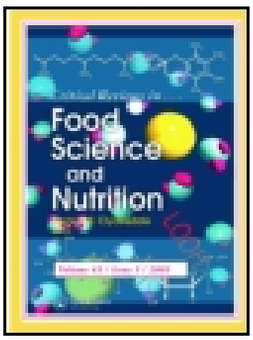

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

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To cite this article: Daotong Li, Pan Wang, Pengpu Wang, Xiaosong Hu & Fang Chen (2017): Targeting the gut microbiota by dietary nutrients: A new avenue for human health, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2017.1363708

To link to this article: https://doi.org/10.1080/10408398.2017.1363708

Accepted author version posted online: 28 Aug 2017.
Published online: 02 Nov 2017.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2017.1363708

Targeting the gut microbiota by dietary nutrients: A new avenue for human health

Daotong Li, Pan Wang, Pengpu Wang, Xiaosong Hu, and Fang Chen

Beijing Advanced Innovation Center for Food Nutrition and Human Health, College of Food Science and Nutritional Engineering, National Engineering Research Center for Fruit and Vegetable Processing, Key Laboratory of Fruits and Vegetables Processing, Ministry of Agriculture; Engineering Research Centre for Fruits and Vegetables Processing, Ministry of Education, China Agricultural University, Beijing, China

ABSTRACT

The gut microbiota is a complex ecosystem consisted of trillions of microbes that have co-evolved with their host for hundreds of millions of years. During the last decade, a growing body of knowledge has suggested that there is a compelling set of connections among diet, gut microbiota and human health. Various physiological functions of the host, ranging from metabolic and immune regulation to nerve and endocrine development, are possibly mediated by the structural components of microbial cell or the products of microbial metabolism, which are greatly influenced by dietary macronutrients and micronutrients. Thus, governing the production and activity of these microbial-associated small molecules and metabolites through dietary intervention may provide promising strategies for the improvement of human health and disease. In this review article, we first provide an overview of current findings about the intimate interrelationships between diet and gut microbiota. We also introduce the physiological effects of some microbial-associated small molecules and metabolites on the host as well as the detailed signaling mechanisms.

Abbreviations: AHR, aryl hydrocarbon receptor; BSN, bile salt hydrolase; CA, cholic acid; CARD9, caspase recruitment domain family member 9; CAZymes, carbohydrate-active enzymes; CDCA, chenodeoxycholic acid; CNS, central nervous system; DCs, dendritic cells; DCA, deoxycholic acid; FFAR: free fatty acid receptor; Fgf, fibroblast growth factor; FXR, farnesoid X receptor; GF, germ free; GLP, glucagon-like peptide; HDAC, histone deacetylase; HFD, high fat diet; IL, interleukin; ILCs, innate lymphoid cells; LCA, lithocholic acid; LPS, lipopolysaccharide; MCA, muricholic acid; PSA, polysaccharide A; PYY, plasma peptide YY; SCFAs: short-chain fatty acids; SPF, specific pathogen free; TLR, toll-like receptor; TMA, trimethylamine; TMAO, trimethylamine N-oxide; T_{reg} cells, regulatory T cells; βMCA, beta-MCA

KEYWORDS

Gut microbiota; Dietary nutrients; Metabolites; Signaling mechanisms; Human health

1. Introduction

From primitive tribes to modern society, we humans live on the earth by acquiring necessary energy and nutrients from foods that commonly consumed. As the improvement of living standard, people are being more concerned about the nutritional value of foods than ever before. As a matter of fact, foods may not only include the basic nutrients that meet the requirements of the body, but also provide carbon and nitrogen resources that are essential for large numbers of microorganisms colonizing the distal part of the gastrointestinal tract: the gut microbiota, which previously was just known to be involved in nutrient and energy harvest, while now is gradually recognized as a neglected "metabolic organ" and to play a critical role in modulating host physiology.

The gut microbiota is composed of approximately 100 trillion microbes that belong to three main types of life including bacteria, archaea and eukarya (Eckburg et al., 2005). Approximately more than 1,200 human intestinal bacterial species have been identified, and importantly, a substantial proportion of bacterial members may be isolated and cultured *in vivo* (Browne et al., 2016). In addition, the gut microbiome, which is referred as whole genes of gut microbes, comprises about 500 times genes higher than the human genome (Bäckhed et al., 2005; Qin et al., 2010; Li et al., 2014). Recently, accumulating evidences have confirmed the association between dysbiosis of gut microbial composition and etiology or development of a wide range of human metabolic, immunological and neurological diseases (Li et al., 2016). However, how the disruption of gut microbiota causally or consequentially relates to various physiological functions of the host remains to be discovered and is an interesting area of recent research.

The gut microbiota can be greatly affected by diet. Specific dietary components have a profound influence on the composition and function of the gut microbiota, as well as the production of microbial-associated small molecules and metabolites, which can transmit cross the intestinal epithelium directly or indirectly, and further exert widespread impacts on different organs of the host (Ozdal et al., 2016) (Figure 1). Thus, understanding how our gut microbiome associates with dietary nutrients and how the microbial-derived small molecules and metabolites affect host physiology are of great importance and

CONTACT Fang Chen chenfangch@sina.com College of Food Science and Nutritional Engineering, China Agricultural University, No.17, Qinghua East Road, Haidian District, Beijing, 100083, China.

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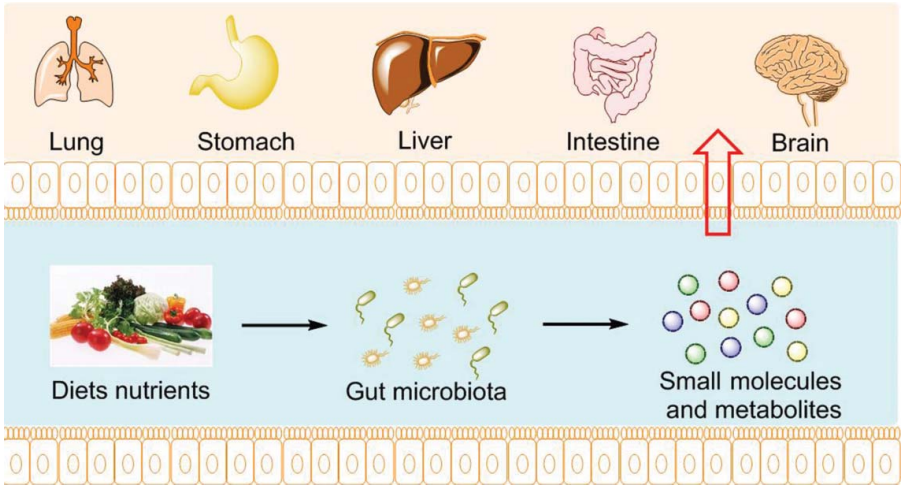

Figure 1. Simplified introduction of diet nutrients-gut microbes-host health axis. Dietary nutrients have impacts on the the production of microbial-modulated small molecules and metabolites, which further pass through the intestinal epithelium and regulate the physiological functions of various organs of the host.

valuable for establishing a detailed framework to examine the casual relationships among diet, gut microbiota and host health, as well as developing novel dietary nutrients targeting the gut microbiota.

