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Review

Microbes in Health and Disease: Human Gut Microbiota

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Abstract: Humans and microbes (e.g., bacteria, fungi, and microalgae) have coexisted and coevolved toward reciprocal adaptation. As omics technologies have rapidly advanced, the relevance of microbes to human health and disease as well as other fields has been progressively unraveled. This review focuses on the human gut microbiota, which is an emerging focus of microbiological research. This review synthesizes recent advances in exploring the fundamentals and multiple functions of the human gut microbiota and its associations with human health and diseases as well as microbiota-targeted therapies.

Keywords: microbe; role; human health; disease; gut microbiota; metabolism; immunity; gut–brain axis

1. Introduction

Microbes (bacteria, archaea, fungi, protists, and microalgae) are microscopic organisms that are distributed ubiquitously in various aquatic, terrestrial, and air environments (e.g., freshwater lakes, seawater, hot springs, soil, sand, rock, disserts, and glaciers), and they also live in and on the bodies of organisms [1]. Microbes maintain the global biogeochemical cycles and flow of energy [2], and they find wide applications in industry [3], agriculture [4,5], and pharmaceutics and therapy [6] as well as bioremediation [7]. Particularly, they play important roles in determining the state of human health, disease, and well-being [8] (Figure 1). These are discussed below.

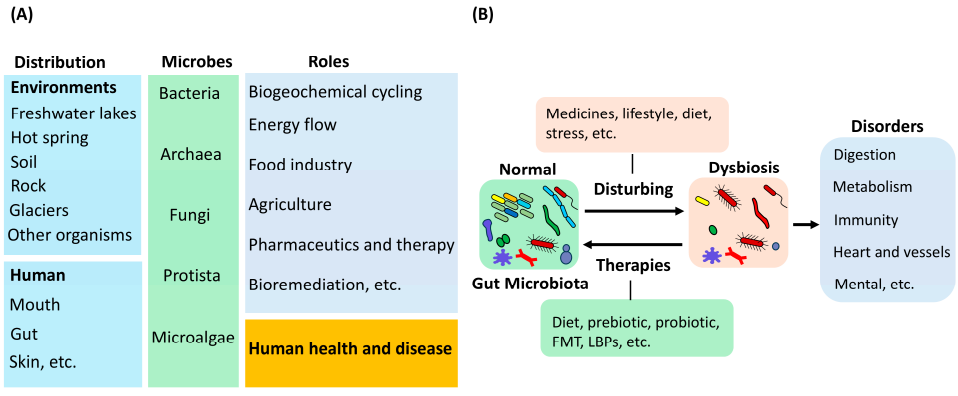

Figure 1. Illustration of (**A**) distribution and classification of microbes and their roles in various fields and (**B**) the causes and therapies for the dysbiosis of human gut microbiota and associated disorders in digestion, metabolism, immunity, heart and vessels, and mental state.

Specifically, over 1 trillion (10^{12}) microbial species [1], ~10^{30} bacteria, ~10^{27} fungi, ~10^{29} archaea, and ~10^{27} protists live in the earth's ecosystem [9]. And ~3.8×10^{13} bacteria live in and on an adult human body [10]. Microbes account for ~17% of the global carbon biomass [9]. Additionally, microalgae (cyanobacteria and eukaryotic microalgae) are important photosynthesizing microbes that convert sunlight and carbon dioxide into

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oxygen and biomass [11]. Cyanobacteria alone contribute more than 50% of atmospheric oxygen, 10% of global photosynthetic primary production [12], and at least 2.32×10^{14} g of carbon biomass [13]. In nature, bacteria, archaea, and fungi serve as key decomposers and break down non-living matter into simple, bioavailable compounds so that living organisms utilize them as nutrients [2]. Certain prokaryotes are the only organisms on earth that are capable of performing nitrogen fixation, nitrification, and denitrification as well as dissimilatory sulfate reduction and anaerobic sulfide oxidation, which are the key biochemical processes in the global nitrogen and sulfur cycles [14]. For example, nitrogen gas is inaccessible for all but nitrogen-fixing prokaryotes [15]. Under the catalysis of nitrogenases, these nitrogen-fixing prokaryotic specialists (e.g., rhizobia and certain species of cyanobacteria and Actinobacteria) convert nitrogen gas into ammonia, which is subsequently utilized as nutrients by organisms [16]. Additionally, the biological oxidation of reduced inorganic sulfur compounds (e.g., sulfides) is exclusively executed by archaea and bacteria that can be aerobic and anaerobic [17]; phototrophic purple and green sulfur bacteria are the common anaerobic sulfur-oxidizing prokaryotes [18]. Therefore, microbes constitute important primary producers and decomposers, and they maintain the carbon, nitrogen, and sulfur cycles as well as the flow of energy on the earth.

