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Invited Mini Review

The gut microbiota: a key regulator of metabolic diseases

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The prevalence of obesity and type 2 diabetes, two closely linked metabolic disorders, is increasing worldwide. Over the past decade, the connection between these disorders and the microbiota of the gut has become a major focus of biomedical research, with recent studies demonstrating the fundamental role of intestinal microbiota in the regulation and pathogenesis of metabolic disorders. Because of the complexity of the microbiota community, however, the underlying molecular mechanisms by which the gut microbiota is associated with metabolic disorders remain poorly understood. In this review, we summarize recent studies that investigate the role of the microbiota in both human subjects and animal models of disease and discuss relevant therapeutic targets for future research. [BMB Reports 2016; 49(10): 536-541]

THE MICROBIOTA IN THE GUT MUCOSA

The human gut is populated with as many as 100 trillion (10^{14}) cells, including bacteria, fungi, viruses, and other microbial and eukaryotic species (1, 2). These complex, heavily diverse communities provide tremendous enzymatic capability and thus play a fundamental role in manipulating host physiology (3, 4). It is well established that five bacterial phyla, *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia*, are dominant components of the human gut microbiota (5). More than 90% of the bacterial populations are gram-negative anaerobes and include the predominant genera *Bacteroides*, *Eubacterium*, *Bifidobacterium*, and *Fusobacterium* (6). Additionally, the gut microbiota is indispensable for carbohydrate fermentation and nutrient absorption (1), protection of pathogenic bacteria (7), and regulation of metabolic disorders (8).

The host intestine is unique with respect to its constant exposure to a plethora of antigens from daily food intake and exogenous bacteria. The resident gut microbiota contains a number of components able to activate both innate and adaptive immunity responses (3, 9). For example, the majority of intestinal bacteria are gram-negative anaerobes equipped with diverse agents, such as lipopolysaccharide (LPS) and flagella, allowing for innate signaling to intestinal epithelial cells through toll-like receptors (TLRs) (10). Segmented filamentous bacteria (SFB) embedded in the ileum can also stimulate adaptive, T helper 17 (T_H17) responses and induce the production of mucosal immunoglobulin A (IgA) antibody (11). In addition, commensal microbe-derived butyrate is associated with regulatory T (Treg) cell differentiation in the colon (12).

THE GUT MICROBIOTA AND METABOLIC DISORDERS

According to the World Health Organization, more than 1.9 billion adults were overweight in 2014, with over 600 million of those adults classified as obese. Obesity results from energy imbalance and is associated with other metabolic complications such as type 2 diabetes. The relationship between gut microbiota and metabolic diseases was first reported by the laboratory of Jeffrey Gordon at Washington University. Specifically, the Gordon laboratory demonstrated that leptin-deficient mice, notable for their excessive appetite and profound obesity, contained fewer *Bacteroidetes* and more *Firmicutes* than control mice (13). This study provided the first direct evidence of differences in the microbial communities of lean vs. obese animals. In support of this finding, a follow-up study from the Gordon laboratory observed fewer *Bacteroidetes* and more *Firmicutes* in obese human subjects than in lean subjects (14). Furthermore, the proportion of *Bacteroidetes* increased with either fat- or carbohydrate-restricted diet and subsequent weight loss. In people who lost weight after a gastric bypass procedure, increased levels of *Bacteroides* and *Prevotella* were negatively correlated with energy intake and adiposity (15). Other studies, however, have not observed a shift in the ratio of *Bacteroidetes* and *Firmicutes* in human subjects with weight loss (16-18). Thus, although it is possible that certain microbial species in the human gut contribute to weight gain and others contribute to weight loss, it is also possible that any observed changes in the gut microbiota are the result of weight shifts.

To address this concern, microbiota transplantation ex-

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periments have since been adopted. An initial study conducted by Gordon *et al*. demonstrated that conventionalization of germ-free mice with a normal microbiota resulted in increased body fat content and insulin resistance within 14 days, despite reduced food intake (19). This study provided the first mechanistic evidence that gut microbes can increase the host's ability to store body fat. Furthermore, germ-free mice that received gut microbes from an obese twin donor showed an increase of total body and fat mass as well as obesity-associated metabolic phenotypes compared with those that received a lean twin's microbiota (20). Interestingly, the gut microbiota from a lean mouse could invade the microbiota of an obese mouse and provide protection from weight gain, but this influence was dependent on diet. Other studies have demonstrated that germ-free mice transplanted with obesity-associated microbiota gained weight, but not to an excessive, obese level (21). Thus, the role of diet and other factors need to be considered.