In this review, we summarize important findings with regard to the relationships between diet and gut microbiota. We also highlight several examples of microbial-associated small molecules and metabolites associated with dietary nutrients and the mechanisms by which these components regulate host physiological functions at the signaling level. We hope this review can provide valuable information for people when choosing dietary nutrients to improve health and disease.

2. Diet and gut microbiota

2.1. Diet and mammalian gut microbiota

The symbiotic relationships between mammals and associated gut microbes have co-evolved for hundreds of millions of years (Moeller et al., 2016). This co-evolution has made the huge microbial community develop enormous functions that the host does not evolve wholly on their own, such as degrading indigestible plant-derived polysaccharides, protecting against enteropathogens, educating immune system and synthesizing essential amino acids and vitamins (Gill et al., 2006). It has been demonstrated that there is significant difference in the gut microbial composition among herbivore, omnivore and carnivore, and the microbial diversity increases from carnivore to omnivore to herbivore (Ley et al., 2008). Moreover, although mammalian gut microbiomes share a wide range of functional cores, the abundance of shared functions is different (Muegge et al., 2011). Specifically, herbivorous fecal microbiomes contain more abundant enzymes involved in biosynthesis pathways such as glutamate biosynthesis, whereas the enzymes that significantly increased in carnivorous fecal microbiomes are degradation pathways such as glutamine degradation (Muegge et al., 2011). These findings suggest that diet may be a strong selective force driving the co-evolution between mammals and their symbiont gut microbiota, and understanding the functional relationships between gut microbiome and diet may provide a novel perspective to study the history of mammalian evolution.

2.2. Dietary components and human gut microbiota

Human studies have demonstrated that long-term diet is strongly correlated with microbiome enterotype clustering, that is, protein and animal fat are associated with *Bacteroides* enterotype, whereas carbohydrates and simple sugars are associated with *Prevotella* enterotype (Wu et al., 2011). In addition, the structure, function as well as the metabolic activity of the intestinal microbiota can also be impacted by short-term intake of 'animal-based diet' or 'plant-based diet' (David et al., 2014). Notably, rhythmic food intake of the host leads to daily diurnal fluctuations of the gut microbiome (Zarrinpar et al., 2014; Thaiss et al., 2014), further confirming the critical role of dietary effects in shaping and modifying the composition and function of the human gut microbiota (Faith et al., 2011).

It is accepted that dietary polysaccharides in plant fibers provide key energy sources for the growth of countless microbes in the gut. Thus, the composition and function of the gut microbiota can be largely influenced by dietary fiber consumption. For instance, following 3-day consumption of barley kernel-based bread (rich in soluble dietary fiber), glucose metabolism is significantly improved in specific individuals whose gut microbial composition exhibits an increase ratio of *Prevotella*/*Bacteroides*, indicating that *Prevotella* may be involved in beneficial effects of dietary fibers on glucose metabolism (Kovatcheva-Datchary et al., 2015). Moreover, by comparing the gut microbial composition, as well as plasma and urinary metabolome between healthy human vegans and omnivores, a recent study reports that vegans have a higher level of gut microbial metabolites than omnivores, though the difference in gut microbiota composition is slight (Wu et al., 2016).

The type of dietary lipids can also affect the gut microbial composition and host metabolism (Caesar et al., 2015). For example, the gut microbiota of mice fed with lard (rich in saturated fatty acids) has increased abundance of harmful bacteria such as *Bilophila*, whereas mice fed with fish oil (rich in

polyunsaturated fatty acids) have increased abundance of beneficial bacteria such as *Lactobacillus* and *Akkermansia muciniphila* (Caesar et al., 2015). Importantly, lard feeding-induced gut dysbiosis results in increased production of microbial-derived factors, which may participate in the induction of white adipose tissue inflammation through chemokine CCL2-mediated signaling (Caesar et al., 2015).

Accumulating data suggest that food additives, which are regularly consumed worldwide, can disturb the homeostasis of the gut microbiota. For example, chondroitin sulfate, a common dietary supplement, is metabolized by *Bacteroides thetaiotaomicron* to release sulfate, which is favorable for the colonization of a harmful sulfate-reducing bacteria *Desulfovibrio piger* in the intestine (Rey et al., 2013). In addition, compared to the mice with water or glucose administration, mice with chronic consumption of non-caloric artificial sweeteners develop significant glucose intolerance, which can be improved through antibiotic treatment. Interestingly, sweeteners can directly alter the structure and function of the gut microbiota *in vitro* (Suez et al., 2014). Similarly, dietary emulsifiers can also induce low-grade intestinal inflammation, metabolic syndrome and altered gut microbial composition (Chassaing et al., 2015). Notably, transferring the disturbed gut microbiota caused by food additives into germ free (GF) mice reproduces the similar metabolic disorders observed in vivo, suggesting that food additives-induced adverse metabolic effects may be driven, in part, by the dysbiosis of the gut microbiota (Suez et al., 2014; Chassaing et al., 2015). Thus, these findings indicate that deep understanding of the metabolic role of gut microbiome in complex interaction with these artificial food additives should be a prerequisite for the safety assessment before their massive usage.

2.3. Gut microbiota of people from different geographic regions

Studies comparing the gut microbiota of people from different geographic regions also provide evidences for the role of dietary patterns in determining the features of gut microbial composition. For instance, the gut microbiota of hunter-gatherers from the Hadza of Tanzania has higher level of microbial diversity and richness than that of Italian individuals (Schnorr et al., 2014). Similarly, the distal gut of healthy children from Bangladesh also exhibits a greater bacterial diversity compared to that of U.S. children (Lin et al., 2013). The gut microbiota of the African children has increased abundance of Firmicutes and decreased abundance of Bacteroidetes when compared with that of European children (De Filippo et al., 2010). Notably, the specific short-chain fatty acids (SCFAs)-producing bacteria enriched in the gut of the African children, such as *Xylanibacter, Prevotella, Butyrivibrio* and *Treponema*, may result from their characteristic dietary habits (low in fat and animal protein and rich in starch, fiber, and plant polysaccharides), and these bacteria may help local people maximize the energy intake from indigestible plant components (De Filippo et al., 2010). Moreover, there are also significant differences in the fecal microbiota composition when comparing the rural Papua New Guineans, Malawians and Amerindians to the US residents (Yatsunenko et al., 2012; Martínez et al., 2015). Collectively, these findings indicate that there is significant difference in the gut microbial composition of people between developing and developed countries, and dietary effects may to a large degree contribute to this variation.

