The Gut Microbiome Influences Host Endocrine Functions

Marialetizia Rastelli,[1,2] Patrice D. Cani,[1,2] and Claude Knauf[2,3]

[1]Université Catholique de Louvain, UCLouvain, Walloon Excellence in Life Sciences and BIOtechnology (WELBIO), Metabolism and Nutrition Research Group, Louvain Drug Research Institute, B-1200 Brussels, Belgium; [2]NeuroMicrobiota, European Associated Laboratory (INSERM/UCLouvain), B-1200 Brussels, Belgium; and [3]Institut de Recherche en Santé Digestive et Nutrition (IRSD), Institut National de la Santé et de la Recherche Médicale (INSERM), U1220, Université Paul Sabatier (UPS), 31024 Toulouse Cedex 3, France

ORCiD numbers: 0000-0002-4499-978X (M. Rastelli); 0000-0003-2040-2448 (P. D. Cani).

ABSTRACT The gut microbiome is considered an organ contributing to the regulation of host metabolism. Since the relationship between the gut microbiome and specific diseases was elucidated, numerous studies have deciphered molecular mechanisms explaining how gut bacteria interact with host cells and eventually shape metabolism. Both metagenomic and metabolomic analyses have contributed to the discovery of bacterial-derived metabolites acting on host cells. In this review, we examine the molecular mechanisms by which bacterial metabolites act as paracrine or endocrine factors, thereby regulating host metabolism. We highlight the impact of specific short-chain fatty acids on the secretion of gut peptides (*i.e.*, glucagon-like peptide-1, peptide YY) and other metabolites produced from different amino acids and regulating inflammation, glucose metabolism, or energy homeostasis. We also discuss the role of gut microbes on the regulation of bioactive lipids that belong to the endocannabinoid system and specific neurotransmitters (*e.g.*, γ-aminobutyric acid, serotonin, nitric oxide). Finally, we review the role of specific bacterial components (*i.e.*, ClpB, Amuc_1100) also acting as endocrine factors and eventually controlling host metabolism. In conclusion, this review summarizes the recent state of the art, aiming at providing evidence that the gut microbiome influences host endocrine functions via several bacteria-derived metabolites. ***(Endocrine Reviews 40: 1271 – 1284, 2019)***

General Overview of the Gut Microbiome

The term *microbiota* indicates a complex and dynamic microbial community residing in a specific habitat. In detail, the human microbiota consists of the totality of microorganisms inhabiting the human body, mainly on the skin, the genitals, and the intestine. Although almost all body surfaces are colonized, most microbes reside in the intestine and are known as the gut microbiota (1).

Importantly, different types of microorganisms constitute the gut microbiota; in addition to bacteria, archaea, fungi, viruses, and phages also colonize the intestine. To date, studies of host–gut microbiota interactions have focused mainly on investigating the bacteriome (the totality of bacteria composing the gut microbiota). However, the mycobiome, virome, and phageome are also attracting increasing attention in this field (1, 2).

Consequently, the interactions between intestinal bacteria and human cells are currently the best described and will be the subject of this review. Here, the more general term *gut microbiome* will be used to refer to the gut bacteria.

The development of culture-independent methods consisting of the sequencing of massive amounts of DNA have substantially contributed to the development of the field. Since their introduction in 2005, next-generation sequencing technologies have enabled advantageous, high-throughput, low-cost, and fast sequencing. Microbial diversity has been determined via two different sequencing approaches: amplicon sequencing and shotgun metagenomics (3). In the amplicon sequencing approach, specific regions of the microbial DNA are amplified (*i.e.*, 16S rRNA gene)

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ESSENTIAL POINTS

- The gut microbiome helps to regulate host metabolism
- Numerous metabolites produced by gut microbes act on specific host receptors
- Short-chain fatty acids trigger the secretion of gut peptides (*i.e.,* glucagon-like peptide-1, peptide YY)
- Gut microbes regulate the production of endocannabinoids and neurotransmitters
- Bacterial components (*i.e.,* ClpB, Amuc_1100) act as endocrine factors controlling host metabolism

and then sequenced, facilitating a taxonomic or phylogenetic analysis (Fig. 1). Functional information could also be extrapolated. On the other hand, the shotgun metagenomics approach sequences the entire genome of the organisms in the sample. After sequencing, the reads are assembled together, allowing the identification of large numbers of coding and noncoding sequences. This approach enables a taxonomic analysis, but it is specifically intended for use in functional analyses. Metabolic pathways have been reconstructed based on enzyme coding genes (4).

According to the most recent estimates, the intestine of a man with a standard weight hosts 3.9×10^{13} bacteria, which reside mainly in the colon, with a bacteria–to–human cell ratio of ~1:1 (Fig. 1) (5). By metagenomic sequencing of fecal samples of 1070 people from three different continents (America, Asia, and Europe), a catalog of the genes expressed by the human microbiome was created in 2014; this nonredundant catalog counts ~10 million bacterial genes, a number 500 times greater than the number of genes in the human genome (6). In this same study, it was calculated that each fecal sample contained an average of 762,655 gut bacterial genes, meaning 38 times more genes than the human genome (6, 7).

Although the number of gut bacterial genes per individual has not been calculated but only estimated, the aforementioned numbers emphasize the importance of the metabolic capacity of the gut microbiome, which is predicted to be even higher than the host metabolic capacity.

At the taxonomic level, ~90% of gut bacteria belong to the phyla Firmicutes, Bacteroidetes, and Actinobacteria, with the remaining portion belonging to Proteobacteria and Verrucomicrobia. Initially, an increase in the Firmicutes to Bacteroidetes ratio was associated with obesity in humans and rodents (8, 9); however, the lack of consistency between studies (10, 11) prompted an in-depth analysis at the taxonomic level (*i.e.,* family, genus, and species). Researchers have not yet defined which level of taxonomic investigation is the most suitable, because the metabolic activity of the gut microbiome and the interaction with the host increase the complexity of the analysis (1).

A complementary approach to analyze the gut microbiome consists in investigating the collection of genes harbored by the gut microbes. For example, a low number of gut microbial genes (*i.e.,* a low gene count) is associated with an unhealthy state, as characterized by higher adiposity, insulin resistance, dyslipidemia, and low-grade inflammation (12). Several other studies have confirmed the positive correlations between a high basal gene count, healthier metabolic status, and better outcomes after dietary restriction (13, 14), thus supporting the importance of the evaluation of the gene richness.

Recently, Vandeputte *et al.* (15) identified new perspectives for the investigation of gut microbiome by suggesting that quantifying the absolute number of bacteria (microbial load or cell counts) is a reliable approach for investigating the intestinal microbiome and, conversely, highlighting the potential limitations associated with the relative quantification and absolute quantification of gut bacteria.

