Mechanisms of food allergy

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Although oral tolerance is the normal physiologic response to ingested antigens, a breakdown in this process appears to have occurred in the past 2 decades, leading to an increasing prevalence of sensitization to food allergens. Over the past decade, basic research has intensified in an attempt to better understand the mechanisms leading to sensitization and disease versus desensitization and short- and long-term tolerance. In this review we assess various factors that can influence tissue and immune responses to food antigens, the current understanding of immune tolerance development, the role of the gastrointestinal microbiota, and current knowledge regarding immunologic mechanisms involved in desensitization and sustained unresponsiveness, although perhaps the latter is more appropriately termed remission. (J Allergy Clin Immunol 2018;141:11-9.)

Key words: *Food allergy, sensitization, tolerance, desensitization, sustained unresponsiveness, remission, allergen immunotherapy, microbiota*

Abbreviations used
AD: Atopic dermatitis
Breg: Regulatory B
DC: Dendritic cell
EC: Epithelial cell
FoxP3: Forkhead box P3
ILC: Innate lymphoid cell
ILC3: Type 3 innate lymphoid cell
OIT: Oral immunotherapy
Treg: Regulatory T

The prevalence of food allergy is increasing, and the development of more accurate diagnostic methods, prevention, and treatment require a better understanding of the underlying mechanisms. Oral tolerance is the normal physiologic response to ingested antigens, and a breakdown in this process results in sensitization to food allergens.[1]

Studies for a better understanding of the mechanisms leading to sensitization and disease versus desensitization and short- and long-term tolerance are being pursued intensively.[2] A number of animal models have been developed to investigate cellular and molecular events, which lead to food allergen sensitization and anaphylaxis.[2-5] One key finding has been that oral administration of a protein to an animal normally induces tolerance but can result in sensitization and allergic disease.[6] The responses in animal models have been shown to be influenced by a long list of factors that damage the epithelial barrier (Box 1).[7-10] These models also suggest that sensitization to food allergens can actually occur through other sites, such as the airways or skin, in contrast to the intestine, where oral tolerance is typically the default response.

The results of these murine models also support the observation that early skin barrier disruption caused by inflammation or genetic defects (eg, filaggrin gene mutations) are associated with increased rates of food sensitization in human subjects.[11] However, studies on IgE responses and digestibility of food proteins suggest that the oral route of exposure is also an important path for sensitization to food allergens.

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Terms in boldface and italics are defined in the glossary on page 12.

This review presents an overview of mechanisms of food allergy, focusing in particular on pathways leading to immune tolerance. In addition, it includes suggestions for new nomenclature on the definition of sustained unresponsiveness, desensitization, and tolerance.

ANTIGEN-SPECIFIC IMMUNE RESPONSE DEVELOPMENT TO FOOD ANTIGENS

Sensitization to food antigens can take place in the gastrointestinal tract, oral cavity, and skin and occasionally in the respiratory tract. After ingestion, the vast majority of food proteins are broken down largely by gastric acid and digestive enzymes in the stomach and intestine. Subsequently, the remaining intact food proteins and peptides are transported from the lumen to the mucosa through gut epithelial cells (ECs) and by specialized ECs called M cells that are localized above Peyer patches.

In addition, direct sampling of ingested antigens/allergens can occur when mucosal dendritic cells (DCs) extend dendrites into the gut lumen. In the mucosa DCs internalize and process these proteins and peptides and move to T-cell areas of draining lymph nodes, where the DCs can interact with naive T cells and present antigen on ***MHC class II*** molecules (Fig 1).[12] The activation of

GLOSSARY

CD28: A protein expressed on T cells that provides costimulatory signals required for T-cell activation and survival, cytokine production, and T_H2 development.

CD80 AND CD86: Also known as B7-1 and B7-2, CD80 and CD86 are proteins expressed on dendritic cells, activated B cells, and monocytes that work in tandem to provide a costimulatory signal necessary for T-cell activation and survival. They are ligands for the T-cell proteins CD28 and cytotoxic T lymphocyte–associated protein 4.

CCR6: A protein that belongs to family A of the G protein–coupled receptor superfamily that is expressed preferentially by immature dendritic cells and memory T cells. The ligand of this receptor is macrophage inflammatory protein 3α. CCR6 is known to be important for B-lineage maturation and antigen-driven B-cell differentiation and is thought to regulate the migration and recruitment of dendritic and T cells during inflammatory and immunologic responses.

