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Review

Impacts of Gut Bacteria on Human Health and Diseases

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Abstract: Gut bacteria are an important component of the microbiota ecosystem in the human gut, which is colonized by 10^{14} microbes, ten times more than the human cells. Gut bacteria play an important role in human health, such as supplying essential nutrients, synthesizing vitamin K, aiding in the digestion of cellulose, and promoting angiogenesis and enteric nerve function. However, they can also be potentially harmful due to the change of their composition when the gut ecosystem undergoes abnormal changes in the light of the use of antibiotics, illness, stress, aging, bad dietary habits, and lifestyle. Dysbiosis of the gut bacteria communities can cause many chronic diseases, such as inflammatory bowel disease, obesity, cancer, and autism. This review summarizes and discusses the roles and potential mechanisms of gut bacteria in human health and diseases.

Keywords: gut bacteria; human health; cancer; obesity

1. Introduction

The human gut mucosa consists of epithelial cells, lamia propria, and the muscularis mucosae, which is colonized by 10^{14} microbes [1]. The number of these microbes is ten times more than the human cells

Gut bacteria are important components of the microbiota ecosystem in the human gut. Commensal bacteria colonize in the gut shortly after birth and comprise approximate 1000 species, most of which are unknown species belonging to anaerobic strains [2,3]. The composition and temporal patterns of gut microbiota in infants varies widely and is very different from those in adults. Furthermore, the intestinal microbiota stabilizes to a more adult-like profile around the age of one year, usually after the introduction of solid foods [4]. In addition, the composition of the gut bacteria community in the stomach and colon is distinctive, which is mainly due to different physicochemical conditions, such as intestinal motility, pH value, redox condition, nutrients, host secretions (e.g., gastric acid, bile, digestive enzymes, and mucus), and the presence of an intact ileocaecal valve [5]. Additionally, they can be influenced by many factors, such as the use of antibiotics, illness, stress, aging, bad dietary habits and lifestyle [5,6].

Usually, gut bacteria and the host live in a commensal manner. On the one hand, they can supply essential nutrients, synthesize vitamin K, aid in the digestion of cellulose, and promote angiogenesis and enteric nerve function [7–9]. *Bacteroidetes* and *Firmicutes* are the main bacteria in the metabolism of undigested food remnants. They help to digest dietary fiber and polyphenols by a complex metabolic energy-harvesting mechanism, which is based on cross-feeding and co-metabolism. In return, commensal bacteria take advantage of theprotective and nutrient-rich environment of the host [10]. Yet, specialized gut bacteria perform reductive reactions such as methanogenesis, acetogenesis, nitrate reduction, and sulfate reduction [11]. On the other hand, commensal bacteria and probiotics can promote barrier integrity, and prevent antigens and pathogens from entering the mucosal tissues [12]. Besides, commensal bacteria contribute to the host defense by regulating the homeostasis of the host immune system [13]. However, gut bacteria can be potentially harmful when the gut ecosystem undergoes abnormal changes. Dysbiosis of the gut bacteria communities in patients or animal models may cause allergy, inflammatory bowel disease (IBD), obesity, diabetes, and even cancer [8,9]. The composition of gut bacteria can indicate the risk of diseases in each person [14]. Herein, this review summarizes and highlights the roles and potential mechanisms of gut bacteria in human health and diseases. Understanding of the relationship between gut bacteria and human health can be helpful for targeting new probiotic treatments and novel strategies in treating and managing a wide variety of human diseases. The literature was sought from the databases PubMed and ISI Web of Knowledge, and the references cited were mainly original articles from 2005–2014.

2. Gut Bacteria in Health

The main gut bacterial phyla, in the order of numerical importance, are *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, *Verrucomicrobia* and *Fusobacteria* [15]. *Firmicutes* are gram-positive bacteria with a low G + C content, including the large class of *Clostridia* and the lactic acid bacteria, while *Actinobacteria* are gram-positive bacteria with a high G + C content, including *Colinsella* and *Bifidobacterium* spp. Lactic acid bacteria and *Bifidobacteria* are two important types of gut bacteria, which are autochthonous ones from birth or acquired from digested food. *Lactobacillus* and *Leuconostoc* spp. are the main lactic acid bacteria found in the human intestine. *Bifidobacterium* spp. is the predominant bacteria found among the first colonizers of newborns, and persists at a low level in adults [16]. Gut bacteria play an important role in human health, including contributing to the host gut

defense system and helping the gut to maintain normal function, while its composition can be influenced by the host (Figure 1).

