Nutrition Research 112 (2023) 30–45

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/NTR

Review

The microbiome as a major function of the gastrointestinal tract and its implication in micronutrient metabolism and chronic diseases

Dingbo Lin[a,*], *Denis M. Medeiros*[b]

[a] *Department of Nutritional Sciences, Oklahoma State University, Stillwater, OK 74078*
[b] *Division of Molecular Biology and Biochemistry, University of Missouri-Kansas City, Kansas City, MO 64108*

ARTICLE INFO

Article history:
Received 5 January 2023
Revised 22 February 2023
Accepted 25 February 2023

Keywords:
Intestinal immunity
Meta-omics
Microbiome homeostasis
Microbiome-host interaction
Precision microbiome

ABSTRACT

The composition and function of microbes harbored in the human gastrointestinal lumen have been underestimated for centuries because of the underdevelopment of nucleotide sequencing techniques and the lack of humanized gnotobiotic models. Now, we appreciate that the gut microbiome is an integral part of the human body and exerts considerable roles in host health and diseases. Dietary factors can induce changes in the microbial community composition, metabolism, and function, thereby altering the host immune response, and consequently, may influence disease risks. An imbalance of gut microbiome homeostasis (i.e., dysbiosis) has been linked to several chronic diseases, such as inflammatory bowel diseases, obesity, and diabetes. Remarkable progress has recently been made in better understanding the extent to which the influence of the diet–microbiota interaction on host health outcomes in both animal models and human participants. However, the exact causality of the gut microbiome on the development of diseases is still controversial. In this review, we will briefly describe the general structure and function of the intestine and the process of nutrient absorption in humans. This is followed by a summarization of the recent updates on interactions between gut microbiota and individual micronutrients, including carotenoids, vitamin A, vitamin D, vitamin C, folate, iron, and zinc. In the opinion of the authors, these nutrients were identified as representative of vitamins and minerals with sufficient research on their roles in the microbiome. The host responses to the gut microbiome will also be discussed. Future direction in microbiome research, for example, precision microbiome, will be proposed.

Abbreviations: BCO1, β-carotene oxygenase 1; DHA, dehydroascorbic acid; GI, gastrointestinal; GMT, gut microbiome transplantation; IBS, irritable bowel syndrome; MT, metallothionein; RA, retinoic acid; RAL, retinal; ROL, retinol; SCFA, short-chain fatty acid; SFB, segmented filamentous bacteria; SNP, single nucleotide polymorphism; VDR, vitamin D receptor; ZIP, zinc transporter; ZnT, Zn transporter.

* Corresponding author at: Department of Nutritional Sciences, Oklahoma State University, Stillwater, OK 74078, USA. Tel.: 1-405-744-5215; Fax: 1-405-744-1357.
E-mail address: dingbo.lin@okstate.edu (D. Lin).

https://doi.org/10.1016/j.nutres.2023.02.007
0271-5317/

1. Introduction

The function of the large intestine is first and foremost its importance for water and electrolyte absorption and as a storage container for fecal material. In comparison, the small intestine has a villa to enhance nutrition absorption because of increased surface area. Although the large intestine does not have a villa, it appears that the large intestine has the crypts of Lieberkuhn, where copious levels of mucus are produced [1].

Although the large intestine is more limited with digestion and absorption, the number of reactions in the large intestine should not be minimized. The large intestine contains a few hundred of most species of microorganisms in human bodies [2]. The oral cavity has approximately 700 species of bacteria that can promote health [3]. The microbiome is considered an organ and is the largest one in humans. Alteration of microbiome homeostasis is critical for human health. The risk of colon cancer, irritable bowel syndrome (IBS), high blood cholesterol, and weight control are some examples of the benefits of many microorganisms constituting the microbiome.

Prebiotics are much different that probiotics [4,5]. These are food compounds that promote the growth of beneficial bacteria. Nondigestible carbohydrates will cause the growth of the beneficial (*Lactobacillus*) microorganisms and decrease deleterious bacteria in the gut such as *Escherichia*. Resistant starches such as oligofructose are prebiotics beneficial to the large intestine. Short-chain fatty acids (SCFAs) through dietary fiber fermentation in the large intestine promote an environment beneficial for bacterial growth [6].

The gut microbiome is an integral part of the human body and exerts considerable roles in host health and diseases. The gut microbiome homeostasis can be altered by multiple factors, including but not limited to genetic mutations, unhealthy diets, lifestyle, and stress. An imbalance of gut microbiome homeostasis (i.e.) dysbiosis, has been linked to several chronic diseases. This dysbiosis can also be potentially reversed, to some extent, by the alteration of diets and other factors, thereby promoting human health (Fig. 1). This paper focuses on the newer science of the microbiome in response to micronutrients. Here, we selected specific vitamins and minerals that influence the microbiome and vice versa, some of which have been given minimal attention. Specifically, we reviewed significant papers on the roles of microbiome–micronutrient communications starting with antioxidant vitamin C, followed by folate. Fat-soluble vitamin D, vitamin A, carotenoids, and the trace elements iron and zinc will also be reviewed. There is limited information on the roles of some other micronutrients and the microbiome. Table 1 lists these micronutrients' functions for host health but not the microbiome because not much information is available on nutrient metabolism in the gut microbiome. Finally, we discussed the potential limitations of current studies in elucidating the function of the microbiome and the emerging strategy for the precision microbiome.

2. Small intestine in nutrient digestion and absorption

Before discussing the microbiome, key biochemical reactions in the upper gastrointestinal (GI) tract are helpful. Enterocytes not only provide the entry site for nutrient absorption, but also are an integral part of nutrient digestion. Several carbohydrate-digesting enzymes, including disaccharidases (e.g., lactase, maltase, sucrase) and α-1-6 dextrinase, as well as enterokinase, are associated with the brush border membrane of the enterocyte [6]. Proteases specific for short-chain peptides are located within enterocytes and play a significant role in finalizing protein digestion.

Several transport proteins are located on the luminal surface and the basolateral surface of enterocyte which facilitates absorption [6]. For example, lipid-soluble substances, such as lipid-soluble vitamins, are primarily incorporated into chylomicrons and lipoproteins within enterocytes, which then enter the lacteal in the central region of the villi. The small intestine absorbs the bulk of the nutrients, whereas some absorption also occurs in the stomach and colon.

3. Large intestine

A further review of what occurs in the large intestine is a major key in understanding the effects on our health. The large intestine is inhabited by more than 400 different species of bacteria [7]. Some bacteria produce nutrients that can be absorbed, including vitamins K, D, and biotin, and nonnutrients such as SCFAs (such as acetic, propionic, and butyric acids). Feces are composed of approximately 30% bacteria, 10% to 20% fat, 10% to 20% inorganic matter, 2% to 3% protein, and 30% undigested fibers and dried components of digestive juices, such as bilirubin and its metabolites [8]. The coloring of feces is primarily attributable to the presence of stercobilin and urobilin, which are metabolites of bilirubin. The pH of feces is slightly acidic (pH = 6.6) [8]. The odorous characteristics of feces are due to the presence of bacterial by-products, such as indoles, skatole, mercaptans, and hydrogen sulfide, and are highly individualized based on diet and colonic bacterial profile. Fermentation is a process by which carbohydrates and proteins are digested and used for energy in this anaerobic metabolism. Vitamin K and biotin are synthesized by colonic bacteria [6]. SCFAs, such as acetate, propionate, and butyrate, have several functions. Butyrate synthesis may help to maintain the integrity of the colonic cells [6].

The colonic cell epithelium is covered by a mucus layer composed of mucins secreted by goblet cells and contains 2 layers: (1) the outer mucus layer, which is loose and thick, with diverse intestinal bacteria; and (2) the inner mucus layer that is dense and thin, almost without any bacteria [9], though commensal segmented filamentous bacteria attach to the ileal epithelium (see vitamin A section) The mucosal layer acts as a barrier to physically protect the epithelial cells that line the gut to protect it from pathogenic microbes. The mucus layer viability depends on genetic and environmental factors. The gut microbiota may change the mucus layer directly or

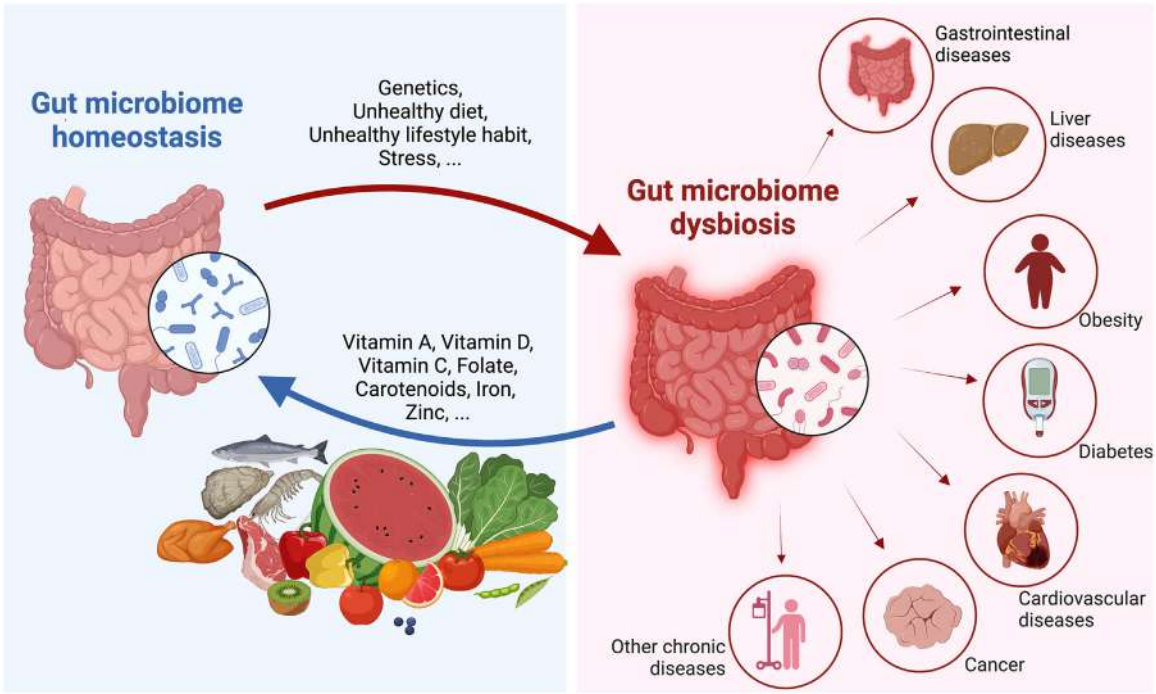

Fig. 1 – Gut microbiome homeostasis determines health and/or diseases. An alteration of gut microbiome homeostasis caused by changes in genetics, nutrition status, lifestyle, and other factors can lead to microbiome dysbiosis, which in turn results in chronic diseases. Increased intake of micronutrients and other food-bioactive compounds can reshape the gut microbiome, and thus can be beneficial for the prevention of chronic diseases. The figure was produced using Biorender software.

indirectly. Once there is a disruption between the mucus layer and microbiota, pathogenic microbes can attach and encroach upon the mucus layer, leading to GI disease.

