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Molecular and cellular mechanisms of food allergy and food tolerance

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Ingestion of innocuous antigens, including food proteins, normally results in local and systemic immune nonresponsiveness in a process termed oral tolerance. Oral tolerance to food proteins is likely to be intimately linked to mechanisms that are responsible for gastrointestinal tolerance to large numbers of commensal microbes. Here we review our current understanding of the immune mechanisms responsible for oral tolerance and how perturbations in these mechanisms might promote the loss of oral tolerance and development of food allergies. Roles for the commensal microbiome in promoting oral tolerance and the association of intestinal dysbiosis with food allergy are discussed. Growing evidence supports cutaneous sensitization to food antigens as one possible mechanism leading to the failure to develop or loss of oral tolerance. A goal of immunotherapy for food allergies is to induce sustained desensitization or even true long-term oral tolerance to food allergens through mechanisms that might in part overlap with those associated with the development of natural oral tolerance. (J Allergy Clin Immunol 2016;137:984-97.)

Key words: *Food allergy, microbiome, sensitization, desensitization, immunotherapy, tolerance, regulatory T cells, basophils, mast cells, dendritic cells*

Abbreviations used

APC:	Antigen-presenting cell
DC:	Dendritic cell
DNFB:	2,4-Dinitrofluorobenzene
EPIT:	Epicutaneous immunotherapy
Foxp3:	Forkhead box protein 3
GALT:	Gut-associated lymphoid tissue
GPR:	G protein–coupled receptor
M cell:	Microfold cell
MLN:	Mesenteric lymph node
OIT:	Oral immunotherapy
OVA:	Ovalbumin
SCFA:	Short-chain fatty acid
SLIT:	Sublingual immunotherapy
Treg:	Regulatory T

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To maintain immune tolerance, the immune system must not only be able to distinguish self from nonself antigens but also to discriminate between innocuous nonself and threatening nonself antigens. The gastrointestinal tract represents a unique challenge to the immune system in making these distinctions and in maintaining tolerance for several reasons. It is the largest interface between the body and the external environment, with the intestinal mucosa having a surface area of more than 300 m^2.[1] As such, it encounters a huge quantity and diversity of foreign antigens representing nonself antigens (ie, >30 kg of food proteins each year),[2] as well as the products of trillions of resident bacteria representing more than 1000 species.[3]

Maintaining tolerance requires complex interactions between nonimmune cells and cells making up the gut-associated lymphoid tissue (GALT), which contains 10^{12} lymphoid cells per meter of gut and more immunoglobulin-producing cells than the rest of the body.[4,5] These cells must act in concert to limit inflammatory responses to resident bacteria and food proteins that could lead to tissue injury, keep microbes confined to the gut, and recognize and respond to pathogens that can cause tissue injury or disease. Failure to achieve an appropriate balance in these roles can lead to a loss of tolerance, resulting in inflammatory diseases, such as inflammatory bowel disease, or responses to innocuous food antigens, such as those occurring in patients with celiac disease and ***IgE***-mediated food allergies.

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Terms in boldface and italics are defined in the glossary on page 985.

GLOSSARY

α4β7: An integrin expressed on lymphocytes that is shown to promote T-cell homing into gut-associated lymphoid tissues through its binding to mucosal addressin cell adhesion molecule, which is present on high endothelial venules of mucosal lymphoid organs.

ANTIGEN-PRESENTING CELLS (APCs): Cells that present antigens through MHCs on their surfaces to T-cell receptors on T cells.

Ara h 1, Ara h 2: Proteins found in peanuts that are known to be food antigens.

αVβ8: A member of the integrin family of transmembrane proteins that mediates cell-cell and cell–extracellular matrix adhesion.

B220: A CD45 isoform and a commonly used B-cell marker predominantly expressed on all mouse B lymphocytes.

BUTYRATE: A short-chain fatty acid and major microbial fermentation metabolite in the lumen of the colon that has been shown to be a critical mediator of the colonic inflammatory response. Without butyrates for energy, colon epithelial cells undergo autophagy and die.

CCR7: A chemokine receptor involved in the adhesion and migration of immune cells. Signals mediated by this receptor regulate T-cell homeostasis in lymph nodes and facilitate DC migration (eg, from the gut to the mesenteric lymph nodes).

CCR9: A chemokine receptor involved in the adhesion and migration of immune cells. CCR9 has also been shown to promote the migration of T lymphocytes (T cells) to the gastrointestinal tract.

CD11c: A cell-surface molecule expressed on many immune cells, with especially high abundance on many dendritic cells.

CD14: A coreceptor for bacterial LPS and other pathogen-associated molecular patterns, such as lipoteichoic acid, which is expressed on subsets of monocytes, dendritic cells, and other hematopoietic cells.

CD45: A receptor-linked protein tyrosine phosphatase that is expressed on all leukocytes.

CHOLERA TOXIN: A highly toxic protein secreted by the bacterium *Vibrio cholerae*, which causes severe gastric inflammation in animals. It is often used as an adjuvant to induce an immune response in biological experiments.

CpG SITES: Regions of DNA where a cytosine nucleotide occurs next to a guanine nucleotide separated by only 1 phosphate. Methylation of the cytosine within CpG sites of a gene can turn the gene off through epigenetic regulation.