Overall, despite the technical and conceptual progress achieved in the study of the gut microbiome, we still lack a gold-standard method; the best strategy relies on the use of complementary approaches (taxonomic profiling, functional metagenomic analysis, and gene count) and the analysis of multiple samples over time to obtain a comprehensive picture of the composition and numbers of metabolites (*i.e.,* metabolome) involved in this complex and dynamic biological system. Many improvements are still needed, and many questions are still matters of debate (1).

In the next part of the review, we will describe several microbial metabolites and microbial components that contribute to the host–gut microbiome dialogue. Those bacterial-derived molecules can locally interact with the host (*i.e.,* activating receptors expressed on intestinal cells or on intestinal nervous terminations) but can also exert their action distally, after entering the circulation. Independent of the mechanism of action (paracrine, endocrine, or nervous) microbiota-derived metabolites and microbial components influence host endocrine function.

What Are the Different Metabolites Produced by the Gut Bacteria?

Short-chain fatty acids

The human gastrointestinal (GI) tract is highly specialized for the digestion and absorption of different

nutrients that are present in our food. Actually, almost all the fat contained in a meal is absorbed, and a very minor portion (<5 g/d) will escape the digestion and eventually reach the colon to be excreted. Numerous factors are implicated in this complex process, including bile acids and different lipases, and the fatty acids are eventually actively transported into intestinal epithelial cells. The upper GI tract is also very efficient at digesting and absorbing simple sugars and most of the amino acids derived from the digestion of proteins contained in the diet.

Conversely, the human gut is unable to digest all the different types of carbohydrates present in our diet. The chemical features of those fibers vary according to the source, such as cereals, fruits, and vegetables. Therefore, numerous carbohydrates escape digestion in the upper GI tract and become so-called dietary fiber. Hence, dietary fibers are used as an energy source by specific gut bacteria. The diverse enzymatic machinery of some bacteria contributes to the metabolization of these nondigestible carbohydrates into different molecules, such as short-chain fatty acids (SCFAs) (*e.g.,* acetate, butyrate, and propionate) (Fig. 2).

SCFAs have been investigated in numerous conditions, and their impacts on host health are well documented (16–18). Besides acting locally, those compounds have endocrine properties and reach different organs located at various distances from the GI tract, such as the liver, adipose tissue, brain, and muscles (19, 20). Consequently, their physiological effects range from the regulation of energy, glucose, lipid metabolism, and inflammation to the modulation of immunity and cancer (16). Thus, these microbial metabolites have numerous physiological roles.

Forty years ago, the pioneering studies by Daniel Jenkins *et al.* (21, 22) revealed an irrefutable link between the ingestion of "nonabsorbable" carbohydrates and glucose metabolism. In these studies, the authors initially postulated that the bulking effects (*i.e.,* water retention) of the nondigestible carbohydrates ingested, such as guar gum or pectin, explained the mechanisms underlying the beneficial effects (21–23). Today, the positive association between fibers and health has undeniably been confirmed; however, the mechanisms are more complex than the bulking effect. During the last 20 years, numerous studies have discovered that different nondigestible carbohydrates are, in fact, fermented by the gut bacteria that are present in the lower part of the gut.

SCFAs and gut peptides in rodents

The different mechanisms by which specific fermentable fibers are fermented into SCFAs and

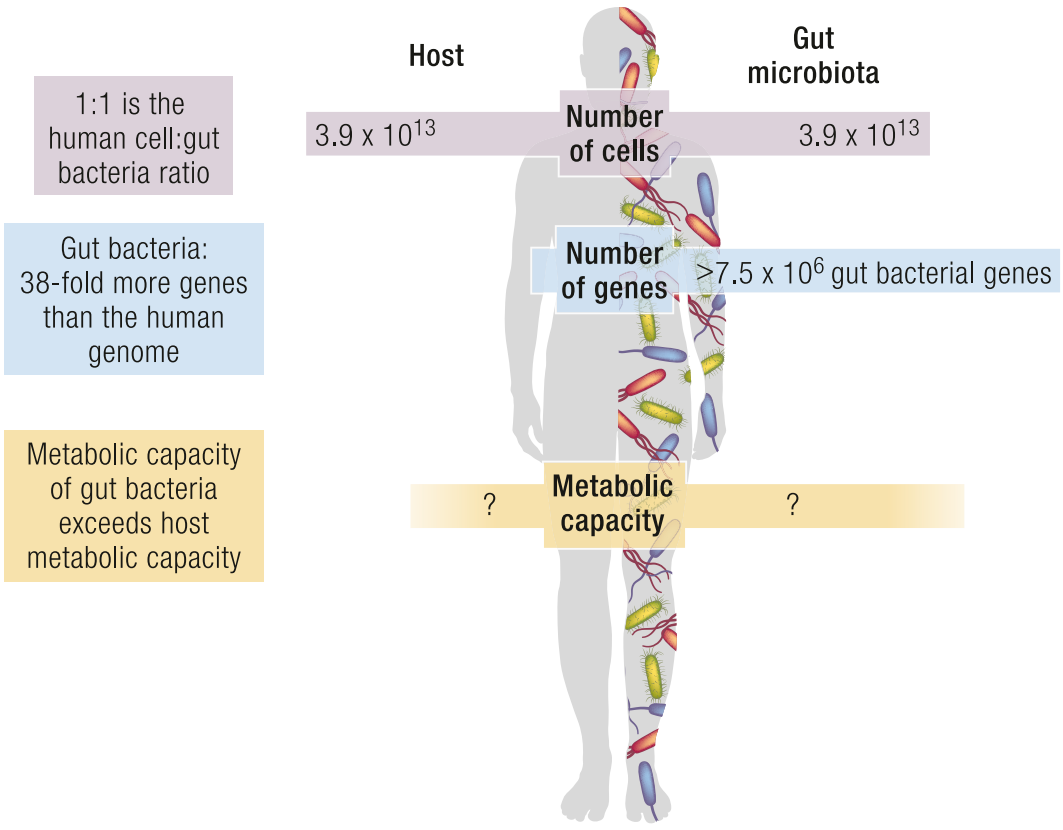


Figure 1. Host and gut microbiota in comparison: the numbers. In recent decades, bacteria composing the gut microbiota have been investigated. Today we know that the intestine of a healthy man hosts a number of bacteria that is comparable to the number of cells composing his body (excluding red blood cells); on average, a stool sample contains >7.5 million bacterial genes, ~38 times more genes than are expressed by the human genome. All these data suggest that the metabolic capacity of the gut microbiota can exceed the host's metabolic capacity. However, numerical evidence is still lacking in this sense.

