CHAPTER 6

Negative Interactions with the Microbiota: IBD
Nita H. Salzman and Charles L. Bevins*

Abstract
Mucosal surfaces are colonized by a complex microbiota that provides beneficial functions under normal physiological conditions, but is capable of contributing to chronic inflammatory disease in susceptible individuals. Of the mucosal tissues, the mammalian intestine harbors an especially high number of microbes with a remarkable diversity. Inflammatory bowel disease (IBD) is a group of chronic relapsing inflammatory disorders of the intestinal mucosa. Evidence from human studies and animal models provides compelling support that intestinal microbes play a key role in disease pathogenesis. While the existence a specific causative pathogen is possible, it appears more likely that intestinal microbes normally present as commensal microbiota may trigger inflammation and perpetuate disease in genetically susceptible individuals. There may be also a shift in the makeup of the commensal flora to a nonphysiologic composition that is more prone to disease (termed dysbiosis). Evidence supports that genetic susceptibility stems from one or more defects in mucosal immune functions, including microbe recognition, barrier function, intercellular communication and antimicrobial effector mechanisms. It is quite plausible to imagine that the chronic inflammation of IBD may in some cases be a normal immune response to an abnormal adherent invasive microbiota and in other cases an over exuberant immune response to an otherwise normal commensal microbiota.

Introduction
The complex ecosystems that colonize mammalian mucosal surfaces serve essential beneficial functions for the host, yet the parameters that define a healthy microbiota are poorly defined. Unlike bacterial-host interactions involving defined pathogens, negative interactions between commensals and host are less clear-cut. The pathology may be caused by an abnormal microbiota (dysbiosis), immune defects in the host and in some instances a combination of both (Fig. 1). Some of the pathological conditions associated with commensals include the following: bacterial vaginosis, where evidence suggests an association with dysbiosis; erythema toxicum neonatorum, hair follicle penetration by commensals, which may likely reflect an immature immunity of newborns; necrotizing enterocolitis, a complex and catastrophic illness of premature infants, which is likely associated with an immature mucosal immune system in combination with dysbiosis; cystic fibrosis, which is more clearly a host defect; celiac disease, in which the presence of dysbiosis has been noted; and finally inflammatory bowel disease (IBD), where dysbiosis and host immunity likely share a role in pathogenesis. This chapter will focus on the latter group of negative interactions in the intestine characterizing IBD.

*Corresponding Author: Charles L. Bevins—Department of Microbiology and Immunology, University of California Davis School of Medicine, Davis, CA 95616, USA. Email: clbevins@ucdavis.edu

Host Factors |
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Complex Microbiota

Host Factors | Abnormal Microbiota
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HEALTH |
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DISEASE

Figure 1. Simple model for balance of host-microbe interactions at mucosal surfaces. Under normal conditions, a mature fully functioning host defense system strikes balance with an abundant and complex microbiota. An imbalance leading to disease may result from either deficiencies in host factors (genetically inherited, age-related, concurrent illness, etc.), or unfavorable alteration in the composition of commensal microbiota or via virulence factors of pathogens.

**IBD**

IBD encompasses at least two groups of disease entities: ulcerative colitis (UC) and Crohn's disease (CD). These are chronic intestinal inflammatory diseases that appear to be immune mediated, but are of largely unknown etiology. UC is characterized by mucosal inflammation limited to the large bowel. Grossly, UC shows a region of continuous colonic involvement, often affecting the entire colon. Histologically, the acute phase is characterized by crypt abscesses and ulcers that extend to the muscularis mucosa and is associated with a mixed inflammatory infiltrate in the lamina propria. The definitive treatment for UC involves resection of the entire large bowel and rectum, with the construction of an ileal pouch-anal anastomosis. Some patients develop significant inflammation in the ileal pouch, resulting in a secondary inflammatory disease, pouchitis. Pouchitis is associated with the clinical symptoms akin to IBD and although its etiology is unclear, pouchitis is also thought to represent an imbalance of host-microbe interactions at the intestinal mucosa, similar to IBD. CD is characterized grossly by discontinuous mucosal involvement (skip lesions) that can occur anywhere in the GI tract and favors involvement of the terminal ileum. Often CD will involve only the ileum, both ileum and colon, or sometimes only the colon. Histologically, inflammation is noted to be transmural, ulceration and crypt abscesses are less pronounced, and granulomas are often present. Despite gross and microscopic differences, there may be considerable overlap in the presentation of IBD, often making precise categorization within this group of diseases a challenge. Variations in both inherited susceptibility and clinical phenotypes suggest that neither UC nor CD is a homogeneous disorder, but rather a spectrum of diseases.

**Evidence of Bacterial Involvement in Intestinal Inflammation**

**Animal Models**

The significance of intestinal bacteria in inciting and perpetuating colitis has been demonstrated in a variety of murine models of IBD. Spontaneous development of colitis has been seen in a variety of rodent models, including the IL-10 knock out (K/O) mouse, IL-2 K/O mice, T-cell receptor K/O mice and HLA-B27 rats when the animals are maintained under conventional (specific pathogen free) conditions. When these rodent strains are raised in germ-free conditions, colitis is either absent or much attenuated. Other murine colitis models, such as the SCID mouse that has been repopulated with CD4⁺ CD45 RB-hi T-cells show improvement with antibiotic treatment, also suggesting the involvement of bacteria in the development and persistence of colitis.

These findings in animal models support a current hypothesis of CD pathophysiology, where an inappropriate immune response to intestinal commensal bacteria is thought to fuel mucosal