

Vaccine Approaches for Food Allergy

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Abstract The prevalence of food allergy appears to be increasing. Hypersensitivity reactions to foods account for significant morbidity and mortality. The current standard of care for treatment of food allergies is limited to diligent dietary avoidance and prompt pharmacotherapy should an unexpected ingestion result in a reaction. Complex interactions between dietary antigens, the gastrointestinal flora, and the gut associated mucosal system drive host immune responses towards oral tolerance or hypersensitivity. Oral tolerance is achieved by regulatory T cell suppression of immune responses and by clonal anergy. Many novel therapies to treat food allergies are currently under investigation. Most utilize antigen-specific strategies in an attempt to induce oral tolerance. Oral immunotherapy (OIT) has been the focus of much attention. Early studies had established the safety and efficacy of OIT, but its ability to induce long-term tolerance versus a state of desensitization remains to be firmly established. Nevertheless, recent advances in our understanding of oral tolerance induction has increased optimism that disease-modifying therapies for food allergies will soon be the standard of care.

Abbreviations

OIT	Oral immunotherapy
IgE	Immunoglobulin E
APC	Antigen presenting cell
MHC	Major histocompatibility complex

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PBMC	Peripheral blood mononuclear cell
FOXP3	Forkhead box P3
IPEX	Immune dysregulation, polyendocrinopathy, enteropathy, X-linked
FAHF-2	Food allergy herbal formula 2

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1 Background

Food allergy is the result of complex immune-mediated responses to food proteins. Approximately 6% of children less than 3 years of age and 4% of adults suffer from food allergies (Sicherer and Sampson 2006). However, public perception of food allergy is much higher (Woods et al. 2002). The prevalence of food allergy appears to be on the rise. Evidence suggests that peanut allergy has risen sharply, approaching epidemic proportions (Sicherer and Sampson 2007). However, there is a paucity of well-designed prospective studies to accurately define the burden of food allergies worldwide. Future studies incorporating double-blinded placebo-controlled oral food challenges, the gold standard method for diagnosing food allergies, are needed to fill this void.

Food allergy can result from multiple deviations in immune responses to food antigens. The underlying immune mechanisms of food allergies can be classified into three general categories: immunoglobulin E (IgE)-mediated (i.e. anaphylaxis and urticaria), cell-mediated (i.e. protein enterocolitis), and a combination of IgE and cell-mediated mechanisms (i.e. atopic dermatitis and eosinophilic esophagitis). In IgE mediated food allergies, patients have a break in tolerance and make IgE to food antigens. Upon subsequent ingestions of the food, IgE binds to the food antigen and causes degranulation of mast cells which results in the symptoms of anaphylaxis. Interestingly, a small number of foods account for most food allergies (cow's milk, egg, soy, wheat, seafood, and nuts). However, any food is capable of inducing an abnormal immune response.

Although a small number of foods account for most food allergies, the distribution of these food allergies differ between children and adults. Adults are more likely to have allergies to peanut, tree nuts, and shellfish while children are more likely to have allergies to cow's milk, egg, soy, and wheat in addition to nuts and shellfish (Ando et al. 2007). Also in adults, food allergies are generally persistent and lifelong. However, in children, IgE-mediated allergy to cow's milk, egg, soy, and wheat are typically outgrown in childhood (Ando et al. 2007). It was previously thought that allergies to these foods were outgrown by the age of 5, but recent reports suggest that the time to outgrow these specific food allergies may be later at age with 79% outgrowing milk allergy by age 16 (Skripak et al. 2007; Savage et al. 2007). However, childhood allergies to peanuts, tree nuts and seafood tend to persist into adulthood (Sicherer and Sampson 2007).