2.4. Carbohydrate-active enzymes (CAZymes) enriched in gut microbiome

One important function of the gut microbiome is degradation and fermentation of the dietary nutrients. For instance, plant- and animal-derived dietary glycans, much of which cannot be digested by the enzymes encoded in human genome, can be degraded by intestinal microorganisms (Koropatkin et al., 2012). Indeed, diverse chemical composition of dietary glycans requires abundant enzymes existed in the gut microbiome for the effective fermentation of these complex carbohydrates (Koropatkin et al., 2012). CAZymes, including glycosyl transferase, carbohydrate esterase, glycoside hydrolases and polysaccharide lyases, play crucial roles in the synthesis, degradation and modification of complex carbohydrates such as plant polysaccharides (El Kaoutari et al., 2013). Even a mini-microbiome model containing 177 sequenced human gut bacterial members has approximately 16,000 different CAZymes (El Kaoutari et al., 2013).

Horizontal gene transfer is one possible factor contributing to the diverse enzymes and functional genes presented in the human gut microbes. For instance, porphyranases, a group of CAZymes identified in one marine bacteria, are commonly detected in the Japanese intestinal microbiota, but not in the microbiota of North American individuals (Hehemann et al., 2010). Dietary habitat of Japanese people (seaweed is a main food source) may provide an opportunity for the transfer of these enzymes from marine microbes to the human gut microbes (Hehemann et al., 2010). Thus, different human gut-associated microbes have a high convergence of several carbohydrate-active enzyme genes (Lozupone et al., 2008). However, some gut symbionts such as *Bacteroides cellulosilyticus* WH2, the genome of which is enriched in more CAZymes than other member of *Bacteroidetes*, can successfully compete with other bacteria for dietary polysaccharide utilization (McNulty et al., 2013). A recent study reveals the mechanisms by which a single gut bacteria *Bacteroides thetaiotaomicron* degrades rhamnogalacturonan-II, a known most structurally complex glycan, by using some previously undiscovered glycoside hydrolase enzyme families and activities, highlighting the importance of discovering new CAZymes in the gut microbiome (Ndeh et al., 2017).

2.5. Dietary features and gut microbial establishment

Dietary features are important factors influencing the establishment of gut microbiota in early life (Yatsunenko et al., 2012). It is well established that there are significant differences in the gut microbiome configuration between breast-fed and formula-fed infants (Yatsunenko et al., 2012; Zivkovic et al., 2011; Bäckhed et al., 2015). Generally, the gut microbiota of breast-fed infants has abundant probiotic bacteria such as *Bifidobacterium* and *Lactobacillus* (Zivkovic, German, Lebrilla, and Mills 2011). However, several pathogens including *Escherichia coli* and *Clostridium difficile* are often presented in the gut

microbiota of formula-fed infants (Penders et al., 2005). At the functional level, the gut microbiome of formula-fed infants is enriched in genes involved in bile acid biosynthesis and methanogenesis, whereas the microbiome of breast-fed infants is enriched in genes involved in biosynthesis and metabolism of amino acids and vitamins (Bäckhed et al., 2015). The human milk contains large number of bioactive substances that have diverse beneficial effects on the health status of infants. By transplanting the gut microbiota of a Malawian infant with severely undernutrition to GF mice or piglets, a recent study demonstrates that sialylated oligosaccharides in breast milk can produce a microbiota-dependent promotion on the growth and metabolism of infants (Charbonneau et al., 2016). Whether breast milk contains other bioactive components that can promote the growth of probiotic bacteria needs to be further investigated. Overall, these findings suggest that rational dietary intervention approaches favoring the establishment and shaping of a "healthy gut microbiota" in infancy will be crucial for the health throughout life.

2.6. Western-style diet, obesity and gut microbiota

It has been estimated that the prevalence of global obesity will reach about 20% by 2025 (NCD Risk Factor Collaboration (NCD-RisC) 2016). Notably, westernized dietary habit is likely an important force driving the development of obesity and obesity-associated metabolic disorders, such as type 2 diabetes and cardiovascular disease.

Extensive previous studies have investigated the associations between Western-style diet, obesity and gut microbiota. The gut microbiota of mice fed on a diet rich in saturated and unsaturated fats has a significantly higher abundance of Firmicutes and lower abundance of Bacteroidetes when compared with that of mice fed on a diet rich in complex plant polysaccharides (Turnbaugh et al., 2008). The analogous difference in microbial composition is also observed in obese *ob/ob* mice when compared to their lean counterparts (Ley et al., 2005). The increased abundance of Firmicutes may result from the significant increase of a bacterial member *Mollicutes*, which has a competitive advantage to the nutrient milieu of Western diet such as import and processing of simple sugars (Turnbaugh et al., 2008). These results indicate that the gut microbiota of obese mice may have an increased capacity of energy harvest from dietary nutrients (Turnbaugh et al., 2006).

The gut microbiota of obese mice may also affect host physiology by regulating host genes involved in the metabolism of dietary nutrients. For instance, the gut microbiota enhances the storage of triglycerides in adipocytes through suppressing the expression of a circulating lipoprotein lipase inhibitor fasting-induced adipose factor in the gut epithelium (Bäckhed et al., 2004). The gut microbiota is also able to reduce fatty acid oxidation in skeletal muscle and liver via inhibiting the activity of phosphorylated adenosine monophosphate-activated protein kinase (Bäckhed et al., 2007).

Westernized dietary habit is characterized by a higher intake of animal protein and fat as well as a lower intake of dietary fiber. Though the beneficial effects of dietary fiber on human health have been documented for decades (Burkitt and Trowell 1977), the mechanisms by which dietary fibers interact with the gut microbiota are still not fully understood. It has been reported that mice with high fiber consumption are protected against dextran sulphate sodium-induced colitis via GPR43- and GPR109AA-dependent inflammasome activation in the gut epithelium (Macia et al., 2015). Moreover, high-fiber diet is effective in preventing the development of allergic airway disease in both young and adult mice through increasing the production of SCFAs (Thorburn et al., 2015). A recent study shows that dietary fiber deprivation leads to a gut microbiota configuration characterized by the proliferation of mucus-degrading bacteria which choose host mucus as an alternative nutrient. Importantly, this fiber-deprived gut microbiota can enhance the disease susceptibility to a gastrointestinal pathogen *Citrobacter rodentium* by damaging the barrier function of colonic mucus layer (Desai et al., 2016).

As described in preceding sections, increased intake of dietary fiber results in a high level of gut microbial diversity, which may partly explain the lower prevalence of metabolic diseases in rural Africans than that of urban Westerners (Schnorr et al., 2014). Indeed, a high level of gut microbial diversity is of great significance for the maintenance of intestinal homeostasis, because it can help resist the perturbation and better adapt to a wide range of environmental factors such as dietary changes (Turnbaugh et al., 2009; Lozupone et al., 2012). A recent study reports that western-style diet will result in a "westernized microbiota", which may lead to the extinction of several gut bacterial lineages by generations (Sonnenburg et al., 2016). Moreover, individuals with increased risks of obesity-related metabolic disorders or inflammatory phenotypes often have a low level of microbial gene richness, while it can be improved through the intervention of long-term fiber consumption (Le Chatelier et al., 2013; Cotillard et al., 2013).

