The role of intestinal microbiota in energy metabolism and metabolic disorders

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Abstract

Obesity and its associated metabolic disorders are a worldwide epidemic. In humans, obesity causes changes in gut microbial composition. Analysis of the consequences of these changes for host energy metabolism, particularly in the context of obesity, requires good experimental models. The use of gnotobiotic animal models has indicated new mediators and molecular targets that suggest a metabolic dialogue between the gut bacteria and the host. The discovery of the impact of a high-fat diet on metabolic disorders linked to gut microbiota has revealed bacterial components (lipopolysaccharides and Toll-like receptors) as potential targets in the management of obesity and related disorders. In animal models, it has been possible to effect specific changes to the gut microbiota through food components with prebiotic properties, thereby decreasing obesity and its associated metabolic alterations, including inflammation. The relevance of this approach in the management of obesity in humans is supported by a number of intervention studies. A metagenomic and integrative metabolomic approach could help in the discovery of which bacteria, among the trillions in the human gut, are specifically involved in the control of host energy metabolism. This knowledge could be relevant for future therapeutic developments in the prevention of obesity and related metabolic disorders.

Key words:
Gut microbiota, obesity, prebiotics, inflammation, gut peptides

Host–microbe interactions: symbiotic control of energy metabolism

The human intestine contains a diverse collection of micro-organisms comprising trillions of bacterial cells and harbouring probably the most complex microbial ecosystem. It is now recognized that the gut microbiota plays a more important role in maintaining human health than previously thought [1]. Continuing advances in genomic technology are revealing our microbial partners (the human microbiota), namely through the Human Microbiome Project [2, 3]. Eighty to ninety percent of bacterial phylotypes are members of two phyla: the Bacteroidetes (e.g. *Bacteroides, Prevotella*) and the Firmicutes (e.g. *Clostridium, Enterococcus*, *Lactobacillus, Ruminococcus)*, followed by the Actinobacteria (e.g. *Bifidobacterium*) and the Proteobacteria (e.g. *Helicobacter, Escherichia*) [4, 5].

The gut microbiota has particular genetic and metabolic attributes that enable the host to live in symbiosis with these 'external' cells, which are tenfold more numerous than the number of cells in the human body [1, 6, 7].

Experimental data collected in several recent reviews explore how the gut microbiota is able to control host energy metabolism [8–10]. Studies performed in germ-free mice support the role of the gut microbiota in sparing and harvesting energy for the host [11]. Initial studies by Backhed et al. [11, 12] found that germ-free mice, compared with conventionally raised mice bearing gut microbiota, had lower fat mass and were protected against obesity induced by a high-fat diet and against associated metabolic disorders. Even though a recent study noted that the absence of gut microbiota does not provide general protection from obesity induced by a high-fat diet [13], the comparison of mice growing with and without gut microbes has enabled the identification of new targets in the control of obesity.

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The gut microbiota may improve the host's digestion/absorption of ingested nutrients by promoting intestinal monosaccharide absorption [11]. By ingesting nutrients that escape digestion to the upper part of the gut, the host feeds the gut microbes, which are then able to ferment non-digestible food components into short-chain fatty acids (acetate propionate, butyrate). These

are absorbed in the lower gut, thereby harvesting energy. However, this process of 'energy harvest' represents a minor part of potential energy recuperation in (over)fed animals. The gut microbiota is also able to boost host anabolic processes, such as hepatic *de novo* lipogenesis and lipoprotein lipase-driven adipocyte fatty acid storage. Some authors have proposed that this latter effect implicates gut microbe-dependent intestinal expression of a lipoprotein lipase inhibitor (FIAF, fasting-induced adipose factor) [11], while others have reported that intestinal production of FIAF/Angptl4 is not causally implicated in gut microbiota-induced fat storage [13]. The presence of the gut microbiota also reduces liver and skeletal muscle AMP-activated protein kinase-dependent fatty acid oxidation. These data suggest an increase in anabolic/catabolic balance, which could contribute to the relative increase in fat mass occurring in conventional vs. germ-free mice following a high-fat diet [12].