Additionally, microbes play crucial roles in the food and beverage industry [3], agriculture [4], and pharmaceutics and therapy [6] as well as bioremediation [7]. For example, some special microbes, including the fungal baker yeast *Saccharomyces cerevisiae*, fungal molds (e.g., *Aspergillus* and *Mucor*), and bacteria (e.g., *Streptococcus* and *Lactobacillus*), are involved in the manufacturing of some internationally and locally common fermented foods (e.g., bread, wine, yogurt, and Chinese soybean curd) [3,19,20]. In the process of making bread, baker yeasts are added to the dough and convert sugar to alcohol and CO_2 as the products of alcoholic fermentation; they simultaneously synthesize other metabolites under anaerobic conditions, resulting in an increase in the volume of dough and a change in flavor [3]. In the process of manufacturing yogurt, lactic acid-producing bacteria (e.g., *Streptococcus thermophilus* and *Lactobacillus bulgaricus*) are added to heat-processed milk [20]. Under appropriate anaerobic conditions, they convert the glucose of milk lactose to lactic acid, which lowers the pH value of milk and causes the coagulation of milk protein, generating the solid curd yogurt [20]. Additionally, some cyanobacterial species (e.g., *Spirulina*) are food and dietary supplements in some regions [21]. In agriculture, nitrogen-fixing bacteria (belonging to plant growth-promoting rhizobacteria (PGPRs)) have been utilized as biofertilizers to improve the growth of plants by increasing the bioavailability of nitrogen in the soil [4], along with other beneficial bacteria (e.g., auxin-producing PGPR, cytokinin-producing PGPR, PGPR with antifungal activity, and biopesticides) [5]. Moreover, antimicrobial-producing microbes (e.g., *Streptomyces* and *Bacillus*) have been utilized to manufacture medical antibiotics (e.g., penicillin and cephalosporin) in pharmaceutics [6]. Of note, engineered microbes have been recently constructed and utilized in clinical trials for the treatment of various non-cancer and cancer diseases (e.g., inflammatory bowel disease, diabetes, hyperammonemia, oral mucositis, human papillomavirus (HPV)-positive cancers, and prostate cancer) [22]. For example, a transgenic bacterium, *Lactococcus lactis* (*LL-Thy12*), that expressed interleukin-10 showed improved outcomes for treating Crohn's disease in a phase I trial [23]. A novel engineered bacterium, *Lactobacillus reuteri* strain PRB782, that secrets high amounts of biologically active cytokine, human interleukin-22, was constructed and held promise as a delivery platform of human interleukin-22 for treating intestinal diseases [24]. Certain microbes (e.g., *Pseudomonas aeruginosa*) have been utilized as an eco-friendly bioremediation tool because of their microbial ability to degrade organic or inorganic pollutants [7,25].

In particular, microbes inhabiting the human body have recently received increasing attention because of their tight associations with human health and disease [8]. In and on an adult human body, there are over 10,000 microbial species [26]. The collection of all these microbes is called the human microbiota. Based on the living location of microbes, the human microbiota can be further divided into the gut microbiota, skin microbiota, oral

microbiota, etc. As DNA sequencing, bioinformatics, and omics technologies have rapidly developed, we have discovered the tight association of the human microbiota with the state of human health and disease at the mechanistic level. As illustrated in Figure 1B, an imbalance (or dysbiosis) in the human gut microbiota causes digestive, cardiometabolic, immune, and neural diseases, etc. [27]. Nowadays, the gut microbiota has become a focus of microbiological research in the study of human health and disease.

Here, we focus on the human gut microbiota and synthesize recent advances in the exploration of the fundamentals of the human gut microbiota and their associations with human health and disease as well as therapies.

2. Human Gut Microbiota

2.1. Distribution and Composition

The gut microbiota is the largest microbial community [28] and comprises primarily bacteria followed by fungi, archaea, protista, and vira [29]. According to the DNA sequencing data, bacteria, fungi, archaea, protista, and vira accounted for ~93%, ~0.1%, ~0.8%, ~0.2%, and ~5.8% of the total DNA, respectively [29], as illustrated in Figure 2A. The number of bacteria in the gut microbiota of an adult body is estimated to be ~38 trillion, and this number is close to that of the total human cells (~37 trillion) in the body [10]. Most gut bacteria inhabit the colon (~0.4 L), with a cell density of 10^{11} bacteria per milliliter, whereas relatively few microbes inhabit the stomach and small intestine [10]. As illustrated in Figure 2B, the human gut microbiota comprises the two most dominant phyla: Firmicutes and Bacteroidetes, followed by Actinobacteria, Proteobacteria, Synergistetes, Verrucomicrobia, Fusobacteria, etc. [30]. Recently, a group of non-photosynthetic cyanobacteria (class Melainabacteria) was discovered in the human gut [31], and their relevance to human health and disease has attracted attention [32]. Within the Firmicutes phylum, the dominant genera include *Clostridium*, followed by *Faecalibacterium*, *Blautia*, *Ruminicoccus*, etc.; the dominant genera within the phylum Bacteroidetes include *Bacteroides*, *Prevotella*, etc.; and the dominant genera of the phylum Actinobacteria include *Bifidobacterium*, *Collinsella*, *Actinomyces*, etc. [33–35]. As illustrated in Figure 2C, the gut fungi are dominated by the yeasts *Saccharomyces*, *Malassezia*, and *Candida* [36]. *Saccharomyces cerevisiae* is known as brewer's yeast and baker's yeast and has been widely utilized in the food and beverage industry, as described above in the Introduction Section. It has been found in the guts of both healthy individuals and patients with inflammatory bowel disease (IBD), and it is less abundant in IBD patients compared to health subjects [37]; it can promote the intestinal epithelia's production of uric acid, which increases gut permeability and eventually exacerbates intestinal diseases [38]. Additionally, it was found in the gut microbiota of certain populations with deficits in attention and executive function; speculatively, it is associated with chronic, low-grade production of ethanol by *S. cerevisiae* in gut [39]. The yeast *Malassezia* belongs to normal human commensal flora and is also an opportunistic pathogen that causes both skin and systemic diseases [40]. *Malassezia* in the gut microbiota was associated with IBD, colorectal cancer, hepatic disease, Alzheimer's disease, sclerosis, and pancreatic cancer [41]. *Candida* belongs to common commensal and opportunistic pathogen, and it can cause a life-threatening bloodstream infection (termed candidemia) [42]. *Candida albicans* in the gut microbiota is thought to be both beneficial and detrimental to human health, *Candida* in the gut is suggested to be an important source of bloodstream infection by *Candida* (candidemia) [43], and increased *Candida* was also found to be associated with other diseases (e.g., IBD, alcoholic liver disease, primary sclerosing cholangitis, asthma, ankylosing spondylitis, and uveitis [44].