3. Microbial-derived small molecules

Large amounts of microbial-derived small molecules or bacterial components from the gut microbiota are considered to be important for the normal development of host immune functions, especially during early life after birth. However, disruption of the homeostatic relationships between gut microbiota and immune system may lead to the development of several immune-related health problems. Life-styles and diets may also be associated with the progressive increase of autoimmune diseases such as asthma and allergies, emphasizing the intimate interrelationships among diet, gut microbiota and host immune system. Thus, targeting the production of microbial-derived small molecules by dietary intervention may provide an applicable strategy for the maintenance of microbial-immune homeostasis.

3.1. Lipopolysaccharide (LPS)

LPS, a major component of the outer membrane of Gram-negative bacteria, is able to elicit strong immune response and inflammation. The gut microbiota contains abundant bacterial species with diverse structural composition of LPS (Berg 1996). In healthy humans, the plasma LPS concentration is significantly increased after a high fat diet (HFD) meal (Erridge et al., 2007). In mice, HFD-induced metabolic endotoxemia is

characterized by increased level of plasma LPS. Interestingly, continuous subcutaneous infusion of LPS causes several metabolic syndromes such as increased body weight and insulin resistance in wild-type, but not in CD14 (an innate immune receptor for LPS) mutant mice. These findings suggest that LPS-induced low-grade inflammation is a possible factor responsible for the occurrence of metabolic diseases (Cani et al., 2007a).

Antibiotic treatment of both HFD-fed and *ob/ob* obese mice decreases the level of plasma LPS (Cani et al., 2008). Alternatively, prebiotic oligofructose treatment also improves glucose homeostasis and inflammation development in HFD-fed mice possibly through selectively increasing the intestinal bacteria *Bifidobacterium*, which is negatively correlated with plasma LPS (Cani et al., 2007b). These findings indicate that gut microbiota is the main source for the circulating LPS in metabolic diseases. Indeed, another study further confirms this notion by detecting large numbers of live intestinal bacteria in adipose tissue and blood during the early onset of HFD-induced diabetes, suggesting that a certain amount of LPS can pass through the intestinal epithelium and reach specific tissues to induce chronic inflammation (Amar et al., 2011).

The theory of intestinal bacterial translocation highlights the importance of gut microbiota in the pathogenesis of metabolic diseases such as obesity. During the process of intestinal bacterial translocation, gut-derived LPS first adheres to mucosal surface and then co-localizes with dendritic cells (DCs) (Amar et al., 2011). The intestinal epithelial and immune cells have several microbial pattern recognition receptors such as nod-like and toll-like receptors (TLR) for the recognition of LPS (Amar et al., 2011). Furthermore, LPS is internalized by intestinal epithelial cells and is transported it to the Golgi compartment, where newly formed chylomicrons may promote its incorporation into mesenteric lymph nodes and further delivery into the circulation (Hornef et al., 2002; Vishnyakova et al., 2003; Ghoshal et al., 2009). It should be noted that gut-derived LPS can also be absorbed into lymph and circulation via paracellular route (passive diffusion) or transcellular route (active absorption) (Hersoug et al., 2016). Given the important role of intestinal epithelium in preventing the translocation of LPS, prebiotic administration can improve HFD-induced endotoxemia by improving the compromised gut barrier integrity in *ob/ob* mice (Cani et al., 2009). Moreover, oral supplementation with alkaline phosphatase secreted by intestinal cells is also able to prevent HFD-induced metabolic syndrome and endotoxemia (Bates et al., 2007; Kaliannan et al., 2013) (Figure 2).

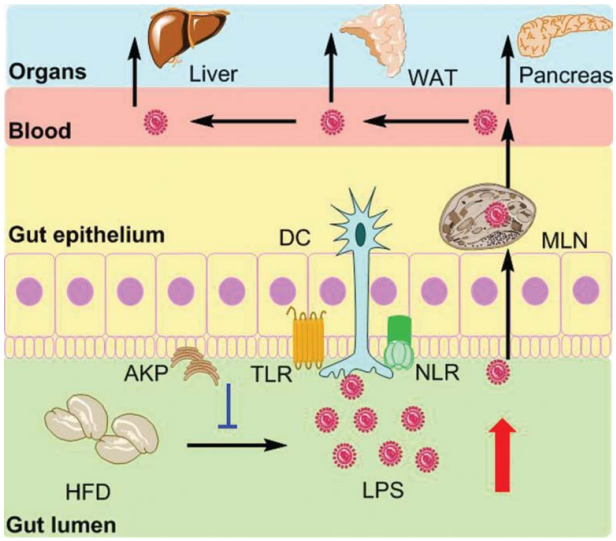

Figure 2. The process of intestinal translocation of LPS. HFD induces increased levels of LPS, which will pass though the intestinal epithelial and reach the LMN. During this process, TLR and NLR of intestinal epithelial cells and DCs are involved in the recognition of LPS. Furthermore, LPS arrives at specific organs such as liver, WAT and pancreas to cause inflammatory responses and metabolic disorders. However, AKP secreted by intestinal epithelial cells can detoxify LPS and prevent HFD-induced endotoxemia. AKP, alkaline phosphatase; DC, dendritic cell; HFD, high fat diet; LPS, lipopolysaccharide; MLN, mesenteric lymph node; NLR, nod-like receptor; TLR, toll-like receptor; WAT, white adipose tissue.

3.2. Polysaccharide A (PSA)

PSA is an important immunomodulatory bacterial molecule that mediates the co-evolution between gut microbiota and host immune system. It has been demonstrated that PSA is required for the modulation of $CD4^+$ T-cell homeostasis and cytokine production by human gut symbiotic *Bacteroides fragilis* (Mazmanian et al., 2005). Moreover, PSA produced by *Bacteroides fragilis* has a protective effect against inflammatory colitis through suppressing the production of pro-inflammatory interleukin (IL)-17 in intestinal immune cells and inducing the generation of IL-10-producing $CD4^+$ T cells (Mazmanian et al., 2008). Furthermore, by suppressing TLR-2-mediated immune responses in $Foxp3^+$ regulatory T cells (T_{reg} cells), *Bacteroides fragilis* can use PSA for its commensal colonization in a unique mucosal niche of the gut (Round et al., 2011). Notably, the conversion of $CD4^+$ T cells into $Foxp3^+$ T_{reg} cells is an important mechanism by which PSA induces gut mucosal tolerance during commensal colonization (Round and Mazmanian 2010). Overall, these studies about PSA functions provide examples illustrating how host immune system distinguishes between pathogenic microbes and beneficial bacteria of gut microbiota. Further research is required to develop appropriate dietary strategies that help maintain host-commensal symbiosis through modulating PSA-mediated host immune responses.

4. Microbial-modulated metabolites

Apart from influencing the composition of intestinal microbial community, complex dietary components that cannot be fully metabolized by the host can be degraded by gut microbes to produce large number of metabolites, which serve as crucial messengers driving continuous communications between the host and the gut microbiota. In this section, we will highlight prominent examples of microbial-modulated metabolites associated with dietary nutrients, as well as the mechanisms of how these metabolites influence host physiology at the molecular level.

