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Microbiome response to diet: focus on obesity and related diseases

Nathalie M. Delzenne[1] · Julie Rodriguez[1] · Marta Olivares[1] · Audrey M. Neyrinck[1]

Abstract
Numerous studies in humans and animal models describe disturbances of the gut microbial ecosystem associated with adiposity and hallmarks of the metabolic syndrome, including hepatic and cardiovascular diseases. The manipulation of the microbiome, which is largely influenced by the diet, appears as an innovative therapeutic tool to prevent or control obesity and related diseases. This review describes the impact of nutrients on the gut microbiota composition and/or function and when available, the consequences on host physiology. A special emphasis is made on the contribution of bacterial-derived metabolites in the regulation of key gut functions that may explain their systemic effect.

Keywords Microbiota · Metabolic disorders · Obesity · Nutrition

1 The role of the gut microbiota in host physiology

Microbial cells are present in numbers (~10^{14}) as compared to human cells with an overwhelming majority (> 99%) located in the gut [1]. The gut microbiome contains all domains of microbial life at very different relative concentrations in term of total DNA: bacteria (~93%), vira (~5.8%), Archaea (~0.8%), Eukarya (~0.2%), and fungi (~0.1%) [2]. Although recent works highlighted that fungi, protozoa and microbial eukaryotes constitute a smaller but potentially important part of the gut microbiome, bacteria and Archaea have received most of the attention in human microbiome studies [1, 3, 4]. The gut bacteria belong mostly to 5 phyla which populate the large intestine. Approximately 90% of bacterial species belong to the phyla Firmicutes (i.e. *Bacillus* spp.) and Bacteroidetes (*Bacteroides* spp.), with the other important phyla being Actinobacteria (*Bifidobacterium* spp.), Proteobacteria (*Escherichia, Helicobacter*), and Verrucomicrobia (*Akkermansia* spp.) [5]. However, there is a large diversity between subjects, which confers a high interindividual variability in terms of microbiome composition [6].

✉ Nathalie M. Delzenne
nathalie.delzenne@uclouvain.be

[1] Metabolism and Nutrition Research Group, Louvain Drug Research Institute, UCLouvain, Université catholique de Louvain, Brussels, Belgium

The gut microbiota interacts with the "host" organisms by several ways. The gut microbiota, and more precisely some bacterial metabolites or components, are able through the interaction with specific receptors, by modulating cell host gene expression or post-translational processes, or simply by acting as metabolic substrates in eukaryotic cells, to influence host immunity, metabolism, neuro-endocrine function, and behavior [7–11]. For example, short chain fatty acids (SCFA) such as acetate, propionate, or butyrate, produced upon the microbial fermentation of carbohydrates and fibers, may influence the production of gut hormones (like glucagon-like peptide 1) by the endocrine L cells, thereby having a beneficial impact on appetite or glucose homeostasis [12–14]. However, as detailed later on, even if SCFA like butyrate are often considered as interesting bioactive metabolites in the control of health and physiology, an increase in fecal SCFA has also been correlated with obesity. Other bacterial co-metabolites (meaning metabolites produced from sequential microbial and host enzymes), like bile acids, may also modulate the endocrine function of the gut [15]. The last section of this review will elaborate the molecular mechanisms involved in the regulation of host metabolism by the bacterial co-metabolites.

In the field of obesity and related metabolic disorders, a lot of studies have been done in order to evaluate the characteristics of the gut microbes that can be associated with the presence of obesity, but also and mostly with the occurrence of related pathologies such as diabetes, cardio-metabolic risk, and more recently, psychological disorders [16–18]. The gut microbiota from twins discordant for obesity modulate adiposity and metabolic phenotypes when inoculated in mice [19], supporting a causal role of the gut microbiota in the

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occurrence of the metabolic disorders. A *contrario*, the inoculation of the gut microbiota (fecal material transfer, FMT) from non-diabetic patients to diabetic individuals allows to improve insulin resistance in part of the cohort. The effect, when present, is reversible- even if it persists several weeks after the FMT. The efficacy of the approach is clearly dependent on the recipient gut microbiota composition [20].

Multiple meta-analyses have investigated the differences in the gut microbiomes of obese and lean patients [21–25], one concluding that *Roseburia* and *Mogibacterium* are significantly enriched in obese individuals whereas *Anaerovorax*, *Oscillibacter*, *Pseudoflavonifractor*, and *Clostridium* IV are depleted [24]. In the most recent meta-analysis, they concluded that obesity is associated with high levels of short chain fatty acids (SCFA, acetate, propionate and butyrate) but not gut microbiota richness at the phylum level [25]. In fact, the extent of the microbial changes is very variable across studies and seems to be highly dependent of potential confounders, especially the diet.

