

Immune mechanisms in food allergy

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The term "food allergy" encompasses a group of distinct clinicopathologic entities which have in common an immunologic basis, and in which an abnormal or exaggerated immunologic response to a specific food protein (allergen) leads to disease. One practical classification scheme (Table 1) divides food hypersensitivity diseases into two categories, the first being IgE-mediated diseases, and the second being immune complex and delayed hypersensitivity induced diseases [1]. The IgE-mediated food hypersensitivity reactions are usually immediate in onset. The pathologic basis for such a reaction is the crosslinking of food allergen-specific IgE molecules on the surface of mast cells and basophils following ingestion of the specific food allergen to which the individual is sensitive. This results in a variable clinical picture which may involve gastrointestinal reactions, including vomiting, nausea, and diarrhea; hives and angioedema, asthma and rhinitis, and, in severe cases, overt anaphylaxis.

In two specific clinical situations, that of food-induced eczema and food-induced eosinophilic gastroenteritis, target tissues exhibit cellular infiltrates reminiscent of late phase IgE-mediated reactions. One possibility is that there is a specific enhancement of the pathologic process in individuals susceptible to these diseases by an intrinsic abnormality of the skin or gastrointestinal tract. The second possibility is that these

Table 1. Food Hypersensitivity Classification

I. IgE-Mediated

A. Immediate

- Gastrointestinal
- Hives, angioedema
- Rhinitis, asthma
- Anaphylaxis

B. Immediate and Late Phase

- Eczema
- Eosinophilic gastroenteritis

II. Immune Complex/Delayed Hypersensitivity

- Gluten-sensitive enteropathy
- Food protein-induced enterocolitis syndromes

individuals suffer from frequent and recurrent mast cell degranulation which leads to a prolonged or continuous late phase reaction and subsequent pathology leading to eczema and gastroenteritis.

For diseases in the second category of food hypersensitivity reactions, evidence has accumulated that implicates both immune complex and delayed hypersensitivity mechanisms. Gluten-sensitive enteropathy is technically a food allergy where there is an abnormal immunologic response to gluten. The food protein induced enterocolitic syndromes as described in infants and children may follow the formation and local deposition of immune complexes and the genesis of delayed hypersensitivity reactions. It should be noted that there is also evidence for IgE-mediated phenomena in some children with food protein induced enterocolitis, and the involvement of one immunologic effector system does not necessarily exclude the involvement of multiple effector mechanisms.

Specific treatment for food hypersensitivity requires the appropriate application of medicines that are able to have an impact on a specific immunologic effector system. The most obvious example of this is IgE-mediated mast cell and basophil dependent immediate reactions to foods. The selection of medications for this disease is best explained by examining the number of mast cell mediators that result from mast cell activation. Thus, the degranulation of mast cells results in the rapid release of granule-associated mediators, in particular histamine, and the generation of lipid-derived mediators, the most striking of which are the leukotrienes and platelet activating factor (Table 2). In addition, there are specific cytokines, including those previously identified only in lymphocytes and monocytes, that are also synthesized by mast cells thirty minutes to two hours following activation [2].

The ideal treatment in such a disease is obviously to avoid the precipitating factor altogether, in this case the food that induces mast cell degranulation. Thus the need for diagnostic techniques in the identification of the foods that induce these immediate reactions. If a reaction does take place the most effective strategy is to attempt to limit mast cell degranulation and the resultant release of mediators. This is the basis of

Table 2. Mast Cell Mediators

I. Granule-Associated

- Histamine
- Proteases
- Heparin/chondroitin sulfate E

II. Lipid-Derived

- Prostaglandins
- Thromboxanes
- HETES
- Leukotrienes
- PAF

III. Cytokines

- Lymphokines
- Monokines

the strategy of employing epinephrine to treat patients with systemic reactions to a specific food protein. Following mast cell degranulation, there may be some benefit from antihistamines which block the action of the granule-derived histamine, and with time it is hoped that similar antagonists will be available to block the actions of leukotrienes and platelet activating factor.

