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Food allergy: recent advances in pathophysiology and treatment

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Food allergies are adverse immune reactions to food proteins that affect up to 6% of children and 3-4% of adults. A wide range of symptoms can occur depending on whether IgE or non-IgE mediated mechanism are involved. Many factors influence the development of oral tolerance, including route of exposure, genetics, age of the host, and allergen factors. Advances have been made in the understanding of how these factors interact in the pathophysiology of food allergy. Currently, the mainstay of treatment for food allergies is avoidance and ready access to emergency medications. However, with the improved understanding of tolerance and advances in characterization of food allergens, several therapeutic strategies have been developed and are currently being investigated as potential treatments and/or cures for food allergy.

Key Words: food hypersensitivity; allergy; anaphylaxis; oral tolerance; immunotherapy

INTRODUCTION

Food allergies are adverse immune reactions to food proteins that can range from immediate, potentially life-threatening reactions to chronic disorders such as atopic dermatitis and allergic gastrointestinal disorders. While many studies have investigated the prevalence of food allergies, few population studies have used the gold standard double-blind, placebo-controlled food challenges (DBPCFC) to confirm the diagnosis of food allergy, which can lead to an overestimated prevalence. A meta-analysis focusing on milk, egg, peanut, and seafood allergy found the prevalence of food allergies to be approximately 3.5%.[1] The majority of the studies included in this meta-analysis used self-reports of food allergy, many utilized skin prick testing and food-specific IgE levels to confirm sensitization to the food allergens, and fewer employed DBPCFCs. The prevalence of food allergies has also been documented to have increased in the last 10-15 yrs, particularly in developed countries. Specifically, studies on peanut allergy in the US and UK indicate that the number of children affected has doubled, with the prevalence now over 1%.[2,3]

The most common food allergens causing reactions in children include milk, egg, wheat, soy, peanuts, tree nuts, fish and shellfish. While the majority of children outgrow their allergy to milk, egg, wheat and soy, allergies to peanut, tree nuts, fish and shellfish often persist into adulthood. The persistence of food allergy is variable, depending on the specific food allergen. Recent reports indicate that it is taking longer for children to outgrow their milk and egg allergy, with most developing tolerance in their teenage years rather that in early school-age as previously thought.[4,5] In contrast, only 20% of children with peanut allergy and 9% with tree nut allergy will develop tolerance.[6,7]

The key to management of food allergies consists of education about food allergen avoidance and the use of emergency medications (e.g., epinephrine) for the treatment of allergic reactions. Although this approach is generally effective, avoidance can be very difficult since many common food allergens are ubiquitous in the diet.[8] Therefore, patients and their families often experience a significant negative impact on their quality of life.[9] Furthermore, food allergic reactions are potentially life-threatening,[10-12] with peanuts and tree nuts accounting for 80% of food-induced fatal anaphylaxis cases. Severe reactions can occur both inside and outside of the home, and victims are often not aware that the products they were eating contained the food allergens.

This review will focus on the immunopathophysiology of food allergy and discusses therapeutic strategies currently being in-

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vestigated with the aim of long-term treatment and possible cure of food allergy.

TYPES OF FOOD ALLERGY

Immune reactions to foods can be IgE-mediated, cell-mediated or result from a combination of IgE and non-IgE mechanisms (Table 1). IgE-mediated reactions occur within 2 hrs of exposure. Binding of food allergens by specific IgE on effector cells, such as basophils and mast cells, leads to mediator release (i.e. histamine, tryptase, cysteinyl leukotrienes, prostaglandin D_2) causing a variety of symptoms that typically affect the cutaneous, respiratory, gastrointestinal and/or cardiovascular systems. Serum IgE and prick skin testing measure allergen-specific IgE, and these provide an indication of the likelihood of allergic reaction with exposure to the food allergen, however the type of reactions that occur are unpredictable in severity. Predictive values for serum food-specific IgE levels and prick skin testing have been published for the major food allergens, and levels above the 95% positive predictive value are highly indicative of clinical reactivity.[13-17] It has also been shown that the rate of decline in food specific IgE levels over time has predictive value for the development of tolerance.[18]