The nutrition of the individuals appears as the most important element that shapes the gut microbiome [26]. Conversely, the gut microbiota characteristics may influence the response to dietary intervention. The tie between diet and gut microbiota may partly explain why microbiota alterations are associated with an obese phenotype in observational studies in humans (for a systematic review [27]), and can also explain the interindividual response to dieting in the specific context of obesity [28, 29]. For those reasons, we will first illustrate how energy intake, dietary habits but also specific nutrient ingestion, may influence the gut microbiota composition and activity, thereby having an influence on host metabolism.

2 Effect of nutrition on gut microbiota composition and activity in the context of obesity

Gut microbiota composition can be highly variable between individuals and diet is thought to explain over 50% of these microbial structural variations in mice and 20% in humans signaling the potential for dietary strategies in disease management through gut microbiota modulation [30, 31]. Changes in diet have been shown to rapidly affect the composition of the gut microbiota [26]. Although time of intake and eating patterns have recently been shown to significantly affect gut bacterial makeup, diet composition remains the primary modulator of bacterial richness and abundance in the gastrointestinal tract [32]. Fiber and macronutrient (fat, sugar, and protein) contents are especially important in determining microbiota composition and its effect on health outcomes and behavior.

2.1 Impact of energy intake and weight loss-driven dieting on gut microbiota

Numerous animal studies demonstrated that high caloric diet, in particular high-fat (HF) diet, induced dysbiosis contributing to obesity-related metabolic disorders (for review, see [33]). Modulation of the gut microbiota by dietary shifts is complex and also confounded by host metabolic responses to specific diets. HF diets have been shown to alter richness of the microbiota [34]. The microbiota analysis, often performed in caecal content in mice studies, allowed to point out in most studies, a shift in phyla (with an increase in Firmicutes and a decrease in Bacteroidetes), as described in the first studies relating dysbiosis in humans; however, a controversy exists showing, in some studies, the inverse shift in phyla proportion [35, 36]. More specific changes in bacterial populations have also been described such as a decrease in Verrucomicrobia (*Akkermansia muciniphila*), a mucin-degrading bacterium that has been inversely associated with body fat mass and glucose intolerance in mice [37]. In humans, it was shown that subjects with higher *A. muciniphila* and gene richness are metabolically healthier before and after the dietary intervention consisting into 6-wk energy-restricted, high-protein diet followed by another 6 wk. of weight maintenance [38]. It is known that diets proposed to lose weight in humans that are based on a high intake of protein but low intake of fermentable carbohydrate, may alter microbial activity and bacterial populations in the large intestine and thus impact on gut health. One study reported that the *Roseburia* spp. and *Eubacterium rectale* subgroup of cluster XIVa decreased as carbohydrate intake decreased in healthy obese volunteers [39]. In addition, the abundance of those butyrate-producing bacteria well correlated with the decline in fecal butyrate. It is unknown whether the relatively short period of reduced butyrate and short-chain fatty acids (SCFA) supply to the colonic mucosa would have long-term consequences for gut health. Such considerations may become important if low-carbohydrate diets are consumed for longer periods without ensuring that adequate forms of appropriate fermentable substrates comprise part of the diet. In a more recent study, they demonstrated that short-term caloric restriction (CR) increased *Lactobacillaceae, Erysipelotichaceae*, *Bacteroidaceae* and *Verrucomicrobiaceae*, the latter represented by *A.muciniphila* [40]. Those microbiota alterations during CR dictates the tone of the immune response and contributes to the increased fat cell browning, fat loss, and to several metabolic improvements such as increased insulin sensitivity. Rapid weight loss using a very low-calorie diet (VLCD) is effective in short term studies or to prepare morbidly obese subjects for bariatric surgery [41]. These diets are typically very low in carbohydrate and fat content while keeping an optimal protein content. The effects of VLCD inducing 10% weight loss on fecal microbiota and bile acid content and composition were examined in obese women [42]. This study shows that the core microbiome was preserved

during VLCD-induced weight loss, but with a reduction in the abundance of the genus *Roseburia* whereas the abundance of a bacteria from *Christensenellaceae* family (unknown genus) increased. In addition, a significant fall in fecal total bile acid concentration and reduced deconjugation and 7-α-dihydroxylation accompanied those changes and individual fecal bile acids correlated with altered gene expression pathways in adipose tissue. While only a few potential microbial metabolites such as SCFA and secondary bile acids with bioactive properties have been often studied, many other microbial metabolites are currently being explored or remain unknown.

