Interaction Between Obesity and the Gut Microbiota: Relevance in Nutrition

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Abstract

This review examines mechanisms by which the bacteria present in the gut interact with nutrients and host biology to affect the risk of obesity and associated disorders, including diabetes, inflammation, and liver diseases. The bacterial metabolism of nutrients in the gut is able to drive the release of bioactive compounds (including short-chain fatty acids or lipid metabolites), which interact with host cellular targets to control energy metabolism and immunity. Animal and human data demonstrate that phylogenic changes occur in the microbiota composition in obese versus lean individuals; they suggest that the count of specific bacteria is inversely related to fat mass development, diabetes, and/or the low levels of inflammation associated with obesity. The prebiotic and probiotic approaches are presented as interesting research tools to counteract the drop in target bacteria and thereby to estimate their relevance in the improvement of host metabolism.

Contents

INTRODUCTION

The role of gut microbes in human physiology was largely underestimated until the 1980s for several reasons. First, only a small fraction of bacteria could be cultured, and therefore the role and the taxonomy of billions of bacteria were unknown. Moreover, interest in the metabolic role of bacteria was mostly focused on their potential to ferment nutrients and produce harmful toxins. As a consequence, medical research was mainly devoted to addressing how to fight microbes (pathogens) to avoid a worldwide epidemic or to manage infections responsible for severe diseases and mortality. These views have changed in the past decade. The gut microbiota has been reconsidered in a more positive way. The concepts of probiotics and prebiotics, based on the rationale that some bacteria act positively on host health, have clearly affected this evolution (99, 103). There is no doubt today that the gut microbiota help balance key vital functions for the host, including immunity and nutritional status, and participate in health maintenance (27, 105). Obesity is now considered an inflammatory disease and results from unbalanced nutrition. Therefore, it is conceivable that changes in the gut microbiota composition and/or function (named dysbiosis) must be taken into account when evaluating the elements driving adiposity and related metabolic disorders. The challenge today is to identify beneficial bacteria able to control adiposity and related metabolic disorders and to estimate the relevance of nutritional approaches to promote those bacteria in obesity for improving host health. This review discusses mechanisms by which gut microbes interact with nutrients and host biology to influence fat mass development and associated diseases and describes the pathophysiological relevance of the phylogenic changes that occur in the microbiota of obese versus nonobese individuals.

THE GUT MICROBIOTA: A COMPLEX SYMBIOTIC SYSTEM

To assess the relevance of the gut microbiota in obesity, it is crucial to understand how gut microbes interact with the host and participate in the metabolic response to diet. Most of the

effects linked to the gut microbiota depend on the production of bacterial metabolites, which promote competitive interactions between gut bacteria (i.e., via bacteriocins) (in situ effects) or reach host tissues to act as metabolic regulators (systemic effects).

Short-Chain Fatty Acids as Mediators of the Interaction Between Gut Microbes and the Host

For example, the microbial fermentation of carbohydrates in the gut produces short-chain fatty acids (SCFAs) (acetate, propionate, butyrate, and lactate). The simple drop in pH driven by SCFAs has been proposed to be involved in the maintenance of microbial ecosystems (46). The profile of SCFAs in the gut reflects the metabolic cooperation between different microbial types because no genus of bacteria can hydrolyze all substrates (nutrients) and none produce all four SCFAs upon carbohydrate fermentation (75). SCFAs can be captured by host cells through specific monocarboxylate transporters (MCTs), and they can then act as metabolic substrates or regulators. SCFAs have different metabolic features. Butyrate is used as an energy substrate for colonocytes, whereas acetate is potentially used as a cholesterol or fatty acid precursor. Propionate is a gluconeogenic substrate in the liver, but it may also counteract de novo lipogenesis from acetate or glucose in the same tissue (3, 41). More recently, SCFAs have been identified as the physiological ligands of G-coupled receptors GPR43 and 41 (also called free fatty acid receptor 2 and 3, respectively), which are expressed in several cell types (immune cells, endocrine cells, and adipocytes) and in a wide variety of host tissues (70, 108). Thus SCFAs, which are considered as indirect nutrients produced by the gut microbiota, have a role in the regulation of energy metabolism, immunity, and adipose tissue expansion and in modulating cancer cell development (34, 53, 88, 112, 126). SCFAs produced by fermentation have been proposed as drivers of the adipose tissue expansion observed in conventionalized (harboring gut microbiota) versus germ-free mice (10). Moreover, the activation of GPR43 by the SCFAs acetate and propionate contributes to the inhibition of lipolysis and to adipocyte differentiation, thereby promoting the expansion of adipose tissue in high-fat-diet-fed animals (12, 53). In addition, transcriptomic analysis of the cecal microbial genome (microbiome) revealed a shift in the gut microbiota in favor of carbohydrate fermentation in obese mice fed a Western diet (117). Therefore, could polysaccharide fermentation in the gut be regarded as potentially harmful in the context of obesity? This idea is refuted by the observation that adding fermentable carbohydrates with prebiotic properties (inulin-type fructans) into the diet does not increase, but even lessens, fat mass development in obese mice or human subjects (17, 18). Interestingly, the supplementation with those prebiotics blunts the overexpression of GPR43 occurring in high-fat-fed animals, a phenomenon that contributes to lower adiposity (43). Below, we discuss further the potential mechanism by which nutrients with prebiotic properties can be helpful in the management of obesity.

