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THE GUT MICROBIOME AND DISEASE

The Microbiome in Inflammatory Bowel Disease: Current Status and the Future Ahead

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Studies of the roles of microbial communities in the development of inflammatory bowel disease (IBD) have reached an important milestone. A decade of genome-wide association studies and other genetic analyses have linked IBD with loci that implicate an aberrant immune response to the intestinal microbiota. More recently, profiling studies of the intestinal microbiome have associated the pathogenesis of IBD with characteristic shifts in the composition of the intestinal microbiota, reinforcing the view that IBD results from altered interactions between intestinal microbes and the mucosal immune system. Enhanced technologies can increase our understanding of the interactions between the host and its resident microbiota and their respective roles in IBD from both a large-scale pathway view and at the metabolic level. We review important microbiome studies of patients with IBD and describe what we have learned about the mechanisms of intestinal microbiota dysfunction. We describe the recent progress in microbiome research from exploratory 16S-based studies, reporting associations of specific organisms with a disease, to more recent studies that have taken a more nuanced view, addressing the function of the microbiota by metagenomic and metabolomic methods. Finally, we propose study designs and methodologies for future investigations of the microbiome in patients with inflammatory gut and autoimmune diseases in general.

Keywords: Microbiota; Crohn's Disease; Ulcerative Colitis; Metagenomics.

Over the past decade, inflammatory bowel disease (IBD) has emerged as one of the most studied human conditions linked to the gut microbiota.[1,2] IBD comprises both Crohn's disease (CD) and ulcerative colitis (UC), which together affect more than 3.6 million people.[3] Large-scale studies of human genetics across a total of 75,000 cases and controls have revealed 163 host susceptibility loci to date.[4] These loci are enriched for pathways that interact with environmental factors to modulate intestinal homeostasis.[5] The incidence of the disease has been on the rise over the past few decades, further highlighting the role of environmental factors in this disease. IBD was once a very rare disorder and only began to rise dramatically in incidence in the second half of the 20th century in North America and Europe, at times doubling every decade; it has expanded into developing countries in the past 2 decades, although there are more cases of UC than CD in the developing world.[6] In addition, several twin studies have shown that the concordance rate for IBD between monozygotic twin pairs is significantly less than 50%, with the least concordance in CD.[7] IBD is thus a multifaceted disorder in which not only germline genetics and the immune system but also several environmental factors play an important role.[8] One such factor, the gut microbial community, is gaining increasing attention for its influence on many aspects of health in general[9] and IBD in particular (Table 1).

The gut microbiota, the largest reservoir of microbes in the body, coexists with its host in variable concentrations throughout the gastrointestinal tract, reaching an upper level in the colon of 10^{11} or 10^{12} cells/g of luminal contents.[10] This community performs a range of useful functions for the host, including digesting substrates inaccessible to host enzymes, educating the immune system, and repressing the growth of harmful microorganisms.[11] The extensive use of low-resolution surveys of the microbial community structure in the past, as well as renewed efforts using next-generation

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Abbreviations used in this paper: **CD, Crohn's disease; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; iCD, ileal Crohn's disease; SCFA, short-chain fatty acid; T2DM, type 2 diabetes mellitus; UC, ulcerative colitis.**

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Table 1. Changes in the Microbiome Linked to IBD

Microbial composition	Decrease in α diversity
	Decrease in *Bacteroides* and Firmicutes
	Increase in Gammaproteobacteria
	Presence of *E coli*, specifically adherent-invasive *E coli*
	Presence of *Fusobacterium*
	Decrease in Clostridia, Ruminococcaceae, *Bifidobacterium*, *Lactobacillus*
	Decrease in *F prausnitzii*
Microbial function	Decrease in SCFAs, butyrate
	Decrease in butanoate and propanoate metabolism
	Decrease in amino acid biosynthesis
	Increase in auxotrophy
	Increase in amino acid transport
	Increase in sulfate transport
	Increased oxidative stress
	Increase in type II secretion system, secretion of toxins

sequencing for a high-resolution description of composition, function, and ecology,[12,13] have improved our overall understanding of the role of the gut microbiota in health, a prerequisite for the study of disease-related dysbiosis. Several factors can intervene with microbial gut community composition, including genetics, diet, age, drug treatment, smoking, and potentially many more (Figure 1).[14] The relative importance of each of these factors is still unclear, but several of them are directly or indirectly linked to the disease state.

