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The gut microbiota: A treasure for human health☆

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ABSTRACT

The interplay between the host and host-associated gut microbiota is an area of increasing interest during the recent decade. From young infants to elderly people, from primitive tribes to modern societies, accumulating evidence has suggested the association of critical physiological roles of gut microbiota in the pathogenesis of a variety of human metabolic, immunological and neurological diseases. Importantly, it appears that the relationship between the gut microbiota and disease is bidirectional, instead of causal or consequential. Personalized nutritional and therapeutic strategies targeting the gut microbiota such as prebiotics, probiotics, drugs and fecal microbiota transplantation may create a new era in the human health.

Contents

Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; ASD, autism spectrum disorder; BBB, blood-brain barrier; CVD, cardiovascular disease; CDI, *Clostridium difficile* infection; CD, Crohn's disease; DSS, dextran sulphate sodium; eCB, endocannabinoid; Fiaf, fasting-induced adipose factor; FMT, fecal microbiota transplantation; FOS, fructooligosaccharides; GPR, G protein-coupled receptor; GABA, γ-Aminobutyric acid; GF, germ-free; GLP-1, glucagon-like peptide 1; HFD, high fat diet; IBD, inflammatory bowel disease; IL-1, interleukin-1; IGN, intestinal gluconeogenesis; IBS, irritable bowel syndrome; KO, knockout; LPS, lipopolysaccharide; LPL, lipoprotein lipase; MyD88, myeloid differentiation factor-88; NAFLD, non-alcoholic fatty liver disease; NLR, nod-like receptors; NOD, nonobese diabetic; Nod1, nucleotide-binding oligomerization domain 1; PYY, peptide YY; PAI-1, plasminogen activator inhibitor-1; SFB, segmented filamentous bacteria; SCFAs, short-chain fatty acids; SPF, specific pathogen free; T_{FH}, T follicular helper; TLR, Toll-like receptor; TMAO, trimethylamine *N*-oxide; TNF-α, tumor necrosis factor-α; T1D, type 1 diabetes; T2D, type 2 diabetes; 5-HT, 5-hydroxytryptamine.

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1. Introduction

The reciprocal co-evolution between mammals and their gut microbes has lasted for hundreds of millions of years (Ley et al., 2008). Scientific efforts for understanding the relationships between humans and human-associated microbial communities are never stopped and have made a great progress in the achievements of Human Microbiome Project (Human Microbiome Project Consortium, 2012) and MetaHit Project (Qin et al., 2010). We now have a better understanding of a complex ecosystem residing within our distal intestinal tract: the gut microbiota, especially the role it plays in our health and disease (Qin et al., 2010).

The human gut microbiota which is composed of approximately 10 to 100 trillions of microorganisms is estimated to outnumber human body cells by a factor of ten (Bäckhed et al., 2005). It means that, as a whole "superorganism", the body made up of 10% of our cells and the rest 90% comprises of microbial cells (Zhao, 2013). Moreover, the whole genome of the gut microorganisms which is known as the gut microbiome comprises about 150 times more genes than the human genome (Qin et al., 2010). Previous studies have defined numerous functional features of the gut microbiome, such as fermentation of indigestible dietary polysaccharides, synthesis of essential amino acids and vitamins, and metabolism of xenobiotic drugs (Gill et al., 2006; Qin et al., 2010; Yatsunenko et al., 2012; Cabreiro et al., 2013). The cross-talks between the gut microbiota and other body parts including the metabolic, immune and nervous system have become the topics of study over the past decade.

In this review article, we highlight the important findings which are published during the recent decade with regard to the subject of gut microbiota and its association with human health and disease. We first summarize the general features of the gut microbiota, and describe the characteristics of gut microbiota from specific age groups of people and different geographic regions. Next, we focus on discussing the relationships between the gut microbiota and three major types of human diseases i.e. metabolic, immunological, and neurological diseases. Finally, we propose four promising therapeutic approaches including prebiotics, probiotics, drugs and fecal microbiota transplantation (FMT) to be utilized in the improvement of human health through modulating the gut microbial ecology.

2. General characteristics of gut microbiota

2.1. Composition

The human intestinal microbiota is a large and diverse community containing several types of life: bacteria, archaea, eukarya, viruses and parasitea (Lozupone et al., 2012; Reyes et al., 2010). The total number of microbial cells in the intestinal tract constitutes around 10^{13}–10^{14} (Ley et al., 2006a). It has been estimated that over 1000 bacterial species inhabit within the human intestinal tract (Qin et al., 2010). The vast majority of bacterial species belong to two most common bacterial phyla: Bacteroidetes and Firmicutes (Bäckhed et al., 2005; Eckburg et al., 2005). With the advancement of modern bioinformatic techniques such as targeted 16S rRNA pyrosequencing and un-targeted whole-genome metagenomic sequencing, a number of novel microbes are gradually being detected. More importantly, it is now recognized that a large proportion of human gut microbes can be cultured in vitro under strict anaerobic conditions (Goodman et al., 2011; Walker et al., 2014; Browne et al., 2016).

2.2. Diversity and dynamics

Homeostasis of the gut microbial communities is characterized by the co-existence of various microbial species in low or in high abundance (Arumugam et al., 2011). Healthy people often has a high level of gut microbial richness, while a people with ill health such as obesity and low-grade inflammation has lower gut microbial species (Le Chatelier et al., 2013; Cotillard et al., 2013). In view of ecology, the more abundant biodiversity an ecosystem has, the better ability it would have to resist the perturbation from outside environment (Turnbaugh et al., 2009). In fact, competitive interactions of the increased microbial species may help in maintaining the gut microbiome stability (Coyte et al., 2015).

The gut microbial ecology is dynamic and this means that not all bacterial members can colonize the gut permanently. The co-evolution between the commensal microbes and their host drives them in developing numerous mechanisms in favor of their colonization. For instance, *Lactobacillus rhamnosus* GG adheres efficiently to the human intestinal mucus by encoding a mucus-binding pili protein (Kankainen et al., 2009). Another example includes *Bacteroides fragilis* which produces multiple surface capsular polysaccharides for colonizing the intestinal tract (Liu et al., 2008). These indigenous commensal bacteria also play crucial roles in defending against the invasion of exogenous opportunistic pathogens through the mechanism of competitive exclusion (Belzer and de Vos, 2012). For example, *Bifidobacterium longum* subsp. *longum* JCM 1217^T protects against *E. coli* O157:H7-induced enteropathogenic infection by promoting acetate-mediated defense functions of host colonic epithelial cells (Fukuda et al., 2011).

2.3. Differences and similarities

It has been established that there is significant inter-individual variation in the gut microbiota composition among populations (Turnbaugh et al., 2009; Qin et al., 2010; Human Microbiome Project Consortium, 2012). Based on the enrichment of one group of bacterial genera and function, the human gut microbiome could be divided into three enterotypes: *Bacteroides* enterotype, *Prevotella* enterotype and *Ruminococcus* enterotype (Arumugam et al., 2011). The different fermentable substrates in the colon may lead to the enriched genera in each enterotype (Arumugam et al., 2011). Although this clustering method is still under debate (Jeffery et al., 2012; Wu et al., 2011), it indicates that different individuals may have varied responses to the same diet or drug. This highlights the importance of gut microbiota in developing personalized nutritional and therapeutic strategies (Arumugam et al., 2011).

Although significant inter-individual variation in the abundance of bacterial phyla exists, different individuals share similar abundances of several 'core' metabolic and functional pathways including fructose/mannose metabolism, amino-sugar metabolism and N-glycan degradation (Turnbaugh et al., 2009). Within a healthy population, most microbial metabolic and functional pathways are evenly distributed across different body habitats (Human Microbiome Project Consortium, 2012). Interestingly, the similarity of gene functions was even observed between mice and human gut microbiome (Xiao et al., 2015).

3. The gut microbiota in specific age groups

3.1. The gut microbiota in early establishment

The establishment and colonization of gut microbiota is a complex process, in which a number of microbe-microbe and microbe-host interactions are involved. A healthy gut microbial ecology is established in infancy and early childhood which is very crucial for health maintenance throughout life. The factors affecting the early establishment of gut microbiota during infancy were listed in Table 1.

The unborn infants are thought to be sterile in the uterine environment. However, the presence of some bacteria in the amniotic fluid (DiGiulio et al., 2008), placenta (Satokari et al., 2009), umbilical cord blood (Jiménez et al., 2005) and meconium (Jiménez et al., 2008) suggests the existence of a prenatal mother-to-infant transmission of commensal bacteria. Moreover, maternal factors, such as prenatal stress (Bailey et al., 2004), antibiotic therapies (Faa et al., 2013) and prolonged gestational period (Azad et al., 2013), may also lead to a disturbed intestinal microbial colonization of the infants.