Cell-mediated reactions to foods include food protein-induced enterocolitis syndrome (FPIES) and proctocolitis. FPIES is characterized by repetitive vomiting and diarrhea at least 2 hrs after ingestion of the food trigger, with common ones including milk, soy and grains. Dehydration often occurs, with hypotension and metabolic acidosis ensuing in severe cases.[19] The immediate treatment for symptoms includes intravenous fluid hydration. As in other food allergies, food avoidance is important. Periodic re-evaluation with physician-supervised oral food challenges are advised to determine whether the allergy has been outgrown. Food protein-induced proctocolitis is commonly triggered by cow's milk and soy, and symptoms can be triggered by exposure through maternal breast milk. Infants are generally brought to medical attention for evaluation of blood streaked stools. These infants are otherwise well in terms of growth and do not generally suffer adverse effects from blood loss, such as anemia. Symptoms resolve with maternal and infant avoidance of milk, and the majority of children outgrow this allergy by 1 yr of age.[20]

Atopic dermatitis and eosinophilic gastroenteropathies are triggered by a combination of IgE and cell-mediated processes. Approximately 35% of children with moderate-severe atopic dermatitis have food allergies as a trigger.[21] Removal of culprit foods results in significant improvement in skin symptoms for these children. In an international multicenter study of children with atopic dermatitis, a close association between early-onset, moderate-to-severe eczema and egg sensitization was found.[22] Children who developed atopic dermatitis after 12 months of age were less likely to have concurrent food allergies.

Table 1. Types of food allergy

Disorder	Mechanism	Clinical features	Immunopathology	Common food triggers
Urticaria/angioedema, anaphylaxis	IgE	Cutaneous, gastrointestinal, respiratory symptoms	Cross-linking of IgE results in release of mediators	Major allergens - Milk, egg, wheat, soy, peanut, tree nuts, fish and shellfish
Oral Allergy syndrome	IgE	Mild oropharyngeal symptoms primarily (pruritus, angioedema)	Primary sensitization to pollen proteins which are homologous to food proteins in certain fruits/ vegetables	Raw fruits and vegetables
Food-dependent, exercise-induced anaphylaxis	IgE	Food triggers anaphylaxis only if ingestion is followed by exercise	Enhanced mast cell releasability and altered intestinal permeability when food ingestion is followed by exercise	Wheat, shellfish and celery are the most commonly reported triggers
Atopic dermatitis	Mixed IgE/ non-IgE	Chronic inflammatory skin disease, pruritic	IgE-mediated activation of cutaneous mast cells; late phase infiltration of inflammatory cells, including eosinophils and T cells	Egg, wheat, milk, soy, and others
Eosinophilic gastroenteropathies	Mixed IgE/ non-IgE	Dysphagia, poor growth, abdominal complaints (nausea, vomiting)	Eosinophilic infiltration of the gastrointestinal tract, mediators of eosinophils play a role (i.e. IL-5, eotaxin)	Multiple foods
Food-protein induced enterocolitis	Non-IgE	Delayed emesis, diarrhea 2 hours following ingestion, severe cases – hypotension in 15%	Increased TNFα, decreased TGFβ	Milk, soy, grains
Food-protein induced proctocolitis	Non-IgE	Blood-streaked stools in infants	Eosinophilic infiltration in the colon	Milk and soy, can occur via breastmilk

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Allergic eosinophilic esophagitis (AEE) and allergic eosinophilic gastroenteritis (AEG) are inflammatory disorders characterized by high numbers of intraepithelial eosinophils in the gastrointestinal tract.[23-25] Although the etiology is still unclear, many patients have IgE-mediated food and aeroallergen sensitization. In a series of over 500 people with AEE, the main food triggers were milk, egg, wheat, corn, beef, chicken, barley, oats, rice, and peanuts.[26] Although the majority of patients responded to elemental diets, only 11 patients experienced resolution of their AEE and eventually resumed an unrestricted diet without medications. Since this is a mixed IgE and cell-mediated process, prick skin testing and serum specific IgE levels may not identify all the allergic triggers. Atopy patch testing has been investigated as an additional diagnostic tool to identify foods that cause delayed symptoms.