subsequently improve metabolism were initially discovered in preclinical models using inulin-type fructans as prebiotics (*e.g.,* inulin or oligofructose) (24) (Table 1). In a series of studies, our group and other researchers have investigated the molecular mechanisms by which a diet enriched with prebiotics decreased the body weight, fat mass gain, insulin resistance, and energy intake in rodents with genetically or diet-induced obesity (27–31). Seeking to determine a mechanism that explains the lower food intake and improved glucose tolerance observed upon prebiotic treatment, we reasoned that the improvements in glucose levels, insulin sensitivity, and energy intake were due to the modulation of gut peptides produced by the L-cells located in the lower part of the gut and the production of glucagon-like peptide-1 (GLP-1) (32). Hence, we measured the levels of GLP-1 and found that the improved phenotype was associated not only with higher levels of GLP-1 in the portal vein blood but also with a higher GLP-1 content and proglucagon mRNA expression in the intestinal segments (*i.e.,* ileum and colon) (28–30). Later, these effects were also accompanied by an increased level of peptide YY (PYY) and more enteroendocrine L-cells (33, 34) (Fig. 2). Currently, these effects are not exclusively limited to one type of fermentable carbohydrate, such as inulin-type fructans. Indeed, resistant starches and arabinoxylans are other fermentable, nondigestible carbohydrates that produce effects similar to inulin-type fructan prebiotics, namely decreased food intake, fat mass, and body weight gain, together with increased plasma GLP-1 and PYY levels (35–38). Similarly to the inulin-type fructans, the microbial fermentation of all these fibers leads to the production of large amounts of various SCFAs. Interestingly, the chemical structure of the fermentable fibers is also directly associated with the profile of SCFAs; in other words, the quantity of butyrate, acetate, or propionate produced depends on the type of fibers, because inulin is described as propionigenic, whereas resistant starches are more butyrogenic. The different pathways involved in the biosynthesis of SCFAs upon nondigestible carbohydrate fermentation and the cross-feedings observed between bacteria have been described [for a review see (39)]. Therefore, the profile of SCFAs will directly depend on the microbiome composition and hence the potential metabolic impact on host health.

SCFAs bind to and activate specific G protein–coupled receptors such as GPR-43 (also referred to as FFAR2, or free fatty acid receptor 2) and GPR-41

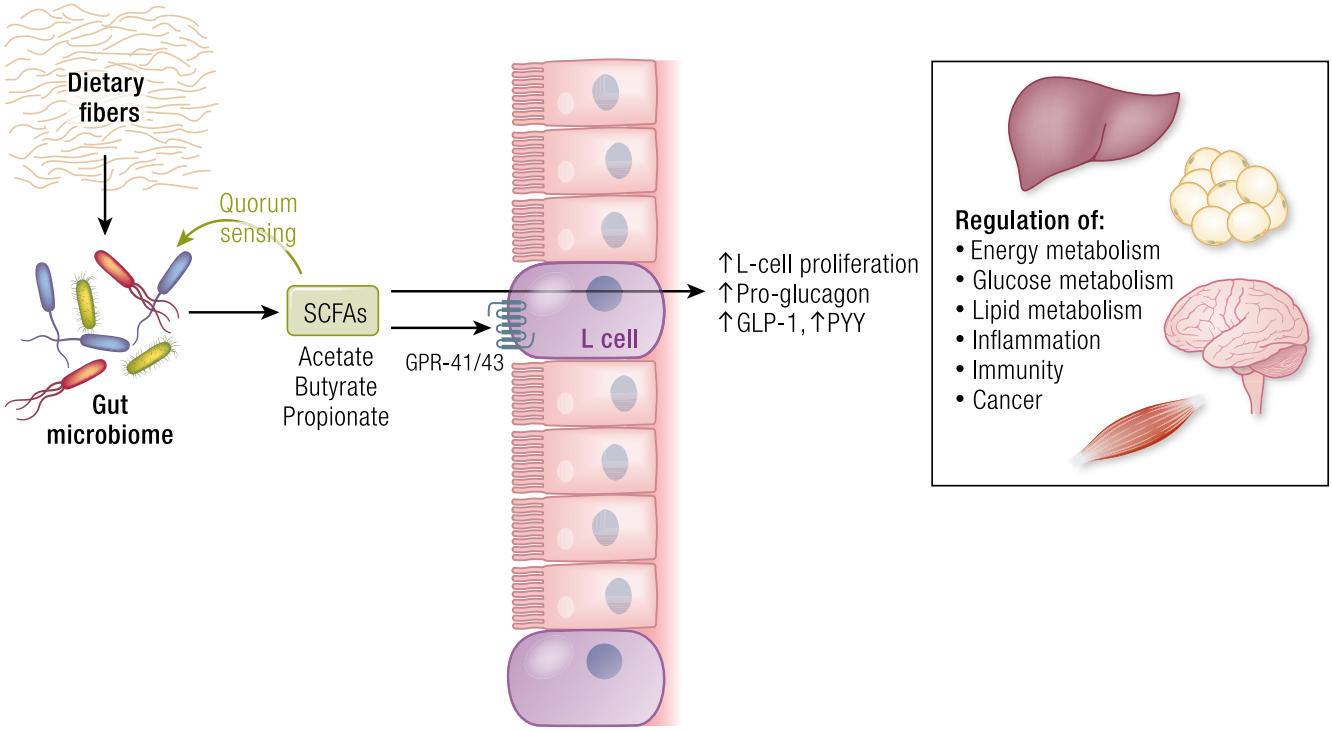


Figure 2. Microbiota-derived SCFAs influence host endocrine functions. Dietary fibers are substrates of the microbial enzymatic machinery; they are fermented in SCFAs (namely acetate, butyrate, and propionate). SCFAs influence host metabolism by acting locally on receptors expressed by the intestinal enteroendocrine L-type cells (*i.e.,* GPR-41, GPR-43) or distally, after entering the circulation and being transported to other organs (liver, adipose tissue, brain, and muscle). Importantly, SCFAs can also be sensed by the gut bacteria themselves and regulate pathogenic colonization, depending on their concentration. This type of cell-to-cell interaction is known as quorum sensing.