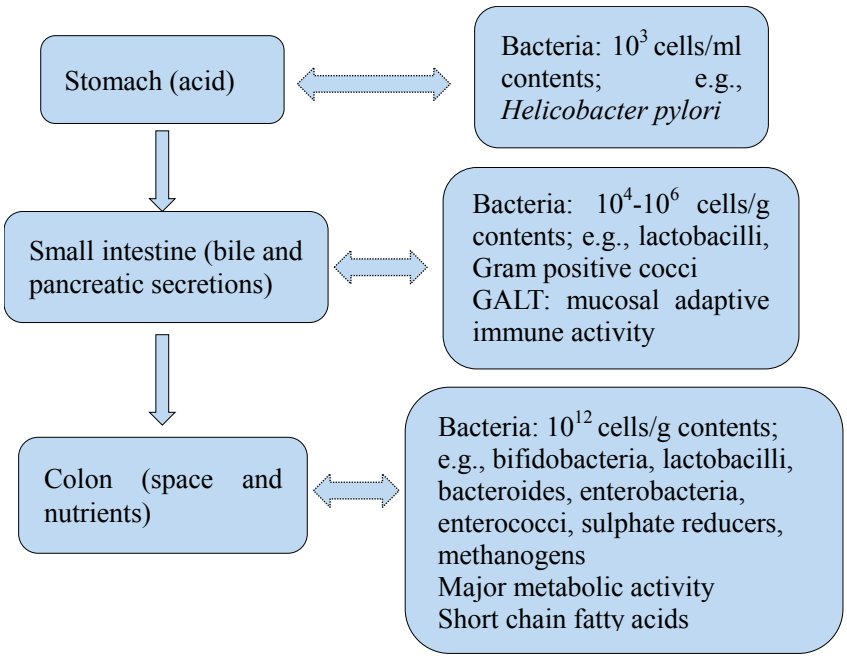

Figure 1. Reciprocal relationship between human gut bacteria and the host.

2.1. Gut Bacteria and Gut Immune System

The gut resists pathogenic bacteria through two barriers, the mechanical barrier and the immune barrier. The mechanical barrier consists of a single layer of polarized intestinal epithelial cells, the enterocytes and mucus. On the other hand, secreted immunoglobulin A (IgA), intraepithelial lymphocytes, macrophages, neutrophils, natural killer cells, Peyer's plaques, and mesenteric lymph node compose the immune barrier. Commensal bacteria and probiotics can promote the integrity of gut barriers. Commensal bacteria contribute to the host gut defense system mainly by resisting the invasion of pathogenic bacteria and helping the development of the host immune system. Gut bacteria maintain resistance against the colonization of pathogenic bacteria by competing for nutrients and attachment sites on the mucosal surface in the colon, a phenomenon collectively known as "colonization resistance" [17]. The invasion of pathogenic bacteria is also prevented by commensal bacteria due to the reduction of the intestinal pH by the production of lactate and short-chain fatty acids (SCFAs) [9]. Another way is by producing toxic or carcinogenic metabolites to inhibit the growth or kill potentially pathogenic bacteria, together with volatile fatty acids that can inhibit the colonization of pathogenic bacteria. For example, proteolytic fermentation in the distal colon could produce toxic, carcinogenic metabolites such as bacteriocins, ammonia, indoles, and phenols by gut bacteria [18]. Lipopolysaccharides (LPSs) and peptidoglycan (PGN) components in the bacterial cell wall are two kinds of pathogen-associated molecular patterns, and they can individually or synergistically activate nuclear factor κB (NF-κB) effector and further induce the production of inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β) and antimicrobial peptides in the defense against foreign pathogens. Chronic stimulation of pattern-recognition receptors (PRRs) by PGN can

also minimize excessive tissue injury induced by intestinal antigen-presenting cells, which can produce inhibitory cytokines such as transforming growth factor β (TGF-β) and IL-10 via nuclear oligomerization domain-2 dependent pathways [19].

Peyer's patches, lamina propria lymphocytes, intra-epithelial lymphocytes and mesenteric lymph nodes constitute gut-associated lymphoid tissue (GALT), which is the main part of the gut immune system. Gut bacteria prime the dendritic cells (belonging to lamina propria lymphocytes) of the immune system. *L. plantarum* was suggested to regulate human intestinal epithelial tight-junction proteins and show protective effects against chemical-induced disruption of the epithelial barrier [12]. It has been found that antibody repertoire diversification occurred in GALT after birth and was stimulated by gut bacteria in sheep, cattle, pigs, and rabbits [20]. It was hypothesized this action may also occur in humans. Gut bacteria including *Bacteroides fragilis* and *Bacillus* are probably required for the normal development of GALT and mucosal immunity in all mammals. They are also required for somatic diversification of immunoglobulin (Ig) genes. Gut bacteria colonization induces a conspicuous response of the gut immune system to the production of IgA, which plays a critical role in regulation of gut bacterial communities in the small intestine. Another factor that may play an active role in the induction of local immune responses is the ILs, which may function as sensors of gut bacteria [10].

