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THE IMMUNOLOGICAL ROLE OF MICROBIOTA IN THE HUMAN INTESTINE AND THE BIDIRECTIONAL COMMUNICATION OF THE GUT-BRAIN AXIS

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ABSTRACT

A group of microorganisms, such as bacteria, viruses, and fungi, located in the same specific environment is called microbiota. These microorganisms have biological effects and regulate the human body, especially at the intestinal level. Microbiota is ubiquitous in the soil, and in humans, it is mainly found in the intestine, particularly in the colon. It controls almost all biological functions and has adapted to live in symbiosis with the human body without causing damage. The microbiota maintains human health and plays an important role in metabolism and regulation of immune functions. The concentration of microorganisms in the intestine is influenced by various factors such as diet, age, genetics, and health conditions and varies from individual to individual. The intestinal microbiota plays a key role in the digestion of complex carbohydrates, proteins, and other nutrients. The microbiota synthesizes essential vitamins such as vitamin K and B which are important for energy metabolism, red blood cell formation, and DNA synthesis. Through hydrolysis, the microbiota can influence xenobiotic metabolism with the modification of environmental toxins and plays a crucial role in the production of mucus. In addition, the bacteria of the microbiota promote the secretion of antimicrobial peptides such as defensins and cathelicidins that inhibit pathogenic microorganisms. The microorganisms that make up the microbiota have an effect on the modulation of both the innate and adaptive immune system. Gut microbes can influence the maturation and activity of antigen-presenting dendritic cells, and in the adaptive response, they can differentiate T cells. The human microbiota is a good example of symbiosis and cooperation between different types of organisms that provide an advantage to the parties.

KEYWORDS: *Microbiota, intestine, immunology, gut-brain axis, microorganism*

INTRODUCTION

The microbiota is a collection of microorganisms such as bacteria, viruses, and fungi that have adapted to living in a specific environment where they have evolved and are specialised in carrying out specific biological effects (1). The microbiota also includes the virome, the genetic material of viruses (2). However, here in this article, we will mainly discuss bacteria because there are more advanced techniques available for their study. Most of the bacteria are

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extremophiles and anaerobes so they live in the dark and without oxygen; and today we know that bacteria are 60/80% Gram-positive, 20/40% Gram-negative, and 60/80% anaerobic.

Microbiota are found in nutrient-rich and nutrient-poor soils where they ferment, break down organic matter, and fix nitrogen, converting atmospheric nitrogen into a form that plants can use (7). Microbiota are found in marine environments where they have adapted to photosynthesize efficiently in low-light conditions near the ocean surface. Microbiota found in deep waters derive energy from chemicals such as hydrogen sulfide, which are emitted from the Earth's crust rather than from sunlight (8). In addition to being found almost ubiquitously in soil, microbiota is also found in the human gut.

Microbiota largely regulate the human body, especially at the intestinal level (3). In the last 10 years, there has been much discussion about microbiota because new technologies have allowed the knowledge and discovery of these microorganisms. The internal surface of the gastrointestinal tract is about 200-300 square meters. In human feces, it is believed that there are 109 virus-like particles per gram, of which bacteriophages are the prevalent enteric viruses. For every human cell, there are at least 10 microbial cells. The gut microbiota is made up of 1,014 microbes, approximately 3 million genes, and 300-1,000 species of bacteria (this is a vague number because there is ongoing research on this topic), and has control over almost all functions of the body, both at the metabolic and physiological levels (4). The remarkable quantity of bacteria present together with our eukaryotic cells has allowed us to define man as a "superorganism", whose genomic structure includes both its genome and the genome of all resident microorganisms (5).

In the past, the intestine was not given this great importance. Other organs were considered more noble and the intestine was considered a peripheral organ of secondary importance. Today, it is considered just as important as other systems because it contributes to the state of health.

DISCUSSION

The microbiota is a group of living microorganisms in a specific location which forms a community that has adapted to living in a specialized environment. In the human body, these microorganisms coexist in natural symbiosis with the human host without causing damage (6), particularly in the colon, where they are adapted to efficiently ferment dietary fiber to produce short-chain fatty acids, which are important for host health. The species and number of microorganisms in the microbiota can vary greatly.