Table 1. Definitions

Prebiotics
Among the different types of fermentable dietary fiber, a specific family called prebiotics is defined as "a substrate that is selectively utilized by host microorganisms, conferring health benefits" (24). The term *prebiotic* thus refers to specific compounds that escape digestion in the upper part of the GI tract and are metabolized by specific bacteria.
Probiotics
Probiotics are "live microorganisms that, when administered in adequate amounts, confer a health benefit to the host" (25).
The Endocannabinoid System: A Glimpse
The ECS comprises several bioactive lipids (*N*-acylethanolamines and 2-acylglycerols), as well as the receptors that are activated by those lipids (*e.g.*, CB1, CB2, GPR119, TRPV1, PPARα) and the enzymes involved in the synthesis and degradation of those same lipids (NAPE-PLD, DAGL, FAAH, NAAA, and MAGL).
The ECS is ubiquitous and modulates glucose and lipid metabolism, food intake, and inflammation.
An extensive review describing the ECS and the crosstalk between the ECS and the gut microbiome has been published (26).

(also referred to as FFAR3). More than 15 years ago, Brown *et al.* (40) identified the endogenous ligands of these receptors that are expressed in a wide variety of tissues and cell types, ranging from endocrine cells to adipocytes and immune cells (41, 42). Importantly, both GPR-41 and GPR-43 are expressed on enteroendocrine L-cells; therefore, those receptors are directly contacted by the SCFAs produced by the local microbiome (43). Thus, the modulation of the proportion and quantity of SCFAs will activate these GPRs and eventually promote the secretion of gut peptides such as GLP-1 and PYY (43–45) (Fig. 2). The role of the microbiome in controlling the production of these gut peptides has been observed in different genetically modified mice models lacking either GPR-43 or GPR-41. Mice lacking these receptors display altered secretion of GLP-1 and PYY after exposure to SCFAs or specific prebiotics (39, 46, 47). Aside from the role of SCFAs and GPR-43 in the secretion of GLP-1 by L-cells, other molecules influenced by the microbiota can also stimulate GLP-1 secretion. Indeed, the gut microbiota regulates both bile acid synthesis and the production of secondary bile acids (48). Bile acids bind to the membrane receptors TGR5 (Gpbar1) expressed on the L-cells. The activation of TGR5 improves liver metabolism and glucose tolerance in obese rodents by a mechanism regulating intestinal GLP-1 production (49). In the adipose tissue, TGR5 stimulation induces expression of the enzyme 2-iodothyronine deiodinase (D2), which produces the activated form of thyroid hormone, thereby increasing thermogenesis (50).

Another mechanism linking bile acids and metabolism is related to the activation of the farnesoid X receptor, which is known to regulate glucose tolerance and insulin sensitivity but via mechanisms other than enteroendocrine regulation (51).

SCFAs and gut peptides in humans

In addition to the numerous data regarding SCFAs and fibers in rodents, human studies have also reported changes in gut peptide production after modification of the gut microbiome induced by the administration of fermentable fibers. Nonetheless, the general impacts on food intake, glucose metabolism, and body weight are far less important that the effects observed on rodents. Although discrepancies exist in the magnitude of the impact on these parameters, they are still interesting to consider when using dietary fiber as a nutritional adjuvant to global and multidisciplinary therapeutic care. Notably, the use of microbially fermented compounds in medical care has been reported for two decades. Indeed, in a 1996 study, Ropert *et al.* (52) first reported a correlation between levels of lactulose, which is fermented by the gut microbiome, in healthy volunteers with higher daily production of gut peptides. In 2003, the administration of oligofructose at a dosage of 20 g/d for 1 week was reported to significantly increase plasma GLP-1 levels after a meal (53). Moreover, several studies reported that modulation of the gut microbiome with nondigestible carbohydrates increases satiety and reduces food intake, with an impact on energy intake. Nevertheless, none of these studies have investigated the gut peptides (54, 55). In 2006, we reported that modulation of the microbiome induced by oligofructose (8 g twice daily for 14 days) significantly increased satiety and reduced hunger and the prospective desire to ingest food (56), effects associated with higher blood GLP-1 and PYY levels (57). Since the publication of these articles, several other studies have confirmed that the consumption of fermented carbohydrates affects appetite sensations in different cohorts, including obese volunteers (58–66); for a review, see (67).

However, very few studies have simultaneously investigated the complex modulation of the gut microbiome, production of different metabolites (*i.e.*, the metabolome), levels of SCFAs, and metabolic effects on subjects with type 2 diabetes. In 2018, Liping Zhao *et al.* (68) performed an in-depth investigation of this problem by conducting a randomized clinical study investigating the impact of modulation of the microbiome with isoenergetic diets that differed in their concentrations of prebiotics (including whole grains and traditional Chinese medicinal foods). They causally linked the improved microbial and metabolic profile by using gut microbiota transplantation into germ-free mice. They concluded that the changes in the microbiome induced by increasing the consumption of nondigestible carbohydrates was sufficient to improve the metabolic parameters of patients with type 2 diabetes. However, although the levels of SCFAs correlated with improvements in several metabolic parameters and increased blood levels of GLP-1 and PYY, the researchers have not been able to ascertain beyond a doubt whether the combination of SCFAs and gut hormones completely explains the observed results. Therefore, whether modulation of the gut microbiota upon fiber intake fully explains the mechanism by which metabolism is improved remains to be demonstrated.

Microbial metabolites derived from amino acids and their impacts on host metabolism

Microbial amino acid–derived metabolites: the bad side?

A decade ago, Newgard *et al.* (69) highlighted a positive correlation between the levels of branched-chain amino acids (BCAAs) and related metabolites and insulin resistance by performing metabolomic profiling of healthy subjects and patients with metabolic disorders. This pioneering study also provided the proof of concept that some amino acids contribute to the onset of metabolic disorders because rats exposed to a high-fat diet enriched with BCAAs exhibited higher BCAA contents in their skeletal muscles and insulin resistance (Fig. 3). According to the authors, the increased pool of circulating BCAAs was of dietary origin (69). Recently, the positive correlation between serum BCAA levels and insulin resistance has been confirmed in humans (70). Here, gut bacteria have been proposed as a source of BCAAs,