Other Potential Mediators

Other molecules in addition to SCFAs can be released by gut microbes and are able to play a role in host metabolism regulation. Lipid metabolites such as conjugated linoleic acids (CLAs) (42, 63, 122) or bile acids (110), gases such as methane or H_2S (79, 100), and heteropolysaccharides such as lipopolysaccharide (LPS) or peptidoglycan (16, 29) bind to specific receptors and thereby change the expression of genes and/or the metabolic activity of host cells. Some of them can play a harmful role in the context of obesity. For example, LPS is found in a significantly higher level in the serum of obese individuals. This creates a metabolic endotoxemia that drives obesity, insulin resistance, and systemic inflammation (16). Other substances have been proposed as beneficial in controlling obesity-related diseases; these include CLAs, which are produced from polyunsaturated fatty

Gut microbiota: microorganisms (virus, bacteria, archae, and moods) present in the gastrointestinal content

Probiotics: live microorganisms that when administered in adequate amounts, confer a health benefit on the host

Prebiotics: selective stimulation of growth/activity(ies) of a limited number of microbial genus(era)/species in the gut microbiota that confer(s) health benefits to the host

Dysbiosis: phylogenic and metabolic changes occurring in the microbiota during specific pathophysiological conditions

SCFAs: short-chain fatty acids

Microbiome: microbial genome

CLAs: conjugated linoleic acids

LPS: lipopolysaccharide

acids by bacteria considered beneficial, such as bifidobacteria (56, 122).

FIAF: fasting-induced adipose factor

Molecular Host Response Toward the Gut Microbiota

In addition to the release of bioactive compounds, the presence of the gut microbiota also provokes changes in the expression of genes coding for peptides in host tissues, which control energy homeostasis and nutrient availability. Backhed and coworkers (10) were the first to demonstrate that colonizing germ-free mice with gut microbiota leads to a drop in the intestinal expression of angiopoietin-like factor IV [also called fasting-induced adipose factor (FIAF)], thereby blunting the inhibition of lipoprotein lipase in the adipose tissue; this explains why conventionalized mice are more sensitive than germ-free mice to fat storage when fed a high-fat diet. Several other proteins/systems (such as the endocannabinoid system) are influenced by gut colonization and/or are changed upon dietary modulation of gut microbiota composition, which are implicated in the control of inflammation, gut barrier function, gut motility, nutrient oxidation, and storage (84). Those targets are summarized in **Figure 1**.

The Metabolomic Approach to Assess Microbe, Nutrient, and Host Interactions

Interestingly, the characteristics of gut microbiota print a metabolic signature in host biological fluids (urine, blood) (9, 15, 31). The profile of microbial-derived metabolites—for example, bile acids or hippurate—is different in obese and in lean individuals (30, 121). The changes in the profile of microbial metabolites in biological fluids can be related to the level of specific families of bacteria, on the one hand, and on associated host phenotypic alterations, such as lipid accumulation in the liver tissue, on the other hand (30). Stable isotope–based techniques can be used to assess the serum and urinary profile of microbial metabolites produced from nutrients (119). There is no doubt that these metabolomic approaches will be helpful in the future to identify biomarkers reflecting interactions between gut microbiota, host, and nutrients.

COMPOSITION OF THE GUT MICROBIOTA IN OBESE VERSUS LEAN INDIVIDUALS: OBSERVATIONAL STUDIES IN ANIMALS AND HUMANS

The composition of the gut microbial community is different in each individual, according to his or her age, growth, and dietary habits, as well as environmental factors. **Figure 2** summarizes which individual and environmental factors can drive changes in gut microbiota composition upon the development of obesity. Lessons can be taken from the observed differences in the composition of the gut microbiota in obese versus lean individuals and from the description of the impact of interventions (dieting, surgery, probiotics, and prebiotics) on the gut microbiota in obese individuals.

Changes in Phylogenic Distribution in Obese or Diabetic Versus Healthy Individuals

16S ribosomal RNA gene (16SrRNA) sequence-based analytical methods have shown that Firmicutes, Bacteroidetes, and Actinobacteria constitute over 90% of the phyla and dominate the gut microbiota (96). Each phylum is subdivided into class, order, family, genus, and species. Most data reported until now observed changes at the phylum level, but numerous studies have also identified the potential impact of one or several specific species that may play an important role in host metabolism.

Studies in animals. The first demonstration of a specific change in the gut microbial community between obese and lean phenotypes was made in genetic obese (*ob/ob*) mice (71). The microbiota of obese mice were associated with changes in phyla proportions leading to fewer Bacteroidetes and more Firmicutes in

ob/ob than lean +/+ or *ob/+* littermates (71). At that time, no causal relationships were demonstrated between these two phyla and the development of obesity, and the role that specific species of these phyla have in obesity has not been investigated. We were the first to demonstrate that high-fat-diet feeding profoundly affects the gut microbial community, resulting in a significant modulation of dominant microbial populations in the gut microbiota of mice within four weeks. We observed a reduced number of the newly recognized Gram-negative operating taxonomic units, *Bacteroides*-like Mouse Intestinal Bacteria, which reside within the Cytophaga-Flavobacter-*Bacteroides* phylum. *Eubacterium rectale-Clostridium coccoides* group and bifidobacteria were also significantly decreased in obese mice, whereas no changes in Lactobacilli/Enterococci and *Bacteroides* were observed (16). A longer period of treatment with a high-fat diet (14 weeks) provoked similar changes in the gut microbiota, with a significant decrease in the family Enterobacteriaceae and in *Bacteroides* spp. (24). In a recent study, Murphy et al. (85) explored the effects of a high-fat diet and genetic obesity on the gut microbiota over time. The authors found an increase in Firmicutes in both high-fat-fed and *ob/ob* mice. They also described a decrease in Proteobacteria and *Bifidobacterium* spp. upon high-fat-diet feeding (85).

