Digestive Diseases and Sciences (2020) 65:695–705
https://doi.org/10.1007/s10620-020-06118-4

REVIEW

Healthy Human Gastrointestinal Microbiome: Composition and Function After a Decade of Exploration

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Published online: 18 February 2020

Abstract

The human gastrointestinal (GI) tract contains communities of microbes (bacteria, fungi, viruses) that vary by anatomic location and impact human health. Microbial communities differ in composition based on age, diet, and location in the gastrointestinal tract. Differences in microbial composition have been associated with chronic disease states. In terms of function, microbial metabolites provide key signals that help maintain healthy human physiology. Alterations of the healthy gastrointestinal microbiome have been linked to the development of various disease states including inflammatory bowel disease, diabetes, and colorectal cancer. While the definition of a healthy GI microbiome cannot be precisely identified, features of a healthy gut microbiome include relatively greater biodiversity and relative abundances of specific phyla and genera. Microbes with desirable functional profiles for the human host have been identified, in addition to specific metabolic features of the microbiome. This article reviews the composition and function of the healthy human GI microbiome, including the relative abundances of different bacterial taxa and the specific metabolic pathways and classes of microbial metabolites contributing to human health and disease prevention.

Keywords Microbiome · Human · Healthy · Metabolites

Abbreviations

GI	Gastrointestinal
HMP	Human Microbiome Project
MetaHIT	Metagenomics of the Human Intestinal Tract
IBD	Inflammatory bowel disease

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Introduction

The healthy human microbiome consists of 30-plus trillion microorganisms per person including mostly bacteria, viruses (bacteriophages and human viruses), and yeast [1]. Human microbes reside on the skin, in the oral cavity, and in the gastrointestinal (GI), respiratory, and genitourinary tracts, accounting for 1–3% of our total body weight. The human GI tract contains relatively rich and complex microbial communities in healthy individuals. Intestinal microbes harbor genes that encode for thousands of microbial enzymes and metabolites [2, 3]. These metabolic pathways and microbial compounds facilitate digestion and assimilation of dietary nutrients, while fostering maturation and proper function of the immune and nervous systems.

The Human Microbiome Project (HMP) and the Metagenomics of the Human Intestinal Tract (MetaHIT) initiatives were the first large-scale microbiome projects defining composition and function of the healthy human microbiome [4, 5]. These endeavors provided the foundation for understanding of the physiology and functional properties of host-associated microbial communities. With the advent of new technologies like next-generation sequencing, whole-genome shotgun sequencing, global metabolomics, and advanced computational strategies along with humanized animal models and culture-based human organoid systems, understanding of the microbiome is rapidly progressing [6].

The GI microbiome is a dynamic and functional interface between the external environment, food, and the human body [7]. Distinct luminal- and mucus-associated ecosystems found throughout the length of the GI tract are influenced by various factors including age, diet, antibiotic/medication ingestion, and other exposures. Alterations in GI microbiome diversity have been attributed to disease phenotypes such as colorectal cancer, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and diabetes [8–12]. Here we review how GI microbiome composition and function affect human health and consider future investigations to further elucidate the healthy human GI microbiome.

Characteristics of a Healthy GI Microbiome

The microbiome is dynamic and changes spatially and temporally, and in relation to an individual's health status. Microbes colonize the human body and shift in composition as humans age, with a gradual increase in microbial diversity during childhood and relative stabilization during adolescence and adulthood [13]. Breastfeeding seems to play a significant role in the formation of early-life microbiome with a predominance of *Bifidobacterium* and *Bacteroides* species in breastfed infants [14, 15]. Breastfeeding appears to have long-term effects on the microbiome and its effects on the immune system and GI tract [16, 17]. The childhood/adolescent microbiome is enriched in *Bifidobacterium* spp., *Faecalibacterium* spp., and members of the *Lachnospiraceae* family [13]. Interestingly, children's gut communities were enriched in functions that may support ongoing development. In contrast to infant and childhood microbiomes, the adult microbiome is more stable and is shaped more by environment than by genetics. As humans age, microbial diversity increases steadily in healthy individuals [17–19]. Decreased microbial diversity has been associated with various disease states [20–22].