The microbiota plays an important role in maintaining human health by influencing various physiological functions, especially metabolism and immune regulation (9). The human gut microbiota is composed of a diverse population of bacteria, viruses, fungi, and protozoa. The most common bacteria are:

- Firmicutes (e.g., *Lactobacillus, Clostridium*)
- Bacteroidetes (e.g., Bacteroides, Prevotella)
- Actinobacteria (e.g., Bifidobacterium)
- Proteobacteria (e.g., *Escherichia coli*)

This microbial composition is influenced by various factors such as diet, age, genetics, and health conditions, and varies from individual to individual (10).

The gut microbiota contributes significantly to the digestion of complex carbohydrates, proteins, and other nutrients, which the human host cannot fully break down on its own (11). Microbes ferment indigestible polysaccharides, such as cellulose and resistant starch, into short-chain fatty acids like butyrate, propionate, and acetate. Butyrate is an important energy source and promotes intestinal barrier integrity (12). Propionate affects hepatic gluconeogenesis and reduces cholesterol synthesis, and acetate enters the systemic circulation and serves as a substrate for lipogenesis (12).

Gut bacteria metabolize dietary proteins into bioactive molecules such as branched-chain amino acids, amines, and phenolic compounds. However, excessive protein fermentation can also produce toxic metabolites such as ammonia and hydrogen sulfide (13). The microbiota synthesizes essential vitamins such as vitamins K and B (B12, biotin, folate), which are essential for energy metabolism, red blood cell formation, and DNA synthesis (14). Some strains of bacteria also produce cofactors such as bile acids, which aid in lipid digestion and cholesterol metabolism (15).

The gut microbiota also plays a crucial role in drug metabolism and detoxification. Microbes in the gut can activate or inactivate drugs through enzymatic transformations, such as hydrolysis, reduction, or conjugation; they can influence xenobiotic metabolism, modifying environmental toxins, food additives, and drugs, which can affect drug efficacy and toxicity (16).

Microbial fermentation of dietary fiber produces short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate, which regulate immune functions by influencing T regulatory (Treg) cells, dendritic cells, and macrophages (17). For example, butyrate has anti-inflammatory properties and promotes Treg cells that control immune homeostasis (18). The microbiota is involved in the function of the intestinal barrier, a critical interface between the external environment

and the immune system (19). The intestinal microbiota enhances this barrier by strengthening tight junctions by enhancing the expression of proteins that maintain tight junctions between epithelial cells. Additionally, the microbiota mediates the production of the mucus layer. Microbes stimulate goblet cells to secrete mucus, which forms a physical barrier that protects epithelial cells from pathogens. Furthermore, commensal bacteria promote the secretion of antimicrobial peptides such as defensins and cathelicidins, which inhibit pathogen colonization (20).

The microbiota modulates the intestinal immune system, having a profound effect on both the innate and adaptive immune systems. In the host innate immune response, pattern recognition receptors (PRRs) detect molecular patterns associated with microbes via receptors, such as Toll-like receptors (TLRs), on epithelial and immune cells (21). This recognition triggers immune responses to eliminate pathogens while maintaining tolerance to commensals. Gut microbes can influence the maturation and activity of dendritic cells, which are key cells that present antigens and educate the adaptive immune system.

In the adaptive immune response mediated by Treg cells, the differentiation of Tregs is induced by some bacterial species such as Bacteroides fragilis, which helps maintain tolerance to commensal bacteria and prevent excessive immune responses that could lead to inflammation (22). Moreover, the gut microbiota stimulates B cells to produce secretory IgA, an antibody that coats the intestinal mucosa and prevents pathogens from adhering to the intestinal lining (23).

The gut microbiota helps the immune system distinguish between harmful pathogens and harmless commensals. This process is essential for preventing autoimmune diseases and allergies. Commensal bacteria outcompete pathogenic bacteria for nutrients and attachment sites, a phenomenon known as colonization resistance. They also produce antimicrobial substances that inhibit the growth of pathogens. When the gut microbiota is out of balance (dysbiosis), it can lead to several diseases such as inflammatory bowel disease (IBD), metabolic disorders, and immune-related diseases (24).

