Mechanisms of allergic diseases

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Immunopathophysiology of food protein–induced enterocolitis syndrome

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There is increasing recognition of the non–IgE-mediated gastrointestinal food allergy known as food protein–induced enterocolitis syndrome (FPIES), with several recent publications summarizing the clinical experience with FPIES in the United States, the United Kingdom, Europe, and Australia. Our understanding of the mechanisms linking food exposure to typical symptoms of vomiting, hypotension, and diarrhea has lagged far behind our understanding of the immune mechanisms of IgE-mediated food allergy. The goal of this overview is to summarize and critique the current state of knowledge of the immunology of FPIES and to identify major gaps in our knowledge that need to be addressed to make significant gains in developing therapies and prevention strategies for FPIES. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

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Food allergy is an umbrella term for any immunologically mediated adverse reaction that occurs reproducibly after exposure to a given food,[1] including both IgE-mediated and non–IgE-mediated reactions. Within the non–IgE-mediated food allergies are the eosinophilic gastrointestinal disorders triggered by food: food protein–induced enterocolitis syndrome (FPIES) and food protein–induced proctocolitis. IgE-mediated food allergy and eosinophilic esophagitis are now well-described entities, with robust clinical and basic science research programs ongoing to understand the immune mechanisms of these disorders.[2,3] In contrast, our understanding of FPIES and proctocolitis falls far behind our understanding of other food-induced allergic disorders. In the past 2 years, there have been publications from 3 centers describing their extensive clinical experience with FPIES,[4-6] and in this issue Nowak-Wegrzyn[7] provides a comprehensive review of the clinical features of FPIES. The purpose of this review is to assess the state of our knowledge of the immune mechanisms of FPIES.

Abbreviations used
BLG: β-Lactoglobulin
FPIES: Food protein–induced enterocolitis syndrome
NK: Natural killer

ACUTE VERSUS CHRONIC REACTIONS TO FOODS IN PATIENTS WITH FPIES

Reactions of profuse vomiting and lethargy occurring within 2 to 4 hours of food ingestion are commonly termed acute FPIES,[8,9] whereas a subacute or chronic form of FPIES has also been described in association with ongoing antigen exposure.[6,10,11] In the late 1960s and early 1970s, several groups described their experience with cohorts of infants presenting with a pattern of adverse reactions, primarily to milk, that they termed cow's milk intolerance, malabsorption syndrome associated with milk intolerance, cow's milk allergy, or cow's milk enteropathy.[8,10,12-14] These infants presented with vomiting, diarrhea, and failure to thrive. Symptoms resolved on a milk elimination diet and recurred on challenge, and infants commonly outgrew their adverse reactions to milk within the first year of life.

In many of these early studies, biopsy specimens were obtained at the time of admission during chronic milk exposure, after a milk elimination diet when symptoms resolved, and after milk challenge when symptoms recurred. These studies demonstrated marked changes in ***intestinal architecture*** that were triggered by milk in the diet.[12,13,15] These changes in intestinal architecture have led to comparisons with celiac disease; however, there is little to suggest that the pathophysiologic mechanisms are similar between the 2 diseases. In the Finnish FPIES cohorts 2 patterns based on the kinetics of symptoms after milk challenge were described: approximately half of the patients experienced an early response of vomiting and diarrhea appearing within 24 hours of milk challenge, and half had a delayed response appearing only after chronic milk ingestion.[10] Infants were described as progressing from an early response to a delayed response with age as they outgrew their adverse reactions to milk.[15] Recent descriptions of clinical experience with cohorts of FPIES (2 in the United States, 1 in the United Kingdom, 1 in Italy, and 1 in Australia) report only rare instances of delayed or chronic FPIES.[4-6,16,17] Much of our understanding of the gastrointestinal

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Terms in boldface and italics are defined in the glossary on page ■■■.

immune events during FPIES is derived from studies on milk enteropathy; it is not clear whether similar mechanisms might be at play in acute FPIES reactions.

ALLERGENS INDUCING FPIES OR MILK ENTEROPATHY

FPIES is presumed to be caused by the protein component of foods, similar to IgE-mediated food allergy. This is supported by reports in which children with FPIES or enteropathy were challenged with purified milk allergens. Freier et al[14] described 6 infants with milk-induced enteropathy whose symptoms improved on a milk elimination diet. These infants were subsequently challenged with purified milk allergens (***caseins***, ***β-lactoglobulin*** [BLG], ***α-lactoglobulin***, and BSA), with the finding that BLG was the only antigen that induced acute symptoms in the majority of infants (5/6) at a dose present in 30 mL of milk. In a cohort described by Kuitunen et al,[10] the majority of infants challenged with purified milk allergens reacted to both casein and BLG.