2 Immune Responses to Food Antigens and Mechanisms of Oral Tolerance

The lumen of the gastrointestinal tract is the largest immunologic organ in the body (Chehade and Mayer 2005). Histologically, it is characterized by a layer of connective tissue containing lymphocytes covered by a mono-layer of epithelium which lines the lumen. A number of local and systemic immunological changes take place when antigens interact with host defense mechanisms in the gastrointestinal tract. The initial host defenses against ingested antigens are nonspecific and include digestion, mucus barriers and secretion of nonspecific antimicrobial peptides called defensins (Sicherer and Sampson 2008). As antigens that survive digestion, enter the lumen of the small intestine, they are sampled by the immune system via several mechanisms (Burks et al. 2008). Dendritic cells within the lamina propria can extend arms between epithelial cells into the lumen of the gastrointestinal tract and thereby bind enteral antigens. Particulate antigens from the lumen can be presented to dendritic cells within the lamina propria by M cells associated with Peyer's patches. T cells and macrophages in the lamina propria can sample soluble antigens via either transcellular or paracellular transport by epithelial cells. Epithelial cells that express MHC class II molecules (Scott et al. 1980; Mason et al. 1981) can also present dietary antigens to T cells.

By sampling enteral antigens in the intestine, the immune system, in the presence of other stimulatory signals, may induce an immune response to the antigen. Secondary adaptive systemic responses to ingested antigens are characterized by production of antigen specific serum and mucosal antibodies as well as generation of antigen specific T cells. Although the gastrointestinal tract is capable of making immune responses to foreign food proteins, with rare exceptions, most food proteins and commensal bacteria sampled by the immune system of the gastrointestinal tract do not stimulate immune responses. Rather, a state of immunological tolerance usually prevails.

Immunological tolerance or oral tolerance occurs when humoral or cellular immune responses to a dietary antigen are suppressed following prior oral exposure to the antigen (Chehade and Mayer 2005; Faria and Weiner 2005). The mechanisms involved in oral tolerance likely evolved over time in mammals to prevent hypersensitivity to the multitude of food and microbial antigens the immune system encounters in the gastrointestinal tract. Oral tolerance is achieved by regulatory T cell suppression of immune responses, by clonal anergy and by clonal deletion. Low dose antigen exposure leads to regulatory T cell suppression, while high dose antigen exposure leads to clonal anergy or clonal deletion (Friedman and Weiner 1994). All three mechanisms likely work simultaneously (Faria and Weiner 2005) to induce oral tolerance to food antigens. Food allergy occurs when tolerance to a food is either not achieved, or when it is disrupted.

Regulatory T cells orchestrate tolerance via important suppressive cytokines such as IL-4, IL-10 and TGF- β (Chehade and Mayer 2005); CD8⁺ suppressor T cells (Bland and Warren 1986); and CD4⁺ helper T cells (Chen et al. 1995; Barone et al. 1995; Garside et al. 1995). The cytokine profile associated with food allergy was nicely demonstrated by (Beyer et al. 2002). Duodenal mucosal lymphocytes of children with gastrointestinal illnesses related to milk were cultured with milk *in vitro*. Stimulation of these lymphocytes with milk protein resulted in the production of the T_H2 cytokines IL-5 and IL-13, while IL-10 and TGF- β expression was relatively low.

Regulatory T cells likely play an important role in the development of tolerance when a food allergy is outgrown. In a study of children with non IgE-mediated cow's milk allergy, those children who outgrew their allergy had higher levels of CD4⁺CD25⁺ T cells and reduced *in vitro* responses to bovine β -lactoglobulin in peripheral blood mononuclear cells (PBMCs) than children with persistent allergy. Interestingly, an increased *in vitro* response to β -lactoglobulin occurred in the PBMCs collected from children who outgrew the allergy following removal of CD25⁺ cells (Karlsson et al. 2004).

Because of the likely importance of regulatory T cells in establishing oral tolerance, poor regulatory T cell activity is probably a contributing factor to the development of food allergy. The transcription factor, forkhead box P3 (FOXP3), is expressed on CD4⁺CD25⁺ regulatory T cells (Khattari et al. 2003; Fontenot et al. 2003). FOXP3 is thought to block development of both T_H1 and T_H2 immune responses (Ostroukhova et al. 2004), and mutations in the gene encoding FOXP3 result in immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome (Bennett et al. 2001). Food allergy is associated with a variant of IPEX that is caused by a deletion in the noncoding region of FOXP3 that impairs mRNA splicing. This variant of IPEX I is also characterized by severe enteropathy and atopic dermatitis (Torgerson et al. 2007). Because of the involvement of mutations in FOXP3 in IPEX syndrome with food allergy, it seems possible that children with food allergies may have disruptions in T cell regulatory activity.