Delivery mode is an important factor influencing the colonization of gut microbiota in the early stage of life (Dominguez-Bello et al., 2010). Vaginally delivered infants acquire bacterial communities similar to their mother's vaginal microbiota, whereas infants delivered via cesarean section harbor bacterial communities that are more similar to their mother's skin microbiota (Dominguez-Bello et al., 2010). The gut microbiota of infants born through cesarean section has a lower total microbial diversity and delayed colonization of Bacteroidetes compared with that of infants born vaginally (Jakobsson et al., 2014). The aberrant gut microbial colonization caused by cesarean section may contribute to the increased risks of acquiring several immune disorders such as asthma and diabetes in later life (Cardwell et al., 2008; Thavagnanam et al., 2008).

Oral and skin microbes from the mother can be transferred to the gut microbiota of new-born infants (Dominguez-Bello et al., 2010; Bäckhed et al., 2015). Moreover, the early exposure to a wide range of microbes from surrounding environment is crucial for the development of a healthy immune system (Ege et al., 2011), which play a critical role on the normal intestinal microbial establishment (Hwang et al., 2012). Dysregulation of gut microbiota composition during infancy was associated with the increasing prevalence of numerous allergic diseases, such as asthma (Abrahamsson et al., 2014), atopic eczema (Abrahamsson et al., 2012) and allergic rhinitis (Bisgaard et al., 2011).

The structure and composition of infant gut microbiota is unstable in the first year of life (Palmer et al., 2007). During this period, feeding mode is considered as a key factor influencing the gut microbiota (Bäckhed et al., 2015). The complex oligosaccharides in human milk could promote the growth and colonization of beneficial microbiota such as *Bifidobacteria* in infant gut (Zivkovic et al., 2011). A recent finding reported that sialylated human milk oligosaccharides were required for the microbiota-dependent promotion of infant growth and metabolism (Charbonneau et al., 2016). However, infants fed with formula are more often colonized with potential pathogens such as *Escherichia coli* and *Clostridium difficile* compared with infants fed with breast (Penders et al., 2006). Overall, these findings indicate that breast-fed infants may have a healthier gut microbial ecology when compared to the formula-fed infants.

It is until about three years after birth that an adult-like configuration of gut microbiota is established (Yatsunenko et al., 2012). During this period, gene functions of the infant gut microbiome change from the earliest lactate utilization to an adult microbiome such as plant polysaccharide breakdown, vitamin biosynthesis and xenobiotic degradation (Koenig et al., 2011). However, specific life events such as illness, dietary changes and antibiotic treatment may cause abrupt shifts in the infant gut microbial composition (Koenig et al., 2011).

3.2. The gut microbiota in the elderly

It is accepted information that the structure of the human gut microbiota changes with aging. The intestinal bacterial composition in the healthy elderly subjects displayed significant inter-individual variation, and was characterized by higher proportions of pathogenic *enterobacteria* and lower proportions of probiotic *Bifidobacteria* (Hopkins and Macfarlane, 2002; Woodmansey et al., 2004; Bartosch et al., 2004; Mueller et al., 2006; Claesson et al., 2011; Zwielehner et al., 2009; Mariat et al., 2009). Interestingly, centenarians, people who have lived for over 100 years, also exhibited a higher abundance of facultative anaerobes such as Proteobacteria and a lower abundance of anti-inflammatory *Faecalibacterium prauznitzii* compared with the young and elderly individuals (Biagi et al., 2010). A recent study reported that the gut microbiota of elderly subjects with long-stay care had a high proportion of phylum Bacteroidetes and genera *Parabacteroides*, *Eubacterium*, *Anaerotruncus*, *Lactonifactor* and *Coprobacillus*, whereas community-dwelling elderly subjects harbored a high proportion of phylum Firmicutes and genus *Coprococcus* and *Roseburia* (Claesson et al., 2012).

Nutritional behaviors and life styles may be critical factors contributing to the featured gut microbial composition in elderly people (Claesson et al., 2012). Developing specific prebiotics and/or probiotics to precisely modify and establish the early childhood gut microbiota is urgently required (Yatsunenko et al., 2012).

4. The gut microbiota in different geographic regions

It was reported that there were significant differences in both the gut microbial composition and functions between the U.S. and Malawian/Amerindian populations (Yatsunenko et al., 2012). A significantly higher abundance of Bacteroidetes and lower abundance of Firmicutes were observed in the fecal microbiota of children from a village of rural Africa when compared with that of European (Italy) children (De Filippo et al., 2010). In the gut of rural African children, the relatively high abundance of specific bacterial genera (*Xylanibacter*, *Prevotella*, *Butyrivibrio* and *Treponema*) might help in maximizing the energy extraction from indigestible dietary polysaccharides (De Filippo et al., 2010). Another study showed that Bangladeshi children exhibited a greater gut bacterial diversity than U.S. children (Lin et al., 2013). In addition, the gut microbiota of rural Papua New Guineans had a higher α

Table 1
Factors affecting the early establishment of gut microbiota.
Adapted from Munyaka et al. (2014).

Stages	Factors
Before birth	Maternal conditions (uterine environment, stress, antibiotic use and gestational period)
During birth	Delivery mode (cesarean section and vaginal delivery)
After birth	Contact with mothers (suckling, kissing and caressing); exposure to environmental pathogens; feeding mode (breastfeeding and formula feeding); specific life events (illness, dietary changes and antibiotic treatment)

diversity, but lower β diversity than that of the urban US residents (Martínez et al., 2015). The variation of the gut microbial structures between the rural Hadza hunter-gatherers in Tanzania and urban Italians might contribute to their different fecal metabolite profiles (Schnorr et al., 2014).

Based on the impacts of long-term diets, the gut microbiota composition could be clustered into two enterotypes: *Bacteroides* enterotype was correlated with the diet rich in animal protein and saturated fats, whereas *Prevotella* enterotype was correlated with the diet rich in carbohydrates and simple sugars (Wu et al., 2011). Accordingly, dietary differences may to a large extent contribute to the variation of gut microbiome composition between urban societies and rural areas (Wu et al., 2011; David et al., 2014). Moreover, "Westernized diet" should be taken into consideration because it has caused extinctions of some gut microbes over generations (Sonnenburg et al., 2016).

5. The association between the gut microbiota and human diseases

So far, the gut microbiota is considered as a key "organ" that affects the host biology which means that if the gut microbiota compromises the whole body gets affected. The dysbiosis of gut microbiota has been thought to be associated with the development and progression of diverse human diseases. In this review article, we clustered these diseases into three major types: metabolic diseases, immunological diseases and neurological diseases, and discussed the relationships between the gut microbiota and human diseases.

5.1. Metabolic diseases

5.1.1. Obesity

It is known that obesity is caused by a dysregulation of energy balance where the amount of energy intake from the food exceeds the expenditure in the body (Turnbaugh et al., 2006). A number of studies have demonstrated that obesity is highly relevant to the altered composition of gut microbiota. An increased abundance of Firmicutes and decreased abundance of Bacteroidetes was observed in the fecal microbiota of obese *ob*/*ob* mice when compared to their lean counterparts (Ley et al., 2005). Similar results were also confirmed in the high fat diet (HFD)-induced obese mice (Turnbaugh et al., 2008). Increase in the relative abundance of Firmicutes might be attributable to the enrichment of one bacterial class *Mollicutes*, the genome of which was enriched in the import and fermentation of simple sugars and complex carbohydrates (Turnbaugh et al., 2008). However, the relevance of Firmicutes/Bacteroidetes ratio in human obesity was reported in some studies (Ley et al., 2006b) but not all (Duncan et al., 2008; Schwiertz et al., 2010; Le Chatelier et al., 2013).

Several mechanisms by which gut microbial community influences the pathogenesis of obesity-associated metabolic syndromes have been elucidated (Fig. 1). Generally, the gut microbiota, as an important environmental factor, may affect host metabolism by two possible pathways: one is extracting energy and nutrients from foods and the other one is affecting the host gene expression involved in energy metabolism (Fig. 1).