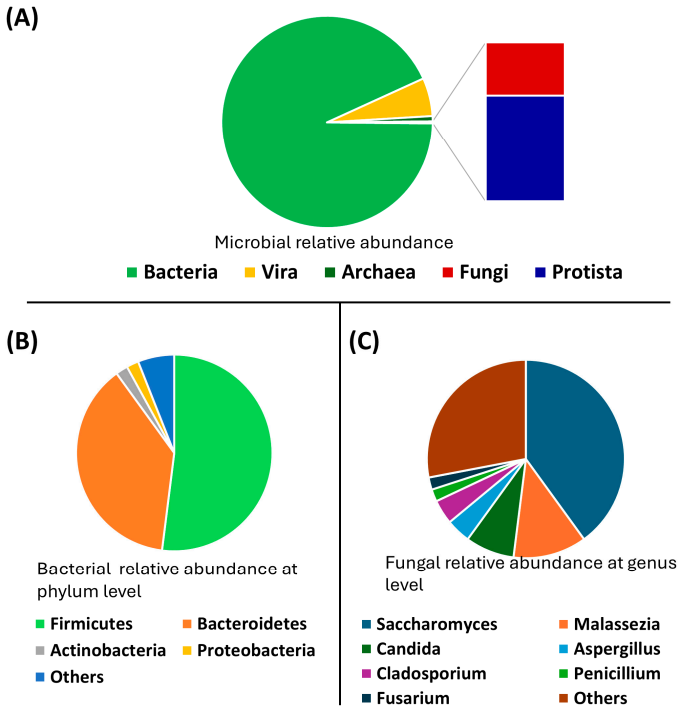

Figure 2. (**A**) The relative abundance of bacteria, vira, archaea, fungi, and protista in total DNA of fecal sample as evaluated according to the previous sequencing findings reviewed by Shkoporov and Hill (2019) [29]. (**B**) The relative abundance of common dominant microbes at the phylum level that represents the approximate estimate from the study by Nam et al. (2011) [45]. (**C**) The relative abundance of common fungal members at the genus level that represents the approximate estimate from the study by Nash et al. (2017) [36].

2.2. Origin and Development

Although recent studies have indicated that the existence of microbes in the fetal intestine remains controversial [46], the prevailing viewpoint supports the hypothesis of a sterile womb. The neonatal gut is colonized immediately by microbes during and after birth. The gut microbiota subsequently rapidly develops and undergoes succession in composition and abundance, which is classified into primary, secondary, and late stages of succession in early, adult, and late life, respectively [47]. Colonization of the gut microbiota after birth is a highly dynamic process and is tied inextricably to host genetics, delivery mode, feeding pattern, etc. [48]. The neonatal gut microbiota contains relatively few diverse microbes and is dominated by facultative anaerobes (e.g., Enterobacteriaceae), which consume oxygen and create anaerobic conditions for the subsequent colonization of obligate anaerobes (e.g., *Bifidobacteria*) [49]. As infants grow, the gut microbiota becomes increasingly complex and reaches an adult-like gut composition by 2–5 years of age [48]. The adult gut microbiota is relatively stable until the elderly age. The elderly adult gut microbiota harbors fewer *Bifidobacteria*, *Lactobacillus*, etc., which are dominant in younger adults [47]. The composition of the human gut microbiota exhibits interindividual variation, which is dependent on age, sex, diet, medication, state of health and disease, etc. [50].

Recently, increasing efforts have been made to understand the impact of plant-based diet [51], food additives [52], and antibiotics [53] on the human gut microbiota and health. For example, a recent review showed that a plant-based diet increased butyrate-producing bacteria and, accordingly, the level of short-chain fatty acids because of the digestion of plants by the gut microbiota and that a plant-based diet versus conventional diets brought short- to moderate-term beneficial effects in healthy subjects compared to patients with obesity, cardiovascular disease, and rheumatoid arthritis [51]. A recent longitudinal study of aging demonstrated the beneficial effects of a plant-based diet and the positive association of a healthful plant-based diet with polysaccharide-degrading bacteria (*Faecalibacterium praus-*

nitzii, *Eubacterium eligens*, and *Bacteroides thetaiotaomicron*) and a negative association with *Blautia hydrogenotrophica*, *Dorea* sp. CAG 317, *Eisenbergiella massiliensis*, etc. [54]. Food additives (potassium sorbate, cinnamaldehyde, stevia, carrageenan-kappa, etc.) have caused the alteration of gut microbiota in in vitro gut microbiota and animal studies [52,55]; for example, cinnamaldehyde decreased and stevia increased Shannon α-diversity in human microbiota batch experiments; cinnamaldehyde increased *Escherichia/Shigella* and *Klebsiella* and decreased Firmicutes (e.g., *Faecalibacterium* and *Subdoligranulum*); and carrageenan-kappa increased *Escherichia/Shigella* and sodium sulfite, polysorbate-80 increased *Bilophila*, and polysorbate-80 decreased *Faecalibacterium* and *Subdoligranulum* [55]. Synthetic antimicrobial food preservatives (sodium benzoate, potassium sorbate, and ethylparaben) and three biogenic antimicrobial preservatives (lysozyme, nisin, and ε-polylysine) significantly affected gut microbiota in a study of healthy mice, while multiple antimicrobial preservatives (e.g., sodium benzoate, ethylparaben, sodium nitrate, sodium propionate, natamycin, nisin, and lysozyme) increased *Proteobacteria*, which is indicative of a potential dysbiosis effect on the gut microbiota [56]. The utilization of broad-spectrum antibiotics is associated with a dysbiosis of the gut microbiota that results in various diseases (e.g., *Clostridioides difficile* infection) [57]. Among the studied antibiotics, vancomycin decreased gut microbiota diversity; the relative abundance of *Coprococcus eutactus*, *F. prausnitzii*, and *Anaerostipes caccae* (SCFA-producing Firmicutes); and the level of short-chain fatty acids (butyrate and acetate), but it increased *Enterobacteriaceae* and *Enterococcus* and the level of primary bile acids [58]. Vancomycin is also more likely to cause pathogen susceptibility compared to other common antibiotics (ampicillin, azithromycin, ciprofloxacin, etc.) [58]. Therefore, precision, narrow-spectrum antibiotics represent the future direction of antibiotic development to minimize dysbiosis of the gut microbiota.