MECHANISM OF FOOD ALLERGY

Normally, there is a delicate balance of the gastrointestinal mucosal immune system distinguishing between potentially harmful pathogens, beneficial commensal bacteria, and harmless food allergens which do not induce active immune responses. The mechanisms by which ingested proteins are able to interact with unique populations of antigen presenting cells leading to suppression of cellular and humoral immune responses has been termed oral tolerance. This has been demonstrated in a murine model in which subcutaneous antigen exposure resulted in cell-mediated and humoral responses to the antigen *in vitro*, but mice that were first orally exposed to the antigen then immunized subcutaneously had decreased immune responses *in vitro*.[27] Transfer of T cells from the orally fed mice to naïve mice resulted in decreased immune responses as well. Different mechanisms of tolerance can occur depending on the dose of allergen exposure. Studies suggest that "high dose" tolerance is due to deletion of effector T cells, whereas "low dose" tolerance involves activation of regulatory T cells.[28]

Loss of oral tolerance can occur or may be bypassed by antigen presentation via alternative routes, such as through cutaneous exposures or via the respiratory tract. Using a murine model, epicutaneous or epidermal exposure to peanut was demonstrated to induce Th2 immune responses and promoted allergic sensitization.[29] In addition, higher rates of peanut allergy have been found in children with atopic dermatitis who used topical creams containing peanut oil (OR 6.8).[30] Respiratory exposures are seen in pollen-food syndrome (PFS), an IgE-mediated allergy that is due to cross-reacting proteins in pollens (the initial sensitizing allergen) and foods, which results in oropharyngeal symptoms to raw fruits and vegetables.[31]

Breakdown of oral tolerance can also occur as a result of defective regulatory T cells. The disorder of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is due to a mutation in the FOXP3 gene, a transcription factor on CD4+CD25+ regulatory T cells that has been implicated in blocking Th1 and Th2 responses. Atopic dermatitis and food allergies are known manifestations of this disorder.[32] The importance of T regulatory cells in tolerance was also demonstrated in a study of non-IgE milk allergy. The development of tolerance to milk was associated with higher numbers of circulating CD4+CD25+ regulatory T cells.[33]

Host factors

Several host factors can influence the development of food allergies. Different mouse strains are not equally susceptible to food allergies,[34,35] suggesting that genetic predisposition is important. Furthermore, the age of exposure to food allergens can determine whether tolerance or allergy develops. In a murine model, sensitization occurred when mice were orally fed ovalbumin in the first week of life, however, tolerance was induced when the mice were orally exposed to ovalbumin at 2-3 weeks of age.[36] In humans, epidemiologic studies show a higher rate of food allergies in young children as compared to adults,[1] suggesting that gut maturity may be a factor in the development of food allergies. On the other hand, population studies suggest that early introduction may be beneficial in some cases. In Israel, where infants are fed peanut proteins starting at an early age, there is a lower incidence of peanut allergy as compared to the UK where peanut is not introduced to children until a much later age.[37] The Learning Early About Peanut Allergies (LEAP) study is currently exploring the role of timing of peanut allergen exposure in the development of peanut allergy.

Several studies suggest that disruption of normal gut barrier functions, such as gastric pH and commensal bacteria, can increase the risk of food allergies. Gastric digestion normally serves to breakdown food proteins, and in many cases destroys immunogenic epitopes in the process. The role of gastric acidity was investigated by Untersmayr et al.[38] using a murine model. Mice fed caviar extract in combination with antacids had elevated specific IgE and demonstrated immediate skin reactivity to the protein after immunization. However, mice which were not fed antacids did not demonstrate these immunologic responses, suggesting that use of antacid medications increased the risk of food allergen sensitization. In a human study of 152 patients on antacid treatment for dyspepsia, increased food allergen sensitization was seen in 25% after 3 months.[39] Gastric enzymes can affect allergenicity of food proteins. Specifically, the allergenicity of ovomucoid has been demonstrated to be reduced after gastric digestion.[40] Additionally, commensal bacterial serve an important role. Mice raised in a germ-free environment do not develop normal tolerance,[41] and mice treated with antibiotics or those lacking in toll like receptor 4 (TLR4) are more easily sensitized to peanut than wild-type control mice.[42]

Additional host factors can modulate the clinical response of food allergy. For example, asthma has been shown to be a risk factor for more severe anaphylaxis. In a study of fatal food aller-

gic reactions, the majority of victims had underlying asthma.[11] Host factors such as exercise, use of medication (alcohol, aspirin, beta-blockers, angiotensin converting enzyme inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants), and concurrent infection may increase the severity of anaphylactic reactions or diminish the efficacy of epinephrine.[43,44] Recently, low serum platelet-activating factor acetylhydrolase (PAF-AH) activity has been found to be a risk factor for more severe food-induced anaphylaxis.[45]