Much of the initial focus on the microbiome has been centered around the understanding of its impact in disease leading to the concept of dysbiosis or shifts in the normal gut microbiome structure. Shifts in the microbiome are influenced by diet, antibiotics, socioeconomic status, and geography [23, 24]. However, it is still unclear whether these changes in microbiome composition are a cause or consequence of epithelial function alteration and disease. One of the features of a healthy microbiome is its resilience, its ability to return to an equilibrium state, and resistance to

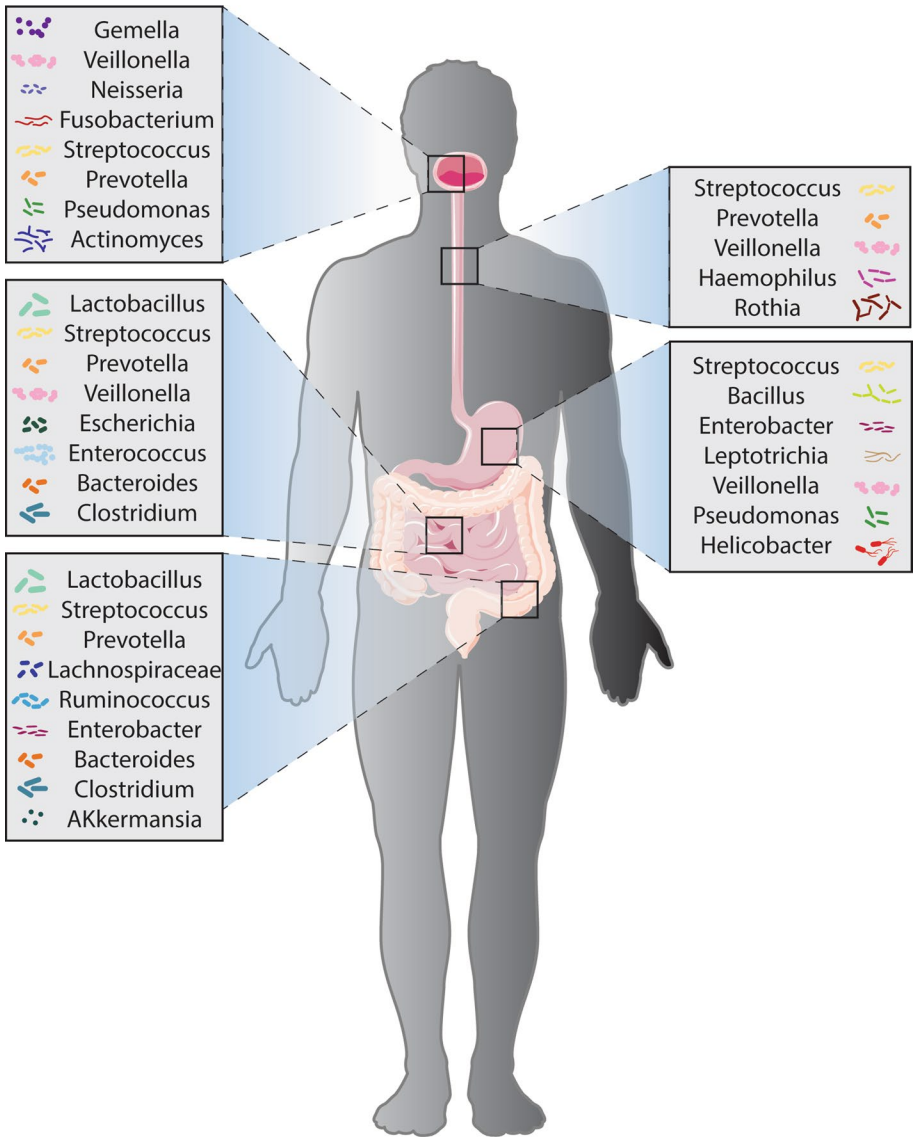

Fig. 1 Human microbiome composition varies by location in the GI tract. Predominant bacterial genera in the oral cavity, esophagus, stomach, small intestine, and colon are delineated in this figure

perturbations. A significant degree of interpersonal diversity even in the absence of disease in the human microbiome makes defining an idealized community of specific microbes difficult [25, 26]. The variation of the microbiome between the individuals is thought to be driven by ecological processes that shape various ecosystems [27, 28]. Rather than an idealized community of microbes, a healthy microbiome can be characterized by a shared set of metabolic modules or functions [18, 29].

