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EDITORIAL

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Update on the gut microbiome in health and diseases

Maurizio Salvadori, Giuseppina Rosso

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Abstract

The Human Microbiome Project, Earth Microbiome Project, and next-generation sequencing have advanced novel genome association, host genetic linkages, and pathogen identification. The microbiome is the sum of the microbes, their genetic information, and their ecological niche. This study will describe how millions of bacteria in the gut affect the human body in health and disease. The gut microbiome changes in relation with age, with an increase in *Bacteroidetes* and *Firmicutes*. Host and environmental factors affecting the gut microbiome are diet, drugs, age, smoking, exercise, and host genetics. In addition, changes in the gut microbiome may affect the local gut immune system and systemic immune system. In this study, we discuss how the microbiome may affect the metabolism of healthy subjects or may affect the pathogenesis of metabolism-generating metabolic diseases. Due to the high number of publications on the argument, from a methodologically point of view, we decided to select the best papers published in referred journals in the last 3 years. Then we selected the previously published papers. The major goals of our study were to elucidate which microbiome and by which pathways are related to healthy and disease conditions.

Key Words: Gut microbiome; Dysbiosis; Pathobionts; Gut-brain axis; Heart-brain axis; Metabolic diseases; Omics techniques

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Core Tip: Gut microbiome has relevant importance in healthy and diseased subjects. The production of several metabolites from the gut microbiome influences the immune system, brain, lung, heart, and metabolism. In the case of normal indigenous microbiota, metabolites produced have a benign action and contribute to the health. By contrast, the presence of pathobionts with their products may affect the different organs and produce diseases. The study of the gut microbiome is a difficult one and different omics technologies should be applied. The large quantity of studies highlights the relevance of the gut microbiome in health and disease.

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INTRODUCTION

More than 150,000 papers with “Microbiome” in the title or abstract have been published since the term was introduced in 2001. Early-stage reports were cross-sectional studies of the microbiota at different body sites, associations with disease markers, and diseases themselves. More recently, three relevant projects, the Human Microbiome Project[1], the Earth Microbiome Project[2], and next-generating sequencing[3], have advanced novel genome associations, host genetic linkages, and pathogen identification. Current studies have principally focused on the functional or mechanistic aspects of differences in microbial composition.

In particular, a study from Gao *et al*[4] found that the more relevant studies cover six important aspects of microbiome research. They include best practices for analyzing microbiomes, the regulation of gut microbiomes in the human immune system, how microbiomes affect immune sensing, the role of microbiomes in the gut-brain interaction, the application of microbiomes in maternal and newborn health, and the study of nutri-microbiome epidemiology.

Due to the high number of publications on the argument, from a methodologically point of view, we decided to select the best papers published on referred journals in the last 3 years. Then, going in a backward way, we selected the previously published papers.

The aim of this study was to clarify the relationship between microbiome and healthy and disease conditions. In particular, we looked for which microbiome products and metabolites are involved in this relationship and which organs are strictly connected to microbiome normal or modified composition.

Before discussing the gut microbiome, and its function and its relationship with health and disease, exact definitions are needed for a correct understanding.

DEFINITIONS

Frequently, the terms microbiota and microbiome are mutually used, but they have a different significance. **Table 1** shows the exact definitions needed to be understood.

Microbiota are defined as the microorganisms (bacteria, archaea, viruses, fungi) that live in the human body in healthy conditions. All of these microorganisms make up the microbiome. The microbiome is the sum of microbes, their genetic information, and their ecological niche. The metagenome is the totality of genes from the genomics of a mixed microbial population that provides information about genetic potential. Indigenous microbiota are the resident microbiota resident in the healthy subjects. Dysbiosis is the change in indigenous microbiota composition causing disease. Pathobionts are the microbiota causing disease.

GUT MICROBIOME

The microbiome is spread across different organs and tissues of the human body, but the most important and best studied is the gut microbiome. A total of 10^{14} bacteria already represent the gut microbiome, and 10^{11} bacteria flow each day from the pharynx to the stomach. Changes in the gut microbiome are associated with diseases, but frequently, it is not known if this is a cause or an effect.

Under normal conditions, formation of the adult microbiome occurs over the first 3 years of life and is affected by life events such as weaning, starting solid food, and primarily cessation of breastfeeding. At birth, the most common bacteria are aerobic bacteria such as *Enterococcus* and *Staphylococcus*. Later, anaerobes prevail, with a prevalence of *Firmicutes* and *Bacteroidetes*[5]. Several studies have documented the distribution of normal gut flora in the different parts of the intestine in adults as shown in **Table 2**[6-8].