CYTOTOXIC T LYMPHOCYTE–ASSOCIATED PROTEIN 4 (CTLA-4): A receptor that functions as an inhibitory signal that downregulates immune responses when bound to CD80 and CD86. CTLA-4 is constitutively expressed in regulatory T cells but is only upregulated in conventional T cells after activation.

GM-CSF: Also known as colony-stimulating factor 2, GM-CSF is a monomeric glycoprotein secreted by macrophages, T cells, mast cells, natural killer cells, endothelial cells, and fibroblasts and functions as a cytokine. GM-CSF functions as a white blood cell growth factor and stimulates stem cells to produce granulocytes (neutrophils, eosinophils, and basophils) and monocytes.

GRANYZMES A AND B: Serine proteases that are released by cytoplasmic granules within cytotoxic T cells and natural killer (NK) cells. They induce programmed cell death in the target cell, thus eliminating cancerous or infected cells. In NK cells and T cells the granzymes are packaged in cytotoxic granules with perforin. Granzyme A is the most abundant and activates a novel programmed cell death pathway, whereas granzyme B activates apoptosis through activation of caspases (especially caspase-3), which in turn cleaves many substrates, including caspase-activated DNase to execute cell death.

IL-1β: A member of the IL-1 cytokine family that is produced by activated macrophages as a proprotein, which is proteolytically processed to its active form by caspase 1. IL-1β is an important mediator of the inflammatory response and is involved in a variety of cellular activities, including cell proliferation, differentiation, and apoptosis.

IL-6: A cytokine also known as IFN-β2, IL-6 is implicated in a wide variety of inflammation-associated disease states, has been associated with the maturation of B cells, and has been shown to act as an endogenous pyrogen capable of inducing fever in patients with autoimmune diseases or infections.

IL-22: A cytokine that has important functions in host defense at mucosal surfaces, as well as in tissue repair. It is unique in that it is produced by immune cells, including T_H cell subsets and innate lymphocytes, but acts only on nonhematopoietic stromal cells, in particular epithelial cells, keratinocytes, and hepatocytes.

IL-35: An IL-12 family cytokine produced by regulatory, but not effector, T and B cells and plays a role in immune suppression.

MHC CLASS II: A complex critical in initiating immune responses, MHC class II is found on antigen-presenting cells and presents antigen derived from extracellular proteins to T-cell receptors.

OX40 AND OX40 LIGAND: Members of the tumor necrosis factor superfamily expressed on a variety of cells, including activated $CD4^+$ and $CD8^+$ T cells. The OX40–OX40 ligand complex has been shown to regulate cytokine production from T cells, antigen-presenting cells, natural killer cells, and natural killer T cells while modulating cytokine receptor signaling. This complex plays a central role in the development of multiple inflammatory and autoimmune diseases, making them ideal therapeutic candidates.

PROGRAMMED CELL DEATH 1 (PD-1): A cell-surface receptor that plays an important role in downregulating the immune system and suppressing inflammatory T-cell activation. PD-1 is an immune checkpoint that serves the dual role of promoting apoptosis in antigen-specific T cells while simultaneously reducing apoptosis in regulatory T cells.

γ/δ T CELLS: A small subset of T cells comprising the highest abundance of T cells in the gut mucosa that possess a distinct T-cell receptor (TCR) on their surface. These T cells have a TCR that is made up of one γ chain and one δ chain, unlike most T cells, which are αβ T cells.

TGF-β: A cytokine secreted by many cell types, including macrophages, that controls proliferation, cellular differentiation, and inflammatory processes in a variety of cells. It also plays a role in T-cell regulation and differentiation.

TOLL-LIKE RECEPTOR 4 (TLR4): A member of the Toll-like receptor family, TLR4 is a human transmembrane protein that belongs to the pattern recognition receptor family. Its activation leads to activation of the innate immune system through an intracellular signaling pathway, nuclear factor κB, and inflammatory cytokine production. TLR4 recognizes LPS, which is a component present in many gram-negative bacteria and select gram-positive bacteria. Its ligands also include several viral proteins, polysaccharides, and a variety of endogenous proteins.

TOLL-LIKE RECEPTOR 8 (TLR8): A member of the Toll-like receptor family, TLR8 is an endosomal receptor that recognizes single-stranded RNA (ssRNA) and can recognize ssRNA viruses, such as influenza, Sendai, and Coxsackie B viruses.

TYPE 3 INNATE LYMPHOID CELLS (ILC3s): Defined by their production of the cytokines IL-17A, IL-22, or both. They are the innate counterpart to T_H17 cells, sharing the common transcription factor of retinoic acid–related orphan receptor γt.

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