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Gut Microbiota and Host Metabolism: What Relationship?

Gilles Mithieux

Institut National de la Santé et de la Recherche Médicale, U1213, Lyon, Université Lyon 1, Villeurbanne, and Université de Lyon, Lyon, France

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Abstract
A large number of genomic studies have reported associations between the gut microbiota composition and metabolic diseases such as obesity or type 2 diabetes. This led to the widespread idea that a causal relationship could exist between intestinal microbiota and metabolic diseases. At odds with this idea, some compelling studies reported that global changes in microbiota composition have no effect on the host metabolism in obese mice or humans. However, specific bacteria are able to confer host metabolic benefits, such as *Akkermansia muciniphila* or *Prevotella copri*, when they are given by gavage in obese mice. A crucial link by which gut bacteria communicate with the host mucosa is based on metabolites or low-molecular-weight compounds. Among them, short-chain fatty acids produced from the fermentation of dietary fibers initiate beneficial effects on the host metabolism via the activation of intestinal gluconeogenesis (a mucosal function exerting antidiabetic and anti-obesity effects through the activation of gut-brain neural circuits). However, fermentation of short-chain fatty acids is a function that is widespread among the main bacterial phyla and thus weakly depends on microbiota composition. Therefore, even if some bacteria may confer on the host metabolic benefits, the causal role of microbiota in metabolic diseases is not established.
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Introduction

In the last decades, the expanding obesity epidemic has constituted an increasing disquieting threat for human wellbeing and health. Obesity, indeed, is associated with a variety of deleterious effects on health, including, e.g., type 2 diabetes and associated macro- and microvascular diseases. In this context, the possible role that intestinal microbiota might play in metabolic diseases has been an emerging field attracting more and more attention. The fact that high-throughput sequencing approaches of the microbiota genome are nowadays available has definitely favored the explosion of this field, especially in the context of human health. Thus, a huge number of studies have reported various types of association between the microbiota composition in health and metabolic diseases

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E-Mail karger@karger.com
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Gilles Mithieux
UMR INSERM U855, Faculty of Medicine Laennec Lyon-East
7–11 rue Guillaume Paradin
FR–69372 Lyon Cedex 08 (France)
E-Mail gilles.mithieux@inserm.fr

as obesity or type 2 diabetes, either in rodents [1–3] or in humans [4–7]. The growing interest in the influence of intestinal microbiota on diseases has now expanded to "non-metabolic" illnesses such as intestinal or mental disorders [8], disorders of the immune system [9], or neurodegenerative disorders, such as Alzheimer disease or multiple sclerosis [10].

In the field of metabolic diseases, obesity and deregulated glucose control has been associated with an altered, especially poorly diversified gut microbiota, which led to the concept of "dysbiosis," whereas leanness and metabolic health has been associated with a higher gut microbial diversity [6, 11]. Accordingly, dietary interventions assumed to favor metabolic health, i.e. based on protein supplementation [5, 11] or on supplementation in soluble dietary fibers, were shown to increase intestinal microbiota diversity in obese people [5, 12, 13]. These studies initiated the widespread idea that gut microbiota dysbiosis could have a causal role in determining the evolution toward obesity and deregulated glucose metabolism and further type 2 diabetes [4–7, 11]. However, that dietary habits and food quality have the capacity to influence metabolic health is a long-known observation [14]. Moreover, that metabolic diseases alter host metabolism is a tautology. To firmly ascertain that microbiota is a causal link in metabolic diseases, manipulating microbiota composition per se should be able to influence host metabolism (Fig. 1). A comparable rationale could be done for the role of microbiota in "non-metabolic" diseases, which may (or may not) be under a control by dietary habits.

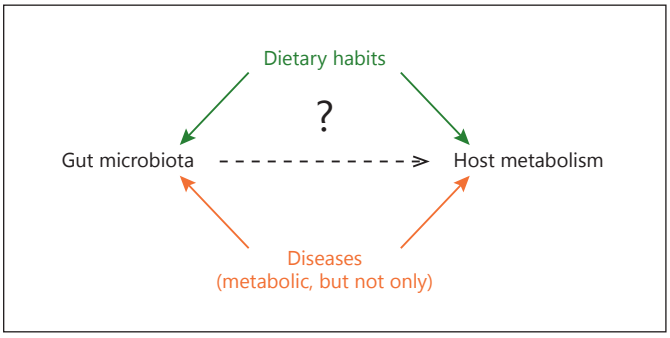

Fig. 1. Relationships between gut microbiota and host metabolism: established (solid line) and hypothetical (dashed line).