4.1. SCFAs

SCFAs, including acetate, propionate and butyrate, are the end bacterial fermentation products of dietary fiber in the colon. It has been known that SCFAs contribute to an important proportion of energy sources for the host (den Besten et al., 2013). Moreover, recent studies have provided numerous evidences

that SCFAs are critical signaling factors by which gut microbiota regulates host development and homeostasis even under steady-state conditions. For instance, microglia is the macrophage located throughout the brain and spinal cord and is crucial for the immune response in the central nervous system (CNS). The microglia of GF mice displays significant immaturity and malformation compared with that of specific pathogen free (SPF) mice. However, the defective functions of microglia in GF mice are partially restored by SCFAs supplementation (Erny et al., 2015). Similarly, compared with SPF mice, GF mice exhibit increased permeability of blood-brain barrier, which can also be improved by SCFAs treatment (Braniste et al., 2014).

G protein-coupled receptors free fatty acid receptor (FFAR) 2/GPR43 and FFAR3/GPR41 are two well known receptors of SCFAs (Brown et al., 2003; Le Poul et al., 2003; Nilsson et al., 2003). GPR43 is mainly expressed in immune cells such as neutrophils and monocytes, whereas GPR41 is widely expressed in different tissues (Brown et al., 2003; Le Poul et al., 2003). An early study demonstrates that GPR41 expression in gut epithelium is required for gut microbiota-dependent decrease of intestinal transit rate and increase of energy harvest from diet (Samuel et al., 2008). Moreover, a recent study reports that GPR43-deficient mice exhibit obesity under HFD induction, whereas mice with GPR43 overexpression in adipose tissue are lean. Interestingly, both of the phenotypes can be abrogated by antibiotic treatment (Kimura et al., 2013). These findings suggest that SCFAs receptors play crucial roles in connecting diet, gut microbiota and host health.

4.1.1. Acetate

Accumulating evidences show that acetate plays an important role in regulating metabolic functions of the host. For instance, in a human pilot study, acetate significantly increases the plasma peptide YY (PYY) and glucagon like peptide (GLP)-1 levels in six hyperinsulinaemic female subjects (Freeland and Wolever 2010). Acetate can reduce appetite by promoting glutamate-glutamine transcellular cycle and increasing lactate and γ-Aminobutyric acid (GABA) production in hypothalamic arcuate nucleus (Frost et al., 2014). A recent study demonstrates that gut microbiota-dependent acetate production results in parasympathetic nervous system activation, and consequently driving glucose-stimulated β-cell insulin secretion in HFD-induced mice (Perry et al., 2016). This study may explain why increased concentration of acetate is observed in the feces of obese people (Schwiertz et al., 2010). Indeed, by acting as a ligand for GPR43, acetate inhibits insulin-mediated fat accumulation by suppressing insulin signaling in adipocytes (Kimura et al., 2013). Taken together, these findings indicate that acetate is able to regulate cellular process directly by functioning as a signaling molecule or affect host physiology indirectly via the activation of nervous system.

Recent studies also confirm that acetate exerts multiple effects on the modulation of immune system. For example, acetate feeding suppresses the development of allergic airway inflammation through promoting Foxp3-regulated T_{reg} cell numbers and function (Thorburn et al., 2015). Moreover, acetate can directly induce T-cell differentiation into effector and T_{reg} cells via the regulation of mTOR–S6K pathway (Park et al., 2015). In colonic epithelial cells, GPR43 is required for acetate-induced K^+ efflux, hyperpolarization as well as inflammasome activation (Macia et al., 2015). In addition, acetate produced by probiotic *Bifidobacterium* improves the defense functions of gut epithelial cells and protects the host against enteropathogenic *Escherichia coli* O157:H7-induced lethal infection (Fukuda et al., 2011) (Table 1).

4.1.2. Propionate

Early studies have demonstrated that propionate can be served as a primary substrate for hepatic gluconeogenesis and the beneficial effects of propionate on host metabolism may be partly mediated through its influences on hepatic carbohydrate metabolism in the liver (Anderson and Bridges 1984; Venter et al., 1990). Propionate is able to stimulate the release of anorectic gut hormones PYY and GLP-1 from human colonic cells *in vitro*. However, gut hormone release is induced following short-term, but not long-term propionate supplementation, suggesting that short-term stimulation may contribute to the beneficial effects of propionate on host metabolism (Chambers et al., 2015).

Besides liver and intestine, propionate also displays active effects on the immune and nervous system. Propionate is able to promote Foxp3 and IL-10 expression in colonic T_{reg} cells via the regulation of GPR43-mediated histone deacetylase (HDAC) inhibition (Smith et al., 2013). In the lung, propionate enhances bone marrow hematopoiesis, impairs the ability to activate T helper type 2 effector cells, and exerts a protective effect against allergic airway inflammation in a GPR41-dependent manner (Trompette et al., 2014). However, propionate suppresses food intake, stimulates gut hormone secretion, and protects against diet-induced obesity through a GPR41-independent mechanism (Lin et al., 2012). Moreover, by regulating

Table 1. Effects of acetate on host functions and the signaling mechanisms.

Target site	Function	Signaling mechanism	Selected references
Plasma	Increase PYY and GLP-1 secretion		Freeland and Wolever, 2010
Hypothalamic arcuate nucleus	Reduce appetite	Glutamate-glutamine transcellular cycle and lactate and GABA production	Frost et al., 2014
β-cell	Stimulate insulin secretion	Parasympathetic nervous system activation	Perry et al., 2016
Adipocytes	Inhibit fat accumulation	GPR43 activation	Kimura et al., 2013
T-regulatory cell	Promote cell number and function	Foxp3 signaling	Thorburn et al., 2015
T-cell	Promote differentiation into effector and T_{reg} cells	mTOR–S6K pathway	Park et al., 2015
Colonic epithelial cells	Induce K^+ efflux, hyperpolarization and inflammasome activation	GPR43 activation	Macia et al., 2015
Gut epithelial cells	Improve defense functions		Fukuda et al., 2011

GPR41-mediated activity of sympathetic nervous system, propionate can control energy expenditure and maintains metabolic homeostasis (Kimura et al., 2011). Similarly, the activation of intestinal gluconeogenesis by propionate is also via a GPR41-mediated gut-brain neural circuit mechanism (De Vadder et al., 2014). Thus, these data indicate that microbial-derived propionate may affect host physiology by different mechanisms, which may be attributable to the functions of propionate on specific tissues (Lin et al., 2012) (Table 2).