Table 1 Definitions related to gut microbiome and its action

Terminology	Significance
Microbiota	All microorganisms living in the gut
Microbioma	Sum of microbes, their genetic information, and their ecological niche
Metagenome	Total genes providing information on genetic potential
Indigenous microbiota	Resident gut microbiota in the healthy subjects
Dysbiosis	Modification of the composition of gut microbiota causing diseases
Pathobionts	Gut microbiota causing diseases

Table 2 Distribution of normal gut flora in different parts of intestine

Intestine sections	Function	Normal flora
Stomach	Acid production, pepsin, amylase, CFU < 10 ³ /mL	<i>Lactobacillus</i> ; <i>Streptococcus</i> ; <i>Helicobacter pylori</i>
Small intestine: Duodenum, jejunum	Pancreatic enzymes, bicarbonate ions, bile salts, CFU: 10 ³ -10 ⁴ /mL	<i>Lactobacilli</i> ; <i>Enterococci</i> , <i>Streptococci</i> ; <i>Actinobacteria</i>
Small intestine: Ileum	CFU: 10 ³ -10 ⁹ /mL	<i>Enterococcus</i> ; <i>Bacteroidetes</i> ; <i>Lactobacillus</i> ; <i>Clostridium</i> ; <i>Corynebacteria</i>
Large intestine: Cecum, colon	Mucus and bicarbonate; CFU: 10 ¹⁰ -10 ¹² /mL	<i>Bacteroidetes</i> ; <i>Clostridium</i> ; <i>Eubacterium</i> ; <i>Ruminococcus</i> ; <i>Streptococcus</i> ; <i>Enterococcus</i> ; <i>Lactobacillus</i> ; <i>Fusobacteria</i>

CFU: Colony-forming unit.

FACTORS INFLUENCING THE GUT MICROBIOME

The Human Microbiome Project data suggest that the unperturbed microbiome is stable over short periods and that there is a degree of resilience of the microbiome due to several factors. In addition to age, several factors affect the composition of the gut microbiome, such as diet, host genetics, exercise, smoking, and drugs[9]. A vegetarian and rich fiber diet has a beneficial effect on the gut microbiome, favoring an increase in *Firmicutes* and *Bacteroidetes*[10,11]. Several genes associated with innate immunity influence the microbiome[12]. A recent study from Chen *et al*[13] documented the influence of host genetics on the gut microbiome. Exercise is associated with a beneficial effect on gut microbiome composition, as documented by Hughes *et al*[14] and Mailing *et al*[15]. It has also been documented that athletes have a reduced rate of inflammatory markers[16] and exercise has been proposed to reduce dysbiosis[17]. No smoker subjects showed an increase in the fecal microbiota of *Firmicutes* and *Actinobacteria*[18]. The same author in a different study found differences in the oral gut microbiota in smokers with respect to no smokers[19]. Several drugs have a powerful effect on microbiome composition. Antibiotics may damage the microbiome in two different ways. On the one hand, by destroying beneficial microbes, antibiotics may cause dysbiosis[20]. On the other hand, destroying beneficial microbes blocks the mechanism by which they inhibit pathogens[21]. These effects on the gut microbiome are related to the type of antibiotics and the treatment duration. Worse effects on the microbiome have been described with the use of clindamycin[22], clarithromycin, ciprofloxacin[23], and vancomycin[24]. All of these antibiotics cause a reduction in *Bacteroides* variety and *Ruminococcus*. Regarding non-antibiotic drugs, there is a complex bidirectional interaction between their use and the gut microbiome[25]. On the one hand, these commonly used drugs alter the gut microbiome composition and function; on the other hand, gut microbes can contribute to drug efficacy and safety by enzymatically transforming drug structure and altering drug bioavailability, bioactivity, or toxicity. Knowing these interactions enables interventions to modulate the gut microbiome and optimize treatment efficacy.

According to the Belgium Flemish cohort[26] and the Twins United Kingdom cohort[27], the most common no antibiotic drugs associated with microbiome modification and dysbiosis are proton pump inhibitors (PPIs), statins, laxatives, metformin, and angiotensin-converting enzyme inhibitors. PPIs, by changing microbiome composition may favor the colonization of pathogens such as *Clostridium difficile* and *Salmonella*[28,29]. Metformin, used to treat type 2 diabetes, increases *Escherichia coli* and reduces *Intestinibacter*, favoring dysbiosis and causing gastrointestinal side effects [30,31]. Studies conducted in the United Kingdom, the Netherlands, and Belgium have documented modifications in microbiome composition after the prolonged assumption of laxatives, statins, and antidepressants[26,27,32].

FUNCTIONS OF THE MICROBIOME

Metabolic function

The gut microbiota has the capacity to metabolize dietary fibers not metabolized by digestive enzymes[33]. In this way, the microbiome provides additional energy by metabolizing large polysaccharides and alcohols. The MEROPS database showed that the microbiome produces proteases that are able to metabolize different substances in the large intestine[34, 35]. Additionally, beneficial effects produced by the microbiome are related to the production of several vitamins[36,37]. A study by Afzaal *et al*[38] showed the principal metabolites produced by gut microbiota in normal conditions and their functions (Table 3)[39-49].

Structural function

Under normal conditions, the microbiome contributes to maintaining the integrity of the gut epithelium. In this condition, cytokines present in the gut lumen do not pass through the gut epithelium. This function may be altered by pathogens such as *E. coli* and *C. difficile*. The dysbiosis produced by these bacteria facilitates the back diffusion of cytokines[50,51].

Protective function

The intestinal surface represents an important barrier, and the microbiome contributes to its stability[52]. The production of short-chain fatty acids (SCFAs) by the microbiome provides further energy for the epithelium and strengthens this barrier[53,54]. Table 4 shows examples of gut microbiome-derived metabolites and their beneficial effects on healthy conditions. In order of the metabolites, the pathway involved, the microbial agent responsible, and the health benefits produced, this information is shown in Table 4[55-70].