4. Overview of the intestinal microbiome

Over the past few decades, there has been significant growth of interest, research, and understanding related to the intestinal microbiome, especially as it relates to nutrition-related health aspects. Although the microbiome is often associated with the bacteria in the lower part of the digestive tract, the term broadly refers to the total genetic material of all the microbes, including bacteria, fungi, protozoa, and viruses, which are located on and inside the human body. According to the National Institutes of Health's National Human Genome Research Institute, the number of human genes approximates 30,000. Although estimates vary, collectively the number of genes of the microbiome may outnumber humans 10-fold and the total mass of the microbiome may approximate 5 lb in an adult male [10].

The term microbiota refers to the community of microorganisms themselves. Most of the attention is focused on the digestive tract, with emphasis on the large intestine. Although a newborn's digestive tract is sterile at birth, it becomes populated with microorganisms quickly. The bacteria coat the mucus lining of the GI tract and estimate the bacterial density in the distal portions of the gut (i.e., colon). This bacterial density reaches around $\sim 10^{11}$ to 10^{12} colony-forming units per gram of luminal content. Studies have revealed more than 1000 different types of bacteria in humans and those in the digestive tract [11].

The stomach and small intestine have relatively few microbes as colonization is largely limited by the acidic environment in the stomach and the presence of bile, digestive enzymes, and mechanical activities of peristalsis [10]. The large intestine is home to hundreds of species of bacteria (300–1000). The greater majority is limited to just a few dozen of those species. The main types of bacteria in the colon are obligate anaerobes. The most abundant bacteria are members of the genus *Bacteroides*, anaerobic gram-positive cocci, such as *Peptostreptococcus* sp., *Eubacterium* sp., *Lactobacillus* sp., and *Clostridium* sp. [12].

The large intestine produces a biofilm composed of mucus. This mucus is dynamic and has endogenous bacteria interacting with it. The mucus is a source of carbohydrates, and several bacterial species can use mucus glycan as a carbon source. Glycan alteration and availability may modify the composition of the microbiota. The mucus layer also is a major component of innate immunity [13].

Intestinal bacteria have an important role in maintaining immune and metabolic homeostasis. There appears to be a connection between the type of bacterial population as a function of inflammatory bowel disease, aging, obesity, and smoking [14]. Collectively, the microbiota is shaped by genetics, environment, diet, and lifestyle factors [10].

The role of nutrients in the microbiome has been studied to a limited extent. We present the impact of vitamin C, folate,

Table 1 – The function of select vitamins and minerals in humans

Nutrient	Functions
Vitamin D	1) Exerts effect of binding to DNA via vitamin D receptor 2) Calcium and phosphorus homeostasis 3) Cell differentiation 4) Regulation 5) Diseases Renal disease, cancer, autoimmune and inflammation, cardiovascular, sarcopenia, type 2 diabetes, gestational diabetes
Vitamin A	1) Vision 2) Cell differentiation 3) Cancer 4) Glycoproteins 5) Reproduction 6) Antioxidant functions
Carotenoid	1) Antioxidant 2) Gene expression regulation
Folate	1) Amino acid metabolism, methyl-folate trap, single-carbon metabolism
Vitamin C	1) Antioxidant
Iron	1) Iron homeostasis 2) Hemoglobin 3) Iron storage proteins 4) Transferrin 5) Iron-responsive element binding protein 6) Enzyme activity
Zinc	1) Zinc-containing proteins a) Zinc finger proteins, metal transcription factor-1, metallothionein b) Zinc transporters a. Influx into the enterocyte (e.g., ZIP-4) b. Efflux out of the enterocyte and intracellular transport

Abbreviation: ZIP, zinc transporter.

carotenoids, vitamin A, vitamin D, zinc, and iron. These nutrients were chosen by the authors with major criteria that there is some evidence of their roles in the microbiome.

5. Vitamin C and other redox-active food compounds on the gut microbiome

Vitamin C (also known as ascorbic acid or ascorbate) is an essential nutrient for human health. Humans are 1 of the mammals that are not able to de novo synthesize vitamin C because of the lack of gulonolactone oxidase, the key enzyme in its synthesis pathway [15]. Food sources of vitamin C primarily include fruits and vegetables, such as cauliflower and kiwifruits. In foods, most vitamin C is found in a reduced form (e.g., ascorbate), although small amounts of the oxidized form called dehydroascorbic acid (DHA) are also present. DHA conversion to ascorbate relies on DHA reductase with hydrogens provided by glutathione [7].

Vitamin C exhibits antioxidant and anti-inflammatory properties. Excess intake of vitamin C (supplementation) may lead to some health concerns, for example, an increased risk for kidney stones [16]. A severe deficiency of vitamin C causes scurvy, which is no longer common. However, mild to moderate deficiencies of vitamin C are found in up to 30% of American populations [17]. Epidemiological and clinical studies indicate that the decreased intake of vitamin C and/or lowered plasma vitamin C levels are linked to the development of chronic diseases, such as obesity, diabetes, and cancer [18,19]. Classically, low vitamin C results in an imbalance of redox cascades and oxidative stress, which has commonly been blamed as a stimulating factor in triggering the etiology of chronic diseases in humans. Most recent work also reveals that vitamin C deficiency-altered gut microbiome composition and function are linked to the progression of these chronic diseases [20,21].

Vitamin C and/or foods containing high redox-active compounds (including vitamin B_2, vitamin C, vitamin E, polyphenols, carotenoids, and other phytochemicals) are beneficial for increased diversity and function of the gut microbiome in healthy individuals and/or centenarians [17,20–25]. The abundance of *Bifidobacterium* and *Akkermansia* is relatively enriched, and the production of fecal SCFAs is enhanced in these populations who typically have high vitamin C levels [20–25].

Increased intake of vitamin C and other redox-active compounds are also positively associated with the alteration of the gut microbiome and the promotion of health conditions in diseased animal models and human subjects. The intake of vitamin C and vitamin E negatively correlates with *Bacteroides* in adults with cystic fibrosis [26]. Consumption of nopal, a vegetable rich in vitamin C, polyphenols, and other antioxidants, increased the richness of intestinal *Bacteroides fragilis*, reduced hepatic steatosis, and attenuated oxidative stress in adipose and brain tissues in rats fed a high-fat diet [27]. Kiwifruits are a good source of vitamin C. A clinical feeding study demonstrated that kiwifruit supplementation for 12 weeks elevated plasma vitamin C levels, reduced insulin resistance, and improved blood glucose control in prediabetic participants, accompanied by an increase in the relative abundance of *Coriobacteriaceae* [28]. Feeding of 2-O-β-d-glucopyranosyl-ascorbic acid, a vitamin C derivative isolated from goji berry fruits (*Lycium barbarum*), altered gut microbiota composition and improved disease conditions in mouse models of dextran sodium sulfate–induced colitis mice and cyclophosphamide-treated immunosuppression [29–31]. Vitamin C supplementation could also improve cardiovascular and hypertension conditions in rats [32–34].

Mechanistically, Pierre et al. demonstrated by using gut microbiome transplantation (GMT) to germ-free interleukin-10 knockout mice that vitamin C–rich redox active compounds' diets reshaped the gut microbial composition and function to mitigate intestinal inflammation. This might at least be partially through enhanced T cell–mediated adaptive immunity [35]. A GMT study also confirms the antiobesity property of *camu camu*, an Amazonian fruit rich in redox active compounds, was due to an alteration of the gut microbiome community [36]. In both of these GMT studies, the particular taxa involved had not been identified. Of note, these microbiome studies using these whole foods, containing high vitamin C and other bioactive compounds (such as fibers and other phytochemicals), may not conclude that vitamin C is the sole contributor to the alteration of the gut microbiome and phenotypes observed.

6. Gut microbiome–derived folate does not meet human needs

Folate is an essential water-soluble nutrient and exerts global physiological roles in cell survival and death. In coordination with riboflavin, pyridoxal phosphate, and cobalamin, folate is vital to amino acid metabolism and the 1-carbon cycle in the synthesis of intermediate metabolites to produce nucleotides, red blood cells, and methyl groups for subsequent methylation in DNA, RNA, and/or protein molecules [7]. Deficiency of folate results in numerous health conditions, including but not limited to neural tube defects, macrocytic anemia, hyperhomocysteinemia, homocystinuria, and stroke [37–39].

Humans are unable to make folate by themselves and meet their needs largely by dietary intake [7]. Larger doses of folate may be required for patients with single nucleotide polymorphisms (SNPs) in 5-methyl tetrahydrofolate reductase and other folate-related metabolic genes. SNPs inactivate 5-methyl tetrahydrofolate reductase, thereby suppressing 5-methyl-tetrahydrofolate production [40].

Dietary folates impact the composition and function of the gut microbiome. High plasma levels of folate and cobalamin levels are positively correlated with the enhanced richness of some commensal bacteria, such as *Bifidobacteria, Akkermansia*, and *Faecalibacterium*, which are also accompanied by a decrease in plasma homocysteine levels [41,42]. On the other hand, deficiencies of folate and cobalamin alter the richness of *Bacteroidia* and *Clostridia* in amyloid-β–infused rats with Alzheimer's disease–like dementia [43]. Furthermore, maternal folate deficiency can also impact infant gut microbiome composition [44], which in the long term, may suppress the development of the immunity system in infants [44–47]. A caution on these findings is that many are correlation studies that do not reflect cause and effect.

Gut microbiota can produce certain amounts of folate, cobalamin, riboflavin, and pyridoxal phosphate, which do not meet human needs [48]. The gut microbe *Lactobacillus reuteri* has diverse functions in modulating human cytokine production and synthesis of folate and cobalamin [42]. Roth et al. reported that *L reuteri 6475* produces 2-carbon-transporting folate in the form of 5,10-ethenyl-tetrahydrofolate polyglutamate [49]. *Bifidobacterium* is another bacterial genus that has been extensively confirmed to produce folate and other vitamins [50]. Microbiome-derived folates are primarily absorbed in the colon, whereas dietary folates are largely absorbed in the small intestine [51].

The mechanism of action of microbiota-generated folates is not well established. A vast majority of experimental findings are interpreted through the foundation of folate metabolism and function in mammalian cells [51]. Future studies are needed to precisely distinguish gut microbe–produced folates from dietary folates and to validate whether gut microbiota–synthesized folate is essential only for the function of local/intestinal tissues.

7. Carotenoids' interaction with the microbiome

Carotenoids are fat-soluble pigments often found in colorful foods, such as fruits, vegetables, egg yolks, and some seafood. They are 40-C organic molecules with or without ionone rings. There are only about a dozen carotenoids identified in the human plasma, although more than 700 carotenoids have been found in nature. Some carotenoids, named pro-vitamin A carotenoids, can be catabolized into retinal (RAL) by β -carotene oxygenase 1 (BCO1) symmetric cleavage at the 15, 15′ site, such as β-carotene, α-carotene, and β-cryptoxanthin [52–54]. There is a subgroup of oxygenized carotenoids, called xanthophylls, such as lutein and zeaxanthin. Lutein and zeaxanthin are widely distributed throughout human bodies and are highly accumulated in the human macula [53]. β-carotene oxygenase 2, asymmetrically cleaves at the 9′ and 10′ sites and is the sole xanthophyll cleavage enzyme found in the inner membranes of mammalian mitochondria [53,54]. Low plasma carotenoid levels are found in patients with chronic diseases, such as obesity, type 2 diabetes, cancer, osteoporosis, and macular degeneration [55–57].

In terms of carotenoid metabolism, experimental data largely collected from animal and/or cell culture studies suggest that dietary carotenoid metabolism is insufficient; only 10-20% of the amount ingested is absorbed in the human small intestine. Most dietary xanthophylls reach the large intestine. In vitro studies suggest that xanthophylls are not well recovered in the colonic fraction either (only 10-50%) [55]. Thus, carotenoids could be "fermented" in the gut by an unclear mechanism, possibly by members of the gut microbiota.

