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The Immunopathogenic Role of Food Hypersensitivity in Atopic Dermatitis

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Food hypersensitivity is reported to play an immunopathogenic role in atopic dermatitis in approximately one-third of children. In 320 selected children with moderate to severe atopic dermatitis, 63% of children were found to have food hypersensitivity by double-blind placebo-controlled food challenges. Both IgE-mediated mast cell and mononuclear cell activation appear responsible for the eczematous lesions resulting from ingestion of food allergens. ***Key words:*** **Atopic dermatitis; Food hypersensitivity; Double-blind placebo-controlled food challenge; Histamine-releasing factor.**

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Atopic dermatitis (AD) is one form of eczema which generally begins in early infancy and is characterized by extreme pruritus, typical distribution, chronically relapsing course, and association with asthma and allergic rhinitis (1). A variety of factors are known to exacerbate flares of AD, including irritants, heat, humidity, infection, stress, and allergens. The role of food allergy in the pathogenesis of AD has been disputed for nearly a century (2). In a recent study of children with AD seen at a university hospital's dermatology and allergy clinics, double-blind placebo-controlled oral food challenges (DBPCFC) revealed that in approximately one-third, food hypersensitivity had contributed to their skin symptoms (3). As discussed below, a single ingestion of food allergen in the DBPCFC is unlikely to provoke an eczematous lesion, but chronic ingestion of a food allergen [or repeated positive oral food challenges] can result in classical changes of AD.

In the past 10 years, 320 patients with AD have been evaluated for evidence of food hypersensitivity. As indicated in Table I, these patients ranged in age from 6 months to 25 years. They were highly atopic, with 45% having both asthma and allergic rhinitis at the time of initial evaluation. Only 23% of the patients had AD alone at the initiation of study. Patients were hospitalized at a Clinical Research Center [RR-00052] for evaluation by DBPCFCs. Foods suspected by history or results of prick skin tests or RASTs were excluded for 10 to 14 days prior to admission. In addition, antihistamines were withheld for 1 to 2 weeks prior to admission. Once hospitalized, patients were treated aggressively with hydrating baths, lubricating creams, topical corticosteroids, and antibiotics until cutaneous pruritus and erythema essentially cleared. Following 3 to 4 days of medical therapy in the hospital, DBPCFCs generally could be initiated. The DBPCFC consists of administering up to 10 g of dehydrated food or placebo substitute over a period of 60–90 min, starting with 250–500 mg and doubling the dose every 15 min until 10 g has been delivered (4). The dehydrated food is mixed in a liquid which is flavored so that it is indistinguishable from the placebo. The Clinical Research Center dietitian prepares and randomizes all challenges so that neither the physicians, research nurses, parents, nor patients know the contents of the challenge material. All challenges are scored on a standardized scoring form (5). A challenge is considered positive and discontinued if objective symptoms develop [eg. morbilliform rash, vomiting, wheezing, etc.]. The food challenge is considered negative if the patient tolerates the full challenge without developing obvious symptoms. Once the blinding has been broken, the patient is fed a large portion of all foods which did not elicit symptoms during the challenge. The food is prepared in the usual fashion and administered openly under observation to confirm the negative result of the DBPCFC.

As shown in Table II, DBPCFCs provoked a variety of symptoms within minutes or up to 2 h. Cutaneous reactions developed in 75% of positive challenges, but symptoms were confined to the skin alone in only 30% of positive responses. At the time of first evaluation, skin symptoms provoked by DBPCFCs usually consisted of a markedly pruritic, erythematous, morbilliform rash which developed at patients' predilection sites for eczema. Urticarial lesions were rarely seen. Interestingly, urticaria was seen in follow-up challenges conducted 1 to 2 years later in patients who had experienced clearing of their eczema while adhering to an appropriate allergen elimination diet, but who remained food sensitive. Although history had not suggested other food-induced complaints, gastro-intestinal symptoms developed in 41% of patients [nausea, abdominal cramping, and vomiting and/or diarrhea], upper respiratory symptoms, especially laryngeal edema [sensation of itching and tightness in the throat, persistent throat clearing with dry hacking cough, and hoarseness] in about one-third, and wheezing in about 10% of positive chal-

Table I. *Patients with atopic dermatitis evaluated for food hypersensitivity*

Patients enrolled	320
Median age: 4.4 years [3 mos–30 yrs]	
Number with elevated serum IgE	256 (80%)
Median: 3,400 IU/ml	
Number with positive family history	304 (95%)
Number with concomitant atopic disease at the time of diagnosis:	
Allergic rhinitis	25%
Asthma	10%
Both asthma & allergic rhinitis	45%
Neither	20%

Table II. *Results of 1,521 initial food challenges in 320 patients with atopic dermatitis*

Negative food challenges:		948
Positive food challenges:		573
Cutaneous symptoms:	424 (74%)	
[Skin only – 150 (26%)		
Gastrointestinal symptoms:	303 (53%)	
Respiratory symptoms:	263 (46%)	
Nasal:	166 (29%)	
Laryngeal:	114 (20%)	
Pulmonary:	56 (10%)	

lenges. As indicated in Table III, relatively few foods induced food allergic symptoms, despite a wide range of foods tested. Egg, peanut, and milk accounted for over two-thirds of the reactions documented by DBPCFC.