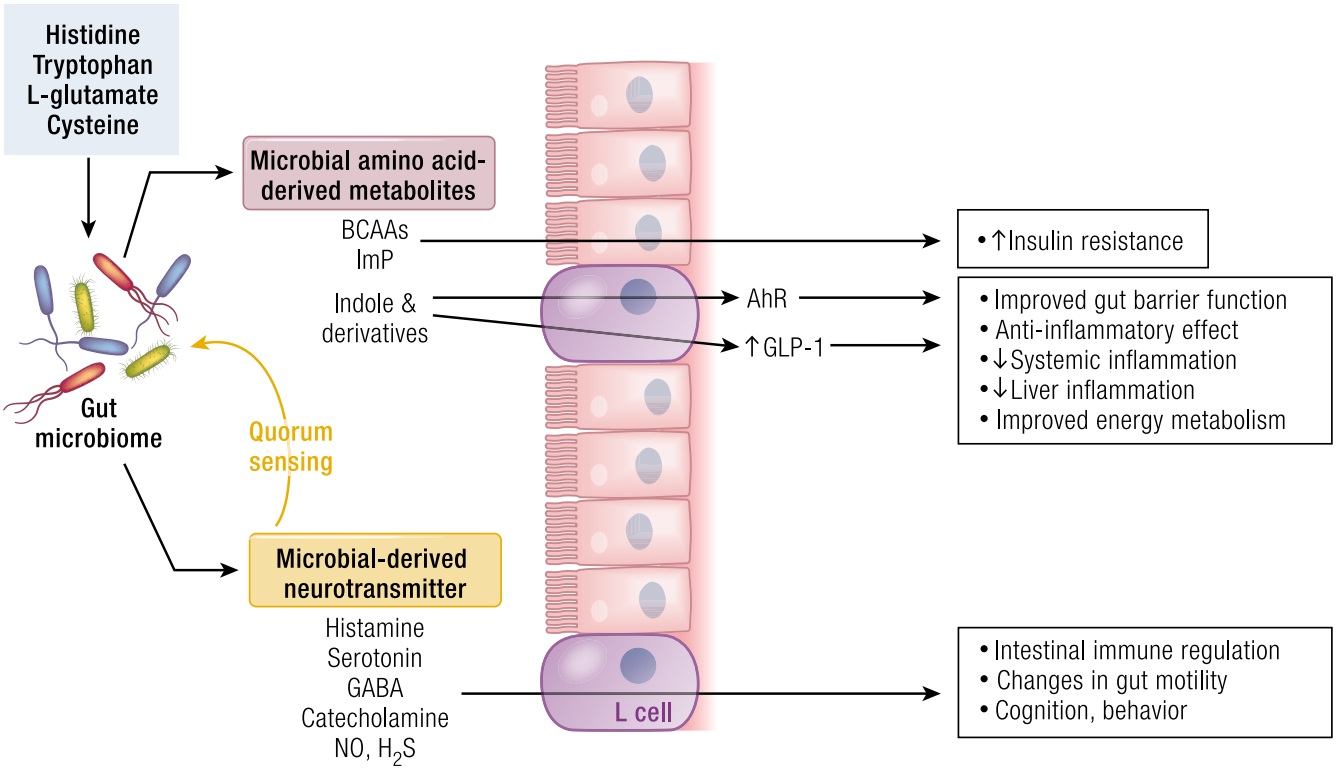


Figure 3. Microbial metabolites derived from amino acids influence host endocrine functions. Some amino acid–derived compounds negatively affect host metabolism. For example, bacterial-derived BCAAs are positively correlated with insulin resistance in humans and rodents. Imidazole propionate (ImP), a bacterial metabolite derived from histidine, also contributes to insulin resistance. Other bacterial metabolites such as indole and derivatives, produced mainly via tryptophan metabolism, have beneficial effects on host metabolism. Indole and derivatives activate the aryl hydrocarbon receptor (AhR). Gut microbes also influence host metabolism by synthesizing neurotransmitters (histamine, serotonin, GABA, catecholamine) or gaseous neurotransmitters (NO and H_2S). In addition to bacteria-to-host interaction, microbial neurotransmitters also contribute to bacteria–bacteria interaction (*i.e.*, quorum sensing), influencing microbial adaptation to the environment and pathogenesis.

because the gut microbiome of insulin-resistant people was enriched with enzymes for BCAA biosynthesis and depleted for enzyme for BCAA uptake. *Prevotella copri* and *Bacteroides vulgatus* were identified as the bacterial species driving this phenotype. *In vivo* studies confirmed the causal role of *P. copri*: administration of this bacterium to high-fat diet–fed mice increased serum BCAA levels and lowered insulin sensitivity. Although no positive correlation was found between *P. copri* abundance and homeostatic model assessment of insulin resistance in mice, the authors concluded that dysbiosis of gut microbiota affects the host serum metabolome and contributes to insulin resistance. Subsequently, other studies also reported a significant relationship between a higher proportion of BCAAs in the serum and insulin resistance (71, 72).

A recent study by Koh *et al.* (73) identified a direct link between the amino acid histidine and insulin resistance. More precisely, the microbial metabolization of histidine into imidazole propionate constitutes a major risk factor for the onset of insulin resistance and eventually type 2 diabetes (Fig. 3). Using metabolomic approaches, the authors observed higher levels of imidazole propionate in subjects with type 2 diabetes than subjects with a normal glucose tolerance (73). By using different molecular and *in vivo* models, the authors finally discovered that imidazole propionate directly contributes to glucose disorders by activating the p38γ/p62/mTORC1 pathway and subsequently inhibiting insulin receptor substrate activity. This study is one of the few examples showing how preliminary findings and correlations may ultimately be translated into mechanisms explaining how a specific microbial metabolite contributes to the onset of a metabolic disorder. However, although the study is interesting from a mechanistic point of view, it has never been demonstrated that reducing this metabolite can prevent or improve glucose metabolism. In addition, this mechanism is probably not uniquely involved in alteration of the insulin signaling pathways, because it has also been demonstrated that low-grade inflammation can contribute to insulin resistance.

Although not directly considered an amino acid, trimethylamine *N*-oxide (TMAO) is another bacterial metabolite derived from dietary choline and L-carnitine. These compounds are abundant in the diet. Numerous studies have shown that TMAO levels were strongly associated with cardiovascular risks in both human and animal studies (71, 74–76). From a mechanistic point of view, TMAO triggers platelet hyperresponsiveness and thrombosis, therefore increasing the development of atherosclerotic risk (71, 74–76).

Interestingly, because TMAO is produced by the hepatic conversion of trimethylamine (TMA) (originating from bacteria) into TMAO, recent studies have focused their attention on modulation of the bacterial enzyme responsible for transforming choline and L-carnitine into TMA. Roberts *et al.* (77) decided to use an inhibitor targeting the major microbial TMA-generating enzymes (CutC and CutD). In animal models, they demonstrated that a single oral dose of such an inhibitor reduced the levels of TMAO and platelet activation as well as thrombus formation. Therefore, this approach paves the way to using molecules targeting microbiome activity instead of changing the composition of the microbiome or the dietary sources of TMAO precursors. However, what are the potential unspecific targets on the host, is this kind of approach translationally applicable in humans harboring different risk factors, and is this approach not bypassing the expected dietary approaches for such patients? All these questions remain unanswered and warrant deeper investigation.

Microbial amino acid–derived metabolites: the good side?