Our understanding of the carotenoid–gut microbiome interaction is still at an early stage. There is no solid and mechanistic evidence to elucidate how carotenoids exactly alter gut microbiome composition and function [58]. Previous work from our group and others in animal models and human participants suggest that carotenoids, primarily β-carotene, astaxanthin, and zeaxanthin, enhance large intestinal tight junction protein expression, reduce proinflammatory cytokine, and alter the gut microbiota in a pattern suggesting their anti-inflammatory properties [59–65]. For example, we reported that astaxanthin intake is associated with the increased abundance of *Actinobacteria, Bifidobacterium*, and *Akkermansia muciniphila* in mice, suggesting that these microbes have a potential property to reduce inflammation [65].

Carotenoid biosynthesis by gut microbiota is underexplored. According to the gene prediction of the human microbiome sequence, carotenoids could be possibly produced by gut microbes in the human gut. Early work indicated that bacteria (sometimes referred to as carotenogenic bacteria), can synthesize carotenoids, such as *Firmicutes* to *Bacteroidetes, Actinobacteria, Proteobacteria,* and *Verrucomicrobiota* [66–69]. However, there are only carotenoid precursors, 4, 4′-diaponeurosporenes (with a 30 carbon basic structure), but not typical C40 carotenoids synthesized in some lactic acid bacteria (Fig. 2) [66,67,70–72]. Altogether, carotenoids are vital for human health. From an evolutionary perspective, the expression of carotenoid precursor genes and the synthesis of carotenoids (or carotenoid precursors) could be beneficial for gut microbiota survival and stress responses, although future research is warranted to fully discover the interplay of carotenoids with gut microbiome in health and diseases.

8. Vitamin A: more than meets the eye

Vitamin A is a fat-soluble and essential nutrient for human beings. There are 2 forms of vitamin A in the diet: preformed vitamin A (retinol and retinyl esters) and provitamin A carotenoids that can be converted to vitamin A by BCO1 catabolism [7,54]. Retinol (ROL) is a predominant form of the vitamin binding to retinol-binding proteins, such as RBP4 in circulation [73]. Intercellular metabolism of ROL is possibly through key enzymes, for example, ROL dehydrogenase and RAL dehydrogenase in the production of RAL and retinoic acid (RA), respectively [7]. In terms of genetic contributions to human vitamin A status, SNPs are the most common genetic variations that have been most well-studied in humans [74]. To date, there are at least rs1501299, rs6564851, rs12934922, and rs11646692 SNPs identified in the human BCO1 gene. Individuals, particularly vegetarians and vegans who rely highly on plant-derived provitamin A carotenoids as their vitamin A sources, are at higher risk for vitamin A deficiency when they carry BCO1 SNPs, as these mutations suppress BCO1 enzymatic activities in the conversion of provitamin A carotenoids to RAL [75,76].

Vitamin A metabolites exert distinct functions in human health and immunity. A deficiency of vitamin A alters the gut microbiome composition. A great number of publications show that changes in vitamin A–associated gut microbiome richness differ by sex/gender, age, lifestyle, eating behavior, and overall health conditions [48]. The role of vitamin A deficiency in the interplay between immunity and gut microbiome in humans is limiting. Infants up to 2 years of age were studied to research a combination of these variables [77]. Vitamin A supplementation affected the abundance of fecal *Bifidobacterium*, a beneficial commensal, or *Proteobacteria*, a phylum containing enteric pathogens. Boys had an increase in *Bifidobacterium* with vitamin A supplementation and girls did not have any change. The authors concluded that vitamin A did improve the health of the infants through this observation, but additional studies on humans are needed. The results appeared to be marginal because only 1 sex was impacted [77]. Studies with adults may be preferred in the future to further elucidate how vitamin A plays a role at the interface of host-commensal-pathogen interactions.

Most recent studies in animal models reveal that the irreversible conversion of ROL to RA in the small intestine by gut microbiota is vital to the host mucosal immunity and infection (Fig. 2) [78–84]. RA is a key player in the maturation and activation of type 3 innate lymphoid cells [78]. Promising findings confirmed that, at least in rodent models, commensal microbiota is essential to convert dietary ROL to RA in mucus layers and subsequent regulation of mucosal immunity. Sano et al. presented that segmented filamentous bacteria (SFBs) directly contact the mucosal cells in the ileum and induce serum amyloid A proteins, leading to the promotion of local effector Th17 responses [79]. Bang et al. further discovered that serum amyloid A proteins deliver ROL to myeloid cells in the lamina propria through low-density lipoprotein receptor-related protein 1, where ROL is catabolized to RA and thereby activates $CD4^+$ T cells and B cells, resulting in the promotion of adaptive immunity [80,81]. Further, other commensal bacteria, such as *Lactobacillus* spp, *Bacillus cereus, Faecalibaculum rodentium,* and *Bifidobacterium bifidum* can convert dietary retinol to RA in the mucus layer by microbial aldehyde dehydrogenase [82–84]. Then RA can be absorbed into the enterocytes and interacts with the RA receptor, thereby regulating gene expression related to adaptive immunity against enteric infection in mice [82–84].

Collectively, commensal bacteria and SFBs in the small intestine can promote the host's local mucosal immunity through control of dietary vitamin A metabolism (e.g., conversion of ROL to RAL and/or RA) (Fig. 2). On the other hand, there is no evidence to support that gut microbiota can synthesize retinol de novo thus far. However, microbiome homeostasis can be bidirectionally regulated by vitamin A metabolism in mammals.

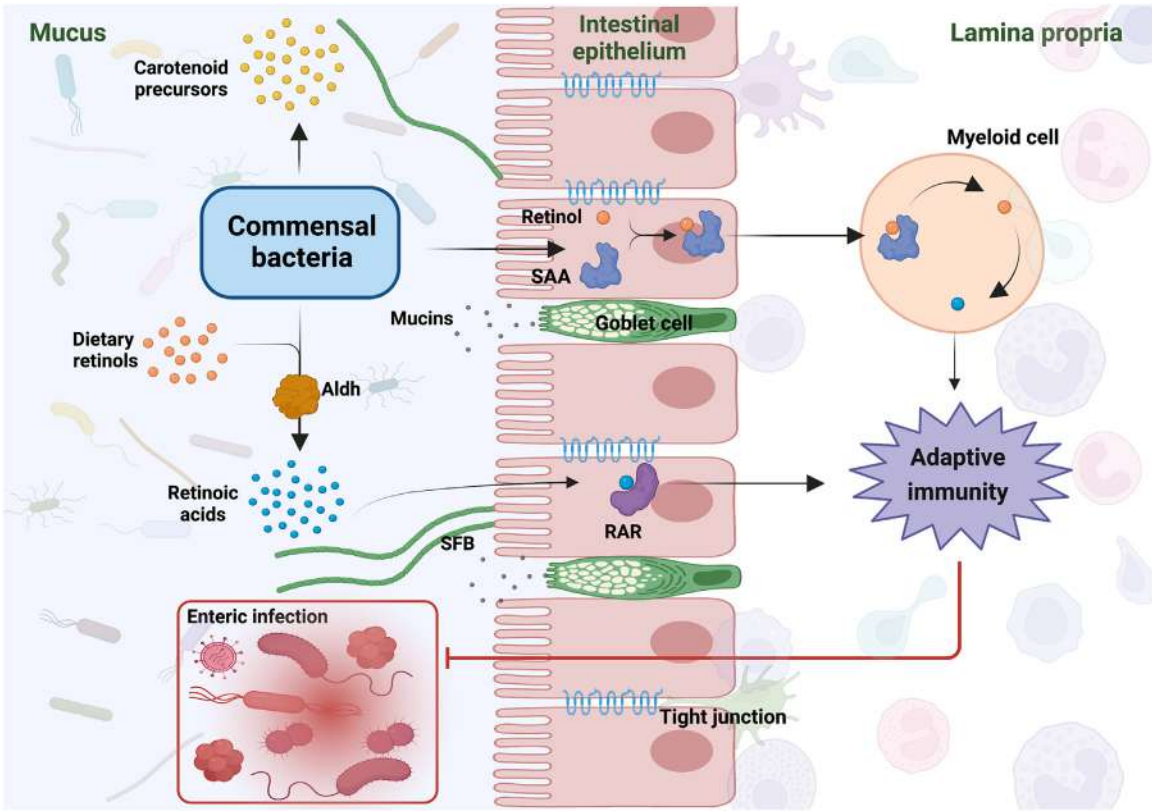

Fig. 2 – The complexity of the intestinal metabolism of carotenoids and vitamin A in mammals. Some commensal bacteria are capable to synthesize carotenoid precursors (a form of 30 carbon [C30] carotenoids) in the lumen of the human gut, though the fate of these newly synthesized carotenoid precursors is unknown. Commensal bacteria and/or segmented filamentous bacteria (SFBs) can convert dietary vitamin A into retinoid acid (RA) in the mucus layer; SFBs also can upregulate serum amyloid A proteins (SAAs), a retinol-binding protein in the intestinal cells, to deliver retinol (ROL) to myeloid cells for further conversion to RA, thereby altering intestinal adaptive immunity against enteric infection in mice. Goblet cells secret mucin proteins into the lumen in the formation of mucus. The figure was produced using Biorender software.

9. Vitamin D: a hormone communicating with the microbiome

Vitamin D is 1 of the most important vitamins because it also has a role as a hormone, thus allowing a greater number of reactions it is responsible for. This vitamin is found in bacteria, fungi, protozoans, and viruses [7]. A lack of vitamin D can lead to inflammatory diseases, such as IBS, Crohn disease, and ulcerative colitis. These diseases interact with genes, environment, and gut microflora [85,86]. Dietary supplementation of vitamin D is associated with the mitigation of IBS [87]. This vitamin requires a nuclear receptor as a partner and, specifically, the gut epithelium is restored to normal in the host by the vitamin D/nuclear receptor complex. This suggests the complex may inhibit inflammation in IBS [88,89]. The microbiome has these receptors that influence xenobiotic metabolism, fat storage, and renewal of GI epithelial cells [88,89].

It appears that the roles of vitamin D influence the immune system as an immune mediator [89]. Vitamin D deficiency is more common in patients with IBS compared with healthy populations. The active form of vitamin D (1,25-$(OH)_2$-vitamin D_3) regulates the GI microbiome and promotes anti-inflammatory and tolerogenic immune responses [89]. Innate immunity as a result of vitamin D_3 induces antimicrobial compounds by promoting T cells and cytokines in the host [90].

An unanswered question is "How does deletion of vitamin D affect the microbiota metabolites?" [89,91]. Mice with tissue-specific vitamin D receptor (VDR) deletions that are tissue-specific in intestinal epithelial cells and myeloid cells were used to answer this question [92]. Microbiota metabolites from the host carbohydrates, proteins, lipids, and bile acids were changed in mice with the deletion of VDR [91]. Deletion of VDR affected 84 of more than 700 biochemicals because VDR status compared with 530 changes resulting from a high-fat diet [91].

Multiple sclerosis is a neuroinflammatory disease. The progression of this disease can be modulated by the gut microbiota, diet, and vitamins A and D [93]. The mechanisms of how the microbiome impacts vitamin D metabolism and multiple sclerosis are mixed. Microbiota-derived metabolites can also regulate VDR gene expression in the host, thus indirectly impacting vitamin D metabolism and function [93]. A high saturated-fat diet induces gut microbiome compositional shifts and functional changes, and subsequential intestinal inflammation, thereby altering the blood–brain barrier and resulting in neuroinflammation [94].