Relationship between the gut microbiome and immune system

The gut microbiome has important effects on the local and general immune systems. The local gut microbiome drives the maturation of gut-associated lymphoid tissue (GALT)[71] and maintains barrier function by mucus production and antimicrobial peptide production. In addition, GALT has specific influences on inflammatory *vs* no inflammatory cell phenotypes. One-sixth of the cells of the gut epithelium are represented by T lymphocytes. In addition, B lymphocytes, dendritic cells, and plasma cells are present in lymphoid tissue, principally in the colon mucosa or in Peyer's patches[72, 73].

Indigenous microbiota or pathobionts may differentiate T helper (Th) cells into Th1, Th2, Th17, and regulatory T (Treg) cells *via* the production of microbiota metabolites. Filamentous bacteria induce the growth of Th17 and Th1; *Clostridia* stimulate Tregs and the anti-inflammatory cytokine interleukin 10 (IL-10). *B. fragilis* stimulates IL-10 and Tregs. By contrast, excessive stimulation of Th1 and Th2 cells due to the condition of dysbiosis may cause excessive production of proinflammatory cytokines[74]. Intestinal colonization has an important role in the development of tolerance[75]. This fact is relevant in the prevention of immune-mediated diseases. Indeed, the loss of immune tolerance may cause the development of allergic diseases or autoimmune diseases. Dysbiosis caused by *E. coli* or *C. difficile* is associated with eczema or atopic dermatitis. The production of SCFAs has a double effect. They constitute the main energy substrate for enterocytes and stimulate the maturation and correct function of Tregs[76]. Several axes have been established between the gut microbiome and different organs. In the case of dysbiosis they can generate diseases. The gut-brain axis may generate stress, anxiety, depression, schizophrenia, cognitive decline, and autism. The gut-brain endocrine axis generates regulatory, metabolic, behavioral, and hormonal disorders. The gut-heart axis generates cardiovascular diseases, atherosclerosis, thrombotic events, and hypertension. The gut-lung axis generates chronic obstructive pulmonary disease. The gut-liver axis generates liver inflammation, hepatocellular carcinoma, and non-alcoholic fatty liver. The gut-pancreas axis generates diabetes and pancreas cell inflammation. The gut-bone axis generates bone demineralization and osteoporosis. The gut-muscle axis generates muscle impairment, fragility, and sarcopenia. The gut-skin axis generates acne, psoriasis, atopic dermatitis, wrinkles, and aging. The gut-reproductive axis generates infertility, ovarian dysfunction, ovarian cancer, and postmenopausal osteoporosis. The gut-kidney axis generates chronic kidney disease, acute kidney injury, inflammation, nephrolithiasis, and nephropathy. The gut-bladder axis generates urinary tract infection and an overactive painful bladder. Some of these axes will be discussed below.

Gut microbiome and the brain

Recently, significant studies have documented the existence of the so-called "gut-brain axis." This is a bidirectional communication system between the gut and brain. On the one hand, the brain may control gastrointestinal functions such as peristalsis, mucus production, and the gut immune system[77]. On the other hand, the gut microbiome releases SCFAs and other metabolites influencing brain function, whereas several neurotransmitters are involved in the bidirectional communication between the host and the microbiota[78].

The gut microbiome may affect the brain directly by the gut nervous system, sending signals to the brain or indirectly by the production of intestinal hormones or transforming diet components into substances such as SCFAs, neurotransmitters such as serotonin, gamma amino butyric acid (GABA), tryptophan, and vitamins that influence the blood-brain barrier (BBB) and cerebral functions[79].

In healthy conditions, bacteria such as *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, and *Streptococcus* are among the principal producers of neurotransmitters[80,81]. In addition, SCFAs affect the BBB, and several other immune pathways affect behavior, memory, and locomotion[82,83].

Table 3 Metabolites produced by gut microbiota and their functions

Metabolites	Functions	Ref.
Bile acid metabolites; including deoxycholic acid and lithocholic acid	Regulate bile acid, cholesterol, lipid, glucose, and activate host nuclear receptors and cell signaling pathways	Ramirez-Macias <i>et al</i> [39]
Short-chain fatty acids metabolites	Regulate food intake and insulin secretion, also aid in maintaining body weight	Psichas <i>et al</i> [40]
Branched-chain fatty acids including isobutyrate	Histone deacetylase inhibition, increased histone acetylation	Mischke <i>et al</i> [41]
Indole derivatives including indoxyl sulfate and IPA	IPA exhibits neuroprotective effects, acts as a powerful antioxidant and regulates intestinal barrier function	Hendrikx <i>et al</i> [42]
Lipopolysaccharide, peptidoglycan, lipoteichoic acid	Epigenetic regulation of genes in colorectal cancer, modulation of chromatin structure and transcriptional activity	Lightfoot <i>et al</i> [43]
Phenolic derivatives include 4-OH phenylacetic acid, urolithins, enterodiol and 9-prenylaringenin	Exhibit antimicrobial effect, maintain intestinal health and protect against oxidative stress	Larrosa <i>et al</i> [44]
Choline metabolites include choline, trimethylamine N-oxide, and betaine	Regulating lipid metabolism, and glucose synthesis contribute to the development of cardiovascular disease	Smallwood <i>et al</i> [45]
Polyamines include putrescine, spermidine and spermine	Sustaining the high proliferation rate of intestinal epithelial cells enhances intestinal barrier integrity and enhances the systematic adaptive immune system	Rooks <i>et al</i> [46]
Vitamins including thiamine (B1), riboflavin (B2), niacin (B3), pyridoxine (B6) panthothenic acid (B5), biotin (B7), folate (B11, B9), cobalamin (B12), and menaquinone (K2)	Help in red blood cell formation, DNA replication, and repair, work as an enzymatic co-factor, and enhance immune functioning	Nicholson <i>et al</i> [47]
Ethanol	Protein fermentation metabolism may be involved in NAFLD progression	Yao <i>et al</i> [48]
Hydrogen sulfide	Reduction/neutralization of reactive oxygen species	Afanas'ev <i>et al</i> [49]

IPA: Indole-3-propionic acid; NAFLD: Non-alcoholic fatty liver disease.

