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Interplay between obesity and associated metabolic disorders: new insights into the gut microbiota

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Obesity and associated metabolic disorders are worldwide epidemic. The literature provides new evidence that gut microbiota dysbiosis (at the phyla, genus, or species level) affects host metabolism and energy storage. Here we discuss new findings that may explain how gut microbiota can be involved in the development or in the control of obesity and associated low-grade inflammation. New powerful molecular biology methods and the use of gnotobiotic animal allowed to analyze the molecular link between gut bacteria and the host. Moreover, even if more studies are needed to unravel how changing gut microbiota impacts on the development of obesity and related metabolic alterations, probiotic and prebiotic approach appear as potential interesting treatments to reverse host metabolic alterations linked to gut microbiota dysbiosis.

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In the early 1900s, two Nobel prizes in physiology and medicine were awarded to scientists who established the link between microbes and human health. The first one, Robert Koch, linked microbes to infectious diseases; while the second one, Ilya Mechnikov, was the first to propose the use of live microorganisms to maintain human health. Now, an intricate set of relationships between microbiota and humans has been unraveled. The human gut microbiota has been shaped by the continuous coevolution history of host–microbe interaction. This means that both, human and microbes have inherited from their intimate association. Finally, the development of this complex symbiosis probably depends on interactions between host–microbe genetics and the environment [1,2•]. Given the hotspot of the wide diversity of putative relationship between the gut microbiota, obesity and associated disorders, the present review focuses on novel studies investigating this interplay.

Scanning the belly: trillions of workers only for your daily health

Over the past years, numerous studies have deciphered key aspects of the mammalian host–gut microbiota relationship. The human intestine contains a diverse collection of microorganisms totalizing around trillions of bacterial cells, harboring probably the most complex microbial ecosystems. It is now recognized that the gut microbiota plays an even more important role in maintaining human health than previously thought [3••]. Nowadays, the exact composition of the gut microbiota is unknown; however, continuing advances in genomic and information technologies are starting to unravel our microbial partners (the human microbiota), through the Human Microbiome Project [4,5•]. Recently conducted investigations have shown that 80–90% of the bacterial phylotypes are members of two *phyla*: the Bacteroidetes (e.g. *Bacteroides* and *Prevotella*) and the Firmicutes (e.g. *Clostridium*, *Enterococcus*, *Lactobacillus*, *Ruminococcus*), followed by the Actinobacteria (e.g. *Bifidobacterium*) and the Proteobacteria (e.g. *Helicobacter*, *Escherichia*) [6,7]. It is becoming evident that the gut microbiota provides us with essential genetic and metabolic attributes, sparing us from the need to evolve on our own. In the gut, for example, this includes nutrient and drug metabolism, epithelial cells proliferation, immune system and barrier function against enteric pathogens, synthesis and bioavailability of several vitamins [3••,8••,9•]. Today more attention is paid to the role of interplay between gut microbiota and host energy-related metabolic functions. Most research activities in this field have unveiled a glimpse into the mechanism of action and potential therapeutic role of nonpathogen bacteria (probiotics) on mucosal immunity, inflammatory bowel diseases, allergic diseases, etc. [10–13]. Nonetheless, most of the clinical studies have been designed to explore pathological situations rather than physiological or mild impaired health situation.

