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Food Allergy: Our Evolving Understanding of Its Pathogenesis, Prevention, and Treatment

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Abstract Food allergy is defined as an IgE-mediated hypersensitivity response to ingested food with allergic symptoms ranging from urticaria to life-threatening anaphylaxis. Food allergy is thought to develop because of (1) failed induction of tolerance upon initial exposure to food antigen or (2) breakdown of established tolerance to food antigen. We review current understanding of the pathogenesis, epidemiology, and natural history of food allergy, including the unconventional IgE-mediated food allergy to mammalian meat known as alpha-gal food allergy. We highlight emerging data on food allergy treatment and prevention, emphasizing the growing appeal of manipulating the gut microenvironment using probiotics and helminth products to blunt systemic allergic responses to food.

Keywords Food allergy · Probiotics · Helminth · Peanut allergy · Microbiota · Alpha-gal

Food allergy is defined as an IgE-mediated hypersensitivity response to ingested food with allergic symptoms ranging from urticaria to life-threatening anaphylaxis. IgE-mediated hypersensitivity reactions to food are typically acute in onset, developing less than 2 h after the ingestion and usually within minutes. Symptoms can involve any organ system, but commonly involve cutaneous, oropharyngeal, gastrointestinal, and respiratory systems [1]. The symptoms that result from food allergies can negatively impact the lives of patients and their families with physical, social, and financial consequences that diminish quality of life [2, 3]. Not surprisingly, there is great interest in treating food allergy and preventing it, particularly in high-risk, genetically susceptible individuals. We review current understanding of the pathogenesis, epidemiology and natural history of food allergy. We highlight emerging data on food allergy treatment and prevention, emphasizing the growing appeal of manipulating the gut microenvironment to blunt systemic allergic responses to food.

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Pathogenesis of Food Allergy

Food allergy is thought to develop because of (1) failed induction of tolerance upon initial exposure to food antigen or (2) breakdown of established tolerance to food antigen. Ordinarily, different components of the intestinal immune system integrate signals from intestinal luminal antigens derived from food and resident gut flora and communicate with the systemic immune system to generate tolerance to dietary antigens (Fig. 1) [4]. Food-allergic patients may have a defect in one or multiple components of the intestinal immune system, including the intestinal epithelial barrier, phagocytic innate immune cells, tolerogenic antigen presenting cells (APCs) and regulatory cells of the adaptive immune system. They develop a CD4+ T helper 2 (Th2) skewed immune response to orally delivered food antigens, triggering production of cytokines IL-4, IL-5, and IL-13. This prompts B cell activation and class switching, generating food antigen-specific IgE. Secreted IgE binds the surface of basophils and tissue resident mast cells. When the host is re-exposed to food antigen, it binds food-specific IgE attached