A vitamin D deficiency may lead to increased colorectal cancer risk. A case-control study of human fecal microbiota with vitamin D supplementation was conducted. The data were adjusted for vitamin D and other risk factors and revealed that the microbiome with an increased *Bifidobacteria/Escherichia* ratio is thought to decrease colorectal cancer risk [95].

Tabatabaeizadeh et al. reported compositional changes in the microbiome of adolescent girls given vitamin D supplements, *Bacteroidetes* and *Lactobacillus* decreased with vitamin D supplementation, whereas *Firmicutes* and *Bifidobacterium* increased [96]. This demonstrates the impact that a high vitamin D intake can change the composition of the gut microbiome in humans. Future studies are needed for a better understanding of the mechanisms and the benefits achieved by which vitamin D affects the gut microbiome [96].

10. Zinc: an essential nutrient for the gut microbiome and the host immunity

Zinc is a trace element and exerts many functions in host cells and the gut microbiome (Fig. 3). In the host GI tract, dietary zinc is liberated to the free form from dietary protein before absorption in the enterocyte and gut microbes. At physiologic levels of intestinal zinc, the predominant mechanism of absorption appears to be transporter-mediated via divalent metal transporter 1, zinc transporter 4 (ZIP4), and ZIP14 [97–103]. Zinc also diffuses through the intestinal mucosa into the lamina propria by paracellular diffusion [7]. Absorbed zinc is exported out of the enterocyte by Zn transporter 1 (ZnT1) [98–101]. ZnT7 and ZIP7 are carriers in the intracellular transport of zinc. Metallothionein (MT) is a zinc-binding protein to store zinc as an intracellular buffering pool in the mucosa and other types of cells (Fig. 3). Zinc supplementation in humans can decrease inflammation of the GI tract. This observation may lead to an increase in MT levels, followed by a decrease in inflammation [99,104–106]. On the other hand, low MT expression is present in inflammatory bowel disease patients [106] and intestinal colitis rodents [107].

Zinc is an essential trace nutrient for gut microbiota as well, though the information on the metabolic mechanism is still limited. Therefore, as shown in Table 2, a list of several zinc-dependent enzymes and their functions in mammalian cells would be beneficial for understanding zinc metabolism in gut microbiota. Presumably, there would be some similar or comparable metabolic features in these microbes, compared with mammals. Zinc homeostasis in gut microbes is maintained by zinc uptake via ZnuABC and ZupT transporters and zinc export by exporters ZntA and ZitB (Fig. 3) [104,105,108,109]. For some *Enterobacteriaceae* with limited zinc availability from the environment (as being sequestrated by calprotectin) and/or the deletion of zinc transporters, their colonization in the inflamed gut is enhanced via a zincophore-mediated zinc acquisition mechanism in zinc-limited media [110].

The studies demonstrated that zinc could affect gut microbiome composition and function [104]. Abnormal gut physiology and microbiota composition may result in an increase in inflammatory proteins during pregnancy [111]. On the other hand, microbiota composition, gut pathology, and cytokines can be rescued by an amino acid–conjugated zinc complex, suggesting that a zinc deficiency may contribute to abnormal gut–brain signaling by altered physiology and microbiota composition [112]. In school-age children, zinc deficiency is associated with the elevation of serum inflammatory cytokines, an increase in the Shannon index (an indicator of alpha diversity of microbial communities) of the fecal microbiome, and enhanced richness in fecal *Coprobacter, Acetivibrio, Paraprevotella*, and *Clostridium_XI* [113]. In contrast, increased zinc in the gut results in the alteration of gut microbiota that appears linked to inflammation and pancreatitis, autism spectrum disorder, attention deficit disorder, attention deficit hyperactivity disorder, and fetal alcohol syndrome [114].

It appears that there is a zinc competition among the microbiota population in the GI tract. Zinc uptake by a high-affinity ZnuABC transporter is required for *Campylobacter jejuni* survival and growth in chickens with a normal microbiota but not when chickens are raised with a limited microbiota [115]. Without the ZnuABC transporter, *C jejuni* is unable to replicate or colonize in the GI tract [115], implicating that limiting zinc levels in chicken could limit human infection caused by *C jejuni*.

In addition to the deleterious changes mentioned earlier in zinc deficiency, autism spectrum disorder appears limited to gut problems and altered microbiota. Mice made zinc deficient in the prenatal stage appear to have autism spectrum behavior [111]. Biological studies collectively exhibit altered gut physiology and proinflammatory signaling. Neuroinflammation and gut composition are similar to autism spectrum disorder in humans [111].

Excess diet zinc can decrease the level of antibiotics to confer susceptibility to *Clostridium difficile* [116]. The Zn-binding S100 protein calprotectin shows antimicrobial effects against *C difficile* through chelating zinc in the lumen, which leads to limited zinc availability for this pathogen colonization in the gut [116–118].

On *C difficile* invasion, the intestinal immune system is activated, and calprotectin is released from the activated immune cells, particularly neutrophils, and eventually translocated across the intestinal epithelial cells. Calprotectin is a calcium- and zinc-binding protein, that can be used as an indirect marker of intestinal inflammation. Calprotectin released from the gut can bind zinc and limit the availability of zinc for pathogen colonization in the gut (Fig. 3) [109,116].

Another zinc transporter, ZIP8, is used as a host defense mechanism as well. A defect in ZIP8 gene impairs the host's defense against pneumonia because it can facilitate bacterial effects [119]. Variants of myeloid-specific ZIP8 can decrease the uptake of zinc and lead to intestinal microbiome dysbiosis and an increase in susceptibility to *Streptococcus pneumoniae* infection in the lung tissues of mice. In summary, zinc is a cofactor essential for microbiota–host communication. Possible perturbations in zinc homeostasis may impact the host immunity in the host and microbiome communities (Fig. 3) [120].

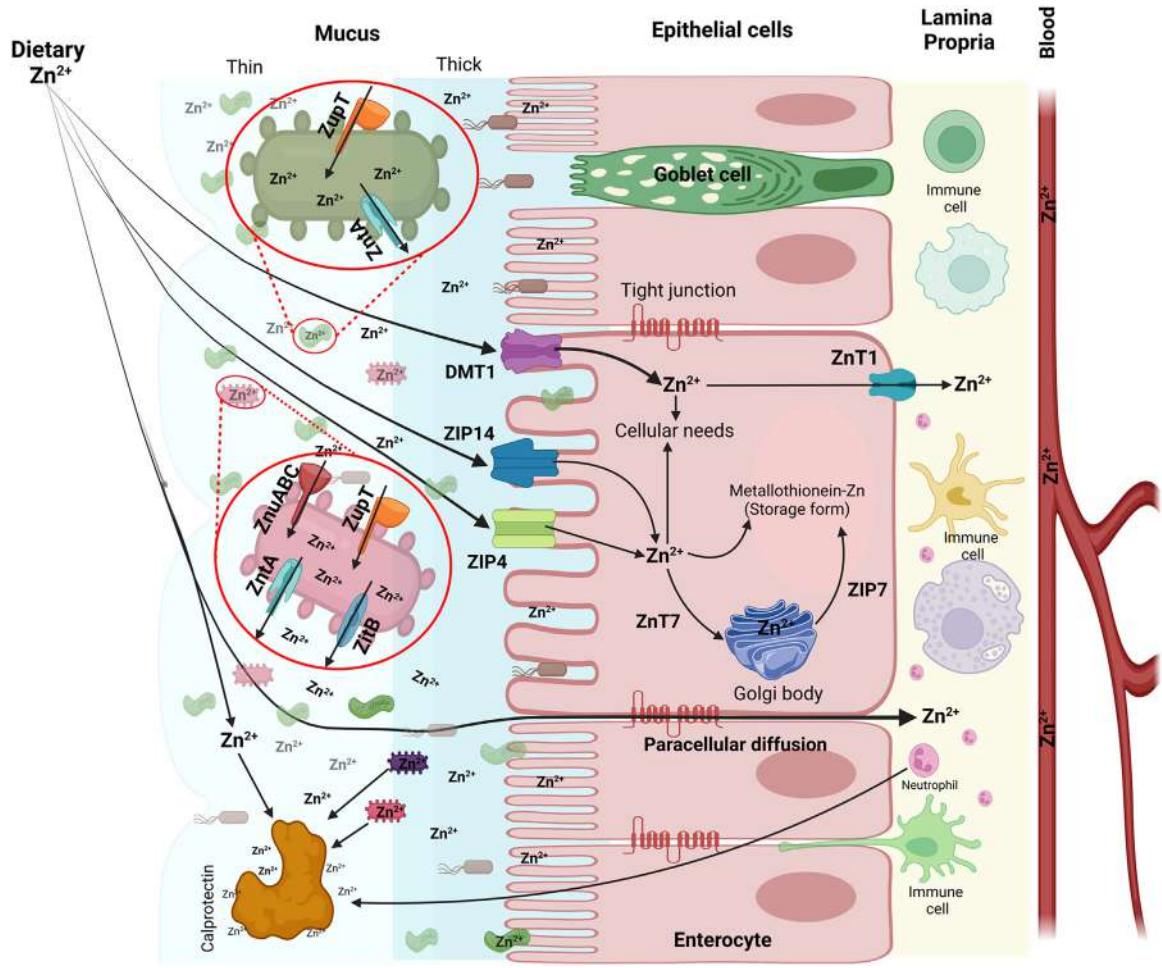

Fig. 3 – Zinc is an essential nutrient for gut microbiota and host cells. After digestion, zinc is absorbed through divalent metal transporter 1 (DMT1) and zinc transporters 4 and 14 (ZIP4 and ZIP14). Zinc also diffuses through the intestinal mucosa into the lamina propria by paracellular diffusion. Zinc is exported out of the enterocyte to the blood by the Zn transporter 1 (ZnT1) and picked up by blood proteins. ZnT7 and ZIP7 are carriers in the intracellular transport of zinc. Metallothionein (MT) is a zinc-binding protein to store zinc. Zinc homeostasis in gut microbes is maintained by zinc uptake via ZnuABC and ZupT transporters and export by exporters ZntA and ZitB. On pathogen infection, the intestinal immune system is activated and calprotectin is released from the activated immune cells, particularly neutrophils, and translocated across the intestinal epithelial cells into the lumen. Calprotectin, a calcium- and zinc-binding immune protein, can bind zinc and limit the availability of zinc for pathogens' colonization in the gut. The figure was produced using Biorender software. ZIP, zinc transporter.