Metagenomic analysis showed that the gut microbiome of obese *ob*/*ob* mice was enriched in the degradation of indigestive dietary polysaccharides such as starch, sucrose and galactose. This indicates that the gut

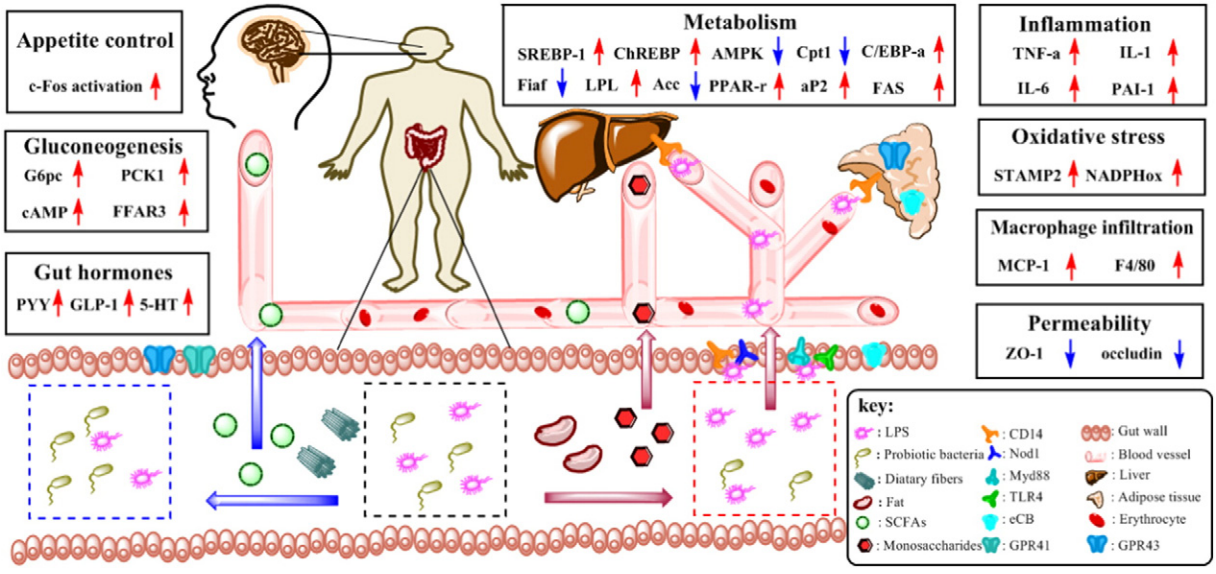

Fig. 1. Mechanisms of the gut microbiota modulating host metabolism. Intestinal commensal bacteria promote uptake of monosaccharides by extracting energy and nutrients from foods. HFD results in dysbiosis of gut microbiota composition characterized by increased levels of LPS, which are able to pass through intestinal tract and reach to every organ of the body through the transportation of the blood. Immune-related receptors (Nod1, CD14, TLR-4, Myd88) and gut permeability proteins (ZO-1, occludin) are involved in the process of intestinal bacterial translocation. In the peripheral organs such as liver and adipose tissue, LPS cause metabolic symptoms via regulating the expression of genes involved in metabolism (SREBP-1, ChREBP, AMPK, Cpt1, C/EBP-α, Fiaf, LPL, Acc, PPAR-γ, aP2, FAS), inflammation (TNF-α, IL-1, IL-6, PAI-1), oxidative stress (MCP-1, NADPHox,) and macrophage infiltration (F4/80, STAMP2). The eCB system also participates in this inflammatory-associated modulation. SCFAs (acetate, propionate and butyrate), fermentation products of dietary fibers metabolized by intestinal bacteria can promote the release of gut hormones (PYY, GLP-1 and 5-HT) by activating SCFAs receptors (GPR41, GPR43). These gut hormones act as critical modulators in colonic mobility and platelet function. SCFAs also promote the expression of IGN genes (G6pc, PCK1, cAMP, FFAR3), which are crucial in the regulation of glucose tolerance and insulin sensitivity. In addition, gut microbiota have an impact on appetite control associated with c-Fos activation in hypothalamic neurons, possibly via increasing the circulatory GLP-1 and PYY levels. 5-HT, 5-hydroxytryptamine; AMPK, adenosine monophosphate-activated protein kinase; aP2, adipocyte fatty acid-binding protein 2; C/EBP-α, CCAAT/enhancer-binding protein-α; cAMP, cyclic adenosine monophosphate; ChREBP, carbohydrate response element binding protein; Cpt1, carnitine:palmitoyl transferase-1; eCB, endocannabinoid; FAS, fatty acid synthase; FFAR3, free fatty acid receptor 3; Fiaf, fasting-induced adipose factor; G6pc, catalytic subunit of glucose-6-phosphatase; GLP-1, glucagon-like peptide 1; GPR41, G protein-coupled receptor 41; HFD, high fat diet; IGN, intestinal gluconeogenesis; IL-1, interleukin-1; LPL, lipoprotein lipase; Acc, acetylCoA carboxylase; LPS, lipopolysaccharide; MCP-1, monocyte chemotactic protein-1; Myd88, myeloid differentiation factor-88; Nod1, nucleotide-binding oligomerization domain 1; PAI-1, plasminogen activator inhibitor-1; PCK1, phosphoenolpyruvate carboxykinase 1; PPAR-γ, peroxisome proliferator activated receptor-γ; PYY, peptide YY; SREBP-1, sterol response element binding protein 1; STAMP2, six-transmembrane protein of prostate 2; TLR-4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; ZO-1, zonula occludens-1.

microbiota of *ob*/*ob* mice had increased capacity of food energy harvest compared with that of their lean littermates (Turnbaugh et al., 2006).

Germ-free (GF) mice with gut microbial colonization exhibited a significant increase in body fat content (Bäckhed et al., 2004). Gut microbial colonization promoted lipoprotein lipase (LPL)-mediated triglyceride storage in GF mice adipocytes though inhibiting the intestinal expression of fasting-induced adipose factor (Fiaf) (a circulating LPL inhibitor) (Bäckhed et al., 2004). Moreover, the expression of phosphorylated adenosine monophosphate-activated protein kinase (AMPK) and acetylCoA carboxylase (Acc), as well as the activity of carnitine: palmitoyl transferase-1 (Cpt1) was significantly decreased in GF mice with gut microbial colonization. These results indicate that gut microbiota was able to promote fat accumulation by inhibiting AMPK-dependent fatty acid oxidation (Fig. 1) (Bäckhed et al., 2007). In addition, the intestinal microbiota could also promote fat accumulation via suppressing the production of functional beige fat in white adipose tissue (Suárez-Zamorano et al., 2015).

It is accepted that a low-grade systemic inflammation is an important factor responsible for the early onset of obesity (Cani et al., 2007a, 2008). Continuous subcutaneous infusion of lipopolysaccharide (LPS), a cell wall component of Gram-negative bacteria, resulted in increased body weight and adipose tissue depots, as well as the upregulation of several inflammatory factors including tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6 and plasminogen activator inhibitor-1 (PAI-1) (Cani et al., 2007a). Importantly, antibiotic treatment markedly reduced body weight and plasma LPS levels in both HFD-fed and *ob*/*ob* mice. These data indicate that gut microbiota may cause obesity-associated metabolic disorders, to some extent, through LPS-dependent inflammatory mechanisms (Cani et al., 2008) (Fig. 1).

Whether the inflammatory regulator LPS in the plasma is originated from intestinal microbial communities? Indeed, large number of intestinal bacterial DNA were detected in the mesenteric adipose tissue, mesenteric lymph nodes and the blood of mice after HFD feeding, indicating that these intestinal bacterial components might be able to pass through the wall of intestinal tract and reach specific tissues (Amar et al., 2011). The process of intestinal bacterial translocation required the participation of several pathogen receptors such as nucleotide-binding oligomerization domain containing-1 (Nod1), CD14 and myeloid differentiation factor-88 (Myd88) (Amar et al., 2011). Moreover, innate immune toll-like receptor (TLR) 4 is also a key receptor for the recognition of microbial pathogen LPS by enterocytes (Neal et al., 2006) (Fig. 1).

The endocannabinoid (eCB) system has been identified as another crucial modulator in the development of gut microbiota-mediated obesity. Gut microbiota alteration resulted in the change of cannabinoid 1 (CB1) receptor expression in the colon (Muccioli et al., 2010). Consequently, activation of the eCB system increased the gut permeability by decreasing the expression of two tight junction proteins occludin and zonula occludens-1 (ZO-1) (Muccioli et al., 2010). In the adipose tissues, eCB system activation also promoted adipogenesis via increasing the expression of genes involved in the adipocyte differentiation and lipogenesis (Muccioli et al., 2010) (Fig. 1). *N*-acylphosphatidylethanolamine phospholipase D (NAPE-PLD) is an enzyme responsible for the synthesis of endocannabinoid *N*-acylethanolamines. Specific deletion of *Napepld* gene in the mice adipose tissue led to obesity, insulin resistance, altered lipid metabolism and browning process, and gut microbiota transfer could partially reproduce these phenotypes (Geurts et al., 2015) (Fig. 1).

Short-chain fatty acids (SCFAs), such as acetate, propionate and butyrate, are the main fermentation products of dietary fibers metabolized by intestinal bacteria. A number of studies have demonstrated that SCFA signaling pathways are involved in the gut microbiota-mediated host metabolism (Tazoe et al., 2008; Breton et al., 2015) (Fig. 1).