4.1.3. Butyrate

Butyrate, one of the most abundant SCFAs presented in the colonic lumen, plays critical roles in regulating gastrointestinal motility and enteric nervous system (Louis and Flint 2007; Soret et al., 2010). The normal colonocytes use microbial-produced butyrate as a primary energy source for important metabolic processes such as β oxidation, TCA cycle and oxidative phosphorylation. However, colonocytes of GF mice undergo increased autophagy, which can be restored with butyrate supplementation (Donohoe et al., 2011). Moreover, butyrate can also have an effect on the promotion of brain neural proliferation and neurogenesis (Kim et al., 2009; Yoo et al., 2011). An early study reports that dietary supplementation of butyrate can prevent obesity and insulin resistance by promoting energy expenditure and mitochondria function in skeletal muscle and brown fat (Gao et al., 2009). A recent finding suggests that cAMP-dependent induction of intestinal gluconeogenesis may contribute to the beneficial effects of butyrate on glucose and energy homeostasis (De Vadder et al., 2014).

Interestingly, there are some contradictory effects of butyrate on the growth of colonocytes. For instance, butyrate promotes the proliferation of normal colonocytes by acting as an oxidative energy source, whereas it inhibits the growth of cancerous colonocytes by altering the expression of many genes involved in cell proliferation, apoptosis, and differentiation (Donohoe et al., 2012). The metabolic differences of normal colonocytes and cancerous colonocytes (Warburg effect) may be responsible for the opposing effects (Donohoe et al., 2012). As a HDAC inhibitor, butyrate can inhibit the proliferation of intestinal epithelial stem/progenitor cells through a Foxo3-dependent mechanism (Kaiko et al., 2016). However, in a mice model of colorectal cancer ($Apc^{Min/+}MSH2^{-/-}$), butyrate induces aberrant proliferation and transformation of colon epithelial cells via the activation of Wnt/β-catenin signaling pathway (Belcheva et al., 2014). Overall, these findings indicate that the effects of butyrate on the growth of colonocytes may be dependent on the dose of treatment or the metabolic and genetic backgrounds of cells.

Butyrate is also critical for the maintenance of intestinal immune homeostasis. For instance, butyrate can modulate immune responses of intestinal macrophages and DCs via the inhibition of HDAC (Singh et al., 2010; Chang et al., 2014). Additionally, by activating GPR109A, a cell surface G-protein–coupled receptor expressed at high level in normal colon cells but low level in colon cancer cells, butyrate induces the expression of anti-inflammatory molecules in macrophages and DCs and enables them to support differentiation of T_{reg} cells and IL-10-producing T cells, thereby suppressing colonic inflammation and carcinogenesis (Furusawa et al., 2013; Singh et al., 2014). Notably, the differentiation of periphery T_{reg} cells can also be induced by butyrate treatment (Arpaia et al., 2013) (Table 3).

4.2. Bile acids

The synthesis of primary bile acids takes place in the liver, where at least 17 different enzymes are involved in the modification, cleavage and conjugation of cholesterol (Russell 2003) (Figure 3). This complex process mainly comprises two pathways: the classical (or neutral) pathway and the alternative (or acidic) pathway (de Aguiar Vallim et al., 2013). Prior to secretion, bile acids are conjugated with taurine (mouse) or glycine (human), and are then stored in gallbladder until released into duodenum after a meal (de Aguiar Vallim et al., 2013). Approximately 95% of secreted bile acids are then reabsorbed in ileum and transported back to liver via the process of enterohepatic circulation (de Aguiar Vallim et al., 2013). Cholic acid (CA) and chenodeoxycholic acid (CDCA) are the primary bile acids formed in humans, whereas CA and muricholic acid (MCA), predominantly beta-MCA (βMCA), are the primary bile acids synthesized in rodents (de Aguiar Vallim et al., 2013).

It should be noted that a small percentage of primary bile salts can enter the large intestine, where they are deconjugated and converted into secondary bile acids deoxycholic acid (DCA) and lithocholic acid (LCA) through gut bacteria-mediated activity of C24 amide hydrolysis and 7α-dehydroxylation (Wahlström et al., 2016). Bile salt hydrolase (BSN) is the first step for bacterial metabolism of conjugated primary bile acids (Jones et al., 2008). It has been reported that BSN activity is generally conserved and enriched in all major bacterial

Table 2. Effects of propionate on host functions and the signaling mechanisms.

Target site	Function	Signaling mechanism	Selected references
Liver	Regulate gluconeogenesis and carbohydrate metabolism		Anderson and Bridges, 1984; Venter et al., 1990
Colonic cells	Stimulate PYY and GLP-1 secretion		Chambers et al., 2015
Colonic T_{reg} cells	Promote Foxp3 and IL-10 expression	GPR43-mediated HDAC inhibition	Smith et al., 2013
Lung	Enhance bone marrow hematopoiesis and decrease T helper type 2 effector cell activity	GPR41 activation	Trompette et al., 2014
Sympathetic nervous system	Control energy expenditure and maintain metabolic homeostasis	GPR41 activation	Kimura et al., 2011
Intestine	Activate gluconeogenesis	GPR41-mediated gut-brain neural circuit	De Vadder et al., 2014

Table 3. Effects of butyrate on host functions and the signaling mechanisms.

Target site	Function	Signaling mechanism	Selected references
Colon	Regulate gastrointestinal motility and enteric nervous system		Louis and Flint, 2007; Soret et al., 2010
Colon	Regulate β oxidation, TCA cycle and oxidative phosphorylation	As a primary energy source	Donohoe et al., 2011
Brain	Promote neural proliferation and neurogenesis		Kim et al., 2009; Yoo et al., 2011
Skeletal muscle and brown fat	Promote energy expenditure and mitochondria function		Gao et al., 2009
Intestine	Regulate glucose and energy homeostasis	cAMP-dependent gluconeogenesis	De Vadder et al., 2014
Normal colonocytes	Promote proliferation	As an oxidative energy source	Donohoe et al., 2012
Cancerous colonocytes	Inhibit growth	Regulation of genes involved in cell proliferation, apoptosis, and differentiation	Donohoe et al., 2012
Intestinal epithelial stem/ progenitor cells	Inhibit proliferation	Foxo3-dependent HDAC inhibition	Kaiko et al., 2016
Colon epithelial cells of $Apc^{Min/+}MSH2^{-/-}$ mice	Induce proliferation	Wnt/β-catenin signaling	Belcheva et al., 2014
Intestinal macrophages and DCs	Modulate immune response	HDAC inhibition	Singh et al., 2010; Chang et al., 2014
Intestinal macrophages and DCs	Promote differentiation of T_{reg} cells and IL-10-producing T cells	GPR109A activation	Furusawa et al., 2013; Singh et al., 2014
Periphery T_{reg} cells	Promote differentiation		Arpaia et al., 2013

divisions and archaeal species of gut microbiome and may help facilitate a survival advantage for microbial colonization to intestine by mitigating the toxic effects of conjugated primary bile acids (Jones et al., 2008). Consequently, 7α-dehydroxylation is the most important metabolic process for DCA and LCA production, which are mainly carried out by gut bacteria belong to genus *Clostridium*, such as *C. scindens, C. hiranonis, C. hylemonae* (Clostridium cluster XVIa) and *C. sordelli* (Clostridium cluster XI) (Ridlon et al., 2006) (Figure 3).