Structural Composition of the GI Microbiome

The human GI tract is a complex system that begins at the esophagus and ends at the anus with most data obtained to date from the distal colonic microbiota due to the practical considerations of specimen collection. Important physiologic conditions like pH, bile content, and transit time vary along the GI tract and contribute to distinct microbial communities inhabiting the upper and lower GI tract [30]. In this section, we review what is known about the composition of healthy bacterial communities in the oral cavity, esophagus, stomach, small intestine, and colon (Fig. 1).

Oral Cavity

The oral cavity is comprised of several microbial environments including the tonsils, teeth, gums, tongue, cheeks, hard and soft palates. It is the opening to the GI tract where food enters and is mixed with saliva. More than 1000 taxa have been found in the oral cavity so it has its own database known as the Human Oral Microbiome Database [31]. Six major phyla comprise 96% of the taxa

including *Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Spirochaetes,* and *Fusobacteria* [31]. In saliva of healthy patients, the predominant genera are *Gemella, Veillonella, Neisseria, Fusobacterium, Streptococcus, Prevotella, Pseudomonas,* and *Actinomyces* [32]. Different locations within the oral cavity have varying degrees of biological diversity [33].

Esophagus

Food is transported down the esophagus from the oral cavity to the stomach. Similar to the oral cavity, the most abundant bacteria in the human esophagus belong to the phylum *Firmicutes* and the genus *Streptococcus* [34], likely derived from the oral cavity [30, 35]. Shotgun sequencing has revealed three distinct community types in the esophagus of healthy subjects [36]. Communities are dominated either by *Streptococcus* (*Streptococcus mitis/oralis/pneumoniae*), *Prevotella* (*Prevotella melaninogenica and Prevotella pallens*) and *Veillonella*, or *Haemophilus* (*Haemophilus parainfluenzae*) and *Rothia* (*Rothia mucilaginosa*). Similar to other GI sites, age contributes to the structure of the esophageal microbiome, but interestingly composition appears to be independent of proton-pump inhibitor use or gender [36]. Overall, there are limited studies to suggest altered microbiome composition associated with esophageal diseases so further studies are necessary to better elucidate disease pathogenesis.

Stomach

The stomach is the first digestive organ of the body. It contains proteolytic enzymes and gastric acid that processes the food that is ingested. Due to its acidic environment, the growth of many bacteria is inhibited. The harsh environment is thought to serve as a protective mechanism against pathogens. Despite the low pH, a diverse microbiota can be found in the stomach. The genera commonly found in the corpus and antrum include *Bacillales incertae sedis*, *Streptococcaceae*, *Enterobacteriaceae*, *Leptotrichiaceae*, *Veillonellaceae*, and *Pseudomonadaceae* [32, 35]. Individuals can be divided into the two major groups: groups with and without *Helicobacter pylori*. In patients with abundant *H. pylori*, a greater number of bacteria belonged to the phylum *Proteobacteria* and the gastric microbiomes yielded lower overall alpha diversity [32, 37]. When looking at the gut microbiome of individuals with *H. pylori*, there is increased abundance of *Succinivibrio*, *Coriobacteriaceae*, *Enterococcaceae*, and *Rikenellaceae* [38].