Not all amino acid–derived metabolites directly correlate with insulin resistance or altered glucose metabolism. Different microbial metabolites derived from tryptophan may alter metabolism (78). For example, metabolism of tryptophan by gut microbes leads to the production of several molecules, including indoles and their derivatives (Fig. 3). In fact, different indole derivatives have been shown to act as endocrine molecules that are able to directly activate aryl hydrocarbon receptor. Among these molecules, indole-3 propionic acid (IPA), indole-3-acetaldehyde, indole-acrylic acid, indole-3 aldehyde, and indole-3 acetate have been described. For instance, IPA has been shown to improve metabolism by reinforcing the gut barrier function, increasing the immune response, and exerting anti-inflammatory effects on different animal models (79, 80). In two recent human studies, IPA was associated with a lower risk of developing type 2 diabetes, mainly by protecting β cell function and eventually increasing insulin secretion. Moreover, the abundance of this metabolite inversely correlates with low-grade inflammation (81, 82). Interestingly, in addition to the role of SCFAs in stimulating GLP-1 secretion, indole and indole-3 acetate modulate host metabolism by either reducing liver inflammation or stimulating L-cells to secrete GLP-1 (83–85).

Neurotransmitters

Gut microbes are also able to synthetize "classical" neurotransmitters derived from amino acids and gaseous neurotransmitters (Fig. 3). Those neurotransmitters have a local impact on gut physiology (*e.g.,* motility, intestinal hormone release) and a "central" impact (*e.g.,* cognition, behavior) via the link between the enteric nervous system and the brain.

First, gut microbes can secrete histamine (86). Histamine is a monoamine synthetized after decarboxylation of the amino acid histidine. Recently, Barcik *et al.* (87) showed that the quantity of histamine-secreting microbes is significantly increased in the gut of patients with asthma, suggesting that bacterial histamine could participate in the regulation of gut immunity.

Another neurotransmitter derived from amino acids is serotonin. Gut serotonin is known to have a large impact on physiological processes, including gut motility and immunity (88). Most intestinal serotonin has an endogenous origin (*i.e.,* by enterochromaffin cells) (89). Nevertheless, by using germ-free and gnotobiotic mice recolonized with specific pathogen-free fecal microbiome, Hata *et al.* (90) discovered that bacteria can produce the free serotonin *via* the deconjugation of glucuronide-conjugated serotonin by bacterial enzymes. Germ-free mice show diminished monoaminergic activity associated with an overactive hypothalamic-pituitary-adrenergic axis, suggesting that gut microbiota can affect systems implicated in the psychopathology of depression (91, 92). In support of this finding, administration of the probiotic *Bifidobacterium infantis* to conventionalized mice increased the circulating level of tryptophan, decreased the ratio of kynurenine to tryptophan, and reduced products of serotonin breakdown in the brain, suggesting that the probiotic has antidepressant properties (92). Although it is clear from this study that intestinal microbiota can affect central neurotransmission, those findings must be interpreted with caution. In fact, in treated mice no behavioral improvement was observed by forced swim test, no significant changes in central serotonin level were found, and hypothalamic-pituitary-adrenergic axis activity did not improve (measured in terms of hypothalamic expression of vasopressin and corticotrophin-releasing factor or by plasma corticosterone concentration) (92).

Numerous articles show that gut microbes can also produce γ-aminobutyric acid (GABA), and a recent review from Xu *et al.* (93) clearly describes the mode of GABA synthesis by the decarboxylation of L-glutamate catalyzed by glutamate decarboxylase. It is the case for culturable bacteria from the human gut, such as *Lactobacillus brevis* and *Bifidobacterium dentium*, which are two major producers of gut GABA (94). GABA transporters are localized on the blood-brain barrier, but they are more likely to be involved in GABA efflux (95); therefore, it is still unknown whether gut microbiota–derived GABA can reach the central nervous system.

Finally, the gut microbiome can also produce catecholamines, such as norepinephrine and dopamine (96), that have an effect on local and central physiology, as described earlier. Importantly, microbium-derived catecholamines are unlikely to exert their action directly in the brain, because they cannot cross the blood-brain barrier (97). Some authors showed that luminal gut (*i.e.,* bacterial) dopamine plays a crucial role as a proabsorptive modulator of water transport in the colon (96). However, we are only beginning to discover the role of bacterial catecholamines in host physiology.

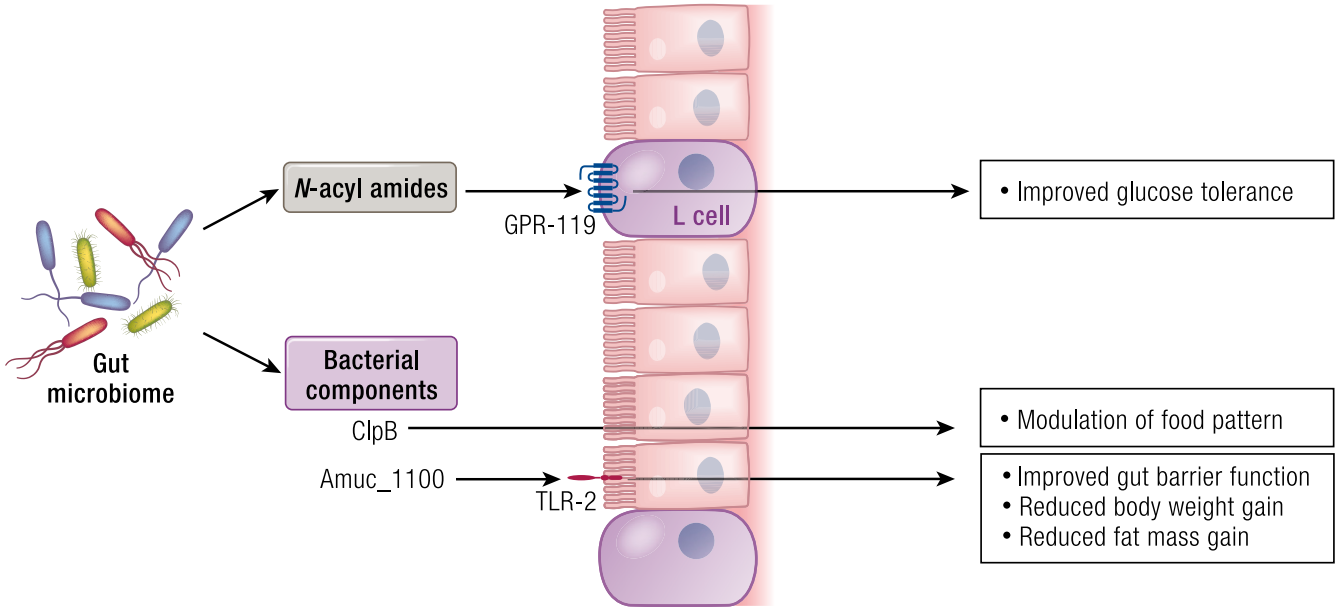
Second, gut microbes are also able to release various types of gases composed of nitrogen, oxygen, hydrogen, methane, and carbon monoxide (98, 99) (Fig. 3). As explained by Scaldaferri *et al.* (98) in a review published in 2013, "intestinal gases are the expression of metabolic activity of gut microbiota in the gut," and variations in the production of intestinal gas could be observed in some pathological states. In addition to this well-characterized metabolic activity, some bacterial-produced gases are considered as neurotransmitters or "gasotransmitters," as described for nitric oxide (NO) and hydrogen sulfide (H_2S) (100), two gasotransmitters well known to modify the gut physiology. To give some physiological examples, bacteria are able to produce NO *via* bacterial NO synthase enzyme (such as *Bacillus subtilis*) (101) and H_2S from cysteine (102). These two gaseous neurotransmitters cross the epithelium and modify gut function. Very recently, a new concept has emerged demonstrating that the inhibition of proximal gut motility improves hyperglycemia observed during type 2 diabetes (103, 104). Because NO (103, 104) and H_2S (105) exert tonic inhibition of smooth muscle cells, one could speculate that gut microbiome could have a direct impact on gut muscle relaxation and then participate in the control of glycemia *via* this novel mechanism of action.

