Diet Effects in Gut Microbiome and Obesity

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Abstract: The 100 trillion microbes in human gut coevolve with the host and exert significant influences on human health. The gut microbial composition presents dynamic changes correlated with various factors including host genotypes, age, and external environment. Effective manipulation of the gut microbiota through diets (both long-term and short-term diet patterns), probiotics and/or prebiotics, and antibiotics has been proved being potential to prevent from metabolic disorders such as obesity in many studies. The dietary regulation exerts influences on microbial metabolism and host immune functions through several pathways, of which may include selectively bacterial fermentation of nutrients, lower intestinal barrier function, overexpression of genes associated with disorders, and disruptions to both innate and adaptive immunity. Discoveries in the interrelationship between diet, intestinal microbiome, and body immune system provide us novel perceptions to the specific action mechanisms and will promote the development of therapeutic approaches for obesity.

Keywords: diet, gut microbiota, obesity, prebiotic

Introduction

Our human gut is colonized with a complex community of 100 trillion microbe cells, which is 10-fold the number of eukaryotic cells in the human body, and it is estimated that they represent 150 times unique genes than our own genome. Culture-independent methods such as 16S ribosomal RNA analysis revealed that the adult microbiota is rich in the level of bacterial species (1000 to 1150 species; Qin and others 2010) but limited in the phylotypes of which mainly are *Firmicutes* and *Bacteroidetes*, constitute over 90% of the gut bacteria cells (Ley and others 2006a, 2006b; Turnbaugh and Gordon 2009).

The microbiota (commensal and symbiotic microbes reside in our guts) varies between individuals but studies of microbiome (microbial metagenome sequences) have demonstrated that the functional gene repertoires exhibit great similarity among individuals especially adults (Turnbaugh and others 2009c).The composition of gut microbiota within an individual is inherently associated with host genotypes and age and moreover presents dynamic changes affected by external factors such as diets, antibiotics, and prebiotics and probiotics, which may result in dysbacteriosis (Figure 1).

Accumulating evidence indicates that a dysfunctional microecosystem (such as a decrease in microbial diversity) may relate to enteral inflammation such as inflammatory bowel disease (IBD; Macfarlane 2009) and several extra-intestinal diseases such as obesity (Ley and others 2005; Turnbaugh and others 2006), diabetes (Creely and others 2007; Cani and others 2008), liver disease (Brun and others 2007; Yin and others 2010), cardiometabolic complications (Shen and others 2013), and even cancer (Scanlan and others 2008; Tlaskalova-Hogenova and others 2011). Thus, making clear the mechanisms of gut microbiota acting on host metabolism and regulating the microbial composition through diets, prebiotics and probiotics, and antibiotics exerts significant influences on human health.

The dietary regulation exerts influences on microbial metabolism and host immune functions through several pathways of which may include selectively bacterial fermentation of nutrients, lower intestinal barrier function, overexpression of genes associated with disorders, and disruptions to intestinal function by causing both innate- and adaptive-immune responses (Kau and others 2011; Shulzhenko and others 2011). The majority of gut microbes play as crucial vehicles in the host metabolism by improving energy harvest from foods, for example they are able to degrade the polysaccharide that is indigestible to the host. Besides they can improve mucosal immunity, intestinal permeability, and modulate the host-derived compounds, thus having a profound effects on human life (Hooper and others 2002; Ley and others 2005).

Better understanding of the interrelationship between diet, intestinal microbiome and body immune system are fundamental in the development of therapeutic approaches for various diseases to benefit human health. In this review, we demonstrate the dynamic changes of gut microbiota associated with human genotypes, age, and dietary factors. Moreover, we highlight dietary effects on the shifts of gut microbiota, and the mechanisms through which resulting in obesity and other related disorders such as type 2 diabetes and several cardiovascular diseases. Finally, the association between the regulation of gut microbiota and intestinal metabolism that closely related to obesity were discussed, too.

The Dynamic Changes of Gut Microbiota are Associated with Human Genotypes, Age, and Dietary Factors

Host genotypes

Gut microbial composition of the kinship relationships resemble with each other more than unrelated individuals (Dicksved and others 2008; Turnbaugh and others 2009c), suggesting that the genetic background may be an important factor in selecting and shaping the intestinal microbiota. A study of 645 mice with the use of quantitative trait loci (QTL) detection approach (an analysis to test whether specific taxa cosegregate as quantitative traits with linked genomic markers) revealed that for 18 host QTL, the host genetic variation is correlated with relative abundances of specific microbial taxa, including at least one taxon from each of the *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, and *Actinobacteria* phyla (Benson and others 2010). Another clinical study of familial Mediterranean fever (FMF) patients by mutations in the MEFV gene—which encodes the pyrin, a regulatory protein of innate immunity demonstrated