Other studies have confirmed the strong impact of dietary fat on the composition of the gut microbiota in mice. Turnbaugh et al. (115) used metagenomic approaches to demonstrate that diet-induced obesity was associated with a bloom in Mollicutes, a class of bacteria belonging to the Firmicutes phylum, and a relative suppression of the Bacteroidetes phylum. Specific changes within the Firmicutes phylum occurred upon high-fat-diet feeding, which led to a drastic increase in the Erysipelotrichi class (i.e., *Clostridium innocuum*, *Eubacterium dolichum*, and *Catenibacterium mitsuokai*), representing 16% of the total 16S rRNA sequences (117). Hildebrandt et al. (59) found that mice fed a high-fat diet for three months exhibited higher Clostridiales and fewer Bacteroidales orders, also supporting the increase in the proportion of corresponding phyla (increased Firmicutes-to-Bacteroidetes ratio). Interestingly, and in accordance with the decrease in Bacteroidetes and with previous findings (24), the families Bacteroidaceae, Prevotellaceae, and Rickenellaceae were decreased in high-fat-fed mice (59). A recent study by Zhang et al. (127) found that four different lineages within the Erysipelotrichaceae responded differentially to a high-fat diet. In this study, the authors found that the family Bifidobacteriaceae (e.g., bifidobacteria) was present in lean control mice but completely disappeared in diet-induced obese mice. The decrease in *Bifidobacterium* spp. has also been confirmed in a model of genetic obese and diabetic rats (*fa/fa* rats) (121), whereas we found, by using high-throughput culture-independent approaches (e.g., 454 bar-coded pyrosequencing of the 16S-ribosomal-RNA) (68, 69), that *Bifidobacterium* spp. were virtually absent in obese (*ob/ob*) mice (P.D. Cani, personal communication).

Altogether, these animal studies strongly support the idea that obesity, and more likely high-fat diets, might be directly involved in the modulation of gut microbiota composition both at the phylum and genus levels. They also point out reproducible changes in the gut microbiota associated with obesity, such as an increase in Firmicutes phylum or a decrease of *Bifidobacterium* spp. Several bacteria that are less well known, namely Desulfovibrionaceae, were positively associated with obesity and/or type 2 diabetes (59, 127).

Studies in humans.

Changes at the phylum level: confirmation for increased Firmicutes and controversies about Bacteroidetes. In 2006, one year after their first observation in experimental animals (71), Ley et al. (72) confirmed that obese subjects had a larger proportion of Firmicutes and relatively fewer Bacteroidetes than did lean subjects. In this study, they also showed that the ratio of Firmicutes to Bacteroidetes approached a profile from a lean subject after weight loss

(following either a low-fat or a low-carbohydrate diet). In accordance with these data, Turnbaugh et al. (116) focused their analyses on the gut microbiota of 154 monozygotic or dizygotic twin-pair individuals concordant for their lean or obese phenotype and their mothers. First, they found a decrease in phylogenic microbial diversity in obese subjects as well as a reduced representation of the Bacteroidetes and more Actinobacteria (116). Although a recent study confirmed a reduction of Bacteroidetes in obese patients (6), Duncan et al. (45) did not detect any differences for this phylum between obese and nonobese subjects. Moreover, no significant changes were observed when they examined the percentage of Bacteroidetes in the feces of obese subjects under controlled weight-maintenance diets or a weight-loss program (45). Furthermore, a sequencing-based study performed by Zhang et al. (128) demonstrated that obese subjects harbored even more Bacteroidetes than normal-weight individuals. In addition, they found an enrichment of the Prevotellaceae (belonging to the Bacteroidetes phylum) in the obese patients (128). Finally, Schwiertz et al. (104) found that the ratio of Firmicutes to Bacteroidetes changed in favor of the Bacteroidetes in overweight and obese subjects. From those studies, it appears that the level of Bacteroidetes phylum does not change in the same way in obese individuals. The relevance of Firmicutes phylum is supported by the observation that surgical treatment of obesity (gastric bypass) strongly increased Gammaproteobacteria (members of the family *Enterobacteriaceae*) and proportionally decreased Firmicutes (128).

***Changes at the genus/species level: not enough bifidobacteria, too much* Staphylococcus aureus.** Interesting data have come from the observed changes in the species or genera of bacteria related to overweight and obesity. Kalliomaki et al. (61) have shown that the *Bifidobacterium* spp. number was higher in children who exhibited a normal weight at seven years than in children becoming overweight. This supports the idea that differences in the gut microbiota composition may precede becoming overweight (61). In this study, the authors also observed a reduced *Staphylococcus aureus* count in normal-weight children compared to children who became overweight several years later. In accordance with this report, Collado et al. (32) observed more *Bacteroides* spp. and *Staphylococcus aureus* in the fecal sample of overweight compared to normal-weight women. They also found a positive correlation with the total *Bacteroides* spp. and weight and body mass index (BMI) (before and during pregnancy). Interestingly, they discovered that bifidobacteria were present in higher numbers not only in normal-weight compared with overweight women but also in women with lower weight gain during pregnancy (32). More recently, Santacruz et al. (101) compared the gut microbial community between 34 normal-weight and 16 overweight women, before and after pregnancy. Interestingly, they found lower *Bifidobacterium* spp., but contrary to the previous study, fewer *Bacteroides* spp. in overweight women as compared with normal-weight women. In addition, *Staphylococcus, Escherichia coli, and Enterobacteriaceae* were significantly higher in overweight compared with normal-weight women (101). Importantly, *Bifidobacterium* and *Bacteroides* were inversely correlated with body weight, whereas an opposite trend was found for *Staphylococcus*, *Escherichia coli*, and *Enterobacteriaceae* (101). Increased numbers of *Bifidobacterium* were also correlated with women who had normal weight gain compared with those with excessive weight gain over pregnancy.

