cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

REVIEW

Microbial Activities and Intestinal Homeostasis: A Delicate Balance Between Health and Disease

Christina L. Ohland[1] and Christian Jobin[1,2]

[1]Department of Medicine and [2]Department of Infectious Diseases and Pathology, University of Florida, Gainesville, Florida

SUMMARY

This review discusses the equilibrium between host and microbial community in the context of health and disease. The focus is on bi-directional pressures between prokaryotes and eukaryotic cells, as well as inter-bacterial interactions resulting in alterations to the microbiota.

The concept that the intestinal microbiota modulates numerous physiologic processes, including immune development and function, nutrition and metabolism, and pathogen exclusion, is relatively well established in the scientific community. The molecular mechanisms driving these various effects and the events leading to the establishment of a "healthy" microbiome are slowly emerging. This review brings into focus important aspects of microbial/host interactions in the intestine and discusses key molecular mechanisms controlling health and disease states. We discuss the evidence of how microbes interact with the host and one another and their impact on intestinal homeostasis. ***(Cell Mol Gastroenterol Hepatol 2015;1:28–40; http://dx.doi.org/10.1016/j.jcmgh.2014.11.004)***

Keywords: Bacterial Communication; Bowel Disease; Host-Microbe Interactions; Inflammatory; Microbiome.

Appearances can be deceiving. Despite what you see in the mirror, humans are more prokaryotic than eukaryotic, as the bacteria in and on our bodies outnumber our own cells 10 to 1.[1] Microbes are embedded in our biological system and are deeply integrated in our daily life, and an emerging field of research has tackled the inter-kingdom communication network present in the walking mixed cultures we call people.

The gastrointestinal (GI) tract has the highest density and variety of bacteria in the human body (approximately 100 trillion microbes made up of >1000 species) due to the ideal growth conditions provided by this organ. In the colon, there are up to 10^{12} microbes per gram of luminal content which accounts for 60% of fecal weight.[2,3] A healthy adult's intestinal microbiome is diverse, relatively stable over time, and dominated by two phyla, Bacteroidetes and Firmicutes (~95%). Nevertheless, there is considerable interindividual variability at the species level due to genetic, environmental, and nutritional factors.[4] Diet in particular has been shown to rapidly shift this community,[5] resulting in geographic region-specific microbial signatures as seen in rural African children eating a fiber-rich diet compared to their European counterparts.[6] Although understanding the bacterial species present in the gastrointestinal tract is important, recent work has shifted the focus to the existence of a core enteric metabolome, which has the potential to change the way we look at how our gut functions.[7] Because bacterial genes have many overlapping and redundant functions, the end result of their combined metabolism and catabolism can ultimately have a tremendous impact on the intestinal environment and host physiology. As we discuss later, these microbial-derived products are a main component of the host-bacteria and bacteria-bacteria communication network essential to intestinal homeostasis.

External pressures, such as infection or antibiotics, cause a disequilibrium in the microbial community, a phenomenon designated as *dysbiosis* and often associated with pathologies including inflammatory bowel disease (IBD).[8,9] Alternatively, internal pressure resulting from defective host genetics, such as innate and adaptive immune genes, results in mismanagement of the microbiota, again leading to dysbiosis and pathologic conditions seen in the airway,[10] the skin,[11] and the gut.[12,13] IBD is a chronic, relapsing, and remitting inflammatory disease that can be classified as ulcerative colitis (UC) or Crohn's disease (CD). Both forms can be thought of as examples of disrupted communication between the intestinal microbiota and the host. The nature of this communication breakdown is not clear but involves genetic susceptibility related to the epithelial barrier and innate immunity, all of which are important components of host-bacteria interaction.[14]

This review will discuss the complex cross-talk between intestinal cells and the microbiota as well as the antagonistic and mutualistic interactions among enteric bacteria. This multifaceted communication network is what shapes the intestinal environment, drives homeostasis, and is thus essential to understanding how to prevent and treat intestinal disorders such as IBD.

Abbreviations used in this paper: **AMP, antimicrobial peptides; CD, Crohn's disease; CDI, contact-dependent growth inhibition; GI, gastrointestinal; HGT, horizontal gene transfer; IBD, inflammatory bowel disease; MAMP, microbe-associated molecular pattern; QS, quorum sensing; SCFA, short-chain fatty acids; SFB, segmented filamentous bacteria; T6SS, type VI secretion system; UC, ulcerative colitis.**

2352-345X
http://dx.doi.org/10.1016/j.jcmgh.2014.11.004

Host Effects on the Microbiota

Gastrointestinal Tract Environment

The intestinal microbiota is largely acquired during our first few days of life, although recent studies have shown that infants may not be bacteria free at birth.[15,16] Species diversity and stability increase to an adultlike microbiota by the age of 3 years as children are exposed to a new milieu that includes solid food and individuals with different microbiota.[17–19] The wide topologic and geographic differences that microorganisms encounter along the GI tract dictate their environmental niche for growth and ultimately shape the community as a whole (Figure 1).