Gut bacteria and the endocannabinoid system

Gut bacteria produce endocannabinoid mimetics and influence the host metabolism

In 2017, human gut bacteria were reported to produce *N*-acyl amide (Fig. 4). Strikingly, those microbial metabolites structurally mimic the host's endogenous bioactive lipids belonging to the endocannabinoid system (ECS) and have affinity for several host receptors in the GI tract (Table 1) (106). In particular, some of those metabolites act as strong agonists of GPR119. The endogenous ligands of GPR119 are oleoylethanolamide and 2-oleoyl glycerol (2-OG) (107, 108). Both bioactive lipids are members of the ECS, and by activating GPR119 on the enteroendocrine L-cells they trigger GLP-1 secretion and eventually regulate glucose and energy metabolism (106, 109). The structural and functional overlap between bacterial and endogenous metabolites prompted researchers to investigate the effect of microbial *N*-acyl amides on the physiology of the host. Cohen *et al.* (106) administered an engineered bacterium producing *N*-acyl amide (specifically *N*-acyl serinol) to gnotobiotic mice and investigated oral glucose tolerance.

Figure 4. Microbial metabolites and microbial components influence host metabolism. Both bacterial metabolites and bacterial components modulate host physiology by interacting with receptors expressed by the host locally (*i.e.*, in the intestine) or distally. Gut bacteria produce *N*-acyl amide, an endocannabinoid mimetic that influences host glucose metabolism *via* the GPR119 receptor. Moreover, proteins constitutively expressed by symbionts (namely ClpB and Amuc_1100) also modulate host metabolism *via* a paracrine or endocrine action. ClpB is involved in regulation of appetite, whereas Amuc_1100, expressed on the outer membrane of *A. muciniphila*, improves barrier function and partially recapitulates the beneficial effect of the live bacterium.



Treated mice exhibited better oral glucose tolerance than control mice, thus indicating that the microbial-derived *N*-acyl amide directly modulates the physiology of the host (106, 110). However, this study did not investigate whether microbiota-derived *N*-acyl amides exert their action with a paracrine or endocrine mechanism.

Does the gut microbiome modulate intestinal ECS tone or vice versa?

The aforementioned study is the only one showing that gut bacteria produce metabolites analogous to the endocannabinoids; nevertheless, several other studies have also supported the existence of crosstalk between gut bacteria and the ECS of the host. For example, the administration of *Akkermansia muciniphila*, a commensal bacterium known to prevent diet-induced obesity (111, 112), increases the intestinal levels of several 2-acylglycerols (namely, 2-OG, 2-arachidonylglycerol, and 2-palmitoyl glycerol) (111). Those 2-acylglycerols have been implicated in the control of gut barrier and inflammation, and both 2-OG and 2-palmitoyl glycerol have been shown to activate GPR119, thereby stimulating GLP-1 secretion (113, 114). However, in these particular studies, the origins of those 2-acylglycerols were unclear: were they derived from bacteria or the host? This key question remains unanswered.

In another study by our group, variations in gut microbiome composition were associated with alterations in the intestinal ECS, which in turn modulated gut permeability and endotoxemia (113). Indeed, by combining different approaches aimed at modulating the composition of the gut microbiome, such as a high-fat diet, prebiotics, probiotics, antibiotics, or germ-free mice, we discovered a colon-specific modulation of CB1 receptor expression in all these different models. In addition, the levels of bioactive lipids and the expression of enzymes belonging to the ECS in the colon were altered in response to probiotic-induced modulation of the gut microbiome (113). In another recent study we also demonstrated that deletion of the main endocannabinoid-synthesizing enzyme from the intestinal epithelial cells of mice alters the composition of gut microbiome (115).

Although these data are interesting and reveal a direct association between the gut microbiome and the intestinal ECS, numerous questions remain to be addressed. For example, does variation in the composition of the gut microbiome modulate ECS tone? Alternatively, does modulation of the intestinal tone of endocannabinoids drive the alterations in the gut microbiome composition?

Indeed, intestinal endocannabinoids act locally to modulate peristalsis and food intake (116, 117). Therefore, a conceivable hypothesis is that the host's ECS contributes to shape gut microbiome composition by modulating those two variables.

Gut microbiome–ECS crosstalk: beyond the intestine

Crosstalk between the gut microbiome and the ECS is not limited to the intestine. Actually, we observed crosstalk between the gut microbiome and adipose ECS. Almost a decade ago we observed that, similar to the data observed in the colon, changes in gut microbiome composition (induced by prebiotics and antibiotics) modulated the levels of bioactive lipids in adipose tissue and the expression of receptors and enzymes belonging to the ECS (113). More recently, deletion of NAPE-PLD (the main enzyme synthesizing bioactive lipids of the ECS) in adipocytes was shown to induce a shift in the composition of the gut microbiome (118). Strikingly, after consuming a normal diet, adipocyte NAPE-PLD–deficient mice develop obesity, glucose intolerance, and adipose tissue inflammation. The mechanism is directly associated with a decrease in adipose tissue browning and beiging. The mice are unable to maintain their body temperature upon cold exposure. This study was the first to show a direct link between the gut microbiome and adipose tissue browning processes. More strikingly, antibiotic treatments abolished the phenotype linked to deletion of the NAPE-PLD in adipose tissue. Additionally, transferring gut microbiota from knockout mice to germ-free mice transferred the phenotype of obesity and lack of beiging processes. This finding was clearly associated with major changes in levels of bioactive lipids and eventually confirmed the strong association between gut microbes and the endocrine activities of adipose tissue (118). In conclusion, many aspects of this exciting subject remain largely unknown and clearly merit further investigation.