Food allergen factors

Food allergies can produce an array of clinical symptoms. The presence of specific IgE to sequential or conformational epitopes can distinguish between different phenotypes of milk and egg allergy. Several studies show that binding of conformational epitopes is associated with transient allergy to milk and egg whereas binding of sequential epitopes in these proteins is a marker for persistent allergy.[46,47] Recent studies demonstrate that the majority of milk and egg allergic individuals can tolerate extensively heated or baked forms of these foods,[15-18] indicating that these individuals identify conformational epitopes that are disrupted by heating. Furthermore, studies show that different patterns of epitope recognition or epitope diversity may correlate with clinical manifestations of allergic reactions to peanut and milk.[48-51]

Although heating appears to render many proteins less allergenic, heating does not have the same effect on all food proteins. Roasting peanuts involves very high temperatures, and this causes a Maillard reaction leading to increased stability and allergenicity of peanut allergens.[52] This finding may explain the differences in prevalence of peanut allergy in the U.S. where peanuts are primarily consumed in the roasted form and China where boiled or fried peanuts predominate.

Additional properties of peanut make it a highly allergenic protein. Glycosylated Ara h 1, a major peanut allergen, has been shown to act as a Th2 adjuvant by activating dendritic cells to drive Th2 cell maturation.[53] In contrast, deglycoslyated Ara h 1 did not activate dendritic cells. Recently, peanut proteins were shown to have the ability to induce production of complement (C3a) leading to increased platelet-activating factor and histamine production by macrophages, basophils, and mast cells.[54]

THERAPIES

Since no treatments are available to cure or provide long-term remission from food allergy, there is a strong need to develop effective therapies. Several strategies are currently being inves-

Table 2. Allergen-specific approaches for the treatment of food allergy

	Mechanism	Effects	Concerns	Research status
Subcutaneous immunotherapy (SCIT)	Gradual exposure to allergens to induce desensitization or tolerance	Proven therapy for respiratory and venom allergy, equivocal results for oral allergy syndrome	High risk of anaphylaxis in peanut allergy studies	No current studies
Oral immunotherapy (OIT)	Gradual exposure to allergens to induce desensitization or tolerance	Improved clinical tolerance; studies mainly for milk and egg; recent double-blind, placebo-controlled study for milk	Unclear whether the effects are desensitization or induction of tolerance; side effects are common	Clinical
Sublingual immunotherapy (SLIT)	Gradual exposure to allergens to induce desensitization or tolerance	Improved clinical tolerance; largest study for hazelnut allergy	Unclear whether the effects are desensitization or induction of tolerance; side effects are common	Clinical
Recombinant vaccines	Mutate IgE binding sites; proteins stimulate T cells to proliferate, but have greatly reduced IgE-binding capacity	Protection against peanut anaphylaxis in mice; study of Bet v 1 for OAS demonstrated improvement of symptoms	Improved safety profile compared with conventional IT, requires identification of IgE binding sites for each allergen	Preclinical and clinical
Peptide immunotherapy	Peptide fragments contain T cell epitopes, but are not of sufficient length to cross-link IgE and therefore, cannot trigger mast cell or basophil activation;	Protection against peanut anaphylaxis in mice	Improved safety profile compared with conventional IT, requires identification of T cell epitopes for each allergen	Preclinical
ISS-conjugated protein immunotherapy	ISS bound to proteins can act as adjuvants to promote switching to a Th1 response	Protection against peanut sensitization in mice	Concern for excessive Th1 stimulation, and potential for autoimmunity	Preclinical
Plasmid DNA immunotherapy	Allergen gene immunization to promote endogenous allergen production resulting in possible induction of tolerance	Less severe and delayed peanut-induced anaphylaxis in a murine model	Serious concerns regarding safety in view of strain-dependent effects in mice	Preclinical

tigated, both allergen-specific (Table 2) and allergen non-specific (Table 3). Allergen-specific approaches attempt to alter the allergic response to specific food allergens, whereas allergen non-specific treatments are aimed at modulating the overall allergic response. These non-specific approaches would be particularly beneficial for individuals suffering from multiple food allergies.

