Update on Gut Microbiota in Gastrointestinal Diseases

Reviewed by:

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Gut microbiota

Human gastrointestinal system is home for approximately 100 trillion microorganisms, known as the gut microbiota (GM). GM is a complex, dynamic, and spatially heterogeneous ecosystem inhabited by a myriad of microorganisms interacting with each other and with the human host, including bacteria, fungi, archae, and viruses. GM, being metabolically active is associated with various functions, such as nutrition, immune development, and host defense; signifying the key role of GM in the maintenance of human health.[1,2]

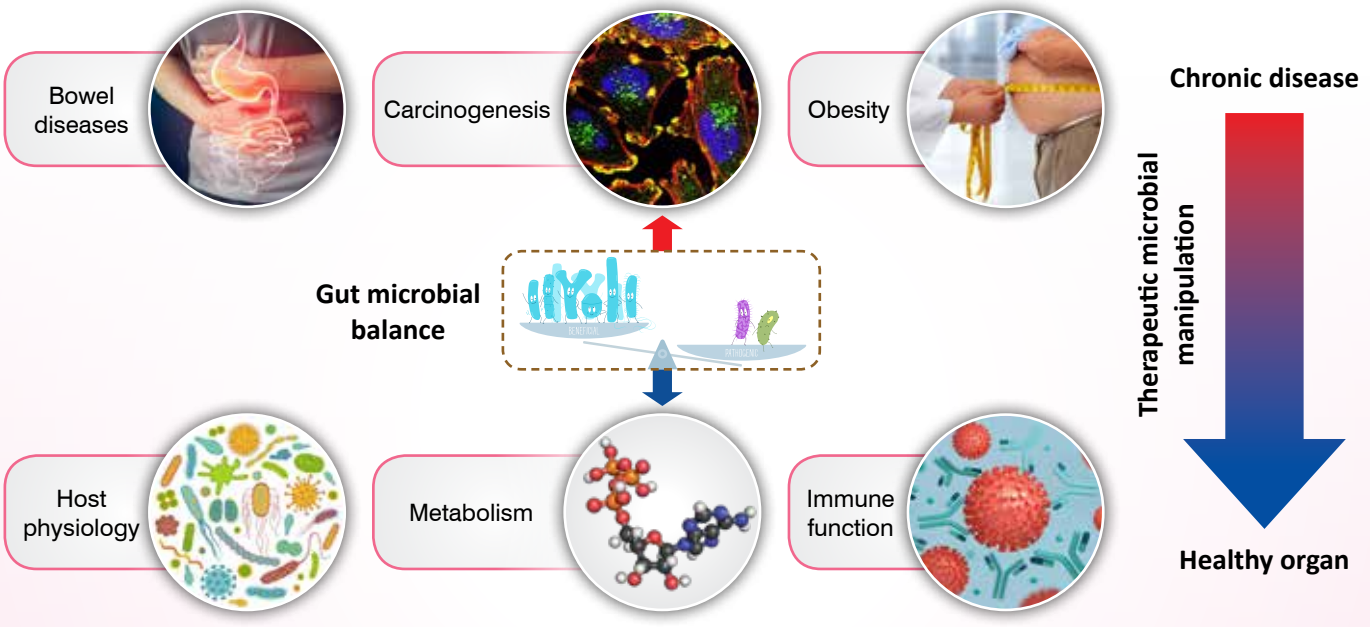
Any imbalance in the composition and function of the gut microbiota results in dysbiosis. Dysbiosis not only results in loss of beneficial microbial input or signaling and a colonization of pathogenic microbes, but is also thought to aggravate inflammatory effects and immune dysregulation associated with human disorders.[1]

Gut microbiota: Function and role in GI health

In healthy individuals, intestinal microbiota is known to exert health benefits with respect to pathogen protection, nutrition, host metabolism and immune modulation (Figure 1).[3,4]