Differential microbial targets in obese and diabetic patients. Specific changes in the gut microbiota have been associated not only with obesity but also with type 2 diabetes. Wu et al. (124) compared the gut microbiota composition from 16 type 2 diabetic patients and 12 healthy subjects. Contrary to data on obese patients, the diversity profiles of both groups were similar (124). Interestingly, following their analysis at the genus level, the authors found

that *Bacteroides* were more prevalent in the type 2 diabetic patients, whereas *Prevotella* was less prevalent in diabetics compared with healthy individuals. Interestingly, they also found a remarkable decline in the *Bifidobacterium* spp. in diabetic patients (124). Larsen et al. (67) have shown a significant decrease in the Firmicutes phylum in individuals with diabetes in comparison with controls. Furthermore, they found a positive correlation between plasma glucose and the ratio of Bacteroidetes to Firmicutes, the ratio of *Bacteroides-Prevotella* to *Clostridium coccoides*, and the *Betaproteobacteria* count. Thus, in this study, persons with type 2 diabetes exhibited a gut microbial community enriched with Gram-negative bacteria (*Bacteroides-Prevotella* and *Betaproteobacteria*), which was correlated to glucose intolerance.

Furet et al. (52) found that the *Bacteroides-Prevotella* group and *Faecalibacterium prausnitzii* species were lower in obese subjects. Interestingly, they showed that the *F. prausnitzii* count was negatively correlated with an inflammatory state and diabetes.

Probiotic and Prebiotic Approaches to Evaluate the Relevance of Specific Bacteria in Obesity and Related Diseases

Even though several observational studies have revealed specific bacteria that are lowered upon obesity or related disorders (such as *F. prausnitzii*, *Bifidobacterium* spp., or lactobacilli), these are often controversial data, which raises questions about their relevance in the control of obesity and diabetes. For example, a study performed on 15 Indian obese female children has shown that *Bacteroides-Prevotella*, *Eubacterium rectale*, *Bifidobacterium* spp., or *Lactobacillus acidophilus* were equivalent between lean and obese subjects. Strikingly, the level of *F. prausnitzii* was even found to be significantly higher in obese compared with nonobese individuals (11). The only way to prove the relevance of specific bacteria in the control of diseases is to counteract their drop quite specifically and to observe any effects on host health.

Treatment with prebiotics and probiotics selectively changes the composition of the gut microbiota in favor of a specific genus and even specific strains (for probiotics). The available intervention studies in animals and humans with these compounds are quite useful in assessing the relevance of selected bacteria in obesity and related diseases (80, 95, 99).

Probiotic approach to estimate the relevance of lactobacilli in obesity and related disorders. The genus *Lactobacillus* spp., belonging to the Firmicutes phylum, has been the subject of considerable controversy in the literature (4, 6, 7, 11, 39, 47, 60, 77, 98, 102). The debate concerns a potential causal link between lactobacilli and obesity. Armougom et al. (6) have compared the gut microbiota composition of obese and lean patients and found that lactobacilli were increased in obese individuals, although those bacteria were detected in less than half of the obese and lean patients (9 of the 20 obese versus 5 of the 20 lean subjects). Balamurugan et al. (11) did not find any relationship between body weight and *Lactobacillus* spp. In addition, weight loss associated with lower energy intake and higher physical activity in overweight adolescents is associated with high fecal lactobacilli counts (102). Moreover, increased *Lactobacillus* spp. numbers were associated with a lower weight gain over pregnancy. In this group, lactobacilli and infant birth weight were also inversely correlated (101).

Several strains of lactobacilli have been tested as a probiotic approach in experimental models of obesity and in humans. Specific strains of *Lactobacillus plantarum* and *Lactobacillus paracesei* spp. reduce adipocyte cell size and body fat in high-fat-diet-fed mice (7, 111). Moreover, the administration of a strain of *Lactobacillus gasseri* to obese and type 2 diabetic patients has been shown to decrease fat mass (visceral and subcutaneous) and BMI (60). In addition, Andreasen et al. (4) have recently demonstrated that the administration of *Lactobacillus* spp. positively impacts insulin sensitivity. Finally, compelling evidence suggests that early gut microbiota modulation with

probiotics (i.e., lactobacilli) strongly reduces the BMI in young children by restraining excessive weight gain during the first years of life (from 0 to 10 years of follow-up) (76). All of these data support an improvement of obesity and related disorders by lactobacilli supplementation. These data raise the questions of whether these effects are strain specific and what the mechanisms are. Currently, few data clearly demonstrate the way in which lactobacilli can counteract adiposity. Changes in the expression of genes coding for proteins, which control fat storage (angiopoietin-like factor 4) and are known to respond to gut microbiota, have been proposed as potential host targets (7).

Prebiotic approaches to estimating the relevance of bifidobacteria in obesity and related disorders. Inulin-type fructans were the first nondigestible carbohydrates considered as prebiotics because they were able to promote a selective and significant increase in bifidobacteria and to improve health in different pathophysiological conditions (99). We have shown that fructan administration was able to increase bifidobacteria levels in high-fat-diet-fed mice quite selectively, without counteracting the drop in Cytophaga-Flavobacter-*Bacteroides* and the *Eubacterium rectale-Clostridium coccoides* group (24). Interestingly, in this study, negative correlations were shown between *Bifidobacterium* spp. numbers and glucose tolerance, visceral fat mass, fasting insulinemia, plasma LPS level, and inflammatory markers.