Small Intestine

The small intestine consists of the duodenum, jejunum, and the ileum and is the location where most nutrient digestion and absorption occur. The duodenum is the portion of the small intestine where the food bolus enters from the stomach, and bile salts from the gallbladder along with pancreatic enzymes start digestion. The intestinal epithelium of the jejunum and ileum is then responsible for nutrient absorption. Metabolism favors simple sugar and amino acid metabolism, so the small intestine is dominated by rapidly dividing facultative anaerobes such as *Proteobacteria* and *Lactobacillales* [39]. This finding was supported by studies analyzing jejunal samples obtained via enteroscopy. One study showed that *Streptococcus, Prevotella, Veillonella, Fusobacterium, Escherichia, Klebsiella,* and *Citrobacter* were abundant, whereas extreme anaerobes like *Alistipes, Ruminococcus,* and *Faecalibacterium* were not present [40]. Also, when the jejunum and ileum contents from three individuals were analyzed, the most common communities consisted of streptococci, lactobacilli, *Gammaproteobacteria,* the *Enterococcus group*, and the *Bacteroides* group [41]. As the small intestine progresses distally in the ileum, the microbial composition becomes more complex and approaches that of the colon in terms of diversity and richness. Vaspapolli et al. found that the duodenum harbored similar genera as the stomach (*Bacillales incertae sedis*, *Streptococcaceae*, *Enterobacteraceae*, *Leptorichiaeceae*, *Veillonellaceae*, and *Pseudomonadaceae),* while the terminal ileum exhibited a composition closer to that of the colon (*Clostridiaceae*, *Lachnospiraceae*, *Peptostreptococcaceae*, *Ruminococcaceae*, *Enterobacteriaceae*, and *Bacteroidaceae*) [32]. These findings demonstrate unique microbial compositional profiles along the length of the small intestine.

Colon

The colon consists of the cecum, ascending, transverse, descending, and sigmoid colon, as well as the rectum. It is the location where water and minerals are absorbed and complex carbohydrate fermentation occurs [42]. Complex foods that have not been digested by the host reach the colon and feed the colonic microbiota. The healthy human colon yields a relatively rich abundance of microbes in the colon, and these communities are highly diverse. The predominant colonic bacterial phyla in the healthy human are *Bacteroidetes*, *Firmicutes*, *Verrucomicrobia*, *Proteobacteria*, and *Actinobacteria* [35]. Few differences have been observed between the ascending and descending colon in terms of microbiome composition, with families from the colon including *Clostridiaceae*, *Lachnospiraceae*, and *Bacteroidaceae* dominating the microbiome structure [32].