Table 4 Examples of gut microbiota-derived metabolites and their beneficial effects on human health

Metabolite	Pathway	Microbial agent	Health benefits
Butyrate	Carbohydrate metabolism	<i>Clostridia</i> ; <i>Faecalibacterium prausnitzii</i> ; <i>Coprococcus catus</i> ; <i>Anaerostipes hadrus</i>	Increased intestinal barrier function; Modulate intestinal macrophage function; Suppression of colonic inflammation; Improvements in insulin sensitivity
Propionate	Carbohydrate metabolism	<i>Blautia obeum</i> ; <i>Coprococcus catus</i> ; <i>Roseburia inulinivorans</i> ; <i>Prevotella copri</i>	Suppression of colonic inflammation; Decreased innate immune response to microbial stimulation; Protection from allergic airway inflammation; Improvements in insulin sensitivity and weight control in obese mice
Indole	Tryptophan metabolism	<i>Lactobacillus</i> ; <i>Bifidobacterium longum</i> ; <i>Bacteroides fragilis</i>	Maintenance of host-microbe homeostasis at mucosal surfaces <i>via</i> IL-22; Increased barrier function; Modulation of host metabolism
Indole-3-aldehyde	Tryptophan metabolism	<i>Lactobacillus</i>	Maintenance of mucosal homeostasis and intestinal barrier function <i>via</i> increased IL-22 production; Protection against intestinal inflammation in mouse models of colitis
Indole-3-propionate	Tryptophan metabolism	<i>Clostridium sporogenes</i>	Maintenance of intestinal barrier function and mucosal homeostasis; Increased production of antioxidant and neuroprotectant products
10-hydroxy-cis-12-octadecanoate	Linoleic acid derivative (lipid metabolism)	<i>Lactobacillus</i>	Maintenance of intestinal barrier function; Decreased inflammation; Increased intestinal IgA production

IgA: Immunoglobulin A; IL-22: Interleukin 22.

It should also be highlighted that the Mediterranean diet rich in vegetables and fibers stimulates the activity and growth of beneficial bacteria for the brain[84]. More than 20% of patients with gut dysbiosis are affected by sleep disorders and depression[85,86].

Similarly, recent studies have documented that microbiota composition differs significantly between healthy controls and patients affected by neurovegetative disorders such as multiple sclerosis (MS), Alzheimer's disease (AD), and Parkinson's disease (PD)[87]. In MS, a higher abundance of *Firmicutes* and the absence of *Fusobacteria* are frequently found [88]. The stool microbial profile of AD patients has a decreased number of *Firmicutes* and *Actinobacteria*. *Firmicutes*, such as

Ruminococcoceae and *Turicibacteriaceae*, are less abundant in these patients[89]. PD patients have a lower production of SCFAs and fewer gut bacteria, such as *Lechnospiraceae* and *Faecalibacterium prausnitzii* producing these substances[90].

In conclusion, several recent studies have documented that a different composition of the gut microbiome may contribute to the development of neurodegenerative disorders causing chronic inflammation of neuronal cells and loss of the BBB.

MICROBIOME IN HEALTH AND DISEASE

Table 4 shows the gut microbiome in healthy conditions. A metabolically healthy microbiota (mainly achieved by a high fiber, low animal fat, and low protein diet and other aforementioned environmental factors) is shown in Figure 1. Microbial production of SCFAs provides an energy source for colonocytes and causes a decrease in luminal pH. The SCFAs acetate, butyrate, and propionate can bind to the G protein-coupled receptor 41 (GPR41) and GPR43, which are expressed on enteroendocrine L cells, and subsequently induce the secretion of glucagon-like peptide 1 and peptide YY, which contribute to increased energy expenditure, reduced food intake, and improved glucose metabolism and insulin secretion[91]. Butyrate is an activator of peroxisome proliferator-activated receptor gamma and a stimulator of β -oxidation and oxygen consumption in the gut, which maintains an anaerobic environment in the gut lumen[92].

Pathobionts often responsible for dysbiosis are shown in Table 5. Figure 2 shows the metabolic pathways induced by gut dysbiosis. A dysbiotic microbiota is often associated with a prolonged colonic transit time, resulting in a shift in colonic metabolism leading to increased microbial proteolysis. Even though the preferred substrate for bacterial fermentation is fermentable dietary fibers, bacteria will not switch to protein metabolism until fermentable polysaccharides are depleted. As a result of increased protein fermentation, branched-chain fatty acids (2-methylbutyrate, isobutyrate, and isovalerate), trimethylamine, organic acids, gases, and trace amounts of phenols, amines, indoles, and ammonia are produced, causing an increase in luminal pH[93]. Together, such changes in the microbial environment and metabolites cause leakage of pathogen-associated molecular patterns, including lipopolysaccharides (LPS), which increase in the blood and trigger systemic low-grade inflammation and insulin resistance[94]. It should be noted, however, that some indole derivatives, such as 3-indolepropionic acid, produced by the fermentation of dietary fibers have been shown to improve glucose metabolism[95].