G protein-coupled receptor 41 (GPR41) and 43 (GPR43) are two important SCFA receptors located in the enteroendocrine cells of intestinal epithelium. Activation of GPR41 and GPR43 by SCFAs promoted the release of 5-hydroxytryptamine (5-HT) and peptide YY (PYY), thereby influencing the colonic mobility (Tazoe et al., 2008). GPR41-dependent production of circulating hormone PYY was also required for increasing gut microbiota-induced efficiency for energy harvest from the diet (Samuel et al., 2008). A recent study reported that gut commensal bacterial protein ClpB had an impact on appetite control associated with c-Fos activation in hypothalamic neurons, possibly through stimulating the release of gut satiety hormone glucagon-like peptide 1 (GLP-1) and PYY in the plasma (Breton et al., 2015) (Fig. 1).

GPR43 was highly expressed in the white adipose tissue of HFD-fed mice. Compared with wild-type mice, *Gpr43*$^{-/-}$ mice with HFD treatment exhibited significant metabolic syndromes such as obesity, insulin resistance and inflammation, which were significantly improved with antibiotic treatment or under GF conditions (Kimura et al., 2013). In addition, GPR41 and GPR43 had also been detected in immune cells such as polymorphonuclear cells, monocytes and dendritic cells (Le Poul et al., 2003; Brown et al., 2003). *Gpr43*$^{-/-}$ mice treated with dextran sulphate sodium (DSS) resulted in significantly worse colonic inflammation compared to wild-type mice. However, gut microbiota-dependent acetate administration markedly improved inflammatory symptoms in wild-type, but not *Gpr43*$^{-/-}$ mice, suggesting the beneficial role of SCFA-GPR43 interactions in the regulation of host inflammatory responses (Maslowski et al., 2009) (Fig. 1).

Intestinal gluconeogenesis (IGN) has a beneficial effect on the regulation of glucose and energy homeostasis. Butyrate directly induced IGN by promoting the activity of glucose-6-phosphatase (G6Pase) and the expression of phosphoenolpyruvate carboxykinase 1 (PCK1). In contrast, propionate-mediated induction of IGN was dependent on a gut-brain communication axis. However, SCFAs-mediated metabolic benefits were abolished in an intestinal-specific dysregulation of IGN (I-G6pc$^{-/-}$) mice model (De Vadder et al., 2014) (Fig. 1).

5.1.2. Type 2 diabetes (T2D)

T2D is a metabolic disorder characterized by the symptom of insulin resistance. Obesity is considered to be linked with the onset of T2D. Recently, increasing evidence indicates that altered gut microbiota is associated with the development of T2D (Larsen et al., 2010; Qin et al., 2012; Karlsson et al., 2013).

16S rRNA pyrosequencing of the gut microbiota showed that the ratio of Bacteroidetes/Firmicutes and the abundance of class *Betaproteobacteria* were higher in T2D subjects when compared with non-diabetic controls. In contrast, the proportion of *Clostridia* was significantly lower in diabetic subjects when compared to the healthy controls (Larsen et al., 2010). To explore whether the dysbiosis of gut microbiota occurs before the onset of diabetes, Zhang et al. (2013) found that the prediabetes subjects had significantly lower abundance of *Verrucomicrobia* when compared with the normal glucose tolerance subjects, indicating that *Verrucomicrobiae* could serve as a potential diagnostic biomarker for the progression of T2D (Zhang et al., 2013).

Metagenomic analysis of the fecal microbiome from 345 Chinese T2D patients and non-diabetic controls showed that several butyrate-producing bacteria such as *Faecalibacterium prausnitzii*, *Roseburia intestinalis* and *Roseburia inulinivorans* were enriched in healthy persons, whereas the opportunistic pathogens including *Clostridium symbiosum*, *Eggerthella lenta* and *Escherichia coli* were enriched in T2D patients (Qin et al., 2012). Microbial functional analysis revealed that pathways, including oxidative stress resistance, methane metabolism and sulphate reduction, were highly enriched in the gut microbiome of T2D patients (Qin et al., 2012). In another study, increased abundance of four *Lactobacillus* species and decreased abundance of five *Clostridium* species were observed in the gut microbiota of European T2D women. Functional pathways of the gut microbiome in T2D populations were enriched in starch and glucose metabolism, fructose and mannose metabolism, as well as ABC transporters and glutathione synthesis, whereas normal glucose tolerance subjects were enriched in flagellar assembly and riboflavin metabolism (Karlsson et al., 2013).

5.1.3. Cardiovascular disease (CVD)

It is known that CVD is the leading cause of death and morbidity worldwide. The gut microbiota of patients with symptomatic atherosclerosis had enriched abundance of the genus *Collinsella*, whereas *Roseburia* and *Eubacterium* and three species of *Bacteroides* were enriched in healthy controls. At the functional level, the gut microbiome of atherosclerosis patients were enriched in genes associated with peptidoglycan biosynthesis, whereas phytoene dehydrogenase genes were enriched in healthy subjects (Karlsson et al., 2012). Compared with normal chow diet fed mice, dietary supplementation with three dietary lipid phosphatidylcholine metabolites choline, trimethylamine *N*-oxide (TMAO) and betaine resulted in the enhancement of atherosclerosis in Apoe$^{-/-}$ mice. However, suppression of the intestinal microbiota by broad-spectrum antibiotics completely inhibited the dietary choline-mediated progression of atherosclerosis in Apoe$^{-/-}$ mice (Wang et al., 2011a). Study in humans further confirmed that the intestinal microbiota played an obligatory role in the production of plasma TMAO which were significantly associated with an increased risk of major adverse cardiovascular adverse events (Tang et al., 2013). Mechanistic study by Zhu et al. (2016) demonstrated that TMAO could directly promote the platelet hyperreactivity by increasing the intracellular Ca^{2+} release and thereby enhancing the potential of thrombosis risk (Zhu et al., 2016). Targeted inhibition of microbial TMA production by a structural analog of choline, 3,3-dimethyl-1-butanol (DMB), has recently been shown to attenuate the development of atherosclerosis in Apoe$^{-/-}$ mice (Wang et al., 2015b).

5.1.4. Liver diseases

Altered gut microbial composition has also been demonstrated to be related with several liver diseases, such as nonalcoholic fatty liver disease (NAFLD) (Jiang et al., 2015), hepatic encephalopathy (Bajaj et al., 2012) and cirrhosis (Qin et al., 2014).

16S ribosomal RNA gene sequencing of the gut microbiota between NAFLD patients and healthy subjects showed that *Alistipes* and *Prevotella* were significantly increased in healthy subjects, whereas *Escherichia*, *Anaerobacter*, *Lactobacillus* and *Streptococcus* were abundant in NAFLD patients (Jiang et al., 2015). Specific bacterial families, such as *Alcaligenaceae*, *Porphyromonadaceae* and *Enterobacteriaceae*, were significantly associated with cognitive impairment and inflammation in hepatic encephalopathy patients (Bajaj et al., 2012). Compared with healthy individuals, the gut microbiota of patients with hepatitis B liver cirrhosis had reduced abundance of *Bacteroides* and *Clostridium*, which were crucial for colonic bile acid metabolism (Wei et al., 2013). Metagenomic analysis of the gut microbiome between patients with liver cirrhosis and healthy subjects showed that high proportions of some oral commensal species including *Veillonella* and *Streptococcus*, and opportunistic pathogenic species such as *Streptococcus anginosus*, *Veillonella atypical* and *Clostridium perfringens* were observed in the liver cirrhosis patients (Qin et al., 2014). At the functional level, microbial functions of liver cirrhosis patients were enriched in ammonia production, phosphotransferase systems and membrane transport, whereas functions including carbohydrate and amino-acid metabolism were enriched in healthy controls (Qin et al., 2014).