Allergen specific therapies

Allergen Immunotherapy

Immunotherapy entails gradual exposure to allergens in the hope of desensitization (temporary loss of responsiveness due to continuous exposure) and/or promoting tolerance (permanent immunologic nonresponse). Although widely used for respiratory allergies, the mechanisms of immunotherapy are not well understood, but is believed to involve initial desensitization of mast cells and basophils, changes in allergen-specific T cell responses and/or induction of regulatory T cells and late effects on effector cells, including eosinophils and B cells.[55] Food specific immunotherapy has been investigated as a potential treatment for food allergy.

Subcutaneous immunotherapy (SCIT) has been used since 1911, and is highly efficacious for allergic rhinitis, asthma and insect sting allergy.[56,57] However, early attempts at using SCIT for food allergies demonstrated unacceptably high rates of severe adverse reactions.[58,59] Since pollen-food syndrome (PFS) occurs due to cross-reactivity with pollens, SCIT would seem to be a logical treatment for PFS as well. Although results demonstrate clinical improvements in many patients, these studies lacked appropriate control groups and relied on self-reported symptoms.[60,61] Furthermore, with difficulties in objective evaluations for improvement in symptoms in PFS and lack of consensus for target doses, SCIT remains an unproven therapeutic approach for PFS.

Given the high rates of adverse reactions with SCIT, alternative routes of administering immunotherapy are being investigated to improve the risk-benefit ratio. There is an expanding body of literature that reports a high rate of efficacy with oral immunotherapy (OIT) (75-86%) with various food allergens.[62] The first double-blind, placebo-controlled OIT study for food allergy in children was performed by Skripak et al.[63] for milk allergy. Twelve patients completed 3-4 months of active treatment. Although no significant changes in specific IgE levels or skin prick test results were observed, there was a significant increase in milk-specific IgG and IgG_4 in the active group. More importantly, the majority of participants experienced reactions during the post-OIT food challenge, demonstrating that complete protection from allergic reactions due to milk was not achieved. Furthermore, all participants continued daily intake of dairy, therefore, it is unclear whether any OIT participants developed tolerance rather than desensitization to milk.

Additional studies have investigated the effects and safety of OIT in varying patient populations and using different dosing regimens. Longo et al.[64] reported on their experience with OIT in a highly milk allergic population. After 1 yr, 36% of the OIT group had unrestricted diets, and more than half (54%) were able to tolerate limited amounts of milk (ranging from 5-150 mL). Adverse reactions were common and occurred in all children on OIT. This study demonstrated that OIT can be effective even for those with the most severe allergies. The authors noted that although adverse events were common, in cases of persistent milk allergy and a high risk of accidental exposures and reactions, the risks of treatment may be acceptable. Staden et al.[65] reported a case series of 9 high-risk children who successfully underwent a rush oral immunotherapy protocol with milk, suggesting that desensitization can be achieved quickly. Adverse effects were frequent, but generally mild.

Recently, Jones et al.[66] reported an open-label peanut oral immunotherapy (OIT) study in which desensitization was successful in 93% of patients. The authors assessed several immu-

Table 3. Allergen non-specific approaches for the treatment of food allergy

	Mechanism	Effects	Concerns	Research status
Anti-IgE	Decreases circulating free IgE, inhibits the early and late phase allergic response, suppresses inflammation and provides improved control for allergic diseases	Provided an improved threshold against peanut-induced reactions in 80% of treated patients	May be useful in combination with immunotherapy	Clinical
Chinese herbal medicine	Inhibit Th2 immune response	Long-term protection from peanut anaphylaxis in a murine model. Also effective in murine model of multiple food allergies	Oral, generally safe and well tolerated; currently in Phase I trial	Clinical
Cytokine/anti-cytokine	Block pro-allergic cytokines	Clinical improvement in patients with eosinophilic esophagitis (IL-5)	Concerns for systemic side effects	Clinical
TLR-9	Induction of Th1-type immune responses	Protect from peanut anaphylaxis in a murine model	Concern for excessive Th1 stimulation, and potential for autoimmunity	Preclinical

nological parameters and presented several interesting results about possible mechanisms of OIT. Declines in skin prick tests and peanut-specific IgE levels and increases in peanut-specific IgG_4 were observed. A significant decrease in basophil activation was detected, as well as increases in several cytokines, including IL-10 and IL-5, which suggests that OIT does not cause the typical downregulation of Th2 and upregulation of Th1 profiles. In addition, T-cell microarrays demonstrated downregulation of apoptotic genes, indicating a potential role for apoptosis in OIT.

