

Food allergy: When mucosal immunity goes wrong

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For someone who has spent his entire career in the field of food allergy, it is extremely gratifying to see the Journal focus on this topic for the second time in less than 1 year. Twenty years ago, only a few articles related to food allergy appeared in the Journal each year. As highlighted in this issue, tremendous advances have been made in our understanding of the mucosal immune system, oral tolerance, the structural properties of allergens, and the immunopathogenesis of food hypersensitivity disorders. Food allergy, which was at the fringe of our specialty 20 years ago, has advanced to become a vibrant subspecialty that is based on rigorous scientific methods and studied by legions of new investigators from a variety of scientific backgrounds. Whereas food allergy had been viewed as a rare disorder, the most recent epidemiologic evidence suggests that it affects up to 8% of children less than 3 years of age¹ and about 4% of the US population.² In addition, food allergy appears to be the single leading cause of anaphylaxis outside of hospitals and likely accounts for about 30,000 cases of anaphylaxis treated in hospital emergency departments each year.³ Despite our many advances, we still have no proactive treatment for food-induced allergic disorders, and we do not understand why some forms of food allergy appear to be increasing (eg, peanut allergy).^{4,5} Nevertheless, our knowledge in this field has been increasing at an exponential rate, and as highlighted in this issue of the Journal, the influx of talented investigators focusing on food allergy promises further great advances in the years to come.

The gastrointestinal tract is the largest immunologic organ in the body, possesses the greatest surface area exposed to the outside environment, and is confronted with the largest antigenic load in the form of dietary proteins, commensal organisms, and pathogens.⁶ The mucosal immune system of the gut has the extraordinary

ability to distinguish between foreign pathogens and safe nutrient proteins and commensal organisms. Chehade and Mayer⁷ provide an excellent review on the most recent information outlining the physiologic and immunologic mechanisms used by the gastrointestinal tract to accomplish its task. Although Merrill Chase provided the first clear evidence of oral tolerance nearly 60 years ago,⁸ demonstrating how the gastrointestinal immune system can actively inhibit immune responsiveness to antigens taken in by the oral route, studies over the past decade have begun to reveal the intricacies of this component of the immune system. Genetic factors, gut flora, antigen dose, and digestive processes influence how antigen-presenting cells (ie, dendritic cells and intestinal epithelial cells) process and present antigens to T cells. In the case of potentially harmful antigens, a subset of CD4⁺ T cells will mount a swift inflammatory response to protect the host, but in the case of dietary nutrients or harmless organisms, T regulatory cells (eg, T_H3, T_R1, and/or CD4⁺CD25⁺ cells) are activated to bring about immune tolerance. In the remarkably few instances in which these responses go wrong, considering the complexities of the gut-associated mucosal immune system, individuals might experience food hypersensitivity or inflammatory bowel disorders.

As depicted in Table I, the expansion of our knowledge of basic immune mechanisms has been accompanied by a growing appreciation for the diversity of food-induced hypersensitivity disorders. Celiac disease provides unique insight into the interaction of genetic susceptibility, the loss of oral tolerance to specific dietary antigens, and the development of inflammation of the gastrointestinal tract, as outlined in the review by James.⁹ It also might shed insight into the underlying immunopathology of other disorders, such as inflammatory bowel disease, which might represent a loss of tolerance to gut microbial flora. Food protein-induced enterocolitis syndrome, first described in young infants by Powell et al,¹⁰ is a non-IgE-mediated disorder that can provoke hypotensive shock. In case studies, Sicherer¹¹ provides the clinical spectrum of this disorder and discusses appropriate evaluation. Although the exact immune mechanism or mechanisms responsible for this syndrome are yet to be delineated, it is clear that a variety of food proteins are capable of inducing protein-induced enterocolitis syndrome and that it is not necessarily limited to the pediatric population.¹² In his review of the unified immune system, Braunstahl¹³ not

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TABLE I. Food hypersensitivity disorders