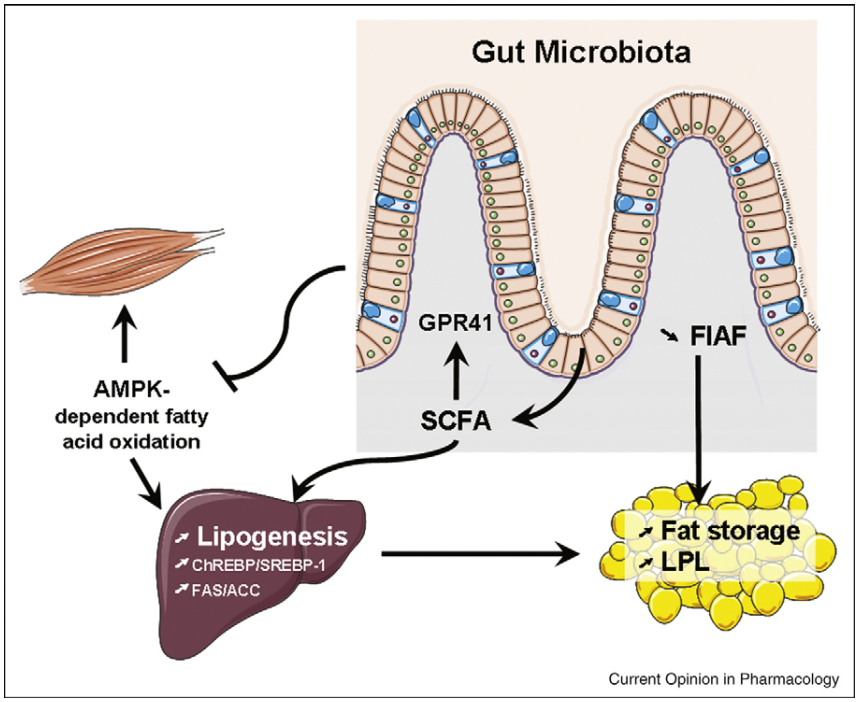
Gut microbiota and energy homeostasis

Unequivocal evidence on the role of the gut microbiota on energy harvesting from the diet, came from studies performed in germ-free mice [14]. Briefly, Backhed *et al.* found that conventionally raised mice contained 40% more total body fat and 47% higher gonadal fat content than germ-free mice, a phenomenon associated with a higher food intake in germ-free mice than in their

counterparts bearing a gut microbiota [14]. To unravel this dichotomy, the authors have proposed several mechanisms. The first pathway proposed by the investigators implied that the gut microbiota promotes intestinal monosaccharides absorption, energy extraction from non-digestible food components (via short chain fatty acids (SCFA) production through the fermentation), hepatic *de novo* lipogenesis, and adipocyte fatty acid storage; this latter effect is driven through lipoprotein lipase (LPL) regulation via the suppression of intestinal expression of a LPL inhibitor (FIAF, fasting-induced adipose factor) (Figure 1) [14]. The second pathway, further explored the underlying mechanisms related to the fact that germ-free mice are protected against high-fat diet-induced obesity and associated metabolic disorders (Figure 1) [15•]. Strikingly, and opposite to the mechanisms proposed in germ-free mice fed a normal chow diet, this study is not completely in favor of a better energy harvest from the high-fat diet. The authors have proposed that the activation of a cellular energy-dependent protein kinase activated in response to metabolic stresses, namely AMP-activated protein kinase (AMPK) could be the key molecular element explaining the relative resistance of germ-free mice to the development of obesity following high-fat diet feeding [15•]. Hence, the presence of a gut microbiota suppresses the liver and skeletal muscle AMPK-dependent fatty acid oxidation. Thus, these last experiments strongly support that a bacterially related factor/mechanism independently of the energy harvesting may be responsible for the development of diet-induced obesity and diabetes (Figure 1).

A third pathway, involving the gut microbiota fermentation end-products, namely the short chain fatty acids, has been recently proposed. SCFA act not only as energy substrates for the host, but also as signaling molecules. They are ligands for at least two G-protein-coupled receptors, GPR41 and GPR43 [16]. In a recent report, Samuel *et al.* have demonstrated that GPR41$^{-/-}$ mice colonized with a model of fermentative microbial community (*B. thetaiotaiomicron* and *M. smithii*) did not gain fat mass at the same extent as wild-type littermates did [17•]. The authors also found that the colonization of wild-type germ-free mice led to increase plasma levels of peptide YY (PYY), whereas this effect was blunted in GPR41$^{-/-}$ mice. PYY has been shown to inhibit food intake, gastric emptying, pancreatic and intestinal secretions, and gut motility [18]. In this study the authors proposed that in the absence of GPR41 signaling, the reduced plasma PYY levels promote an increased gut motility and reduce energy harvest from the diet. However, this last hypothesis, based on the fact that modulation of PYY level

Figure 1



Gut microbiota harvest energy from the diet increases energy storage. Gut microbiota may regulate energy storage: (1) by increasing monosaccharides absorption, (2) by producing lipogenic substrates (short chain fatty acids, SCFA), (3) by increasing hepatic lipogenesis, (4) by suppressing the fasting-induced adipose factor (FIAF) in the gut which in turn increased the enzyme lipoprotein lipase (LPL) activity, (5) by inhibiting AMPK-dependent fatty acid oxidation, and (6) by acting through the SCFA receptor GPR41.

