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Treatment of GIT disorders by optimizing the normal Microbiota: A Review

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Abstract

The human gastrointestinal (GI) tract harbors a complex and dynamic population of microorganisms, the gut microbiota, which exert a marked influence on the host during homeostasis and disease. Multiple factors contribute to the establishment of the human gut microbiota during formative years. Diet is considered as one of the main points in shaping the gut microbiota across life time. Intestinal bacteria play a crucial role in maintaining immune and metabolic homeostasis and protecting against pathogens. The altered gut bacterial composition has been associated with the pathogenesis of many provocative diseases and infections. The interpretation of these studies relies on a better understanding of inter-individual variations, heterogeneity of bacterial communities along and across the GI tract, functional redundancy and the need to distinguish cause from effect in states of dysbiosis. This review summaries our current understanding of the development and composition of the human GI microbiota, and its impact on gut integrity, underlying the need for mechanistic studies focusing on host-microbe interactions.

Keywords: Dysbiosis, symbiosis, pathogens, heterogeneity.

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1. Introduction

1.1 Gastrointestinal disorders

Gastrointestinal diseases refer to diseases involving the gastrointestinal tract, namely the esophagus, stomach, small intestine, large intestine and rectum, and the accessory organs of digestion, the liver, gallbladder, and pancreas. Gastrointestinal disorders include such conditions as constipation, irritable bowel syndrome, hemorrhoids, anal fissures, perianal abscesses, anal fistulas, perianal infections, diverticular diseases, colitis, colon polyps, and cancer. Many of these can be prevented or minimized by maintaining a healthy lifestyle, practicing good bowel habits, and submitting to cancer screening. Gastrointestinal disorders include such conditions as Constipation, Irritable Bowel, Hemorrhoids, Anal fissures, Perianal abscesses Anal fistulas, Perianal infections, Diverticular diseases, colitis. Many of these can be prevented or minimized by maintaining a healthy lifestyle, practicing good bowel habits, and submitting to cancer screening.

2. Gut Microbiota

The human gastrointestinal (GI) tract represents one of the largest interfaces (250–400 m^2) between the host, environmental factors and antigens in the human body. In an average lifetime, around 60 tons of food passes through the human GI tract, along with an abundance of microorganisms from the environment which impose a huge threat on gut integrity [1]. The collection of bacteria, archaea and eukarya colonizing the GI tract is termed the 'gut microbiota' and has co-evolved with the host over thousands of years to form an intricate and mutually beneficial relationship [1]. As a result of the vast number of bacterial cells in the body, the host and the microorganisms inhabiting it are often referred to as a 'superorganism' [2,3]. The microbiota offers many benefits to the host, through a range of physiological functions such as strengthening gut integrity or shaping the intestinal epithelium [4], harvesting energy [5], protecting against pathogens [5] and regulating host immunity [6]. However, there is potential for these

mechanisms to be disrupted as a result of an altered microbial composition, known as dysbiosis. The microbiota in a large number of intestinal and extra-intestinal diseases has become steadily apparent. This review summarises our current understanding of the development and composition of the human GI microbiota, and its impact on gut integrity and host health.

2.1 Composition and structure of the human GI microbiota:

Around a decade ago, most knowledge about the adult human gut microbiota stemmed from labor-intensive culture-based methods [7]. These studies identified 2172 species isolated from human beings, classified into 12 different phyla, of which 93.5% belonged to Proteobacteria, Firmicutes, Actinobacteria, and Bacteroidetes. Three of the 12 identified phyla contained only one species isolated from humans, including an intestinal species, *Akkermansia muciniphila*, the only known representative of the Verrucomicrobia phyla. In humans, 386 of the identified species are strictly anaerobic and hence will generally be found in mucosal regions such as the oral cavity and the GI tract [8]. An extensive catalog of the functional capacity of the human gut microbiome was recently obtained, where 9 879 896 genes were identified through a combination of 249 newly sequenced and 1018 published samples [9].

2.2 Development of the human GI microbiota:

In the early stages of development, the microbiota is generally low in diversity and is dominated by two main phyla, Actinobacteria and Proteobacteria [10,11]. During the first year of life, the microbial diversity increases and the microbiota composition converges towards a distinct adult-like microbial profile with temporal patterns that are unique to each infant [12]. By around 2.5 years of age, the composition, diversity and functional capabilities of the infant microbiota resemble those of adult microbiota. Although in adulthood, the composition of the gut microbiota is relatively stable, it is still subject to perturbation by life events [13]. In individuals over the age of 65, the microbial community shifts, with an increased abundance of Bacteroidetes phyla and *Clostridium* cluster IV, in contrast with younger subjects where cluster XIVa is more prevalent [14]. In contrast, a separate study observed that the microbiota of a young cohort and an elderly population (70 years) were relatively comparable, whilst the diversity of the microbiota from a cohort of centenarians was significantly reduced [15].