IgE mediated	Mixed IgE and cell mediated	Cell mediated
Gastrointestinal		
Oral allergy syndrome	Eosinophilic esophagitis	Food protein–induced enterocolitis
Gastrointestinal anaphylaxis	Eosinophilic gastroenteritis	Food protein–induced proctocolitis
	Infantile colic	Food protein–induced enteropathy Celiac disease
Cutaneous		
Urticaria	Atopic dermatitis	Contact dermatitis
Angioedema		Dermatitis herpetiformis
Morbilliform rashes		
Flushing		
Respiratory		
Acute rhinoconjunctivitis	Asthma	Food-induced pulmonary hemosiderosis (Heiner syndrome)
Acute bronchospasm		
Generalized		
Anaphylaxis		

only outlines the close association between allergic responsiveness of the upper and lower airways but also reminds us that eosinophilic inflammation in the esophagus, stomach, and small intestine have been associated with allergic manifestations in the airway. Given the close relationship of the mucosal immune system in different target organs, neural integration, and extensive cell trafficking, allergic responsiveness to inhaled or ingested allergens in multiple organs should not be unexpected (eg, allergic eosinophilic esophagitis or anaphylaxis).

With the advent of the double-blind placebo-controlled oral food challenge 30 years ago by May,¹⁴ the practice of patients with food allergy avoiding all foods within a specific botanical family or animal species was challenged. Skin testing and RASTs frequently demonstrated the presence of IgE antibodies to most members of botanically related or species-related foods, but oral challenges demonstrated that this cross-reactivity did not translate into clinical symptoms.¹⁵⁻¹⁷ This apparent paradox led to the investigation of food proteins at the molecular level, following the lead of Aas¹⁸ and Elsayed and Bennich,¹⁹ who defined the major codfish allergen, Gad c 1. As reviewed by Breiteneder and Clare Mills in this issue of the Journal,²⁰ more than 100 food allergens have now been identified and sequenced, and the cDNA coding for these proteins has been isolated, sequenced, and cloned. With this information, investigators are developing diagnostic assays for IgE-mediated food-induced allergic reactions that more accurately predict clinical reactivity²¹ and might provide insight into the natural history of clinical reactivity²² and possibly into the severity of food-induced allergic responsiveness,²³ as well as novel therapeutic approaches.²⁴ Breiteneder and Mills show how

viewing food allergens at the molecular level should provide insight into what makes a specific glycoprotein allergenic and how the way it is processed can affect this property. For example, a number of investigators have shown that dry roasted peanuts are more allergenic than boiled or fried peanuts,^{25,26} but it might be the combination of using dry roasted peanuts and the emulsification process used to produce our modern-day peanut butter that has contributed to the increase in peanut allergy over the past decade. It also is apparent that when viewing food allergens at a molecular level, there are a rather limited number of protein families that constitute major food allergens, that share a number of biochemical and physicochemical properties, and that cross the bounds of various plant and animal species, confirming the obsolescence of previous botanical family and animal species avoidance strategies. Furthermore, it has become evident that IgE (and IgG) antibodies might be directed at conformational or sequential epitopes. In disorders such as the oral allergy syndrome, cross-reacting pollen-specific antibodies are directed at conformational epitopes, which explains why some raw fruits and vegetables produce local (oral and pharyngeal) allergic symptoms but the cooked form, which has an alteration of its tertiary structure caused by extensive heating, is ingested with no ill effect. It also likely explains why many young children tolerate cooked forms of milk and egg proteins but react to these foods when they are in their more native state.

Although viewing food allergens at the molecular level should clarify many of the apparent paradoxes of food allergy, it also suggests that simply identifying amino acid sequences will not be sufficient to detect potential allergens. In an original article by Jenkins et al,²⁷ an *in silico* approach using information on known sequence and structural properties of various proteins was applied to characterize major food allergens and determine whether there were unifying characteristics. The authors found that plant food allergens could be classified into 5 structural families, supporting the notion that conserved structural and functional properties of food allergens play a major role in determining allergenicity. They also demonstrated that the 3-dimensional structural analysis of a protein often correlated more closely with its *in vivo* allergenicity than suggested by simple sequence analysis (eg, the extensive binding of Bet v 1 antibodies to the Mal d 1 protein of apples, despite a sequence identity of about 56%).

