-mediated immune response. A phase 1 study (clinicaltrials.gov identifier NCT02851277) is in progress to evaluate the safety, tolerability, and immune response in adults with peanut allergies.

Biologics

In addition to omalizumab, which has shown promise as adjunctive therapy for FA, ANB020 (AnaptysBio, San Diego, California), an anti–IL-33 antibody, is being evaluated in an advanced phase 2 placebo-controlled clinical trial that is designed to determine safety, tolerability, and activity in adult patients with peanut allergy (clinicaltrials.gov identifier NCT02920021). IL-33 is a proinflammatory cytokine that acts upstream of IgE and mediates B-class switching to IgE. Results of a phase 1 study (in healthy volunteers) indicate that ANB020 is well tolerated in healthy volunteers and that a single dose is sufficient to suppress IL-33 function for approximately 3 months after dosing.[59]

Other biologics that target key molecules known to be involved in FA have been developed. A few of these drugs have been approved for the treatment of other allergic diseases or asthma. Anti–IL-5 (mepolizumab and reslizumab) and anti–IL-5R (benralizumab) antibodies have been approved by the FDA for the treatment of asthma.[60] Dupilumab is an antibody directed against the IL-4Rα subunit of IL-4 and IL-13 receptors. It blocks the signaling pathways of IL-4 and IL-13, key cytokines that drive the type 2 inflammatory response. It has been approved for the treatment of moderate-to-severe atopic dermatitis.[61] Other biologics are being tested in clinical trials for various allergic diseases and asthma. QAX576, an anti–IL-13 antibody, was found to be safe and efficacious for eosinophilic esophagitis in a preliminary study of 23 patients.[62] Tezepelumab (AMG 157/MEDI-9929), an anti–thymic stromal lymphopoietin antibody, has been shown to lower rates of clinically significant asthma exacerbations.[63] Results obtained from clinical studies of MEDI-528, an anti–IL-9 antibody, has shown variable results, likely because of the heterogeneous nature of asthma in the populations studied.[64]

Conclusion

Current immunotherapy studies are very encouraging and the lengthy treatment period and relatively high rates of adverse reactions are being addressed through the use of adjunctive therapy, such as anti-IgE antibodies, Chinese herbal therapy, and probiotics. With our increased understanding of the molecular mechanisms

involved in FA and other atopic and immune diseases, we have made tremendous progress in the identification and development of other biologics. In addition to anti–IL-33, which is currently being evaluated for FA, other biologics that alter immune response have been developed and are in varying stages of preclinical and clinical development or have been approved for specific diseases. There is a common mechanism underlying atopic diseases and asthma and an understanding of the mechanisms underlying 1 disease can assist with our understanding and treatments of other immune diseases. For example, omalizumab was initially approved for asthma and subsequently approved for chronic idiopathic urticaria. It also has been shown to be effective for the treatment of FAs. Research into the identification of biomarkers for diagnosis and prognosis is ongoing and soon might assist with the identification of those best positioned to benefit from immunotherapy. The future looks promising. In the past decade, there has been tremendous progress in our understanding of the mechanism underlying FA and an approved treatment is likely within the next few years.

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