DIET ALTERS THE GUT MICROBIOTA

Diet is a major factor in obesity, and it also helps shape the gut microbiota. Human studies from the past decade have revealed that the gut microbiota responds rapidly to large changes in diet; in many cases, the composition and function of the gut microbiota shifts within 1-2 days (22, 23). Despite these rapid dynamics, long-term dietary habits are still critical in determining the gut composition of an individual (24), and the effectiveness of a specific diet largely relies on the initial composition of the gut microbiota (25).

Extensive research has shown that the gut microbiota of a traditional rural population (i.e., high-fiber, low-fat diet) is more diverse and contains distinct taxa than the microbiota of Western populations (i.e., low-fiber, high-fat diet) (26). Preservation of microbial diversity by a high-fiber, low-fat diet allows individuals to maximize energy intake from fiber while also protecting them from inflammation and noninfectious colonic diseases. Although it is unclear whether increased microbial diversity contributes to protection from metabolic diseases, several metagenomics studies indicate that improved outcomes in metabolic diseases are associated with increased microbial diversity (27, 28). For example, a team of researchers sequenced the microbiomes of 169 obese and 123 non-obese individuals and observed that individuals fell into two groups: a group with a low amount of microbial gene diversity and another group with high diversity (27). Those with fewer genes tended to have more pronounced adiposity, insulin resistance, and dyslipidemia than individuals containing more diverse gut microbiotas. Furthermore, obese individuals with lower bacterial diversity showed more weight gain over time. These data imply that manipulation of microbial diversity in the gut could be a promising avenue for amelioration of metabolic disorders.

MICROBIAL REGULATION OF METABOLITES

The gut microbiota produces numerous amounts of metabolites. For example, the microbiota contributes to host metabolic efficiency by increasing energy availability via the production of short-chain fatty acids (SCFAs), such as acetate, butyrate and propionate (29). Previous studies demonstrated that SCFA levels were elevated in obese human subjects and animal models, consistent with the fact that SCFAs provide extra calories to the host (8, 16). Most recently, researchers observed that amplified production of acetate increased the likelihood of obesity by triggering secretion of ghrelin, the appetite-inducing hormone (30). By contrast, other studies have demonstrated that SCFAs directly contribute to host protection from metabolic diseases. For example, SCFAs are an important energy source for gut epithelial cells through activation of G-protein-coupled receptors, such as GPR41 and GPR43, which influence enteroendocrine regulation (31, 32). Butyrate acts as a main energy source for colonocytes (33), and propionate can induce intestinal gluconeogenesis, thus protecting the host from diet-induced obesity via the gut-brain neural axis (34). Interestingly, consumption of a complex diet resulted in increased levels of SCFAs and increased diversity within the gut microbiota (26). Reduced dietary intake of carbohydrates for obese humans, however, resulted in decreased butyrate levels in their feces and correlated with a reduced abundance of butyrate-producing bacteria (i.e., *Roseburia* spp. and *Eubacterium rectale*) (17). Furthermore, levels of propionate specifically correlated with the amount of *Bacteroidetes* in the gut (35).

In addition to the production of SCFAs, the microbiota forms bile acids from host cholesterol. Bile acids are a family of steroid acids synthesized from cholesterol in the liver and mostly secreted into the lumen of the intestine to control the digestion and absorption of dietary fat and fat-soluble vitamins (36). Commensal microbiota plays a pivotal role in the conversion of primary bile acids in the lower part of the small intestine and the colon to generate secondary bile acids (37, 38). Although it has become clear that bile acids act as signaling molecules for metabolic pathways, fundamental questions remain concerning whether additional administration of specific commensal bacteria can regulate bile acid metabolism and the potential role of these altered bile acids in metabolic diseases, such as obesity and type 2 diabetes (39, 40). A recent study demonstrated that the bile acid profiles in the gut and serum of control mice were quite distinct from those of germ-free mice (41), while another animal study reported that taurine-conjugated bile acids were dominant in germ-free and antibiotic-treated mice (42). Furthermore, administration of probiotics altered gut microbiota composition and enhanced bile acid deconjugation and fecal excretion (43). Notably, the increased probiotic bacteria were associated with the induction of hepatic bile acid synthesis via the farnesoid X receptor (FXR) (43). The gut microbiota also

regulates the G-protein-coupled bile acid receptor 1 (known as TGR5) (44). Our group has detected increased levels of bile acids in fecal tissue as well as TGR5 in adipose tissue from *B. acidifaciens*-fed mice (45). Additional studies have suggested that bile acid-TGR5-cAMP signaling pathways enhance energy expenditure in adipose tissue (46, 47). In total, specific commensal microbiota may regulate host metabolic actions through modulation of bile acid synthesis or reabsorption and by interaction with receptors such as FXR and TGR5.