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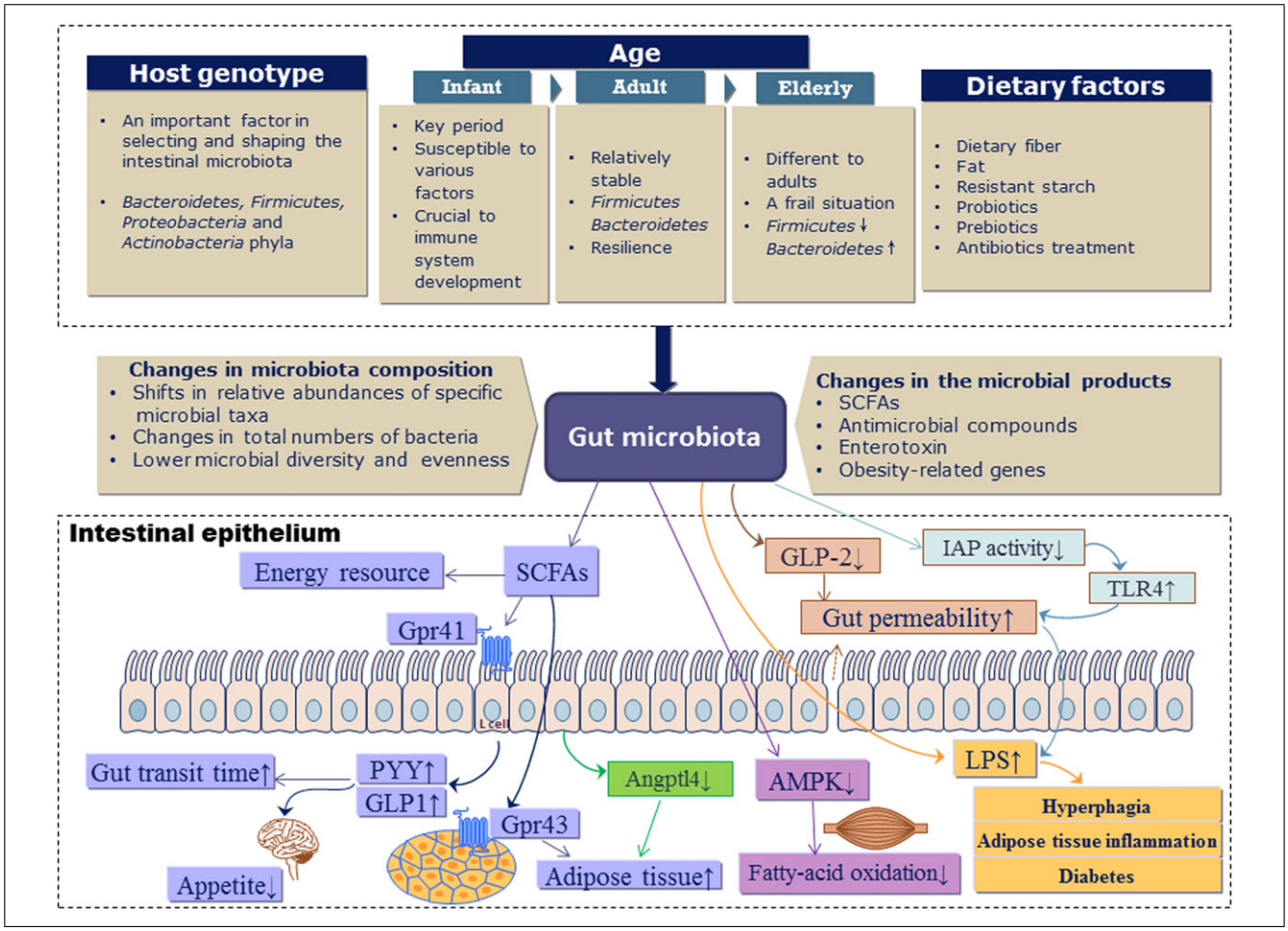

Figure 1—The gut microbial composition presents dynamic changes correlated with host genotypes, age, and dietary factors and antibiotics treatment. Changes in microbiota composition and related microbial products exert influences through complex mechanisms on host immune and metabolic functions resulting in obesity and associated disorders.

significant shifts in bacterial community structure such as decreased total numbers of bacteria, lower diversity, and major changes in bacterial populations within the *Bacteroidetes, Firmicutes,* and *Proteobacteria phyla* (Khachatryan and others 2008).

These findings highlight that there is an interaction between the host genetics and a specific profile of commensal microbiota in the human gut, which will be critical for future studies to understand the association between the composition of gut microbiota and complex diseases.

Age

The gut microbiota in various age groups present different characteristics (Figure 1). To realize the significant features of each group and the reasons for them will help to enhance pertinence and actual effects of further studies.

Infancy is a critical period for intestinal colonization. The newborn infant gastrointestinal tract is almost sterile and initial acquisition of infant gut microbiota can be from vagina, feces, and hospital. The early colonizers after delivery mainly are *Bifidobacterium*, *Clostridium*, *Ruminococcus*, *Enterococcus*, *Enterobacter*, and *Bacteroides* (Favier and others 2002; Marques and others 2010). During the first 2 y of life, the composition of the infant intestine is volatile and susceptible to many factors (O'Toole and Claesson 2010) including delivery mode (Adlerberth and Wold 2009; Dominguez-Bello and others 2010), feeding method (Orrhage and Nord 1999), and environmental factors (such as health care, nutrition, and antibiotics). Accompanied by the fluctuations of bacterial populations, the complexity of the bacterial community evolved gradually toward an adult-like configuration (Palmer and others 2007; EGGESBø and others 2011; Yatsunenko and others 2012).

In adulthood, the gut microbial composition is relatively stable and dominated by *Firmicutes* and *Bacteroidetes*. Although it undergoes multiple perturbations of diets, antibiotics, and/or new species invasion, the conventional microbiota can protect against changes to a certain extent. But if the perturbations overload the capacity of the microsystem can tolerate, shifts in gut microbiota occur and may induce dysbacteriosis resulting in a range of diseases (Lozupone and others 2012).

The human gut microbiota undergoes substantial changes through the aging process as well as the functionality of the host immune system, resulting in a frail situation and a greater susceptibility to infections. Several studies have observed age-related changes in the gut microbiota composition. For example, The dominant roles of *Firmicutes* and *Bacteroidetes* keep unchanged during different life stages but the ratio of *Firmicutes* to *Bacteroidetes* evolves—to be respectively 0.4, 10.9, and 0.6 for infants, adults, and elderly individuals (Mariat and others 2009).