Table 2 – Zinc-dependent enzymes and function in humans

Enzyme	Overall functions
Alkaline phosphatase	Mineralization of bone matrix
Alcohol dehydrogenase	Oxidation of ethanol in the cytosol, primarily in hepatocyte
Angiotensin-converting enzyme	Angiotensin I to II conversion
Aspartate transcarbamylase	Pyrimidine synthesis
Carbonic acid anhydrase	Interconverts CO_2 and H_2O to carbonic acid
Carboxypeptidases A and B	Protein digestion
DNA and RNA polymerases	DNA replication and transcription
Elastase	Connective tissue elastin digestion
Fructose 1, 6-biphosphatatase	Gluconeogenesis (synthesis of carbohydrates from noncarbohydrate sources)
Gustin	Taste acuity
Phosphodiesterase	Cleaves phosphodiester bonds (i.e., nucleic acid)
Lactase dehydrogenase	Reversible oxidation/reduction interconversion of pyruvate and lactic acid
Leukotriene hydrolase	Eicosanoid metabolism
Pyruvate dehydrogenase	Pyruvate to acetyl coenzyme A conversion within the mitochondria
Reverse transcriptase	DNA replication
Superoxide dismutase	Cytosolic antioxidant

11. Iron and the microbiome

Iron is one of the most important trace elements worldwide as insufficient levels of dietary iron are often reported in both industrialized and nonindustrialized nations [121]. There are varying degrees of clinical markers of iron stores. Hemoglobin levels are a crude level of iron status because this marker does not decrease until other stores are depleted. Hematocrit (a percent of the blood composed of red blood cells) is also a crude method. A protein that binds iron and is a sensitive marker of iron status is ferritin [7].

Iron supplements are often administered to correct anemia, especially in infants and children, and efforts to administer iron-fortified powders are often used. It is not uncommon to believe that iron supplements are healthy for young children and infants. Iron deficiency often results in IBS and Crohn disease [122,123]. Supplementation of ferrous sulfate enhanced the richness of *Bacteroides* spp in the microbiome of both healthy and IBS groups [124]. However, hepcidin, a hormone that regulates iron status, can influence iron metabolism, homeostasis, and inflammation. These changes in hepcidin influence inflammatory expression and inflammatory cytokines and can induce hepcidin expression, thereby altering iron homeostasis. Inflammatory bowel disease is greater with higher hepcidin in some studies [125,126]. It is unknown if there is a causal role of iron in IBS because the disease is considered multifactorial [127].

Experiments on infection with *Salmonella enterica* reveal that the iron-deficient group fared better than the iron-sufficient mice [128]. The weight of spleen size adjusted for body weight was greater in iron-sufficient mice. The iron deposition was linked to higher body weight and enteric infection. An increase in colonic iron may adversely affect the gut microbiome in that they decrease the beneficial barrier commensal gut bacteria (e.g., *Bifidobacteria, Lactobacilli*) and increase the abundance of enterobacteria including enteropathogenic *Escherichia coli* [129]. These changes are associated with increased gut inflammation [130,131]. Where enteric infection is common, a different strategy of iron supplementation needs greater research. Surprisingly, this is 1 of the few trace macrobiotics to have a negative outcome on the health of young people.

In addition to iron deficiency impacting the microbiota, the issues of hemochromatosis or excess iron storage can also shift the composition of the microbiota. Studies have been conducted on pigs given increased levels of iron from 50- to 800-mg/kg diets. The tissues accumulated the iron proportional to the increase in dietary iron. *Lactobacillus amylovorus* went down, whereas *Lactobacillus reuteri* increased with increased iron supplementation, thereby suggesting iron levels in the nearly toxic range can increase the composition of certain bacterial species [132].

Colorectal cancer is often linked to anemia and iron deficiency. Oral and intravenous iron often treat the deficiency. However, there is a negative issue in that excess iron can enhance colorectal carcinogenesis [131]. This may likely increase a microbiome shift to pathogenic bacteria from protective bacteria, which promotes inflammation and carcinogenesis.

As summarized earlier, iron deficiency is often corrected by supplementation, especially in young children and pregnant and lactating mothers, and in parts of the world where anemia is frequent. However, it would appear that iron supplementation can have harmful effects, especially in the gut. Public health measures need to be studied to have guidelines on when supplementation should be used and when consumption should be curtailed.

12. Limitations of current studies

Overall, the published research supports the statement that gut microbiome homeostasis is critical for human health. However, there are some concerns about the current microbiome work cited, for example, small sample sizes in some human clinical studies. For animal work, housing conditions (e.g., single or group housing, bedding condition) are commonly underdescribed. Housing is critical because it directly impacts research outcomes. Mice are coprophagic animals. Gut microbiota samples from the same cage of cohoused mice should be considered 1 sample. However, single housing is not a good choice for mice either because they are social animals. Small animal numbers per group and single-sex animals are also commonly found in many studies. Contamination of fecal microbiome samples is also a concern as well. Further, most published works are studies. The causality of the alteration of the microbiome homeostasis to clinical disease outcomes is yet to be established. Functionality studies are also limited. The function of metabolites derived from micronutrient-altered microbiota, such as SCFAs, secondary bile acids, and indole derivatives, needs more extensive investigation. Studies in GMT with a particular taxon but not populations of microbiota community could be expected as well. Taken together, microbiome research is still at an early stage. There is room for improvement in experimental design and data interpretation. Whether alteration of gut microbiome homeostasis can be considered a risk factor for chronic diseases warrants more mechanistic studies.

13. The concept of precision microbiome

Most members of human gut microbiota are oxygen sensitive, grow slowly, and require complex nutrients [133,134]. Isolation and characterization of strict anaerobes are especially challenging. Most current microbiome studies heavily rely on 16S rRNA and metagenomic sequencing to predict compositions and functions [135]. A deeper understanding of the microbiome features of the individuals but not the population could contribute to the future development of a well-defined strategy to meet an individual's need for gut microbiome homeostasis.

The precision microbiome is the concept newly developed to address the health needs from aspects of the microbiome in humans, by personalized multispecies microbiota supplementation, in combination with personalized nutrition. Ultimately, the microbiome homeostasis is achieved through depleting diseases-associated microbiome and enriching beneficial microbiome populations. For example, application of ben-

eficial *Bifidobacterium* and *Akkermansia* in combination with increased intake of nondigestible fibers would be expected to have a synergistic effect on the restoration of gut microbiome homeostasis and the digestive health. Therefore, precision microbiome research will be highly transformative and translational.

16s rRNA sequencing is the most cost-effective approach for research laboratories and clinical diagnosis in microbiome research. However, it also has significant limitations because of the power of sequencing and a bias of primers designed to amply the gene that is not 100% conserved across the microbiota community [136,137]. Large-scale metaomics approaches, such as metagenomics, metatranscriptomics, metaproteomics, and metabolomics, offer great analytical opportunities to understand how gut microbiome maintains its homeostasis and responds to the environment and host as a whole community and as individual strains [138–140]. Application of meta-omics will lead to the identification of microbiome species/strains, characterization of metabolic pathways and metabolites, and development of potential treatments for human diseases [138]. However, metaomics are complex and expensive and rely on other techniques such as statistical and computational assessments and network analyses [140]. Further, the functional analyses in the combination of an anaerobic culture of gut microbiota with microbiome transplant are still warranted to unlock the potential for developing and using isolated taxa and/or metabolites for applications in preventing chronic diseases.

14. Summary

Classically, digestion and absorption have mainly been thought of as the functions of the small intestine. The colon was relegated to fluid absorption and storage of undigested food (fecal matter). We now know that the colon is a major part of the microbiome organ system and plays a vital role in pathogenic and beneficial bacteria homeostasis. In summary, we can link health and disease with the microbiome. Examples of promotion of health with micronutrients, intestine, and microbiome include sufficient and balanced micronutrient availability, maintenance of the gut microbiome homeostasis, integrity of intestinal immunity, and precise regulation of the micronutrients–gut microbiome (the host).

The microbiome in the intestine varies greatly. The microbiome is dynamically shaped/reshaped by diets, environmental factors, and host health conditions. Therefore, this microbial heterogeneity across populations will make it possible for developing future strategies to precisely reengineer the gut microbiota community by the precision microbiome and precision nutrition, thereby promoting human health.

Author Contributions

Dingbo Lin and Denis M. Medeiros conducted the literature search and review and wrote the manuscript.

Sources of Support

Funded by USDA NIFA 2020-67017-30842, 2021-67018-34023, and 2022-67018-36235 (to D. L.).

Declaration of Competing Interest

None.

Acknowledgment

The authors are grateful for the artwork of the graphical abstract and Figs. 1–3 by Yashu Tang and Dr. M. D. Salahuddin at Oklahoma State University.

REFERENCES

[1] Kennedy GA, Strafuss AC. Scanning electron microscopy of the lesions of swine dysentery. Am J Vet Res. 1976;37:395–401 [No DOI available].
[2] Macfarlane GT, Macfarlane S. Human colonic microbiota: ecology, physiology and metabolic potential of intestinal bacteria. Scand J Gastroenterol Suppl. 1997;222:3–9. doi:10.1080/00365521.1997.11720708.
[3] Jenkinson HF. Beyond the oral microbiome. Environ Microbiol. 2011;13:3077–87. doi:10.1111/j.1462-2920.2011.02573.x.
[4] Snelling AM. Effects of probiotics on the gastrointestinal tract. Curr Opin Infect Dis. 2005;18:420–6. doi:10.1097/01.qco.0000182103.32504.e3.
[5] Roberfroid M, Gibson GR, Hoyles L, McCartney AL, Rastall R, Rowland I, et al. Prebiotic effects: metabolic and health benefits. Br J Nutr. 2010;104(suppl 2)):S1–63. doi:10.1017/S0007114510003363.
[6] O'Keefe SJ. Nutrition and colonic health: the critical role of the microbiota. Curr Opin Gastroenterol. 2008;24:51–8. doi:10.1097/MOG.0b013e3282f323f3.
[7] Medeiros DM, Wildman REC. Advanced Human Nutrition, ISBN. Burlington, MA: Jones and Bartlett Learning.; 2023.
[8] Walton C, Montoya MPB, Fowler DP, Turner C, Jia W, Whitehead RN, et al. Enteral feeding reduces metabolic activity of the intestinal microbiome in Crohn's disease: an observational study. Eur J Clin Nutr. 2016;70:-6. doi:10.1038/ejcn.2016.74.
[9] Zhang P. Influence of food and nutrition on the gut microbiome and implications for intestinal health. Int J Mol Sci. 2022;23:9588. http://doi.org/10.3390/ijms23179588.
[10] Cai R, Cheng C, Chen J, Xu X, Ding C, Gua B. Interactions of commensal and pathogenic microorganisms with the mucus layer in the colon. Gut Microbes. 2020;11:680–90. doi:10.1080/19490976.2020.173560.
[11] Rajilić-Stojanovic M, de Vos WM. The first 1000 cultured species of the human gastrointestinal microbiota. FEMS Microbial Rev. 2014;38:996–1047. doi:10.1111/1574/6976.12075.
[12] Aleksandrova K, Romero-Mosquera B, Hernandez V. Diet, gut microbiome and epigenetics: emerging links with inflammatory bowel diseases and prospects for management and prevention. Nutrients. 2017;30:962 doi: 10.3390.

