Duke Master of Biomedical Sciences

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Gut Microbiome Dysbiosis and Its Implications in IBD

Gabriella N. Coen, B.S.

Background

- Inflammatory bowel diseases (IBDs) arise in two main forms: Ulcerative Colitis (UC) and Crohn's Disease (CD).
- UC affects the mucosa and submucosa of the colon and rectum, whereas CD can impact any structure along the GI tract[(1)].
- IBD pathogenesis includes multiple factors such as genetics, environmental exposures, immune system dysfunction, and increasing evidence for an altered gut microbiome[(1)]. The human GI tract houses trillions of microorganisms that function in digestion, immune regulation, and epithelial integrity[(1)].
- Healthy individuals have diverse, beneficial bacteria that provide them these protective gut functions.
- Emerging research is implying patients with IBD have a gut microbial imbalance, or dysbiosis. This can be characterized as having more pathogenic microorganisms than beneficial microorganisms.

Goal

This review explores the current literature on gut microbiome dysbiosis and its implication in IBD. It evaluates how modifying the gut microbiome changes the function of the GI tract. This review will also report current literature regarding microbial metabolite influence, diet impact, and emerging therapeutic strategies by attempting to understand the complex interactions of the gut microbiome and the host immunity.

Methods

This review was curated from PubMed search using the terms "inflammatory bowel disease" AND "gut microbiome". Both primary and secondary research articles were utilized. Papers were included if they discussed IBD inflammation and the gut microbiome.

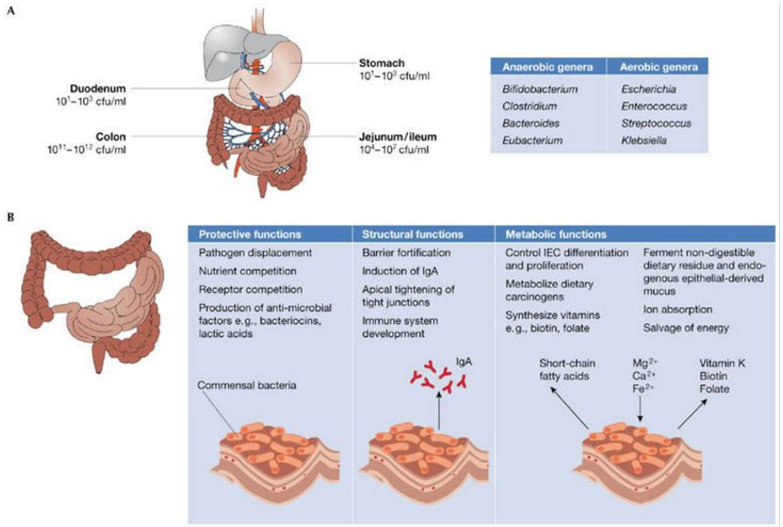

Figure 1. Functions of the intestinal flora. (**A**) Bacteria density increases in the jejunum/ileum from the stomach and duodenum, and in the large intestine, colon-residing bacteria achieve the highest cell densities recorded for any ecosystem. The most common anaerobic and aerobic genera are listed. (**B**) Commensal bacteria exert a miscellany of protective, structural and metabolic effects on the intestinal mucosa.[(12)]

