Cell Host & Microbe
Review

An Integrative View of Microbiome-Host Interactions in Inflammatory Bowel Diseases

Marta Wlodarska,[1,2] Aleksandar D. Kostic,[1,3,4] and Ramnik J. Xavier[1,3,5,6,*]
[1]The Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA
[2]Developmental and Molecular Pathways, Novartis Institutes for BioMedical Research, Cambridge, MA 02139, USA
[3]Center for Computational and Integrative Biology, Massachusetts General Hospital, Boston, MA 02114, USA
[4]Department of Biostatistics, Harvard School of Public Health, Boston, MA 02115, USA
[5]Gastrointestinal Unit and Center for the Study of Inflammatory Bowel Disease, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA
[6]Center for Microbiome Informatics and Therapeutics, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
*Correspondence: xavier@molbio.mgh.harvard.edu
http://dx.doi.org/10.1016/j.chom.2015.04.008

The intestinal microbiota, which is composed of bacteria, viruses, and micro-eukaryotes, acts as an accessory organ system with distinct functions along the intestinal tract that are critical for health. This review focuses on how the microbiota drives intestinal disease through alterations in microbial community architecture, disruption of the mucosal barrier, modulation of innate and adaptive immunity, and dysfunction of the enteric nervous system. Inflammatory bowel disease is used as a model system to understand these microbial-driven pathologies, but the knowledge gained in this space is extended to less-well-studied intestinal diseases that may also have an important microbial component, including environmental enteropathy and chronic colitis-associated colorectal cancer.

Introduction

The past decade has seen a dramatic rise in metagenomic and metabolomic studies of inflammatory bowel disease (IBD) and related inflammatory diseases. The best-understood IBDs include Crohn's disease (CD) and ulcerative colitis (UC), which are chronic inflammatory disorders caused by multiple factors involving host genetics, the environment, and microbes. As a result, we are beginning to develop an ecological or community-wide understanding of the role of the microbiome in intestinal disease. Recently, these findings have begun to be translated into a functional mechanistic interpretation of the microbiome in inflammatory diseases.

In this review, we summarize the latest research on the role of the intestinal microbiome in inflammatory disease with a focus toward functional and mechanistic studies. We begin by exploring functional differences that exist along the length of intestinal tract and how these relate to IBD pathogenesis. We then introduce the major intestinal vulnerabilities that contribute to IBD and discuss functional evidence for how microbes contribute to either exacerbate or prevent onset of disease. Although most studies have focused on the bacterial component of the microbiome, we also discuss recent work that explores the impact of viral and micro-eukaryotic components. IBD can be considered the prototypic example of the potential for commensal microbes to influence intestinal disease, and here IBD is used as a context to interpret the role of the microbiome in other intestinal inflammatory diseases, including environmental enteropathy, celiac disease, and colitis-associated colorectal cancer. Using this integrative approach, we highlight both recent advances in the field as well as opportunities for novel therapeutic strategies for IBDs.

Functional Differences across the Intestinal Landscape

To appreciate how the microbiota influences chronic inflammatory diseases, especially IBD, it is critical to consider the physiological, immunological, and pathological differences along the intestinal tract. These aspects are often overlooked in studies concerned with defining the microbial changes that occur in IBD, yet they will be critical to understand the host pathways involved in disease initiation. Furthermore, many of the studies examining microbial changes in IBD have focused on stool samples, which are incompletely reflective of changes occurring at proximal sites of the intestine or in mucosal-associated communities. Functional differences in regions of the intestine are relevant, as CD can affect various areas of both the small and large intestine, resulting in a segmental pattern of inflammation. In contrast, UC tends to affect the colon, showing continuous inflammation. Here we will describe the major functional differences along the intestine in terms of the composition of the epithelium, total microbial burdens, and secretion of antimicrobial peptides (AMPs) and mucus (Figure 1), focusing on how these functional differences are relevant to understanding and elucidating IBD pathogenesis.

