The Microbiome in Crohn's Disease

Role in Pathogenesis and Role of Microbiome Replacement Therapies

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KEYWORDS

• Crohn's disease • Inflammatory bowel disease • Pathogenesis • Gut microbiota • Microbiome • Fecal microbiota transplantation • Probiotics

KEY POINTS

- Patients with Crohn's disease have decreased microbial diversity, which plays an important role in the pathogenesis of Crohn's disease.
- Microbial restoration therapies are being studied for management of Crohn's disease and may be an adjunct to standard therapies in the future.
- It may be feasible to modify the gut microbiota community structure or function to treat patients with Crohn's disease with targeted therapies via individual agents, such as probiotics, bacterial consortia, or even dietary manipulation.
- Fecal microbiota transplantation should not be performed for Crohn's disease other than in research settings.
- A better understanding of host-microbe interactions in patients with Crohn's disease may help improve management of these patients.

INTRODUCTION

Crohn's disease, a subtype of inflammatory bowel disease (IBD), has been increasing in incidence over the last few decades.[1] Crohn's disease may involve any segment of the gastrointestinal tract and lead to complications, such as strictures and fistulas. The pathogenesis of Crohn's disease is multifactorial and involves the interplay of host genetics, host immune dysregulation, and environmental factors resulting in an aberrant immune response and subsequent intestinal inflammation.[2] The human gut microbiota, harboring more than 100 trillion microorganisms, serves as an important

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component in the pathogenesis of Crohn's disease, by providing antigenic stimuli through altered microbial compositions that promote host-microbe imbalances leading to perturbed intestinal and immune homeostasis. An aggressive T-cell-mediated immune response to specific components of the intestinal microbiota in genetically susceptible hosts results in the inflammation of the bowel of Crohn's disease. Microbial dysbiosis is thought to be associated with either development or exacerbation of underlying Crohn's disease.[3]

CROHN'S DISEASE AND ALTERED MICROBIOME

Bacterial dysbiosis is likely a causative factor and an outcome in patients with Crohn's disease.[4] Although dysbiosis may develop as a result of bowel inflammation, dysbiosis may also have a role in perpetuating chronic inflammation. Studies of the gut microbiota in patients with Crohn's disease demonstrate an increase in pathogenic microorganisms, whereas populations of normal commensal phyla are diminished.[5,6] In one interesting study, pretreatment gut microbial samples from patients with new-onset Crohn's disease demonstrated an increased abundance of Enterobacteriaceae, Pasteurellacaea, Veillonellaceae, and Fusobacteriaceae, and decreased Erysipelotrichales, Bacteroidales, and Clostridiales.[7] Ileal and rectal mucosal samples demonstrated a reduction in Firmicutes, such as *Faecalibacterium prausnitzii*, and increased in Proteobacteria, such as *Escherichia coli*, and in *Veillonella*, *Haemophilus*, and *Fusibacteria*.[7] Similarly, previous studies have shown an increase in mucosa-associated *E coli* in Crohn's disease and several showing a reduction in *F prausnitzii*.[8–10] In another study, there were decreased populations of Bacteroidetes and Firmicutes in patients with Crohn's disease, whereas pathogenic organisms, such as *E coli*, *Campylobacter* species, and *Mycobacterium* species were increased.[11] Patients with Crohn's disease have a greater number of mucosal surface–associated bacteria with higher adherence and invasion compared with healthy control subjects.[12] Gut microbiome profiles from patients with isolated colonic Crohn's disease are more similar to that of healthy control subjects than microbiome profiles of patients with isolated ileal or ileocolonic Crohn's disease.[8–10,13] In one study, increased ileal mucosa-associated *E coli* and reduced ileal *F prausnitzii* was present in patients with ileal but not isolated colonic Crohn's disease.[13] However, studies have shown differences between the mucosa-associated microbiota in isolated colonic Crohn's disease and ulcerative colitis. Therefore, mucosa-associated microbiota changes in Crohn's disease are more marked than stool microbiome changes. The microbiota in isolated colonic Crohn's disease shows changes that tend to be less marked and less consistent than those found in Crohn's disease with ileal involvement. These findings could suggest future studies involving gut microbiome profiles in patients with Crohn's disease should incorporate mucosal microbiome sampling in addition to fecal sampling.

HOST MICROBIOME INTERACTIONS IN CROHN'S DISEASE

Evolution of Microbiome

Following birth, humans develop their gut microbiota through a variety of mechanisms. The mode of delivery (whether vaginal birth or birth by caesarean section), diet, and other environmental factors influence the microbial community as it evolves from a simple community containing a core set of resident bacteria to a more complex, diverse community. In early childhood the microbiota shifts in response to the environment including dietary influences, antibiotic exposure, and illness. Eventually, one's unique microbial community becomes a species-rich, complex community relatively stable and resistant to colonization by enteropathogens. In a healthy individual, the