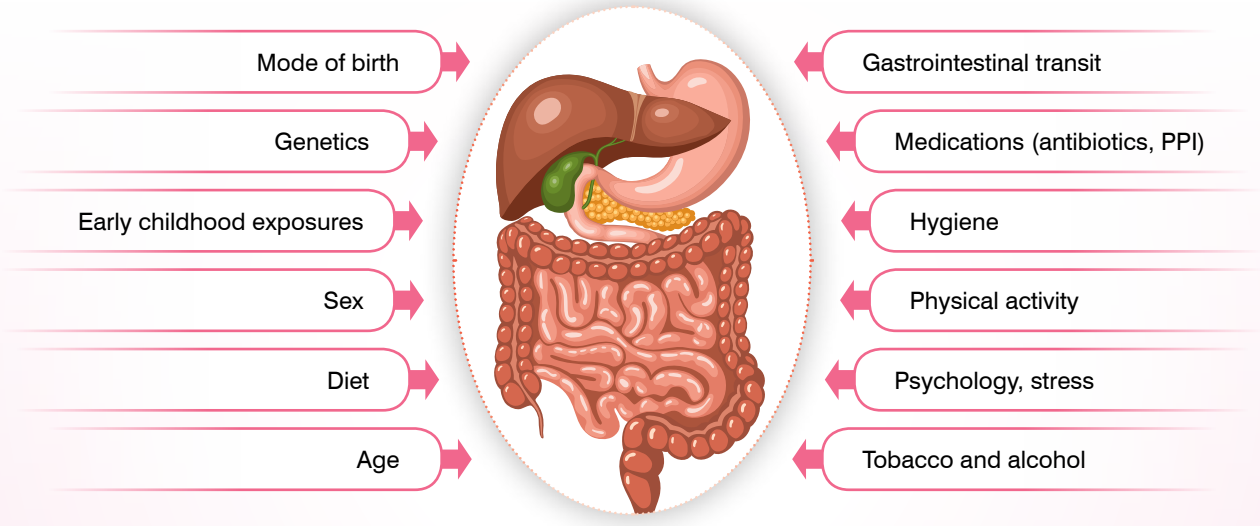
Metabolism: Gut bacteria carry the potential to produce vitamins, synthesize all essential and non-essential amino acids, and carry out biotransformation of bile. Furthermore, microbiome provides the vital biochemical pathways for the metabolism of non-digestible carbohydrates, oligosaccharides that escape digestion, unabsorbed sugars and alcohols from the diet and host-derived mucins. This leads to production of energy and absorbable substrates for the host and energy and nutrients for bacterial growth and proliferation. In colon, metabolism of carbohydrates is a major source of energy.[4]

Figure 1: Gut microbiota in health and disease



Adapted from: Guinane CM, Cotter PD. Role of the gut microbiota in health and chronic gastrointestinal disease: understanding a hidden metabolic organ. Therap Adv *Gastroenterol.* 2013;6(4):295-308.

Figure 2: Factors associated with shaping of gut microbiota



Adapted from: Shin A, Preidis GA, Shulman R, Kashyap PC. The Gut Microbiome in Adult and Pediatric Functional Gastrointestinal Disorders. *Clin Gastroenterol Hepatol.* 2019;17(2):256-274.

Immune modulation: In the gut wall of the host cells, attachment sites present are used by pathogenic bacteria to enter the epithelial cells. However, intestinal bacteria do produce antimicrobial compounds, competing for nutrients and sites of attachment in the gut lining, thereby preventing colonization by pathogens.

Furthermore, it is the interaction between intestinal microbiota and its metabolites that affect the development of host's immune system. Intestinal epithelium is the key connecting link between the immune system and the external environment; such that cells of the intestinal epithelium prevent imposed threat from pathogens by signaling to the innate immune system through specific receptors that recognize and bind to specific molecules associated with bacteria, leading to the production of a host's immune response and the release of protective peptides, cytokines, and white blood cells.[4]

Factors affecting gut microbiota

Host genetics and environmental factors largely define the diversity and composition of GM (Figure 2).

GM diversity varies with age with considerable differences seen at extremes of life. Moreover, distribution and composition of the gut microbiota may also be influenced by with the length of the GI tract and across the lumen, mucus layer, and the epithelium; such that bacterial density may increase from more proximal to distal sites.

Gut microbiota in GI Diseases

Inflammatory bowel diseases

Inflammatory bowel disease (IBD), a chronic, relapsing and remitting inflammatory disorder of the gastrointestinal tract, consists of two major forms, crohn's disease (CD) and ulcerative colitis (UC). It is the interaction between genetic and environmental factors that is associated with deregulated host immune response to gut microbiota.[5]

It has been observed that intestinal dysbiosis has been linked to IBD pathogenesis; such that intestinal areas with higher diversity of bacteria has been associated with greater incidence of CD and UC, such as terminal ileum and colon. Microbiota changes related to IBD patients are summarized in Table 1. Studies have also shown that in IBD, there is more disruption in microbial function (12%) than composition (2%).[5,7]