Sublingual immunotherapy (SLIT), which has been demonstrated to be a safe and effective treatment for allergic rhinitis and asthma, is another attractive option for the treatment of food allergy. Enrique et al.[67] published a randomized double-blind, placebo-controlled study investigating SLIT for hazelnut allergy. Twelve patients with hazelnut allergy (6 with PFS) were treated with SLIT for 5 months using the sublingual-discharge technique. Significant increases in threshold of sensitivity to hazelnut were observed following treatment. There was also an increase in hazelnut-specific IgG_4 and IL-10 after treatment in the active group. Local reactions occurred in 7.4% and systemic reactions were low (0.2%). A follow-up report of 7 patients from the active treatment group who resumed SLIT 4 months after discontinuation demonstrated tolerance of significantly increased doses of hazelnut, decreased specific IgE, and increased specific IgG_4, thus demonstrating the beneficial effect of SLIT even after treatment interruption.[68] A recent randomized, double-blind, placebo-controlled clinical trial of SLIT for peach allergy also reported promising results of improved allergen tolerance that was associated with decreases in skin test reactivity and significant increases in IgE and IgG_4 to Pru p 3.[69]

One multicenter study investigated the effects of birch pollen SLIT for PFS.[70] Twenty patients with pollen-associated apple allergy received 1 yr of SLIT. Although improvement in nasal provocation scores to birch pollen was seen in 9 patients, there was no significant improvement in their apple-induced oral symptoms. In addition, there was no change in specific IgE or IgG_4 to the major apple allergen, Mal d 1, after treatment. The authors concluded that SLIT with birch pollen may have no clinical effect on associated apple allergy.

Overall, immunotherapy appears to be a promising option for the treatment of food allergy, especially as safer routes of administration are being investigated. Additional randomized, placebo-controlled trials are necessary to determine the true efficacy and safety of this method and to standardize extracts, protocols and durations of treatment. Furthermore, studies are needed to clarify whether these clinical improvements are due to true induction of oral tolerance or desensitization and to gain insight into the mechanisms of these treatments.

Modified recombinant vaccines

Modified recombinant food proteins are engineered to decrease IgE binding capacity while retaining the protein's ability to stimulate T cell in order to decrease adverse effects of immunotherapy due to allergen activation of mast cells and basophils. Currently, recombinant peanut,[71,72] apple[73] and fish[74] allergens have been generated. Modified peanut allergens (Ara h 1, 2, 3), altered using site-directed mutagenesis, can stimulate T cells from peanut allergic individuals to proliferate, but have greatly reduced IgE-binding capacity as compared to wild-type peanut protein.[71,72] Heat-killed E. coli (HKE) producing recombinant peanut proteins have been shown to have protective effects in a murine model of peanut anaphylaxis.[75] Peanut-sensitized mice treated with HKE containing modified proteins Ara h 1-3 (HKE-MP123) demonstrated reduced symptom scores during peanut challenge as compared to the placebo-treated group. This protection lasted up to 10 weeks post-treatment in the medium and high dose treated groups. The high-dose treated group demonstrated the most significant decrease in IgE levels and decreased production of IL-4, IL-5, IL-13 and IL-10, and increased IFN-γ and TGF-β production by splenocytes. The mechanisms are hypothesized to involve Th1 cytokines and/or T regulatory cells suppressing Th2 cell activation and mast cell/basophil mediator release on re-exposure to antigen.[76,77] Clinical trials are planned.

SCIT with modified birch pollen allergens (Bet v 1 fragments, Bet v 1 trimer) has been shown to be moderately effective for patients with PFS.[78] Seven, out of 25 patients on active treatment, reported improvement in their oral symptoms as compared to only 1 of 19 placebo-treated patients.