In addition to T regulatory cells, tolerance may also be mediated by clonal anergy or by clonal deletion. Anergy, or T cell nonresponsiveness, happens when T cell receptor ligation occurs in the absence of co-stimulation by either cytokines

such as IL-2, or by lack of CD28 interaction with CD80 and CD86 on APCs (Appleman and Boussiotis 2003). Reactive T cells may also undergo apoptosis through FAS–FAS ligand interactions leading to activation induced cell death (Chen et al. 1995). Clonal deletion, or apoptosis, seem to occur in the setting of ingestion of high doses of antigens while induction of regulatory T cells seem to occur in the setting of low doses of antigen ingestion.

Given our current understanding of the mechanisms of oral tolerance, the possibility of inducing oral tolerance in allergic patients seem feasible. In fact, induction of tolerance to prevent allergy is not a novel concept. In the early 1800s, it was reported that Native Americans consumed poison ivy leaves to reduce the risk of contact reactions to urushiol (Dakin 1829). In the early 1900s, it was reported (Wells 1911) that guinea pigs did not experience anaphylaxis with injection of hen's egg protein following ingestion of it on a regular basis. By the mid-1900s (Chase 1946) reports showed that giving an antigen orally can suppress immune responses by activating T cell responses. In these studies, mice that were immunized subcutaneously responded to subcutaneous boosting with the same antigen with robust *in vitro* humoral and cell-mediated immune responses. However, mice fed with the antigen and boosted subcutaneously, showed blunted *in vitro* responses. Furthermore, when T cells were transferred from mice fed orally with the antigen to naïve mice; decreased *in vitro* immune responses were observed with subcutaneous immunization. The success of these animal studies suggest that induction of oral tolerance in the allergic patient may be feasible.

3 Therapeutic Approaches

The treatment options for food allergy are relatively limited in scope despite the success of immunomodulatory therapies for other allergic disorders. Treatment of hayfever with immunotherapy has been a successful therapeutic approach for years (Noon and Cantab 1911; Freeman 1930) and strong evidence supports the use of venom immunotherapy for Hymenoptera sensitivity (Hunt et al. 1978; Golden et al. 1980).

The current standard of care for managing food allergies is diligent avoidance of the suspected allergic trigger and prompt pharmacotherapy if an allergic reaction occurs. Accidental ingestions of known food triggers are unfortunately common (Yu et al. 2006). Avoidance of specific foods can be arduous for many reasons including the ubiquitous nature of common food allergens and the risk of food cross-contamination. Food avoidance can result in dietary limitations and nutritional deficits, especially for children who must avoid multiple foods. There are many social implications to avoiding foods as well. As for treatment of reactions, administration of epinephrine has associated risks, and severe reactions might not respond to pharmacotherapy.

Because of the difficulty in following elimination diets and the danger of accidental ingestion and reactions to foods, vaccination for food allergies would be

an appropriate therapy for individuals unlikely to naturally develop tolerance. Evidence suggests it might be possible to identify individuals who are less likely to outgrow their food allergy. One group of investigators (Chatchatee et al. 2001) demonstrated this by looking at antibody binding sites on β -casein and κ -casein, two major cow's milk allergens, in milk allergic patients. The sera from a majority of older patients with cow's milk allergy recognized three of the nine IgE binding regions on β -casein and six of the eight IgE binding regions on κ -casein, while sera from younger patients failed to recognize these epitopes suggesting that persistent cow's milk allergy is associated with more antigen recognition. A subsequent study corroborated the use of epitope binding differences to predict persistence of cow's milk allergy (Beyer et al. 2005).

Recent interest in novel treatment approaches for food allergies has sparked a number of therapeutic-based studies (Table 1). Allergen-specific strategies manipulate the immune response to an allergenic food protein to induce a state of desensitization or immune tolerance. Examples include sublingual immunotherapy (SLIT), oral immunotherapy (OIT), immunotherapy with engineered proteins, peptide immunotherapy, plasmid DNA immunotherapy, and immunotherapy utilizing immune stimulatory sequences. The goal of these strategies is to allow consumption of a food without any deleterious effects. Allergen non-specific strategies target various immune mediators to dampen hypersensitivity responses to an allergenic food protein. Examples include Anti-IgE therapy, Chinese herbal medicine, and anti-cytokine treatments.