As summarized in **Figure 2**, prebiotic intervention decreases fat storage in white adipose tissue and in the liver (steatosis), lessens glycemia and hepatic insulin resistance, and decreases endotoxemia and systemic inflammation in several nutritional (high-fat-diet-fed) and genetic (*ob/ob* mice, *fa/fa* rats) obese rodents (17, 22, 25, 26, 35, 37, 38, 99). Some beneficial effects of fructans on BMI, waist circumference, fat mass, and/or insulin resistance were shown in the limited studies available in humans (1, 55, 81, 82, 91, 99).

The correlation between health improvement and the changes in the gut microbiota (in favor of bifidobacteria or others) has never been studied in overweight or diabetic patients. In addition, no studies have been published yet using a probiotic approach to determine whether a specific species of *Bifidobacterium* is associated with body weight gain. This would be useful because it has been shown that weight loss is associated with reduced *Bifidobacterium bifidum* and *Bifidobacterium breve* and increased *Bifidobacterium catenulatum* (102). Those data support the fact that not all bacteria belonging to the same species or group exert the same effect. The relative contribution of the different types of bacteria inside the *Bifidobacterium* spp. merits further investigations in the field of obesity (13, 14, 118). Nevertheless, the prebiotic approach also seems interesting because it may help promote other beneficial bacteria. For example, inulin-type fructans have been shown to increase not only bifidobacteria but also *F. prausnitzii* in healthy volunteers (97). The potential role of *F. prausnitzii* as a modulator of inflammation and diabetes in obese individuals has recently been proposed (52). Therefore, a prebiotic approach as well as a probiotic approach (consisting of the isolation and administration of selected *F. Prausnitzii*) could be relevant in the elucidation of a key role for this novel bacterial target in obesity.

PROBIOTIC AND PREBIOTIC APPROACHES IN THE NUTRITIONAL MANAGEMENT OF OBESITY AND RELATED DISEASES

Involvement of Gut Peptides in the Control of Obesity by Prebiotics

Regulation of appetite. In the past ten years, we and others have contributed to deciphering the complex interactions existing between the fermentation of nondigestible carbohydrates (e.g., inulin-type fructans and resistant starches) by the gut microbiota and the improvement of metabolic disorders (17, 18). Numerous peptides secreted by the enteroendocrine cells present along the gastrointestinal tract are involved in the regulation of energy homeostasis

and/or pancreatic functions. For instance, glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and ghrelin are three peptides able to modulate food intake and energy expenditure (28, 33, 44, 64, 125). Nowadays, changing the gut microbiota composition by prebiotics (inulin-type fructan, oligofructose) (99) leads to a significant decrease in food intake, body weight gain, and fat mass development in rodents. All of these features were associated with an increased production and secretion of two anorexigenic peptides (i.e., GLP-1 and PYY) and with the reduction of one orexigenic peptide (i.e., ghrelin) (**Figure 3**) (19, 20, 40, 65). Those studies revealed an increase in the number of endocrine L cells in the colon of prebiotics-treated animals. When assessing the role of colonic nutrients on obesity, sometimes it is rather difficult to make real distinctions between events related to gut microbiota composition and events related to gut microbial metabolites. This is illustrated by the fact that lactitol or resistant starches, which are both fermentable carbohydrates but which are not producing similar changes in the gut microbiota, exert effects similar to those observed with inulin-type fructan prebiotics; namely, a decrease in food intake and in body weight gain and an increase in plasma GLP-1 and PYY (8, 54, 62, 106, 129, 130).

The effects of prebiotics in humans confirm the relevance of the modulation of gut peptides. Piche et al. in 2003 were the first to report that inulin-type fructan feeding (20 g/d) significantly increased plasma GLP-1 after a meal in humans (94). Two studies, one by Archer et al. (5) and one by Whelan et al. (123), have demonstrated that the gut microbiota fermentation of nondigestible carbohydrates controls food intake behavior and impacts energy intake. We have shown that 16 g/d prebiotics (inulin-type fructans) were associated with greater satiety and reduced hunger and prospective food consumption in healthy subjects; the changes in appetite sensations were accompanied by higher plasma GLP-1 and PYY levels and by a 10% decrease in energy intake upon a controlled meal test day (21, 23). Interestingly, Parnell & Reimer (92) have demonstrated the potential of prebiotics to modulate the gut microbiota in obese patients. After 12 weeks of treatment, they found that obese subjects exhibited a decrease in circulating ghrelin and an increase in PYY.

Although some papers report that acute prebiotic treatment does not necessarily affect appetite sensation (e.g., 93), Tarini & Wolever have shown that a single dose of prebiotics (i.e., inulin) significantly increased postprandial plasma GLP-1 and decreased plasma ghrelin. This contradicts the perceived necessity to wait for persistent and prolonged gut microbiota modulation to allow any effect on gut endocrine function. In a different set of experiments, the same group has shown that the mechanism could be directly dependent on SCFA production following gut microbiota fermentation. The authors proposed that acetate could play a crucial role in this mechanism (50, 51). Interestingly, the modulation of plasma SCFAs was related to changes in gut peptides regulating appetite as well as with lower inflammatory markers in insulin-resistant subjects (50, 51).