It has been unclear which bioactive compounds could reach host targets, but the short-chain fatty acids remain the most studied candidates. Short-chain fatty acids are able to act as signalling molecules in host tissues by linking selected G protein-coupled receptors, Gpr41 and Gpr43 [14]. Their implication in the management of host energy metabolism is supported by the data of Samuel et al. [15], who demonstrated that Gpr41$^{-/-}$ mice colonized with a fermentative microbial community *(Bacteroides thetaiotamicron* and *Methanobrevibacter smithii)* did not gain fat mass to the same extent as wild-type littermates [15]. Other data have shown that short-chain fatty acids (acetate, propionate) may stimulate adipogenesis via Gpr43 activation [16].

Studies in animals and in humans suggest that qualitative changes in the gut microbiota occur with obesity, implying the presence of 'harmful' or 'beneficial' bacteria

One may imagine that the gut microbiota could play a harmful role in the context of obesity, as studies of conventional vs. germ-free mice proved that it contributes to promoting fat mass development. However, both observational and interventional studies in animals and in humans suggest that qualitative changes in the gut microbiota occur with obesity, implying the presence of 'harmful' or 'beneficial' bacteria.

Obesity-induced qualitative changes in the gut microbiota

The composition of the gut microbiota is different in obese compared with lean individuals [4, 8]. Recently, a metagenomic study investigating 154 monozygotic or dizygotic twin pairs concordant for a lean or obese phenotype showed no important overlap of microbiota between individuals or between early changes in the familial context that may have influenced the composition of the microbiota [17]. The study also demonstrated a decrease in phylogenic microbial diversity occurring with obesity [17]. The characterization of several thousand bacterial gene sequences from the gut microbiota of genetically obese ob/ob mice and their lean counterparts revealed that ob/ob mice exhibited a 50% reduction in the abundance of Bacteroidetes and a proportional increase in Firmicutes.

A high-fat diet itself, and not the obese state, may account for the changes in microbiota composition

The first original studies describing qualitative changes of the gut microbiota in obese individuals were published by Ley et al. [18]. In this study, obese individuals were found to have fewer Bacteroidetes and more Firmicutes than were present in lean matched subjects [18]. Interestingly, the authors observed that after 52 weeks of weight loss (following a fat- or carbohydrate-restricted low-calorie diet), the ratio of Bacteroidetes to Firmicutes approached that of a lean-type profile [18]. Hildebrandt et al. [19] compared the effect of a high-fat diet in conventional mice and in RELMb knockout mice, which are resistant to fat-induced obesity. These authors found a decrease in Bacteroidetes and an increase in Firmicutes and Proteobacteria in both genotypes, indicating that a high-fat diet itself, and not the obese state, may account for the changes in microbiota composition. The focus on Bacteroidetes seems to be controversial. Armougom et al. [20] confirmed a reduction in Bacteroidetes in obese patients. However, Duncan et al. [21] detected no differences in the proportion of Bacteroidetes measured in fecal samples in obese and non-obese individuals and no significant changes in the percentage of Bacteroidetes in the feces of obese subjects following weight loss. Zhang et al. [22] found even more Bacteroidetes in obese subjects than in normal-weight individuals. They provided evidence that

