

Classic specific immunotherapy and new perspectives in specific immunotherapy for food allergy

Food allergy is a major cause of life-threatening hypersensitivity reactions. Food-induced anaphylaxis is the most common reason for someone to present to the emergency department for an anaphylactic reaction. The avoidance of the allergenic food is the only method of preventing further reactions that is currently available for sensitized patients. Strict avoidance of specific foods is the accepted treatment of food-induced allergic reactions but is often an unrealistic therapeutic option for food-induced hypersensitivity reactions for the many reasons previously described. Desirable therapeutic strategies for the treatment and prevention of food allergies must be safe, relatively inexpensive and easily administered. Recent advances in the understanding of the immunological mechanisms underlying allergic disease and better characterization of food allergens have greatly expanded the potential therapeutic options for future use. Several different forms of immunomodulatory therapies are currently under investigation: peptide immunotherapy, mutated protein immunotherapy, allergen DNA immunization, vaccination with immunostimulatory DNA sequences and anti-immunoglobulin E (Anti-IgE) therapy.

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Food allergy is a major cause of life-threatening hypersensitivity reactions. Food-induced anaphylaxis is the most common reason for someone to present to the emergency department for an anaphylactic reaction. The avoidance of the allergenic food is the only method of preventing further reactions that is currently available for sensitized patients. This method of prevention is difficult because of accidental food ingestions that occur. With better characterization of allergens and understanding of the immunologic mechanism involved in this reaction, investigators have developed several therapeutic modalities potentially applicable to the treatment and eventual prevention of food allergy. Among the therapeutic options currently under investigation, there is peptide immunotherapy, mutated protein immunotherapy, DNA immunization, immunization with immunostimulatory sequences and anti-IgE therapy. These novel forms of treatment for allergic disease hold promise for the safe and effective treatment of food-allergic individuals and the prevention of food allergy in the future.

Strict avoidance of specific foods is the accepted treatment of food-induced allergic reactions but is often an unrealistic therapeutic option for food-induced hypersensitivity reactions for the many reasons previously described. Food allergens can be hidden in unsuspecting foods, labeling is often misleading, con-

tamination of a safe food occurs when served with a contaminated utensil and several cross-reacting allergens exist.

Desirable therapeutic strategies for the treatment and prevention of food allergies must be safe, relatively inexpensive and easily administered. Recent advances in the understanding of the immunological mechanisms underlying allergic disease and better characterization of food allergens have greatly expanded the potential therapeutic options for future use. Several different forms of immunomodulatory therapies are currently under investigation.

Traditional and novel immunotherapy

Traditional therapies

Immunotherapy for IgE-mediated disease has been used since it was first described nearly a century ago (1). Although injection immunotherapy has traditionally been employed in the treatment of inhalant allergies, such as allergic rhinitis, it has also been used with success in the treatment of food allergy. Injection immunotherapy was first used in the treatment of food allergy when a young child was successfully desensitized to fish (2). In patients with allergic rhinitis experiencing oral allergy symptoms with the ingestion of cross-

reacting allergens in fresh fruits, nuts and vegetables, traditional injection immunotherapy has also been successful in ameliorating the oral allergy symptoms with minimal adverse reactions (3, 4).

Although effective, traditional injection immunotherapy for food allergy is currently not recommended. Recently there was a double-blind, placebo-controlled trial of rush immunotherapy conducted for the treatment of anaphylactic hypersensitivity to peanuts. Patients in the treatment group were able to tolerate increased amounts of peanuts in post treatment food challenges. Unfortunately, an unacceptably high rate of adverse systemic reactions was associated with the rush immunotherapy and maintenance protocols (5, 6). The actual peanut immunotherapy produced so many side effects of treatment that practically it would be impossible to perform on a routine basis. While food desensitization in the oral allergy syndrome has been successful and well tolerated with cross-reacting pollen immunotherapy, the practice of injection immunotherapy for food allergy has been largely abandoned due to the associated risk of serious systemic reactions. Since traditional immunotherapy has been largely impractical for the treatment of most food allergies, several novel therapies are now being explored (Table 1).

Novel therapies

Techniques under current investigation for the treatment of food allergy include: peptide immunotherapy, mutated protein immunotherapy, allergen DNA immunization, vaccination with immunostimulatory DNA sequences and anti-immunoglobulin E (Anti-IgE) therapy.