These data support the idea that among the metabolites produced by the gut microbiota, the SCFAs participate in the release of gut peptides involved in appetite and body weight regulation. However, there is no clear view of the molecular mechanism by which some bacteria or bacterial products are able to increase the differentiation of L cells in the colon. The role of specific gut microbes in these processes remains to be elucidated.

Regulation of glucose homeostasis and gut barrier function. The promotion of gut peptides by a prebiotic approach is a process involved in other biological functions. The invalidation of the GLP-1 receptor by the use of a specific antagonist or by GLP-1 receptor knock-out mice completely abrogates the improvement of hepatic insulin sensitivity and glycemia by prebiotics. These experimental data support the fact that the promotion of GLP-1 production upon prebiotic approach is an essential driver of the improvement of

GLP: glucagon-like peptide

Colonic nutrients: all types of nutrients that can be substantially metabolized by the microorganisms present in the colon

host metabolism in the contact of obesity. In addition, the increase in postprandial GLP-1 secretion occurs in healthy individuals treated with prebiotics, and this is coordinated with a decrease in glucose response (**Figure 3**) (21, 23). The few studies performed in persons with diabetes remain, however, quite controversial in term of prebiotic efficacy (for review, see 99).

L cells also produce other peptides, such as GLP-2, which is relevant to explain the improvement of the gut barrier function by prebiotics in obese animals (26) (**Figure 3**). The modulation of the endocrine function by prebiotics could also contribute to their potential to counteract inflammation associated with obesity (described in the next section).

NASH: nonalcoholic steatohepatitis

NAFLD: nonalcoholic fatty liver disease

Modulation of Obesity-Related Inflammation by Prebiotics and Probiotics

A large body of evidence, mostly from animal studies, has highlighted the interesting concept that putative gut bacterial–derived compounds can affect liver metabolism and cause systemic diseases (89, 90). In view of our experimental data, we have elaborated the concept that the serum level of LPS, a major component of the gram-negative bacteria, increases slightly upon obesity and steatosis, creating a metabolic endotoxemia, but is sufficient to stimulate proinflammatory cytokines and to modify glucose and lipid metabolism in the liver or in the adipose tissue (17, 18, 66, 87). In accordance, it has been proposed that endotoxemia is a major risk for inducing alcoholic liver diseases and hepatic inflammation in nonalcoholic steatohepatitis (NASH) (2, 120) as well as nonalcoholic fatty liver disease (NAFLD) in humans (58, 114). It has been suggested that intestinal bacterial growth could promote gut barrier alteration (i.e., by decreased soluble IgA). Moreover, slight bacterial overgrowth can increase LPS in the enteric cavity, leading to gut mucosal barrier damage and metabolic endotoxemia (73). Importantly, it has been recently demonstrated in humans that both NASH and NAFLD are associated with increased gut permeability (49, 83). We have also demonstrated the alteration of gut barrier function in genetic models of obesity (26). Altogether, these studies strongly suggest a direct link between the gut microbiota, the gut barrier function (leaky gut), and hepatic alterations.

Compelling data obtained in animals and humans provide evidence that changing the gut microbiota by using prebiotics or probiotics has a salutary effect on the development of liver diseases. Briefly, we found that prebiotic feeding reduced liver diseases in several animal models (i.e., diet-induced obesity models and genetic obese rodents *ob/ob*, *db/db*, and Zucker *fa/fa*) as well as in human subjects (25, 26, 35–37, 109). Similarly, changing the gut microbiota by using probiotics significantly suppressed high-fat-diet-induced activation of nuclear factor κ-B signaling involved in the development of high-fat-diet-induced insulin resistance (78). In addition, the administration of probiotic lactobacilli to rats developing alcohol-induced metabolic endotoxemia and liver disease reduced plasma endotoxin levels and the liver pathology score (86). A probiotic mixture of bifidobacteria, lactobacilli, and *Streptococcus thermophilus* has been shown to decrease liver inflammation in genetic obese mice (74) and high-fat-diet-induced hepatic inflammation in young rats (48). The role of probiotics in liver health and overall health has been extensively reviewed elsewhere (57, 107).

The potential of prebiotics to control gut-related inflammation in the context of obesity would involve a specific gut peptide released by L cells, namely GLP-2. In addition, the improvement of the gut barrier function by prebiotics would also implicate a blunting in endocannabinoid system activation (26, 84). Those targets have not yet been studied using a probiotics approach. It is therefore impossible to estimate the relevance of the selective changes in the gut microbiota composition in the improvement of gut barrier function by GLP-2 and the endocannabinoid system.

CONCLUSIONS AND NEW PERSPECTIVES

Taken together, the data currently published suggest that specific changes in the gut

microbiota occur in overweight or obese patients and are either positively or negatively linked with adiposity, inflammation, and glucose or lipid homeostasis. Prebiotic and probiotic approaches are very useful in evaluating the relevance of specific types of bacteria in the occurrence or in the degradation of pathologies associated with obesity, including diabetes and liver diseases. In addition, the fact that colonic nutrients, defined as nutritional substrates for gut microbes, could be helpful in the management of obesity and related disorders, would help identify which type of "dietary fiber" could be proposed in this pathophysiological context. Further research is needed to evaluate the relevance of promising data obtained with probiotic and prebiotic approaches in obese, diabetic, or NASH patients. Studies are also needed to determine whether changes in the gut microbiota and/or activity (SCFAs or other metabolites) are responsible for the promotion of host functions associated with a well-balanced ("healthy") gut microbiota.