In a study explored the gut microbiota composition of 145 elderly (mean age, 75 y) people and 85 health adults (mean age,

35 y) from 4 European countries, higher prevalence of *Enterobacteria* were foundin all subjects independent of the location (Mueller and others 2006). Another published study probed into the age-related differences in the gut microbial composition among young adults, elderly (mean age, 70 y), and centenarians (>100-y old) observed highly similarity in that of the former 2 groups, whereas that of the centenarians showed highly difference. In the centenarians, *Eubacterium limosum* and relatives representative of the long life were more than 10-fold increased. Additionally, the proportion of facultative anaerobes enriched. By contrast, a marked decrease of *Bifidobacteria*, *Faecalibacterium prauznitzii*, and relative symbiotic species with reported anti-inflammatory properties was observed in centenarians (Biagi and others 2010). All these findings suggest that the gut microbial composition of the elderly vary from those in adults.

The innate alteration of human gut microbiota with ageing may have relation to some symptoms of aging such as lower gastrointestinal function (Štšepetova and others 2011). Better understanding of the features presented by different age ranges will help to find the relationship between gut microbiota and age-related illness, and further clarify the pathogenesis.

Dietary effects on gut microbiota

Dietary regulation to the gut microbiota of early life. The development of gut community in early life is important to shape the intestinal microbiota and immune system of the host in later life (Olszak and others 2012).

Feeding type is one of the most essential factors that affect the neonate gut microbiotic composition. Breast-fed infants were mainly colonized with *bifidobacteria* (up to 90% of flora). Human milk oligosaccharides (HMOs) are considered functioning as growth factors for beneficial gut bacteria, as inhibitory receptors binding to different pathogens, and may promote development of the early immune system (Kunz and others 2000; Hemarajata and Versalovic 2012). In contrast, bottle-fed infants harbor more diverse microbiota groups including *Bacteroides, Clostridium*, and *Enterobacteriaceae* (Martin and Walker 2008; Martín and others 2009). The more reasonable nutrition designed formulas nowadays, which contain prebiotics such as galactooligosaccharides (GOS) and fructooligosaccharides (FOS), have been proven to increase the number of *Bifidobacteria* and *Lactobacilli* in the gut.

In contrast, antibiotics play a negative role in the composition of the infant gut microbiota, resulting in decrease of obligate anaerobes (for example, *Bifidobacteria* and *Bacteroides*; Martin and Walker 2008; Reinhardt and others 2009). Reduced bacterial diversity of the infant's intestinal flora precedes asthma (Abrahamsson and others 2013), allergic sensitization, allergic rhinitis, and peripheral blood eosinophilia in the childhood (Bisgaard and others 2011). However, the gut microbiota effect vary with antibiotics (Penders and others 2006). Decreasing excessive use of antibiotics and increasing the use of pre- and probiotics is effective in preventing several important infant diseases such as necrotizing enterocolitis, atopic eczema as well as improving short and long-term health (Wall and others 2009).

To sum up, dietary modulation to the infant microbiota influences the developing immune system and thus affect immunological response to some pathogens in later life.

Long-term dietary regulation derived from different cultures. Dietary history is associated with geography, cultural practices, lifestyle, and socioeconomic status. Significant differences have been found among the gut microbiota of the Russian, American, Danish, and Chinese groups (Tyakht and others 2013). Similarly, comparisons have also been made between Korean gut microbial communities and those members from other countries including the USA, China, and Japan. UniFrac analysis revealed that fecal microbial community of each country member showed slight difference from each other at phyla level, with American had higher *Firmicutes*, Japanese had higher *Actinobacteria*, and Korean and Chinese enriched in *Bacterodetes* (Nam and others 2011). Thereby, gut microbial composition is likely linked to long-term dietary style.

The intestinal microbiomes of rural children in Burkina Faso who consumed a plant-rich diet were compared with that of children from Italy who consumed a low-fiber diet (De Filippo and others 2010) and significant differences of gut flora and opposite trend between the 2 groups were gotten: the African children had lower levels of *Firmicutes* than of *Bacteroidetes* whereas the European children who had high levels of *Enterobacteriaceae* (*Shigella* and *Escherichia*). In specific, the dominant genera of *bacteroides* in the microbiota of African children were the *Prevotella* and *Xylanibacter*, whereas those of the European children were the genera *Bacteroides* and *Alistipes*. *Prevotella* and *Xylanibacter* can ferment both xylan and cellulose in the rural diet of the African children to liberate energy. The *Bacteroides plebeius* coding genes of porphyranases and agarases are significantly more frequent in the gut microbiome of Japanese than that of the North American population, which is associated with the seaweeds-rich diet habits of Japanese since seaweeds is a major resource of the *Bacteroides plebeius* (Hehemann and others 2010). Significant differences in the phylogenetic composition of fecal microbiota were noted between U.S. residents and those from Malawians and Amerindians (Yatsunenko and others 2012). At species level, the non-U.S. adults had a higher prevalence of the *Prevotella* genus than the U.S. residents. The enzyme composition (EC) representation in fecal microbiomes was also compared to see if the distinctive features are evident. The ECs participates in the catabolism of glutamine, simple sugars, sugar substitutes, and host glycans have higher proportional representation in adult U.S. fecal microbiomes, reflecting their typical western diet. In contrast, the EC involved in the degradation of starch was at high level in the Malawian and Amerindian microbiomes, reflecting their corn-dominant diet (Yatsunenko and others 2012) .