DISEASES ASSOCIATED OR RELATED TO DYSBIOSIS

Some diseases associated with gut microbiota abnormalities are shown in Table 6. Neurological diseases associated with gut dysbiosis have already been discussed. Other diseases associated with gut dysbiosis are allergic diseases, inflammatory bowel syndromes or diseases, and metabolic diseases.

Allergic diseases: Gut microbiota dysbiosis is reportedly associated with allergic diseases such as eczema and asthma [96]. Lower levels of gut *S. aureus* and *Clostridium* and higher levels of *Bifidobacterium* are present in children affected by allergic symptoms[97]. The cause has been ascribed to LPS that cause a reduced immune system response[98]. The relationship of gut dysbiosis and asthma or other lung syndromes justifies the term “gut-lung axis”[99].

Irritable and inflammatory bowel syndromes: Irritable bowel syndrome (IBS) is a condition affecting 10% to 20% of adults, and children may also be affected. Bennet *et al*[100] described alterations in the gut microbiome of patients affected by IBS. *Firmicutes* are increased with a reduction in *Ruminococcus* and *B. fragilis*. The result is an excessive increase in SCFAs with consequent increase in serotonin that alters intestinal motility. Inflammatory bowel disease (IBD) is a more severe condition. The most significant types of IBD are ulcerative colitis and Crohn’s disease[101]. Several types of gut dysbiosis have been found in patients affected by IBD. *Bacteroidetes* and *Firmicutes* are decreased[102]. Recently Zhu *et al* [103] found an increase in Proteobacteria and *E. coli*. One of the consequences of such dysbiosis is a reduction in mucus production that allows gut flora to pass more easily across the intestinal barrier, thus enhancing the inflammatory process [104].

Gut dysbiosis and metabolic diseases: The gut microbiota participates in material metabolism to produce metabolites. The gut microbiota can affect the metabolism of glucose, lipids, and proteins by generating a series of metabolites and activating downstream signaling pathways as shown in Figure 3.

Obesity: In addition to genetic and behavioral factors, the gut microbiome has an important role in the genesis of obesity [105]. Obese patient gut flora have higher levels of *Firmicutes* and lower levels of *Bacteroidetes*[106]. Other bacteria found in the gut of obese patients are *Bacteroides*, *Ruminococcus*, and *Staphylococcus*[107]. These bacteria cause the increased degradation of β -glucuronide and aromatic amino acids, higher generation of organic acids and H_2 , and higher biosynthesis of phenylalanine, tyrosine, and tryptophan[108]. In this condition, chronic inflammation is generated by the production of IL-1, tumor necrosis factor alpha, monocyte chemoattractant protein-1, and IL-6. In addition, LPS are produced that bind to the cluster of differentiation 14 receptor on the surface of immune cells to produce further inflammatory factors[109,110].

Type 2 diabetes mellitus: Several studies have documented the influence of the gut microbiome on the pathophysiology of type 2 diabetes mellitus. In this condition, pathogenic flora prevail over protective flora. Gurung *et al*[111] analyzed 42

Table 5 Some examples of potentially harmful gut microbiota bacterial species

Bacteria	Associated physiologic changes	Associated diseases states
<i>Bacteroides</i>	Activate CD4+ T cells	Increased with animal-based diet; Increased in obesity
<i>Bifidophila</i>	Promote pro-inflammatory immunity	Increased in colitis; Decreased in autism
<i>Clostridium</i>	Promote generation Th17 cells	Increased after smoke exposure; Increased in autism and Rett syndrome; Positive correlation with plasma insulin and weight gain; Increased in type 2 diabetes; <i>Clostridium perfringens</i> increased in old age
<i>Escherichia coli</i>	TLR activation	Increased in inflammatory bowel disease; Increased in type 2 diabetes
<i>Neisseria</i>	Sugar fermentation	Only two species are pathogenic: <i>Neisseria meningitides</i> and <i>Neisseria gonorrhoeae</i>

Th17: T helper 17; TLR: Toll-like receptor.

Table 6 Diseases associated with gut microbiota abnormalities

Disease	Features
Irritable bowel syndrome	An abundance of <i>Firmicutes</i> and a decrease of <i>Bacteroidetes</i>
Type I diabetes	In genetically predisposed individuals, autoimmune against pancreatic β -cells. Deficient development or alteration of the microbiota may contribute to dysfunctional immunity with the devastation of autoimmune β -cells and increased leakiness of the intestinal barrier. Variability of microbiomes reduced
Asthma	Outbreaks of <i>Chlamidophila pneumonia</i> during bronchitis and pneumonia development affect the airway microbiome. Gut microbiota is influenced by the introduction of microbiota to the environment, particularly in early life, which helps immune function growth and the development of defending against allergic sensitization
Food-borne pathogens and food poisoning	Opportunistic pathogens (<i>Campylobacter</i> , <i>Salmonella</i> , <i>Escherichia coli</i> , <i>Shigella</i>) disturb the microbiome's balance leading to dysbiosis
Malnutrition	Decrease or missing species that either process food categories efficiently or produce vitamins may reduce the absorption of nutrients. An overabundance of <i>Enetrobacteriaceae</i> can lead to epithelial damage, diarrhea, and limited absorption of nutrients
Depression	In physiologic system, <i>Bifidobacterium infantis</i> , generally found in infants' gastrointestinal tract and administered probiotic drugs, can have antidepressant effects
Anxiety	Oral administration of <i>Campylobacter jejuni</i> subclinical doses in murine models induced anxiety like behavior without stimulating immunity