Educating patients with food allergy to avoid allergenic foods and providing them with medications to treat accidental ingestions have been the mainstays of therapy in the treatment of food-induced allergic disorders. However, in the past several years, a number of proactive therapeutic strategies have entered preclinical and clinical trials. Anti-IgE therapy appeared promising in its first clinical trial,²⁸ and further trials are ongoing. The use of engineered recombinant protein vaccines²⁴ and oligodeoxynucleotide sequences bound to recombinant proteins have shown promise in reversing peanut allergy in murine models of peanut-induced anaphylaxis.²⁹ Three years ago, Li et al³⁰ published a somewhat unorthodox but successful

approach to treating mice with peanut allergy with an herbal preparation, FAHF-1. In this issue of the Journal, Li et al³¹ present a newer generation of the previous herbal formula, FAHF-2, which contains 9 herbs and provides extended protection from allergic symptoms in a murine model of peanut anaphylaxis. The protective effect of FAHF-2 was associated with a decrease in serum peanut-specific IgE levels and significantly reduced peanut-induced splenocyte production of IL-4, IL-5, and IL-13 and modestly increased IFN- γ production *in vitro* compared with that seen in sham-treated mice. Like anti-IgE, FAHF-2 should provide protection to any food inducing an IgE-mediated reaction. If these results can be replicated in clinical trials, a safe and relatively inexpensive treatment for food allergy might be available in the next several years. Perhaps even more exciting, identification and isolation of the active component or components in FAHF-2 responsible for this dramatic downregulation of the allergic response could provide a new class of drugs to treat allergic disorders and provide further insight into the immunopathogenesis of allergic reactions.

As highlighted in this issue of the Journal, great strides are being made in the field of food allergy. Food allergens are being identified and characterized at the molecular level, and immunologic mechanisms responsible for oral tolerance and food hypersensitivity are being defined. Investigators are using this basic information to develop better diagnostic and therapeutic tools with which to manage our patients, and someday soon, we should be able to treat and prevent the development of food-induced allergic disorders.