2.3 Factors shaping the GI microbiota

The microbiota composition is subject to shaping by the host and environmental selective pressures. To protect from injury and maintain homeostasis, the GI tract limits exposure of the host immune system to the microbiota by conscription of a multifactorial and dynamic intestinal barrier. The barrier comprises several integrated components including physical, biochemical and immunological factors [16]. An individual microbe's longevity is determined by whether it is contributing to the range of essential functions on which host fitness relies. It is proposed that organisms who do not contribute advantageous functions are controlled by, and may occasionally be purged during, for example, transferral of the microbiota to a new host [17]. The microbiota can also be shaped by the host immune system. This effect is mostly limited to stratification and compartmentalization of bacteria to avoid the opportunistic invasion of host tissue, whilst species-specific effects are less probable due to the high amount of functional redundancy within the microbiota [18].

2.4 Role of the GI microbiota in health:

Owing to its large genomic content and metabolic complement, the gut microbiota provides a range of beneficial properties to the host. Some of the most important roles of these microbes are to help to maintain the integrity of the mucosal barrier, to provide nutrients such as vitamins or to protect against pathogens. In addition, the interaction between commensal microbiota and the mucosal immune system is crucial for proper immune function.GI microbiota is also crucial to the *de novo* synthesis of essential vitamins which the host is incapable of producing Lactic acid bacteria are key organisms in the production of vitamin B_{12}, which cannot be synthesized by either animal, plants. *Bifido bacteria* are main producers of folate, a vitamin involved in vital host metabolic processes including DNA synthesis and repair. Further vitamins, which gut microbiota have been shown to synthesize in humans, include vitamin K, riboflavin, biotin, nicotinic acid, pantothenic acid, pyridoxine, and thiamine Colonic bacteria can also metabolize bile acids that are not reabsorbed for biotransformation to secondary bile acids All of these factors will influence host health.

2.5 Microbial Flora of the Stomach and Gastrointestinal Tract

The flora of the gastrointestinal tract in humans has been studied intensively. These studies have demonstrated that bacteria are the most numerous microbes present in the stomach and gastrointestinal tract. Sometimes the diet of a human can select for the dominance of one or a few bacteria over other species. The situation is similar in humans. Other factors that influence the bacterial makeup of the human stomach and gastrointestinal tract include age, cultural conditions, and the use of antibiotics. In particular, the use of antibiotics can greatly change the composition of the gastrointestinal flora. Despite the variation in bacterial flora, the following bacteria tend to be present in the gastrointestinal tract of humans and many animals:

Escherichia coli, Clostridium perfringens, *Enterococci*, Lactobacilli, and *Bacteroides.*Only bacteria that can tolerate strongly acidic environments are able to survive in the stomach. One bacterium that has been shown to be present in the stomach of many people is *Helicobacter pylori*. This bacterium is now known to be the leading cause of stomach ulcers. In addition, very convincing evidence is mounting that links the bacterium to the development of stomach and intestinal cancers.In humans, the small intestine contains low numbers of bacteria, some 100,000 to 10 million bacteria per milliliter of fluid. The bacterial flora of this region consists mostly of lactobacilli and *Enterococcus faecalis*.In the large intestine, the bacterial numbers can reach 100 billion per milliliter of fluid. These include anaerobic lactic acid bacteria, *Bacteroides*, and *Bifidobacterium bifidum*. The bacteria numbers and composition in the large intestine is effectively that of fecal material.

3. Role of Microbiota in the Treatment of GIT Disorders

3.1 Constipation:

Constipation means it is hard to have a bowel movement (or pass stools), they are infrequent (less than three times a week), or incomplete. Constipation is usually caused by inadequate "roughage" or fiber in the diet, or a disruption of the regular routine or diet. Constipation causes a person to strain during a bowel movement.

Treatment: You can treat your constipation by, Increasing the amount of fiber you eat.