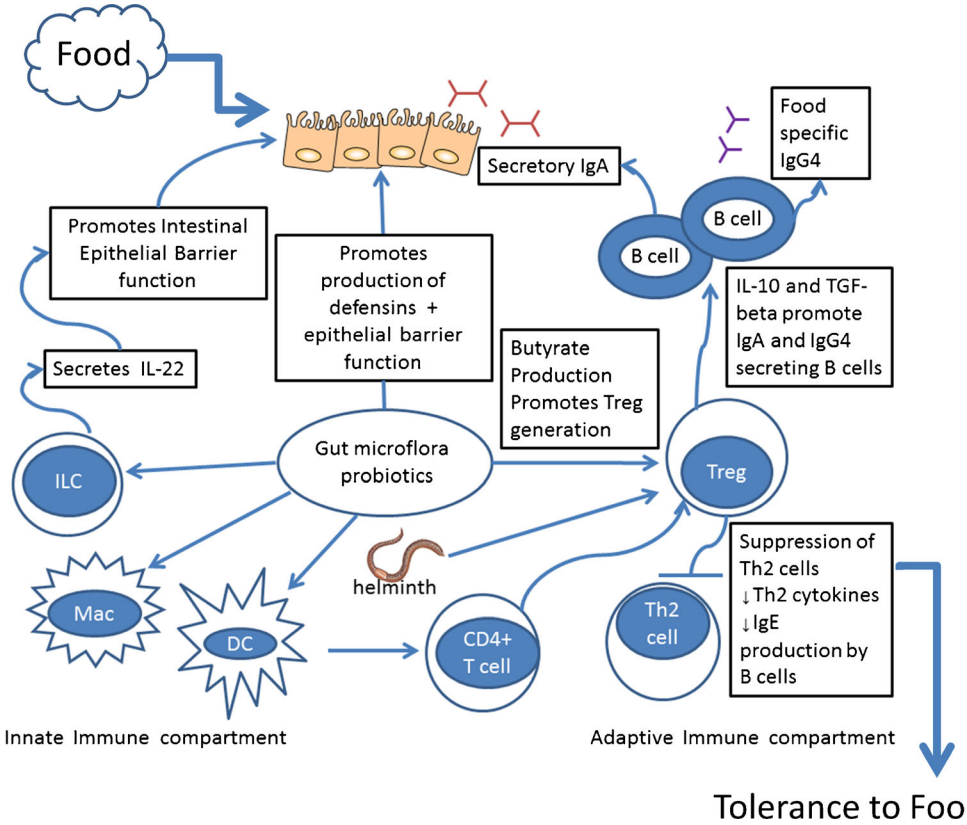

Fig. 1 Commensal gut microflora unite innate and adaptive immune compartments to help generate an immune mileu favoring development of tolerance to orally delivered food antigens. Gut microflora interact with macrophages (Mac), dendritic cells (DC) and innate lymphoid cells (ILC) stimulating production of IL-22 that promotes intestinal epithelial barrier function. Direct crosstalk between gut microflora and intestinal epithelial cells triggers production of defensins which also shore up the epithelial barrier. Tolerogenic DC that take up both gut microflora and food antigen interact with naïve CD4+ T cells from the adaptive immune compartment favoring regulatory T cell (Treg) development. Treg development is also supported by butyrate generated from the breakdown of ingested carbohydrates by commensal flora. Tregs and other tolerogenic cells secrete regulatory cytokines like IL-10 and TGF-beta that favor B cell production and secretion of mucosal IgA further fortifying the intestinal epithelial barrier. Tregs suppress formation of food antigen-specific Th2 effector cells (Th2 cell) decreasing Th2 cytokine production. This prevents food antigen-specific IgE production and promotes food antigen-specific IgG4 production leading to tolerance to food antigen. Probiotics may function like endogenous gut microflora to promote tolerance to dietary antigen. Helminth products may further stimulate production of Tregs and other regulatory cells and cytokines to promote tolerance to foods

to FcEpsilon receptors on mast cell and basophil cell surfaces. Crosslinking these receptors triggers degranulation of these innate immune cells, releasing mediators like histamine that generate the symptoms characteristic of immediate allergic reactions [5].

Epidemiology

The most common allergenic foods in the USA are milk, eggs, peanuts, tree nuts, soy, wheat, fish, and shellfish [6•]. Estimating the prevalence of food allergy is challenging because the gold standard for confirming the diagnosis of food allergy is the double-blind, placebo-controlled food challenge (DBPCFC), a time-consuming and expensive process that can trigger adverse reactions [1]. Thus, most food allergy prevalence estimates rely on self-report and vary in food allergy definitions and study methodology [7]. The prevalence of food allergy in children in the USA based on self-report ranges from 2–10 % [7]. One internet-based study estimated 8 % of children have food allergy with just under one third of these having multiple food allergies [8]. An NHANES study showed a prevalence of 6.53 % from 2007–2010 [6]. Prevalence of self-reported food allergy is similar in other industrialized regions including Canada (6.6 % adults, 7.1 % children) [9] and Europe (5.9 % from 2000–2012) [10].

One study tracking change in prevalence of self-reported food allergy in US adults using the U.S. Food and Drug Administration (FDA) Food Safety Survey found that self-reported food allergy prevalence increased 1.5-fold from 9.1 % in 2001 to 13 % in 2010. In this same study, physician-diagnosed food allergy in adults was 5.3 % in 2001 and only 6.5 % by 2010 [11]. A meta-analysis suggests that the prevalence of self-reported food allergy in the US increased 1.2 % points per decade from 1988–2011 [12]. These findings suggest, but do not confirm, the increasing

prevalence of food allergy. Reasons for this are not fully understood, although a popular hypothesis pinpoints alterations in gut microflora as a possible contributor (see below, The Gut Microbiome in Food Allergy).