REFERENCES

1. Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. *Pediatrics* 1987;79:683-8.
2. Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of seafood allergy in the United States determined by a random telephone survey. *J Allergy Clin Immunol* 2004;114:159-65.
3. Sampson HA. Update of food allergy. *J Allergy Clin Immunol* 2004;113:805-19.
4. Grundy J, Matthews S, Bateman B, Dean T, Arshad SH. Rising prevalence of allergy to peanut in children: data from 2 sequential cohorts. *J Allergy Clin Immunol* 2002;110:784-9.
5. Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol* 2003;112:1203-7.
6. Mayer L. Mucosal immunity. *Pediatr* 2003;111:1595-600.
7. Chehade M, Mayer L. Oral tolerance and its relation to food hypersensitivities. *J Allergy Clin Immunol* 2005;115:3-12.
8. Chase MW. Inhibition of experimental drug allergy by prior feeding of the sensitizing agent. *Proc Soc Exp Biol* 1946;61:257-9.
9. James SP. Prototypic disorders of gastrointestinal mucosal immune function: celiac disease and Crohn's disease. *J Allergy Clin Immunol* 2005;115:25-30.
10. McDonald PJ, Goldblum RM, Van Sickle GJ, Powell GK. Food protein-induced enterocolitis: altered antibody response to ingested antigen. *Pediatr Res* 1984;18:751-5.
11. Sicherer SH. Food protein-induced enterocolitis syndrome: case presentations and management lessons. *J Allergy Clin Immunol* 2005;115:149-56.
12. Sampson HA. Food allergy. Part 2: diagnosis and management. *J Allergy Clin Immunol* 1999;103:981-99.
13. Braunstahl G-J. The unified immune system: respiratory tract—naso-bronchial interaction mechanisms in allergic airway disease 2005;115:142-8.
14. May CD. Objective clinical and laboratory studies of immediate hypersensitivity reactions to food in asthmatic children. *J Allergy Clin Immunol* 1976;58:500-15.
15. Bernhisel-Broadbent J, Sampson HA. Cross-allergenicity in the legume botanical family in children with food hypersensitivity. *J Allergy Clin Immunol* 1989;83:435-40.
16. Bernhisel-Broadbent J, Scanlon SM, Sampson HA. Fish hypersensitivity. I. In vitro and oral challenge results in fish-allergic patients. *J Allergy Clin Immunol* 1992;89:730-7.
17. Sicherer SH. Clinical implications of cross-reactive food allergens. *J Allergy Clin Immunol* 2001;108:881-90.
18. Aas K. Studies of hypersensitivity to fish: a clinical study. *Int Arch Allergy Appl Immunol* 1966;29:346-63.
19. Elsayed S, Bennich H. The primary structure of allergen M from cod. *Scand J Immunol* 1975;4:203-8.
20. Breiteneder H, Mills ENC. Molecular properties of food allergens. *J Allergy Clin Immunol* 2005;115:14-23.
21. Beyer K, Ellman-Grunther L, Jarvinen KM, Wood RA, Hourihane JO'B, Sampson HA. Measurement of peptide-specific IgE as an additional tool in identifying patients with clinical reactivity to peanuts. *J Allergy Clin Immunol* 2003;112:202-8.
22. Jarvinen KM, Beyer K, Vila L, Chatchatee P, Busse PJ, Sampson HA. B-cell epitopes as a screening instrument for persistent cow's milk allergy. *J Allergy Clin Immunol* 2002;110:293-7.
23. Shreffler WG, Beyer K, Burks AW, Sampson HA. Microarray immunoassay: association of clinical history, in vitro IgE function, and heterogeneity of allergenic peanut epitopes. *J Allergy Clin Immunol* 2004;113:776-82.
24. Li XM, Srivastava K, Grishin A, Huang CK, Schofield BH, Burks AW, et al. Persistent protective effect of heat-killed *Escherichia coli* producing "engineered," recombinant peanut proteins in a murine model of peanut allergy. *J Allergy Clin Immunol* 2003;112:159-67.
25. Maleki SJ, Chung SY, Champagne ET, Raufman JP. The effects of roasting on the allergenic properties of peanut proteins. *J Allergy Clin Immunol* 2000;106:763-8.
26. Beyer K, Morrow E, Li XM, Bardina L, Bannon GA, Burks AW, et al. Effects of cooking methods on peanut allergenicity. *J Allergy Clin Immunol* 2001;107:1077-81.
27. Jenkins JA, Griffiths-Jones S, Shewry PR, Breiteneder H, Clare Mills EN. Structural relatedness of plant food allergens with specific reference to cross-reactive allergens: an *in silico* analysis. *J Allergy Clin Immunol* 2005;115:163-70.
28. Leung DY, Sampson HA, Yunginger JW, Burks AW, Schneider L, Wortel CH, et al. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 2003;348:986-93.
29. Li XM, Sampson HA. Novel approaches for the treatment of food allergy. *Curr Opin Allergy Clin Immunol* 2002;2:273-8.
30. Li XM, Zhang TF, Huang CK, Srivastava K, Teper AA, Zhang L, et al. Food allergy herbal formula-1 (FAHF-1) blocks peanut-induced anaphylaxis in a murine model. *J Allergy Clin Immunol* 2001;108:639-46.
31. Srivastava KD, Kattan JD, Zou ZM, Li JH, Zhang L, Wallenstein S, et al. The Chinese herbal medicine formula FAHF-2 completely blocks anaphylactic reactions in a murine model of peanut allergy. *J Allergy Clin Immunol* 2005;115:171-8.