Gut microbiota ultimately contribute to the regulation of incretin hormone secretion through the interaction between the aforementioned metabolites (SCFAs, bile acids) and their receptors (GPR1 and GPR43, TGR5), which are expressed on enteroendocrine L cells (48-52). The stimulated enteroendocrine L cells secrete incretin hormone peptides, such as glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2), and peptide YY (PYY), which in turn stimulate insulin release and decrease blood glucose levels (48). These secreted peptides affect a wide range of organs and tissues to improve insulin sensitivity, glucose tolerance, and energy homeostasis (Fig. 1), thereby contributing to protection in metabolic disorders such as obesity and type 2 diabetes.

MICROBIAL REGULATION OF INFLAMATION

Several lines of evidence point to a role for gut microbiota in the induction of systemic and adipose tissue inflammation (49, 50). For example, the gut microbiota produces substantial amounts of inflammation-inducing factors, including LPS and peptidoglycan. Additionally, monocolonization of *Escherichia coli* into germ-free mice promoted macrophage accumulation in white adipose tissues and polarized macrophages toward inflammation, suggesting that gut microbiota-derived endotoxins, such as LPS, play a role in obesity regulation (10). Furthermore, food-derived microbiota exacerbated C-C motif chemokine ligand 2 (CCL2)-dependent macrophage infiltration in white adipose tissues through TLR signaling (51). In mouse models, obesity is associated with increased numbers of effector T cells and decreased numbers of Treg cells (52, 53). Because many studies have demonstrated that microbiota-generated SCFAs promote anti-inflammatory responses in mucosal and systemic tissues through Treg cells (12, 54, 55), it is tempting to speculate that gut microbiota may control obesity through the generation of Treg cells.

SYMBIONTS IN METABOLIC DISEASES

There are several strategies to control metabolic diseases by a single species of the gut microbiota (Table 1). One such strategy is the consumption of beneficial bacteria as prebiotics or probiotics. For example, *Akkermansia* (*A.*) *muciniphila*, known as the mucin-degrading bacterium (56), can be administered as a prebiotic to reduce the likelihood of obesity and diabetes. This microbe commonly constitutes 3-5% of the human gut microbial community and is more abundant in healthy individuals than in obese/diabetic patients or animals (57-59). In one study, treatment of high-fat diet (HFD)-fed mice with metformin, a widely prescribed type 2 diabetes therapeutic agent, improved the glycemic profile and resulted in a higher abundance of *A. muciniphila* (60). Moreover, oral administration of *A. muciniphila* to HFD-fed mice without metformin treatment led to antidiabetic effects. Interestingly, exposure to the cold resulted in significant changes to gut microbiota composition, and reconstitution of cold-suppressed *A. muci-*

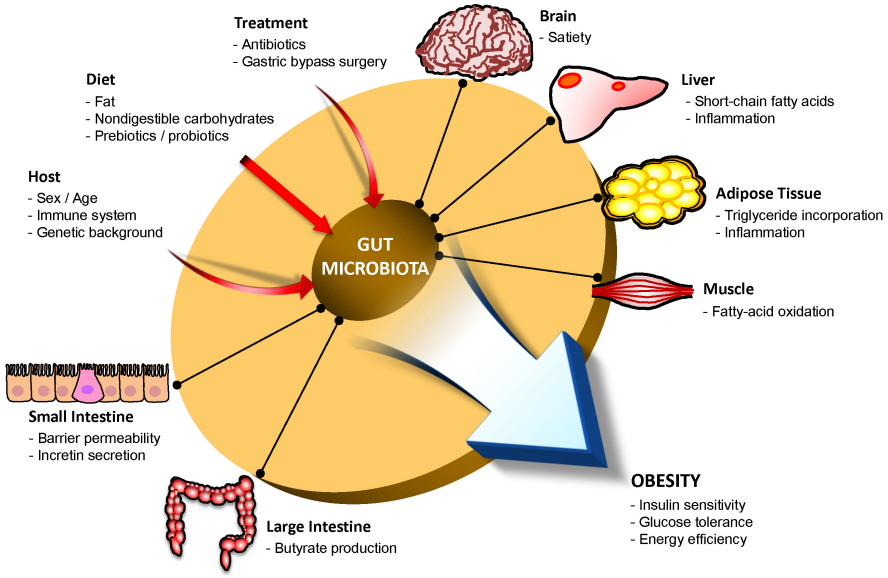

Fig. 1. Interactions between the gut microbiota and host metabolism. The gut microbiota can be influenced by a number of external factors, including host background, diet type, and medical treatments. Imbalance of the intestinal microbiota can lead to severe metabolic disorders (e.g., obesity) by altering host insulin sensitivity or energy homeostasis.