3. Multifunction of the Human Gut Microbiota

As illustrated in Figures 3 and 4, the gut microbiota plays various important roles in (i) digestion and metabolism [59,60]; (ii) colonization resistance against pathogens [61]; (iii) intestinal epithelial homeostasis related to the differentiation and proliferation of the intestinal epithelium; (iv) the development, education, and regulation of immunity; and (v) the development and function of the central nervous system [27], etc. These are further discussed below.

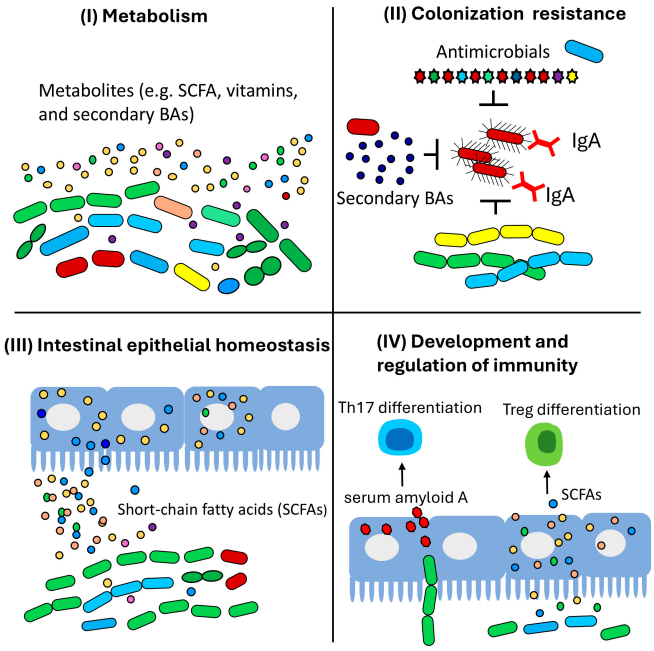

Figure 3. Illustration of the roles of gut microbiota (**I**) in digestion and metabolism, where certain members of gut microbiota are able to digest carbohydrates (indigestible for human) to short-chain

fatty acids (SCFAs) that serve as important energy sources for colonocytes, regulators of immunity, inflammation, metabolism, etc. The gut microbiota can also produce vitamins and participate in the biosynthesis of secondary bile acids. (**II**) In colonization resistance, the gut microbiota resists against the colonization of pathogens via multiple mechanisms associated with the production of antimicrobials, the production of inhibitive compounds (e.g., secondary bile acids that inhibit the germination of *Clostridioides difficile*), the formation of a physical barrier against the proliferation of pathogens, and inducing the immune system to secrete IgA against pathogens. (**III**) In intestinal epithelia homeostasis, for example, SCFAs produced by certain members of gut microbiota not only serve as the energy source of colonocytes but also maintain the structural and functional integrity of physical and chemical barriers of intestinal epithelium. (**IV**) In the development and regulation of immunity, for example, segmented filamentous bacteria among gut microbiota attach to and trigger the epithelium to secrete serum amyloid A. Serum amyloid A is further involved in the differentiation of Th17 cells and the production of Th17 effector cytokines (e.g., IL-17 and IL-22) that are associated with increased resistance against pathogen *Citrobacter rodentium*. SCFAs are involved in the differentiation of T cells into regulatory T cells (e.g., Tregs) and effector T cells (e.g., Th1 and Th17 cells).