The metagenomes of gut microbiota community structures from Russian cities resembled those of Western countries, which is presumably associated with increased consumption of meat products and processed food (Tyakht and others 2013). However, the gut microbiota in rural residents of Russia are distinctly enriched in *Firmicutes* and *Actinobacteria* (both are underrepresented in urban residents), which is presumably associated with high consumption of starch-rich bread and natural products (Tyakht and others 2013).

These findings imply that the dietary habits formed over a long period of time may play a key role in the composition of gut microbiota over other variables such as ethnicity, sanitation, and climate. But the genetic differences in individuals among different countries cannot be neglected. More carefully controlled studies should be carried out to probe into the relationship between long-term dietary patterns and gut microbiota even without genetic factors and other environmental variables.

Short-term regulation by diet patterns and food ingredients. Food ingredients such as polysaccharides, fat, protein, and vitamins consumed by the host can be absorbed and utilized by gut microbiota. The microbial species in humans gut can be more adept at degrading polysaccharides than the hosts themselves, resulting in higher production of short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate. Different

microbial species have their preferential "targets," and diet–microbe interactions within the gut are now thought to play an important role in host health with links to suppression of pathogens, impact on blood lipids, and a reduced risk of developing metabolic disorders (Costabile and others 2008). The research about the diet-related effects on the gut microbiota is of great significance for the human health. For example, the vegetarian diet and the Western diet are 2 distinctly different diet patterns, in which the former is characterized by high fiber and low fat and the latter is the other way around. Several studies have detected the difference of the gut flora composition between the 2 diet patterns. The gut microbiota of vegetarians is dominated by *Clostridium coccoides, Clostridium ramosum* (Finegold and others 1983; Hayashi and others 2002) and in the absent of *Faecalibacterium prausnitzii* (Hayashi and others 2002). The clusters of *F. prausnitzii* were found at high levels in groups who mainly consume fish and meat (Mueller and others 2006).

A more strict-designed recent study observed a vegan or vegetarian diet can significantly change the human gut microbiota compared with the omnivorous controls carefully matched for age and gender. Specifically, a distinct decrease in the counts of *Bacteroides* spp., *Bifidobacterium* spp., *Escherichia coli*, and *Enterobacteriaceae* spp. was found in vegans and vegetarians (Zimmer and others 2011), whereas the total bacteria cells were unchanged. A shift in the fluctuant nonstarch polysaccharides and some other nutrients from meal can rapidly alters the composition of the microbiota (Turnbaugh and others 2009b; Sonnenburg and others 2010; Faith and others 2011; Goodman and others 2011).

Whole grain cereal is rich in dietary fiber and resistant starch (RS) with protection from chronic diseases. A recent *in vitro* study explored the impact of 2 different sized oat flakes on the human gut microbial ecosystem (Connolly and others 2010a). The larger one produced significant increases in *Bifidobacterium* in the latter stages of fermentation whereas numbers declined for the smaller one. Additionally, the smaller one resulted in a significant increase in the *Bacteroidese Prevotella* group. The differences may be due to varying types and levels of dietary fiber present after digestion in particular RS (*Bifidobacterium* are known to ferment this dietary fiber; Connolly and others 2010a).

A study of 10 human subjects under a controlled setting detected marked changes in the microbiota along with a dietary shift from high-fat, low-fiber to low-fat, high-fiber diets within 24 h (Wu and others 2011). But the short time was not sufficient to change the dominant enterotypes distinguished primarily by levels of *Bacteroides* (associated with protein and animal fat) and *Prevotella* (associated with carbohydrates). Thus, altering enterotypes may require a long-term dietary intervention, more in line with the study comparing children from Italy and Burkina-Faso (De Filippo and others 2010; Wu and others 2011). A recent study of 14 overweight men with precisely controlled diets revealed rapid and marked changes in the colonic microbiota and demonstrated the influence of dietary intake with consequences for health (Walker and others 2010). In this study, the subjects were provided successively with a control diet, diets high in resistant starch (RS) or nonstarch polysaccharides (NSPs), and a low carbohydrate weight loss (WL) diet. Detected by qPCR, *Firmicutes* bacteria related to *Ruminococcus bromii* (R-ruminococci) and *Eubacterium rectale* increased in most volunteers on the RS diet, and the *Oscillibacter* group was enhanced by both the RS and WL diets. The *E. rectale* decreased, along with *Collinsella aerofaciens*, on WL diet. However, the starch digestibility estimated from chemical analysis of the diet and of 24 h fecal samples were subject to interindividual variation, with >60% of RS remaining unfermented in 2 volunteers on the RS diet, compared to <4% in the other 12 volunteers. These results may be due to profound differences in the response of the microbial community to dietary change, and in microbial fermentation of dietary substrates in the colon between individuals (Walker and others 2010).

It has been shown that diets high in RS and NSP can respectively benefit insulin sensitivity and phytochemicals release through the microbial fermentative activity in the colon (Gill and Rowland 2002; Robertson and others 2005). Besides, diets containing RS and NSP offer potential benefits in prevention of colorectal cancer through the delivery of fermentation acids, in particular butyrate, to the distal colon (McIntyre and others 1993; Duncan and others 2007). Additionally, studies have found that WL diets have considerable influence on the composition and metabolic outputs of the gut bacterial community (Duncan and others 2007, 2008; Brinkworth and others 2009) .

