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Review Article

Role of the enteric microbiota in intestinal homeostasis and inflammation

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ABSTRACT

The mammalian intestine encounters many more microorganisms than any other tissue in the body thus making it the largest and most complex component of the immune system. Indeed, there are greater than 100 trillion (10^{14}) microbes within the healthy human intestine, and the total number of genes derived from this diverse microbiome exceeds that of the entire human genome by at least 100-fold. Our coexistence with the gut microbiota represents a dynamic and mutually beneficial relationship that is thought to be a major determinant of health and disease. Because of the potential for intestinal microorganisms to induce local and/or systemic inflammation, the intestinal immune system has developed a number of immune mechanisms to protect the host from pathogenic infections while limiting the inflammatory tissue injury that accompanies these immune responses. Failure to properly regulate intestinal mucosal immunity is thought to be responsible for the inflammatory tissue injury observed in the inflammatory bowel diseases (IBD; Crohn disease, ulcerative colitis). An accumulating body of experimental and clinical evidence strongly suggests that IBD results from a dysregulated immune response to components of the normal gut flora in genetically susceptible individuals. The objective of this review is to present our current understanding of the role that enteric microbiota play in intestinal homeostasis and pathogenesis of chronic intestinal inflammation.

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Introduction

The mammalian intestine encounters many more microorganisms than any other tissue in the body thus making this tissue the largest and most complex component of the immune system. Indeed, the healthy human small and large intestine is home to hundreds of trillions of bacteria, viruses, archaea, and fungi [1–5]. It is becoming clear that our coexistence with the gut microbiota represents a dynamic and mutually beneficial relationship that is thought to be a major determinant of health and disease. Because of the potential for intestinal microorganisms to induce local and systemic inflammation, the intestinal mucosal immune system has developed a plethora of mechanisms to protect the host from pathogenic infections while limiting the inflammatory tissue damage that accompanies these innate and adaptive immune responses. Failure to properly regulate these protective immune responses induces a chronic inflammatory response that is thought to be a critical immunopathological mechanism responsible for the development of the inflammatory bowel diseases (IBD; e.g., Crohn disease and ulcerative colitis). These idiopathic inflammatory diseases affect primarily the small and/or large bowel and are characterized by the infiltration of large numbers of inflammatory leukocytes (e.g., neutrophils, monocytes, and lymphocytes) into the intestinal lamina propria, where they directly or indirectly promote tissue injury and dysfunction including edema, loss of goblet cells, fibrosis, erosions, and ulcerations. Although the etiology of IBD remains to be definitively defined, it is becoming increasingly appreciated that chronic intestinal inflammation results from a complex interaction among genetic, immune, and microbial factors [5–7]. Based upon a large body of experimental and clinical evidence generated over the past 20 years, investigators hypothesize that chronic gut inflammation results from a dysregulated immune response to components of the normal gut flora in genetically susceptible individuals [8,9]. The objective of this review is to present our current understanding of the role that commensal enteric microbiota play in intestinal homeostasis and pathogenesis of chronic intestinal inflammation.

Intestinal microbiota in health and disease

Bacterial colonization and redox metabolism

The only time that the human body is devoid of its microbial residents is during gestation. Despite some evidence suggesting that small numbers of bacteria may be present in the amniotic fluid, umbilical cord blood, and/or meconium of healthy neonates [10], it is widely accepted that the fetus is maintained essentially in a germ-free state during development [3]. Upon birth, the newborn becomes colonized with commensal microbiota that arise from the mother's vagina, skin, feces, and breast milk [11,12]. The lactate-metabolizing bacteria *Bifidobacterium* and *Lactobacillus* derived from the vaginal canal and breast milk are the primary microorganisms that initially colonize in the intestinal tract during the first 3 months of life [12,13]. These initial microbial residents lay the foundation for the subsequent colonization of the complex microbial communities that reside within the gut [14]. As the infant grows, phylogenetic diversity of the microbial community increases with bacterial-dependent metabolism becoming more complex and specialized, ultimately establishing the adult intestinal microbiota [13]. There is also a distinct distribution of aerobic and anaerobic bacteria along the length of the gastrointestinal (GI) tract. Although the proximal part of the GI tract has many fewer bacteria than the distal portion, it is colonized by a much higher percentage of aerobic and/or facultative anaerobic bacteria than the distal small bowel and colon (Fig. 1) [5]. Indeed, the distal portion of the GI tract is dominated almost exclusively by enormous numbers of anaerobic bacteria that are 2 to 3 orders of magnitude more prevalent than aerobic bacteria. Interestingly, it has been determined that anaerobic bacteria fail to colonize the newborn gut unless the bowel is first colonized by aerobic and/or facultative anaerobic bacteria [15]. The distribution of oxygen-tolerant and intolerant bacteria within the healthy adult gut not only reflects the luminal oxygen gradient along the length of the GI tract but is also responsible for creating the hypoxic/reducing environment within the distal bowel lumen [15]. The redox relationship between the intestine and its microbiota is poorly understood at the present time. It is well known that the reductive environment does not prevent the production of reactive nitrogen species such as nitric oxide (NO). In fact, the intestinal lumen contains >200 ppb NO [15]. Although nitric oxide synthase-like enzymes have been identified in a select few enteric bacteria, the vast majority of luminal NO is produced by anaerobic bacteria via the reductive metabolism of nitrate and nitrite [15]. The respiration and growth of certain bacteria have been shown to be reversibly suppressed by NO in the presence of low oxygen tension [15,16]. Intestinal bacteria also produce large amounts (millimolar levels) of hydrogen sulfide (H_2S), which is capable of suppressing mitochondrial metabolism in epithelial cells as well [16,17].

Stability and regulation of microbial communities

The healthy adult intestine contains more than 100 trillion (10^{14}) bacteria that have, until recently, been estimated to comprise more than 1000 different species (Fig. 1) [3,5]. More recent studies, using a newly developed method for low-error amplicon sequencing of bacterial 16S ribosomal RNA genes, suggest that the human microbiota actually harbors ~200 strains of bacteria representing slightly more than 100 different bacterial species [18]. Nevertheless, the total number of genes derived from this diverse

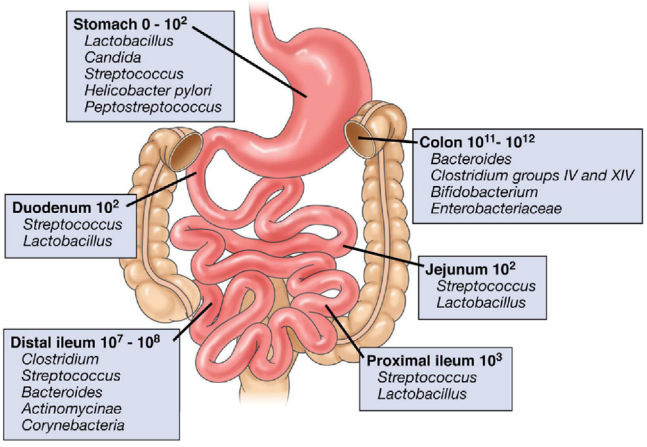

Fig. 1. Composition and luminal concentrations of the major microbial species in various regions of the gastrointestinal tract. Boxes show the numbers of organisms per gram of luminal contents (reproduced from Ref. [5], with permission).