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Innate immune recognition on the intestinal mucosa

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Abstract

The discovery of transcriptionally activating receptors for microbial structures has provided a deeper understanding of how the immune system manages to sense and localize the presence of harmful microbes and target and shape the adequate host response. However, the recognized microbial structures are common to pathogens and commensal microbes and many body surfaces are constantly exposed to environmental microbial ligands and densely colonized by a bacterial flora such as seen for example in the intestinal tract. Thus, mechanisms must exist that facilitate discrimination between benign and beneficial colonization and potentially harmful invasive infection. Identification of the mechanisms involved and characterization of the underlying molecular processes will add to our understanding of mucosal immune defense and might unravel the etiology and pathogenesis of so far undefined inflammatory conditions. Here, we will discuss factors that might be involved to control inappropriate innate immune activation and ensure the host–microbe homeostasis in the intestinal tract.

Keywords: Innate immunity; Intestinal mucosa; Commensal microflora; Host–microbe homeostasis; Inhibition of TLR4 signaling

The anatomical site

The human intestinal epithelium comprises more than 300 m^2 of mucosa and thus represents the largest human body surface constantly exposed to environmental substances, nutrients, and microorganisms. The small intestinal surface is build up from epithelial protrusions called villi and gland-like invaginations called crypts and by its spatial extension allows efficient nutrient and water uptake. The epithelial cell layer is constituted by a number of specialized cell types. The most prominent cell type is the absorptive enterocyte. Enterocytes are covered with finger-like membrane protrusions, microvilli, at the apical surface and tightly connected to each other by firm proteinaceous cell–cell contacts, tight membrane junctions made of adhesion proteins. Enterocytes are constantly created from stem cells at the lower half of the crypts and undergo a specific cell differentiation program while migrating upwards the crypt-villus axis (Pinto et al., 2003). At the villi apex, they are shed in an apoptotic process called anoïkis. Constant proliferation, migration, and differentiation facilitate continuing renewal of the epithelial mucosa and have been estimated to result in replacement of the entire surface epithelium approximately every 2–5 days. Non-enterocytes diverge early during cell differentiation and form Paneth, goblet, and endocrine cells (Yang et al., 2001). Endocrine cells secrete hormone-like peptide mediators involved in regulatory processes of

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gut physiology. Goblet cells or mucin-secreting cells are found scattered over the epithelial surface and produce large amounts of mucus that builds a mucus layer covering the epithelial surface (Walker et al., 1977; Corfield et al., 2000). They also mature during their migration along the crypt-villus axis and are shed off into the lumen (Marshman et al., 2002). Finally, at the lower end of the crypts and proximal to the stem cells, markedly granulated cells can be identified that were first described by the Austrian physiologist Josef Paneth (1857–1890). Paneth cells are restricted to the small intestine and secrete large quantities of antimicrobial peptides. High concentrations of these antimicrobial peptides within the crypt lumen protect the neighboring stem cells to ensure ongoing epithelial renewal and mucosal repair also in the event of microbial challenge. In contrast to the short-lived absorptive enterocytes, Paneth cells have a half-life of approximately 20 days (Fig. 1).

The term lamina propria describes the subepithelial space which is populated by stroma cells as well as cells of the adaptive immune system forming the gut-associated lymphoid tissue (GALT). Antigen uptake occurs at specialized anatomical locations within the small intestine named Peyer's patches (PP). PPs are covered by M (microfold) cells which lack microvilli and possess potent endocytotic activity. M cells overlay aggregates of subepithelial lymphocytes and macrophages and facilitate antigen translocation and the presentation of luminal antigens to these subepithelial professional immune cells (Ermak et al., 1990; Farstad et al., 1994). After antigen presentation, lymphocytes in PPs differentiate into effector lymphocytes and B cells start to produce immunoglobulin A (IgA) (Neutra et al., 1996; Macpherson and Uhr, 2004). Subepithelial polymeric (mostly dimeric) IgA is translocated into the intestinal lumen by the polymeric immunoglobulin receptor (pIgR) and plays an importamt role in the antibacterial host defense (Fagarasan and Honjo, 2003; Wijburg et al., 2006). pIgR is required for the adaptive host defense against enteropathogenic bacteria and is highly expressed in crypt intestinal epithelial cells (Bens et al., 1996; Tang et al., 2006; Wijburg et al., 2006). Mucosal IgA has additionally been shown to possess anti-inflammatory activity by binding to bacterial lipopolysaccharide (LPS), a potent immunostimulatory membrane glycolipid produced by all Gram-negative bacteria (Fernandez et al., 2003). In addition, dendritic cells (DC) sample microbial antigens by cell extensions that breach through the epithelial layer and reach the intestinal lumen (Niess et al., 2005; Uhlig and Powrie, 2003; Neutra et al., 1996). DCs play an important role as regulators of immunity to pathogens, oral tolerance, and intestinal inflammation. It is probable that the functional characteristics of DCs isolated from intestinal tissue is determined by factors produced by resident stroma cells leading to a specialized intestinal DC phenotype (Sierro et al., 2001; Rimoldi et al., 2005; Niess and Reinecker, 2006).

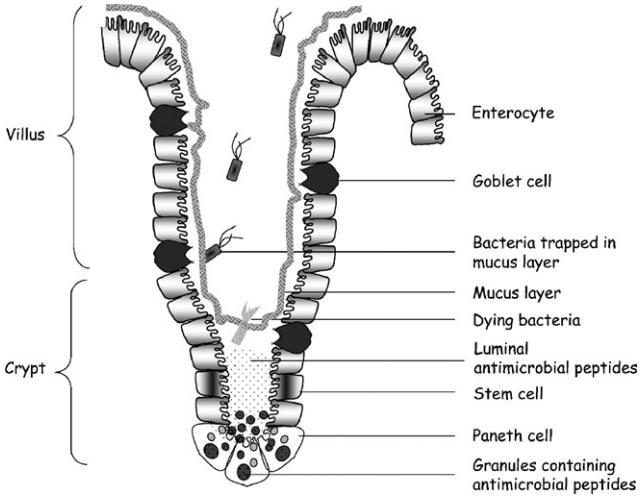

Fig. 1. The anatomical situation at the small intestinal surface.

The intestinal microflora

The intestinal lumen is colonized by a large and very dynamic microbial flora. The number and composition changes considerably within the gastrointestinal tract with moderate numbers but complex bacterial communities in the oral cavity, low to very low numbers in the esophagus, stomach and duodenum and increasing amounts of mostly Gram-positive bacteria along the jejunum and ileum (10^4–10^7/g content). The ileocaecal valve represents an important physical barrier to the caecum and colon which are heavily colonized by a highly diverse and mostly anaerobic Gram-negative flora reaching a density of 10^{14} bacteria/ml and exerting a strong fermenting activity. The diversity of species encompasses around 400 different bacteria (Simon and Gorbach, 1984). Within these, 30–40 different bacterial species make up for 99% of the total population of the intestine (Guarner, 2006). The predominant bacteria are *Bifidobacterium* spp., *Eubacterium* spp., *Clostridium* spp., *Lactobacillus* spp., and *Bacteroides* spp., and only relatively low numbers (<1%) of the *Enterococcus* spp. or members of *Enterobacteriaceae* are found. It is important to note that a large proportion of the enteric microflora is not cultivable by classical microbiological methods (Suau et al., 1999), and only the development of molecular biology techniques and enlarged sequence databases have allowed the identification of new colonizing bacterial species and even archaebacteria within the intestine (Tannock, 2001; Samuel and Gordon, 2006). Not surprisingly, the composition of the normal flora also depends on the age of the