The acidity of the stomach limits bacterial growth and only a sparse microbiota ($<10^1$ bacteria/g of contents) is present.[20] This community predominantly consists of Firmicutes and Actinobacteria, but Bacteroidetes, Proteobacteria, and Fusobacteria are also present.[21,22] Although they are similar at the phylum level to the rest of the GI tract, the relative quantities of each organism differ, indicating that the gastric population is distinct.[23] When *Helicobacter pylori* are present, the stomach microbiota is dominated by this Proteobacterium, and diversity is severely reduced.[21,23,24] In the duodenum, stomach acid is neutralized, and bile acids become the driving force of microbiota modulation in the small intestine. For example, cholic acid has been shown to directly increase the cecal Firmicutes/Bacteroidetes ratio and decrease microbial diversity in vivo.[25] Here, diversity and bacterial load (10^3 bacteria/g) are low, but both factors

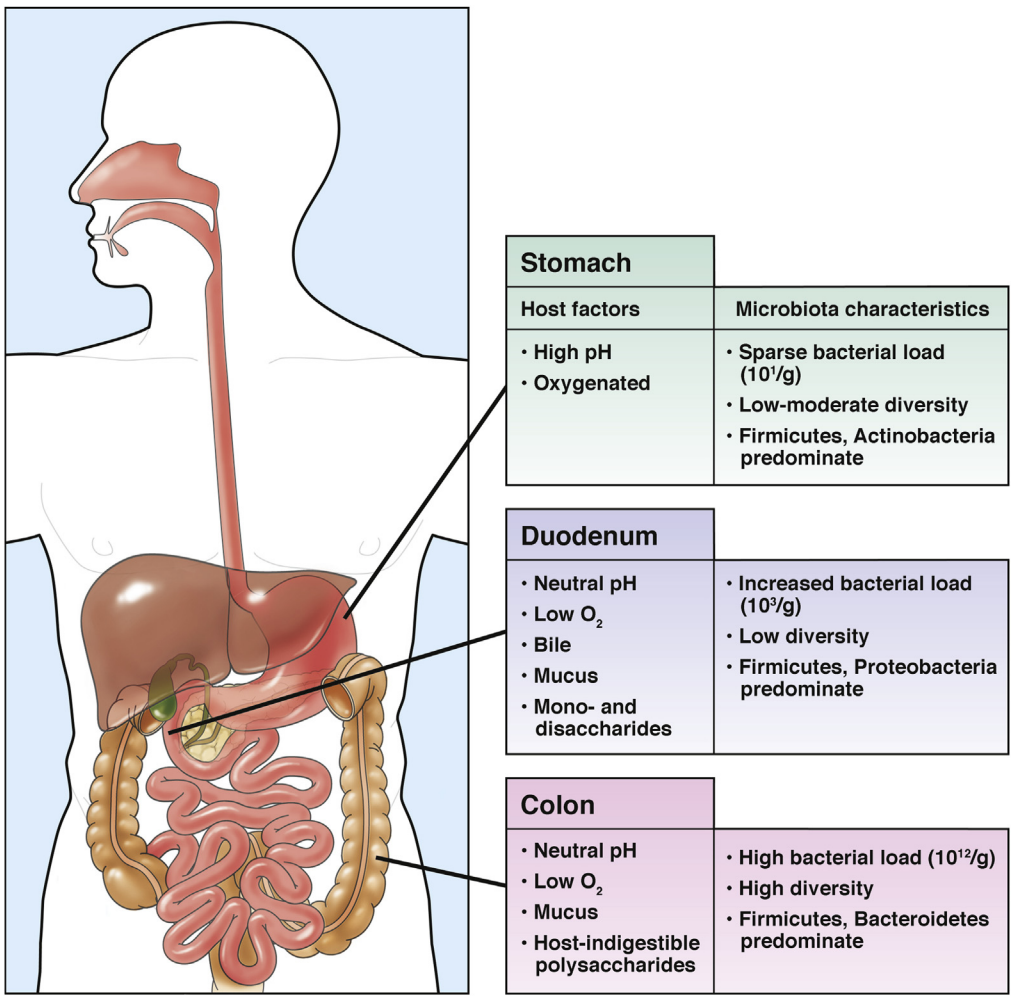

Figure 1. Regional differences in the gastrointestinal tract affect microbial niche. In the stomach, high pH and oxygen content restrict microbial colonization. The major phyla do not significantly differ from those found further along the GI tract, but the predominant bacteria (Firmicutes and Actinobacteria) as well as the species are distinct. Diversity is thought to be moderate, although this may be due to transient organisms. In the duodenum, the stomach acid is neutralized, bile is present, oxygen is reduced by facultative anaerobes, and the host epithelium produces a mucous layer. Most starches have been digested into monosaccharides and disaccharides, which are progressively absorbed throughout the small intestine. These factors result in a microbiota dominated by Proteobacteria and Firmicutes such as Lactobacillales with low bacterial load and diversity. Alternatively, host-indigestible polysaccharides promote the growth of Bacteroidetes and Firmicutes such as Clostridiales in the colon where diversity and bacterial load are high. In addition to these factors, the intestinal barrier and immune system affect which microbes can survive in the gut but do not appear to be region dependent.