studies and found that the protective bacteria were *Bifidobacterium* and *Bacteroides* as well as *Rosaburia* and *Faecalibacterium*. By contrast, *Ruminococcus*, *Fusobacterium*, and *Blautia* are pathobionts that, through the production of LPS, increase the permeability of the intestinal epithelium. In this condition, inflammatory molecules are produced, which increases insulin resistance (Figure 4)[112]. By contrast, protective flora produce IL-10 and other anti-inflammatory cytokines. In addition, protective flora exert their effect through the production of SCFAs and butyrate[113]. SCFAs also act as substrates for lipogenesis and gluconeogenesis in the liver.

Heart disease: Recent studies have also allowed identified a heart-gut axis. As in similar conditions, the effects of this axis are bivalent. Indeed, on the one hand, heart failure induces an increase in permeability of the gut barrier (the so-called leaky gut) with consequent passage of gut microbiota and its products in the circulation inducing inflammation. On the other hand, several products of the gut microbiota entering the blood may induce hypertension, atherosclerosis, and heart failure. The gut flora that is able to induce cardiovascular diseases is composed as follows[108]. There is an increase in Enterobacteriaceae as *E. coli* and *Klebsiella*, and a decrease in *Roseburia* and *F. prausnitzii*[114]. Several metabolic pathways are involved in the gut-heart axis: trimethylamine (TMA) and trimethylamine n-oxide (TMAO), SCFAs, and bile acids [115]. Dietary sources including choline and l-carnitine provide substrates for microbiota-mediated production of trimethylamine. TMA after entering the portal circulation is converted by the hepatic host flavin-containing monooxygenase to TMAO. TMAO can promote atherogenesis and heart failure development. Adverse cardiac remodeling is also associated with elevated TMAO levels[116-118]. A beneficial effect is exerted by SCFAs. SCFAs improve intestinal barrier function by promoting mucous production. In addition, they improve vascular tone through G protein-coupled receptor signaling. Finally, SCFAs activate histone acetyltransferase and inhibit histone deacetylase, thereby inhibiting inflammation and modulating immune cell activation[119].

Bile acids: Bile acids may be modified by the microbiome. They are produced by the liver, and a small portion are metabolized by colon microbiota with the production of secondary bile acids such as deoxycholate, lithocholate, and

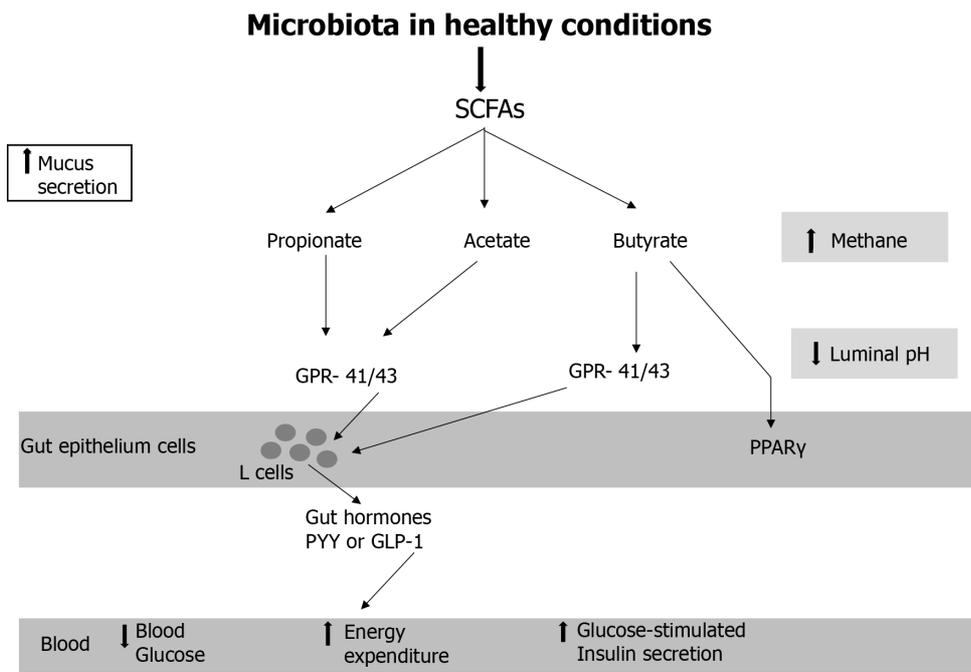


Figure 1 Microbiota in healthy conditions. GLP-1: Glucagon-like peptide 1; GPCR: G protein-coupled receptor; PPAR γ : Peroxisome proliferator-activated receptor gamma; PYY: Peptide YY; SCFA: Short chain fatty acid.