3.1 Allergen-Specific Strategies

3.1.1 Subcutaneous Immunotherapy

Subcutaneous allergen immunotherapy is associated with a variety of allergen-specific immune changes. Allergen-specific IgE initially rises, but later declines as allergen-specific IgG increases. Concomitantly, T_H2 driven immune responses change to a T_H1 phenotype. Subcutaneous peanut immunotherapy was studied (Nelson et al. 1997) in 12 patients of whom 6 were treated with peanut extract and 6 were treated with placebo. All of the treated patients, compared to patients who received placebo, were able to tolerate more peanut protein upon a subsequent double-blinded placebo-controlled peanut challenge. Peanut-specific IgG increased in the treatment group which is relevant, given that allergen specific IgG4 is postulated to act as a blocking antibody. IgG4 is known to increase during prolonged immunotherapy and may act to bind allergen, thereby inhibiting allergen binding to IgE which prevents allergic reactions. No immunological changes were observed in the placebo group. Despite demonstrable clinical efficacy, significant adverse effects were common and this method of immunotherapy for food allergies was therefore abandoned.

Table 1 Potential Therapeutic Strategies to Treat Food Allergies

Strategy	Mechanism	Benefits	Limitations	Status
<i>Allergen-Specific Strategies</i>				
Subcutaneous Immunotherapy	Present antigen at nonmucosal site	Efficacy well-established for venom and aeroallergen hypersensitivity	Significant side effects	Development not actively being pursued
Sublingual and Oral Immunotherapy	Present antigen at mucosal site	Safer than subcutaneous immunotherapy	Long-term tolerance induction uncertain	Multiple protocols under investigation
Immunotherapy with Engineered Food Proteins	Mutation of IgE binding sites prevent IgE activation but preserves T cell responses	Excellent safety profile	Difficult to engineer therapeutic proteins	Human studies planned
Peptide Immunotherapy	Peptides aren't large enough for IgE activation, but T cell responses are preserved	Safer than vaccination with entire allergen	Difficult to produce a validated vaccine	Murine studies only
Plasmid DNA Immunotherapy	Endogenous production of protein results in tolerance	Potential benefit with only one dose	Strainspecific variability in mice	Development not actively being pursued
Immunotherapy with Immune Stimulatory Sequences	Enhances Th1 responses	Increased efficacy and good side effect profile	Conjugation could alter allergen	Murine efficacy established
<i>Allergen Non-Specific Strategies</i>				
Anti-IgE Therapy	Prevents binding of IgE to high-affinity receptors	Could be efficacious for any food allergy	Variable responses in preliminary study	Studies on hold
Chinese Herbal Medicine	Unknown	Could be efficacious for any food allergy	Unknown	Human studies under way
Cytokine Therapies	Dampen hypersensitivity responses	Could be efficacious for any food allergy	Could alter natural immune responses that could be beneficial	Anti-IL-5 studies for eosinophilic esophagitis under way

3.1.2 Sublingual and Oral Immunotherapy

SLIT and OIT have undergone intense scrutiny recently. These strategies aim to first desensitize and then induce long-term tolerance in individuals with food allergies. Most studies utilize similar protocols in which patients are given very small amounts of antigen in a research setting with close observation for adverse effects. Patients then regularly consume the maximum tolerated amount of antigen on a regular basis at home. Clinical efficacy is often assessed with open or blinded food challenges, and serological studies are performed to assess immunological changes.

The efficacy of SLIT for treatment of hazelnut allergy was recently examined (Enrique et al. 2005). Twenty-three hazelnut allergic patients were randomized to either the active treatment group or placebo. Following treatment, efficacy was assessed by double-blinded placebo-controlled hazelnut challenges. The mean amount of tolerated hazelnut inducing symptoms increased from 2.29 to 11.56 g ($P = 0.02$) in the active group versus 3.49 to 4.14 g (not significant) in the placebo group. The active group, in contrast to the placebo group, was characterized by an increase in IgG₄ and IL-10 production.