Natural History of Food Allergy

Roughly 70–80 % of children allergic to egg, milk, wheat, and soy will outgrow these allergies by adolescence [13–18]. Approximately 50 % of children outgrow egg and cow's milk allergy (CMA) by age 6 [19, 20]. In contrast, about 20 % of children with peanut allergy and 10 % with tree nut allergy outgrow these allergies [21, 22]. Recent studies examining the natural history of peanut allergy continue to support this. Arshad et al. observed natural resolution of peanut allergy in 17 % of subjects ages 4 to 10 and 25 % ages 10 to 18 in a birth cohort observed through age 18 [23]. A longitudinal study of children diagnosed with peanut allergy at 1 year of age showed that peanut allergy resolved by age 4 in 22 % of children [24•]. Taken together, these studies show that the majority of peanut-allergic patients remain peanut-allergic through adulthood, providing impetus for research into prevention and treatments for peanut allergy in particular.

Alpha-gal Mammalian Meat Allergy

There is increasing awareness of an unusual IgE-mediated food allergy to mammalian meat known as alpha-gal food allergy. First described in 2009 [25••], alpha-gal food allergy challenges the current paradigm for food allergy. In contrast to conventional food allergies which require IgE antibodies specific to a food protein, alpha-gal allergy is associated with the presence of IgE antibodies against a sugar moiety galactose-alpha-1,3-galactose (also known as "alpha-gal") that lines the surface of non-primate mammalian tissue. Antibodies directed against alpha-gal moieties have a well-established role in acute organ rejection [26]. Preexisting alpha-gal specific IgE antibodies have been implicated in anaphylactic reactions to cetuximab, a chimeric mouse-human IgG1 monoclonal antibody that has the oligosaccharide galactose-alpha-1,3-galactose on the Fab portion of the cetuximab heavy chain [27].

Reactions to alpha-gal are intermittent and may not occur with every allergen exposure. Variability in adverse reactions to alpha-gal depends on how much allergen is ingested which may depend on fat content of the cut of mammalian meat consumed. Additional factors include how much alpha-gal is digested, processed, packaged and presented to the immune system and the underlying state of the immune system at the time—i.e., whether the immune system is activated in the setting of acute or chronic infection, autoimmune disease, malignancy, etc. Unlike other IgE-mediated food allergies, IgE-mediated allergic reactions to alpha-gal in ingested mammalian meat are typically delayed in onset, frequently developing 3–6 h after ingestion, although alcohol and exercise may decrease time frame to reaction [26]. Commins et al. demonstrated this delayed onset of symptoms through open food challenges of patients with a history of severe cutaneous reactions 3 to 6 h after eating beef, pork, or lamb and positive alpha-gal specific serum IgE. By sampling blood hourly during each oral food challenge to check for basophil expression of the activation marker CD63 following in vitro allergen re-stimulation, they showed that basophil activation correlated with the appearance of clinical symptoms [28]. Their findings suggest that, like protein allergen in conventional food allergy, alpha-gal can crosslink alpha-gal-specific IgE bound to basophil FcEpsilon receptors and activate basophils.

Immunomodulatory properties of ticks play an important role in the development of alpha-gal mammalian meat allergy. Several case reports describe patients who previously tolerated mammalian meat developing meat allergy after tick bites [29]. Commins et al. demonstrated that serum IgE antibodies to alpha-gal rise after tick bites from the lone star tick, *Amblyomma americanum* [30••]. Tick bites from *Ixodes ricinus* and *Ixodes holocyclus* have also been reported to generate alpha-gal specific IgE [31]. Reasons for this are not fully understood. Tick bites may drive proliferation of a plasmablast population that produces alpha-gal specific IgE antibodies and repeated tick bites could promote persistence of this population of antibody-producing cells (Commins, personal communication). Over 1000 cases of delayed urticarial or anaphylactic reactions to mammalian meat have been described in the USA, primarily in the southeastern states within the known geographic distribution of *Amblyomma americanum*, including Tennessee, Virginia, North Carolina, Arkansas, and southern Missouri [30••]. Cases described in Australia, Western Europe, Japan, and Korea also link tick bites with sensitization to alpha-gal and subsequent mammalian meat allergy [31]. Additional studies on the prevalence of alpha-gal specific serum IgE in the general population, the prevalence of alpha-gal mammalian meat allergy itself, and continued studies on the immunomodulatory role of tick bites in triggering this allergy will improve understanding of this intriguing food allergy.