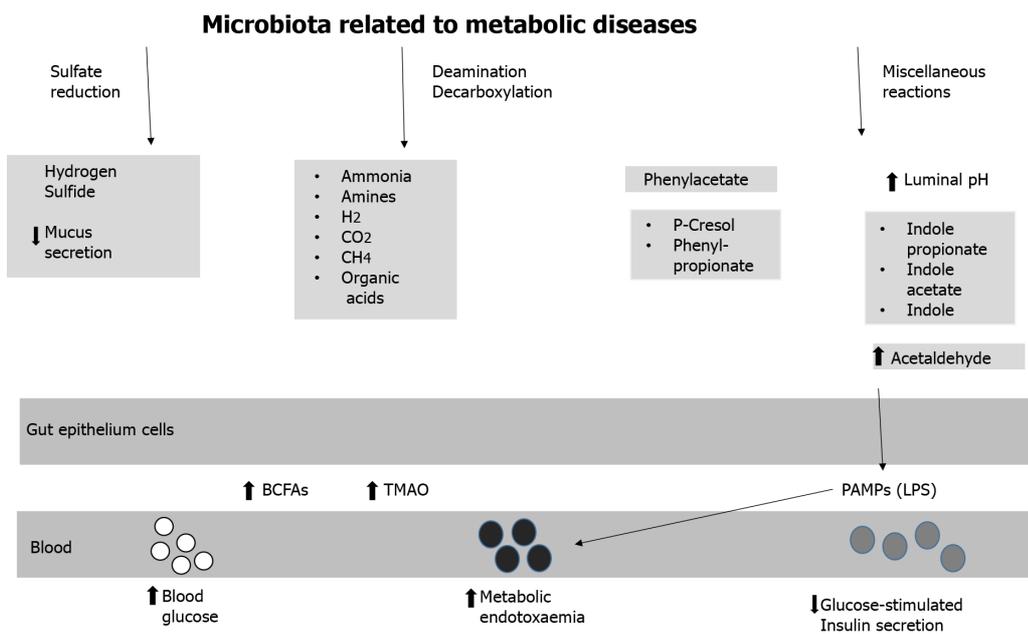


Figure 2 Microbiota related to metabolic diseases. BCFA: Branched-chain fatty acid; LPS: Lipopolysaccharides; PAMP: Pathogen-associated molecular pattern; TMAO: Trimethylamine oxide.

ursodeoxycholate. These secondary bile acids are powerful agonists of the farnesoid nuclear receptor (FXR), which modulates metabolism and inflammation. Therefore, bile acids inhibit the anti-inflammatory activity of FXR. At the cardiovascular level, bile acids favor atherosclerotic disease, cardiac hypertrophy and hypertension[120].

All of these studies are important, but often they are conflicting or have some drawbacks. Some examples are as follows.

The *Firmicutes/Bacteroidetes* ratio is cited in several studies as an important marker of health or disease; however, several of these studies have relevant bias due to methodological procedures or discrepancies in enrolling subjects for the study.

Modification in gut microbiota seems to cause irritable bowel disease, but the microbiota responsible and their metabolites are poorly understood. The same is true for the interrelation between not well defined microbiota and brain

Influence of gut microbiota on glucose, lipid and protein metabolism

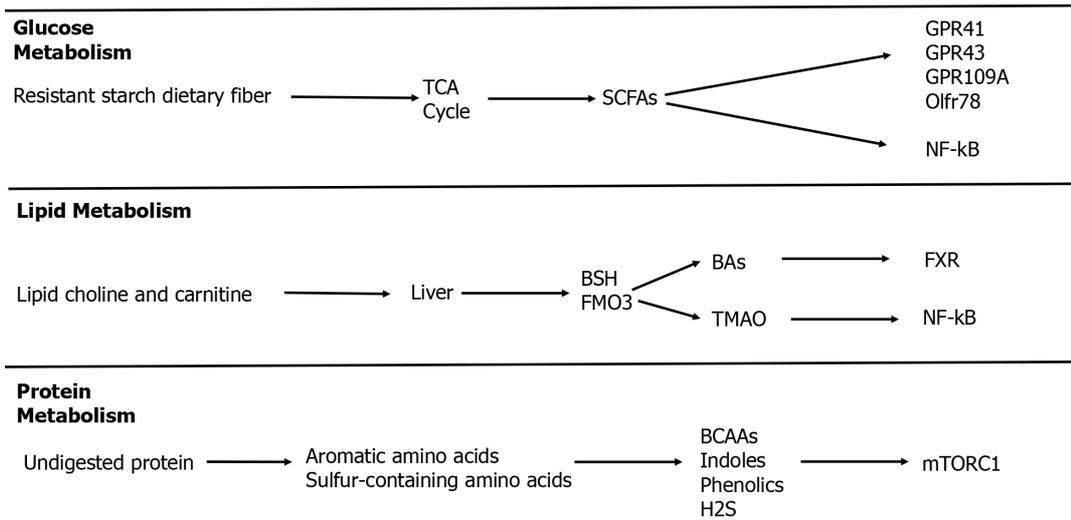


Figure 3 Influence of gut microbiota on glucose, lipid, and protein metabolism. BCAAs: Branched-chain amino acids; BSH: Bile salt hydrolase; FMO3: Flavin monooxygenase 3; FXR: Farnesoid X receptor; GPR: G protein-coupled receptor; Olfr: Olfactory receptor 78; mTORC1: Mammalian target of rapamycin complex 1; NF-kB: Nuclear factor kappa B; SCFAs: Short-chain fatty acids; TGR5: Takeda G protein-coupled receptor 5; TMAO: Trimethylamine N-oxide.