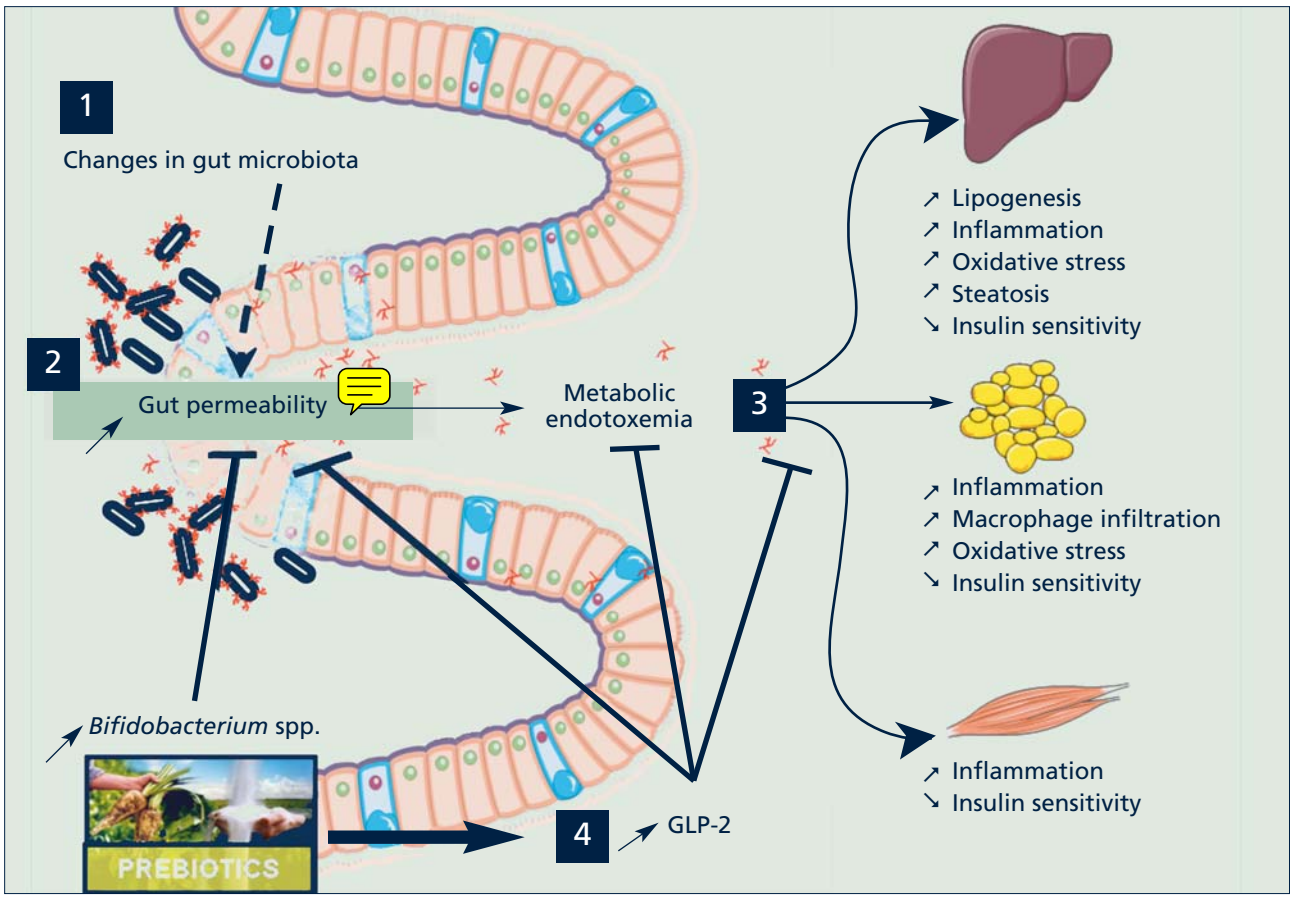

Fig. 1: *Diet- or obesity-associated changes in the gut microbiota promote gut permeability, increase metabolic endotoxemia and trigger the development of metabolic disorders. Adapted from [9]. (1) A high-fat diet changes the composition of the gut microbiota in a complex way. (2) This phenomenon is associated with higher gut permeability, leading to higher plasma lipopolysaccharide levels (metabolic endotoxemia). (3) Metabolic endotoxemia promotes low-grade inflammation-induced metabolic disorders (insulin resistance, diabetes, obesity, steatosis, oxidative stress, adipose tissue macrophage infiltration). (4) Intake of prebiotics modulates the gut microbiota, for instance by increasing Bifidobacterium spp. In addition, the higher endogenous GLP-2 production restores gut barrier function, decreases metabolic endotoxemia and reduces the development of metabolic disorders.*

a subgroup of Bacteroidetes (Prevotellaceae) was significantly enriched in obese individuals. Moreover, these authors showed that surgical treatment for morbid obesity (gastric bypass) greatly increased Gammaproteobacteria (members of the family Enterobacteriaceae) and proportionally decreased Firmicutes [22]. The methodology used for bacterial analysis could explain certain discrepancies between the results published by different groups [23].