Peptide immunotherapy

Use of peptide fragments that contain T cell epitopes that are not of sufficient length to cross-link IgE, is another potential strategy to decrease adverse effects of immunotherapy related to mast cell or basophil activation. A preliminary *in vitro* study using pepsin-digested peanut peptides showed induction of IFN-γ (Th1 cytokine) from peripheral blood mononuclear cells in a concentration-dependent manner.[79] In a murine model of peanut allergy, mice receiving immunotherapy with peptides containing IgE epitopes to the major peanut protein Ara h 2 prior to allergen challenge experienced only mild allergic reactions as compared to sham-treated mice, which exhibited severe anaphylactic reactions.[80] Although these preliminary murine studies are promising, validating the stability and uniformity of peptide mixtures for human use poses a significant challenge.

Immunostimulatory sequence-conjugated protein immunotherapy

Immunostimulatory sequences (ISS), such as CpG oligodeoxynucleotides, bound to proteins can act as adjuvants to promote switching to a Th1 response,[81] thus making the proteins less allergenic. Early studies using ragweed allergen showed

that immunotherapy with ISS in combination with Amb a 1, the major ragweed allergen, promoted Th1 responses and reduced allergenicity in mice, rabbit and primates.[82] The mice then underwent a sensitization protocol to beta-gal. Similarly, mice immunized with beta-galactosidase plus an ISS sequence oligodeoxynucleotide were protected from developing fatal anaphylaxis and had lower plasma histamine levels after allergen challenge compared to the group treated with beta-gal protein alone.[83]

A similar approach was investigated in a murine model of peanut-induced anaphylaxis.[84] Mice treated with ISS-linked Ara h 2 (a major peanut protein) had lower symptoms scores and lower plasma histamine levels following challenge with Ara h 2 compared to the mice treated with ISS-linked Amb a 1. A significantly higher Ara h 2-specific IgG2a levels in the ISS-linked Ara h 2 treated mice was seen, but there was no significant difference in specific-IgE or IgG_1 levels between the two groups. These findings suggest that ISS-conjugated protein immunotherapy may be an effective treatment for food allergy.

Plasmid DNA immunotherapy

Allergen gene immunization is another approach to immunomodulate the allergic response. DNA nanoparticles containing the gene for Ara h 2 was synthesized by complexing plasmid DNA with chitosan and then administered these nanoparticles orally to mice.[85] Immunized mice demonstrated less severe and delayed anaphylactic responses following challenge compared to mice treated with 'naked' DNA or unimmunized mice, and this was associated with decreased IgE levels, lower plasma histamine, and less vascular leakage. Despite promising results in the murine model, concerns regarding use in humans are a potential disadvantage of this technique.

Allergen non-specific therapies

Anti-IgE

Approved for the treatment of asthma with associated environmental allergies, recombinant monoclonal humanized anti-IgE treatment causes decreased circulating free IgE, inhibits the early and late phase allergic response, suppresses inflammation and provides improved control for allergic diseases.[86] A double-blind, randomized, dose-ranging trial in 84 patients with a history of peanut allergy was the first investigation of this for the management of food allergy.[87] Patients were randomized to receive either TNX-901 (150, 300, or 450 mg of anti-IgE antibodies) or placebo for 4 months. Patients receiving the highest dose experienced significant decreases in symptoms with peanut challenge as compared to the placebo group. The median threshold of sensitivity to peanut increased from 178 mg peanut protein (the equivalent to one peanut) to almost 9 peanuts (2.8 grams). Although 25% of patients were able to tolerate over 20 peanuts post-treatment, another 25% failed to develop any change in tolerance to peanut indicating that the treatment response can be variable. Investigation of another anti-IgE preparation, omalizumab (Xolair®, Genentech), for the treatment of peanut allergy was initiated, but discontinued for safety issues related to the protocol.[88]

Combination therapy of anti-IgE and allergen immunotherapy is being investigated as a method to decrease adverse reactions to immunotherapy in order to allow increased safety and efficacy.[89] No data is currently available regarding the effectiveness of this strategy.