In IBD, there is marked reduction in bacterial diversity and stability, linked to decrease in Firmicutes and enriched Proteobacteria and Actinobacteria phyla. Furthermore, metabolites of gut microbes also play a key role in the pathogenesis of IBD. Short chain fatty acids (SCFAs) aids in B-cell development, regulation of mucosal integrity via inflammasome activation and IL-18 production, thus exerting effects on mucal immunity. Moroever bile acids play an immunomodulatory role by direct stimulation of FXR, exerting anti-inflammatory effects and protecting chemically induced colitis. As evident by studies, inositol triphosphate, a metabolite of GM, carries the potential

Table 1: Changes in gut microbiota in IBD

Microbial composition	Microbial function
• Decrease in Bacteroides and Firmicutes • Decrease in alpha diversity • Increase in Gammaproteobacteria • Presence of Escherichia coli, specifically AIEC • Presence of Fusobacterium • Decrease in Clostridia, Ruminococcaceae, Bifidobacterium, Lactobacillus • Decrease in Faecalibacterium prausnitzii	• Decrease in short chain fatty acids, 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

Adapted from: Kostic AD, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease: current status and the future ahead. *Gastroenterology.* 2014;146(6):1489-99.

of antagonizing inhibitory effect of butyric acid on histone deacetylase 3 and inducing the activation of protein deacetylase 3, thus favouring intestinal epithelial cell proliferation and intestinal injury repair and improving inflammatory bowel disease.[2]

Irritable bowel syndrome

Irritable bowel syndrome (IBS), a common gastrointestinal problem in clinical practice is associated with high morbidity, affecting around 11% of population across the globe.[5] Though the pathophysiology of IBS is not known, genetic factors, motor dysfunction of the GIT, visceral hypersensitivity, infection, inflammation, and immunity as well as psychopathological factors are associated with its development. Healthy GM exerts either bactericidal effects or it prevents pathogenic bacteria adherence to gut wall. However, microbial imbalance in the gut promotes bacterial adhesion to gut walls, thus aiding in IBS symptoms development. It is the alteration in the microbial composition in IBS patients along with altered colonic fermentation that is linked to development of IBS symptoms. Furthermore, there is a significant, 2-fold increase in the ratio of Firmicutes to Bacteroidetes in IBS patients.[4]

Significant increase in Ruminococcus, Clostridium, and *E. coli* has also been observed in IBS patients. However, in patients with IBS, UC and CD Faecalibacterium, more specifically *F. prausnitzii*, levels were decreased signifying it as "healthy gut marker." *F. prausnitzii* has a strong anti-inflammatory effect both in vitro and in vivo, maintaining intestinal health.[5]

In IBS-D patients, marked increase in levels of Enterobacteriaceae and significantly lower levels of *Faecalibacterium prausnitzii* was noted, as evident by a group of researchers; signifying an imbalance of advantageous and potentially harmful intestinal bacteria in such patients.[8]

C. difficile infection

C. difficile, an anaerobic, Gram-positive, sporulating, bacterial pathogen, has been considered as primary cause of nosocomial, antibiotic-associated diarrhea. In healthy individuals, gut mircobiota prevents colonization of *C. difficile*, thus arresting its pathogenic activity in the colon, by spore germination and toxin production. However, in patients with *C. difficile* infection bacterial diversity is altered; increase in proteobacteria and reduction of Firmicutes and Bacteroidetes phyla.[5]

Constipation

Microbial imbalance may contribute to functional constipation and constipation-type irritable bowel syndrome; significantly higher level of Firmicutes, including Clostridium species, and a significantly lower level of Actinobacteria and Bacteroidetes in patients with IBS-C has been noted.[9]