Epithelial Layer

Although the small and large intestine have profound functional differences, they share some structural similarities (Figure 1). The small intestine is divided into three functionally distinct segments—the duodenum, jejunum, and ileum—and the function of the epithelium is regulated by the expression of transcription factors specific to each segment. For example, GATA4 is expressed by epithelial cells in the duodenum and jejunum, and reduction of GATA4 expression causes these cells to absorb bile acid, a function normally limited to epithelial cells of the ileum (Beuling et al., 2010). The majority of the digestive and absorptive function of the intestine occurs in the duodenum and jejunum and is facilitated by long villi, as well as microvilli, which contain enzymes that mediate digestion and transport nutrients. One such brush border enzyme is intestinal alkaline phosphatase (IAP), which is highly expressed in the duodenum (Goldberg et al., 2008;

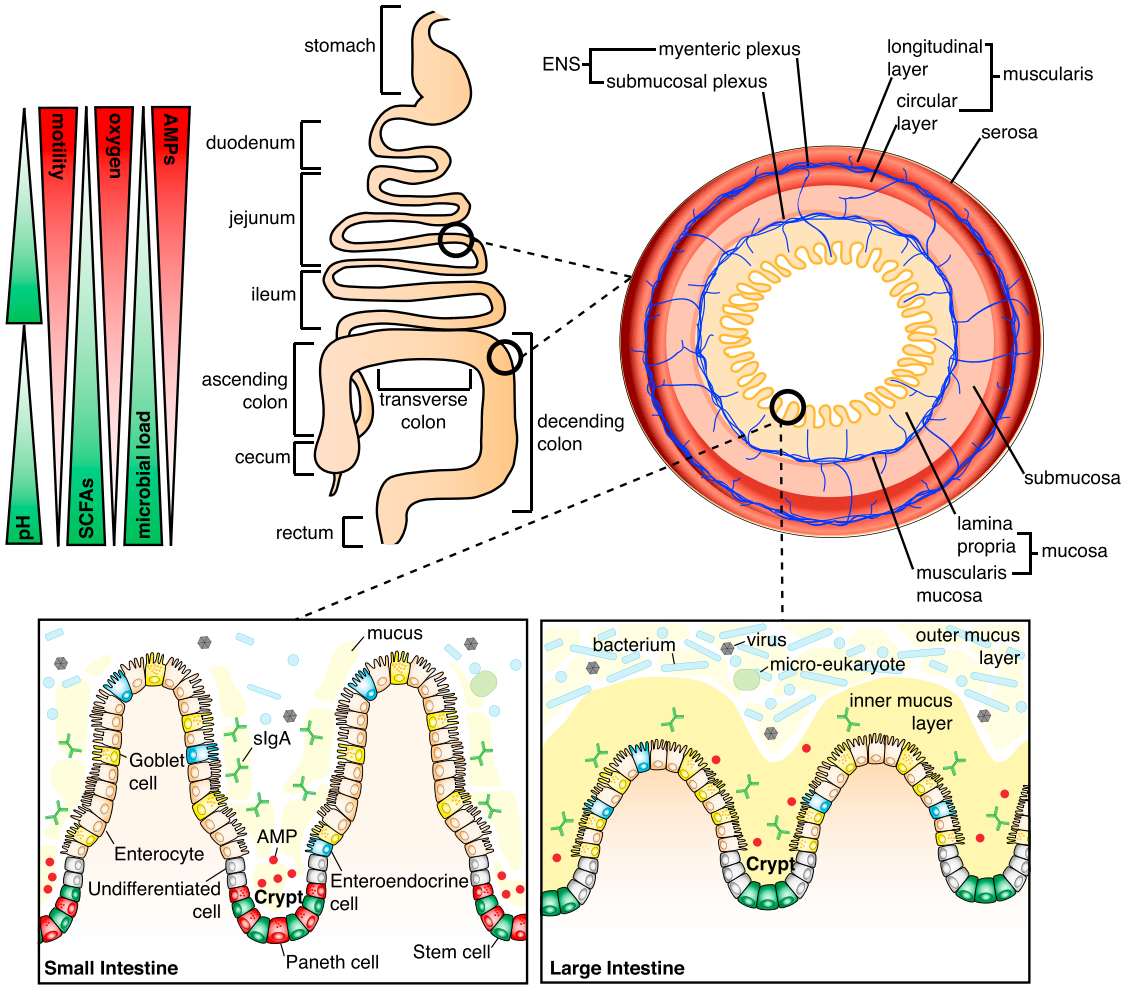

Figure 1. Differentiating Features of the Small and Large Intestinal Landscape

The small intestine begins after the stomach and is composed of the duodenum, jejunum, and ileum. The ileum joins to the large intestine via the cecum. The large intestine is composed of the ascending colon, transverse colon, descending colon, and rectum. The small intestine has higher oxygen levels and antimicrobial peptide (AMP) production, and increased intestinal motility, whereas in the large intestine, the microbial load is the highest and short-chain fatty acids (SCFAs) are abundant. The entire length of the intestine is lined by a single layer of epithelial cells. Below these cells is the lamina propria (LP), composed of connective tissue that provides the blood supply, lymphatic system, and innervation by the submucosal plexus, which are critical to the function of the intestine. Importantly, the LP houses many immune cells of both the innate and adaptive immune system (not shown). Further enteric enervation occurs in the thin layer of smooth muscle, the muscularis mucosa, which separates the LP from the underlying submucosa. Below the submucosa is a thick muscle layer, the muscularis, composed of an inner circular layer and outer longitudinal layer. Between the two muscle layers is the myenteric plexus, an important component