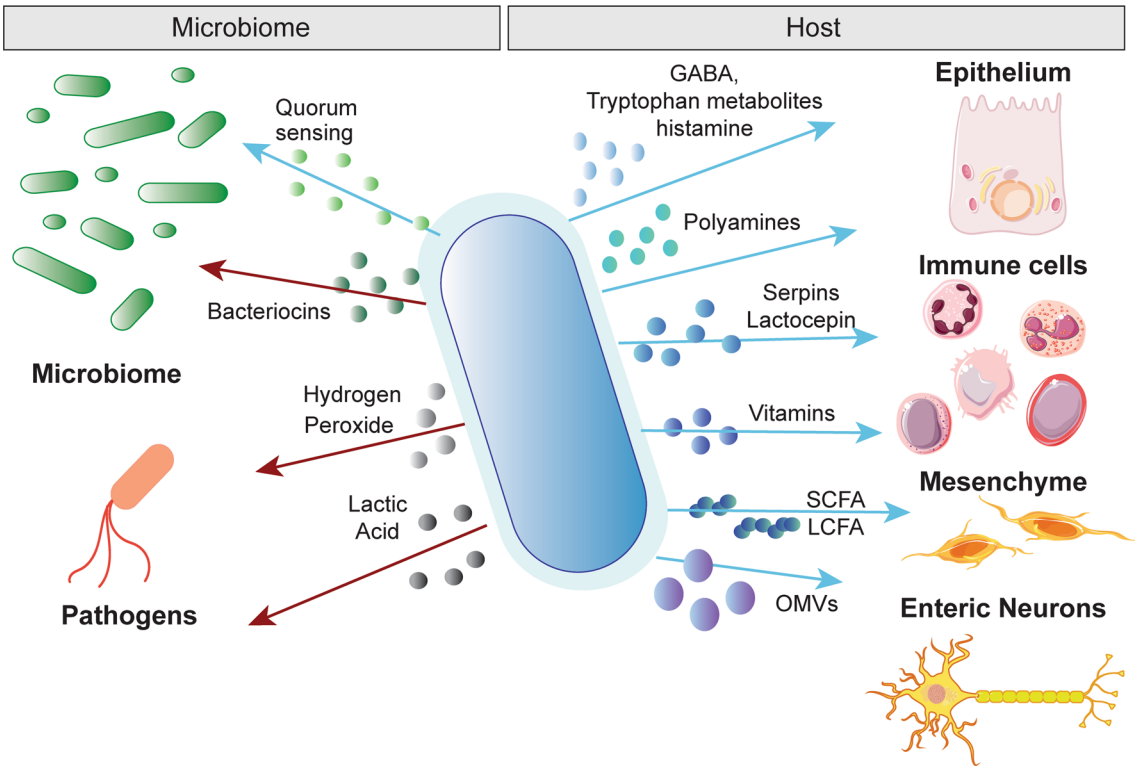

Fig. 2 Microbial metabolites produced in the gastrointestinal tract have diverse functions. The gastrointestinal microbiome can modulate both intra- (microbe–microbe) and inter-kingdom (microbe-host) interactions that can influence human health. Bacteria are involved in quorum sensing and can release bacteriocins, hydrogen peroxide, and lactic acid, which yield effects on the gut microbiome and pathogens. In addition, bacteria can produce gamma-aminobutyric acid (GABA), tryptophan metabolites, histamine, polyamines, serpins, lactocepin, vitamins, short chain fatty acids (SCFA), long chain fatty acids (LCFA), and outer membrane vesicles (OMVs), which can have effects on the human host epithelium, immune cells, mesenchyme, and enteric neurons

A major difference between the small and large intestine is the structure of the mucus layer. In the colon, the mucus forms a stratified layer that is more defined than in the small intestine. The colonic mucus layer consists of an inner mucus layer, physically excludes bacteria, and contains immune effectors that target the microbiota [43]. In contrast, the outer mucus layer is loose and serves as a colonization site for numerous microbes. Due to the structural makeup of the colon, it has been observed that bacteria are organized along the transverse axis of the colon, from the lumen to the mucosa. Microbes that prioritize dietary starches and nutrients reside within the colonic lumen. Organisms that can utilize mucin such as *Akkermansia, Ruminococcus*, and some *Bacteroides* species reside within the outer intestinal mucus layer [44–47]. In addition to nutrient sources, oxygen gradients exist from the intestinal lumen to the mucosa as well as moving down the colon, with consequent effects on microbial composition of the colon. For example, *Proteobacteria* and *Actinobacteria* phyla are found closer to the rectum than feces as a result [48].

Several studies have attempted to define a human intestinal core microbiota. Longitudinal analysis and cross-sectional comparisons of fecal 16S rRNA have revealed that a significant fraction of bacterial phylotypes is continuously present and thus comprises a stable microbial core [49–54]. These core microbes include *Bacteroides*, *Eubacterium*, *Faecalibacterium*, *Alistipes*, *Ruminococcus*, *Clostridium*, *Roseburia*, and *Blautia*; with *Faecalibacterium prausnitzii*, *Oscillospira guillermondii*, and *Ruminococcus obeum* as the top three taxa shared by all adults [55].

Alterations of the colonic microbiota and breaches in the colonic structure have been associated with various disease states. Recent microbiome genome-wide association studies revealed multiple alterations in gut microbiome composition in metabolic disorders and disorders of immunity [56]. Inflammatory bowel disease (IBD) is characterized by immune activation and disrupted intestinal epithelial mucosal barrier function, which can culminate in the inappropriate immune activation against commensal bacteria. Affected sites in IBD are locations with relatively greater bacterial densities such as the distal ileum and cecum. In addition, mucus-degrading bacteria were increased in relative abundance in IBD patients leading to the an increase in available substrates to sustain mucosa-associated bacteria during colitis [57], and large increases in *Ruminococcus gnavus* have been noted in mucosal samples of IBD patients

[56]. In colorectal cancer patients, *Coriobacteriaceae* were found in greater abundance in tumors [8]. Obesity is associated with lower abundances of *Christensenella minuta, Akkermansia muciniphila,* and *Methanobrevibacter smithii* and an overabundance of *Blautia* [56]. The colonic microbiome plays a pivotal role in maintaining intestinal epithelial homeostasis and overall human health.