2.2 Impact of various dietary habits on gut microbiota

Dietary habits (Western, Agrarian and Mediterranean omnivore diets, vegetarian, vegan and gluten-free diets) drive the composition of the gut microbiota and metabolome [43]. The short-term consumption of diets composed entirely of animal or entirely of plant products differently alters microbial community structure and overwhelms inter-individual differences in microbial gene expression [26]. The animal-based diet increased the abundance of bile-tolerant microorganisms such as *Alistipes, Bilophila*, and *Bacteroides* whereas the levels of Firmicutes that metabolize dietary plant polysaccharides (*Roseburia, Eubacterium rectale*, and *Ruminococcus bromii*) decreased [26]. Observational studies including cross-sectional and cohort studies can provide association between dietary habits and gut bacteria, while we are limited by the ability to reveal causal relationships. Westernized diet, defined as high dietary intake of saturated fats and sucrose and low intake of fiber, clearly contribute to the increased occurrence of diabetes and obesity in countries adapting a westernized lifestyle [44]. Western diet induced a less diverse microbiome in US individuals than their rural counterparts whose diet is dominated by plant-based polysaccharides such as corn and cassava [45]. Similarly, traditional diet low in fat and animal protein, and rich in starch, fiber, and plant polysaccharides showed higher diversity in the gut microbiota of children living in a village of rural Africa than those from Europe countries adhering to a typical Western diet, high in fat, animal protein, and sugar, but low in fiber [46]. African children showed a significant enrichment in Bacteroidetes and depletion in Firmicutes with a unique abundance of bacteria from the genus *Prevotella* and *Xylanibacter*, known to contain a set of bacterial genes for cellulose and xylan hydrolysis, completely lacking in the EU children. Conversely, *Enterobacteriaceae* (*Shigella* and *Escherichia*) were significantly underrepresented in African than in European children. In addition, more SCFA were found in African than in European children. The authors surmise that the increase in the Firmicutes/ Bacteroidetes (F/B) ratio in European children, probably driven by their high-calorie diet, might predispose them to future obesity suggesting that this ratio may be considered a useful obesity biomarker. Other diets reported to be associated with changes in gut microbiota composition include Mediterranean diet, vegan diet and vegetarian diet [47–50]. The Mediterranean diet is useful in the prevention of overweight, obesity and metabolic disease. Results obtained in a study investigated in overweight/obese subjects indicate that Mediterranean diet rich in high quality-extra virgin olive oil induces an increase of lactic acid bacteria and could have a potential role in the prevention of inflammation. Another study demonstrated that consumption of two healthy dietary patterns improving insulin sensitivity (Mediterranean diet with 35% of calories as fat (22% MUFA fat, 6% PUFA fat and < 10% saturated fat) and a low-fat diet with <30% total fat (<10% saturated fat, 12%–14% MUFA fat and 6–8% PUFA fat)) restored microbiota dysbiosis in obese individuals [51, 52]. Interestingly, the F/B ratio decreased whereas *Bacteroides, Prevotella* and *Faecalibacterium* genera increased in the obese group after 2 years of consumption of those healthy diets as compared with the baseline. In addition, the consumption of the Mediterranean diet for 2 years increased the abundance of *Ruminococcus* genera and *P. distasonis* as well as butyrate-producing bacteria and/or anti-inflammatory bacterial species like *Roseburia* and *F. prausnitzii*, whereas the consumption of the low-fat diet did not affect the abundance of these genera. In contrast, the consumption of the low-fat diet for 2 years decreased the abundance of *Streptococcus* and *Clostridium* genera whereas the consumption of the Mediterranean diet did not affect the abundance of these genera. It was suggested that high-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome [47]. It is important to emphasize that one recent study revealed that circulating branched-chain amino acids (BCAAs)-valine, leucine, and isoleucine-are significantly lower in vegetarian subjects than those in the omnivorous group [49]. In line with the lower concentrations of BCAAs, meta-transcriptomic analysis shows that the gut microbial pathway for the degradation of BCAAs is significantly upregulated among vegetarians compared with the omnivores. This association remained to be investigated into obese people.