[13] Sender Ron, Fuchs Shai, Milo Ron. Revised estimates for the number of human and bacteria cells in the body. PLoS Biol. 2016;14(8):e1002533. doi:10.1371/journal.pbio.1002533.
[14] Wexler HM. Bacteroides: the good, the bad, and the nitty-gritty. Clin Microbiol Rev. 2007;20:593–621. doi:10.1128/CMR.00008-07.
[15] Koshizaka T, Nishikimi M, Ozawa T, Yagi K. Isolation and sequence analysis of a complementary DNA encoding rat liver L-gulono-gamma-lactone oxidase, a key enzyme for L-ascorbic acid biosynthesis. J Biol Chem. 1988;263(4):1619–21.
[16] Naidu KA. Vitamin C in human health and disease is still a mystery? An overview. Nutr J. 2003;2:7. doi:10.1186/1475-2891-2-7.
[17] Hazan S, Dave S, Papoutsis AJ, Deshpande N, Howell MC Jr, Martin LM. Vitamin C improves gut *Bifidobacteria* in humans. Future Microbiol. 2022 Published online December 8. doi:10.2217/fmb-2022-0209.
[18] Fadupin GT, Akpoghor AU, Okunade KA. A comparative study of serum ascorbic acid level in people with and without type 2 diabetes in Ibadan, Nigeria. Afr J Med Med Sci. 2007;36:335–9.
[19] Singh RB, Ghosh S, Niaz MA, Singh R, Beegum R, Chibo H, et al. Dietary intake, plasma levels of antioxidant vitamins, and oxidative stress in relation to coronary artery disease in elderly subjects. Am J Cardiol. 1995;76:1233–8. doi:10.1016/s0002-9149(99)80348-8.
[20] Pham VT, Fehlbaum S, Seifert N, Richard N, Bruins MJ, Sybesma W, et al. Effects of colon-targeted vitamins on the composition and metabolic activity of the human gut microbiome- a pilot study. Gut Microbes. 2021;13:1–20. doi:10.1080/19490976.2021.1875774.
[21] Chi L, Gao B, Tu P, Liu CW, Xue J, Lai Y, et al. Individual susceptibility to arsenic-induced diseases: the role of host genetics, nutritional status, and the gut microbiome. Mamm Genome. 2018;29:63–79. doi:10.1007/s00335-018-9736-9.
[22] Otten AT, Bourgonje AR, Peters V, Alizadeh BZ, Dijkstra G, Harmsen HJM. Vitamin C supplementation in healthy individuals leads to shifts of bacterial populations in the gut-a pilot study. Antioxidants (Basel). 2021;10:1278. doi:10.3390/antiox10081278.
[23] Wu L, Xie X, Li Y, Liang T, Zhong H, Yang L, et al. Gut microbiota as an antioxidant system in centenarians associated with high antioxidant activities of gut-resident Lactobacillus. NPJ Biofilms Microbiomes. 2022;8:102. doi:10.1038/s41522-022-00366-0.
[24] Kruger MC, Middlemiss C, Katsumata S, Tousen Y, Ishimi Y. The effects of green kiwifruit combined with isoflavones on equol production, bone turnover and gut microflora in healthy postmenopausal women. Asia Pac J Clin Nutr. 2018;27:347–58. doi:10.6133/apjcn.062017.06.
[25] Gomes-Neto JC, Round JL. Gut microbiota: a new way to take your vitamins. Nat Rev Gastroenterol Hepatol. 2018;15:521–2. doi:10.1038/s41575-018-0044-3.
[26] Li L, Krause L, Somerset S. Associations between micronutrient intakes and gut microbiota in a group of adults with cystic fibrosis. Clin Nutr. 2017;36:1097–104. doi:10.1016/j.clnu.2016.06.029.
[27] Sánchez-Tapia M, Aguilar-López M, Pérez-Cruz C, Pichardo-Ontiveros E, Wang M, Donovan SM, et al. Nopal (Opuntia ficus indica) protects from metabolic endotoxemia by modifying gut microbiota in obese rats fed high fat/sucrose diet. Sci Rep. 2017;7:4716. doi:10.1038/s41598-017-05096-4.
[28] Wilson R, Willis J, Gearry RB, Hughes A, Lawley B, Skidmore P, et al. Sungold kiwifruit supplementation of individuals with prediabetes alters gut microbiota and improves vitamin C status, anthropometric and clinical markers. Nutrients. 2018;10:895. doi:10.3390/nu10070895.
[29] Huang K, Dong W, Liu W, Yan Y, Wan P, Peng Y, et al. 2-o-β-d-glucopyranosyl-l-ascorbic acid, an ascorbic acid derivative isolated from the fruits of lycium barbarum l., modulates gut microbiota and palliates colitis in dextran sodium sulfate-induced colitis in mice. J Agric Food Chem. 2019;67:11408–19. doi:10.1021/acs.jafc.9b04411.
[30] Dong W, Huang K, Yan Y, Wan P, Peng Y, Zeng X, et al. Long-term consumption of 2-o-β-d-glucopyranosyl-l-ascorbic acid from the fruits of lycium barbarum modulates gut microbiota in c57bl/6 mice. J Agric Food Chem. 2020;68:8863–74. doi:10.1021/acs.jafc.0c04007.
[31] Huang K, Yan Y, Chen D, Zhao Y, Dong W, Zeng X, et al. Ascorbic acid derivative 2-o-β-d-glucopyranosyl-l-ascorbic acid from the fruit of lycium barbarum modulates microbiota in the small intestine and colon and exerts an immunomodulatory effect on cyclophosphamide-treated balb/c mice. J Agric Food Chem. 2020;68:11128–43. doi:10.1021/acs.jafc.0c04253.
[32] Li Y, Zafar S, Salih Ibrahim RM, Chi HL, Xiao T, Xia WJ, et al. Exercise and food supplement of vitamin C ameliorate hypertension through improvement of gut microflora in the spontaneously hypertensive rats. Life Sci. 2021;269:119097. doi:10.1016/j.lfs.2021.119097.
[33] Li Y, Salih Ibrahim RM, Chi HL, Xiao T, Xia WJ, Li HB, et al. Altered gut microbiota is involved in the anti-hypertensive effects of vitamin C in spontaneously hypertensive rat. Mol Nutr Food Res. 2021;65:e2000885. doi:10.1002/mnfr.202000885.
[34] Anwar F, Alhayyani S, Al-Abbasi FA, Nadeem MS, Kumar V. Pharmacological role of vitamin C in stress-induced cardiac dysfunction via alteration in gut microbiota. J Biochem Mol Toxicol. 2022;36:e22986. doi:10.1002/jbt.22986.
[35] Pierre JF, Hinterleitner R, Bouziat R, Hubert NA, Leone V, Miyoshi J, et al. Dietary antioxidant micronutrients alter mucosal inflammatory risk in a murine model of genetic and microbial susceptibility. J Nutr Biochem. 2018;54:95–104. doi:10.1016/j.jnutbio.2017.12.002.
[36] Anhê FF, Nachbar RT, Varin TV, Trottier J, Dudonné S, Le Barz M, et al. Treatment with camu camu (Myrciaria dubia) prevents obesity by altering the gut microbiota and increasing energy expenditure in diet-induced obese mice. Gut. 2019;68:453–64. doi:10.1136/gutjnl-2017-315565.
[37] Adams JB, Kirby JK, Sorensen JC, Pollard EL, Audhya T. Evidence based recommendations for an optimal prenatal supplement for women in the US: vitamins and related nutrients. Matern Health Neonatol Perinatol. 2022;8:4. doi:10.1186/s40748-022-00139-9.
[38] Rizowy GM, Poloni S, Colonetti K, Donis KC, Dobbler PT, Leistner-Segal S, et al. Is the gut microbiota dysbiotic in patients with classical homocystinuria? Biochimie. 2020;173:3–11. doi:10.1016/j.biochi.2020.02.013.
[39] Valentini L, Pinto A, Bourdel-Marchasson I, Ostan R, Brigidi P, Turroni S, et al. Impact of personalized diet and probiotic supplementation on inflammation, nutritional parameters and intestinal microbiota - the "RISTOMED project": randomized controlled trial in healthy older people. Clin Nutr. 2015;34:593–602. doi:10.1016/j.clnu.2014.09.023.
[40] Brody LC, Conley M, Cox C, Kirke PN, McKeever MP, Mills JL, et al. A polymorphism, R653Q, in the trifunctional enzyme methylenetetrahydrofolate dehydrogenase/methenyltetrahydrofolate cyclohydrolase/formyltetrahydrofolate synthetase is a maternal genetic risk factor for neural tube defects: report of the Birth Defects Research Group. Am J Hum Genet. 2002;71:1207–15. doi:10.1086/344213.