The mechanisms of the interaction between the gut microbiota and liver diseases have been investigated. It has been reported that bacterial DNA was present in blood and mesenteric lymph nodes of rats with CCl4-induced cirrhosis and was associated with several inflammatory markers such as TNF-α and IL-6 (Guarner et al., 2006). High prevalence of small intestinal bacterial overgrowth (SIBO) was observed in patients with cirrhosis (Gupta et al., 2010). The elevated levels of gut-derived LPS promoted liver tumorigenesis in rodents (Yu et al., 2010). However, modulation of the gut microbial ecology by antibiotic rifaximin led to a significant improvement in endotoxemia-associated liver diseases such as hepatic encephalopathy and advanced cirrhosis (Kalambokis et al., 2012; Bajaj et al., 2013). Gut was the major source of endogenous bacteria for the cause of infection and inflammation in mice model of

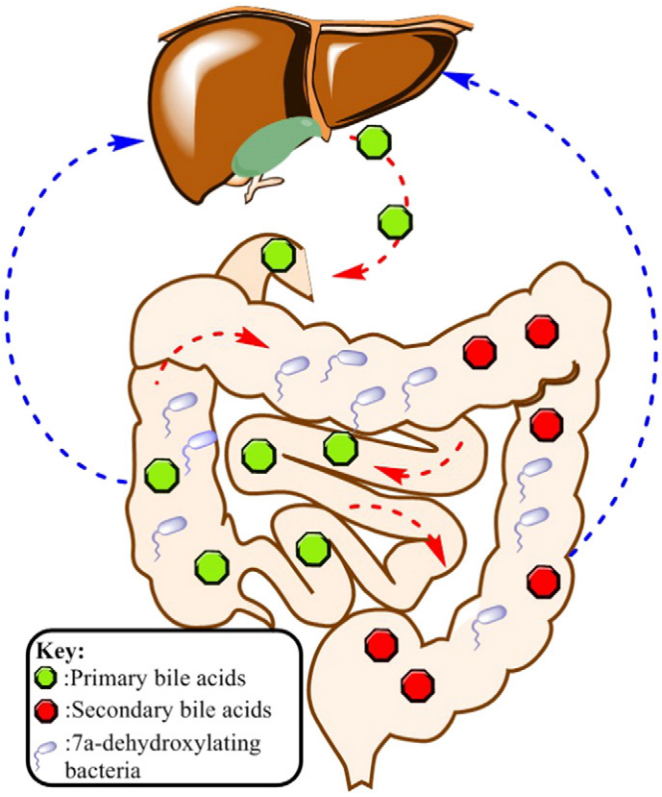

Fig. 2. The interrelationship between gut microbiota and liver by enterohepatic circulation. On one hand, primary bile acids produced in the liver are secreted into the intestinal tract, where they play an important role in regulating the gut microbial composition. On the other hand, primary bile acids which are functionally converted by 7α-dehydroxylating bacteria into secondary bile acids are then reabsorbed into the circulation system. These bacterial metabolites may have a critical impact on hepatic bile acid synthesis.

CCl_4-induced cirrhosis (Gómez-Hurtado et al., 2011). These findings suggest that intestinal bacterial translocation may be a possible factor for the pathogenesis of inflammation-related liver diseases.

Immune responses may be involved in the etiology of microbe-associated liver diseases. In patients with hepatitis C virus infection, the ability of anti-bacterial antibodies in regulating complement-mediated killing of gut bacteria was impaired (Lamontagne et al., 2013). Moreover, intestinal microbiota and TLR 4 activation were required for the promotion of hepatocellular carcinoma (Dapito et al., 2012). A recent study reported that gut microbiota-mediated maturity of liver immunity system played a crucial role in the clearance of hepatitis B virus infection (Chou et al., 2015).

Enterohepatic circulation is another key mechanism bridging the gut microbiota and the liver. In the process of enterohepatic circulation, bile salts synthesized in the liver are secreted into the intestinal tract, where they could be metabolized by intestinal bacteria (Fig. 2) (Ridlon et al., 2006). 7α-dehydroxylating bacteria in the human colon functionally converted primary bile acids into secondary bile acids (Ridlon et al., 2006). In the fecal samples of advanced cirrhotic patients, primary bile acid was associated with high abundance of potentially pathogenic *Enterobacteriaceae*, whereas secondary bile acid was correlated with lower abundance of 7α-dehydroxylating bacteria *Ruminococcaceae* (Kakiyama et al., 2013). Administration of primary bile acid increased the abundance of phylum Firmicutes, specifically the 7α-dehydroxylating bacterial members of *Clostridium* cluster XIVa in rats (Islam et al., 2011). Thus, these findings suggest that bile acid may play an essential role in the regulation of gut microbiota composition.

In return, gut microbial community can also have an active effect on the physical functions of the liver (Fig. 2). Intestinal microbiota affected the hepatic bile acid synthesis via promoting the nuclear receptor

farnesoid X receptor (FXR)-dependent expression of fibroblast growth factor 15 (Fgf15) in the ileum (Sayin et al., 2013). Gut microbiota-mediated metabolism of dietary choline might contribute to the development of NAFLD (Dumas et al., 2006). Moreover, inflammasome deficiency-associated dysbiosis of gut microbiota might also be a determinant factor in the progression of NAFLD (Henao-Mejia et al., 2012).

5.2. Immunological diseases

A key functional role of immune system includes protection of the host against infection from the exogenous opportunistic pathogens. Innate immune system has been demonstrated to play an essential role in maintaining the stability of intestinal microbial ecology (Carvalho et al., 2012).

As the crucial evolutionarily conserved molecules of innate immune system, TLRs act as important mediators in initiating inflammatory and immune defense responses. TLR-5, a transmembrane protein recognizing bacterial flagellin, is highly expressed in the intestinal mucosa (Vijay-Kumar et al., 2010). Compared with the wide-type mice, TLR5-deficient mice exhibited hallmarks of several metabolic syndromes, such as increased body and fat mass, hyperglycemia and insulin resistance, as well as altered gut microbial composition. Interestingly, GF mice colonized with the gut microbiota from TLR5-deficient mice also displayed similar metabolic features (Vijay-Kumar et al., 2010). TLR-5 deficiency also caused increased abundance of *Proteobacteria*, which was associated with the induction of intestinal inflammation (Carvalho et al., 2012). LPS and flagellin were two critical activators driving TLR-5 deficiency-induced gut inflammation (Chassaing et al., 2014a; Chassaing et al., 2014b).

TLR signaling could also be employed by commensal microbes. Human commensal *Bacteroides fragilis* used an immunomodulatory molecule, polysaccharide A, to establish its colonization in a specific mucosal niche of the gut by suppressing TLR2 signaling-dependent T_H 17 cell responses (Round et al., 2011). In addition, TLR signaling-mediated recognition of commensal bacterial products was required for the maintenance of intestinal epithelial homeostasis and the protection against DSS-induced intestinal inflammation (Rakoff-Nahoum et al., 2004).

Paneth cell α-defensins are essential antimicrobial peptides of intestinal innate immunity. Alteration in the expression of Paneth cell α-defensins had a considerable impact on the host commensal microbiota, especially the group of bacteria known as segmented filamentous bacteria (SFB), which was tightly associated with mucosal immunological responses (Salzman et al., 2010). Microbiota-mediated production of REG3β and REG3γ, two antimicrobial peptides produced by Paneth cells, required Myd88 function in the colon (Larsson et al., 2012). Moreover, MyD88-dependent expression of RegIIIγ which is a direct bactericidal C-type lectin that specifically targets Gram-positive bacteria also played a key role in maintaining the host-microbial homeostasis in intestinal mucosal surface (Vaishnava et al., 2011).

Nod-like receptors (NLR) is another group of innate immune molecules involved in the regulation of intestinal homeostasis. The gut microbiota of NOD1-deficient mice was characterized by an increase of total bacterial population, in particular the commensal bacteria *Clostridiales*, Bacteroides and *Enterobacteriaceae* (Bouskra et al., 2008). Moreover, peptidoglycans from commensal gram-negative bacteria activated NOD1-dependent receptor recognition in epithelial cells, thereby inducing the formation of isolated lymphoid follicles in the intestine (Bouskra et al., 2008). Commensal bacteria could also induce the expression of NOD2, which played important role in regulating the intestinal mucosal homeostasis and suppressing the colonization of pathogenic bacteria (Petnicki-Ocwieja et al., 2009). The intestine of Nod2-deficient mice was characterized by increased abundance of Firmicutes, *Bacteroides* and *Bacillus* (Petnicki-Ocwieja et al., 2009). Nod2 deficiency-mediated dysbiosis of gut microbiota increased the risks of DSS-induced intestinal inflammation and tumorigenesis (Couturier-Maillard et al., 2013).

The adaptive immune system is also critical for a sustainable host-microbial relationship. It was reported that the intestinal microbiota of mice lacking both B and T cells ($Rag1^{-/-}$) had an enrichment of bacterium *Akkermansia muciniphila* when compared with that of wild-type mice (Zhang et al., 2015). Gut microbiota-dependent production of IL-1β and IL-6 induced the differentiation of IL-10-producing regulatory B cells in the spleen and the mesenteric lymph nodes (Rosser et al., 2014).

Immunoglobulin A (IgA) is the major effector molecule of the adaptive immunity in the gut (Kawamoto et al., 2014). The maturation and differentiation of $Foxp3^+$ T cells influenced the quantities and qualities of intestinal IgAs thereby maintaining the diversification and richness of gut microbial communities (Peterson et al., 2007; Kawamoto et al., 2014; Palm et al., 2014).