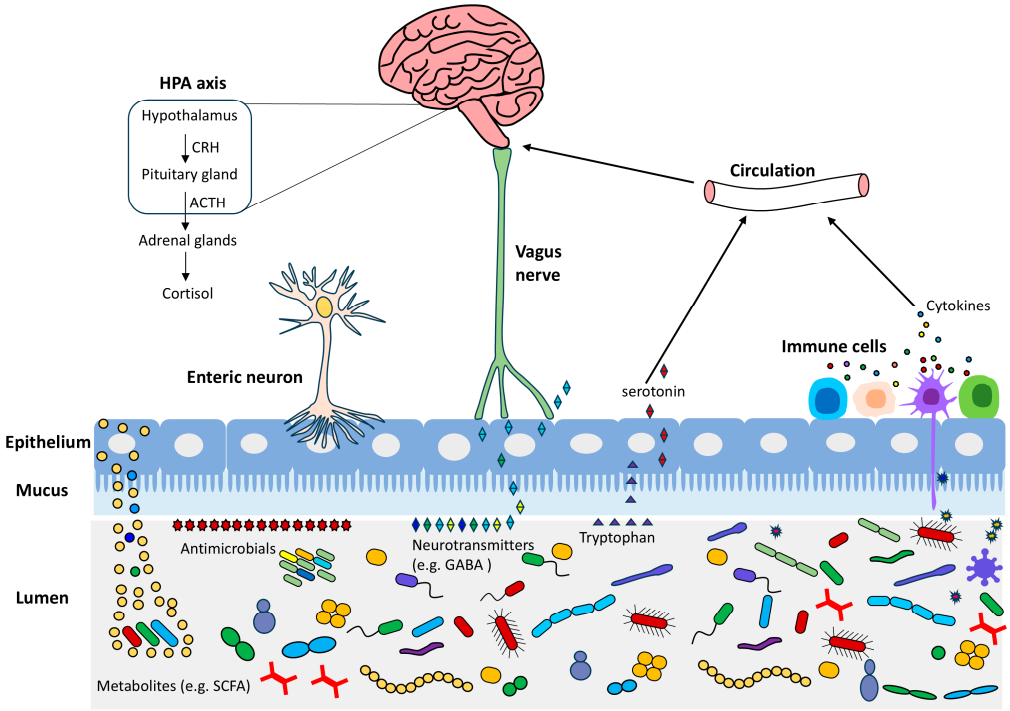

Figure 4. Illustration of the human gut microbiota, intestinal epithelium, host immunity, and gut–microbiota–brain axis. Gut microbes can produce various antimicrobials and neurotransmitters (e.g., gamma-aminobutyric acid (GABA) and serotonin), and the human gut microbiota is also involved in the metabolism of tryptophan, which is the precursor of serotonin. The bidirectional gut–brain axis comprises the central nerve system, autonomic nerve system (ANS), enteric nerve system, hypothalamic–pituitary–adrenal (HPA) axis, circulatory system, immune system, as well as the gut microbiota and involves neuronal, endocrine, and immune pathways. It is hypothesized that the gut microbiota can affect the HPA axis via multiple microbe-associated signals. These stressors or signals stimulate the neurons of the paraventricular nucleus of the hypothalamus to secrete corticotropin-releasing hormone (CRH); subsequently, the CRH is transported and triggers the pituitary gland to release adrenocorticotropic hormone (ACTH), which further stimulates the production and secretion of cortisol in the adrenal glands. Cortisol has multiple roles (e.g., regulating metabolism and neuroimmune signaling).

3.1. Metabolism

Specifically, some gut bacteria within the phylum Firmicutes are important bacterial fermenters and digest carbohydrates (e.g., fiber and resistant starch) that are indigestible for the human body into short-chain fatty acids (SCFAs, e.g., acetate, propionate, and butyrate) [59], as shown in Figures 3 and 4. SCFAs serve as important energy sources for colonocytes, the liver, and peripheral cells [62] and have various functions in the absorption of ions (e.g., Ca^{2+} and Mg^{2+}), inhibition of inflammation, metabolism of lipids and glucose, regulation of the immune response, regulation of appetite, etc. [62,63]. Additionally, some gut microbes are capable of synthesizing vitamins (e.g., vitamin K) [31,60] and metabolizing primary bile acids to secondary bile acids [27,60].

3.2. Colonization Resistance

The gut microbiota suppresses the colonization of pathogens via various mechanisms, such as the production of antimicrobials and nutrient competition (Figure 3). The normal healthy gut microbiota transforms primary bile acids into secondary bile acids, which is regarded as one of important mechanisms in colonization resistance by which the human gut microbiota suppresses the diarrhea-causing gut pathogen *Clostridioides difficile* because secondary bile acids inhibit the outgrowth of *C. difficile* [61].

3.3. Intestinal Epithelial Homeostasis

The gut microbiota maintains intestinal epithelial homeostasis [64,65]. As shown in Figure 4, the intestinal epithelium is a single-cell layer composed of intestinal stem cells and various differentiated cell types (e.g., enteroendocrine cells, goblet cells, enterocytes, Paneth cells, and colonocytes) [64]. The intestinal epithelium provides both physical and chemical barriers to segment gut microbes and the immune system; the physical barrier refers to mucus secreted from goblet cells, the glycocalyx on the microvilli surface of epithelial cells, and the junction between adjacent epithelial cells, whereas the chemical barrier refers to various antimicrobial compounds produced mainly by Paneth cells. [65]. Therefore, the intestinal epithelium constitutes the first line of defense against microbial invasion. The gut microbiota plays crucial roles in maintaining the structural integrity and function of both the physical and chemical barriers of the intestinal epithelium [64]. Specifically, the metabolites (e.g., SCFAs) produced by the gut microbiota serve not only as the primary energy source for colonocyte proliferation, as discussed above, but also as important regulators of both the physical and chemical barriers of the intestinal epithelium. For example, short-chain fatty acids (e.g., butyrate) improve the structural integrity of the intestinal epithelium via upregulating the expression of tight junction proteins (e.g., occludin and zonula occludens-1) [66], which are crucial for the function of tight junctions between adjacent epithelial cells. Butyrate stimulates goblet cells to secrete mucins, which are the major structural protein component of the mucus layer, by upregulating the *MUC* genes that encode the protein backbone of mucin [67]. Butyrate also stimulates small intestinal Paneth cells to secrete the antimicrobial compound α-defensin [68] and induces the production of antimicrobial peptides (RegIIIγ and β-defensins) in intestinal epithelial cells [69]. Additionally, SCFAs regulate the differentiation of intestinal stem cells and promote turnover of the intestinal epithelium [70,71]. Germ-free mice exhibit reduced turnover in epithelial intestinal cells in the small intestine, and normal turnover can be restored by oral administration of short-chain fatty acids [70].

3.4. Development, Education, and Regulation of Immunity

The gut microbiota participates in the development, improvement, and regulation of immunity as well as in the regulation of inflammation [27,72]. The relevance of the gut microbiota to the development of immunity has been demonstrated widely in various germ-free animal model experiments and epidemiological studies [72–76]. For example, compared with conventional animals, a germ-free animal model demonstrated various defects in gut mucosal and systemic immunity, including relatively lower weights of lymph nodes in the

small intestine [77], smaller Peyer's patches, thinner lamina propria, and reduced numbers of $CD4^+$ T cells and IgA-producing plasma cells in the intestine, and these defects were found to be reversible by colonization by the commensal microbiota [74,76]. Reduced numbers of some myeloid cells, differentiated T cells, and B cells in the spleen, liver, etc., were also observed in germ-free or antimicrobial-treated animal models [73]. In epidemiological studies, an increased incidence of immune diseases (e.g., allergic disease) in childhood and infectious diseases has been reported, especially in regions with improved hygienic lifestyles, which is suggested to be associated with decreased exposure to microorganisms or reduced biodiversity of the gut microbiota [78,79]. Together, these findings highlight the relevance of the gut microbiota to the development of normal immunity.