The hypothesis of more specific modulation of the gut microbiota in obesity (instead of findings obtained at phylum level) is supported by several studies. We have previously demonstrated that diet-induced obesity (a high-fat low-carbohydrate diet) in mice markedly reduced caecal *Bifidobacterium* spp. and also reduced *Bacteroides*-related bacteria and *Eubacterium rectale-Clostridium coccoides* content [24, 25]. The decrease in *Bifidobacterium* spp. has also been confirmed in other models of genetically obese diabetic rodents (fa/fa rats) [26]. An interesting study in humans showed that changes in the gut microbiota may precede the development of overweight [27]. Kalliomaki et al. showed that *Bifidobacterium* spp. was higher in children who exhibited a normal weight at 7 years than in children who were becoming overweight. More importantly they observed that the *Staphylococcus aureus* count was lower in children who maintained a normal weight than in children who became overweight some years later. The authors proposed that *S. aureus* may act as a trigger for low-grade inflammation [28], contributing to the development of obesity [24]. In agreement with these findings, Collado et al. [29] observed significant differences in the composition of gut microbiota according to body weight during pregnancy. Interestingly, these authors found significantly higher numbers of *Bacteroides* and *S. aureus* in overweight compared with normal-weight women, and they observed a positive correlation between the number of *Bacteroides* and the women's weight and BMI before and during pregnancy. *Bifidobacterium* was present in higher numbers in normal-weight

than in overweight women and also in women who gained the least weight during pregnancy [29]. These two studies unequivocally support the view that the gut microbiota profile (namely in favour of more bifidobacteria and/or less *S. aureus*) may provide protection against the development of overweight and obesity.

Nevertheless, a recent report has shown that weight loss could be associated with reduced *B. bifidum* and *B. breve* counts and increased *B. catenulatum* [30]. Indeed, *Bifidobacterium* spp. represents an important and complex group of bacteria whose presence is often associated with beneficial health effects. Studies are needed to better understand its relative contribution in obesity and weight management [31–33].

Other selective changes in bacterial composition have been described in obese individuals, in which the relation with fat mass and metabolic disorders has not been proven and is sometimes controversial. The lactobacilli count was found to be higher in obese (8 out of 20) than in lean individuals (1 out of 20) [20]. Paradoxically, weight loss due to calorie restriction and physical activity in overweight adolescents increases the number of lactobacilli [30].

Nutritional modulation of gut microbiota to assess its relevance to obesity

In order to assess the effect of targeted changes in gut microbiota composition on obesity and related disorders, we and others have tested the effect of dietary supplementation with non-digestible/fermentable oligosaccharides in different experimental models of obesity (ob/ob mice, diet-induced obese mice, obese Zucker rats). These are described as prebiotics, because they promote bifidobacteria in the gut and exert effects that are beneficial for the host (reviewed in [34, 35]).

In obese animals fed inulin-type fructans with prebiotic properties, the (recently reviewed) effects were described as:

1. A decrease in food intake through modulation of the production of gastrointestinal peptides (increase in anorexigenic peptide YY and glucagon-like peptide [GLP]-$1_{(7–36)}$ amide; decrease in ghrelin).
2. A decrease in hepatic lipogenesis and steatosis.
3. An improvement in hepatic insulin resistance and a decrease in blood glucose linked to increased production of intestinal incretins (including GLP-1 and glucose-dependent insulinotropic polypeptide [GIP]).
4. A decrease in tissue (liver, adipose tissue, muscle) and systemic inflammation (decrease in circulating lipopolysaccharides [LPS] and proinflammatory cytokines).

This latter effect is linked to a decrease in LPS absorption through an improvement in gut barrier function, driven by GLP-2 *(Fig. 1)* [9, 25, 34, 36–40].

Several studies suggest that the gut microbiota may be involved in the development of low-grade inflammation classically associated with obesity-related metabolic disorders

The 'anti-inflammatory' effect of prebiotics is of particular interest. Several studies suggest that the gut microbiota may be involved in the development of low-grade inflammation classically associated with obesity-related metabolic disorders [24]. We have demonstrated that excess dietary fat facilitates the absorption of highly proinflammatory bacterial LPS from the gut, thereby activating CD14-TLR4, which promotes adipose tissue inflammation and development [24]. Recent data obtained in TLR5 knockout animals suggest that Myd-88-dependent immune mediators such as interleukin-1β and interleukin-18 could trigger gut microbiota-induced obesity [41]. Interestingly, prebiotic treatment is able to decrease interleukin-18 and interleukin-1β serum level in genetically obese mice and in mice fed a high-fat diet [25, 40].