Treatment of GM dysbiosis in GI diseases

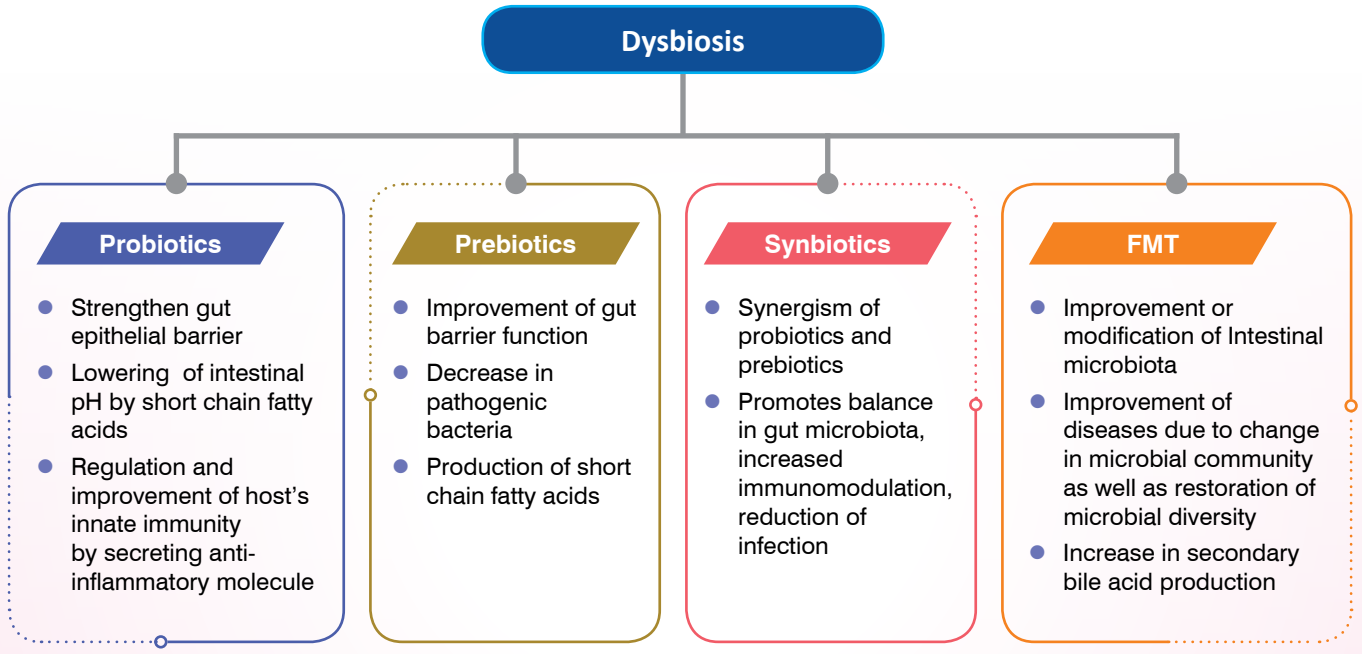
Therapeutic interventions that focus on regulating the composition of GM, gut homeostatis and physical barrier defense should be contemplated as an effective therapeutic strategy to treat chronic disease. These may include use of prebiotics, supplementation with probiotics, reconstitution of bacterial populations by faecal transplantation or antimicrobials to eliminate pathogens or regulate GM incurring benefit to host health (Figure 3).[1,3,5]

Future implication of gut microbiome in health care

Metagenomics might be considered as having the potential future role in diagnosis, prognostication and optimization of therapy as it carries the ability to differentiate individuals according to their gut microbiota profile. It may also in identification of predictors of disease relapse and/or chronicity.

Furthermore, it is important to work on strategies on modulation of gut microbiota and how they might offer a new approach to the prevention and management of a host of clinical symptoms, syndromes, and disorders.[10]

Figure 3: Effect of therapeutic interventions on gut microbiota



Abbreviation: FMT; Fecal microbiota transplantation.

Adapted from: Nishida A, Nishino K, Ohno M, Sakai K, Owaki Y, Noda Y, Imaeda H. Update on gut microbiota in gastrointestinal diseases. *World J Clin Cases.* 2022;10(22):7653-7664.

Conclusion

Gut microbiota, being metabolically active is associated with various functions, such as nutrition, immune development, and host defense; signifying the key role of GM in the maintenance of human health. Any imbalance in the composition and function of the gut microbiota results in dysbiosis. Dysbiosis not only results in loss of beneficial microbial input or signaling and a colonization of pathogenic microbes, but is also thought to aggravate inflammatory effects and immune dysregulation associated with human disorders. Intestinal dysbiosis has been linked to IBD pathogenesis; such that intestinal areas with higher diversity of bacteria has been associated with greater incidence of CD and UC, such as terminal ileum and colon. Moreover, it is the alteration in the microbial composition in IBS patients along with altered colonic fermentation that is linked to development of IBS symptoms. Furthermore, there is a significant, 2-fold increase in the ratio of Firmicutes to Bacteroidetes in IBS patients. Microbial imbalance may contribute to functional constipation and constipation-type irritable bowel syndrome.

Therapeutic interventions that focus on regulating the composition of GM, gut homeostatis and physical barrier defense should be contemplated as an effective therapeutic strategy to treat chronic disease. It is important to work on strategies on modulation of gut microbiota and how they might offer a new approach to the prevention and management of a host of clinical symptoms, syndromes, and disorders.

References

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