of the enteric nervous system (ENS), which functions to coordinate intestinal peristalsis. The outermost covering of the intestine is the serosa. At the mucosal level, the small intestine has long "finger-like" villi that project into the lumen, and which are absent in the large intestine. In the small intestine, the crypts contain stem cells, AMP-producing Paneth cells, and undifferentiated cells; the villi contain the differentiated enterocytes, enteroendocrine cells, and goblet cells. In the small intestine, goblet cells secrete mucus into the lumen, which has a loose, non-adherent consistency. In the large intestine, the crypts lack Paneth cells and contain only stem cells and undifferentiated cells; the differentiated cells include enterocytes, enteroendocrine cells, and goblet cells. Here, enterocytes are involved in the production of AMPs and goblet cells secrete mucus that forms a bilayer structure: the inner and outer mucus layers. Although many of the cell types are shared between the small and large intestine, the function of these cells varies depending on the intestinal location.

Henthorn et al., 1987). IAP functions to hydrolyze monophosphate esters, resulting in detoxification of microbial ligands such as LPS, and is essential to maintain intestinal homeostasis (Bates et al., 2007; Goldberg et al., 2008). Inflamed mucosal tissue from intestines of patients with CD and UC exhibit reduced IAP production; this likely occurs through enhanced Toll-like receptor (TLR) 4 signaling and increased bacterial translocation into the mucosa (Goldberg et al., 2008; Molnár et al., 2012). Inflammatory diseases that affect the small intestine often result in blunting of villi, leading to malabsorption and malnutrition, as seen in celiac disease and environmental enteropathy (Dewar and Ciclitira, 2005; Kelly et al., 2004).

The main functions of the large intestine are the reabsorption of water and uptake of vitamins (e.g., vitamin K, vitamin B12, thiamine, riboflavin). The large intestine is also the site of enzymatic degradation of indigestible fiber by the microbiota, producing short-chain fatty acids (SCFAs). SCFAs, including acetate, propionate, and butyrate, exert a protective effect on epithelial cells and stimulate fluid absorption (Scheppach, 1994). It is well known that UC leads to changes in microbial