Mechanisms Underlying Induction of Tolerance to Foods

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KEYWORDS

• Tolerance • Treg • Foxp3 • IgE • IgG4 • Immunotherapy • Microbiota

KEY POINTS

- Oral tolerance is mediated by allergen-specific Tregs that are generated by mucosal dendritic cells.
- Factors such as intestinal mucin and cytokines produced by epithelial cells and innate lymphoid cells contribute to tolerance by modifying the phenotype of gastrointestinal dendritic cells.
- Oral tolerance by early dietary introduction can prevent peanut allergy in infants at high risk of peanut allergy.
- Humoral mechanisms, in particular the generation of allergen-specific IgG4, are associated with development of tolerance to foods in humans.
- Clinical tolerance induced by immunotherapy is associated with immune changes in basophils, IgG4, allergen-specific Th2 cells, and allergen-specific cells with regulatory markers.

IMMUNE MECHANISMS OF ORAL TOLERANCE

An early description of the phenomenon of oral tolerance was provided by Wells and Osborne in 1911, when they described a series of studies showing that guinea pigs could not be induced to undergo experimental anaphylaxis to corn or oats if it was a component of the diet.[1] In the intervening century, there has been a growing body of literature defining the immune mechanisms of oral tolerance. Classic oral tolerance experiments are performed by feeding of antigen, either a single high-dose

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(50–100 mg) feed or multiple low doses (0.5–1 mg) administered daily by gavage or in the drinking water for 5 to 7 days. Oral tolerance is then defined as the suppression of an immune response elicited by immunization, and commonly measured by reduction in cytokine production by lymph node cells re-stimulated with allergen in vitro, delayed type hypersensitivity reaction (ear swelling on injection), or reduction of anaphylaxis or allergic symptoms.

Role of Regulatory T Cells

The appreciation that oral tolerance was an active regulatory immune response rather than solely caused by deletion or anergy of antigen-specific cells came from studies in which tolerance could be transferred to naive animals through the transfer of CD4+ or CD8+ lymphocytes. Weiner and colleagues[2,3] first described a population of cells termed Th3 cells, that express surface transforming growth factor (TGF)-beta and can be identified by staining for latency-associated peptide. These cells do not express CD25 or Foxp3, and suppress by a TGF-beta–dependent mechanism.[4] In addition to these cells, antigen-specific Tregs expressing the transcription factor Foxp3 are also induced in response to antigen feeding, and these iTregs also suppress through a TGF-beta–dependent mechanism.[5,6] Tr1 cells that are interleukin (IL)-10 dependent and suppress through an IL-10–dependent mechanism are involved in the prevention of colitis and microbial-induced inflammation in the intestine,[7] but most studies have shown that IL-10 is dispensable for the induction of tolerance to food antigens.[6,8] Some of this difference in mechanisms may have to do with the site of regulatory responses. The greatest antigenic burden from food occurs in the small intestine, whereas the greatest antigen burden from the microbiota (and subsequent inflammation) occurs in the colon.

Site of Initiation of Tolerance

The mucosal immune system is the largest lymphoid organ in the body, and comprises organized lymphoid structures and a densely packed population of resident immune cells found in the epithelium and underlying lamina propria. Organized structures include Peyer's patches (PP) and isolated lymphoid follicles that are located within the mucosal tissue, as well as mesenteric lymph nodes (MLN) that drain the intestine via lymphatics. The digestive process breaking down food proteins to small peptides and amino acids that can be absorbed by enterocytes begins in the stomach and continues in the duodenum and jejunum. However, a small percentage of intact protein escapes digestion and is absorbed across the mucosal barrier in a form that is immunologically active (ie, that can be presented by antigen-presenting cells). Antigen can be acquired through several different mechanisms. Microfold or M cells are flattened epithelial cells that overlie PP and are specialized for the uptake of particulate antigens such as viruses and bacteria. Some food antigens have also been shown to be selectively sampled through the PP.[9,10] Soluble food antigens are excluded from passing between enterocytes by tight junctions, but are taken up by fluid phase endocytosis and transported to the underlying immune cells. Recently, a novel mechanism of small intestinal antigen uptake was identified through goblet cell–associated antigen passages or *GAPs*.[11] A conduit was identified in small intestine that rapidly filled with luminal antigen, delivering antigen to lamina propria dendritic cells (DCs). This mechanism of antigen uptake was under the control of cholinergic regulation, showing an important point of control of mucosal immunity by nerves in the gastrointestinal tract.[11] Intestinal mononuclear phagocytes have been shown to extend dendrites between enterocytes, reaching into the lumen and pulling antigen across the epithelium without disrupting the integrity of the tight junctions between cells.[12,13]