The interactions between T follicular helper (T_{FH}) cells and B cells are critical for intestinal IgA production (Kawamoto et al., 2012). Programmed cell death-1 (PD-1) is an inhibitory coreceptor which is highly expressed in T_{FH} cells. PD-1-deficient mice had a significant reduction of anaerobic bacteria and an increased abundance of *Enterobacteriaceae* when compared with wide-type mice (Kawamoto et al., 2012). The altered composition of gut microbiota in PD-1-deficient mice might result from the dysregulation of IgA selection in the germinal center of Peyer's patches (Kawamoto et al., 2012). Similarly, activation-induced cytidine deaminase $(AID)^{-/-}$ mice had an enriched abundance of anaerobic SFB, which might also be due to the absence of hypermutated mucosal IgA (Fagarasan et al., 2002; Suzuki et al., 2004).

Innate and adaptive immune system can cooperatively affect the gut microbiota. For instance, MyD88 signaling deficiency in T cells resulted in reduced T_{FH} cells and IgA-producing B cells and consequently caused the changes in the intestinal microbial community (Kubinak et al., 2015). The gut of $TLR5^{-/-}$ mice exhibited an enrichment of bacterial flagella-related and motility-related genes, which might be due to the decreased production of anti-flagellin antibodies (Cullender et al., 2013).

Overall, the above-mentioned evidence suggests the existence of a bidirectional interaction between the gut microbiota and host immune system, that is, gut microbiota influence the functions of host immune system, and vice versa (Fig. 3). The homeostasis of their relationship

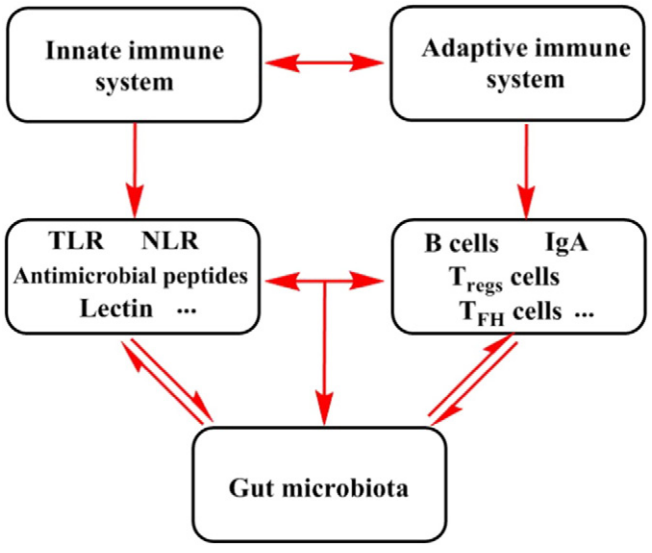

Fig. 3. Relationships between innate immune system, adaptive immune system and the gut microbiota. The interactions between innate immune system and gut microbiota are regulated by several innate immune molecules such as Toll-like receptor (TLR), Nod-like receptor (NLR), antimicrobial peptides and lectin. Moreover, cross-talks between adaptive immune system and gut microbiota are via immune cells including B cells, regulatory T (T_{regs}) cells and T follicular helper (T_{FH}) cells, as well as strain-specific antibody IgA. Furthermore, innate and adaptive immune system can cooperatively affect intestinal microbial communities.

may result from a long-term coevolution between the host and its-associated microbes. However, the disturbance of this balance may contribute to the pathogenesis of diverse immunological diseases.

5.2.1. Inflammatory bowel disease (IBD)

IBD is a group of inflammatory disorders of colon and small intestine which is caused by the attacks from immune system. Intestinal microbiota may play a crucial role in initiation and trigger of the disorders. Compared with healthy people, the gut bacterial species of IBD patients were characterized by an increase of *Ruminococcus gnavus* and a decrease of *Dialister invisus*, *Faecalibacterium prausnitzii* and *Bifidobacterium adolescentis* (Joossens et al., 2011). Moreover, increased abundance of *Actinobacteria* and *Proteobacteria* and decreased abundance of *Bacteroidetes* and *Lachnospiraceae* were detected in the intestinal tract of IBD patients compared with that of non-IBD controls (Frank et al., 2007).

Crohn's disease (CD) is one common form of IBD. The gut microbiota of CD patients was characterized by a significantly lower bacterial diversity than that of healthy people (Manichanh et al., 2006). This might be due to the reduction of *Clostridium leptum*, a phylogenetic group of bacteria belonging to the phylum Firmicutes (Manichanh et al., 2006). Another study showed that the changes in the intestinal microbiota of CD patients included increased abundance of *Enterobacteriaceae* and *Ruminococcus gnavus*, as well as decreased abundance of *Faecalibacterium* and *Roseburia* (Willing et al., 2010). In addition, low proportion of *Faecalibacterium prausnitzii*, one anti-inflammatory commensal bacterium, was also found in the intestine of CD patients and this bacterium was associated with a high risk of endoscopic recurrence following surgical resection (Sokol et al., 2008).

5.2.2. Irritable bowel syndrome (IBS)

IBS is a common functional gastrointestinal disorder with the symptoms including diarrhea, constipation, abdominal bloating and flatulence (Lyra et al., 2009). The etiology is poorly understood and many factors are involved in the disorder. The gut microbiota of IBS patients had a higher abundance of Firmicutes and a lower abundance of Bacteroidetes than that of control subjects (Jeffery et al., 2012). Specifically, IBS patients contained higher numbers of *Dorea*, *Ruminococcus* and *Clostridium*, as well as lower numbers of *Bifidobacterium*, *Faecalibacterium* and methanogens when compared with the healthy controls (Rajilić-Stojanović et al., 2011). *Pseudomonas aeruginosa* and *Staphylococcus aureus* were two possible pathogens responsible for the pathophysiology of IBS (Kerckhoffs et al., 2011; Rinttilä et al., 2011).

Generally, IBS can be classified into three predominant subtypes, i.e. constipation-predominant, diarrhea-predominant and mixed-type (Longstreth et al., 2006). IBS patients with different symptom-subtypes exhibited variable gut microbiota composition (Lyra et al., 2009). *Lachnospiraceae*, a family member of the phylum Firmicutes, was significantly abundant in diarrhea-predominant IBS patients (Krogius-Kurikka et al., 2009). However, constipation-predominant IBS patients had a high abundance of *Veillonella* spp. (Malinen et al., 2005).

5.2.3. Type 1 diabetes (T1D)

T1D is an autoimmune disorder resulting from the T cell-mediated destruction of pancreatic β-cells. The association between intestinal microbiota and the pathogenesis of T1D has been demonstrated in a number of studies (Brugman et al., 2006; Roesch et al., 2009; Hara et al., 2012; Endesfelder et al., 2014).

Children with T1D had reduced gut bacterial diversity when compared with healthy controls (de Goffau et al., 2013). A decrease of Firmicutes and an increase of Bacteroidetes were found in children who gradually developed T1D (Giongo et al., 2011). At the genus level, *Veillonella*, *Clostridium* and *Bacteroides* were significantly higher whereas *Lactobacillus*, *Prevotella* and *Bifidobacterium* were significantly lower when compared to the gut microbiota of T1D children with that of healthy children (Murri et al., 2013; Mejía-León et al., 2014). The intestinal microbiota of T1D children also had a high abundance of class *Bacilli* (notably *streptococci*). In contrast, butyrate-producing bacteria *Clostridium* clusters IV and XIVa were abundant in healthy children (de Goffau et al., 2014). Metagenomic analysis showed that gut microbiome of children with T1D were enriched in functions including stress responses, virulence factors and sulfur metabolism, whereas functions of DNA, RNA and protein metabolism were enriched in healthy children (Brown et al., 2011).

It was interesting that T1D was not developed in MyD88 knockout (KO) nonobese diabetic (NOD) mice ($MyD88^{KO}$ NOD mice). Three intestinal bacterial families *Lactobacillaceae*, *Rikenellaceae* and *Porphyromonadaceae* were significantly increased in the gut of $MyD88^{KO}$ NOD mice when compared with that of wild-type NOD mice. However, diabetes was restored when $MyD88^{KO}$ NOD mice was under germ-free condition or with antibiotic treatment (Wen et al., 2008). Furthermore, wild-type NOD mice colonized with gut microbiota from $MyD88^{KO}$ NOD mice contained increased numbers of *Lachnospiraceae* and *Clostridiaceae*, as well as decreased numbers of *Lactobacillaceae* (Peng et al., 2014). Microbial colonization also resulted in high concentrations of IgA and TGFβ and increased the numbers of $CD103^{+}$ and CD8αβ T cells in the gut, which might contribute to the delayed onset of diabetes in the wild-type NOD mice (Peng et al., 2014).

Collectively, these findings indicate that some bacterial members in the gut may play crucial roles in the initiation or the protection of T1D. Further studies are required to explore the specific functions of these bacteria.