Studies of animals bred under germ-free conditions showed that germ-free animals presented morphological, structural, and functional abnormalities, including "reduced vascularity, digestive enzyme activity, muscle wall thickness, cytokine production and serum immunoglobulin levels, smaller Peyer's patches and fewer intra-epithelial lymphocytes" [21]. Another study showed that animals received cells from germ free mice developed an earlier onset of colitis, and $CD4^+CD62L^-$ cells from germ free mice were not able to ameliorate colitis compared with mice reconstituted with lymphocytes from conventionally housed animals [22]. The study also assumed a lack of Treg cells within germ free mice by observing the higher percentage of $CD4^+GITR^+$ expressing lymphocytes and the production of IL-10 after priming by dendritic cells, which suggested the presence of Treg cells within the $CD4^+CD62L^+$ lymphocyte subset derived from conventional housed mice. Butyrate, produced by commensal microorganisms during starch fermentation, may facilitate extrathymic generation of Treg cells [23].

2.2. Gut Bacteria Benefit the Host

Not only do gut bacteria benefit the host by contributing to the host gut defense system, they also help the gut to maintain normal functions. Gut bacteria benefit the host in a variety of ways, such as regulating gut motility, producing vitamins, transforming bile acid and steroids, metabolizing xenobiotic substances, absorbing minerals, and activating and destroying toxins, genotoxins, and mutagens [24]. The proximal region of colon produces a great quantity of short-chain organic acids, such as acetic, propionic, and butyric acids. Theses organic acids are energy sources for the colonic mucosa and peripheral body tissues, and they are metabolites of undigested complex carbohydrates by colonic bacteria fermentation. In return, theses organic acids affect bacterial growth in the colon by affecting colonic water absorption and decreasing fecal pH. In addition, *Oxalibacterium formigenes*, a betaproteobacterium within the order *Burkholderiales*, which is among the putative core bacteria,

is one of the few colonic bacteria with well-defined health benefits. They regulate the homeostasis of oxalic acid and prevent the formation of kidney stones [25].

Gut bacteria are essential for the transformation of natural compounds (e.g., lignans) to perform their bioactivities. Lignans are present in a wide range of foods, such as flaxseed, vegetable, fruit, and beverages. Lignans afford protection against cardiovascular diseases, hyperlipidemia, breast cancer, colon cancer, prostate cancer, osteoporosis and menopausal syndrome, dependent on the bioactivation of these compounds to enterolactone (ENL) and enterodiol [26,27]. Gut bacteria are required for the production and bioavailability of these enterolignans. Secoisolariciresinol is one of the most abundant dietary lignans, and it can be demethylated and dehydroxylated by two gut bacteria isolated from human feces, named *Peptostre ptococcus* SECO-Mt75m3 and *Eggerthella lenta* SECO-Mt75m2 [28]. Gut bacteria also play an essential role in the metabolism of isoflavones, and the metabolites are more biologically active than their precursors. Isoflavones are structurally similar to the mammalian estrogen, and soy foods are the predominant food sources of them. Isoflavones have protective activity in breast cancer, prostate cancer, cardiovascular disease, osteoporosis, and menopausal symptoms [29]. In addition, De Fillippo *et al.* [14] reported that gut bacteria protected African children from the risk of infectious and noninfectious colonic diseases by coevolving with the polysaccharide-rich diet, which also allowed them to maximize energy intake from fibers.

2.3. Dietary Influence on Gut Bacteria

The colonization of gut bacteria is influenced by many factors, such as the living environment and diet (Figure 2). The feeding ways of infants was reported to impact the composition of gut bacteria. Infants fed with breast milk had higher levels of *Bifidobacteria* spp., while infants fed with formula had higher levels of *Bacteroides* spp., *Clostridium coccoides* and *Lactobacillus* spp. [30–32]. Besides, the host physiologic process, the anatomical structure and physiology of the digestive tract are major factors [24]. They may cause changes to the disease structure in the host. It was proved that diets could impact the composition of gut bacteria. A study showed that mice fed with Western-diet and low-fat-chow-diet displayed different structures of gut bacteria. The relative abundance was increased about 1.2-fold for *Bacteroidetes* and 18-fold for *Proteobacteria*, while was decreased about 1.5-fold for *Firmicutes* in mice fed with Western-diet. Members of the *Desulfovibrionaceae* family were significantly enriched in the cecal contents of healthy mice fed with Western-diet. *Lactobacillus gasseri* species were found representing 4.3% of total bacteria on average, and *Ruminococcus* and other members of *Lachnospiraceae* and *Bacteroidales* were also enriched in mice fed with low-fat-chow-diet. *Lactobacillus gasseri* species were even absent in mice receiving Western-diet [33]. There are also studies reporting that long-term and short-term diets influence the composition and function of the gut microbiota in humans. In a study of diet inventories and 16S rDNA sequencing to characterize fecal samples from 98 individuals, enterotypes were strongly associated with long-term diets, particularly protein and animal fat (*Bacteroides*) versus carbohydrates (*Prevotella*). Microbiome composition changed detectably within 24 h of initiating a high-fat/low-fiber or low-fat/high-fiber diet, but that enterotype identity remained stable during the 10-days in a controlled-feeding study of 10 subjects [34]. Another study showed the short-term consumption of diets composed entirely of animal meat, eggs, and cheeses or plant rich in grains, legumes, fruits, and vegetables, altered microbial community structure

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