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The role of gut microbiota: from gastrointestinal cancer to neurodegenerative diseases

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ABSTRACT
The intestinal milieu harbours the gut microbiota, consisting of a complex community of bacteria, archaea, fungi, viruses and protozoans that bring to the host organism an endowment of cells and genes more numerous than its own. In recent years, an interest in intestinal microbiota-host interactions has increased due to many findings about the impact of gut bacteria on human health and disease. Gut microbiota dysbiosis, defined as marked alterations in the amount and function of the intestinal microorganisms, is correlated with the aetiology of chronic diseases, ranging from cardiovascular, neurologic, respiratory and metabolic illnesses to cancer. In this review, we focus on the interplay among gut microbiota and host to provide a perspective on the role of microbiota in the pathogenesis and progression of various human disorders, highlighting the influence of gut microbiota on cancers in the gastrointestinal tract and on neurodegenerative diseases.

Keywords:
gut, microbiota, gastrointestinal cancers, neurodegenerative disorders.

Background

The human is a superorganism that functions in harmony with trillions of symbiotic bacteria and eukaryotic cells. Human normal microorganism are mainly distributed in the internal cavity of the body, such as respiratory, digestive and urogenital tract, and body surface forming four microecosystem.[1] Of these four site, the gut microbiota has drawn the attention of the scientific community for its clinical significance, and it is now well established that a healthy gut flora is largely responsible for overall health of the host[2]. It has been shown that an imbalance in the gut microbiota, called dysbiosis, is associated with various diseases, ranging from intestinal diseases, like gastric and colorectal cancer, irritable bowel syndrome, and inflammatory bowel disease[3], to other systemic diseases and to central nervous system (CNS) diseases, such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS).[4] Here, we mainly reviewed the influence of gut microbiota on two different fields, cancers in the gastrointestinal (GI) tract and neurodegenerative diseases.

The gut microbiota

The human gut microbiota consists of several types of microbes including bacteria, archaea, eukarya, viruses and parasites. In recent years, the Metagenomics of the Human Intestinal Tract (MetaHIT) and the Human Microbiome Project (HMP) have provided the most integrated view of human-associated microbes. Hugon et al. listed 2172 species isolated in human, which they classified into 12 different phyla, and among these divisions, the Bacteroidetes and the Firmicutes constitute more than 90% of the total population.[5] Traditionally, the Firmicutes: Bacteroidetes ratio has been implicated in predisposition to disease state; however, the significant variability even in healthy individuals that has been observed across recent studies makes the relevance of this ratio debatable.[6]

Microbiota is acquired at birth and develops in parallel with the host playing an important role in maintaining the body healthy through adulthood until death. After birth, microbes rapidly colonize the sterile neonatal GI tract, and the microbiota composition partially depends on the delivery mode and whether breast-feeding is done.[7] The intestines of infants born vaginally are initially colonized by organisms from the maternal vagina, organisms from the genera Lactobacillus and Prevotella, on the contrary in cesarean delivery mostly the maternal skin flora colonizes the infant's intestine with the dominance of Streptococcus, Corynebacterium and Propionibacterium.[8] Thereafter by the age of 3-5 years, the unstable structure and composition of microbiota starts to differentiate and gradually develops to resemble that of adults. In adulthood, the composition and functions of the established microbiota remain the same if there is no change in long-term dietary habits, antibiotics treatment, stress and pathophysiology in adulthood.[9] Indeed, recent evidence has shown that the adult microbiome is not stable as previously believed, and there are many important endogenous and exogenous factors for the composition of the intestinal microbial community, such as genetic factors, sex, dietary habits and food types, drugs and other factors including lifestyle, illness, smoking and drug addiction1. The gut microbiota, which derives its nutrient from host dietary components and shed epithelial cells, is an organ by itself with an extensive metabolic capability and substantial functional plasticity. The normal gut microbiota imparts specific function in host nutrient metabolism, xenobiotic and drug metabolism, maintenance of structural integrity of the gut mucosal barrier, immunomodulation and protection against pathogens.[6] On the contrary, a shift in the balance of microbiota composition such that it may become deleterious to host health is termed dysbiosis. Dysbiosis of the gut microbiome has been implicated in numerous disorders, ranging from intestinal diseases, to more systemic disease and neurological disorders.[10]

Gut microbiota and gastrointestinal cancer

In the past decade, the interaction between microorganisms and tumors have attracted much attention in the efforts understand the possible mechanisms through which the microbiota is involved in cancer prevention, carcinogenesis and therapy. Various studies have demonstrated that impaired microbiota can facilitate carcinogenesis via multiple pathways, and further studies have suggested that the microbiota and his associated metabolites are not only closely related to carcinogenesis by inducing inflammation and immune dysregulation, which lead to genetic instability, but also interfere with the pharmacodynamics of anticancer agents.[11] The link has been found both with local gastro-intestinal cancers, as well as with other distal tumors.[12]

The most well established risk factor for gastric cancer (GC) is Helicobacter pylori infection.[13] Infection by H. pylori can stimulate immune responses and inflammation, regulate many signaling pathways, and induce achlorhydria, epithelial atrophy and dysplasia. [14] Furthermore, H. Pylori also indirectly promotes carcinogenesis by changing the composition of the gastric microbiota. Several studies showed the gastric microbiota arose from patients infected with H. Pylori are different from uninfected people, suggesting an interaction between H. Pylori and gastric microbial community. Though the mechanism of H. Pylori in altering the gastric microbiota remain unclear, all of these findings had shed a light that dysbiosis of gastric microbiota might related to the susceptibility to gastric inflammation and tumorigenicity in patients with H. pylori infection.[15]

