Role of Tolerance in the Development of Eosinophilic Gastrointestinal Diseases

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• Eosinophilic esophagitis • Eosinophilic gastroenteritis
• Oral tolerance • Food allergy

Although the precise link is not completely understood, eosinophilic gastrointestinal diseases (EGIDs) have been shown to be highly associated with atopy. Oral tolerance describes the specific suppression of immune responses to an antigen by prior administration of the antigen by the oral route. Like other allergic gastrointestinal diseases, EGIDs may result from a loss of oral tolerance or a failure in the induction of tolerance. Allergy may be a stimulus for the recruitment of eosinophils to the gastrointestinal tract or may lead to the failure of key regulatory T cells, leading to the loss of immunologic tolerance. Bypassing mechanisms of high-dose tolerance, which include induction of lymphocyte anergy or deletion, may also facilitate the development of EGIDs and other forms of food allergy. Further study to clarify the role of tolerance in the development of EGIDs can help identify potential prevention strategies and therapeutic targets.

EOSINOPHILIC GASTROINTESTINAL DISEASES IN THE SPECTRUM OF FOOD HYPERSENSITIVITY

Gastrointestinal manifestations of food hypersensitivity may range from oropharyngeal pruritus to profuse vomiting and diarrhea and anaphylaxis. Likewise, there is a spectrum of immunologic mechanisms underlying the various forms of food hypersensitivity, from immediate-type IgE-mediated processes to cell-mediated allergy. EGIDs are an increasingly recognized category of disorders characterized by infiltration of the esophageal, gastric, and intestinal walls with eosinophils. Unlike classic IgE-mediated food allergy, eosinophilic esophagitis (EoE) and allergic eosinophilic

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gastroenteritis generally have an insidious onset and result in a range of symptoms, from dysphagia and food impaction to reflux, vomiting, and failure to thrive.

Although dissimilar in their clinical presentations, EGIDs and other forms of food allergy likely have common pathophysiologic mechanisms. Genetic predisposition, allergen sensitization, and environmental factors play important roles in the pathogenesis of these diseases. Although the precise link is not completely understood, EoE has been shown to be highly associated with atopic disease. Sensitization to both food and environmental allergens has been demonstrated in patients with EoE.[1] Studies have shown that a significant proportion of patients with EGIDs have evidence of allergic disease by history or skin testing.[2] In one series of 13 patients, 77% had a history of an allergic disorder (asthma, allergic rhinitis, urticaria, atopic dermatitis, food allergy, or drug allergy) or positive radioallergosorbent testing or skin prick testing.[3] Another study of 21 children revealed that 68% of subjects had a positive result to foods on skin or radioallergosorbent testing.[4]

The mucosal accumulation of eosinophils in the gastrointestinal tract suggests a Th2-mediated process.[1] Murine studies have shown impaired induction of esophageal eosinophilia in response to allergen in mice who are genetically deficient in signal transducer and activator of transcription 6, interleukin (IL)-13, IL-4, and IL-5, providing evidence that allergen-induced EoE is dependent on classic Th2 cytokine signaling.[5] Like other Th2-dependent disease processes, EGIDs likely represent the interplay of extrinsic allergic triggers and intrinsic Th2 cytokines in genetically predisposed individuals.[1] Eosinophils, occasionally discounted as mere markers of disease, likely make important contributions to disease pathogenesis.[1] Eosinophils contain granule proteins, such as major basic proteins 1 and 2, eosinophilic cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase, which have a range of proinflammatory properties. Mast cells and lymphocytes also contribute to the development of disease. (See the articles by authors elsewhere in this issue.)

FUNDAMENTALS OF TOLERANCE

The role of food antigen sensitization is being recognized as a key player in the development of eosinophilic disease. A fundamental principle underlying the development of food allergy is the concept of tolerance. Oral tolerance is used to describe the specific suppression of cellular or humoral responses to an antigen by prior administration of the antigen by the oral route.[6] The lumen of the gastrointestinal tract, the largest immunologic organ in the body, is continually exposed to an array of dietary proteins. Despite the large daily dietary antigen load, most ingested proteins do not provoke local or systemic immune responses. Oral tolerance presumably evolved as an analog of self-tolerance to prevent hypersensitivity reactions to food proteins and bacterial antigens present in the mucosal microbiota.[7] It is a natural immunologic process driven by exogenous antigens, ultimately allowing them to gain access to the body without activating a potentially damaging immune response.

In the mid-twentieth century, Chase[6] established that oral feeding of an antigen induces T cell–mediated inhibition of subsequent immune responses, or oral tolerance (**Fig. 1**). He contrasted the induction of oral tolerance from the generation of strong cell-mediated and humoral responses that follows subcutaneous immunization and booster administration of an antigen. Further experiments demonstrated that the transfer of T cells from antigen-fed ‘‘tolerant’’ mice to naive mice also resulted in reduced in vitro immune responses to subcutaneous immunization.

Antigen exposure in the gut results in several major immunologic responses. The local production and release of noninflammatory secretory IgA antibody is the initial