influences intestinal transit, remains debatable. It is not clear whether lowering GPR41-dependent PYY level actually causes a reduced rate of nutrients delivery to the ileo-colonic segment. Strikingly, opposite to those results, we have shown that the modulation of gut microbiota via specific fermentation of nondigestible carbohydrate, called prebiotics, increased SCFA concentration in the cecum and also increased plasma PYY levels, a mechanism probably contributing the reduction of food intake and fat mass development following prebiotics treatment [19,20]. Therefore, an overproduction of SCFA may occur concomitantly with an increase in secretion of PYY upon gut microbiota changes, and an increase in PYY does not necessarily precludes an increase in energy sparing and fat mass development. Whatever are the mechanisms involved all those experiments strongly support a pivotal role of the gut microbiota in the development of adipose tissue (Figure 1).

Gut microbiota and obesity: the dysbiosis concept

Recently, it has been proposed that alterations in the development or composition of the gut microbiota (known as dysbiosis) participate in the development of obesity. In accordance with this hypothesis, it has been shown, firstly in a rodent model, that obesity can be associated with an altered gut microbiota [6]. Hence, after the characterization of several thousands bacterial gene sequences from the gut microbiota of genetically obese *ob/ob* mice and their lean counterparts, Ley *et al.* pointed out that *ob/ob* mice exhibited a 50% reduction in the abundance of Bacteroidetes and a proportional increase in Firmicutes. Similarly, the same group has also compared the distal gut microbiota of obese and lean human subjects and found that obese people had lower Bacteroidetes and more Firmicutes than did lean control subjects [21]. Interestingly, the authors observed that after weight loss (following a fat restricted or a carbohydrate restricted low-calorie diet), the ratio of Bacteroidetes to Firmicutes approached a lean type profile after 52 weeks of diet-induced weight loss [21]. However, this study did not demonstrate that the relative change in bacterial strains profile lead to the different fates of body weight gain. More recently, Duncan *et al.* performed a similar study, and found data which do not support the hypothesis that the proportions of Bacteroidetes and Firmicutes are different between obese and lean subjects. The authors did not detect any differences between obese and nonobese individuals in terms of the proportion of Bacteroidetes measured in the fecal samples, and no significant changes of the percentage of Bacteroidetes occurred in feces from obese subjects upon weight loss [22].

In accordance with this last study, Zhang *et al.* [23•] found even more Bacteroidetes in the obese subjects than in normal-weight individuals. They provided evidence that a subgroup of Bacteroidetes (*Prevotellaceae*) was significantly enriched in the obese individuals. Moreover, the authors showed that surgical treatment for morbid obesity (gastric bypass) strongly altered the gut microbiota toward an increase in *Gammaproteobacteria* (members of the family *Enterobacteriaceae*) and a proportional decrease in Firmicutes [23•]. Thus, the connection between the relative abundance of Bacteroidetes in obese humans remains a matter of debate. Recently, a metagenomic study, investigating the gut microbiota, addressed how host genotype, environmental exposure, and host adiposity participate to the modulation of the gut microbiome. A total of 154 monozygotic or dizygotic twin pair individuals concordant for their lean or obese phenotype, and their mothers have been taken into account in the study. The authors show that, even though there is no important overlap of microbiota among individuals, early changes in familial context influences the composition of microbiota [24•]. Despite such interfamilial/intrafamilial variations, it exists a remarkably consistent core functions for gut microbes. All together, these data lend credence to the hypothesis that smaller changes or more specific modulation of the gut microbiota community (instead of those obtained at the wide *phylum* levels) are involved in the development of obesity.

Bifidobacteria and obesity: the neglected bacteria genera?

In accordance with such hypothesis, we have recently demonstrated that the development of obesity and type 2 diabetes following a high-fat diet feeding is characterized by specific changes of the bacterial populations, which are predominant in the gut microbiota. We found, in rodents, that diet-induced obesity markedly reduced *Bifidobacterium* spp. number, and also reduced *Bacteroides*-related bacteria, *Eubacterium rectale–Clostridium coccoides* group content [25,26]. This specific decrease in *Bifidobacterium* spp. has recently been confirmed in another model of genetically obese and diabetic rodents (*fa/fa* rats) [27•].