Probiotics. Probiotics are defined as "live microorganisms which, when administered in adequate amounts to allow colonization of the colon, confer a health benefit on the host" (Sanders 2008), of which the most common groups are the genera *Lactobacillus* and *Bifidobacterium* (Parracho and others 2007). Introducing probiotics to human and mice can lead to variations in expression of microbiome-encoded enzymes associated to plant polysaccharide metabolism (McNulty and others 2011). Probiotics have been shown to maintain the normal microbial community structure, inhibit the invasion of pathogens in the human gut by increasing the amount of mucus secretion, improve the mucosal integrity, and reduce the gut permeability (Spinler and others 2008; Saulnier and others 2009; O'Shea and others 2012; Shen and others 2013). The ability of *Bifidobacteria* to improve gut barrier function and reduce the intestinal endotoxin levels has been demonstrated in several studies (Griffiths and others 2004; Wang and others 2004; Wang and others 2006). Furthermore, probiotics can act on the gut immune system and affect the gut epithelia and immune cells sensitivity to microbes in the gut lumen (Thomas and Versalovic 2010). The potential use of probiotics in lowering necrotizing enterocolitis risks in preterm infants and preventing infections in immunocompromised patients are also discussed in some studies (Martin and Walker 2008; Guillemard and others 2010; Mikelsaar and others 2010; Tatum and others 2010).

Moreover, probiotics may function as a supplementary tool to ameliorate obesity and associated disorders (Shen and others 2013; Sommer and Bäckhed 2013). A study on diet-induced obese mice has confirmed the anti-obesity effect of *Lactobacillus rhamnosus* PL60, a human originated bacterium (Lee and others 2006). Another germ-free mice study revealed that *Lactobacillus paracasei* could decrease fat storage along with a high level of Angptl4, which is a circulating lipoprotein lipase (LPL) inhibitor that controls triglyceride deposition into adipocytes (Aronsson and others 2010).

As growth promoters, probiotics have been widely used in the animal farming industry for nearly 50 y, and are experimentally shown to stimulate fattening in poultry (Angelakis and Raoult 2010), livestock (Anadón and others 2006) and mice (Angelakis and others 2012). It is difficult to deny the hypothesis that probiotics may have the same effect in humans by altering the intestinal flora. High level of intestinal lactobacilli can increase risks of obesity and hyperglycemia in healthy adults (Štšepetova and others 2011), but the effects of the probiotics for body weight and obesity are deemed to be strain specific. For example, *Lactobacillus ingluviei*, *Lactobacillus acidophilus* are associated with a weight-gain effect,

whereas *Lactobacillus casei/paracasei*, *Lactobacillus plantarum*, and *Lactobacillus gasseri* showed antiobesity effect (Million and others 2011, 2012). In a rats study compared the effects of 4 *Bifidobacteria* strains on the body weight (BW) gains acquired different results: 1 strain increased BW, 1 strain reduced BW, and the rest 2 had no significant influences on BW (Yin and others 2010). Therefore, the supplementation of probiotics should be detailed in specific strains and carefully evaluated before they are regarded as safe for human use.

Prebiotics. Prebiotics refers to nondigestible food ingredients that selectively stimulate the growth of one or a limited number of microbes in the gut with beneficial effects for host health (Pharmaceutiques 1995; Roberfroid 2007; Saulnier and others 2009; Roberfroid and others 2010).

The prebiotic-rich foods, such as Jerusalem artichokes and chicory, have been reported the ability to regulate gut microbiota by elevating the number of *Bifidobacteria* and *Lactobacilli* (Kleessen and others 2007; Ramnani and others 2010) . To improve their applicability, prebiotics may serve as oral intake ingredients. Supplementation with prebiotics such as fructo-oligosaccharides (FOS) and inulin can promote the growth of beneficial gut bacteria, particularly *Bifidobacterium* and/or *Lactobacillus* (Ramirez-Farias and others 2009; Brignardello and others 2010; Maccarrone and others 2010; Roberfroid and others 2010; Cani and others 2012), and decrease the number of *Clostridium leptum* in some studies (Pyra and others 2012). Interestingly, some fructans are also able to increase other bacteria such as *F. prausnitzii* (Ramirez-Farias and others 2009).

Several mechanisms (Table 1) have been proposed to illustrate the beneficial effects of prebiotic on obesity and related metabolic disease such as type 2 diabetes and several cardiovascular disease : (1) a modulation of gut peptides (glucagon-like peptide 1, peptide YY, and intestinal proglucagon mRNA) with consequences for a decrease in appetite and postprandial glucose excursion responses (Cani and others 2009a; Parnell and Reimer 2009; Everard and others 2011; Hess and others 2011). (2) Increasing endogenous glucagon-like peptide-2 (GLP-2) production resulting in the amelioration of gut barrier functions during obesity and diabetes (Cani and others 2009b). (3) Improving glucose tolerance, target enteroendocrine cell activity, and leptin sensitivity associated with metabolism in obesity and diabetes (Cani and others 2009b; Everard and others 2011). (4) Promoting gut fermentation and modulating GPR43 (a G protein-coupled receptor, linking between gut fermentation processes and white adipose tissue development) expression, thus controlling the development of adipose tissue (Dewulf and others 2011). (5) Regulating inflammatory tone by a decrease in endotoxaemia, plasma, and adipose tissue proinflammatory cytokines, as well as hepatic expression of inflammatory and oxidative stress markers, which may affect host metabolism in obesity and diabetes (Cani and others 2007, 2009b).

Antibiotics. Antibiotics are designed to target pathogenic population and improve our lives by treating infectious diseases. But because most of them have broad-spectrum activity, they can affect other members of the gut microbiota and thereby disrupt their coevolved interactions with the host.