The gut microbiota regulates immune innate and adaptive responses via gut microbiota-associated cellular compounds or metabolites (e.g., short-chain fatty acids and bile acids) [72,80]. For example, segmented filamentous bacteria are an important group of beneficial gut microbes. They attach to epithelial cells in the ileum and trigger epithelial cells to secrete humoral factors (serum amyloid A) that promote Th17 cell differentiation in the lamina propria (Figure 3), and the production of Th17 effector cytokines (e.g., IL-17 and IL-22) is associated with increased resistance against the intestinal pathogen *Citrobacter rodentium* [81]. As important gut fermentation products, short-chain fatty acids regulate the differentiation of T cells into regulatory T cells (e.g., Tregs) and effector T cells (e.g., Th1 and Th17 cells). While effector T cells combat invading microbes and produce proinflammatory cytokines, regulatory T cells control the excessive responses of effector T cells and produce anti-inflammatory cytokines (e.g., IL-10) to limit inflammation and maintain immune tolerance. A delicate balance exists between effector T cells and regulatory T cells in the normal immune system. Short-chain fatty acids inhibit histone deacetylases (HDACs) and subsequently increase the activity of the mTOR pathway, which is important for promoting T-cell differentiation into regulatory T cells (e.g., Tregs) and effector T cells (e.g., Th1 and Th17 cells) and the expression of their cytokines (e.g., IL-10, IFN-γ, and IL-17) [71,82].

3.5. The Gut–Brain Axis

The gut microbiota also participates in the development and function of the central nerve system, as demonstrated in germ-free animal model experiments [83] and human studies [84]. For example, germ-free animal models exhibit decreased anxiety-like behaviors and impaired short-term recognition and working memory [83]. There are remarkable differences in the gut microbiota between healthy subjects and patients with neurodegenerative disorders (e.g., Parkinson's disease) [85]. In a recent comparative analysis of the gut microbiota between Parkinson's disease (PD) subjects and healthy cohabitants, a higher number in *Lactobacillus* and a lower number in the group of *Clostridium coccoides* and *Bacteroides fragilis* were found in PD subjects [86]. Particularly, irritable bowel syndrome (IBS) caused by dysbiosis of the normal gut microbiota is typically associated with mental health disorders (e.g., anxiety and depression) [87].

The mechanisms of modulation by the gut microbiota are executed via the gut–brain axis, which involves bidirectional signaling communication [85]. Structurally, the axis includes the central nerve system (CNS), autonomic nerve system (ANS), enteric nerve system (ENS), hypothalamic pituitary adrenal (HPA) axis, circulatory system, immune system, and gut microbiota [85] (as shown in Figure 4). In addition, the neuronal, endocrine, and immune pathways are involved [85]. Firstly, the gut microbiota can modulate the responses of the central nervous system via direct or indirect control of key neurotransmitters (e.g., γ-aminobutyric acid (GABA), dopamine, and serotonin). The gut microbiota can directly synthesize neurotransmitters and their precursors and regulate the biosynthesis of neurotransmitters [85,88]. The GABA producers include *Lactobacillus*, *Bifidobacterium*, and *Escherichia coli*; the dopamine producers include *Proteus vulgaris*, *Serratia marcescens*, and *Staphylococcus aureus*; and the serotonin producers include *E. coli*, *Streptococcus*, and *Enterococcus* [89]. The gut microbiota is involved in the metabolism of tryptophan, which is the precursor of serotonin [89]. Indigenous gut spore-forming bacteria can also pro-

mote the biosynthesis of serotonin in colonic enterochromaffin cells via the action of their metabolites [90]. Secondly, the gut microbiota not only plays an important role in the development of the HPA axis [91] but also regulates the activity of the HPA axis, which is the major neuroendocrine system in response to stressors, through the action of gut microbiota-associated substances such as bacterial antigens (e.g., lipopolysaccharides), proinflammatory cytokines caused by dysbiosis of the gut microbiota, and short-chain fatty acids produced by gut bacteria fermenters [92]. Thirdly, the gut microbiota controls the maturation and function of microglia [93], which represent the largest population of immune cells in the brain and are essential for brain development and homeostasis [94,95]. Moreover, the gut microbiota can activate immune cells (e.g., macrophages, neutrophils, and dendritic cells) to release proinflammatory cytokines (e.g., IL-1β, TNFα, and IL-6) via microbe-associated molecular patterns (MAMPs, e.g., lipopolysaccharides), these cytokines cross the blood–brain barrier, enter the brain, activate microglia to release proinflammatory cytokines, and amplify the effects of cytokines on the CNS [96]. Moreover, proinflammatory cytokines can activate the kynurenine pathway and decrease the level of serotonin, affecting the response of the CNS [97]. Additionally, gut microbiota-associated substances (e.g., bile acids, peptidoglycan, lipopolysaccharide, and toxins) can directly enter the CNS and regulate the response of the CNS [98].