Studies have (Patriarca et al. 2003) investigated OIT as an approach for treating an assortment of food allergies. Fifty-eight patients were treated with OIT, most with allergy to cow's milk (24), whole egg (13) or fish (10). Most patients (77%) were successfully desensitized, and when compared to control patients with food allergy, OIT patients were characterized by increased food-specific IgG₄ levels and decreased food-specific IgE levels. Other investigators (Meglio et al. 2004) treated 21 children with IgE-mediated cow's milk allergy with OIT. Desensitization was successful in 15 of the 21 children (71.4%). These children were able to consume 200 mL of cow's milk daily. Three of 21 (14.3%) were able to tolerate 40–80 mL of cow's milk daily. However, desensitization was not possible for 3 of the 21 children due to allergic symptoms with ingestion of small quantities of cow's milk. A more recent study (Buchanan et al. 2007) used a 24 month OIT protocol to treat 7 children with egg allergy. At the end of treatment, 4 of the 7 children passed a double-blinded placebo-controlled egg challenge of 10 g of powdered egg white. The remaining 3 children were partially desensitized. However, initial desensitization did not necessarily result in induction of tolerance. Of the 4 children who passed the initial challenge, only 2 passed a second challenge after 3 months off of egg OIT while consuming an egg-restricted diet.

Although these studies revealed encouraging preliminary results, they did not address the possibility of natural tolerance induction with increasing age. Another group of investigators (Rolinck-Werninghaus et al. 2005) reported results from an oral tolerance induction study involving 3 children with either cow's milk or egg allergy. After 37 to 52 week of therapy, patients tolerated either 250 mL of cow's milk or 4.5 g of egg protein. Per the protocol, 2 patients underwent a double-blinded placebo-controlled food challenge following a 2 month elimination diet. The third patient in this study discontinued maintenance daily dosing for only 2 days. All three patients developed moderate symptoms upon re-exposure to the causal food allergen, suggesting initial tolerance was not spontaneous.

A larger study of children with cow's milk or egg allergy utilized the same OIT protocol and an elimination diet control group (Staden et al. 2007). Upon follow-up food challenge, seven of 20 (35%) children in the control group demonstrated tolerance, compared to 16 of 25 (64%) of children showing some level of response in the active treatment group. Nine of 25 (36%) of children treated with OIT showed permanent tolerance, three of 25 (12%) were tolerant with regular ingestion, and 4 of 25 (16%) were considered partial responders. Allergen-specific IgE levels decreased significantly in both the active treatment and control groups. These results appear to validate the use of OIT as a more effective method to achieve oral tolerance than practicing avoidance.

In another study (Longo et al. 2008) 60 children with severe cow's milk allergy and high cow's milk-specific IgE were randomized to either specific oral tolerance induction (30) or a milk free diet (30). After 1 year, tolerance was assessed with either observed open feeding (tolerance induction group) or double-blinded placebo-controlled cow's milk challenges (milk free diet group). All children in the milk free diet group reacted upon re-exposure. Eleven of 30 (36%) of the children in the tolerance induction group became completely tolerant to cow's milk, 16 (54%) were partial responders tolerating 5–150 mL, and 3 (10%) could not complete the study because of persistent respiratory or abdominal symptoms. Specific IgE was significantly lower in half of the children in the treatment group at 6 and 12 months, but was essentially unchanged in the diet elimination group.

The validity of OIT studies has been strengthened by incorporating double-blinded protocols. A new report (Skripak et al. 2008) utilized a randomized, double blinded protocol to assess the effectiveness of OIT for cow's milk allergy. Nineteen children 6–17 years of age completed the study; 12 were randomized to treatment and 9 to placebo. The median baseline dose of cow's milk to induce symptoms was 40 mg for both groups. Upon double-blinded placebo-controlled challenges at the end of the protocol, the median dose to induce symptoms in the active group was 5,140 mg compared to 40 mg in the placebo group ($P = 0.003$). Milk-specific IgG levels increased significantly in the treatment group, but no significant changes in specific IgE levels were observed in either group.