Microbial Functions in the GI Tract

Although microbiome structure varies among healthy individuals, microbial functions are well-conserved [32]. One important function of the microbiome is the generation of microbial metabolites which influence both microbes and host. This section details the functional capacity of the GI microbiota and specifically touches on microbial-derived metabolites that modulate both intra- (microbe–microbe) and inter-kingdom (microbe-host) interactions that impact human health (Fig. 2).

Microbial Metabolites

Secreted microbial compounds can target the microbiome by acting as signaling molecules for inter-bacterial communication. These molecules, known as quorum sensors, can influence bacterial homeostasis, growth, spore formation, programmed cell death, virulence, and biofilm formation [58–62]. Quorum sensing offers advantages to biofilm communities by allowing them to adapt to environmental changes [58–60, 63]. Quorum sensing compounds are grouped into three classes: (1) LuxI/LuxR-type; (2) oligopeptide-two-component-type; and (3) luxS-encoded autoinducer 2 (AI-2) quorum sensing [58]. In intestinal communities, the levels of the quorum sensing compound AI-2 were associated with relatively decreased abundance in *Bacteroidetes* and increased abundance in *Firmicutes* [64]. Additionally, AI-2 also promoted Firmicutes that encoded a LuxS homolog, indicating that a positive feedback loop might exist within the microbiota, whereby AI-2 signaling and downstream responses drive increases in abundance of the AI-2 producers, which then further increases signal levels and amplifies the response throughout the community.

While quorum sensing compounds typically encourage bacterial growth of similar microbes, bacteria also secrete compounds that inhibit the growth of competitors. These antibiotic compounds can be proteins (bacteriocins) or small molecules (lactic acid, hydrogen peroxide (H_2O_2), and reactive aldehydes) and effectively enhance host health through colonization resistance [65, 66]. Bacteriocins target phosphate groups on bacterial cell membranes, deplete the transmembrane potential ($\Delta\psi$), and form membrane pores. These events result in membrane disruption, cellular leakage, and cell death [67–69]. Interestingly, bacteriocins have a synergistic effect with lactic acid, produced commonly by probiotics, and exhibit greater antibacterial activity at lower pH. Lactic acid bacteria (LAB) produce lactic acid as an end product of glucose fermentation [70], which (1) reduces local pH and suppresses colonization and proliferation of potential pathogens, and (2) can penetrate the bacterial cytoplasmic membrane, lower the intracellular pH, and suppress the electron transport system, leading to oxidative stress, DNA damage, and cell death [71–74]. Lactic acid also works synergistically with H_2O_2 to inhibit pathogens and shape microbial communities [71, 75, 76] by damaging bacterial nucleic acids and preventing chromosomal replication [77–80]. Apart from intra-kingdom interactions, L-lactic acid can directly impact host health by suppressing pro-inflammatory responses of immune cells [81]. An isomeric mixture of 3-hydroxypropionaldehyde (3-HPA) also known as reuterin is produced by LAB [82, 83] and inhibits enteric pathogen growth [84–86]. Reuterin is the by-product of glycerol fermentation [87, 88], which is hypothesized to stem from the breakdown of a prevalent bacterial membrane phospholipid phosphatidylethanolamine into glycerol and ethanolamine, suggesting that glycerol is abundant in the GI tract. Like lactic acid, reuterin also mediates inter-kingdom interactions; recent studies have linked reuterin production with iron homeostasis in the host [89, 90].

Microbial Metabolites/Compounds and Their Impact on Host Processes

Bacterial metabolites can also mediate host processes and functionally complement host metabolic capabilities. Certain microbes can generate biologically active compounds including but not limited to, gamma-aminobutyric acid (GABA), tryptophan metabolites, polyamines, and histamine [91–107]. Microbial neuromodulators like GABA may participate in communication with the enteric and central nervous systems, while microbial-derived immunomodulators like histamine interact with intestinal immune cells. Serpins, another example of microbial-derived immunomodulators, are similar to eukaryotic serine protease inhibitors which suppress inflammatory responses by inhibiting elastase activity [108–112]. Similarly, lactocepins are bacterial enzymes which can degrade pro-inflammatory signals [113–115]. For example, *Lactobacillus*-secreted lactocepin selectively degrades lymphocyte recruiting chemokine IP-10, I-TAC and eotaxin, thereby suppressing pro-inflammatory signaling cascades [116, 117].