4. Associations with Human Diseases

Dysbiosis of the normal gut microbiota is associated with digestive, metabolic, cardiovascular, immune, and neural diseases, among others [85,99–103]. In a cross-sectional study including 355 patients with inflammatory bowel disease (IBD), 412 patients with irritable bowel syndrome (IBS), and 1025 healthy controls, similar dysbiotic profiles of the gut microbiome were observed in two main IBD types (Crohn's disease and ulcerative colitis) and were associated with gut inflammation; for instance, an increase in Bacteroides occurred only in IBD patients, and a decrease in butyrate-producing bacteria and increases in *Actinomyces* and *Streptococcus* were observed in IBS patients [104]. A group of special *E. coli* strains (adherent-invasive *E. coli*, AIEC) was identified in patients with Crohn's disease and is characterized by hypermotility and increased acetate consumption, which exacerbates inflammation during mucosal injury [105]. A systematic review revealed that patients with IBS generally had lower gut microbiota diversity; increased Firmicutes, Clostridia, and Clostridiales; a higher Firmicutes/Bacteroidetes ratio at the phylum level; and decreased Bacteroidia and Bacteroidales at lower taxonomic levels compared to healthy controls [106]. While several studies have shown that obese individuals have a relatively high Firmicutes/Bacteroidetes ratio, contradictory observations have been reported in other studies. A recent review revealed that the Firmicutes/Bacteroidetes ratio is not a convincing biomarker of obesity and that the obesity-associated gut microbiota pattern is heterogeneous around the world, although the gut microbiota affects the development of obesity [107]. A metagenome study including 218 Chinese subjects with atherosclerotic cardiovascular disease (ACVD) and 187 healthy controls revealed that compared with healthy controls, ACVD patients had increased *Enterobacteriaceae* and *Streptococcus* [108]. A systematic review of the associations between the gut microbiota and allergic diseases revealed that allergic children had greater numbers of *Bacteroides*; lower numbers of *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*, and *Clostridium*; a higher prevalence of *Bifidobacterium adolescentis*; a lower prevalence of *Bifidobacterium catenulatum* and *Staphylococcus aureus*; and lower bacterial diversity [109].

Allergic diseases include food allergy and non-food allergies (e.g., eczema, asthma, drug allergy, and allergic rhinitis) and are inflammatory disorders resulting from an abnormal immune response to these innocuous substances (termed as allergens) [110]. In the past years, food allergy has become an increasingly prevalent health problem in children and adults around the world [111] and is caused by various factors (dysbiosis of gut microbiota, impaired integrity of intestinal epithelium, etc.) [112]. The mechanisms are associated with the Th2/Th1 and Th17/Th1 ratio imbalance [111]. Immunoglobulin (IgE)-mediated food

allergy is a common pattern; briefly, under certain circumstances (e.g., impaired intestinal epithelium), the allergens trigger the immune response of the T helper 2 (Th2) cells that activate B cells to release IgE antibody [113,114], the allergen-specific IgE binds to basophils and master cells via the high-affinity surface receptors on the surface, and subsequently, various inflammatory mediators (e.g., histamine) are released in repeated exposure to the allergen [110], increasing the vascular permeability and eventually causing the allergic symptoms (urticaria, diarrhea, etc.) [111,115]. Food allergy was found to be associated with gut microbiota in human and animal studies [116–118]. For example, in a Chinese study recruiting 34 infants with food allergy (17 IgE-mediated and 17 non-IgE-mediated) and 45 healthy controls, the food allergy was associated with fewer phyla *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* and fewer genera *Enterococcus* and *Staphylococcus* but with high phylum *Firmicutes* and high family *Clostridiaceae* 1; particularly, IgE-mediated allergy was associated with increased *Clostridium sensu stricto* and *Anaerobacter* and decreased *Bacteroides* and *Clostridium* XVIII, suggesting the relevance of dysbiosis of the gut microbiota in food allergy [119]. In a Canadian study recruiting 166 infants in the first year of life, low fecal microbiota richness at 3 months and a high Enterobacteriaceae/Bacteroidaceae ratio in early infancy were associated with subsequent food sensitization [120]. In a USA study recruiting 141 children aged 3–16 months, children with egg allergy (n = 66) harbored abundant genera from the *Lachnospiraceae* and *Streptococcaceae* families, while controls without egg allergy (n = 75) harbored abundant *Leuconostocaceae* [117]. An animal study previously showed that Clostridia-containing microbiota protected against food allergen sensitization [116], and the anaerobe *Anaerostipes caccae* from the feces of a healthy infant was found to prevent food allergy in mice [121]. The association of non-food allergies with the gut microbiota was also observed [122]. For example, in a large birth-cohort study in the Netherlands, an increased risk of developing eczema among infants was found to be associated with increasing numbers of gut *Escherichia coli*, and the presence of *Clostridium difficile* was associated with an increased risk of developing eczema, recurrent wheezing, and allergic sensitization [122]. In a longitudinal study including 25 infants at high risk for asthma (HR) and 29 healthy controls, HR infants were randomized to daily oral *Lactobacillus rhamnosus* GG (HRLGG) or placebo (HRP) for 6 months, and delayed gut microbiota diversification over the first year of life was observed in HRP subjects; however, the rate of bacterial gut microbiota diversification in HRLGG subjects was comparable to that in healthy controls, suggesting that the associations of childhood atopy and asthma with perturbation and delayed development of early-life gut microbiota can be temporally modified by *Lactobacillus* supplementation [123].

In a study including 25 participants with dementia due to Alzheimer's disease (AD) and 25 control participants, the AD group presented decreased gut microbiota diversity and Firmicutes but increased Bacteroidetes as well as decreased *Bifidobacterium*, and there was a significant association of the cerebrospinal fluid (CSF) biomarker YKL-40 with the abundances of *Bacteroides*, *Turicibacter*, and the genus SMB53 (family *Clostridiaceae*) [124]. A systematic review identified differences in the gut microbiota of 53 microbial families and 98 genera between subjects with Parkinson's disease (PD) and healthy controls. The genera with increasing trends in PD reported in two studies included *Bifidobacterium*, *Alistipes*, *Christensenella*, *Enterococcus*, *Oscillospira*, *Bilophila*, *Desulfovibrio*, *Escherichia/Shigella*, and *Akkermansia*, and the genera with decreasing trends in PD reported in two studies included *Prevotella*, *Blautia*, *Faecalibacterium*, *Fusicatenibacter*, and *Haemophilus* [125].