Both immediate and late-phase effects of ingested food allergens have been recorded during DBPCFCs (6–10). The pruritic, erythematous morbilliform rash, which is a hallmark of the immediate skin response, generally arises abruptly and persists for 30–120 min. Several laboratory findings implicate IgE-mediated cutaneous mast cell activation in the pathogenesis of these lesions induced by positive DBPCFCs: a sharp rise in plasma histamine concentration (9), no change in circulating basophil number, total histamine content, or spontaneous basophil histamine release *in vitro* [indicators of circulating basophil activation] (7), and no significant change in the complement activation products C3a or C5a (10). In addition, several lines of evidence implicate an IgE-mediated late-phase component associated with positive DBPCFCs. Approximately 4–8 h following the onset of the primary skin reaction, many patients develop diffuse pruritus and less frequently, an erythematous macular rash. A significant rise in circulating polymorphonuclear neutrophils was observed in 14/15 patients who experienced a positive challenge, compared with patients experiencing no symptoms [median: 5,904 vs. 3,196 cells/mm^3; $p < 0.01$], and a distinct drop in circulating eosinophils. Utilizing Percoll density gradients, circulating eosinophils were noted to change from a pre-challenge 'normodense' profile to a post-challenge 'hypodense' profile in 3 patients studied to date. Skin biopsies obtained from the sites of challenge-induced morbilliform lesions 8–14 hours following positive food challenges revealed infiltration of eosinophils and deposition of major basic protein in the upper dermis (10).

It is postulated that the repeated ingestion of food allergens by AD patients with food allergy leads to chronic inflammation and pruritus, which provokes frequent scratching and the consequent trauma-induced lichenified lesions. Chronic food allergen ingestion was demonstrated to be associated with the spontaneous production of histamine-releasing factor [HRF] from mononuclear cells *in vitro* (7). The generation of HRF was associated with increased spontaneous basophil histamine release *in vitro*, increased basophil releasibility *in vitro*, and increased cutaneous hyperirritability [a state of increased reactivity to a variety of minor non-specific stimuli, e.g. heat, cold, detergents, etc.]. Spontaneous generation of HRF decreased to normal levels over a 6–9-month period when the food-allergic patients eliminated the appropriate allergens from their diet [mean HRF-induced basophil histamine release: 57.1 ± 9.3% to 2.0 ± 0.8%; $p < 0.001$] (7). In addition, spontaneous basophil histamine release returned to normal levels, basophil releasibility normalized, and cutaneous hyperirritability diminished.

In a prospective follow-up study of 26 patients with AD, those patients with food allergy who were appropriately diagnosed and placed on an allergen elimination diet experienced a marked and significantly greater improvement in their eczematous rash compared with a similar group of patients who did not have food allergy or who did not adhere to the elimination diet (6). Clinical improvements associated with the allergen elimination diet were not limited to the skin in these food-allergic patients. Several patients experienced improvement in asthmatic symptoms as evidenced by improved control in their asthma while reducing their medication requirements. Initial gastrointestinal changes also were noted. In food-allergic children who were found to be ingesting food allergens, absorption of the carbohydrate marker, lactulose, was elevated, indicating abnormal gut wall integrity. However, lactulose absorption returned to normal when the responsible food allergens were eliminated from the diet (13). This study indicated that patients with AD and food hypersensitivity had subclinical malabsorption which was reversed when food allergens were removed from the diet.

Following 1–2 years of strict food allergen avoidance, 75 patients have been rechallenged. Approximately one-third of symptomatic food hypersensitivities were lost at the time of second DBPCFC (9). The likelihood of developing tolerance appeared to be dependent upon the allergen responsible for the reaction, [i.e. the development of tolerance to soy was seen much more frequently than development of tolerance to peanut], and how well the patient adhered to the strict elimination diet. Similar results have been reported in adults with food hypersensitivity (13). Prick skin tests were of no use in monitoring loss of clinical reactivity; the reactivity of prick skin tests at the time of rechallenge did not differ significantly from the results at the time of diagnosis. To investigate whether symptomatic skin reactivity was determined at the

Table III. *Foods eliciting positive reactions in 320 patients evaluated for food hypersensitivity*