There have been a number of developments in the antihistamine category of medications used to treat patients undergoing mast cell degranulation. H1 antagonists have long been available. These medications are effective in decreasing the pruritus and edema associated with mast cell degranulation and abrogating systemic consequences of mast cell degranulation such as hypotension and cardiac arrhythmias. Sedation as a side effect of such drugs has limited their use. More recently non-sedating H1 antagonists have become available and gained wide acceptance due to improved patient compliance. There are also H1 antagonists with prophylactic anti-asthma properties attributed to mast cell stabilization by these drugs. Finally, antagonists that block the H2 actions of antihistamines have been developed as therapy for gastric hypersecretion. These drugs have found clinical acceptance in severe allergic reactions in that they may decrease the hypotensive effects associated with histamine release. In terms of severe reactions to foods, such drugs have been used in conjunction with epinephrine and H1 antihistamines to treat severe cases of anaphylaxis.

Individual antagonists to specific products, however, will never be totally successfully in treating mast cell-dependent reactions. This realization has led to a search for drugs that can be taken orally but stabilize mast cells throughout the body. One drug, cromolyn sodium, is believed to act through mast cell stabilization. Its usage has for the most part been limited to situations where it can be delivered onto mucous membranes and onto the epithelial surfaces of the lung where it is an effective prophylactic medication. It has been suggested as a drug which might be given to prevent systemic reactions to foods. However, as reviewed elsewhere [3], there is no clear evidence that cromolyn sodium can be reliably depended upon to prevent systemic reactions to foods, and particularly, anaphylaxis. Thus the search for an effective oral mast cell stabilizing drug continues. In a similar vein, antihistamines with mast cell stabilizing properties cannot be relied upon to prevent severe systemic mast cell degranulation. The treatment of immediate reactions to foods continues to require a combination of dietary avoidance and treatment of inadvertent exposure (Table 3). Desensitization to food antigens remains an unproven medical possibility.

Table 3. Treatment of IgE-Mediated Food Hypersensitivity.

1. Dietary Avoidance
2. Treat Inadvertent Exposure
 - a. Medic-alert bracelet
 - b. Epinephrine
 - c. Antihistamines
 - d. Seek medical help
3. Unproven: Desensitization
 - Prophylactic medications

As noted previously, some immediate reactions to foods that are dependent upon antigen-specific IgE and mast cell degranulation have a prominent "late phase" component. This is the case in eczema and food induced eosinophilic gastroenteritis. In both diseases the pathology of IgE immediate reactions including hives, angioedema, nausea and vomiting, and anaphylaxis may be seen following inadvertent exposure to foods to which the individual is sensitive. These complications are managed in the same way as IgE-mediated reactions to foods. In addition, the late phase component may require specific strategies. In eczema, efforts are made to maintain moisture in the skin, to use antihistamines to decrease the pruritus, to quickly treat superinfection with systemic antibiotics, and finally to treat severe exacerbations of eczema with topical steroids. Repeated application of topical steroids are known to have a number of local effects, including the apparent ablation of mast cells within the tissues.

Eosinophilic gastroenteritis is by definition a disorder of the stomach and/or small bowel which is characterized by peripheral eosinophilia, eosinophilic infiltrations of the bowel wall, and gastrointestinal problems [4]. Its diagnosis rests on the clinical picture, characteristic radiographic findings, and gastrointestinal biopsy which shows a prominent eosinophilic infiltrate. Patients with eosinophilic gastroenteritis associated with food hypersensitivity may have elevated serum IgE levels, and multiple skin tests positive to a wide variety of food proteins. In some cases it may be useful to exacerbate the disease with specific food challenge to confirm the diagnosis. The treatment of this disease includes the use of elimination diets and treatment of inadvertent exposure (Table 3). In severe cases where an elimination diet does not result in the resolution of symptoms, it may be necessary to institute daily steroids to control the disease. With time, patients with eosinophilic gastroenteritis can generally be managed on every other day steroids as low as 7.5 mg every other day.

Food hypersensitivity reactions due to immune complex and delayed hypersensitivity responses appear to play a prominent role in the genesis of food protein induced enterocolitic syndromes particularly seen in newborns and infants. In this disease sometimes referred to as milk-soy related gastrointestinal disease in children, the clinical picture is one of chronic diarrhea, eosinophilia, and malabsorption. Its onset may be from 2 days to 4 months after birth and there is an increased incidence of atopy in family members. The diagnosis is based on the clinical picture and specific protein challenge. Treatment relies on the identification of the food proteins responsible, and their elimination from the diet. If there is an immediate component, preparation should be made to treat inadvertent exposure. In severe cases steroids may be required.

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