The alterations in the gut microbiota as a result of antibiotic treatment mainly come down to a shift in microbiota composition (Dethlefsen and others 2008; Dethlefsen and Relman 2011), reduced diversity, and/or abundance of bacteroides (Dethlefsen and others 2008; MacFarlane and Macfarlane 2009; Dethlefsen and Relman 2011), and decreased evenness of the community (Dethlefsen and others 2008). But community changes induced by antibiotic treatment varied among individuals, which may be due to the expansion of antibiotic-resistant genes in the gut microenvironment and other indirect factors (Dethlefsen and others 2008).

Disrupted interactions within the gut flora resulting from antibiotic usage are reported in associated with acute (Beaugerie and Petit 2004) and chronic (Flöistrup and others 2006; Marra and others 2006) health problems, such as obesity (Ternak 2005), diarrhea, asthma, and IBD (Guarner and others 2006). Significant and persistent weight gain can occur after treatment with a 6-wk intravenous treatment of vancomycin in patients with infective endocarditis, which might be due to the selection of *Lactobacillus* sp. in the gut microbiota (Thuny and others 2010). Antibiotic therapy can also prevent from obesity as well as improve plasma lipopolysacharides (LPS) levels and glucose tolerance (Kalliomäki and others 2008; Membrez and others 2008).

A study of the infant gut flora following ampicillin and gentamicin treatment indicated that the gut microbiota of the antibiotic-treated infants significantly changed (with a higher proportions of *Proteobacteria* and lower proportions of *Actinobacteria* as well as the genus *Lactobacillus* than the untreated counterparts) and recovery still incomplete after 8 wk, which suggests antibiotics disruption in early life can exert crucial influences on the evolution of the infant gut microbiota (Fouhy and others 2012).

Although the composition of human gut microbiota changes naturally with age, the impact of antibiotic therapy on the elderly intestinal microbiota composition taking into account their residence location (long-term nursing care, rehabilitation wards, day hospitals, and the community) was recently discussed (O'Sullivan and others 2013). The study revealed that a significant structural shift across 9 genera in the antibiotic-treated subjects, including a 7-fold reduction in *Bifidobacterium* spp. numbers. Thus, the long-term health effects following antibiotic therapy on the intestinal microbiota in the elderly should be considered (O'Sullivan and others 2013).

The mechanisms of the microbiota modulation toward host metabolic and immune system induced by antibiotic treatment are complex and largely unclear. The known hypothesizes at present may include (1) Effects on microbial intestinal metabolism: gut bacteria respond to antibiotic usage attenuated the production of SCFAs—which is the main energy source and associated with cell proliferation, differentiation, growth, and apoptosis (Willing and others 2011)—and the capacity to transport and metabolize bile acid, cholesterol, hormones, and vitamins (Pérez-Cobas and others 2013). (2) Perturbation in intestinal homeostasis and the integrity of intestinal defenses: a study with metronidazole-treated mice indicated that disruption of the microbiota with antibiotic resulted in an increased inflammatory tone of the gut, which is characterized by increased bacterial (*C. rodentium*) stimulation of the epithelium, altered goblet cell function, and reduction in mucus thickness. It demonstrates a impaired mucosal barrier and thus contributes to the exacerbated severity of *C. rodentium*-induced colitis (Wlodarska and others 2011). (3) Distribution to the innate immunity: lower diversity of the microbiota following antibiotic treatment can decrease the amount of microorganism-associated molecular pattern (MAMP) recognition receptors, for example Toll-like receptors (TLRs), which are activated by bacterial ligands and thereby weakening the innate immunity (Dessein and others 2009; Wells and others 2010). (4) Regulation of T-cell differentiation and activation: depleting Gram-positive bacteria especially segmented filamentous bacteria population with antibiotics reduces the differentiation of T-helper 17 cells, thus resulting in a

Table 1–Studies of the mechanisms and beneficial effects of prebiotics on obesity and related metabolic disease.