High concentrations of DCA and LCA in blood, bile and feces have been associated with increased risks of cholesterol gallstone disease and colon cancer (Ridlon et al., 2006). Moreover, DCA-provoked senescence-associated secretory phenotype in hepatic stellate cells may also play a key role in promoting obesity-associated hepatocellular carcinoma development (Yoshimoto et al., 2013). However, *Clostridium scindens*, a bile acid 7α-dehydroxylating intestinal bacterium, can protect the host against *Clostridium difficile*-induced intestinal infection by restoring the relative abundance of secondary bile acids (Buffie et al., 2015). Although the exact roles of secondary bile acids in humans are still unclear, the results stated above suggest that secondary bile acids may have dual (beneficial and harmful) functions in regulating host physiology.

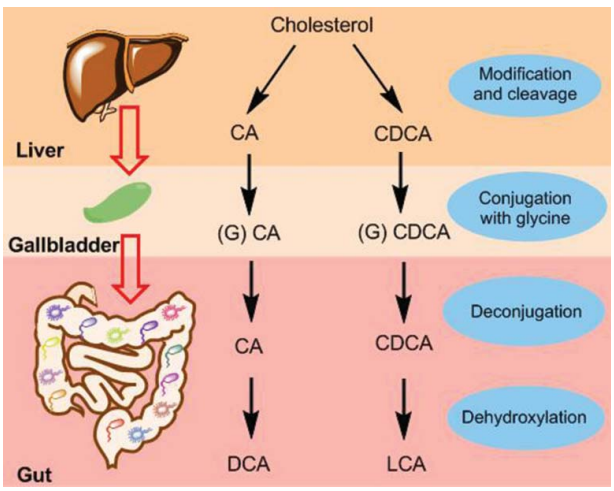

Figure 3. The process of bile acid synthesis and metabolism in humans. In the liver, primary bile acids CA and CDCA are formed through the modification and cleavage by the enzymes. Furthermore, new formed CA and CDCA are then conjugated with glycine and stored in the gallbladder. Consequently, the primary bile acids that enter into the gut can be converted into secondary bile acids DCA and LCA through the metabolism of the gut microbiota. CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; G, glycine; LCA, lithocholic acid.

Except DCA and LCA, other secondary bile acids may also play key roles in regulating gut microbial ecology of the host. For example, isoDCA, the 3β-OH epimer of DCA, can be produced by gut bacteria such as *Ruminococcus gnavus, Clostridium perfringens* and *Eggerthella lenta* (Devlin and Fischbach 2015). Importantly, the conversion of DCA to isoDCA decreases the damage to bacterial cell membrane, thereby favoring the growth of *Bacteroides* (Devlin and Fischbach 2015). Further studies are warranted to study the critical roles of other forms of secondary bile acids in regulating host physiology.

It have been demonstrated that the bile acids pool size is significantly decreased in SPF mice compared to GF mice (Sayin et al., 2013). Since bile acids have direct antimicrobial activities on gut microbes (Begley et al., 2005), administration of bile acids can induce profound alterations in rat gut microbial composition (Islam et al., 2011). However, some intestinal pathogens are bile acids-resistant. For instance, taurine-conjugated hepatic bile acid, the production of which is promoted by a diet high in milk-derived fat, can favor the growth of a sulphite-reducing pathobiont *Bilophila wadsworthia*, thereby resulting in the dysbiosis of intestinal immune homeostasis (Devkota et al., 2012). Moreover, fecal samples of advanced cirrhotic patients have a high abundance of *Enterobacteriaceae*, which is positively correlated with increased concentration of primary bile acid CDCA, while low abundance of 7α-dehydroxylating bacteria *Ruminococcaceae* is associated with decreased concentration of secondary bile acid DCA (Kakiyama et al., 2013). All together, these findings suggest that there is a close connection between gut microbiota and bile acid metabolism.

Farnesoid X receptor (FXR), which is highly expressed in liver and ileum, plays a key role in preventing bacterial

overgrowth and disruption of intestinal epithelial barrier (Inagaki et al., 2006). Moreover, FXR is also a crucial bile acid receptor by which gut microbiota regulates host signaling (Teodoro et al., 2011). For example, gut microbiota suppresses liver bile acid synthesis via increasing FXR-dependent expression of fibroblast growth factor (Fgf)-15 in the ileum (Sayin et al., 2013). Colonization of gut flora with VSL#3 probiotics also promotes fecal bile acid excretion and hepatic bile acid synthesis via the modulation of FXR-Fgf15 axis (Degirolamo et al., 2014). A recent study shows that gut microbiota promotes diet-induced hepatic steatosis and obesity through an FXR-dependent mechanism (Parséus et al., 2016). Moreover, by inhibiting intestinal FXR signaling pathway, the increased tauro-βMCA levels, which is caused by decreased *Lactobacillus* abundance and BSH enzymatic activity, may be responsible for the improvement of tempol on HFD-induced obesity (Li et al., 2013).

4.3. Trimethylamine N-oxide (TMAO)

Dietary foods that is enriched in choline and phosphatidylcholine can be metabolized by gut microbiota to form TMA, which is further transformed into its oxidation product TMAO in the liver (Wang et al., 2011). It has been demonstrated that plasma TMAO level is strongly associated with the development and pathogenesis of cardiovascular diseases (Wang et al., 2011). The mechanisms by which TMAO induce atherosclerosis include: i) promoting macrophage foam cell formation by increasing the expression of macrophage scavenger receptors CD36 and SR-A1 (Wang et al., 2011); ii) suppressing reverse cholesterol transport and altering sterol metabolism (Koeth et al., 2013); iii) increasing thrombosis risk via enhancing intracellular $Ca2^{+}$ release-dependent platelet hyperreactivity (Zhu et al., 2016). L-carnitine, an abundant component in red meat, can also accelerate atherosclerosis through microbiota-dependent TMAO production (Koeth et al., 2013). 3,3-dimethyl-1-butanol, a structural analog of choline which is presented in some balsamic vinegars, red wines as well as cold-pressed extra virgin olive oils, can prevent atherosclerosis development by serving as an inhibitor to block microbiome-dependent TMA production (Wang et al., 2015). Moreover, resveratrol, a natural phytoalexin, is also able to attenuate TMAO-induced atherosclerosis via the inhibition of gut microbial TMA formation (Chen et al., 2016).