3.1.1 Possible alterations of intestinal microbiota in chronic constipation:

Using standard cultural and/or molecular approaches, the quantitative difference among intestinal microbiota species has been extensively studied. Alterations of intestinal microbiota in patients with chronic constipation can be characterized by a relative decrease in obligate bacteria (e.g. *Lactobacillus*, *Bifidobacterium*, and *Bacteroides* spp.) and a parallel increase of potentially pathogenic microorganisms (e.g. *Pseudomonas aeruginosa* and *Campylobacter jejuni*). These alterations may influence intestinal motility and secretory functions by changing the amount of available physiologically active substances and the metabolic environment of the gut.

3.1.2 Possible microbiota-based therapy on chronic constipation

3.1.2.1 Dietary fibre:

Dietary fibre has been recommended on an empirical basis for the management of chronic constipation. As is known, dietary fibres can promote the excretion of intestinal mucin by stimulating the capacity of mucosal protein synthesis. Dietary fibre is broken down in the proximal colon and provides an energy-yielding substrate for microbial fermentation. The result of this is to stimulate the growth of intestinal microbiota and contribute significantly to the stool dry weight. Besides, fibres could promote the excretion of bacterial fermentation products, such as SCFAs, which has pro-motility effects.

3.1.2.2 Prebiotics:

Prebiotics are non-digestible substances that provide a beneficial physiological effect on the host by selectively stimulating the growth or activity of a limited number of favorable indigenous gut bacteria. Prebiotics are subjected to bacterial metabolism in the colon, where they are transformed into lactic and short-chain carboxylic acids. It has been demonstrated that galacto-oligosaccharides seemed to promote the intestinal peristalsis and relieve constipation. The consumption of inulin-type fructans affects intestinal microbiota and stimulates bowel movements normalizing stool frequency in constipated patients.

3.1.2.3 Probiotics:

These are live or attenuated microorganisms defined as being capable of conferring health benefits on their host when they are given in sufficient quantities and administered continuously, beyond any inherent nutritional value. Probiotics have demonstrated beneficial effects in patients with constipation, making them increasingly used as alternative treatment options. Some probiotics, such as *Bifidobacterium lactis* DN-173010 and *Bifidobacterium longum* could modify the metabolic activities of the colonic microbiota and improve lactose digestion in Chinese lactose-intolerant subjects. Probiotic administration may modulate the composition of the intestinal microbiota and consequently induce the alteration of metabolic activities and colonic immunological activities.

3.2 Irritable Bowel Syndrome (IBS):

Irritable bowel syndrome (also called spastic colon, irritable colon, or nervous stomach) is a condition in which the colon muscle contracts more often than in people without IBS. Certain foods, medicines, and emotional stress are some factors that can trigger IBS.

Treatment includes:

Avoiding caffeine, Increasing fiber in the diet, Monitoring which foods trigger IBS.

3.2.1 Modulation of the intestinal microbiota in IBS

3.2.1.1Probiotics:

The term “probiotic” as originally defined by FAO/WHO refers to “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host”[19]. However, in order to be beneficial, probiotic bacteria must be able to survive along the gastrointestinal tract, to resist gastric acid, bile, and pancreatic juice action and to demonstrate functional efficacy.

3.2.1.2 Putative mechanisms of action of probiotics:

As the pathogenesis of IBS is multifactorial, probiotics have been shown effective in modulating several mechanisms that might have a mechanistic role in IBS pathogenesis, including effects on the composition of intestinal microbiota, gastrointestinal dysmotility, visceral hypersensitivity, altered gut epithelium an immune function, luminal metabolism, dysfunction of the gut-brain axis, psychological distress.