Environmental Factors Affecting Microbiome Composition

Diet

One of the most important environmental factors affecting microbial composition is dietary preference, which has been shown to determine microbiome composition throughout mammalian evolution.[15] Although no specific diet has been shown to directly cause, prevent, or treat IBD, it is important to take interactions between nutrients and microbiota into account when studying the role of the microbiome in disease. Thus far, only limited information on this topic has been gathered in humans, undoubtedly as a result of the challenge of setting up a large-scale controlled diet study. Wu et al have shown that long-term dietary patterns affect the ratios of *Bacteroides*, *Prevotella*, and Firmicutes and that short-term changes may not have major influences.[16] In addition, Zimmer et al have studied the impact of a strict vegan or vegetarian diet on the microbiota[17] and found a significant reduction in *Bacteroides* species, *Bifidobacterium* species, and the Enterobacteriaceae, whereas total bacterial load remained unaltered. Since the Enterobacteriaceae are among the taxa that are consistently found to be increased in patients with IBD (see the following text), it would be of value to include both short-term and long-term dietary patterns in future studies of the role of the microbiome in IBD. Given the complexity of dietary effects, including such information will likely only be feasible in a large cohort study.[18]

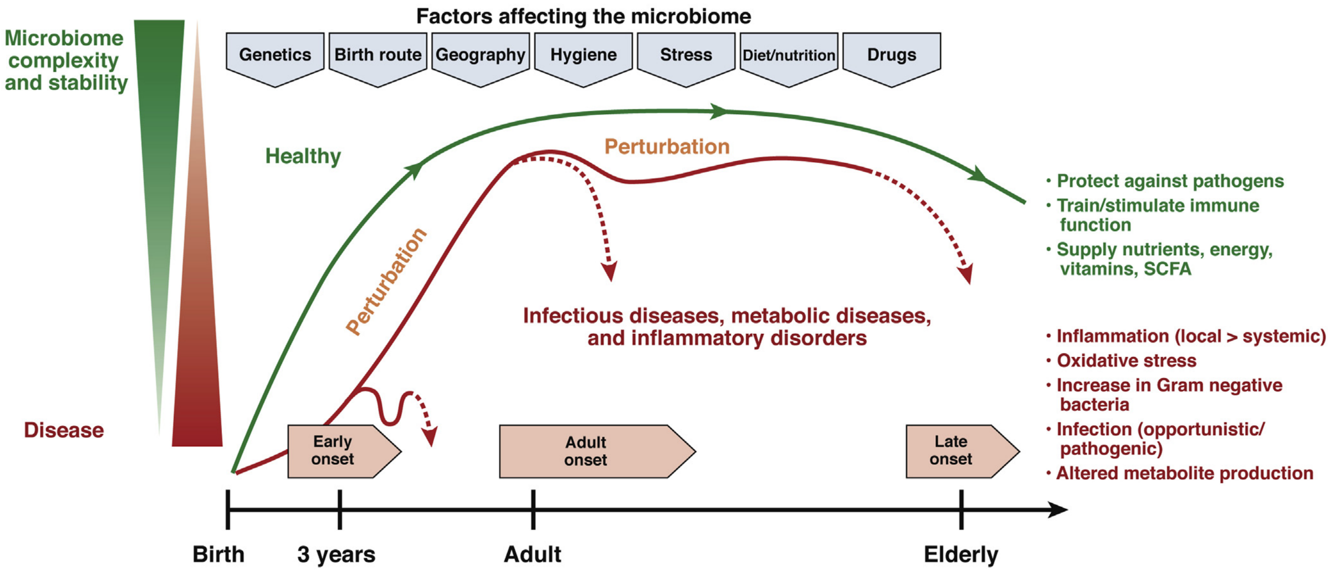

Figure 1. Factors affecting the stability and complexity of the gut microbiome in health and disease. Key characteristics of the microbiome, including stability, resilience, and complexity, are influenced over time from infancy to adulthood and into old age. In the healthy gut, these characteristics contribute to important physiological processes such as protection against pathogens, training of the immune system, and digestion of food to supply energy and nutrients including vitamins and SCFAs. Many factors are indicated to affect the microbiome throughout microbiome development and even established assembly, including genetics, diet, and medication, among others (marked in the *gray boxes* at the top of the figure). Some of these factors can introduce perturbations affecting the complexity and stability of the microbiome, potentially introducing microbial dysbiosis. Features of an imbalanced microbiome include, for example, an increase in gram-negative bacteria linked to an environment of oxidative stress and inflammation and metabolite production.