Interaction between gut microbiome and immune system in dysbiosis condition

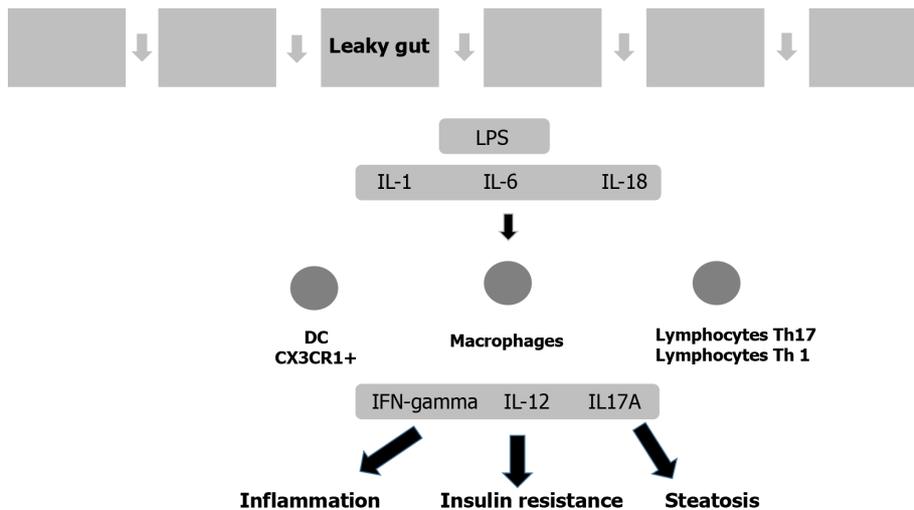


Figure 4 Interaction between gut microbiome and immune system in dysbiosis condition. DC: Dendritic cell; IFN-γ: Interferon gamma; IL-1: Interleukin 1; IL-6: Interleukin 6; IL-18: Interleukin 18; LPS: Lipopolysaccharides.

diseases such as PD and autism. Again, methodological problems and presence of confounders may be the cause.

More importantly, these problems concern the treatment. Indeed, meta-analyses on the use of prebiotics and probiotics have given contradictory results and to date, the majority of authors retain that large-scale randomized controlled studies are needed to evaluate the efficacy of these treatments.

TREATMENT AND PERSPECTIVES

Dysbiosis treatment is based on the use of prebiotics or probiotics. In addition, fecal microbiota transplantation has been proposed. Prebiotics are dietary products that may change the composition and functions of microbiota by enhancing the presence of indigenous microbiota or by favoring the growth of specific bacteria. Probiotics are live beneficial bacteria. Among these favorable effects to re-equilibrate, gut microbiota dysbiosis has been documented by *Akkermansia muciniphila*, *F. prausnitzii*, *B. uniformis*, predator bacteria, and phage therapy[8]. Fecal microbiota transplantation is the process of transplantation of fecal microorganisms from healthy people to re-equilibrate gut microbiota dysbiosis. In the future we can imagine the use of sequester or binding resins to eliminate harmful products or to sequester microbial

metabolites. Other approach is the use of 3, 3-dimethyl-1-butanol to reduce TMAO or TMA-lyase inhibitors. Overall, several problems remain to be resolved.

There is substantial heterogeneity in the microbiota in both normal conditions and dysbiosis. In general, there is not a single bacterium but a collection of bacteria. This collection will likely not be best defined by the individual bacteria but rather by their metabolic capacities. This refers to the enzymes that are expressed, functioning and determining downstream metabolism.

CONCLUSION

The human gut possesses millions of microorganisms that is called microbiota. Microbiota in normal conditions exerts beneficial effects over the whole body and is connected with many organs forming different axis. Several factors may modify the microbiota composition and favor the presence of dangerous microorganisms, better known as pathobionts. This condition is called dysbiosis and is linked with different diseases, such as neurological diseases, metabolic diseases, and circulatory diseases. An understanding of microbiota in both the healthy subject and sick patient and understanding of the biological pathway connecting the gut microbiota with different organs are essential to finding therapeutic measures. The use of probiotics, prebiotics, phages, and feces transplantation represent to date the therapeutic measures more frequently adopted. However, several trials are ongoing looking for new, more efficient therapeutic strategies.

Future directions, among others could be as follows: The development of multiomics techniques such as metagenomics, metabolomics, and metatranscriptomes should be further developed to answer the critical questions of which microbiota are involved in health and disease. Indeed, in addition to metagenomics, the microbiome should also be analyzed by metabolomics studies in order to find its metabolic organization.

In addition, studies on genome-wide association will be used to correlate different genotypes with diseases phenotypes, and studies of metabolome wide association will correlate metabolic phenotypes with disease phenotypes.

The key findings of our study were as follows: (1) In normal conditions, the gut microbiome exerts a beneficial effect on the organism. (2) This is related to the production of several metabolites. (3) Several axis connect the microbiome with several organs. (4) Gut microbiome modifications with the appearance of pathobionts are at the basis of several diseases in different organs.

FOOTNOTES

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