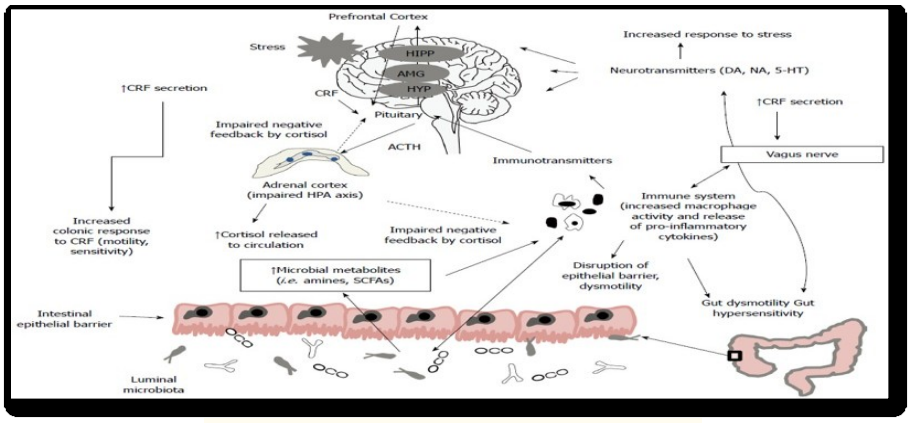

Figure 1: Mechanism of action of probiotics

3.2.1.3 Mechanism of action of probiotics:

Gut microbiota influences the bidirectional communication between the enteric nervous system and the central nervous system, modulating gut development and several physiological functions, including intestinal motility, sensitivity, secretion, and immunity. In irritable bowel syndrome (IBS), the altered composition and/or activity of microbiota may induce a disruption of this communication leading to activation of immune system and production of pro-inflammatory cytokines, production of microbial metabolites as short-chain fatty acids (SCFAs) that are toxic at high concentration, activation of hypothalamic-pituitary-adrenal (HPA) axis with increase of cortisol that feeds back to the pituitary, hypothalamus (HYP), amygdala (AMG), hippocampus (HIPP) and prefrontal cortex to shut off the HPA axis and increase of corticotropin-releasing factor (CRF). These effects lead to alterations of intestinal motility and sensation, disruption of the epithelial barrier and impaired production of neurotransmitters with an increased response to stressful events. On a turn, stress may provoke systemic pro-inflammatory cytokines production that activates the HPA axis that signals to both the enteric nervous system and the central nervous system and may alter microbiota composition [20].

3.3 Intensive faecal microbiota transplantation for active ulcerative colitis

The intestinal microbiota is implicated in the pathogenesis of ulcerative colitis. Faecal microbiota transplantation is a novel form of therapeutic microbial manipulation, but its efficacy in ulcerative colitis is uncertain. We aimed to establish the efficacy of intensive-dosing, multidonor, faecal microbiota transplantation in active ulcerative colitis. Fecal microbiota transplantation (FMT) is the administration of a solution of fecal matter from a donor into the intestinal tract of a recipient in order to directly change the recipient's gut microbial composition and confer a health benefit. FMT has been used to successfully treat recurrent *Clostridium difficile* infection. There are preliminary indications to suggest that it may also carry the therapeutic potential for other conditions such as inflammatory bowel disease, obesity, metabolic syndrome, and functional gastrointestinal disorders. The process usually involves first selecting a donor without a family history of autoimmune, metabolic, and malignant diseases and screening for any potential pathogens. The feces are then prepared by mixing with water or normal saline, followed by a filtration step to remove any particulate matter. The mixture can be administered through a nasogastric tube, nasojejunal tube, esophagogastroduodenoscopy, colonoscopy, or retention enema. Most clinical experience with FMT has been derived from treating recurrent or refractory *Clostridium difficile* infection (CDI). This paper will review the therapeutic potential of FMT in treating CDI, inflammatory bowel disease (IBD), and several other conditions [21].

4. Conclusion

Given the close symbiotic relationship existing between the gut microbiota and the host, it is not surprising to observe a divergence from the normal microbiota composition (generally referred to as dysbiosis) in a plethora of disease states ranging from chronic GI diseases to neurodevelopmental disorders. The function of metabolomics approaches has greatly advanced our understanding of the mechanisms linking the gut microbiota

composition and its activity to health and disease phenotypes. At a functional level, a potential way to describe a 'dysbiotic microbiota' might be one which fails to provide the host with a full complement of beneficial property. Whether dysbiosis of the microbiota is a cause or a consequence of the disease is therefore likely to exacerbate the progression of the disease and affect the type of strategies needed to restore symbiosis. Depending on the type and stage of disease, these include the development of microbiome modulators (e.g. antimicrobials, diet, prebiotics or probiotics) mostly aimed at changing the composition of the host microbiota, or of microbial-based solutions to replace some of the defective microbes and their associated benefits (e.g. specific commensal strains, probiotics, defined microbial communities, microbial-derived signaling molecules or metabolites). Given the contribution of host genetics in many diseases associated with a dysbiotic microbiota, dual therapeutic strategies (e.g. combining immunotherapy and microbiota-targeted approaches) may also be required to restore the environment required to re-establish an effective communication between the host and the targeted microbiota. Success in these endeavors is dependent on our mechanistic understanding of how the microbiota affects and is affected by the host at a molecular and biochemical level.

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