The question of the relevance of gut microbes in alleviating the metabolic syndrome through prebiotics must be raised. As previously described, several reports have shown that obesity induced by dietary manipulation (high-fat feeding) or genetic deletion (leptin-deficient models) is characterized by changes in gut microbiota towards a decreased number of bifidobacteria [26, 42–46]. Importantly, this group of bacteria has been shown to reduce intestinal LPS levels in mice and to improve mucosal barrier function [24, 25, 47, 48]. Taking all the data obtained in obese mice fed a high-fat diet receiving prebiotics or not, we were able to demonstrate a negative correlation between bifidobacteria count and endotoxemia on the one hand, and between bifidobacteria count and fat mass development or insulin resistance on the other [25, 39]. In view of the complexity of the gut microbiota, we cannot absolutely preclude that bifidobacteria are the sole actors in prebiotic improvement of obesity-associated

metabolic disorders, but their increase seems theoretically relevant in the management of these disorders.

Treating obese individuals with prebiotics has been tried in a limited number of studies. Supplementation with an inulin-type fructans prebiotic for 1 year was shown to have a significant benefit in the maintenance of an appropriate BMI and fat mass in non-obese young adolescents [49]. Daily intake of yacón syrup, equating to 0.14 g of fructans per kg per day over 120 days, increased the sensation of satiety and decreased body weight, waist circumference and BMI in obese premenopausal women [50]. A recent clinical trial supports the evidence that prebiotics (short-chain inulin-type fructans) given as a supplement for 3 months decrease food intake, body weight gain and fat mass development in obese subjects. The authors reported a higher postprandial plasma peptide YY levels as well as a drop in ghrelin during a 6-h meal tolerance test [51].

The modulation of gut peptides by fructans-type prebiotics has also been shown in intervention studies in healthy individuals. An increase in postprandial GLP-1, peptide YY and GIP correlated with a decreased glycemic response and a decrease in energy intake in healthy individuals supplemented with inulin-type fructans for 2 weeks [36]. A single dose of inulin given in a high-fructose corn syrup reduced ghrelin and increased plasma GLP-1 levels [52]. However, the effect of acute treatment with prebiotics (8 g of inulin-type fructans with or without 0.3 g of β-glucan) for 2 days did not have any effect on appetite, satiety or food intake, suggesting that an adaptative process (possibly linked to the modulation of gut microbiota) is necessary to observe the satietogenic effect of prebiotics [53]. Of note, no measurement of the gut microbiota composition was performed in these intervention studies, thus rendering difficult the link between the observed effects and gut microbial changes.

Conclusion

The role of the gut microbiota in the control of host energy metabolism is without doubt an important one. Elucidation of the number of specific bacterial phyla/gender/species that correlate with the development of fat mass could help in discovering a new type of 'target' in the management of obesity and related disorders. For this purpose, food components with prebiotic properties are of interest, since they are able to counteract most of the metabolic alterations linked to obesity. Interestingly, their intake promotes the endogenous release of peptides, which are nowadays used as molecules in drug development to control obesity and diabetes (e.g. GLP).

It is likely that targeted modification of the gut microbiota can also be obtained by direct administration of the bacteria. For example, a fermented milk containing a specific strain of lactobacilli *(Lactobacillus gasseri* SBT2055) reduced abdominal adiposity in overweight patients, which suggests that a targeted probiotic approach to modulating the gut microbiota could also be an interesting approach to tackling obesity [54].

A targeted probiotic approach to modulating the gut microbiota could also be an interesting approach to tackling obesity

The gut microbiota is an important target to consider in the management of obesity and related diseases. The advantage of this target is that both nutritional and pharmacological approaches can be developed on the basis of our increasing knowledge of host–microbe interactions.

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