Food Allergy Prevention

There is considerable interest in preventing the development of food allergies, and peanut allergy in particular, since approximately 80 % of peanut-allergic individuals remain peanut-allergic into adulthood. Twenty years ago, expert guidelines for infants with family histories of allergy suggested delaying the introduction of allergenic foods like eggs, peanuts, and tree nuts until ages 2–3 years [32]. However,

additional epidemiologic studies summarized in the American Academy of Pediatrics 2008 clinical report on the role for early nutritional interventions on development of atopic disease showed no strong evidence to support delayed introduction of any complementary solid foods, including commonly allergenic foods, beyond 4-6 months of age to prevent development of allergies to these foods [33••]. In addition, there is no strong evidence that breastfeeding exclusively beyond 4-6 months of age or diet alteration in breastfeeding mothers reduces the risk of allergic sensitization or prevents the development of food allergy in high-risk infants [2, 34•].

The ideal time to introduce commonly allergenic foods like milk, egg, or peanut into a child's diet is still unknown, but a retrospective study involving over 3000 infants suggested that introducing cooked egg into the infant's diet between 4–6 months of age was associated with a lower risk of egg allergy than introducing egg at 10–12 months or older [35]. Similarly, authors of a large scale prospective study involving over 13,000 infants found that infants with IgE-mediated CMA were more likely to have had supplemental cow's milk protein (CMP)-based formulas introduced between 3.5–6.5 months of age compared to non-allergic infants, who received supplemental CMP formula within the first 2 weeks of life. This suggests that early exposure to CMP as a supplement to breastfeeding may prevent development of CMA [36].

Studies also indicate that early peanut ingestion may protect against development of peanut allergy in high-risk children. A 2008 study found that prevalence of peanut allergy in Jewish primary schoolchildren in the UK was nearly tenfold higher than peanut allergy prevalence in a similar population in Israel, even after controlling for differences in atopy, socioeconomic status and genetic background. Israeli infants eat much larger quantities of peanut than British infants with a median monthly peanut consumption of 7.1 g of peanut protein in Israeli infants ages 8–14 months compared to 0 g of peanut protein in this age group in the UK [37]. These findings suggested that early introduction of peanut during infancy might prevent development of peanut allergy. This led to a randomized trial of early peanut consumption in individuals at risk for peanut allergy known as the Learning Early about Peanut Allergy (LEAP) study. The LEAP trial demonstrated that early peanut introduction can be successfully carried out in a population at high risk for developing peanut allergy. In this trial, 640 infants, ages 4 to 11 months, with preexisting egg allergy, severe eczema, or both and with skin prick test sizes to peanut of 4 mm or less were randomly assigned to consume or avoid peanuts until 60 months of age. There was an 11 to 25 % absolute reduction in risk of peanut allergy in this population when peanut was introduced by ages 4–11 months [38••]. Subjects assigned to consume peanut consumed peanuts at least three times weekly with at least 6 g of peanut protein incorporated into the diet each week. In a follow-up study, the LEAP-On study, the investigators explored the persistence of oral tolerance to peanut in subjects randomized to peanut consumption within the first year of life through age 60 months, by determining peanut allergy prevalence in this population at age 72 months, after a 12-month period of peanut avoidance. The prevalence of peanut allergy in this group stayed low, 3.6 % at 60 months in the primary LEAP trial and 4.8 % at 72 months in the follow-up LEAP-On study, in the intention-to-treat populations for both studies. Peanut allergy prevalence was four to fivefold lower in the peanut-consumption group compared to the peanut-avoidance group at the end of both the primary LEAP trial and the follow-up LEAP-On study [39•].

In the follow-up LEAP-On study, adherence to peanut avoidance still allowed for cumulative consumption of up to 18 g of peanut protein in a 12-month period, which might be expected with accidental exposure. While overall adherence to peanut-avoidance was high in the original peanut-avoidance group at 90.4 %, the adherence rate in the original peanut-consumption group was only 69.3 %. The follow-up study was still adequately powered to demonstrate its primary outcome. Moreover, despite variation in overall adherence to peanut-avoidance during the 12-month peanut-avoidance period in the original prolonged peanut-consumption group, the prevalence of peanut allergy remained low in this population, suggesting that subsequent intermittent low-dose consumption of peanut after prolonged consumption does not trigger new-onset peanut allergy [39•].