Dysbiosis in patients with IBD is characterized by reduced diversity and overgrowth of pro-inflammatory bacteria such as Enterobacteriaceae. Dysbiosis in metabolic processes is linked to obesity, type 1 diabetes, and non-alcoholic fatty liver disease, through mechanisms involving endotoxin release. Immune-related dysbiosis has been implicated in the development of autoimmune diseases such as rheumatoid arthritis and allergies due to impaired immune tolerance (25).

The gut microbiota interacts with the brain through the gut-brain axis, influencing mental health. Dysbiosis is associated with mood disorders, such as depression and anxiety, potentially through altered production of neurotransmitters (e.g. serotonin) and immune activation (26).

Probiotics are live beneficial bacteria, such as strains of Lactobacillus and Bifidobacterium, that are used to restore a healthy microbial balance. Prebiotics are non-digestible fibers, such as inulin and fructooligosaccharides, that promote the growth of beneficial bacteria. Fecal microbiota transplantation involves the transfer of fecal matter from a healthy donor to a patient with dysbiosis (27). This approach is successful in treating conditions such as Clostridioides difficile infections and is being studied for other disorders such as IBD and metabolic syndromes (28). Diets rich in fiber and polyphenols are associated with greater microbial diversity and better health outcomes. In contrast, diets high in fat and sugar can lead to dysbiosis. (29).

The microbiota is made up of millions of genes. In a human gene, there are about 100 microbial genes (it is thought to be as many as 150 as of today). The techniques in use today promote a better understanding of bacteria, but there is also a virome, the set of viruses and their genetic heritage. It is believed that there are 109 virus-like particles per gram in human feces and bacteriophages are the prevalent enteric viruses. So, we are in the presence of a numerically very large group of microorganisms (30). What is important in this symbiotic relationship is that we welcome them, allowing them to recover everything they need for their metabolism (darkness, anaerobic conditions, etc.) and they are able to offer us many advantages. These microorganisms have the sole interest of surviving and they transform into pathogens when something changes this balance, so this environment must be protected (31).

Role of the Microbiota in the Gut-Brain Axis

The gut-brain axis is a complex bidirectional communication network that connects the central nervous system (CNS) with the enteric nervous system and the gastrointestinal tract (32). The gut microbiota influences this axis and plays an important role in various neurological, psychological, and metabolic conditions. Gut microbes produce a variety of bioactive molecules that influence brain function and behavior (33). Short-chain fatty acids such as acetate, propionate, and butyrate are produced by bacterial fermentation of dietary fiber. These metabolites modulate the immune system by interacting with G-protein-coupled receptors on immune cells and influence neurotransmitter systems by crossing the blood-brain barrier (BBB) or by acting on vagal afferents. They also regulate processes such as mood, cognition, and inflammation (34) and regulate the integrity of the gut barrier, thereby, influencing systemic inflammation, which may indirectly impact brain function.

Gut bacteria can synthesize several key neurotransmitters, such as serotonin (5-HT) (about 90%) produced in the gut by enterochromaffin cells. Serotonin is critical for regulating mood, sleep, and digestion (35). Some bacteria such as Lactobacillus and Bifidobacterium can produce gamma-aminobutyric acid (GABA), an important inhibitory neurotransmitter that calms neuronal excitability, and dopamine, which affects reward and motivation (36). The gut microbiota influences the availability of tryptophan, which is a precursor to serotonin and kynurenine, which influence pathways linked to mood disorders such as depression.

Furthermore, the gut microbiota can modulate the production of pro-inflammatory (e.g., IL-6, TNF) and anti-inflammatory (e.g., IL-10) cytokines (37). These cytokines can cross the BBB and directly influence brain regions associated with mood and behavior, such as the hippocampus and hypothalamus.

CONCLUSIONS

The microbiota is found in many natural environments where it has adapted to photosynthesize efficiently in low-light conditions. The human intestinal microbiota is essential for the biochemical and immunological homeostasis of the human body. It plays a central role in nutrient metabolism, immune modulation, and protection against pathogens. The interaction between the gut microbiota and the brain is crucial because it involves a variety of molecular and biochemical pathways, with significant implications for neurological, psychological, and immune health. Future studies on the human intestinal microbiota and its interaction with the brain could improve the understanding of pathogenetic mechanisms and open therapeutic possibilities with new drugs for the treatment of many diseases associated with microbiota imbalance.

Conflict of interest

The authors declare that they have no conflict of interest.

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