5. Gut Microbiota-Targeted Therapies

Therefore, gut microbiota-targeted therapeutic strategies have been established to restore the homeostasis of the gut microbiota to improve human health. They include dietary interventions, prebiotics, probiotics, synbiotics, fecal microbiota transplantation (FMT), and bacteriophages [8,126,127].

5.1. Diet

Diet can affect the composition of the gut microbiota [128], in turn affecting the state of health and disease, and beneficial effects have been reported in some diet intervention studies; for example, in a randomized, crossover study that included 13 patients with type 2 diabetes mellitus, the intake of a high-fiber diet was found to improve glycemic control, decrease hyperinsulinemia, and lower plasma lipid concentrations [129].

5.2. Prebiotic

A prebiotic is defined as "a selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefits upon host health" [130]; common prebiotics include fructans, galactans, lactulose, inulin, etc. The use of prebiotics in some clinical trials has been associated with increased gut bifidobacteria and health benefits associated with metabolic health, satiety, bone health, skin health, allergies, and digestion [130,131].

5.3. Probiotic

Probiotics belong to a group of "live microorganisms which when administered in adequate amounts confer a health benefit on the host", according to the definition by the Food and Agriculture Organization (FAO) of the United Nations (FAO) and World Health Organization (WHO) [132], and they include *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, and *Saccharomyces*. The mechanisms of beneficial action of probiotics in the gut involve the production of antimicrobials against pathogens, colonization resistance against pathogens, and the modulation of the immune system [132]. Recently, precision genome editing of probiotics has been proposed to improve the probiotic properties [133].

5.4. Synbiotic

A synbiotic is "a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host" [134]; various types of synbiotics have been described in clinical trials, such as live microorganisms (*Bifidobacterium* and *Lactobacillus* strains) with substrate galacto-oligosaccharides (GOSs) [134].

5.5. Fecal Microbiota Transplantation (FMT)

FMT involves transplanting the gut microbiota of a healthy donor to the colon of a diseased subject. The transplantation routes include upper gastrointestinal routes (e.g., nasogastric/nasojejunal tube, endoscopy, and oral capsules) and lower gastrointestinal routes (e.g., colonoscopy) [135]. The U.S. Food and Drug Administration (FDA) classifies fecal microbiota products that are used to diagnose, prevent, treat, or cure a disease or condition in humans as biological products and has oversight of their safety and effectiveness [136]. The screening of donor and donor stool involves rigorous, multiple-stage protocols (e.g., questionnaires, laboratory stool tests, and blood tests) to ensure the safety of recipients [137]. To date, in clinical trials, FMT has been utilized mainly to treat recurrent *C. difficile* infection (CDI), which is associated with dysbiosis of the gut microbiota caused by the use of broad-spectrum antibiotics, with an overall 91% effect rate at week eight [138]. Very recently, the FDA approved two fecal microbiota products for the treatment of recurrent *C. difficile* infection: Vowst (fecal microbiota spores, live-brpk that contains Firmicutes spores from human feces) and Rebyota (fecal microbiota, live-jslm that contains a broad consortium of microbes prepared from human feces), both of which presented higher success rates for the treatment of recurrent *C. difficile* infection than did the placebo [139,140]. FMT has also been investigated for the treatment of other gastrointestinal (GI) disorders (e.g., irritable bowel syndrome, inflammatory bowel diseases, etc.) and various non-GI disorders (diabetes, obesity, Parkinson's disease, autism, Alzheimer's disease, etc.) [141–144], with promising and mixed results observed, for example, in the treatment of irritable bowel syndrome [141]. Notably, concerns of safety and risk exist in the use of FMT for the treatment of diseases regarding the transmission of infectious diseases, acquisition of noninfectious diseases, and other potential long-term adverse effects [145].

6. Perspectives

The human gut microbiota plays multiple important functions in metabolism, colonization resistance against pathogens, the development and functioning of immunity, and the gut–brain axis. Dysbiosis of the gut microbiota is associated with the development of intestinal, metabolic, cardiovascular, immune, and neural diseases (*C. difficile* infection, inflammatory bowel disease, irritable bowel syndrome, obesity, allergic disease, asthma, anxiety, Alzheimer's disease, etc.). Gut microbiota-targeted therapies (e.g., prebiotics, probiotics, synbiotics, and fecal microbiota transplantation) show improved outcomes. Particularly, two fecal microbiota products have been recently approved by the FDA for treating recurrent *C. difficile* infection. As sequencing, omics, laboratory cultivation, and artificial intelligence (AI) technologies have developed, we are approaching a deeper and more accurate understanding of the causal relationships of the gut microbiota with human health and diseases. In turn, these findings will facilitate the advancement of gut microbiota-targeted therapies toward precision and personalization. There is also an urgent need to address various challenges related to the standardization and regulation of the microbiota therapy. Although fecal microbiota-associated therapies have demonstrated safety and efficacy in treating diseases (e.g., *C. difficile* infection), it remains unclear of the long-term risks of fecal microbiota transplantation. The nature of fecal microbiota transplant is highly complex and depends on the individual host. Firstly, what defines a healthy gut microbiota remains challenging [146]. Secondly, it is time-consuming, expensive, and challenging to conduct the first key step to screen various infectious agents, antimicrobial resistance, and other risk factors, although it is simple in concept. It remains likely that some risk agents are transferred to the patient because of the lack of the knowledge at the time of the screening step. Additionally, there is still a debate on the classification of human stool in the fecal microbiota transplant treatment [147]. While in some countries (e.g., USA and Canada), fecal microbiota transplant is classified as a biological agent or a medicinal product, it is classified as a human tissue or cell product in some European countries [145]. Therefore, future standardization and regulation are needed to ensure the privacy, research ethics, and safety of the treatment.

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