Various factors contribute to colorectal cancer (CRC) and the involvement of the microbiota in colorectal carcinogenesis is becoming increasingly clear. Indeed, many changes in the bacterial composition of the gut microbiota have been reported in CRC, suggesting a major role of dysbiosis in colorectal carcinogenesis. [16,17] Some bacterial species have been identified and suspected to play a role, these species primarily include Streptococcus bovis, H. pylori, Bacteroides fragilis, Enterococcus faecalis, Clostridium septicum and Escherichia coli.[18] Two different hypotheses have emerged to explain contribution of gut microbiota to CRC: the presence of a dysbiotic microbial community with pro-carcinogenic features capable of remodeling

the microbiome as a whole to drive pro-inflammatory responses and epithelial cell transformation, and the "driver-passenger" theory, where intestinal bacteria, termed "bacteria drivers", initiate CRC by inducing epithelial DNA damage and tumorigenesis, in turn promoting the proliferation of passenger bacteria that have a growth advantage in tumor microenvironment. [18]

Gut microbiota and neurodegenerative diseases

At the end of the 19th century, the American scientist Gershon first described the concept of gut-brain connection. Insights into the gut-brain crosstalk have revealed a complex communication system that not only ensures the proper maintenance of gastrointestinal homeostasis, but is likely to have multiple effects on affect, motivation and higher cognitive functions. The complexity of these interactions is enclosed in the denomination of "gut-brain-axis" (GBA).[19] The GBA consists of bidirectional communication between the central and the enteric nervous system (ENS), and both clinical and experimental evidence suggest that gut microbiota has an important impact on GBA interacting not only with intestinal cells and ENS, but also directly with the central nervous system (CNS) through neuroendocrine and metabolic pathways.[20]

The gut microbiota can affect the body's nervous system function in numerous ways, the principal one likely being modulation of the intestinal barrier and tight junction integrity. Furthermore, microbiota can influence ENS activity by production, expression and turnover of neurotrasmitters (serotonin, GABA) and neurotrophic factor (BDNF), can interact with GBA through the modulation of afferent sensory nerves, and can affects mucosal immune activation.[19] At the same time, the CNS can directly impact the gut via sympathetic nervous system or parasympathetic nervous system by the secretion of catecholamines or acetylcholine, which influence ENS circuits.[1]

Given the impact the microbiota has on the development of immune cells and the nervous system, it is possible that this microbial interaction may significantly influence the course of autoimmune CNS diseases such as MS.[21] In the last few years, several studies have demonstrated that patients with MS exhibit gut microbial dysbiosis with both enrichment and depletion of certain bacterial populations compared with healthy controls. Modifications of the intestinal environment induced by either diet or microbiota composition have been linked to the pathogenesis of MS, but the mechanisms underlying this association are still largely unknown. T helper 17 (TH17) cells are key players in MS: effector TH17 cells represent the first wave of pathogenic T cell infiltrating the CNS because of their ability to efficiently breach the blood-brain barrier, and several studies demonstrated that effector TH17 cells that trigger brain autoimmunity originate in the intestine. TH17 cell differentiation in the small intestine is regulated by the whole microbial community composition and also by some specific bacteria. MS patients which high disease activity and increased intestinal TH17 cells, frequently show a higher Firmicutes: Bacteroidetes ratio with an increase in Streptococcus and a decrease in Prevotella strains compared to healthy controls and MS patient with no disease activity.[22]

ALS belong to neurodegenerative diseases characterized by the loss of motor neurons. To date, the pathogenesis of ALS remains unclear and is likely multifactorial, and the pathophysiology may be related to the gastrointestinal tract.[23] Indeed, as widely reviewed by McCombe et al., theoretical reasons support the hypothesis of the involvement of gut microbiota in the pathogenesis of ALS, including connections with the impaired metabolism, host immunity, and production of toxins that induce brain damage.[24] Most of the experimental evidence of gut dysbiosis comes from studies on mouse models for ALS. In the G93A-SOD1 transgenic mice models for ALS, it was shown that the impaired intestinal epithelium and tight junction potentially contributed to the progression of ALS, and that replenishment of probiotics and the relevant metabolites thereof ameliorated the motor ability of mice.[25] In general, a few studies have been performed on human ALS, and with conflicting results. Brenner et al., and similarly Rowin et al., showed a low diversity of intestinal microbial composition in fecal samples of ALS compared to controls, inferring that there is no direct and significant gut microbiota–disease correlation.[24] Conversely, Mazzini et al. highlighted an altered ALS gut microbiota by quantitative PCR analysis. Specifically, the authors showed a cluster distinction between bacterial profiles of ALS patients compared to controls, especially related to an increase of Escherichia coli and Enterobacteria, and a decrease of Clostridium and yeast.[26] Fecal microbiota transplantation (FMT) has emerged as a promising strategy to restore gut microbiota dysbiosis involved in complex pathologies including neurodegenerative diseases. To this regard, a very recent paper has proposed a multicenter randomized double-blind clinical trial employing FMT as a therapeutic intervention for ALS patients at an early stage, opening new avenues for the treatment of neurodegenerative diseases by acting on the microbiota modulation.[24]

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