5.3. Neurological diseases

The association between the gut microbiota and brain development and behavior is an area of increasing interest. It has been reported that GF mice displayed increased motor activity and reduced anxiety-like behaviors when compared with the specific pathogen free (SPF) mice (Diaz Heijtz et al., 2011). GF mice also had significant social impairments and were more susceptible to the restraint stress than SPF mice (Sudo et al., 2004; Desbonnet et al., 2014). However, antibiotic treatment to SPF mice increased exploratory behavior and the expression of brain-derived neurotropic factor (BDNF) in the hippocampus (Bercik et al., 2011a). Blood-brain barrier (BBB) is thought to play an important role in controlling the exchange of molecules and nutrients between the brain and blood. GF mice had increased permeability of BBB when compared with SPF mice (Braniste et al., 2014). Fecal transfer from mice with normal gut microbiota into GF mice or treatment of GF mice with bacteria that produce SCFAs decreased the permeability of BBB (Braniste et al., 2014). Moreover, gut microbiota was also crucial for the maturation and function of microglia in the brain (Erny et al., 2015).

The relationship between the gut microbiota and brain may be bidirectional. Exposure to the social disruption stressor resulted in the increased abundance of *Clostridium* and decreased abundance of *Bacteroides*, which were correlated with the increased circulating cytokine levels (Bailey et al., 2011). In addition, early life stress could also lead to an altered gut microbial composition (O'Mahony et al., 2009; De Palma et al., 2015; Park et al., 2013).

These findings provide strong evidence for the existence of a microbiota-gut-brain axis and underscore the essential role of gut microbiota in the regulation of its homeostasis (Clarke et al., 2013; Gareau et al., 2011).

5.3.1. Autism

Autism spectrum disorder (ASD) is a group of serious neurodevelopmental disorders characterized by the presence and severity of stereotypic behavior and deficits in language and social interaction. Children with autism often have frequent gastrointestinal problems and the intestinal microbes may play a role in the onset of this disorder (Bolte, 1998; Finegold et al., 2002; Song et al., 2004).

Desulfovibrio, a sulphate-reducing bacterial genus, may contribute to the development of regressive autism (Finegold et al., 2012). A microbially-modulated metabolite, 4-ethylphenylsulfate (4EPS), was able to induce ASD-related behavioral abnormalities (Hsiao et al., 2013).

It has been reported that autistic patients exhibited abnormal composition of intestinal microbiota. At the phylum level, high levels of Bacteroidetes were found in the autistic children, while Firmicutes were abundant in the control subjects (Finegold et al., 2010). Autistic children had higher abundance of toxin-producing bacterial group of *Clostridium histolyticum*, as well as lower abundance of the carbohydrate-degrading bacteria *Prevotella*, *Coprococcus* and unclassified *Veillonellaceae* than healthy controls (Parracho et al., 2005; Kang et al., 2013). Moreover, high abundance of *Sutterella* species was only found in the intestines of children with autism and gastrointestinal dysfunction, but not in the children with only gastrointestinal dysfunction (Williams et al., 2012).

5.3.2. Multiple sclerosis

Multiple sclerosis is an immune-mediated central nervous system (CNS) inflammatory disorder characterized by progressive deterioration of neurological function. Mice in experimental autoimmune encephalomyelitis (EAE) model produced many features of multiple sclerosis (Lee et al., 2011). Compared with SPF mice, GF mice displayed attenuated symptoms of EAE, which were significantly promoted following intestinal colonization with SFB (Lee et al., 2011). Bacteria-mediated signals from the gut to the brain might be transduced directly via peripheral vagal afferent nerves (Gaykema et al., 2004; Goehler et al., 2005; Goehler et al., 2008). Accordingly, intestinal microbiota might be an important regulator in the initiation of spontaneous demyelinating autoimmune disease (Berer et al., 2011).

6. Therapeutic strategies modulating the gut microbiota

The intestinal microbiota has been applied as a potential target for nutritional and medical intervention. In the following section, we summarize important strategies that effectively modify intestinal microbial ecology for the improvement of human health.

6.1. Prebiotics

Prebiotics have been defined as "non-digestible food ingredients that benefit the host by selectively stimulating the growth or activity of one or a limited number of bacteria in the colon" (Gibson and Roberfroid, 1995). Dietary carbohydrates including resistant starches, non-starch polysaccharides and oligosaccharides can reach the large intestine directly by escaping the digestion of host enzymes and act as the major substrates for the growth of gut bacteria with specific carbohydrate enzymes (Walker et al., 2011). It is important to note that host-producing carbohydrates such as mucins and chondroitin sulphate can be fermented by intestinal microbes (Roberfroid et al., 2010). The fermentation end products can be utilized by diverse gut bacteria via metabolic cross-feeding (Belenguer et al., 2006). Fructooligosaccharides (FOS) and galactooligosaccharides (GOS) are two well-known dietary prebiotics, which are widely used for improving metabolic disorders (Scott et al., 2011; Walton et al., 2012).

It has been demonstrated that prebiotic FOS selectively increased the number of *Bifidobacterium*, which were positively correlated with improvements of body weight, endotoxaemia and inflammatory disorders (Cani et al., 2007b). Metagenomic sequencing analysis showed that gut microbial functions including "cell motility", "chemotaxis and flagellar assembly", which were enriched in mice during HFD induction, were significantly reduced upon FOS administration (Everard et al., 2014). The anti-diabetic effects of FOS were attenuated after the use of GLP-1 receptor antagonist or in GLP-1 receptor knockout (GLP-1R$^{-/-}$) mice (Cani et al., 2006). Moreover, GLP-2-dependent improvement of gut barrier function also contributed to the beneficial effects of FOS (Cani et al., 2009b). Importantly, the production of GLP-1 and GLP-2 might result from gut microbiota-induced increase of enteroendocrine L-cells (Everard et al., 2011).

A recent study reported that water extract of *Ganoderma lucidum* (Ling Zhi), a traditional Chinese medicine, reduced HFD-induced obesity in mice by modulating gut microbiota dysbiosis (Chang et al., 2015). Dietary supplementation with fully soluble fructan promoted gut microbial fermentation and secretion of gut peptide GLP-1 and PYY, which are the key regulators for appetite regulation and glucose homeostasis (Cani et al., 2009a). Long-term supplementation of oligofructose also resulted in decreased concentrations of ghrelin in the plasma of overweight and obese adults (Parnell and Reimer, 2009). However, the mechanism by which oligofructose suppresses ghrelin secretion and whether the lowered plasma ghrelin levels is related to the altered gut microbiota composition still needs to be further explored.

As more and more beneficial intestinal bacteria are being found with the application of advanced sequencing techniques, the definition of prebiotics should be more specific, for instance, which beneficial bacteria are promoted and which disease or disorder can be improved. In addition, except the traditional non-digestible carbohydrates, whether other large-molecule phytochemicals can be developed as novel prebiotics remains to be determined. Finally, although the beneficial effects of prebiotics on immune function have been reported (Vulevic et al., 2008), evidence about the role of prebiotics in ameliorating neurologic disorders is relatively scarce and requires to be established.

6.2. Probiotics

According to the definition from the Food and Agriculture Organization of the United Nations and the World Health Organization, probiotics are "live microorganisms which provide a health benefit on the host when administered in adequate amounts" (Araya et al., 2002). *Bifidobacterium* and *Lactobacillus* are two well-known probiotics widely used for improving human health. Oral administration of 8-strain probiotic compound VSL#3 effectively attenuated liver injury and maintained intestinal barrier function in mice via a PPARγ-dependent mechanism (Ewaschuk et al., 2007). A recent study showed that the beneficial impacts of three probiotics, *Lactobacillus paracasei* CNCM I-4270, *Lactobacillus rhamnosus* I-3690 and *Bifidobacterium animalis* subsp. *lactis* I-2494, on HFD-induced metabolic syndromes in mice were strain-specific (Wang et al., 2015a). Given the functions of probiotics in improving metabolic- and immune-related diseases have been well summarized (Hashemi et al., 2016), the following mainly focused on the critical roles of probiotics in the improvement of neurological disorders.

γ-Aminobutyric acid (GABA) is an important neurotransmitter of CNS. *Lactobacillus rhamnosus* administration was able to alleviate anxiety-like behaviors in mice by modulating vagus nerve-dependent expression of GABA receptors in the brain (Bravo et al., 2011). In a placebo-controlled study, probiotic *Lactobacillus casei* strain Shirota had an influence in ameliorating the symptoms of depression and anxiety in patients with chronic fatigue syndrome (Rao et al., 2009). Moreover, *Lactobacillus reuteri* could modulate enteric nervous system, whereas the mechanism of action is still unknown (Wang et al., 2010).