Animal model and experimental design	Flora change with prebiotics	Mechanism	Functions on disease	Reference
HF-feeding mice vs normal chow-fed control mice and HF-OFS-treated mice	*Bifidobacterium* spp.↑	Glucose tolerance↑, glucose-induced insulin secretion↑;normalized inflammatory tone endotoxaemia↓, plasma and adipose tissue proinflammatory cytokines↓	Improving high-fat-diet-induced diabetes in mice	Cani and others 2007
10 healthy adults (5 men and 5 women) were randomly divided into 2 groups: received either 16 g prebiotics/d or 16 g dextrin maltose/d for 2 wk		Plasma glucagon-like peptide 1↑ and peptide YY concentrations↑	Changes in appetite sensation and glucose excursion responses after a meal	Cani and others 2009
1. ob/ob mice (Ob-CT): prebiotic treatment (Ob-Pre) *vs* control (Ob-Cell) 2. Ob-CT and Ob-Pre mice were treated with GLP-2 antagonist or saline 3. Ob-CT mice were treated with a GLP-2 agonist or saline	*Bifidobacterium* spp.↑	Inflammatory tone (plasma LPS and cytokines↓, hepatic expression of inflammatory and oxidative stress markers↓); the endogenous intestinotrophic proglucagon-derived peptide (GLP-2) production↑, intestinal permeability↓	Improving inflammation and metabolic disorders during obesity and diabetes; improve gut barrier functions	Cani and others 2009
ob/ob mice or diet-induced obese and diabetic mice: chronically fed with prebiotic-enriched diet or with a control diet	*Firmicutes* ↓ *Bacteroidetes* ↑	Glucose tolerance↑, L-cell number↑(intestinal proglucagon mRNA expression ↑and plasma glucagon-like peptide-1 levels↑), fat-mass development↓, fat oxidative stress↓, and low-grade inflammation↓, leptin sensitivity↑	Exerting effects on host metabolism in obesity and diabetes	Everard and others 2011
Male C57bl6/J mice: fed a standard diet or an HF diet without or with Inulin-type fructans (ITF) (0.2 g/d per mouse) during 4 wk	*Bifidobacterium* spp.↑ *Roseburia* spp. ↓ *C. coccoides*↓	Peroxisome proliferator activated receptor γ (PPAR-γ)–activated differentiation factors↓, GPR43 expression↓, the subcutaneous adipose tissue↓	A beneficial effect on obesity and with potential decrease in PPAR-γ–activated processes	Dewulf and others 2011
Male lean and obese JCR:LA-cp rats: received different dose of inulin and oligofructose	*Firmicutes*↓ *Bacteroidetes* ↑ *Bifidobacteria* and *Lactobacillus*↑(in a dose-dependent manner)	Caecal proglucagon and peptide YY mRNA levels↑, plasma ghrelin response↓ (in a dose-dependent manner)	Dose-dependent regulation of the appetite effects and energy expenditure may have therapeutic potential for obesity	Parnell and Reimer 2012
20 healthy subjects: assigned to receive 2 separate doses of 0, 5, or 8 g of short-chain fructooligosaccharide (scFOS)		Gastrointestinal tolerance ↑, breath hydrogen↑(in a dose-dependent manner), the appetite effects was not obvious	The potential of scFOS as a dietary intervention is still remained to be seen	Hess and others 2011
48 healthy adults with a body mass index (in kg/m^2) > 25 consumed 21 g oligofructose/d or a placebo (maltodextrin) for 12 wk		Plasma ghrelin response↓ and peptide YY↑	The potential to promote weight loss and ameliorate satiety hormone concentrations and glucose regulation in overweight adults	Parnell, and Reimer 2009
Male, diet-induced obese Sprague–Dawley rats: fed with high-fat/-sucrose diet plus either metformin (MET) or oligofructose (OFS) or both	*Bifidobacteria* ↑ *Clostridium leptum* ↓	Fat mass↓, hepatic total glycerin↓, glucose-dependent insulinotropic polypeptide (GIP) secretion↓, leptin↑, AMPKα2 mRNA and phosphorylated acetyl CoA carboxylase (pACC) levels↑, plasma DPP4 activity↓	The potential to improve metabolic outcomes associated with obesity	Pyra and others 2012

depletion of the secretion of related pro-inflammatory cytokines (Ivanov and others 2009).

Gut Microbiota and Obesity

Obesity, now considered a worldwide epidemic, is a major health problem in both developed and developing countries (Eckel and others 2004). It has many complications such as type 2 diabetes mellitus, hypertension, obstructive sleep apnea syndrome, and ischemic heart disease (Steelman and others 2002). More recently, obesity is even recognized as a risk factor for cancer (Khandekar and others 2011; Yoshimoto and others 2013). The causes behind obesity appear to be multiple and involve genetic background, disequilibrium in the energy balance, living a sedentary lifestyle, and other environmental factors (Friedman 2009). For the past few years, obesity has been associated with a modification in microbiota, including a higher *Firmicutes/Bacteroidetes* ratio (Ley and others 2006a) and a decrease in *Methanobrevibacter smithii* (Turnbaugh and others 2006). Additionally, it has been shown that the gut microbiota of nonobese individuals is more diverse than that of obese individuals (Turnbaugh and others 2009a). The mechanisms by which gut microbiota affect obesity in humans are complicated and largely unknown, the proposed statements may consist of: an excessive bodily energy harvest, higher levels of SCFAs to promote adipogenesis, overexpression of the obesity-related genes, and increased production of LPS by gut microbiota causing obesity and Inflammation (Figure 1).

An excessive energy intake of the host

Several obese mice and humans studies have observed significant shifts in the intestinal phyla usually with an increase in *Firmicutes/Actinobacterium* and a reduction in *Bacteroidetes* (Waldram and others 2009; Ley 2010; McNulty and others 2011). These microbiota changes resulted in an increased capacity for the fermentation of carbohydrates (Turnbaugh and others 2006; Turnbaugh and others 2009c) and further an increased concentration of the end product—SCFAs, mainly acetate, propionate, and butyrate—which are crucial energy substrates of the host (Turnbaugh and Gordon 2009). However, some studies failed to disclose the relationship between the dominant gut phyla and obesity (Duncan and others 2008; Connolly and others 2010b). These contradictory results probably due to the individual variations and effects of multiple environmental factors inevitably. In another example, *Bacteroides thetaiotaomicron* along with *M. smithii* are colonized in germ-free mice. Since *M. smithii* uses the production of *B. thetaiotaomicron* (formate) as substrate for methanogenesis, on the one hand the degradation of carbohydrate is enhanced thus improving bodily energy gain (Samuel and Gordon 2006); however, a higher concentration of methane is associated with a higher body mass index and is a predictor of significantly overweight (Basseri and others 2012).