[41] Gurwara S, Ajami NJ, Jang A, Hessel FC, Chen L, Plew S, et al. Dietary nutrients involved in one-carbon metabolism and colonic mucosa-associated gut microbiome in individuals with an endoscopically normal colon. Nutrients. 2019;11:613. doi:10.3390/nu11030613.
[42] Spinler JK, Sontakke A, Hollister EB, Venable SF, Oh PL, Balderas MA, et al. From prediction to function using evolutionary genomics: human-specific ecotypes of Lactobacillus reuteri have diverse probiotic functions. Genome Biol Evol. 2014;6:1772–89. doi:10.1093/gbe/evu137.
[43] Park S, Kang S, Sol Kim D. Folate and vitamin B-12 deficiencies additively impair memory function and disturb the gut microbiota in amyloid-β infused rats. Int J Vitam Nutr Res. 2022;92:169–81. doi:10.1024/0300-9831/a000624.
[44] Babakobi MD, Reshef L, Gihaz S, Belgorodsky B, Fishman A, Bujanover Y, et al. Effect of maternal diet and milk lipid composition on the infant gut and maternal milk microbiome. Nutrients. 2020;12:2539. doi:10.3390/nu12092539.
[45] Chittaranjan Y. Vitamin B12: an intergenerational story. Nestle Nutri Inst Workshop Ser. 2020;93:91–102.
[46] Cerdó T, Diéguez E, Campoy C. Infant growth, neurodevelopment and gut microbiota during infancy: which nutrients are crucial? Curr Opin Clin Nutr Metab Care. 2019;22:434–41. doi:10.1097/MCO.0000000000000606.
[47] Rubini E, Schenkelaars N, Rousian M, Sinclair KD, Wekema L, Faas MM, et al. Maternal obesity during pregnancy leads to derangements in one-carbon metabolism and the gut microbiota: implications for fetal development and offspring wellbeing. Am J Obstet Gynecol. 2022;227:392–400. doi:10.1016/j.ajog.2022.04.013.
[48] Pham VT, Dold S, Rehman A, Bird JK, Steinert RE. Vitamins, the gut microbiome and gastrointestinal health in humans. Nutr Res. 2021;95:35–53. doi:10.1016/j.nutres.2021.09.001.
[49] Röth D, Chiang AJ, Hu W, Gugiu GB, Morra CN, Versalovic J, Kalkum M. Two-carbon folate cycle of commensal Lactobacillus reuteri 6475 gives rise to immunomodulatory ethionine, a source for histone ethylation. FASEB J. 2019;33:3536–48. doi:10.1096/fj.201801848R.
[50] He Q, Zou T, Chen J, He J, Jian L, Xie F, You J, Wang Z. Methyl-donor micronutrient for gestating sows: effects on gut microbiota and metabolome in offspring piglets. Front Nutr. 2021;8:675640. doi:10.3389/fnut.2021.675640.
[51] Engevik MA, Morra CN, Röth D, Engevik K, Spinler JK, Devaraj S, et al. Microbial metabolic capacity for intestinal folate production and modulation of host folate receptors. Front Microbiol. 2019;10:2305. doi:10.3389/fmicb.2019.02305.
[52] Wyss A. Carotene oxygenases: a new family of double bond cleavage enzymes. J Nutr. 2004;134:246S–250S. doi:10.1093/jn/134.1.246S.
[53] von Lintig J, Hessel S, Isken A, Kiefer C, Lampert JM, Voolstra O, et al. Towards a better understanding of carotenoid metabolism in animals. Biochim Biophys Acta. 2005;1740:122–31. doi:10.1016/j.bbadis.2004.11.010.
[54] Lindqvist A, He YG, Andersson S. Cell type-specific expression of beta-carotene 9′,10′-monooxygenase in human tissues. J Histochem Cytochem. 2005;53:1403–12. doi:10.1369/jhc.5A6705.2005.
[55] Rubin LP, Ross AC, Stephensen CB, Bohn T, Tanumihardjo SA. Metabolic effects of inflammation on vitamin A and carotenoids in humans and animal models. Adv Nutr. 2017;8:197–212. doi:10.3945/an.116.014167.
[56] Amengual J, Widjaja-Adhi MAK, Rodriguez-Santiago S, Hessel S, Golczak M, Palczewski K, et al. Two carotenoid oxygenases contribute to mammalian provitamin A metabolism. J Biol Chem 2013;288:34081–96. doi:10.1074/jbc.M113.501049.
[57] Wu L, Guo X, Wang W, Medeiros DM, Clarke SL, Lucas EA, et al. Molecular aspects of β, β-carotene-9′, 10′-oxygenase 2 in carotenoid metabolism and diseases. Exp Biol Med (Maywood). 2016;241:1879–87. doi:10.1177/1535370216657900.
[58] Djuric Z, Bassis CM, Plegue MA, Ren J, Chan R, Sidahmed E, et al. Colonic mucosal bacteria are associated with inter-individual variability in serum carotenoid concentrations. J Acad Nutr Diet. 2018;118 606–616.e3. doi:10.1016/j.jand.2017.09.013.
[59] Honarbakhsh M, Malta K, Ericsson A, Holloway C, Kim YK, Hammerling U, et al. β-carotene improves fecal dysbiosis and intestinal dysfunctions in a mouse model of vitamin A deficiency. Biochim Biophys Acta Mol Cell Biol Lipids. 202;1867:159122. doi: 10.1016/j.bbalip.2022.159122.
[60] Holloway C, Zhong G, Kim YK, Ye H, Sampath H, Hammerling U, et al. Retinoic acid regulates pyruvate dehydrogenase kinase 4 (Pdk4) to modulate fuel utilization in the adult heart: Insights from wild-type and β-carotene 9′,10′ oxygenase knockout mice. FASEB J. 2022;36:e22513. doi:10.1096/fj.202101910RR.
[61] Rinninella E, Mele MC, Merendino N, Cintoni M, Anselmi G, Caporossi A, et al. The role of diet, micronutrients and the gut microbiota in age-related macular degeneration: new perspectives from the gut–retina axis. Nutrients. 2018;10:1677. doi:10.3390/nu10111677.
[62] Schmidt KM, Haddad EN, Sugino KY, Vevang KR, Peterson LA, Koratkar R, et al. Dietary and plasma carotenoids are positively associated with alpha diversity in the fecal microbiota of pregnant women. J Food Sci. 2021;86:602–13. doi:10.1111/1750-3841.15586.
[63] Frankenfeld CL, Hullar MAJ, Maskarinec G, Monroe KR, Shepherd JA, Franke AA, et al. The gut microbiome is associated with circulating dietary biomarkers of fruit and vegetable intake in a multiethnic cohort. J Acad Nutr Diet. 2022;122:78–98. doi:10.1016/j.jand.2021.05.023.
[64] Xie J, Liu M, Liu H, Jin Z, Guan F, Ge S, et al. Zeaxanthin ameliorates obesity by activating the β3-adrenergic receptor to stimulate inguinal fat thermogenesis and modulating the gut microbiota. Food Funct. 2021;12:12734–50. doi:10.1039/d1fo02863d.
[65] Wu L, Lyu Y, Srinivasagan R, Wu J, Ojo B, Tang M, et al. Astaxanthin-shifted gut microbiota is associated with inflammation and metabolic homeostasis in mice. J Nutr. 2020;150:2687–98. doi:10.1093/jn/nxaa222.
[66] Misawa N, Maoka T, Takemura M. Carotenoids: carotenoid and apocarotenoid analysis-use of E. coli to produce carotenoid standards. Methods Enzymol. 2022;670:87–137. doi:10.1016/bs.mie.2022.03.019.
[67] Kanamoto H, Nakamura K, Misawa N. Carotenoid production in oleaginous yeasts. Adv Exp Med Biol. 2021;1261:153–63. doi:10.1007/978-981-15-7360-6_12.
[68] Tian B, Hua Y. Carotenoid biosynthesis in extremophilic Deinococcus-Thermus bacteria. Trends Microbiol. 2010;18:512–20. doi:10.1016/j.tim.2010.07.007.
[69] Shindo K, Misawa N. New and rare carotenoids isolated from marine bacteria and their antioxidant activities. Mar Drugs. 2014;12:1690–8. doi:10.3390/md12031690.
[70] Takemura M, Takagi C, Aikawa M, Araki K, Choi SK, Itaya M, et al. Heterologous production of novel and rare C30-carotenoids using Planococcus carotenoid biosynthesis genes. Microb Cell Fact. 2021;20:194. doi:10.1186/s12934-021-01683-3.
[71] Hagi T, Kobayashi M, Nomura M. Whole-transcriptome analysis of oxidative stress response genes in carotenoid-producing Enterococcus gilvus. Biosci Biotechnol Biochem. 2018;82:1053–7. doi:10.1080/09168451.2017.1399790.

[72] Ohki S, Hagi T, Nakano K, Shiroma A, Tamotsu H, Shimoji M, et al. Complete genome sequence of carotenoid-producing enterococcus gilvus cr1, isolated from raw cow's milk. Microbiol Resour Announc. 2018;7 e00988–18. doi:10.1128/MRA.00988-18.
[73] Kanai M, Raz A, Goodman DS. Retinol-binding protein: the transport protein for vitamin A in human plasma. J Clin Invest. 1968;47:2025–44. doi:10.1172/JCI105889.
[74] Shastry BS. SNP alleles in human disease and evolution. J Hum Genet. 2002;47:561–6. doi:10.1007/s100380200086.
[75] Leung WC, Hessel S, Méplan C, Flint J, Oberhauser V, Tourniaire F, et al. Two common single nucleotide polymorphisms in the gene encoding beta-carotene 15,15′-monoxygenase alter beta-carotene metabolism in female volunteers. FASEB J. 2009;23:1041–53. doi:10.1096/fj.08-121962.
[76] Lietz G, Lange J, Rimbach G. Molecular and dietary regulation of β,β-carotene 15,15′-monooxygenase 1 (BCMO1). Arch Biochem Biophys. 2010;502:8–16. doi:10.1016/j.abb.2010.06.032.
[77] Nazmul HM, Ahmad SM, Kalanetra KM, Taft DH, Alam JJ, Afsana K, al et. Neonatal vitamin A supplementation and vitamin A status are associated with gut microbiome composition in Bangladeshi infants in early infancy and at 2 years of age. J Nutr. 2019;149:1075–88. doi:10.1093/jn/nxz034.
[78] van de Pavert SA, Ferreira M, Domingues RG, Ribeiro H, Molenaar R, Moreira-Santos L, et al. Maternal retinoids control type 3 innate lymphoid cells and set the offspring immunity. Nature. 2014;508:123–7. doi:10.1038/nature13158.
[79] Sano T, Huang W, Hall JA, Yang Y, Chen A, Gavzy SJ, et al. An IL-23R/IL-22 circuit regulates epithelial serum amyloid a to promote local effector th17 responses. Cell. 2015;163:381–93. doi:10.1016/j.cell.2015.08.061.
[80] Gattu S, Bang YJ, Pendse M, Dende C, Chara AL, Harris TA, et al. Epithelial retinoic acid receptor β regulates serum amyloid A expression and vitamin A-dependent intestinal immunity. Proc Natl Acad Sci U S A. 2019;116:10911–16. doi:10.1073/pnas.
[81] Bang YJ, Hu Z, Li Y, Gattu S, Ruhn KA, Raj P, et al. Serum amyloid A delivers retinol to intestinal myeloid cells to promote adaptive immunity. Science. 2021;373:eabf9232. doi:10.1126/science.abf9232.
[82] Woo V, Eshleman EM, Hashimoto-Hill S, Whitt J, Wu SE, Engleman L, et al. Commensal segmented filamentous bacteria-derived retinoic acid primes host defense to intestinal infection. Cell Host Microbe. 2021;29 1744–1756.e5. doi:10.1016/j.chom.2021.09.010.
[83] Bonakdar M, Czuba LC, Han G, Zhong G, Luong H, Isoherrannen N, et al. Gut commensals expand vitamin A metabolic capacity of the mammalian host. Cell Host Microbe. 2022;30 1084–1092.e5. doi:10.1016/j.chom.2022.06.011.
[84] Cao YG, Bae S, Villarreal J, Moy M, Chun E, Michaud M, et al. Faecalibaculum rodentium remodels retinoic acid signaling to govern eosinophil-dependent intestinal epithelial homeostasis. Cell Host Microbe. 2022;30 1295–1310.e8. doi:10.1016/j.chom.2022.07.015.
[85] Ananthakrishnan AN. Epidemiology and risk factors for IBD. Nat Rev Gastrolentol Hepatol. 2015;12:205–17. doi:10.1038/nrgastro.2015.34.
[86] Desai MS, Seekatz AM, Koropatkin NM, Kamada N, Hickey CA, Wolter M, et al. A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. Cell. 2016;167 1339–1353.e21PMID: 27863247. doi:10.1016/j.cell.2016.10.043.
[87] Wellington VNA, Sundaram VL, Singh S, Sundaram U. Dietary supplementation with vitamin D, fish oil or resveratrol modulates the gut microbiome in inflammatory bowel disease. Int J Mol Sci. 2022;23:206. doi:10.3390/ijms230102106.
[88] Sun J. Dietary vitamin D, vitamin D receptor, and microbiome. Curr Op Clin Nutr Met Care. 2018;2:471–4. doi:10.1097/MCO.0000000000000516.
[89] Fletcher J, Cooper SC, Ghosh S, Hewison S. The role of vitamin D in inflammatory bowel disease: mechanism to management. Nutrients. 2019;11:1019. doi:10.3390/nu11051019.
[90] Gubatan J, Moss AC. Vitamin D in inflammatory bowel disease: more than just a supplement. Curr Op Gastro. 2018;34:217–25. doi:10.1097/MOG.0000000000000449.
[91] Chatterjee I, Lu R, Zhang Y, Zhang J, Dai Y, Xia Y, et al. Vitamin D receptor promotes healthy microbial metabolites and microbiome. Sci Rep. 2020;10:7340. doi:10.1038/s41598-020-64226-7.
[92] Leyssens C, Verlinden L, Hertogh, Gysemans C, Mathieu C, Carmeliet G, et al. Impact on experimental colitis of vitamin D receptor deletion in intestinal epithelial or myeloid cells. Endochrinology. 2017;158:2354–66. doi:10.1210/en.2017-00139.
[93] Riccio P, Rossano R. Diet, gut microbiota, and vitamins D and A in multiple sclerosis. Neurotherapeutics. 2018;15:75–91. doi:10.1007//s13311-017-0581-4.
[94] Correale J, Hohlfeld R, Baranzini SE. The role of the gut microbiota in multiple sclerosis. Nat Rev Neurol. 2022;18:544–58. doi:10.1038/s41582-022-00697-8.
[95] Gandini S, Bonial M, Haukka J, Bymes G, Cox B, Sneyd MS, et al. Meta-analysis of obeservational studies of serum 25-hydroxyvitain D levels and colorectal, breast and prostate cancer and colorectal adenoma. Int J Cancer. 2011;128:1414–24. doi:10.1002/ijc.25439.
[96] Tabatabaeizadeh SA, Fazeli M, Meshkat Z, Khodashenas E, Esmaeli H, Mazloum S, et al. The effects of high doses of vitamin D on the composition of the gut microbiome of adolescent girls. Clin Nutr ESPAN. 2020;35:103–8. doi:10.1016/j.clnesp.
[97] Lichfer LA, Cousins RJ. Mammalian zinc transporter: nutritional and physiological regulation. Annu Rev Nutr 2009;29:153–76. doi:10.1146/annurev-nutr-033009-083312.
[98] Harris ED. Cellular transporters for zinc. Nutr Rev. 2002;60:121–4. doi:10.1301/00296640260085877.
[99] Cousins RJ, Blanchard RK, Moore JB, Cui L, Green CL, Liuzzi JP, et al. Regulation of zinc metabolism and genomic outcomes. J Nutr. 2003;133(5 suppl 1):1521S–1526S. doi:10.1093/jn/133.5.1521S.
[100] Cousins RJ. Gastrointestinal factors influencing zinc absorption and homeostasis. Int J Vitam Nutr Res. 2010;80:243–8. doi:10.1024/0300-9831/a000030.
[101] Eide DJ. Zinc transporters and the cellular trafficking of zinc. Biochim Biophys Acta. 2006;1763:711–22. doi:10.1016/j.bbamcr.2006.03.005.
[102] Kambe T. An overview of a wide range of functions of ZnT and Zip zinc transporters in the secretory pathway. Biosci Biotechnol Biochem. 2011;75:1036–43. doi:10.1271/bbb.110056.
[103] Hashimoto A, Mg Kambe T. Zn and Cu transport proteins: a brief overview from physiological and molecular perspectives. J Nutr Sci Vitaminol (Tokyo). 2015;61(suppl):S116–18. doi:10.3177/jnsv.61.S116.
[104] Xia P, Lian S, Wu Y, Yan L, Quan G, Zhu G. Zinc is an important inter kingdom signal between the host and microbe. Vet Res. 2021;2:39. doi:10.1186/s13567-021-00913-1.
[105] Hood MI, Skaar EP. Nutritional immunity: transition metals at the pathogen-host interface. Nat Rev Microbiol. 2012;10(525–37). doi:10.1038/nrmicro2836.
[106] Chasapsis CT, Loutisdou AC, Spiliopoulou CA, Stefanidou ME. Zinc and human health: an update. Arch Toxicol. 2012;86:521–34. doi:10.1007/s00204-011-0775-1.