Chinese herbal medicine

A 9-herb formula based on Traditional Chinese Medicine is currently under investigation as a treatment of food allergy. It is named the food allergy herbal formula (FAHF-2) and is effective in a murine model of peanut-induced anaphylaxis.[90] Peanut-allergic mice treated with FAHF-2 had no signs of anaphylaxis after peanut challenge, but all sham-treated mice had severe symptoms of anaphylaxis, decreased rectal temperatures, elevated plasma histamine, and marked vascular leakage. There were also associated decreases in peanut-specific IgE levels and Th2 cytokine production (IL-4, IL-5, IL-13). The protective effects of FAHF-2 were demonstrated to last up to 6 months post-therapy, which represents about 25% of the lifespan of the mouse.[91] Furthermore, these effects are not peanut-specific; treatment has been shown to modulate the allergic response in a murine model of multiple food allergies.[92]

Peliminary studies with purified human peripheral blood mononuclear cells from peanut-allergic individuals showed that cells stimulated with crude peanut extract in the presence of FAHF-2 had a decrease in antigen-dependent T-cell proliferation. A dose-dependent decrease in Th2 cytokine production (IL-5 and IL-13) and increase in IFN-γ production were also seen, indicating that FAHF-2 specifically inhibits the Th2 response.[93] Recently, the U.S. FDA approved a botanical drug IND for FAHF-2 and a Phase I trial is currently underway.

Cytokine/Anti-cytokine

Allergic diseases develop in part because of imbalances in T helper (Th) type 1 and type 2 cytokines. Strategies to block proallergic cytokines have been investigated as potential therapeutic approaches. Use for management of allergic asthma has been most widely investigated, however, applications in the field of food allergies are emerging.

Eosinophilic esophagitis (EE) is a inflammatory disorder characterized by high numbers of intraepithelial eosinophils in the esophagus.[23-25] Data from murine models of EE and analysis of human esophageal tissue demonstrate the presence of T cells and mast cells along with eosinophils, indicating that a Th2-based inflammatory process is a key feature of EE.[94,95] Since IL-5, a major Th2 cytokine, is a regulator of eosinophil function and survival, anti-IL-5 (mepolizumab) has been investigated as a treatment for EE.[96] Promising results were seen in an open-la-

bel phase I/II study of anti-IL-5 in 4 adults with EE. Decreases in peripheral and esophageal eosinophilia and symptomatic improvement were seen after 3 monthly infusions of anti-IL-5 (750 mg intravenously).

Recombinant IL-12 has also been investigated for the treatment of allergic disorders because IL-12 promotes the development of Th1 effector cells and inhibits Th2 class switching. Beneficial effects of reducing blood and sputum eosinophil numbers in asthmatic patients have been seen, however, significant systemic toxicities pose a significant barrier to use.[97] A less toxic route of intranasal administration of IL-12 using the nonpathogenic lactic acid bacteria (*Lactococcus lactis*) as a vehicle has been investigated in a murine model. Pretreatment of mice with *L. lactis* strains expressing bovine-lactoglobulin (BLG) with an IL-12-producing *L. lactis* protected sensitized mice against intranasal challenge with BLG antigen.[98]

Toll-like receptors

Since stimulation of toll-like receptor 9 (TLR9) can lead to strong mucosal and systemic Th1-type immune responses, the effects of a synthetic TLR9 agonist has been investigated in a murine model of food allergy.[99] After oral administration, decreased gastrointestinal inflammation and protection from peanut-induced anaphylaxis was observed during or after peanut sensitization. Decreases in IgE and increases in IgG2a levels were also detected. The authors postulated that these effects were due to TLR9 agonist induction of Th1-type immune responses.

Additional strategies currently being investigated for other allergic disorders

A novel human immunoglobulin Fc-Fc fusion protein, cross-linking the high-affinity FcRI and low-affinity FcRIIb on mast cells and basophils leading to inhibition of degranulation, has been developed.[100] The same group has also developed a human gamma-allergen fusion protein to achieve the same inhibition in an allergen-specific manner.[101] The Fc-Fel d 1 fusion protein inhibited Fel d 1-mediated degranulation in purified human basophils from cat allergic patients and blocked the allergic responses in a mouse model. Since many food allergens are already well-characterized, a similar approach can be taken for food allergy.

CONCLUSIONS

We are continuing to gain more insight into the immune mechanisms leading to the loss of oral tolerance and development of food allergies. A complex combination of host factors and food allergen properties interact to determine whether tolerance or allergy develops in a given individual. With increased knowledge of these various factors, potential treatments can be developed. Currently, a variety of promising therapeutic strategies are being investigated. These, either alone or in combination, will hopefully provide long-term treatment options and potentially a cure for food allergy.

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