CX3CR1: A chemokine receptor involved in the adhesion and migration of immune cells. It is expressed on a subset of phagocytic cells in the small intestine.

DENDRITIC CELLS (DCs): Professional antigen-presenting cells that link the innate and adaptive immune systems by capturing and then presenting antigens to T cells.

FOLLICULAR HELPER T (T_{FH}) CELLS: A specific subset of effector T cells that traffic to the B-cell areas of secondary lymphoid tissues, such as through interactions mediated by the chemokine receptor CXCR5 and its ligand, CXCL13. T_{FH} cells can regulate antigen-specific B-cell development and antibody production.

HAPTENS: Small molecules that elicit an immune response only when covalently bound to a large carrier, typically a protein antigen.

IgA: The main immunoglobulin found in mucous secretions. Secretory IgA is resistant to degradation by proteolytic enzymes in the gastrointestinal tract, where it provides protection against pathogens.

IgE: An antibody (immunoglobulin) associated with type 2 immunity, including allergic responses. Found only in mammals, IgE antibodies bind allergens and can help to enhance host resistance to parasites (eg, helminths and protozoans) and increase resistance to venoms in mice. When bound to allergens and FcεRI on basophils and mast cells, antigen- and IgE-induced aggregation of FcεRI can trigger release of histamine, proteases, prostaglandins, leukotrienes, chemokines, and cytokines.

IgG_4: A subtype of immunoglobulin IgG, IgG_4 can be produced in part to dampen inflammation by helping to curtail Fc receptor (FcR)–mediated processes.

IL-5: A major maturation and differentiation cytokine expressed by T_H2 cells and eosinophils in mice and human subjects. IL-5 has been shown to play an instrumental role in eosinophilic inflammation in patients with allergic diseases.

IL-6: A cytokine implicated in a wide variety of inflammation-associated disease states, it is involved in the maturation of B cells and has been shown to be an endogenous pyrogen capable of inducing fever in patients with autoimmune diseases or infections.

IL-10: A cytokine produced primarily by monocytes and, to a lesser extent, by lymphocytes (particularly Treg cells) and mast cells that has pleiotropic effects in immunoregulation and inflammation by limiting the immune response to pathogens and thereby limiting damage to the host.

IL-22: A cytokine that has important functions in host defense both at mucosal surfaces and in tissue repair. It appears to be unique in that it is produced by immune cells, including T-helper cell subsets and innate lymphocytes, but acts mostly on nonhematopoietic stromal cells, in particular epithelial cells, keratinocytes, and hepatocytes.

IL-25: A cytokine known to be involved in mucosal immunity. It induces production of the type 2 cytokines IL-4, IL-5, and IL-13.

IL-33: Belonging to the IL-1 family of cytokines, IL-33 potently drives production of type 2 cytokines. It is a ligand for IL-33 receptor (IL1RL1), an IL-1 family receptor that is selectively expressed on T_H2 cells and mast cells.

INHIBITORY FCγ RECEPTORS: Receptors that downregulate the immune complex–mediated inflammatory responses on phagocytes and IgE- and antigen-induced activation of mast cells and basophils when cross-linked with stimulatory Fcγ receptors (FcγRs).

INNATE LYMPHOID CELLS (ILCs): Innate immune cells that belong to the lymphoid lineage but cannot respond in an antigen-specific manner because they lack a B- or T-cell receptor. ILCs are a recently described group of cells with physiologic functions analogous in some ways to helper T cells and cytotoxic natural killer cells. They have a role in protective immunity and the regulation of homeostasis and inflammation. Their dysregulation has been shown to contribute to immune pathology and diseases, such as allergy and autoimmune disease.

MHC CLASS II: A complex that presents antigen derived from extracellular proteins to $CD4^+$ T cells.

MHC TETRAMERS: Fluorescently labeled tetrameric MHC-peptide complexes that enable the direct detection, quantification, and phenotypic characterization of antigen-specific T cells by using flow cytometry.

MICROFOLD CELLS (M CELLS): Specialized epithelial cells of the gastrointestinal tract that sample antigens.

OVALBUMIN: The most abundant protein found in egg white, ovalbumin is a well-characterized allergen used in immunologic studies in mice.

OX40–OX40 LIGAND: Members of the TNF superfamily expressed on a variety of cells, including activated $CD4^+$ and $CD8^+$ T cells. The OX40-OX40 ligand (OX40L) complex has been shown to regulate cytokine production from T cells (including differentiation to T_H2 cells), antigen-presenting cells, natural killer cells, and natural killer T cells and also modulate cytokine receptor signaling. In mice Treg cells can directly inhibit the FcεRI-dependent degranulation of mast cells through cell-cell contact involving OX40-OX40L interactions between Treg cells and mast cells, respectively. The OX40-OX40L complex plays a central role in the development of multiple inflammatory and autoimmune diseases.

PROPIONATE: A short-chain fatty acid and a major microbial fermentation metabolite in the human gut with putative health effects that extend beyond the gut epithelium.

RETINOIC ACID: A metabolite derived from retinol (vitamin A) that plays important roles in cell growth and differentiation, including differentiation of Treg cells.

STAPHYLOCOCCAL ENTEROTOXIN B: A superantigen produced by the bacterium *Staphylococcus aureus* that elicits cytokine release.

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