The striking findings from the LEAP and LEAP-On studies demonstrating benefit with early peanut introduction for the majority of study subjects at high-risk for peanut allergy encouraged experts from several different professional societies to recommend early peanut introduction in high-risk infants ages 4–11 months under an allergist's supervision [40]. Whether alternative doses of peanut besides the 6–9 g of peanut consumed per week in the LEAP study can induce tolerance to peanut remains unclear, as does the treatment duration time required to ensure sustained tolerance to peanut. It is also unknown if high-risk individuals have an increased risk of developing peanut allergy if peanut consumption is stopped before 60 months or with more sporadic peanut feeding. Moreover, recent consensus guidelines on early peanut introduction do not apply to children at low risk for peanut allergy. Development of more extensive guidelines on early introduction of peanut-containing foods into the diets of more general pediatric populations, not just "high-risk" as defined by the LEAP study, is ongoing [40].

The Gut Microbiome in Food Allergy

An estimated 10^{14} microbes inhabit the human intestinal lumen performing numerous functions critical for human health [41•]. Multiple experimental models indicate that maintaining

tolerance to these commensal gut flora helps establish and sustain host tolerance to food [4]. Some hypothesize that environmental, dietary, and medical practices of industrialized nations have altered the gut commensal microbiota leading to an upswing in food allergy prevalence. Industrialized populations are exposed to antibiotics through their extensive use in agriculture to promote livestock growth and through medically prescribed antibiotics [42]. Mouse models have shown that neonatal antibiotic treatment can alter gut microbial diversity in fecal and ileal samples [43, 44••, 45]. Stefka et al. demonstrated that the altered gut microenvironment enhances food allergen sensitization in a murine model of peanut allergy [44••]. Human studies looking at 16S ribosomal RNA profiling of the gut microbiome in pediatric populations have also found associations between altered gut microbial populations and prevalence of food allergen sensitization [46, 47]. Researchers have noted differences in gut microbiota of children with food allergy and their food allergy-free counterparts [48, 49]. Hua et al. used data on self-reported food and environmental allergies and fecal 16S ribosomal RNA sequence data from the American Gut Project to demonstrate that adult allergic participants in the study had fecal microbial communities significantly different than those in non-allergic participants. Subjects with nut and seasonal allergies had more *Bacteriodales* and a reduction in *Clostridiales* taxa [50], recently shown in animal models to be integral to intestinal barrier integrity [44••].

Probiotics, defined as ingested microbes that provide health benefits to the host, may play a role in preventing food allergy. Mouse studies have shown that germ-free mice, which lack normal commensal microbes, have significantly underdeveloped regulatory T cell compartments and humoral IgA compartments, immune components considered critical for establishing tolerance to dietary antigens [42]. Stefka and colleagues demonstrated that sensitization to peanut is enhanced in both germ-free mice and mice that have received antibiotics in the neonatal period dramatically altering their normal gut commensal flora. The researchers also established that microbiota from the *Clostridia* class had allergy-protective properties in this peanut allergy model. When microbes from this class were reintroduced to antibiotic-treated mice, they prevented sensitization to peanut. *Clostridia* colonization triggered production of the cytokine IL-22, known to modulate intestinal barrier permeability [51, 52]. These researchers showed that treating mice who received antibiotics as neonates with either oral *Clostridia* or exogenous parenteral IL-22 was sufficient to reduce serum concentrations of peanut allergens Ara h6 and Ara h2 [44••]. This study suggests that populating the gut with appropriate microflora may reinforce intestinal barrier epithelial function, possibly preventing the development of food allergy.

Human studies using probiotics to try to prevent or treat food allergy have shown variable results. Probiotics studied so far in clinical trials for allergy prevention and treatment include the early gut colonizers and facultative anaerobes *Lactobacillus* and *Streptococcus* and later gut colonizer and obligate anaerobe *Bifidobacterium* [41•]. Bernini Canini and colleagues in a prospective clinical trial showed that supplementing extensively hydrolyzed casein formula (EHCF, a formula typically given to children with CMA) with *Lactobacillus GG* (LGG) increased the rate at which infants with CMA were tolerized to CMP when compared to infants fed with EHCF alone. These infants were able to tolerate cow's milk for at least 6 months after a double-blind placebo-controlled food challenge confirmed initial tolerance to cow's milk [53]. Subsequent studies looking at the composition of fecal microbiota in LGG-supplemented EHCF-fed infants showed increases in the number of genera producing the short chain fatty acid butyrate, an energy source for colonocytes that has also been linked to maintaining regulatory T cell populations and epithelial barrier function [42, 49]. By contrast, in a double-blind placebo-controlled trial with 119 infants with CMA fed either extensively hydrolyzed formula (EHF) supplemented with *Lactobacillus casei* and *Bifidobacterium lactis* or EHF alone, CMA infants fed EHF plus probiotics acquired tolerance to CMP at the same rate as CMA infants given EHF alone [54]. Discrepancies in these studies' findings may be due to differences in probiotic strains used, dose administered, study population and study design.