Bifidobacteria infantis displayed potential antidepressant properties by suppressing the release of pro-inflammatory cytokines in the blood and reducing concentrations of 5-hyroxyindole acetic acid and dihydroxyphenylacetic acid in the brain (Desbonnet et al., 2008, 2010). Another study demonstrated that the protection of *Bacteroides fragilis* against CNS demyelination was dependent on the production of capsular polysaccharide A (Ochoa-Repáraz et al. 2010). Moreover, DSS-induced anxiety-like behavior in mice could be normalized with the administration of probiotic *Bifidobacterium longum* NCC3001 (Bercik et al., 2011b). The anxiolytic effect of *B. longum* administration was possibly via activating vagal pathways in the enteric nervous system (Bercik et al., 2011b).

Except *Lactobacillus* and *Bifidobacterium*, other bacteria have also been found to have probiotic activity. *Akkermansia muciniphila* is a mucin-degrading bacteria that belongs to the phylum of Verrucomicrobia (Derrien et al., 2004). Its abundance was negatively correlated with several diseases such as IBD (Png et al., 2010), obesity (Santacruz et al., 2010) and even autism (Wang et al., 2011b). Administration of *Akkermansia muciniphila* resulted in the improvement of gut barrier function, metabolic endotoxemia and adipose tissue inflammation in HFD-induced obesity (Everard et al., 2013). Thus, *Akkermansia muciniphila* might be critical for the maintainance of a healthy gut microbial ecology (Belzer and de Vos, 2012).

With the development of high-throughput sequencing, more and more bacteria with probiotic activity will be found. But how to obtain specific conditions to culture them is still a big challenge. However, it is still not clear whether these novel probiotics are absolutely safe to human health when introduced into the body. Thus, future works focusing on the fully understanding of the microbe-host relationships are warranted. Gnotobiotic animals are valuable tools used to evaluate the physiological functions of each probiotic strain.

6.3. Drugs

It has been well established that individuals have different responses to the same drug (Evans and Relling, 2004). The gut microbiota may be an important environmental factor that influences the inter-individual variations in drug efficiency. For instance, there is significant correlation between the intestinal bacterial metabolites secondary bile acids and individuals' variable responses to simvastatin treatment (Kaddurah-Daouk et al., 2011). In addition, predose production of bacteria-mediated *p*-cresol affected a person's capacity for acetaminophen sulfonation (Clayton et al., 2009).

Currently, we still know little about how our intestinal microbes modulate drug metabolism. Yet, some drugs may exert their pharmacological efficiency by influencing gut microbial composition. Neonatal treatment with glycopeptide antimicrobial drug vancomycin suppressed clinical onset of diabetes in NOD mice and increased the number of bacterium *Akkermansia muciniphila* (Hansen et al., 2012). Moreover, ezetimibe was able to modulate cholesterol metabolism in mice possibly through increasing the abundance of *Lactobacillus* (Catry et al., 2015).

Metformin, a widely prescribed drug for the treatment of T2D, extended the lifespan of *Caenorhabditis elegans* by altering the folate and methionine metabolism of the co-cultured *Escherichia coli* (Cabreiro et al., 2013). Moreover, metformin also improved metabolic disorders and adipose tissue inflammation in HFD-fed mice. These improvements were companied by an increase of mucin-producing goblet cells and an enrichment of bacterium *Akkermansia muciniphila* (Shin et al., 2014). In T2D patients with metformin administration, serum levels of bile acid and gut hormone PYY were significantly correlated with the relative abundance of Bacteroidetes and Firmicutes (Napolitano et al., 2014). A recent study showed that T2D patients with metformin treatment exhibited an enrichment of *Escherichia* species, which might be associated with its adverse effects such as bloating (Forslund et al., 2015).

Gegen Qinlian Decoction (GQD) is a traditional Chinese herbal formula, which has been recorded to treat diarrhea for a long history. A recent study reported that a beneficial bacteria *Faecalibacterium prausnitzii*, which was negatively correlated with reduced levels of glycated hemoglobin (HbA1c) and fasting blood glucose, was significantly enriched in the gut of T2D patients with GQD treatment (Xu et al., 2015). Berberine is a component of the Chinese herb *Coptis chinensis*. Two SCFA-producing bacteria *Allobaculum and Blautia*, as well as the fecal concentrations of total SCFAs were significantly increased in HFD-fed rats with berberine administration (Zhang et al., 2012a). Moreover, both *Coptis chinensis* and berberine could reduce the ratios of Firmicutes or Bacteroidetes to total bacteria in HFD-induced mice (Xie et al., 2011).

Taken together, these findings suggest that the therapeutic effects of some drugs may, at least in part, depend on modulating the composition and/or the metabolism of gut microbes. Thus, gut microbiota can be manipulated to increase pharmacological efficiency or to decrease adverse effects (Jia et al., 2008). Decreasing the number of harmful bacteria and increasing proportions of beneficial bacteria such as SCFA-producing bacteria can be considered as new parameters for the evaluation of drug's therapeutic index. Understanding the mechanism of our gut microbiota in drug metabolism is crucial to treat diseases and improve human health.

6.4. Fecal microbiota transplantation (FMT)

Gut microbiota transplantation, also known as "fecal bacteriotherapy", is defined as the transfer of the fecal suspension from a healthy donor into the gastrointestinal tract of a patient for the treatment of specific diseases. It had been recorded as an ancient therapeutic method to treat food poisoning or diarrhea during the Dong-jin dynasty in the 4th century China (Zhang et al., 2012b). In the 16th century, the fecal suspension, which was called "yellow soup" in traditional Chinese medicine, was used for the treatment of numerous gastrointestinal disorders (Zhang et al., 2012a). In the 17th century, FMT was used in veterinary medicine in Europe to cure animals that were unable to ruminate (Zhang et al., 2012b). The first use of FMT in modern medicine was reported in 1958 with the successful treatment of patients with pseudomembranous colitis (Eiseman et al., 1958).

Clostridium difficile infection (CDI), a gastrointestinal disease caused by bacteria *Clostridium difficile*, is the most common cause of hospital-acquired diarrhea and has caused a global healthcare problem (Di Bella et al., 2015). Numerous case reports and case series have demonstrated that FMT is a promising therapeutic approach for the treatment of recurrent and refractory CDI (Aas et al., 2003; Brandt et al., 2012; Kelly et al., 2012; Youngster et al., 2014) since the first use of FMT for CDI treatment was reported in 1983 (Schwan et al., 1983).

Mice infected with *C. difficile* 027/BI displayed a reduction in the intestinal bacterial diversity (Lawley et al., 2012). In humans, patients with FMT treatment had increased gut bacterial diversity, specifically characterized by increased abundance of *Bacteroidetes* and *Clostridium* clusters IV and XIVa as well as decreased abundance of *Proteobacteria* (van Nood et al., 2013). A recent study demonstrated that *Clostridium scindens*, a bile acid 7α-dehydroxylating intestinal bacterium, ameliorated CDI via a secondary bile acid-dependent mechanism (Buffie et al., 2015).

FMT appears to be a promising therapy for the treatment of numerous diseases (Rossen et al., 2015). However, the mechanism by which FMT normalizes intestinal microbial homeostasis remains to be elucidated. Standardized methodologies for FMT including donor screening, stool preparation and routes of administration are necessary to reduce the risk of adverse events and improve the efficacy and safety for better clinical application.

7. Conclusion and future perspective

In this review article, we summarized the characteristics of gut microbiota in specific age groups. An essential step for the health improvement throughout life is by establishing a "healthy gut microbiota" at an early age. Targeting the gut microbiota by dietary fibers may help resist the diseases and extend the life span. Diet and lifestyle are crucial environmental factors that result in different gut microbiome between rural and urban communities.

We systematically described the associations between the gut microbiota and three clustered diseases including metabolic, immunological and neurological diseases, respectively. Numerous diseases are associated with the dysbiosis of gut microbiota, indicating the key role of gut microbiota in human health is connecting all parts of the body into a whole organized system. More importantly, it appears that the

relationship between the gut microbiota dysbiosis and the occurrence of some diseases is neither causal nor consequential, but bidirectional. Thus, the gut microbiota may directly or indirectly participate in the initiation of diverse diseases.

Finally, potential nutritional and therapeutic strategies modifying the gut microbiota (prebiotics, probiotics, drugs and FMT) are introduced for treating or preventing diseases. Further researches focusing on elucidating the underlying mechanisms are warranted. Nevertheless, there is no doubt that the development and application of these approaches will bring great opportunities for the improvement of human health.

It should be emphasized that the development of advanced sequencing techniques has expanded the depth of our insights into the intestinal microbial communities. Discovering new bacterial species with specific functions results from the perfect combination of traditional and modern microbiological techniques. At the same time, application of precise gene editing tools will also be helpful to create some bacterial species with multiple health-promoting effects.

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