SUMMARY POINTS

1. The gut microbiota helps balance key vital functions for the host, including immunity and nutritional status.
2. The changes in the gut microbiota composition and/or activity may be implicated in the control of inflammation, fat storage, and altered glucose response in obese patients.
3. Short-chain fatty acids appear to be "indirect nutrients" produced by the gut microbiota that can modulate adiposity and immunity.
4. Probiotics and prebiotics are interesting research tools to assess the relevance of specific bacteria in obesity.
5. Prebiotics may lessen obesity and related metabolic stress by modulating gut peptides involved in the control of appetite and gut barrier function.

FUTURE ISSUES

1. A future challenge in nutrition is to assess and confirm in human studies the relevance of colonic nutrients able to selectively promote beneficial bacteria (probiotics, prebiotics, and others) to control adiposity and related metabolic disorders.
2. The analysis of the metabolic phenotype in biological fluids will be helpful in identifying novel biomarkers, reflecting the nutrition-driven changes in the gut microbiota composition and/or activity.

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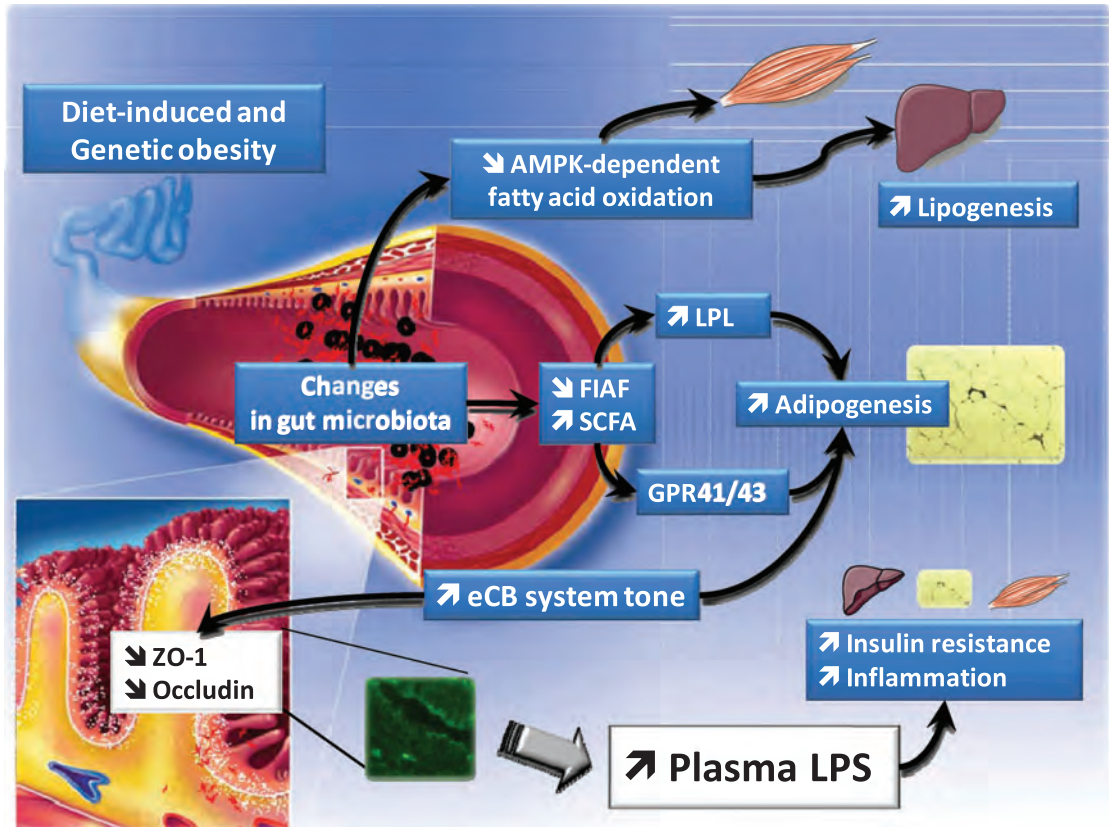

Figure 1

Gut microbiota might be involved in energy storage through various mechanisms. The fermentation of carbohydrates by the gut microbiota is associated with higher short-chain fatty acid (SCFA) production and absorption. They can be used as lipogenic substrates in host tissues but would act on adiposity mostly by promoting fat storage via the activation of specific receptors (GPR43 and 41). The presence of the gut microbiota suppresses the intestinal synthesis of the fasting-induced adipose factor (FIAF or angiopoietin-like factor IV), an effect that drives the activity of the enzyme lipoprotein lipase (LPL) and fat storage in the adipose tissue. In addition, hepatic and muscle fatty acid oxidation can be altered by the gut microbiota through a 5′ adenosine monophosphate-activated protein kinase (AMPK)-dependent mechanism. Finally, the low-grade inflammation and insulin resistance observed in obesity can be triggered by alteration of the gut barrier (namely by a decrease in tight junction proteins ZO-1 and Occludin) and by activation the endocannabinoid (eCB) system tone, leading to higher plasma lipopolysaccharide (LPS) levels. Those events contribute to fat storage, mostly associated with excess in dietary fat intake.