In another study, children considered high-risk for developing atopic disease were fed standard infant formula or a nonhydrolyzed fermented infant formula containing heat-killed *Bifidobacterium breve C50* and *Streptococcus thermophilus 065*. Researchers found no statistically significant difference in the incidence of CMA between the two groups based on history and oral challenge even though infants fed the fermented formula with heat-killed probiotics were more likely to have negative skin prick tests to CMP [55]. Allen and colleagues also found reduced skin prick test sensitivity to CMP or hen's egg protein at age 6 months in children fed with *Lactobacillus* and *Bifidobacterium* daily from birth through 6 months born to women given the same probiotics daily from 36 weeks gestation to delivery when compared to mothers and infants fed with placebo [56]. These studies suggest that probiotics modulate development of allergic sensitization to foods as measured by allergy skin prick testing, but this does not automatically translate into food allergy prevention. Probiotic preparation, for example, live vs. heat-killed, may impact whether probiotic supplementation prevents food allergy.

Clearly, more studies are warranted to identify the appropriate probiotic strains, preparations, and doses to use to try to prevent or treat food allergy. Several studies, however, have shown no harm associated with probiotic supplementation

[57, 58]. Despite conflicting findings on the benefits of probiotics in allergic disease, emerging data in the field is promising enough for the World Allergy Organization to support the use of probiotics in (1) pregnant women at high risk for delivering an allergic child (2) breastfeeding mothers with infants at high risk for allergy, and (3) infants at high risk for developing allergy with the caveat that evidence backing these recommendation is of low quality [59].

Emerging Therapies to Treat Food Allergy: Probiotics and Helminth Products

There are no FDA-approved cures or disease-modifying therapies for food allergy. Management of food allergy involves counseling patients to strictly avoid culprit food allergens and carry antihistamines and an epinephrine autoinjector in case of accidental exposure [1, 5]. Given the considerable anxiety for patients and families surrounding food allergy and the challenge of strict avoidance, there is strong interest in long-term therapeutic solutions for food allergy. Currently, all therapies for food allergy are investigational.

By increasing the amounts of target allergen delivered to the host until a maintenance dose is reached, allergy immunotherapy seeks to reprogram the immune system, halting Th2-skewed immune responses to allergens. Mechanisms behind allergy immunotherapy are not completely understood but seem to involve generation of regulatory T cells that inhibit or modify allergen-specific responses by pathogenic B and T cells through secretion of IL-10, TGF-beta, and other regulatory cytokines and by promoting generation and release of allergen-specific IgG4 antibodies over IgE [60•].

For many patients and families, having access to therapies promoting desensitization would be satisfactory. Food-allergic individuals are desensitized when the amount of food required to generate an adverse allergic response is increased from baseline. Desensitization requires continuous administration of food allergy immunotherapy. Creating therapies that promote desensitization and ultimately generate tolerance (or sustained unresponsiveness to food) is the goal for many in food allergy immunotherapy development. Tolerance is achieved when an individual can eat the food without developing symptoms even after prolonged avoidance of the food [1, 5].

Emerging therapeutic techniques to treat food allergy including subcutaneous immunotherapy (SCIT), oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT), recombinant vaccines, immunobiologics, and herbal therapeutics have been reviewed extensively elsewhere [3, 5, 60•, 61, 62]. Here, we highlight possible roles for probiotics and helminths as food allergy OIT adjuvants since they impact both the gut microenvironment and the systemic immune system.