Outcomes of Changing Microbiota

In disagreement with the concept of a causal relationship between microbiota and metabolic diseases, some compelling studies have shown that changing microbiota has no effect on host metabolism. For example, a study addressed the question of the role of intestinal microbiota in the proneness of C57BL/6J mice to diet-induced obesity. It appeared that C57BL/6J mice grown in the Jackson animal facility partially resisted to diet-induced obesity compared to their counterpart mice with the same genetic background grown in the facility of another producer: Taconic Farm. Large differences in the intestinal microbiota composition were highlighted between mice from the two facilities [15]. This was in line with the idea that the microbiota could have a role in the issue. Various manipulations were done to cross-transfer the main diverging bacteria species between mice from the two colonies. This remained without any effect on their susceptibility to obesity. Even a complete exchange of the gut microbiota from Jackson to Taconic Farm and vice-versa, after elimination of the original microbiota with antibiotics treatment, was without effect: mice from Jackson colonized with the microbiota of Taconic Farm continued to partially resist to diet-induced obesity compared with mice from Taconic Farm colonized with the microbiota from Jackson [15]. These data disagreed with the concept that the gut microbiota per se could importantly influence the development of obesity in mice.

Another striking study was performed in 57 obese patients with altered glucose control, featured from various parameters. The patients were treated for 7 days with different antibiotic cocktails to deplete original intestinal microbiota. They were studied for the same metabolic parameters before, and after the treatment, and next 8 weeks after the treatment, which was a time where their microbiota was still dramatically modified compared with the situation before the treatment [15]. However, no change in any of the metabolic parameters was evidenced either after the antibiotic treatment or after the 8-week follow-up, suggesting again that the gut microbiota does not exhibit the capacity to markedly influence the host metabolism [16].

It must be mentioned that in a high number of experimental studies, an obesity-prone phenotype could be successfully conferred on germ-free mice upon transferring the microbiota from obese mice [see, for example, 1]. However, one must bear in mind that germ-free mice are far from constituting a satisfactory control mouse model. Because of the absence of intestinal bacteria, the efficiency of food is very weak in germ-free mice. They eat much more than conventional mice to hardly gain weight and they resist to diet-induced obesity. Therefore, they gain

weight even after colonization by a gut microbiota from lean mice. Moreover, the intestine of germ-free mice suffers from several defects. Particularly, their gastrointestinal nervous and immune systems are very immature, and accordingly conventionalization partially corrects these defects [17, 18]. More importantly, the gut barrier permeability is markedly altered in germ-free mice, which makes their intestine leaky and especially permeable to a variety of compounds, such as inflammatory lipopolysaccharides [19]. This might explain their proneness to alterations in energy homeostasis or metabolic control when they are colonized with dysbiotic microbiota.

These points have been emphasized in an elegant recent study, in which dysbiotic microbiota from previously obese mice were transferred in mice treated by antibiotics to deplete gut microbiota, a treatment which did not alter intestinal permeability [20]. In this case, antibiotic-treated colonized mice did not develop obesity or deregulated glucose control. What is more, when they were challenged with a high-fat diet, they resisted obesity and alterations in metabolic control. This strongly suggests that "dysbiotic" intestinal microbiota may be adaptive and confer protection against deregulations in metabolic control, instead of being deleterious and causal in the disease [20].

Therefore, from the viewpoint of the author, the causal role of intestinal microbiota in the deregulation of energy homeostasis in metabolic diseases is not established.

Benefits Provided by Specific Bacteria

If experiments of changing the whole gut microbiota have not clearly supported a causal role of the whole microbiota in metabolic control, it remains that the transfer of specific bacteria species could have a significant impact in the regulation of energy homeostasis. Perhaps the best example is *Akkermansia muciniphila*, a bacterium residing within the mucus layer and deriving nutrient sourcing from it. *Akkermansia* abundance is decreased in obese mice and restored to normal upon fiber feeding [2]. Given by gavage to diet-induced obese mice, *Akkermansia* corrects deregulated glucose control, notably decreasing the circulating levels of inflammatory lipopolysaccharides and improving the gut barrier [2]. Importantly, a protein that binds Toll-like receptor 2 and is able to restore normal gut permeability and to recapitulate partly the benefits conferred by the living bacteria was identified in the membrane of the bacterium, thus providing a putative mechanistic insight into the phenomenon [21].

A second example is *Prevotella copri*, a bacterium proliferating in human subjects that positively respond to prebiotic feeding in terms of glucose control [13]. *Prevotella* given by gavage in mice contributes to the improvements in glucose control in the presence of dietary fiber. Interestingly, *P. copri* is a succinate-producing bacterium. It was shown elsewhere that succinate is a major bacterial metabolite produced in response to fiber feeding in mice and provides metabolic benefits via its role as a substrate of intestinal gluconeogenesis (IGN) [22]. IGN indeed is a gut function initiating various metabolic benefits by generating a gut-brain nervous signal that positively interferes in energy homeostasis and glucose control [23]. Finally, *Prevotella* was shown to act positively in glucose control both by activating IGN as a substrate, but also via succinate-independent mechanisms, which remain to be deciphered [13, 22].

