Oral Tolerance Development and Maintenance

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KEYWORDS

• Food allergy • Immune tolerance • Microbiome • Mucosal immunity
• Immunotherapy • $CD4^+$ T cells • Dendritic cells

KEY POINTS

- The gastrointestinal tract has an abundant mucosal immune system to develop and maintain oral tolerance.
- The oral route of administration takes advantage of the unique set of immune cells and pathways involved in the induction of oral tolerance.
- Food allergy results from a loss of oral tolerance toward ingested antigens.
- Oral immunotherapy is thought to initiate desensitization through interaction of an allergen with mucosal dendritic cells that initiate downstream immune system modulation through regulatory T cells and effector T cells.

INTRODUCTION

Tolerance is the the ability to endure what one cannot avoid and is also referred to as an accepted dispensation to particular rules. When applied to orally administrated antigen, the definition of tolerance represents the capacity of the immune system to adapt to innocuous dietary proteins and commensal bacteria because we are unable to avoid them. These antigens are detected in the gut epithelium and lamina propria (LP) within minutes after consumption,[1] suggesting a critical role of the gastrointestinal (GI) tract in oral tolerance development. Currently, it is postulated that this state of unresponsiveness to ingested antigens is initiated by tolerogenic CD103 + DCs residing in the GI LP.[2] Following capture of luminal antigens, these cells migrate to the draining lymph node to present antigen-derived epitopes to induce antigen-specific regulatory CD4 + T cells. Failure to develop oral tolerance can lead to a cascade of adverse reactions such as immunoglobulin E (IgE)-mediated food allergies, celiac disease, autoimmune diseases, and infections. These immune-related disorders have emerged as

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Immunol Allergy Clin N Am ■ (2017) ■–■
https://doi.org/10.1016/j.iac.2017.09.003
immunology.theclinics.com

major health problems worldwide because of the rapid increase in prevalence over the past decade.[3] Food-induced allergic reactions are an immediate, adverse reaction triggered predominantly by cross-linking of food-derived antigen-specific IgE bound to the high-affinity IgE receptor FcεR on mast cells after reexposure to allergen.[4,5] These allergic reactions can cause clinical symptoms ranging from mild mouth itching and abdominal pain to life-threatening anaphylaxis. Standard of care is allergen avoidance and prompt treatment of allergic reactions when they develop after accidental ingestion. One promising area of current investigation is the use of oral immunotherapy (OIT) as a method to eventually restore oral tolerance to food. Improving the understanding of oral tolerance mechanisms will aid in the reduction of food allergy prevalence rates through preexposure prophylaxis (due to natural tolerance development) and create new strategies for food allergy therapy (due to induced tolerance).

THE GASTROINTESTINAL MUCOSA: A UNIQUE PLACE IN ORAL TOLERANCE DEVELOPMENT

The GI tract is exposed to a large array of non-self-antigen on a continual basis, including numerous commensal bacteria and well over 30 kg of food proteins per year.[6] Nevertheless, the GI immune system does not elicit cellular or humoral immune responses to these harmless antigens because it protects against pathogenic microbes. This phenomenon of balancing the immune response to commensal microbes and food has been termed “oral tolerance” and refers to local and systemic immune unresponsiveness to orally administered soluble antigens. It may develop naturally or be induced by allergen immunotherapy. The GI mucosa is the largest immunologic site in the body designed to distinguish between beneficial and harmful components in the gut to maintain systemic immune tolerance.[7,8] It is composed of 3 major compartments: the epithelial layer, the LP, and the gut-associated lymphoid tissue (GALT), where adaptive immune responses are initiated.[9] Immune responses in the gut are efficiently induced in mesenteric lymph nodes (mLN) and Peyer patches (PP), which are the main components of the organized GALT. PPs are lymphoid-cell accumulation areas found in the submucosa, primarily the small intestine, and consist of B-cell follicles and surrounding T-cell areas. Intestinal epithelial cells form a tight and selective barrier that allows highly controlled paracellular and transcellular transport of molecules or antigens necessary to the induction of appropriate immune responses in the gut.[10] The barrier function of the GI tract is aided by the presence of a protective, hydrophobic mucus-coated surface that traps antigen and dimeric IgA that binds food proteins. Together this prevents absorption of antigen across the intestinal epithelium.[11] However, an estimated 2% of gut luminal food proteins pass through the gut epithelium intact and are disseminated locally or systemically through the circulation or the lymphatic system.[12] Tissue-resident T lymphocytes are abundant in the GI immune system and play important roles in mucosal immunity and oral tolerance.[13] Their adaptation to these environments requires constant discrimination between natural stimulation coming from harmless microbiota and food, and pathogens that need to be cleared. Several factors are involved to ensure durable tolerance to harmless intestinally derived antigens, including the dose, nature, and routes of antigen entry at sensitization. Physical barriers, digestion, and composition of the intestinal flora are also thought to contribute to the ability to develop oral tolerance.[14] The microbiome is a complex collection of resident bacteria in the gut and elsewhere that can profoundly impact immune responses in the GI tract. For instance, gut microbiota has been associated with increased production of IgA that may protect against food allergy by neutralizing food antigens and limiting their access to the immune system.[15,16]