Peanut allergy has been the focus of attention for immunotherapy due to prevalence acceleration, severity, and persistence. Investigators (Reese et al. 1999) recently reported results from an ongoing placebo-controlled peanut OIT study. Five patients received immunotherapy with peanut protein and five received placebo. Following the treatment phase, all children underwent an oral challenge with peanut flour. Upon challenge, the placebo patients tolerated a median cumulative dose of 460 mg (~ 1 peanut), but all patients in the active treatment group tolerated 5,000 mg (~ 13 peanuts) ($P = 0.008$). Mean peanut-specific IgE levels did not change significantly throughout the study period, but titrated skin tests were significantly improved in the treatment group compared to placebo.

These studies suggest OIT is safe and efficacious. However, important questions need to be answered prior to adopting OIT as standard therapy.

Larger studies incorporating randomized double-blinded protocols are needed to further assess dose and safety, in addition to the ability of OIT to induce long-term clinical tolerance. Nevertheless, this type of treatment strategy shows great promise, especially for those who are unlikely to become tolerant to a food spontaneously such as those with peanut allergy.

3.1.3 Immunotherapy with Engineered Food Proteins

Immunization with altered allergenic food proteins is a concept gaining interest. With this strategy, IgE-binding epitopes are engineered to attenuate IgE immune responses yet permit T cell stimulation. This approach has shown promise in a murine model of peanut allergy (Li et al. 2003). In this study, single amino acids were altered in the Ara h1, Ara h2, and Ara h3 binding epitopes of peanut proteins. These modified proteins were administered rectally with heat killed *E. coli* to C3H/HeJ peanut-sensitized mice. Following oral peanut challenge 10 weeks later, these mice were protected from anaphylaxis. The mice that received the largest dose showed significantly reduced production of IL-4, IL-13, IL-5, and IL-10. Production of IFN- γ and TGF- β was significantly increased. Efficacy and safety of these modified peanut proteins in humans remain to be elucidated.

3.1.4 Peptide Immunotherapy

Vaccination with a combination of small peptides that together extend across the entire native allergenic protein theoretically could preserve T cell activation while avoiding IgE-based immune responses. IgE recognizes conformational epitopes of larger peptides and proteins while T cell receptors recognize small linear peptides of 8 to 10 amino acids. By immunizing with small peptides, T cell activation could occur while IgE binding would be lost. One study utilizing this strategy in a murine model of peanut allergy suggested potential benefit (Li et al. 2001). However, production of a validated vaccine would be difficult due to the complexity of the stability and combination of multiple peptides in one vaccine (Sicherer and Sampson 2008).

3.1.5 Plasmid DNA Immunotherapy

Vaccination with allergen-encoding bacterial plasmid DNA is an interesting strategy. In theory, a protein endogenously produced by a host should result in tolerance. Although this type of treatment successfully prevented peanut allergy in AKR/J mice (Roy et al. 1999), strain-dependent variable responses have been observed (Li et al. 1999) in other studies. Consequently, variability of response in humans would be a valid concern.

3.1.6 Immunotherapy with Immune Stimulatory Sequences

Yet another vaccine strategy is to use immune stimulatory sequences (i.e. CpG) to enhance Th1 responses. A group of investigators (Kattan et al. 2003) orally sensitized C3H/HeJ mice with peanut and cholera toxin, followed by either treatment with intranasal CpG or no treatment. Upon subsequent peanut challenge, none of the CpG-treated mice experienced anaphylaxis. In contrast, 67% of the untreated mice showed signs of anaphylaxis. Treated mice, compared to untreated mice, had higher body temperatures, lower levels of peanut-specific IgE, higher levels of peanut-specific IgG2a, and lower levels of IL-5 in splenocyte supernatants. CpG has also been used as an adjuvant with ovalalbumin in SLIT studies in sensitized mice. Mice that received SLIT containing CpG had elevated mucosal IgA titers in the absence of elevated IgE titers, suggesting that the addition of CpG to immunotherapy may promote a Th1 response.