[107] Tsuji T, Naito Y, Takagi T, Kugai M, Yoriki H, Horie R, et al. Role of metallothionein in murine experimental colitis. Int J Mol Med 2013;31:1037–46. doi:10.3892/ijmm.2013.1294.
[108] Hantke K. Bacterial zinc uptake and regulators. Biometals. 2001;14:239–49. doi:10.1023/a:1012984713391.
[109] Lopez CA, Beavers WN, Weiss A, Knoppel RJ, Zackular JP, Chazin W, et al. The immune protein calprotectin impacts Clostridioi difficile metabolism through zinc limitation. Am Soc Micro. 2019;10 eo2289-LT. doi:10.1128/mBio.10eO2289-19.
[110] Behnsen J, Zhi H, Aron AT, Subramanian V, Santus W, Lee MH, et al. Siderophore-mediated zinc acquisition enhances enterobacterial colonization of the inflamed gut. Nat Commun. 2021;12:7016. doi:10.1038/s41467-021-27297-2.
[111] Sauer AK, Malijauskaite S, Meleady P, Boeckers TM, McGourty K, Grabrucker AM. Zinc is a key regulator of gastrointestinal development, microbiota composition and inflammation with relevance for autism spectrum. Cell Mol Life Sci. 2021;79:46. doi:10.1007/s00018-021-04052-w.
[112] Sauer AK, Grabrucker AM. Zinc deficiency during pregnancy leads to altered microbiome and elevated inflammatory markers in mice. Front Neurosci. 2019;29. doi:10.3389/fnins.2019,01295.
[113] Chen X, Jiang Y, Wang Z, Chen Y, Tang S, Wang S, et al. Alteration in gut microbiota associated with zinc deficiency in school-age children. Nutrients. 2022;14:2895. doi:10.3390/nu14142895.
[114] Skalny AV, Aschner M, Lei XG, Gritssenko VA, Santamaria A, Alekseenko SI, et al. Gut microbiota as a mediator of essential and toxic effects of zinc in the intestines and other tissues. Int J Mol Sci. 2021;22:13074. doi:10.3390/ijms222313074.
[115] Gielda LM, DiRita VJ. Zinc composition among the intestinal microbiota. mBio. 2012;3 e00171–12. doi:10.1128/mBio.00171-12.
[116] Zackular JP, Moore JL, Jordan AT, Juttukonda LJ, Noto MJ, Nicholson MR, et al. Dietary zinc alters the microbiota and decreases resistance to Clostridium difficile infection. Nat Med. 2016;11:1330–4. doi:10.1038/nm.4174.
[117] Farr D, Nag D, Chazin WJ, Harrison S, Thummel R, Luo X, et al. Neutrophil-associated responses to vibrio cholerae infection in a natural host model. Infect Immun. 2022;90:e0046621. doi:10.1128/iai.00466-21.
[118] Lopez CA, Beavers WN, Weiss A, Knippel RJ, Zackular JP, Chazin W, et al. The immune protein calprotectin impacts clostridioides difficile metabolism through zinc limitation. mBio. 2019;10 e02289–19. doi:10.1128/mBio.02289-19.
[119] Samuelson DR, Smith DR, Cunningham KC, Wyatt TA, Hall SC, Murry IJ, et al. ZIP8 mediated intestinal dysbiosis impairs pulmonary host defense against bacterial pneumonia. Int J Mol Sci. 2022;23:1022. doi:10.3390/ijms23031022.
[120] Samuelson DR, Hag S, Knoell DL. Divalent metal uptake and the role of ZIP8 in host defense against pathogens. Front Cell Dev Biol. 2022;10:924820. doi:10.3389/fcell.2022.924820.
[121] Mantadakis E, Chatzimichael E, Zikidou P. Iron deficiency anemia in children residing in high and low-income countries: risk factors, prevention, diagnosis and therapy. Mediterr J Hematol Infect Dis. 2020;12:e2020041. doi:10.4084/MJHID.2020.041.
[122] Mahadea D, Adamczewska E, Ratajczak AE, Rychter AM, Zawada A, Eder P, et al. Iron deficiency anemia in inflammatory bowel diseases-a narrative review. Nutrients. 2021;13:4008. doi:10.3390/nu13114008.
[123] Cherayil BJ, Ellenbogen S, Shanmugam NN. Iron and intestinal immunity. Curr Opin Gastroenterol. 2011;27:523–8. doi:10.1097/MOG.0b013e32834a4cd1.
[124] Poveda C, Pereira DIA, Lewis MC, Walton GE. The impact of low-level iron supplements on the faecal microbiota of irritable bowel syndrome and healthy donors using in batch cultures. Nutrients. 2020;12:3819. doi:10.3390/nu12123819.
[125] Collins JF, Wessling-Resnick M, Knutson MD. Hepcidin regulation of iron transport. J Nutr. 2008;138:2284–8. doi:10.3945/jn.108.096347.
[126] Nemeth E, Ganz T. Regulation of iron metabolism by hepdicin. Annu Rev Nutr. 2006;26:323–42. doi:10.1146/annurev.nutr.26.061505.111303.
[127] Bek S, Teo YN, Tan XH, Fan KHR, Kristie HR, Siah KTH. Association between irritable syndrome and micronutrients: a systematic review. J Gastroenterol Hepatol. 2022;37:1485–97. doi:10.1111/jgh.15891.
[128] Hoffmann A, Haschka D, de Souza LV, Tymoszuk P, Seifert M, von Raffay L, et al. Baseline iron status and presence of anaemia determine the course of systemic *Salmonella* infection following oral iron supplementation in mice. EBioMedicine 2021;71:103568. doi:10.1016/j.ebiom.2021.103568.
[129] Ippolito JR, Piccolo BD, Roberson MS, Barney DE, Ali J, Singh P, et al. Iron deficient diets modify the gut microbiome and reduce the severity of enteric infection in a mouse model of S. Typhimurium-induced enterocolitis. J Nutr Biochem. 2022;107:109065. doi:10.1016/j.jnutbio.2022.109065.
[130] Paganini D, Zimmermann MB. The effects of iron fortification and supplementation on the gut microbiome and diarrhea in infants and children: a review. Am J Clin Nutr. 2027;106:1688S–93S. doi: 10.3945/ajcn.117.156067.
[131] Mahalhal A, Williams JM, Johnson S, Ellaby N, Duckworth CA, Burkitt MD, et al. Oral iron exacerbates colitis and influences the intestinal microbiome. Plos One. 2018;13:e0202460. doi:10.1371/journal.pone.0202460.
[132] Chen S, Wu X, Wang X, Shao Y, et al. Responses of intestinal microbiota and immunity to increasing dietary iron using a piglet model. Front Cell Dev Biol. 2020;8:603392. doi:10.3389/fcell.2020.603392.
[133] Browne HP, Forster SC, Anonye BO, Kumar N, Neville BA, Stares MD, et al. Culturing of 'unculturable' human microbiota reveals novel taxa and extensive sporulation. Nature. 2016;533:543–6. doi:10.1038/nature17645.
[134] Rajakovich LJ, Fu B, Bollenbach M, Balskus EP. Elucidation of an anaerobic pathway for metabolism of l-carnitine-derived γ-butyrobetaine to trimethylamine in human gut bacteria. Proc Natl Acad Sci U S A. 2021;118:e2101498118. doi:10.1073/pnas.2101498118.
[135] Arboleya S, Ang L, Margolles A, Yiyuan L, Dongya Z, Liang X, et al. Deep 16S rRNA metagenomics and quantitative PCR analyses of the premature infant fecal microbiota. Anaerobe. 2012;18:378–80. doi:10.1016/j.anaerobe.2012.04.013.
[136] Woo PCY, Lau SKP, Teng JLL, Tse H, Yuen K-Y. Then and now: use of 16S rDNA gene sequencing for bacterial identification and discovery of novel bacteria in clinical microbiology laboratories. Clin Microbiol Infect 2008;14:908–34. doi:10.1111/j.1469-0691.2008.02070.x.
[137] Gupta S, Mortensen MS, Schjørring S, Trivedi U, Vestergaard G, Stokholm J, et al. Amplicon sequencing provides more accurate microbiome information in healthy children compared to culturing. Commun Biol. 2019;2:291. doi:10.1038/s42003-019-0540-1.
[138] Zhang X, Li L, Butcher J, Stintzi A, Figeys D. Advancing functional and translational microbiome research using meta-omics. Microbiome. 2019;7:154. doi:10.1186/s40168-019-0767-6.

[139] Altay O, Nielsen J, Uhlen M, Boren J, Mardinoglu A. Systems biology perspective for studying the gut microbiota in human physiology and liver diseases. EBioMedicine. 2019;49:364–73. doi:10.1016/j.ebiom.2019.09.057.

[140] Jiang D, Armour CR, Hu C, Mei M, Tian C, Sharpton TJ, et al. Microbiome multi-omics network analysis: statistical considerations, limitations, and opportunities. Front Genet. 2019;10:995. doi:10.3389/fgene.2019.00995.