Bacterial components: the new frontiers of endocrine factors

As detailed in previous sections of this review, bacterial metabolites influence the host metabolism, but specific bacterial components may also act as factors modulating host endocrine functions. Recent evidence has provided insights into some constitutive microbial proteins that are able to influence host physiology. Notably, this topic is a new field of investigation in this area of research.

In 2014, a bacterial protein mimicking the host's hypothalamic peptide was identified *via* a proteomic approach (119). Specifically, bacterial caseinolytic protease B (ClpB) showed sequence homology with host peptide α-melanocyte-stimulating hormone. Mice immunized with ClpB exhibit increased levels of the α-melanocyte-stimulating hormone autoantibody and increased food intake compared with control mice (119). Consistent with these findings, mice force fed with the wild type strain of *Escherichia coli* exhibit altered food behaviors compared with mice administered a strain of *E. coli* lacking ClpB, thus confirming the involvement of ClpB in the modulation of the host's food pattern (119). In humans, eating disorders are associated with autoantibodies against neuropeptides (120, 121), consistent with the higher plasma ClpB levels detected in patients with eating disorders than in healthy subjects (122).

The same team of researchers also suggested an autoantibody-independent role for ClpB in modulating food intake. Indeed, a colonic infusion of proteins from *E. coli* (containing ClpB) stimulates the release of intestinal anorexigenic hormones, whereas intraperitoneal administration of the proteins activates anorexigenic neurons in the hypothalamus (123).

Evidence of a role for bacterial proteins in modulating host metabolism was also provided by the study by Plovier *et al.* (112). Indeed, in their study they found that daily oral administration of the bacterial protein Amuc_1100, expressed on the outer membrane of *A. muciniphila,* improves the gut barrier function and partially recapitulates the beneficial effects of the live bacterium (112). The proposed mechanism involves activation of a receptor of the innate immune system, Toll-like receptor 2.

Along the same lines, a recent study has described the production of some proteins displaying high homology with human peptide hormones, such as insulin and IGF-1, by viruses of the human microbiome. *In vitro* and *in vivo* studies have shown that those viral insulin/IGF-1–like peptides modulate the host's physiology (124).

It Is Not Only About Bacteria–Host Interaction

Up to now we have focused mainly on bacteria–host interaction. Nevertheless, it is important to highlight that some of the bacterial metabolites described earlier can also target or be sensed by the gut bacteria themselves, thus contributing to a cell-to-cell interaction known as quorum sensing. For instance, SCFAs have beneficial or inhibitory role on pathogen colonization, depending on their concentration (125, 126). Moreover, bacteria-produced biogenic amines can also modulate bacterial behavior. For instance, histamine is produced by the bacteria to maintain intracellular pH homeostasis and can be used to generate energy by exploiting proton motive force (126). On the other hand, serotonin, adrenaline, and noradrenaline are sensed by pathogens and play a role in pathogenesis (126–128). NO is also sensed by bacteria and regulates cell-to-cell interaction (129, 130). However, nothing is known about the role of NO in the GI tract in the contest of quorum sensing.

Overall, concerning the gut microbiome, bacteria-to-bacteria interaction is still a new field of investigation [for review, see (125, 126)]. We firmly think that this subject warrants further investigation. Undeniably, the

intestinal microbiome is an extremely complex and dynamic community of living bugs constantly competing for nutrients and survival, and therefore cell-to-cell interaction surely plays a major role in shaping the composition of the gut microbiome.

Conclusions

Currently, in experimental models the role of the gut microbiome as an endocrine organ is undeniable and supported by numerous data. Nevertheless, the precise roles of the different microbes that reside in our gut and their incredible capacities to generate complex molecules has opened Pandora's box. Indeed, the development of novel high-throughput sequencing techniques designed to decipher the composition of the gut microbiome has led to an incredible number of publications. However, the causality between gut microbes and host diseases remains poorly defined and sometimes over-interpreted (1, 131). Certainly, numerous studies have linked the composition of the gut microbiome (at both taxonomic and functional levels) with different diseases. In addition to these correlations, most studies that have identified potential mechanisms have been performed in rodents and warrant confirmation in humans. Although the use of animal models is often viewed as caveat, we must acknowledge that this field of investigation is blooming and represents a new era of research in the field of endocrinology. However, we are still far from using microbial metabolites or specific gut bacteria to replace drugs currently used to target the endocrine system. It is also important that scientists jumping into the field remain cautious when concluding that one metabolite or one bacterium explains the overall phenotype observed. As a matter of fact, integrative physiology is the result of complex interactions occurring between different cells or organs, finely tuned. Nevertheless, we anticipate that numerous microbial components that are able to influence the host's physiology will be discovered, and some will become future therapeutics.

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Correspondence and Reprint Requests: Patrice D. Cani, PhD, UCLouvain, LDRI, WELBIO (Walloon Excellence in Life Sciences and Biotechnology), Metabolism and Nutrition Research Group, Avenue Emmanuel Mounier, 73 Box B1.73.11, B-1200 Brussels, Belgium. E-mail: patrice.cani@uclouvain.be.

Disclosure Summary: P.D.C. and C.K. are co-founders of Enterosys S.A. (Labège, France). P.D.C. is co-founder of A-Mansia Biotech S.A. (Belgium) and inventor on patent applications PCT/EP2013/073972, PCT/EP2016/071327, and PCT/EP2016/060033 (filed in the European Patent Office, Australia, Brazil, Canada, China, Eurasian Patent Organization, Israel, India, Hong Kong, Japan, South Korea, Mexico, New Zealand, and the United States) for the therapeutic use of *A. muciniphila*. M.R. has nothing to disclose.

Abbreviations

2-OG, 2-oleoyl glycerol; BCAA, branched-chain amino acid; ClpB, caseinolytic protease B; ECS, endocannabinoid system; GABA, γ-aminobutyric acid; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; H_2S, hydrogen sulfide; IPA, indole-3 propionic acid; NO, nitric oxide; PYY, peptide YY; SCFA, short-chain fatty acid; TMA, trimethylamine; TMAO, trimethylamine *N*-oxide.