Among the studies relating a dysbiosis of the gut microbiota during obesity, numerous human studies have pointed out changes in bifidobacteria level.

A recent paper has shown for the first time in human that differences in the gut microbiota may precede overweight development [28•]. Kalliomaki *et al.* have shown that *Bifidobacterium* spp. number was higher in children who exhibited a normal-weight at seven years than in children developing overweight. More importantly they observed that the *Staphylococcus aureus* counting was lower in children who maintain a normal-weight than in children becoming overweight several years later. The authors proposed that *S. aureus* may act as a trigger of low-grade inflammation [29], contributing to the development of obesity [25]. In agreement with these last findings,

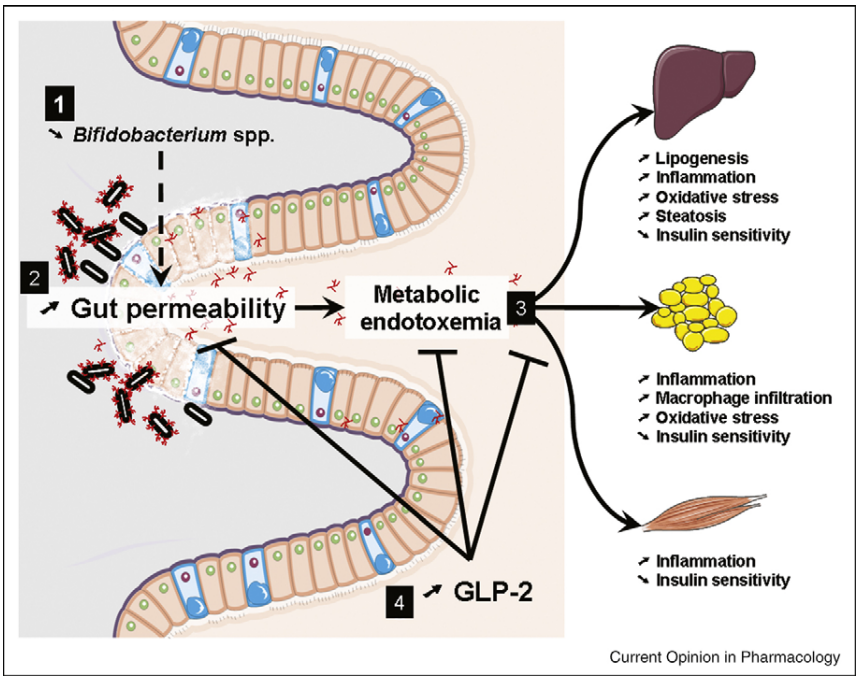
Collado *et al.* observed significant differences in gut microbiota composition according to the body weight during pregnancy. Interestingly, they found significantly higher numbers of *Bacteroides* group and of *S. aureus* in the overweight state compared with normal-weight women, and they established a positive correlation between the number of *Bacteroides* on the one hand, and the weight and BMI (before and over pregnancy), on the other hand. The *Bifidobacterium* group was present in higher numbers in normal-weight than in overweight women and also in women with lower weight gain over pregnancy [30]. These two studies unequivocally support that the gut microbiota profile (in favor of a higher bifidobacteria and a lower number of *S. aureus*) may provide protection against overweight and obesity development. Nevertheless, a recent report has shown that weight loss could be associated with reduced *Bifidobacterium bifidum* and *Bifidobacterium breve* counts and increased *Bifidobacterium catenulatum* [31]. Indeed, *Bifidobacterium* spp. represent an important group of bacteria whose presence is often associated with beneficial health effects [32•]. However, the complexity of this important *genus* is being unraveled [33,34]. Therefore, more studies are needed to unravel the role of specific *Bifidobacterium* species in obesity and weight management.