Peripheral to the field of energy homeostasis, a relevant study highlighted the beneficial role of specific bacteria in the deregulated comportment of the offspring of pregnant mice subject to maternal immune activation (MIA). In the offspring, MIA promotes dysbiosis and disorders in gut function (altered permeability) associated with features of neurodevelopmental disorders evoking autism spectrum disorder in humans. Treatment of the MIA offspring with *Bacteroides fragilis*, a bacterium previously shown to correct the gastrointestinal disorders accompanying colitis [24], corrected the main bacterial types altered in dysbiotic microbiota, improved gut permeability and ameliorated most of the behavior disorders [25]. What was the most important here is that a bacterial metabolite, 4-ethylphenylsulfate (4EPS), was markedly increased in the plasma of the MIA offspring and restored to normal after *B. fragilis* treatment. Injected in naïve mice, 4EPS was able to induce the behavior disorders observed in MIA offspring [25]. This provided a putative mechanistic link between the microbiota function and the alterations in behavior. Therefore, if changing the whole microbiota has a weak impact on the host metabolism (see above), the capacity of some specific bacteria to improve it seems clearer, even if mechanistic insights are still to be comprehensively deciphered.

Microbiota and Metabolism: What Molecular Links?

The latter study underscored a key point, the role of bacterial metabolites in the communications between the microbiota and the host. But in exceptional (pathological) situations in which the gut barrier permeability is im-

portantly impaired, and in which high molecular weight compounds such as LPS or even bacteria are susceptible to be translocated, the bacteria are separated from the gut mucosa by the mucus layer thickness [see, for example, 2]. This makes that metabolites or low-molecular-weight compounds most likely represent the only communication links between the bacteria and the host mucosal functions and then the host metabolism in physiological situations. We emphasized this in a recent study pertaining to the metabolic benefits associated with feeding a soluble fiber-enriched diet [3]. It was confirmed that fiber feeding induced a large diversification of gut microbiota composition associated with a marked shift in the ratio of the two main bacterial phyla (increase in Bacteroidetes, decrease in Firmicutes) [3, 5, 12, 13]. However, the mechanism explaining the benefits did not involve microbiota changes but instead they involved the activation of the IGN function [3] (see above). Like succinate, short-chain fatty acids (SCFAs) (particularly propionate and butyrate) initiate within the gut mucosa several complementary mechanisms issuing in the activation of IGN. Interestingly, mice with loss of function of IGN did not exhibit metabolic benefits, although they exhibited increased production of SCFAs and the diversification of microbiota associated with fiber feeding [3]. Therefore, the fermentation of fiber into SCFAs (and succinate) and the capacity of the host mucosa to derive from these moieties the gut-brain glucose signal triggered by IGN, and not the changes in microbiota composition, are the key events in the fiber-associated benefits.

This study also emphasizes that the microbiota "function" (production of SCFAs), rather than the microbiota "composition," is essential to generate the benefits linked to fibers. It is noteworthy that SCFA-producing bacteria are largely spread in the two preponderant bacterial phyla (Bacteroidetes and Firmicutes) [26, 27]. The latter, however, vary in opposite senses in obesity versus leanness. Therefore, the gut microbiota representative of obesity is capable of producing SCFAs as that representative of leanness. Moreover, the fiber-induced benefits take place in both lean and obese mice [3]. It is also noteworthy that SCFAs are produced by the gut microbiota from the fermentation of amino acids in the case of protein-enriched diets [28, 29], whereas animal meat or vegetarian food rapidly initiates very different evolutions in the microbiota composition [5]. It is noteworthy that protein-enriched diets initiate benefits on host metabolism comparable to fiber-enriched diets [23, 26]. Therefore, the dietary status can dramatically modify the microbiota composition, while initiating comparable metabolic benefits and comparable production of bacterial metabolites. One may thus envision that microbiota changes characterize any situation associated with nutritional alterations, including those associated with gastrointestinal (or other) diseases. In this case, the variations in microbiota composition could be a consequence rather than a cause of metabolic alterations. Finally, one may speculate that the genetic diversity of the gut microbiota population and its food-dependent versatility likely constitutes a key element allowing the host to derive optimal metabolic benefits from the varying conditions of food sourcing occurring under natural (or physiopathological) conditions.

Conclusions

To sum up, the causal role of intestinal microbiota in the initiation of metabolic diseases does not seem clearly established. Moreover, changing the microbiota composition could be of low usefulness to improve energy homeostasis in situations of obesity and deregulated metabolic control. It remains that some specific bacteria are able to exert beneficial effects on deregulated energy homeostasis when they are given by gavage in obese mice. This warrants that the translation of data obtained from mouse studies into well-controlled studies in humans should be considered in the future. An important point to keep in mind is that the physiological way by which gut bacteria interact with the host metabolism is based on metabolites or low-molecular-weight compounds. Therefore, one can hope in the near future to learn a lot from metabolomics of bacterial products associated with well-conducted mechanistic approaches.

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Disclosure Statement

The author has no conflict of interest to disclose relating to this paper.

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