3.1.7 Diet-Specific Tolerance Promotion

Perhaps intervening to promote development of tolerance early in life can be an effective strategy. This idea is based on an observation that infants in Israel who regularly consume snacks with peanut protein have a lower rate of peanut allergy than Jewish infants in the United Kingdom who are not fed peanut containing snacks (Levy et al. 2003). The Learning Early About Peanut Allergy Study is investigating the possibility of early tolerance induction by enrolling 480 children between the ages of 4 and 10 months with eczema and/or egg allergy. This cohort of children has a 20% chance of developing peanut allergy based on previous studies of patients with eczema and/or other food allergies. The participants will be randomized to either avoid peanut protein until the age of 3 or to ingest about 6 g of peanut protein per week. The development of peanut allergy at 5 years will be compared (http://leapstudy.com/study_about.html, accessed 20 April 2009).

3.2 Allergen Non-Specific Strategies

3.2.1 Anti-IgE Therapy

Anti-IgE therapy for food allergy is a reasonable strategy to treat food allergies because IgE plays an essential role in food-induced anaphylaxis. One dosing study (Leung et al. 2003) used humanized monoclonal anti-IgE, TNX-901, for patients with immediate hypersensitivity to peanut using a double-blinded placebo-controlled protocol. Patients who received 450 mg of TNX-901 had significantly increased thresholds of reaction from 178 mg ($\sim \frac{1}{2}$ peanut) at baseline to 2.8 g (~ 9 peanuts) ($P < 0.001$) of peanut flour during oral challenge.

However, individual responses were inconsistent and not all patients would likely be protected from peanut induced anaphylaxis while on monoclonal IgE.

3.2.2 Chinese Herbal Medicine

Another treatment strategy for food allergy is the use of Chinese herbal medicine. Although the primary mechanism of action of Chinese herbal medicine is not clear, it is gaining acceptance as a legitimate treatment strategy for allergic disorders based on results of animal studies. In one particular study (Srivastava et al. 2005) the effects of food allergy herbal formula 2 (FAHF-2), a combination of specific Chinese herbs, on peanut allergic mice was investigated. Sensitized mice were treated for 7 weeks with either FAHF-2 or placebo and then challenged at weeks 1, 3, or 5 post therapy. All placebo treated mice exhibited signs of anaphylaxis and elevated plasma histamine levels following challenges. However, FAHF-2-treated mice showed no signs of anaphylaxis or significant changes in plasma histamine levels. Treated mice showed significantly lower serum peanut-specific IgE levels as long as 5 weeks post therapy. Splenocyte stimulation in vitro with peanut protein resulted in significantly lower levels of IL-4, IL-5, and IL-13 and higher levels of IFN- γ in treated mice. Although mechanistically this strategy is not well-defined, it clearly deserves further attention as a potential therapeutic approach in humans, given the promising results seen in murine studies.

3.2.3 Cytokine Therapies

Manipulation of cytokine levels might diminish hypersensitivity responses to foods. In one study of cytokine therapy, investigators (Frossard et al. 2007) transfected *Lactococcus lactis* to secrete murine IL-10. They then administered the IL-10 to young mice prior to oral sensitization with β -lactoglobulin. Administration of IL-10 resulted in significantly lessened anaphylaxis upon oral challenge, in addition to dampened serum antigen-specific IgE and IgG₁ production. Another study (Ando et al. 2007) targeted TGF- β in a murine model of food allergy. Mice that were orally fed TGF- β and ovalbumin had lower antigen-specific IgE and IgG1 antibodies, T cell reactivity, and immediate-type skin reactivity compared to mice fed only ovalbumin.

4 Conclusions

As our understanding of the mechanisms of food antigen processing, food hypersensitivity and the development of oral tolerance continue to grow, it is logical to explore new therapeutic approaches to treat and/or prevent food allergies. Recent studies using novel therapeutic approaches to treat food hypersensitivity have

shown promise. Further studies are needed to better understand the efficacy and safety of these treatment modalities. Vaccination strategies will require further investigation to determine whether long-term tolerance can be induced, versus short-term desensitization. Studies should include larger numbers of patients with double-blinded placebo-controlled protocols, and immunological changes should be further elucidated. Clearly, the implementation of these novel treatments should be limited to the research setting and not in clinical practice. However, remarkable progress within the field of food allergy treatment has increased expectations that disease-modifying therapies will be the standard of care in the not so distant future.

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