Gut microbiota and low-grade inflammation associated with obesity

Obesity is characterized by a cluster of several metabolic disorders (insulin resistance, type 2 diabetes, dyslipidemia, and hypertension) [35] characterized by a low-grade inflammation [36–38]. Although several elegant studies suggest that the gut microbiota exert a crucial role in the development of fat mass and energy homeostasis, it remains to be demonstrated how the gut microbiota can be involved in the development of a low-grade inflammation classically associated with the metabolic disorders related to obesity. Therefore, we turned to the following question: *Can we attribute the low-grade inflammatory process observed during obesity and metabolic diseases to the gut microbiota*?

On the basis of the recent demonstration that obesity and insulin resistance are associated with a low-grade inflammation, we have proposed several mechanisms linking gut microbiota to the development of obesity and metabolic disorders. Recently, we have identified the lipopolysaccharide (LPS, a membrane component of Gram-negative bacteria) as the triggering factor of the early development of inflammation and metabolic diseases [25]. In fact, we have demonstrated that excess dietary

Figure 2



Changes in gut microbiota (following high-fat diet or obesity) promote gut permeability, increase metabolic endotoxemia and trigger the development of metabolic disorders. (1) For instance, high-fat diet feeding changes the gut microbiota composition in a complex way with a specific decrease in *Bifidobacterium* spp. (2) This phenomenon is associated with a higher gut permeability leading to a higher plasma LPS levels (metabolic endotoxemia). (3) Metabolic endotoxemia promotes low-grade inflammation-induced metabolic disorders (insulin resistance, diabetes, obesity, steatosis, oxidative stress, and adipose tissue macrophage infiltration). (4) To increase endogenous GLP-2 production restores gut barrier function, decreases metabolic endotoxemia, and the development of metabolic disorders.

fat facilitates the absorption of highly proinflammatory bacterial LPS from the gut [25]. In a series of experiments in mice, we showed the interplay between gut microbiota and obesity-related inflammatory disorders. Firstly, we discover that a high-fat diet increases plasma LPS levels, defined as 'metabolic endotoxemia'; secondly, we found that fat feeding changes the bacterial populations (e.g. decreased bifidobacteria) [25,26] and thirdly, we identified that fat feeding and obesity increases gut permeability [39] (Figure 2). To demonstrate that gut microbiota plays a crucial role in the development of metabolic endotoxemia and metabolic diseases associated with obesity (diet-induced obesity or genetically obese mice *ob/ob*), we used different tools to change gut microbiota composition and activity. For instance, we found that drastic changes in the gut microbiota through antibiotic treatment completely blunted the metabolic endotoxemia, and the related metabolic disorders (e.g. glucose intolerance and insulin resistance) [39]. Interestingly, several reports have shown that obesity induced following dietary manipulations (high-fat feeding) [25,26,39,40] or genetic deletion (leptin-deficient models) [27•] is characterized by changes in gut microbiota toward a decreased number of bifidobacteria. Importantly, this group of bacteria has been shown to reduce intestinal LPS levels in mice and to improve the mucosal barrier function [41–45]. We thus asked the following question: *Can we attribute the development of gut permeability observed during obesity to the decrease of bifidobacteria*?

In accordance with this hypothesis, we had previously shown that feeding mice with prebiotics restored the number of intestinal bifidobacteria and reduced the impact of high-fat diet-induced-metabolic endotoxemia and inflammatory disorders [26,46] (Figure 2). However, the mechanisms by which these specific changes in the gut microbiota (prebiotics) improved metabolic endotoxemia — in the particular context of obesity — were not fully understood. Recently, we demonstrated in obese *ob/ob* mice that a selective modulation of the gut microbiota improved intestinal permeability and inflammatory markers [47•]. We found that the modulation of gut microbiota controls and increases endogenous production of the intestinotrophic peptides glucagon-like peptide-2 (GLP-2), and consequently improves gut barrier functions by a GLP-2-dependent mechanism [47•] (Figure 2).

Conclusion

The evident progress and the development of powerful methods deciphering the complexity of the gut microbiota raise several new questions related to the mechanisms by which gut bacteria interact with the host. Overall the demonstrations that gut microbiota dysbiosis might be involved in the obese phenotype — through the regulation of energy balance, low-grade inflammation, and the development of metabolic disorders — suggest that targeted manipulation of the gut microbiota could be an interesting approach in the follow-up of overweight and obese patients.

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