Peptide immunotherapy. Traditional injection immunotherapy for food allergy has been avoided due to untoward side effects, namely anaphylaxis and death. Peptide immunotherapy utilizes peptide fragments containing T cell reactive epitopes rather than complete protein molecules. Theoretically, these peptide fragments are unable to crosslink two IgE molecules required to activate mast cells, but do appear to render T cells unresponsive to subsequent allergen exposure (7). In one study utilizing peptide immunotherapy, the investigators injected cat allergic patients with T cell reactive peptide fragments containing dominant cat allergen epitopes. Patients tolerated the injections with few, mild adverse reactions. Although peptide immunotherapy is not currently being used in the treatment of IgE-mediated disease, they were able to demonstrate that cat allergic patients treated with the peptide fragments had statistically significant improvement in nasal, lung and total symptom scores when compared to placebo-treated subjects after exposure to a "cat

room" (8). Another study demonstrated that pepsin-digested peanut allergen contains T cell epitopes but no IgE-binding epitopes. Interferon-gamma (IFN- γ), a Th1 cytokine, was induced by pepsin-digested peanut in a concentration-dependent manner (9). While peptide immunotherapy for food allergy has not yet reached clinical trials, studies are encouraging and suggest the potential role for peptide immunotherapy in the future therapy of food allergy.

Mutated protein immunotherapy. With greater understanding of the allergic mechanism and better characterization of allergens, we and others are developing techniques that appear to be both safe and effective in the treatment of food allergy. This type of immunotherapy can be achieved through alteration of the primary amino acid sequences of IgE-binding allergenic epitopes of the major allergens present in foods. Such an effort has been shown to substantially alter IgE antibody binding with both major peanut allergens as well as shrimp allergens ranging from reduced binding to complete abolishment of binding. The major peanut allergens, Ara h 1 and Ara h 2, have had mutations made to their cDNA and then mutated less-allergenic proteins were expressed (10). The T cell epitopes were not altered by mutating the IgE-binding sites. Patients with peanut hypersensitivity had dramatically reduced peanut-specific IgE binding to the mutated peanut protein when compared to the wild type peanut protein. In animal studies with peanut-allergic mice the mutated protein significantly reduced the amount of peanut-specific IgE antibody produced by the peanut-allergic animal, as well as reduced their clinical symptoms on peanut challenge (11). Designing molecules in the future that have reduced or abolished IgE binding while preserving their ability to stimulate T cells should result in the availability of safe and effective therapeutics for the treatment of food allergy. Furthermore, alteration of such molecules in foods theoretically could help substantially to reduce the incidence of food-induced anaphylactic reactions in such sensitized patients.

DNA immunization. Another novel approach to the treatment of food allergy currently under investigation is DNA immunization. DNA immunization employs the subcutaneous injection of a plasmid DNA (pDNA) vector encoding a specific allergenic protein. The pDNA sequence is taken up by antigen-presenting cells (APC). Once inside the cell, the DNA encoding allergen is transcribed and translated. The allergen is then presumably presented on the surface of the APC in the context of the major histocompatibility complex (MHC) to T cells. This endogenously produced allergenic protein or protein

Table 1. Potential immunotherapeutic strategies for the treatment of food allergy

Therapy	Type of allergy	Route	Immunologic mechanism	Risks
Traditional injection immunotherapy	Oral allergy syndrome	Subcutaneous	Increase IgG-blocking antibodies, decreases specific-IgE	Safe, when performed properly
Peptide immunotherapy	IgE-mediated food allergy	Subcutaneous	Immune deviation from Th1 to Th2	Appears safe
Mutated protein immunotherapy	IgE-mediated food allergy	Subcutaneous, intranasal and oral	Immune deviations from Th1 to Th2 (?)	Appears safe
DNA immunization	IgE-mediated food allergy	Subcutaneous and oral	(Subcutaneous) immune deviation from Th1 to Th2, (oral) increase levels of allergen specific secretory IgA in gut, and increase systemic IgG	Unknown
Immunostimulatory sequences	IgE-mediated food allergy	Subcutaneous	Immune deviation from Th1 to Th2	Appears safe
Anti-IgE therapy	IgE-mediated food allergy	Subcutaneous	Depletes IgE, blocks IgE from binding to high affinity IgE-receptor (FcεRI). Downregulates IgE receptor production	Appears safe

fragment induces a Th1 phenotypic response with upregulation of IFN- γ , an increase in IgG₂ and suppression of allergen-specific IgE production (12, 13). Oral delivery of DNA immunizations has also been described. It has been utilized as an immunoprophylactic strategy to modulate peanut antigen-induced anaphylaxis (14). In this model, the oral delivery of DNA complexed to chitosan, a biocompatible polysaccharide, also favored a Th1 response and suppressed the Th2 allergic immune response.