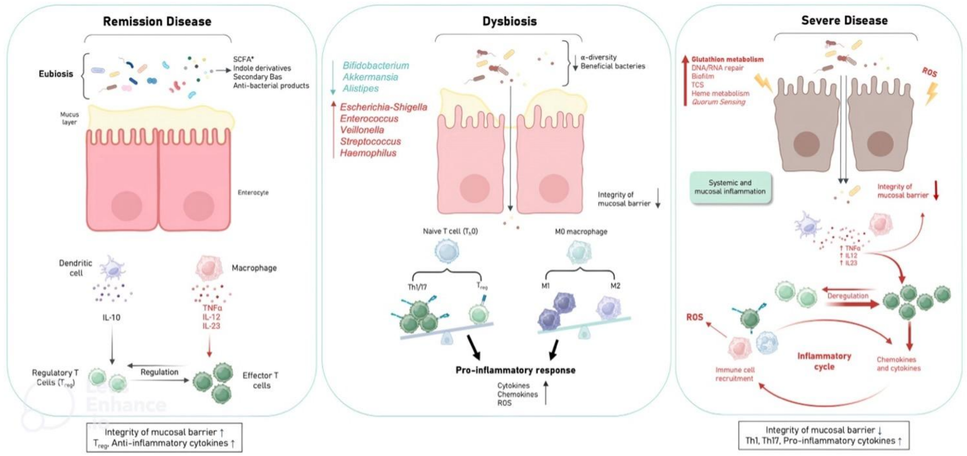

Figure 2. Schematic of the mechanism hypothesis of gut microbiota dysfunction in relation to CD severity. Disease in remission is characterized by integrity of the mucosal barrier; presence of Treg; anti-inflammatory cytokines due to eubiosis and microbial pathways involving amino acid biosynthesis (glutamate (EGFR activation), tryptophan (indole derivatives: AhR activation), carbohydrate biosynthesis (SCFAs (butyrate, acetate, propionate): GPR activation), lipid biosynthesis (secondary BAs: TGR5 and FXR activation). ROS production by immune cells is also prevented by ubiquinone biosynthesis. Mild to moderate disease is characterized by the establishment of dysbiosis with the loss of beneficial anti-inflammatory bacteria and the presence of pro-inflammatory bacteria, thus decreasing the basal beneficial metabolism to down regulate inflammation leading to mucosal barrier damage, over ROS production, pro-inflammatory responses pro-inflammatory cytokines. Severe disease is characterized by loss of mucosal barrier integrity; presence of Th1, Th17; pro-inflammatory cytokines with excessive amounts of ROS (DNA, RNA repair; glutathione metabolism), microbial virulence factors to invade the host (TCS, quorum sensing, heme metabolism) and to evade host defenses (biofilms). (Treg, Regulatory T cells; EGFR, epidermal growth factor receptor; AhR, aryl hydrocarbon receptor; SCFA, short chain fatty acids (Butyrate, acetate, propionate); GPRs, G protein-coupled receptors; Ba, bile acids; FXR, farnesoid X receptor; TGR5, G protein-coupled bile acid receptor 1; TCS, two-component systems; ROS, Reactive oxygen species).[(1)]

Future Research

Targeting the microbial dysbiosis in IBD patients have the potential for symptoms relief. Approaches including prebiotics, probiotics, microbiome-derived metabolite supplementation, dietary intervention, and fecal microbiota transplantation (FMT) show promise for these patients. However, more research and clinical trials are needed to specify effective and safe treatment regimens for IBD patients.

Conclusion

The complex interactions between the gut microbiome and the host immune system have increasing evidence to imply its role in the pathogenesis of IBD. Dysbiosis, reduced beneficial bacteria as compared to pathogenic bacteria, disrupts homeostasis in the GI tract. Compromised epithelial barrier integrity through a reduction of SCFA, primarily butyrate, contributes to chronic inflammation. While current therapies focus on immunosuppression, emerging therapies are examining the effectiveness and safety of microbiome-targeted approaches. The diversity of gut microbiomes between individuals poses challenges that point toward individualized therapy regimens. Continued research utilizing high-throughput DNA sequencing, metabolomics, and longitudinal cohort studies provide insight into the connections between the science and possible treatments. Closing the gaps in knowledge of the gut microbiome and its role in chronic inflammation could provide innovative and effective treatment options that improve patient outcomes for those with IBD.

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Finding #1

Patients with IBD have an altered microbiome composition, indicative of gut microbiome dysbiosis.

- Patients with IBD exhibit a decrease in beneficial, anti-inflammatory bacteria (*Faecalibacterium, Bifidobacterium, Roseburia, Blautia*) & an increase in pathogenic, pro-inflammatory bacteria (*Escherichia coli, Enterococcus, Streptococcus, Proteobacteria*).
- Adherent-invasive *Escherichia coli* (AIEC) are increased in CD patients. AIEC invades epithelial cell barriers, survives intracellularly within macrophages, and replicates in the host cell cytoplasm. They set off a very strong inflammatory response[(4)].

Finding #2

IBD patients have been shown to have a decrease in the bacteria that produce SCFAs, notably *Firmicutes* and *Roseburia*

- SCFAs provide protective functions: epithelial barrier integrity, thicker mucous layer, modulation of reactive oxygen species, and regulation of T-cell activity.
- SCFAs decrease gut inflammation by reducing the NF-kB signal cascade & enhancing anti-inflammatory cytokines, such as IL-10.

Finding #3

High-fiber diets increase *Bifidobacterium*, SCFAs, and decrease CRP levels.

- *Bifidobacterium* aids in metabolizing dietary fiber, and therefore produces metabolites (SCFAs) that modulate host immunity.
- Low-fiber and Western diets have been seen to exacerbate inflammation by increasing microbial dysbiosis.
- Only limited information about diet has been gathered on human subjects, as producing a large-scale diet study has several limitations.

Finding #4

Gut microbiome composition might be a predictor of IBD onset in individuals pre-diagnosed.

- *R. torques* were positively correlated with individuals who developed CD. *R. torques* is a mucin degrader.
- *Roseburia* and *Blautia* were negatively correlated with the individuals who developed CD.
- *Roseburia* might have a potentially protective function against IBD, as they have been seen to increase the presence of T-regulatory cells and decrease proinflammatory cytokine, IL-17[(9)].