OIT involves ingesting gradually increasing doses of allergenic food and is the most effective experimental therapy available to induce desensitization to foods, including milk, egg, and peanut [63–66]. Whether OIT can induce sustained unresponsiveness is controversial. Published OIT trials do not follow patients long enough and/or do not have all the appropriate controls to distinguish between immunotherapy-induced sustained unresponsiveness and subjects naturally outgrowing their allergy during the treatment course [67]. Adverse reactions, though typically mild and limited to the oropharynx, occur in virtually all patients, contributing to poor OIT adherence [61, 62, 68]. Animal and human studies assessing the ability of probiotics to enhance OIT efficacy and safety are scant. In a mouse egg allergy model, treating egg-allergic mice with egg-specific OIT plus the probiotic *Clostridium butyricum* was more effective at alleviating intestinal allergic inflammation in egg-allergic mice than egg-specific immunotherapy alone or probiotic alone [69]. The one published human study exploring the efficacy of probiotic-supplemented OIT was done in peanut-allergic children. Subjects received either placebo or peanut OIT and *Lactobacillus Rhamnosus CMCC 1.3724* for 18 months. Nearly 90 % of subjects receiving peanut OIT and probiotics were desensitized to peanut as compared to only 7 % of subjects receiving placebo. 82 % of patients treated with peanut OIT and probiotics who then strictly avoided peanuts for 2–5 weeks after completing 18 months of therapy showed sustained unresponsiveness to peanut upon repeat oral challenge compared to only 3.6 % of patients on placebo [70•]. There was no peanut OIT-only arm in this study, so the relative contributions of probiotics vs. OIT in generating desensitization and sustained unresponsiveness to peanut are not clear. It is also unclear if the addition of probiotic-supplemented OIT decreased the number of adverse reactions or improved adherence to therapy compared to OIT alone. Additional studies exploring the ability of probiotics to improve safety and efficacy of OIT are needed.

Helminth infection, like probiotics, can alter gut microenvironment and systemic host immune responses. While acute helminth infection generates Th2-mediated immune responses, helminths also trigger host production of immunoregulatory lymphocytes and cytokines that assist in helminth immune evasion and promote chronic helminth infection [71]. Epidemiologic studies demonstrate that chronic helminth infection can protect against allergic disease [72]. Bashir et al. showed that mice infected with the helminth *Heligmosomoides polygyrus* were not sensitized to peanut in a mouse model of peanut allergy. Anaphylactic signs and peanut-specific IgE were significantly muted in helminth-infected mice while helminth-free mice developed anaphylaxis and elevated serum peanut-specific IgE.

The immunoregulatory effect of helminth infection depended on IL-10 [73]. Jouvin and Kinet performed a small study in six adults with peanut or tree nut allergy, feeding subjects ova from the pig helminth *Trichuris suis*. Subjects did experience mild spontaneously resolving gastrointestinal side effects and transient eosinophilia following eight oral doses of 2500 ova every other week. However, no subject dropped out or was removed from the study due to adverse events. This small study had no placebo control group and was not designed to assess whether *T. suis* ova treatment cured food allergy. One subject lost skin prick test reactivity to peanut following *T. suis* ova treatment, but the remaining five subjects had no change in skin prick test reactivity or allergen-specific IgE levels [74•]. No studies have explored OIT plus helminth products to treat food allergy. These studies would be intriguing because the immunoregulatory environment triggered by helminths might enhance inhibition of pathogenic allergen-specific immune responses. Future studies are needed to address possible therapeutic roles for helminths in treatment of food allergy.

Conclusion

Advances made in our understanding of the pathogenesis, epidemiology, and natural history of food allergy have fueled development of strategies to prevent and treat food allergy. From early introduction of commonly allergenic foods to the diets of children at high-risk for developing food allergy to modulating the gut microenvironment and systemic immune response with probiotics and helminth (Fig. 1), discovering new ways to prevent and treat food allergy will expand knowledge of the immunology behind maintaining tolerance to dietary antigens.

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Compliance with Ethical Standards

Conflict of Interest Dr. Iweala declares no conflicts of interest. Dr. Burks has the following disclosures: Advisory Board: Stallergenes; NIH AITC; Competing Relationships: Allergen Research Corporation - Grantee; National Institutes of Health - Grantee; FARE - Chair, Research Advisory Board; Hycor Biomedical - Grantee; Consultant: GLG Research; Adept Field Solutions; Genentech; First Manhattan Co; Insys Therapeutics; ActoGeniX; SRA International; Sanofi US Services; Valeant Pharmaceuticals North America LLC; Stocks: Alltertein; Mastcell Pharaceuticals.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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