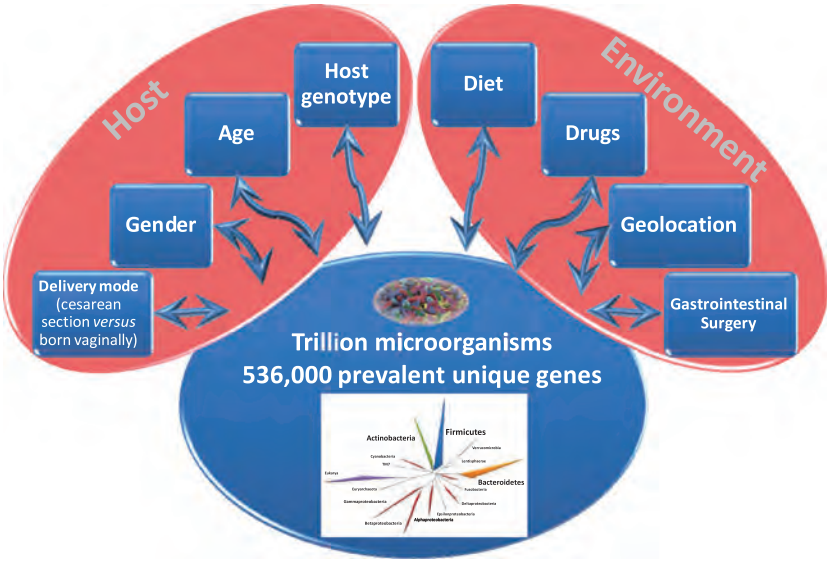

Figure 2

The gut microbiota is a complex ecosystem acting in symbiosis with the host. The gut microbiome encodes a consortium of genes exceeding the human genome by a magnitude of 150. These trillions of cells are shaped by numerous factors directly dependent on the host and including the delivery mode (cesarean versus vaginal), by the gender, the age, and the host genotype. The gut microbiota is also modified according to different environmental factors including diet, drugs (e.g., antibiotics, antiulcer drugs), geolocation (e.g., American versus Japanese), and gastrointestinal surgeries. Finally, different pathophysiological backgrounds (i.e., body mass index, nonalcoholic fatty liver diseases, and cardiovascular diseases) have been linked with changes in the gut microbial community. Whether these changes are associated or causative remains to be determined.

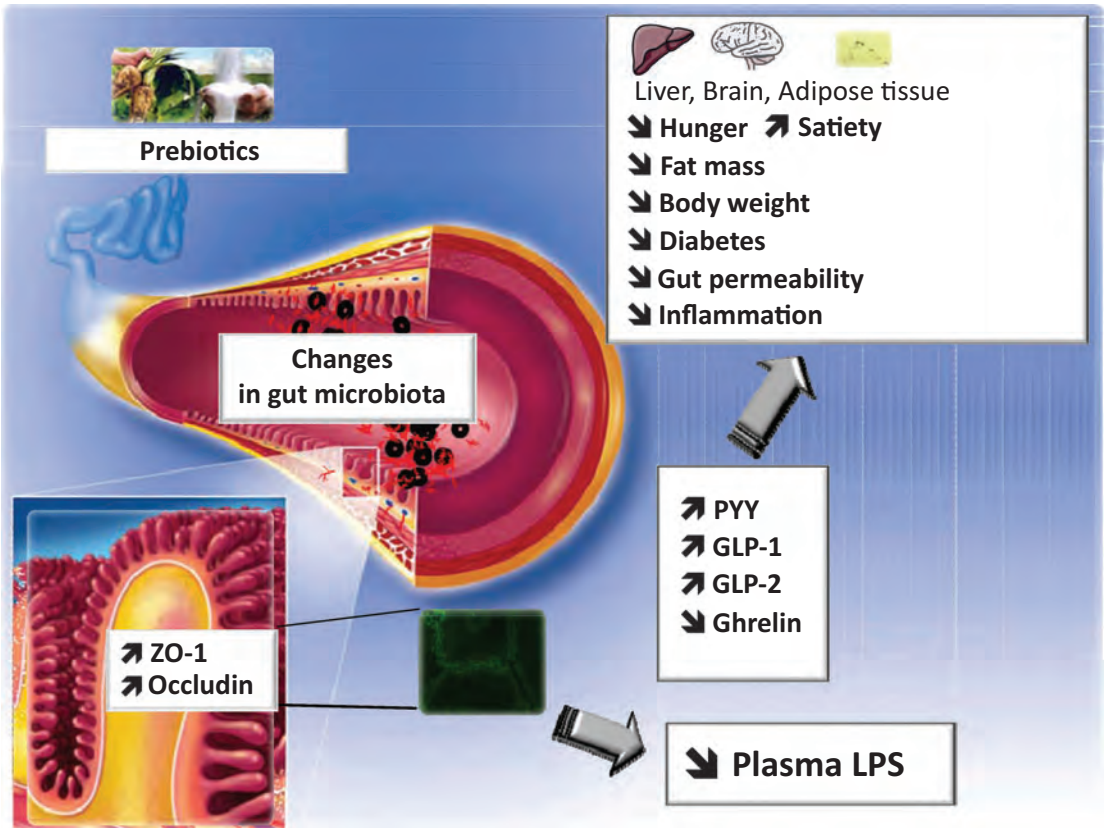

Figure 3

Prebiotic-induced changes in the gut microbiota improve obesity and related metabolic disorders. Prebiotics change the composition of the gut microbiota. This is associated with restored tight-junction protein (ZO-1 and Occludin) distribution and localization. Hence, the gut permeability is decreased and plasma lipopolysaccharide (LPS) levels (metabolic endotoxemia) are lowered. The modulation of the gut microbiota is associated with specific changes in the plasma gut peptide profiles [enhanced glucagon-like peptide-1 (GLP-1), GLP-2, and peptide YY (PYY), and reduced ghrelin]. Altogether, these effects are associated with a decrease in hunger, body weight, fat mass, type 2 diabetes, gut permeability, and low-grade inflammation characterizing obesity.

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Contents

Indexes

Errata

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