Immunization with immunostimulatory sequences. Another DNA immunization technique under investigation is immunization with pDNA conjugated to immunostimulatory sequences (ISS). These ISS contain unmethylated cytosine and guanine dinucleotide repeat motifs. These CpG motifs stimulate APCs and natural killer cells to secrete IFN- γ and IL-12, cytokines that promote immune deviation toward the Th1 phenotype and away from the allergic Th2 phenotype (15). These ISS stimulate immune deviation to the Th1 phenotype when administered in several ways. They can be administered with DNA encoding the allergen (DNA immunization) (16), when given alone (17), or when conjugated with allergen. Although the majority of these DNA immunization techniques have been studied in the mouse model, a recent report describes enhanced immune deviation to the Th1 phenotype and reduced allergenicity after injection immunotherapy with the major ragweed allergen, Amb a 1, conjugated to ISS in mice and rabbits, as well as in primates (18).

Anti-IgE immunotherapy. In general, the immune response to allergen immunotherapy is allergen specific, making treatment of multiple allergies complex and expensive. Often patients are allergic to more than one allergen. Ideally, one would prefer to utilize a single therapy to combat the entire allergic mechanism, one therapeutic option effective for

multiple inhalant allergies as well as food allergies. One such therapy, already in clinical trials, involves the use of anti-IgE antibodies. Immunoglobulin E (IgE) exists freely circulating or attached to mast cells and basophils. When two mast cell-bound IgE molecules are crosslinked by antigen, the cell is activated, and vasoactive mediators are released. Anti-IgE, a humanized mouse monoclonal IgG antibody, directed against the human IgE molecule, binds to freely circulating IgE and not to mast cell- or basophil-bound IgE. Once circulating IgE is bound by anti-IgE, it is unable to bind to its specific high-affinity receptor (FcεRI) on mast cells and basophils. These antigen-antibody complexes are then cleared from the circulation. Several clinical trials involving patients with allergic rhinitis (19) and allergic asthma (20) have been completed. Statistically significant reductions in medication use, allergic symptoms, and airways hyperreactivity have been described with its use. Reductions in total serum IgE levels to less than 1% of pretreatment levels were noted in addition to downregulation of the high-affinity IgE-receptor (FcεRI) (21). Although anti-IgE therapy is expensive and requires frequent administration to maintain the IgE-deficient state, it could theoretically be used quite effectively in conjunction with other therapeutic modalities. For example, pretreatment with anti-IgE could potentially prevent the systemic reactions experienced with peanut immunotherapy (6) while achieving the beneficial effects of desensitization. This promising technique is currently under investigation in patients who have food allergy.

Conclusion

Food allergy affects approximately 6–8% of children and 1–2% of adults. For those patients, and the families of patients, who have anaphylactic reactions, food allergy can be devastating. Reactions can range from mild urticarial reactions to severe anaphylactic shock and death from allergenic foods consumed unknowingly. The only preventative measure currently available for food allergy is strict avoidance of the

incriminating food, which is often very difficult. Immunotherapy will be available in the near future as a safe and potentially effective therapy for the treatment of food allergy.

Thus, there is a variety of new treatments on the horizon to directly diminish the sensitivity of food allergic individuals by reducing the possibility of anaphylactic reactivity of such sensitized individuals upon inadvertent interaction with food allergens. We believe that these new developments certainly should

raise the standard of treatment of food-induced allergic reactions and make their diagnosis, treatment and care more effective in the future. The idea that food-allergic individuals can simply avoid those foods to which they are sensitized has not worked as effectively as needed, sometimes with tragic consequences. New therapies on the horizon should help the physician to greatly improve care of food-induced allergic reactions while reducing the risk of anaphylaxis in these patients.

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