Overview of Gut Immunology
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Abstract
The gastrointestinal tract (GI tract) plays dual roles in human physiology: digestion and uptake of nutrients and the more daunting task of maintaining immune homeostasis (protecting the body from potentially harmful microbes, while inducing tolerogenic responses to innocuous food, commensals and self-antigens). The unique architecture of the GI tract facilitates both of these functions; multiple levels of infolding results in an immense overall surface area that allows maximal nutrient absorption while housing the largest number of immune cells in the body. This review will focus on how mucosal immune responses generated in the GI tract are organized and controlled. The gastro-intestinal associated lymphoid tissue (GALT), which is composed of discrete inductive and effectors sites, is able to discriminate between harmful and harmless antigens while maintaining homeostasis. Inductive sites are organized into specialized aggregations of lymphoid follicles called Peyer's patches (PP), while effector sites are more diffusely dispersed. The separation of these sites serves to limit and control immune responses. In addition to its distinct architecture, the GI tract has specialized immune cells that aid in promoting a tolerogenic response to orally introduced antigens, (e.g., subsets of dendritic cells (DCs) and regulatory T-cells (T_R)). Secretory IgA (sIgA), which is produced in appreciable quantities at mucosal surfaces, also promotes an anti-inflammatory environment by neutralizing immune stimulatory antigens. The mechanisms of induction tolerance are currently poorly understood; however, this tolerant environment limits potentially damaging inflammatory responses to inappropriate stimuli.

Introduction: Tolerance vs. Inflammation
The GI tract has the difficult task of protecting the body from potentially pathogenic organisms (PPOs) while at the same time providing an environment tolerant to commensal microbes, dietary antigens, and self-antigens. Mucosal surfaces are the site of entry for many pathogens; however these regions of high susceptibility are also constantly mounting immune responses, whether inflammatory or tolerogenic, to the numerous antigens that come into contact with the mucosa. Because the majority of antigens that come in contact with mucosal surfaces are nonharmful, the majority of immune responses elicited in these regions induce tolerance. Systemic nonresponsiveness to antigens that are introduced orally is a phenomenon known as oral tolerance.

There are multiple mechanisms involved in induction of tolerance in the GI tract (Table 1). Mechanisms broadly fall into two categories: antigenic ignorance and active tolerance. Antigenic ignorance involves preventing antigens and microbes from gaining access to the immunoreactive areas within the GI tract. Active tolerance involves induction of antigen specific and nonspecific anti-inflammatory responses and/or deletion of reactive immune cells. In studies of oral tolerance in mice, low-dose oral antigens led to an active suppression of the gut immune response while high-dose feeding regimens led to anergy. Oral tolerance is typically characterized by the

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Table 1. Mechanisms of immune tolerance in the GI tract. Many of the factors within the gastrointestinal tract sway immune responses towards a tolerant environment

<table>
<thead>
<tr>
<th>Mechanisms of Immune Tolerance in the GI Tract</th>
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<tr>
<td>• Production of secretory IgA (sIgA)</td>
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<tr>
<td>• Preference for Th2 responses</td>
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<td>• Unique anatomical design</td>
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<td>• Presence of specialized immune cells</td>
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<td>• Specialized adhesion molecules and chemokine receptors</td>
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<td>• Effects of the indigenous microbiota</td>
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suppression of the systemic Th1 response to antigens and elevated levels of IL-10, TGF-β, and antigen-specific sIgA at the mucosal surface. The Th2 response also promotes the induction of tolerance in the gut. Production of IL-4 and IL-5 during Th2 responses acts synergistically to enhance IgA production. These cytokines also act to further inhibit the Th1 response.

Several factors can prevent induction of oral tolerance as demonstrated in animal models. Co-inoculation of antigen along with an adjuvant, such as cholera toxin or saponin, will provoke a robust immune response. In addition, deletion of the indigenous microbiota using either germfree animals or broad spectrum antibiotics prevented induction of oral tolerance. While tolerance may be the default response, the GI tract must also protect against PPOs, which include both "professional" and "opportunistic" pathogens. "Professional" or toxin-producing pathogens are acquired from exogenous sources, causing harm to the host (e.g., E. coli O157:H7). "Opportunistic" pathogens are often normal members of the microbiota but can cause harm to the immune suppressed host often due to overgrowth (e.g., Candida albicans). Both innate and adaptive responses collaborate in controlling infections by PPOs and preventing systemic dissemination via the GI tract to the bloodstream. The dynamic interactions that occur in the normal gut create an environment that is tolerant to dietary antigens, protective against potential pathogens, and able to maintain gut immune homeostasis.

Gastrointestinal Tract Architecture

The architecture of the gastrointestinal tract is designed to facilitate the dual roles handled by the organ: nutrient uptake and defense against PPOs. The vast surface area of the GI tract (~200 m²) is the result of several levels of invagination at the tissue (Kerkring folds), cellular (villi) and membrane levels (microvilli). At the cellular level, villi are lined with intestinal epithelial cells (IECs) that have absorptive microvilli to optimize the absorption of nutrients released during digestion. The tips of these microvilli form the filamentous brush border glyocalyx (FBBG) that is composed of a layer of membrane-anchored glycoproteins, which allow nutrients to cross, while restricting entry of whole bacteria or large molecules. To block entry and/or reduce damage caused by PPOs, the GI tract has an effective repertoire of defense mechanisms. The protective defenses of the GI tract include physical barriers, antimicrobial compounds and specialized immune responses. The luminal contents are separated from underlying lymphoid tissue by the intestinal epithelium, which serves as a restrictive physical barrier held together by intercellular tight junctions that can block extremely small molecules (>2 kDa). Antimicrobial peptides, mucins and trefoil peptides also act to restrict pathogen access to mucosal surfaces. In addition to these host factors, the indigenous microbiota plays an active role in not only preventing establishment of PPOs via competitive exclusion, but also by influencing the gut immune responses (discussed later).

The architecture of the gastrointestinal associated lymphoid tissue (GALT) is designed to limit and control immune responses via separation of inductive and effector sites. Inductive sites consist of organized aggregation of lymphoid follicles and include the Peyer's patches (PP) and mesenteric