Short-chain fatty acids (SCFAs) implicated in immune regulation, pH regulation, sodium and water absorption, and

mucus secretion [66, 118, 119] are an important microbial by-product of complex carbohydrate fermentation in the intestine. The most abundant and well-studied SCFAs are acetate, propionate, and butyrate; however, the intestinal composition of SCFAs is contingent on microbial composition, diet, and intestinal pH [120–123]. SCFAs are absorbed by host epithelial cells and diminished in concentration from the proximal to the distal colon [124–128]. In addition to epithelial cells, SCFA transporters are found on immune, enteroendocrine, kidney and brain cells [127–137] reflecting the diverse effects of SCFAs on host physiology. In addition to SCFAs, microbes can produce long-chain fatty acids (LCFAs) [138–141] known to reduce hepatic triacylglycerols and inhibit atherosclerosis [142, 143].

Select intestinal microbes are able to produce vitamins, essential nutrients required for growth and immune function, which are primarily absorbed in the colon [144–151]. Genomes of gut microbes yield enzymatic pathways involved in vitamin synthesis for eight different B complex vitamins: biotin (B7), cobalamin (B12), folate (B9), niacin (B3), pantothenic acid (B5), pyridoxine (B6), and riboflavin (B2) [152]. Metagenomic studies have also indicated the enrichment of microbial enzymatic pathways for vitamin precursors in the gut and have emphasized the production of vitamins through coordinated bacterial cross-feeding [153]. Interestingly, recent studies have linked vitamin deficiencies with antibiotic-diminished gut microbiota, solidifying a distinct contribution of microbial vitamins to host health that differs from vitamin supplementation in the diet [154]. Key modifications of microbial vitamins like mono- and polyglutamylated folate influence their absorption and function in the host [155–157], which further supports the significance of microbial micronutrients in host health.

Outer membrane vesicles (OMVs) are another key immunomodulatory factor produced by our gut microbiota [158–160]. OMVs typically harbor a number of soluble proteins which can signal to multiple cell types, including cells in the innate and adaptive immune systems [161]. *Bacteroides fragilis* OMV delivery of polysaccharide capsular antigen (PSA) has been widely studied for its immunomodulatory effects. *B. fragilis* OMVs were found to modulate CD4+ T cell homeostasis and cytokine production [162] and directly modulate dendritic cells (DCs) [163, 164]. These immunomodulatory functions have been shown to benefit intestinal inflammation [165] and CNS inflammation [166–168].

Conclusions

The human gastrointestinal microbiome is essential to maintaining human health. Despite technological advances in human microbiome research, the individual composition, functional features, and interactions between human host and microbes remain to be elucidated. These studies emphasize the importance of a healthy GI microbiome and the key roles of bacterial metabolites in fine-tuning the host response. Additional studies may provide more precise etiologic explanations for the interactions between the host and human microbiome. As we begin to understand the composition and function of the healthy microbiome, we may be able to identify individual species and strains which can be tailored for specific targets of interest.

Funding This study was supported by the NIH T32 Grant 5T32DK007664-28 awarded to WR, NIH U01CA170930 Grant awarded to JV, the NLM Training Program in Biomedical Informatics and Data Science T15LM007093 (SCD) awarded to JV, and the Digestive Diseases Center which is funded by NIH/NIDDK P30 DK56338-06A2 Grant awarded to JV.

Compliance with Ethical Standards

Disclosures JV receives unrestricted research support from BioGaia AB, a Swedish probiotics company. JV serves on the scientific advisory board of Seed, a USA-based probiotics/prebiotics company. JV serves on the scientific advisory board of Biomica, an Israeli informatics enterprise, and on the scientific advisory board of Plexus Worldwide, a USA-based nutrition company.

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