Despite the differing findings regarding the role of casein in these 2 cohorts, these findings support the concept that adverse reactions are in fact triggered by the protein fraction of milk. In the case series by Freier et al,[14] infants were described as reacting to BLG that had been boiled for 70 minutes, indicating that ***denaturing*** of the protein did not reduce its immunogenicity. In contrast, the majority of children with IgE-mediated food allergy can tolerate extensively heated milk.[18] This suggests that recognition by the immune system of ***conformational epitopes*** is not playing a role in FPIES. Threshold doses of foods causing symptoms in patients with FPIES are generally in the gram range[16]; in patients with IgE-mediated food allergy, these doses are in the microgram to milligram range.[19] However, there have been case reports of children with active FPIES induced by casein ***hydrolysate formula***[20] or reacting to antigens transmitted through breast milk,[11,21,22] showing that low-abundance antigen can infrequently trigger symptoms.

FPIES can be triggered by foods other than milk, although cow's milk is the most common cause. Many of the foods that trigger FPIES reactions are also IgE-mediated food allergens, including soy, fish, wheat, and egg.[4,5] In adults shellfish have been described to cause non–IgE-mediated reactions consistent with FPIES.[23] However, other foods reported to trigger FPIES are not common IgE-mediated food allergens. Rice is the third most common cause of FPIES in US cohorts, followed by oats.[4,5] Banana, sweet potato, and green peas have all been described as triggers of FPIES, as have meats, including chicken and beef. This list indicates that many common foods have the potential to induce FPIES when introduced to susceptible infants. This is in sharp contrast to celiac disease, in which pathology is triggered by a well-defined antigen ***(gluten)*** found in a restricted subset of foods. Although FPIES can be induced by a very broad spectrum of foods, there is selective food recognition on an individual basis, and children can be reactive to 1, 2, or multiple foods. A positive food challenge reaction to soy reduces subsequent reactions to soy challenge, whereas a positive food challenge reaction to milk does not affect a subsequent reaction to soy.[24] Thus there is clear specificity in the response to foods. This feature of recognition, combined with the common resolution of FPIES with age, suggests that FPIES, like IgE-mediated food allergy, is an inappropriate adaptive immune response to foods.

Furthermore, the timing of adverse reaction onset is consistent with the time required to generate an adaptive immune response. Symptoms to cow's milk typically begin within 2 weeks of

GLOSSARY

CASEINS, β-LACTOGLOBULIN, α-LACTOGLOBULIN: Caseins make up about 80% of the proteins in cow's milk. β-Lactoglobulin and α-lactoglobulin are whey proteins.

CONFORMATIONAL EPITOPE: Nonsequential amino acid residues that become spatially juxtaposed in a folded protein form an available surface on a molecule that is recognized by an antibody.

CYTOTOXIC GRANULES: A principal component of cytotoxic T-lymphocyte effector function. The major components of cytotoxic granules are perforin and granzymes. Perforin disrupts target cell membranes. Granzymes are serine proteases that can cleave substrates or induce protease cascades to promote apoptosis.

DENATURING: Modifying the molecular structure of a protein, especially by using heat, acid, alkali, or UV radiation, so as to destroy or diminish some of the original properties.

GLUTEN: A water-insoluble storage protein moiety of certain cereal grains, including wheat, barley, and rye. Storage proteins (gluten) in wheat are composed of gliadin and glutenin.

HOMING RECEPTOR: Adhesion molecules expressed on lymphocytes. Gut-homing T cells express the α4β7 integrin, which binds to mucosal addressin cell adhesion molecule 1 on gut endothelial cells, and CCR9, a chemokine receptor that binds to the chemokine CCL25 expressed by intestinal epithelial cells. A subset of T cells (intraepithelial lymphocytes) express an integrin (CD103) that allows binding to E-cadherin on the intestinal epithelium.

HYDROLYSATE FORMULA: A formula that has been exposed to either enzymatic or chemical treatments designed to reduce proteins to small peptides. The goal of hydrolysis is to alter the functional properties of ingredients. Hydrolysis reduces IgE reactivity but might not eliminate it completely.

INTESTINAL ARCHITECTURE: In general, there are 5 layers to the small intestinal wall: mucosa, submucosa, circular muscularis, longitudinal muscularis, and serosa. The mucosal surface contains finger-like projections called villi, and the epithelial cells lining the mucosa contain microvilli, which enhance the absorptive surface of the intestine. In addition to absorptive columnar epithelial cells, secretory epithelial cells, including goblet cells, Paneth cells, and enterochromaffin cells, are found within the epithelial layer. The lamina propria is the layer beneath the epithelium and contains connective tissue, lymphocytes, plasma cells, macrophages, dendritic cells, mast cells, and eosinophils.

INVARIANT NATURAL KILLER (NK) T CELLS: A subset of lymphocytes that express surface molecules characteristic of both NK and T cells. NKT cells recognize self-lipids and foreign lipids bound to CD1, a class I MHC–like molecule. They are capable of rapidly secreting cytokines after stimulation. The T-cell receptor α chains in invariant NKT cells have limited diversity and are characterized by a unique Vα24-Jα18 rearrangement.

TGF-β: A regulatory cytokine produced by stromal and hematopoietic cells. TGF-β inhibits proliferation of T and B cells, inhibits activation of macrophages, induces IgA production by B cells through isotype switching, and increases collagen synthesis from fibroblasts to promote tissue repair. Regulatory T-cell production of TGF-β can block T_H1 and T_H2 development in $CD4^+$ T cells.

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