Food	No. of pats	% RX's.
Egg	106 (4)	30%
Milk	78 (17)	22%
Peanut	54 (28)	15%
Soy	33 (1)	9%
Wheat	18	5%
Fish	11	3%
Beef	9	3%
Chicken	6	2%
Pork	3	1%
Potato	4 (1)	1%
Others	30 (4)	9%
Total	352	100%

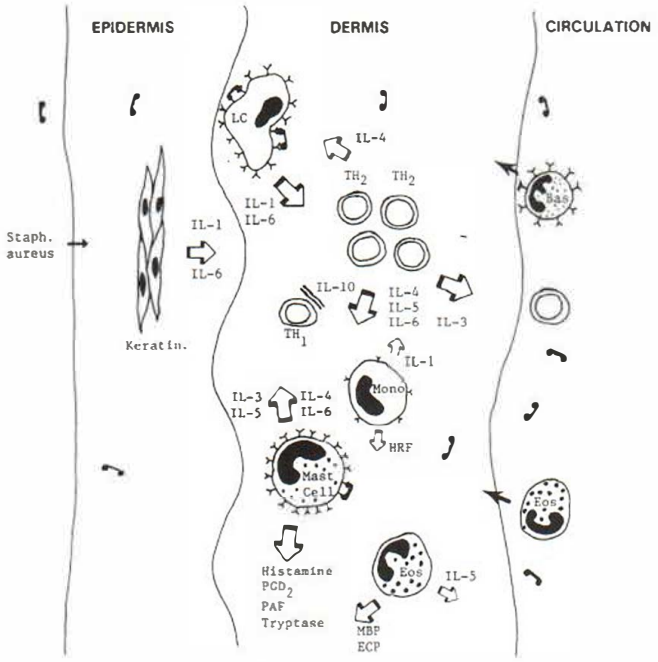

Fig. 1. Food allergens [ ] transported by the circulation or through minute fissures in the epidermis to the dermis activate local mast cells and Langerhans cells which secrete a variety of mediators and cytokines capable of attracting inflammatory cells into the skin. TH_1 = $CD4_+$ lymphocytes secreting IL-2, IFN-, and GM-CSF; TH_2 = $CD4_+$ lymphocytes secreting IL-4, IL-5, IL-3, IL-6, IL-10, and GM-CSF; *Eos* = eosinophils; *Baso* = basophils; and *Keratin* = keratinocytes.

target organ level, the response of cutaneous mast cells to contact with various allergens was assessed by introducing food allergens into skin blister chambers raised on 6 patients. The chamber blister fluid was then monitored for changes in mediator and cell content (14). No differences in immediate or late-phase [4–12 h] histamine or PGD_2 concentrations were seen between food allergen to which the patient was skin test and challenge positive ['relevant'] and food antigen to which the patient was skin test positive and challenge negative ['irrelevant' food allergen]. Based on this study and previous studies documenting the absorption of food antigens in most individuals (15), the difference between sensitized patients with or without clinical reactivity is not determined at the level of the sensitized mast cell. It appears that other elements such as local cytokine production or factors intervening between the absorption of allergen at the level of the gastrointestinal tract and the response at the target organ [e.g. allergen clearing, allergen modification] contribute to clinical reactivity.

As depicted in Fig. 1, food allergens may be absorbed through the gastrointestinal mucosa and transported by the circulation to the skin or may enter through small fissures in the epidermis. Once in the dermis, food allergens may activate local mast cells to release histamine, prostaglandins, and a number of cytokines including IL-3, IL-4, IL-5, and IL-6 (16). The release of these mediators and cytokines would promote local vasodilation and edema, attract eosinophils, basophils, lymphocytes and monocytes, induce FcE_{II} receptors on local Langerhans cells, and promote the proliferation of mast cells. Activated eosinophils would release major basic protein, eosinophil cationic protein, and IL-5, which promote local inflammation and further eosinophil infiltration. IgE-bearing Langerhans cells from AD patients have been shown to be efficient allergen presenting cells for lymphocytes (17). T cell cloning experiments have shown that allergen-specific TH_2 cells are prevalent in lesional skin of AD patients (18). Allergen-induced activation of TH_2 cells would generate an interleukin profile [IL-4, IL-5, IL-3, IL-6, IL-10, and GM-CSF] which would inhibit a typical cell-mediated response and favor further infiltration of allergic inflammatory cells. Repeated allergen-activation of mast cells leads to diminished histamine release, as shown *in vitro* and in rodent models (19), which would mask an obvious correlation between allergen ingestion on a daily basis and skin symptoms. However, the repeated mediator and cytokine release from skin mast cells ['late-phase Type I hypersensitivity] and the allergen-induced activation of Langerhans cells and lymphocytes [Type IV hypersensitivity] would lead to the chronic inflammatory changes seen in the skin of patients with atopic dermatitis.

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