Table 1. Gut microbiota associated with obesity

Microbes	Mechanisms	References
Bacteroidetes /*Firmicutes* ratio ↓	Enhance dietary energy recovery	Ley et al (2005, 2006)
Methanobrevibacter smithii ↓	Increase energy harvest	Samuel et al (2007)
Bacteroidetes /*Firmicutes* ratio ↑	Increase SCFA levels	Schwiertz et al (2010)
Bacteroides (*B.*) *cellulosilyticus* ↓ *B. vulgatus* ↓ *B. thetaiotaomicron* ↓ *B. caccae* ↓ *B. uniformis* ↓	High invasiveness into the gut	Ridaura et al (2013)
Akkermansia muciniphila ↓	Improve glucose homeostasis	Santacruz et al (2010)
Bacteroides acidifacients ↓	Activate lipid oxidation	Yang et al (2016)

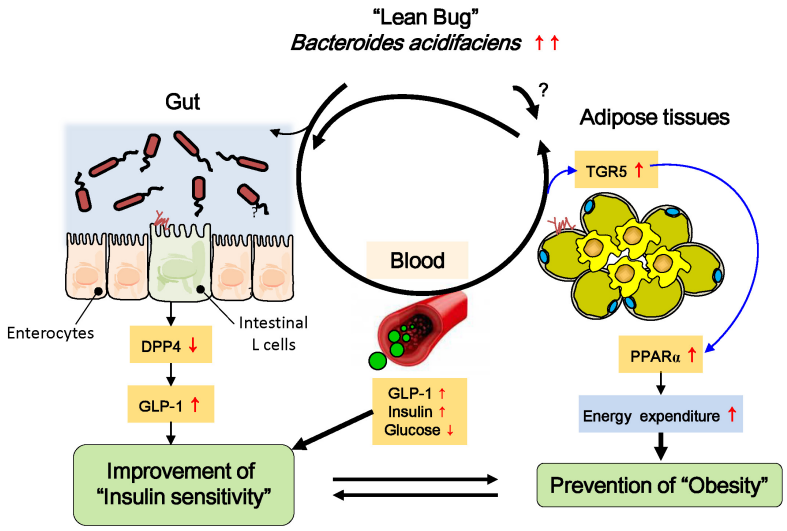

Fig. 2. Proposed mechanism for modulation of host insulin sensitivity by *Bacteroides acidifaciens* (BA). The selected commensal bacterium (i.e., BA) causes intestinal epithelial cells to secrete lower amounts of dipeptidyl peptidase-4 (DPP-4) in the gut and increased levels of glucagon-like peptide-1 (GLP-1), which may contribute to glucose homeostasis. At the same time, increased levels of bile acids (i.e., cholate and taurine) may contribute to GLP-1 activation in the intestine and to peroxisome proliferator-activated receptor α (PPARα) activation through TGR5 in adipose tissues, ultimately resulting in fat oxidation and improved insulin sensitivity.

niphila reduced caloric uptake (61).

Gordon *et al*. reported lean phenotypes in mice that were correlated with *Bacteroides* species, such as *B. cellulosilyticus*, *B. uniformis*, *B. vulgatus*, *B. thetaiotaomicron*, and *B. caccae* (20). Oral administration of the *B. uniformis* CECT 7771 strain ameliorated HFD-induced metabolic dysfunction in obese mice (62). Our group has recently reported that HFD-fed mice given *B. acidifaciens* for 10 weeks gained less fat mass and body weight than those given PBS alone (45). We have suggested that peroxisome proliferator-activated receptor α (PPARα)-mediated fat oxidation in adipose tissues and an expanded half-life of GLP-1 are involved in the regulation of host adiposity and insulin resistance by *B. acidifaciens*. Furthermore, metabolites secreted by *B. acidifaciens* may play a critical role in maintaining low levels of dipeptidyl peptidase-4 (DPP-4) in the gut (45) (Fig. 2). It would be interesting to conduct a follow-up study to identify underlying mechanisms how beneficial symbionts working on and soluble factors produced by those bacterium and their cross-talks.

CONCLUSIONS AND PERSPECTIVES

It is likely that nothing is simple when considering the link between diet, gut microbes, and metabolic diseases. Although mechanistic studies in animal models have produced valuable insight and revealed potential therapeutic targets, future studies are challenged with translating these findings into the human patient.

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