Regulation in SCFAs to activate adipose tissue development

Apart from being an important energy sources, the SCFAs are ligands for specific G-protein–coupled receptors (GPCRs)—Gpr41 (expressed by a subset of enteroendocrine cells in the gut epithelium) and Gpr43 (is activated by SCFAs and expressed in intestine, adipocytes, and immune cells, suggesting involvement in lipid and immune regulation; Brown and others 2003; Le Poul and others 2003)—which may promote energy absorption and/or triglyceride synthesis and may further affect immune and inflammatory responses (Maslowski and others 2009). Studies on Gpr41+/+ and Gpr41−/− mice revealed that the former group are significantly fatter than the latter counterparts no matter they were normally raised or gnotobiotic. And it indicated that the knockout of Gpr41 is corresponding with decreased expression of PYY, an intestinal secreted hormone negatively regulating gut motility, satiety, and energy expenditure (Samuel and others 2008). A study with Gpr43-deficient mice fed a high-fat diet has shown lower body fat mass in them as well as lower levels of liver triglycerides and plasma cholesterol, suggesting the inhibiting effect of Gpr43 in energy expenditure and triglyceride synthesis (Bjursell and others 2011).

Expression of obesity-related genes in the host

Angiopoietin-like protein 4 (Angptl4), also called fasting-induced adipose factor (Fiaf), is a circulating lipoprotein lipase inhibitor expressed in the intestine and selectively inhibited in the gut epithelium by the microbiota resulting in accumulation of adipocyte triglycerides (Backhed and others 2004, 2007). Correspondingly, the overexpression of Angptl4 reduces adipose tissue weight by stimulating triglyceride metabolism (Mandard and others 2006). Moreover, downregulated expression of AMP-activated protein kinase (AMPK) by gut microbiota induces inhibition of fatty-acid oxidation resulting in obesity (Bäckhed and others 2007).

High levels of LPS induced by gut microbiota

In both studies of humans and mice, positive correlations have been found between energy intakes and plasma LPS levels (Cani and others 2007; Amar and others 2008). LPS is a compound from Gram-negative bacterial cell walls whose concentration is up along with an increase in the proportion of Gram-negative bacteria induced by a fat-rich diet (Cani and others 2007; Amar and others 2008). Excessive high level of LPS (defined as metabolic endotoxemia) is related to gut, hepatic, and adipose tissue inflammation and diabetes through complex mechanisms (Cani and others 2007; Amar and others 2008; Seki and Brenner 2008; Fei and Zhao 2013). Another possible mechanism proposed is that high-fat feeding triggers alterations in intestinal microbiota, followed by a decrease in IAP activity and an increase in TLR4 activation in the gut wall, then leading to an increase in luminal LPS and gut permeability (de La Serre and others 2010). Enhanced gut permeability could increase plasma levels of LPS, finally resulting in an appearance of hyperphagia and obesity (de La Serre and others 2010). Germfree mice colonized with *Enterobacter cloacae* B29 (an endotoxin-producing bacterium) isolated from a morbidly corpulent human's gut induced obesity and insulin resistance characterized by high levels of circulating endotoxin and deteriorative inflammatory status (Fei and Zhao 2013). Meanwhile, the symptoms are more apparent on a high-fat diet than a normal chow diet. It is a commendable interpretation of the diet-microbiota-LPS-obesity association (Fei and Zhao 2013).

Conclusions and Prospects

In this review, we have summarized the crucial roles of genetic, physiological, and dietary factors in gut microbiota composition, and further discussed the interactions between gut microbiota and obesity. But the interrelationship between the microbiota, the environment, and human health is a profound and complex problem, especially the exact mechanisms through which microbes regulate the host metabolism. A metabolomics study has shown the pathway linking dietary lipid intake, intestinal microbiome, and atherosclerosis, which provides opportunities for the development

of novel therapeutical approaches for atherosclerotic heart disease (Wang and others 2011). Deeper analysis into microbial metagenomics, metatranscriptomics, and metabonomics to get a better understanding of the specific functional genes and their mechanisms for health is of great significance. Besides, more research is needed to understand how the inter-individual variation is modified by age and genetic environmental factors and how to make a distinction between bacterial groups those are beneficial and those are detrimental to health. Advanced culture-independent approaches and bioinformatics tools facilitate the large-scale sequencing of human gut microbiome. However, most of data acquired to date have been from fecal samples while ignoring the microbial metabolism occurring in small intestinal. Thus, using these meta-omics–based methods to track the changes of microbial metabolism in different gut site over time is a major challenge.

Experimental animal models, particularly the "humanized" germ-free mice and/or genetically modified mice, help to identify the correlations between dietary components and gut microbial communities as well as the relevant mechanisms impacting host metabolism. To confirm the effects of gut microbiota on human metabolic disorders and long-term state of health, well-controlled clinical-level studies must be carried out.

As probiotics and/or prebiotics are increasingly used in industrial food such as fermented milk products contain *Bifidobacterium*, *Lactobacillus*, and/or xylooligosaccharide, the application of both in modulating gut microbiota composition is a potential therapeutic use. However, attentions should be paid to the exploration of new-type prebiotics and the safety of probiotics, as well as the unpleasant side effects from both. For example, *in vitro* studies have investigated the prebiotic potential of a konjac glucomannan hydrolysate (GMH), polydextrose, and several polyols using batch culture fermentations (Beards and others 2010; Connolly and others 2010b). Probiotics effects on body weight and obesity are recognized to be strain specific and dose dependent, thus it is essential to enforce stringent level of control before they are regarded as safe for human use. Synbiotics, in which probiotics and prebiotics are used in combination, are normally used to regulate the composition of the gut microbiota contributing to health care or disease prevention (Vitali and others 2010). As the exact molecular mechanisms underlying their health benefits have remained largely unclear, carefully designed clinical trials should be performed in urgently needed.

In conclusion, manipulation of the gut microbiota by integrated factors significantly affects the host metabolism. Discoveries in this area provide us novel perceptions to the micrbiota–host interactions and will promote the development of therapeutic approaches for obesity and its complications.

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