4.4. Indole derivatives

Gut bacteria such as *Lactobacilli* reuteri and *Lactobacilli johnsonii* can metabolize tryptophan into indole derivatives that are involved in the regulation of gut immune homeostasis by functioning as aryl hydrocarbon receptor (AHR) ligands (Zelante et al., 2013). It has been demonstrated that AHR is a highly conserved transcription factor that is crucial for the postnatal expansion, maintenance, and function of $ROR\gamma t^{+}$ innate lymphoid cells (ILCs) (Qiu et al., 2012), as well as the formation of intestinal lymphoid follicles (Kiss et al., 2011). $AHR^{-/-}$ mice display decreased IL-22 production, which may result from deficiency of natural killer $p46^{+}$ and lymphoid tissue-inducer-like ILCs (Lee et al., 2011). Moreover, AHR activation by dietary ligands from cruciferous vegetables is required for the maintenance of intraepithelial lymphocytes at the epithelial sites. However, AHR deficiency or the absence of AHR activation leads to reduced epithelial turnover, impaired microbial control and increased intestinal immunopathology (Li et al., 2011). Furthermore, AHR pathway activation promotes cytochrome P4501 (CYP1) enzyme activity in intestinal epithelial cells, which have an important feedback role in the metabolic clearance of AHR ligands, thereby decreasing the protection against *Citrobacter rodentium*-induced intestinal infection (Schiering et al., 2017). Thus, increasing the availability of AHR ligands such as indole derivatives through microbiota-based dietary supplementation is critical for the maintenance of intestinal immune homeostasis. Further studies are needed to determine whether there are other microbial metabolites associated with dietary nutrients as the AHR ligands.

Caspase recruitment domain family member 9 (CARD9) is an important inflammatory bowel disease susceptibility gene involved in immune response to gut bacteria. $Card9^{-/-}$ mice display an altered gut microbiota characterized by impaired ability of tryptophan metabolism and decreased production of AHR ligands. The altered gut microbiota in $card9^{-/-}$ mice may contribute to the increased sensitivity of $Card9^{-/-}$ mice to colitis (Lamas et al., 2016). Indole derivatives also have an effect on the regulation of CNS functions. For example, AHR expression in astrocytes limits CNS inflammation, potentially via the control of cytokine signaling 2-dependent NF-κB activation. Dietary supplementation with indole derivatives activate AHR signaling in astrocytes, thereby suppressing CNS inflammation (Rothhammer et al., 2016).

4.5. Retinoic acid (RA)

RA is an important vitamin A metabolite that implicated in the regulation of immune homeostasis. Notably, the expression of RA-associated genes is highly increased in the peripheral lymph nodes of SPF mice when compared with that of GF mice, suggesting that gut microbiota may play a crucial role in promotion of RA-mediated secondary lymphoid organ development (Zhang et al., 2016). Moreover, vitamin A insufficiency also causes impaired mucosal and systemic $CD4^{+}$ T cell responses during *Toxoplasma gondii* infection, which can be restored by RA treatment. However, the effects of RA on T cell function are abrogated by the antagonism of RA receptor (RAR) or the deficiency of RARα ($Rar\alpha^{-/-}$), suggesting the importance of RA-RARα signaling axis in the promotion of T cell activation during immune tolerance (Hall et al., 2011). Taken together, these findings highlight strong correlations between nutritional metabolism and immune regulation. However, whether the gut microbiota is involved in RA production has yet to be determined.

5. Other microbial-associated molecules and metabolites

Apart from the above mentioned components, a vast number of other microbially produced and modulated metabolites as well as their functions on host physiology and pathology have been studied recently.

Succinate, an important metabolite produced by gut microbiota during fermentation of dietary fiber, improves glucose

and insulin tolerance by activating intestinal gluconeogenesis and decreasing hepatic glucose production (De Vadder et al., 2016). Urolithin A is an microbial metabolite of the natural compound ellagitannin from pomegranate fruit. Urolithin A administration extends lifespan in *C. elegans* and improves muscle function in rodents through induction of autophagy in mitochondria (Ryu et al., 2016). Moreover, gut microbial metabolites taurine, histamine, and spermine can positively or negatively modulate NLRP6 inflammasome signaling, epithelial IL-18 production and antimicrobial peptide secretion in the gut, thereby contributing to the construction of a symbiotic host-microbiome intestinal microenvironment (Levy et al., 2015). Another study reports that increased levels of several gut microbial products such as 4-ethylphenylsulfate and indolepyruvate are presented in serum of mice with autism spectrum disorder (Hsiao et al., 2013). However, which specific gut bacteria is responsible for the production of these metabolites and whether dietary changes can have an impact on the production of these metabolites remains to be further investigated.

Anthocyanins are a group of flavonoids that are abundant in various colorful fruits and vegetables. Microbial metabolism of anthocyanins results in the production of protocatechuic acid, which prevents the development of atherosclerosis via promoting miRNA-10b-mediated reverse cholesterol transport in macrophages (Wang et al., 2012). Moreover, a recent study demonstrates that dietary flavonoids apigenin and naringenin may impact host energy expenditure by increasing the expression of thermogenic factor uncoupling protein 1 in brown adipose tissue. In contrast, the weight management effects of these flavonoids can be abrogated by HFD treatment, which causes an altered gut microbiome characterized by elevated levels of flavonoid-degrading bacteria (Thaiss et al., 2016).

6. Conclusion and future perspective

In this review article, we provide an overview about the pivotal role of dietary nutrients in shaping and influencing the composition, function and metabolism of the gut microbiota. Generally, the findings described here suggest that high fiber intake appears to be an effective dietary strategy improving health and reducing the risk of diseases. From the perspective of improving gut microbial ecology, the health benefits of plant fiber are not only attributed to the consumption of complex plant polysaccharides which provide important energetic substrates for the growth of beneficial bacteria in the gut, but also due to the production of large amounts of microbial metabolites such as SCFAs and indole derivatives which are involved in regulating key physiological functions in immune system, metabolic system and nervous system of host. In contrast, western-style diet may lead to a dysbiotic gut microbiota, which is characterized by the prolonged loss of several crucial microbial lineages, genes and functional pathways that have demonstrated to be strongly associated with the increasing prevalence of obesity and other metabolic syndromes. Accordingly, detailed understanding of the intricate relationships between diet and gut microbiota may provide a new avenue for human health improvement.

One increasing research interest regarding the relationships between gut microbiota and diet is the production of numerous microbial-associated small molecules and metabolites as well as their functional roles in host biology. We also highlight prominent examples of how these microbial-associated components impact host physiology and pathology at the signaling level. It can be assumed that these metabolites may play an obligatory role in connecting host and microbiota and driving a close interaction between them. Future studies will be needed for determining whether there exists other novel microbial-associated compounds associated with dietary nutrients and their bioactive functions. Understanding their key roles in host health and disease is an important step for developing and designing next generation of dietary nutrients targeting the gut microbiota.

It should be noted that the goal of improving health by dietary nutrients can be achieved by using integrated multi-omics approaches, such as transcriptomics, metagenomics, metatranscriptomics and metabolomics, which may help provide a global landscape of the host-microbe interactions under dietary intervention. Moreover, gnotobiotic model with sequenced commensal human gut bacteria will give a comprehensive knowledge about how individual microbial member in response to specific dietary nutrients.

Acknowledgments

This work was supported by the Beijing Municipal Science and Technology Project under Grant D161100005416001; and the Chinese Universities Scientific Fund under Grant 2016SP003.

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