Even if it is controversial, an increase in Firmicutes and a decrease in Bacteroidetes were reported in obese mice and humans with high BMIs [53, 54]. Intake of whole foods, such as cereals, fruits and vegetables, produced anti-obesity effects and may confer health benefits to the host. However, consumption of whole foods may lead to a decrease in abundance of Firmicutes (e.g. navy bean consumption [55]) and *Clostridium* (e.g. tomato and pomegranate juice consumption [56]) whereas some of them increased the abundance of Bacteroidetes and its members (*Bacteroides, Prevotella*) in obese mice (e.g. lingonberry, strawberry, navy bean [55, 57–60]).

2.3 Impact of dietary fibers on gut microbiota in obesity

Almost all types of dietary fiber (DF) are fermentable, entirely or to some degree [61]. Some fibers are rapidly fermented by

the colonic microbiota, whereas others are fermented more slowly, and in some instances to a limited extent. However, a classification according to the fermentability has not been yet established since the evaluation has not been performed systematically for all DF. The importance of DF for gut microbiota composition and function has been extensively studied. DF may modify microbiota abundance, diversity and metabolism including SCFA production. An interesting systematic review published in 2020 reported all intervention studies performed upon the past 20 years with intact cereal fibers, their active subfractions, and their effect on gut microbiota composition, in healthy adult subjects [62]. Despite the common characteristic of being non-digestible in the human small intestine, the DF widely differ from each other by their chemical structure, that influences their fermentation, by the bacterial enzymatic systems. We focused our description on DF with prebiotic properties, defined as a "substrate that is selectively utilized by host microorganisms conferring a health benefit" [63]. One of our review summarizes the main effects of DF with prebiotic properties in intervention studies in humans, with a particular emphasis on the effects of arabinoxylans and arabinoxylo-oligosaccharides on metabolic alterations associated with obesity [61]. More recently, Nie et al. reported all intervention studies in which gut microbiota, satiety, energy intake, postprandial glucose, insulin resistance, and low-grade inflammation were improved due to nondigestible oligosaccharides supplementation in obese humans [64]. Importantly, a multicenter intervention trial in obese patients presenting co-morbidities has been conducted during the FOOD4GUT project devoted to better understand how inulin-type prebiotics present in food play a role on gut microbiota homoeostasis and health (https://sites.uclouvain.be/FOOD4GUT/). It consists in a single blind randomized control trial in which obese patients were asked to consume 16 g native inulin daily combined with recipes based on vegetables naturally rich in inulin-type fructan for 10–16 weeks. As expected, we observed an important increase in the relative abundance of Actinobacteria and *Bifidobacterium* which is in line with the recent systematic review of human studies in adult individuals showing the effects of inulin on the gut microbiome [65]. However, the large increase in *Bifidobacterium* appears as a signature of inulin intake rather than a driver of prebiotic-linked biological outcomes [66]. In fact, the prebiotic decreased also specific bacteria, *Desulfovibrio* and *Clostridium* sensu stricto that were associated with the improvement of anthropometry.

2.4 Impact of lipids on gut microbiota in obesity

Several studies have reported an important role of dietary lipids on the gut microbiota composition and function [67]. These interactions between lipids and gut microbiota result in the control of body weight and energy metabolism and have been well documented during the last decade. However, the effects of the qualitative modulation of dietary fatty acid content on the gut microbiota composition and the consequences on the host metabolism is poorly described. An elegant study assessed the impact of different fat sources on the gut microbiota composition by feeding mice isocaloric diets that differed in fat composition (lard or fish oil, enriched in saturated or polyunsaturated lipids, respectively) [68]. After 11 weeks, saturated lipids from lard promoted obesity, increased inflammation in white adipose tissue and induced significant changes in the gut microbiota composition. Indeed, a lard-enriched diet led to a lower bacterial diversity associated with an increase of *Bacteroides*, *Turicibacter* and *Bilophila* genera whereas it decreased *Bifidobacterium* and *Adlercreutzia* (from Actinobacteria), *Lactobacillus* and *Streptococcus* (two-lactic acid producers) and *Akkermansia* genera. Very nicely, the transfer of gut microbiota from mice fed polyunsaturated lipids from fish oil counteracted both adiposity and inflammation observed into recipient mice fed lard, proving that gut microbiota contributes to phenotypic differences in mice fed lard or fish oil [68]. Another study showed that different dietary fat profiles led to distinct intestinal and metabolic outcomes that are independent of obesity [69]. Indeed, HF diet with saturated lipids induced insulin resistance, gut permeability and mesenteric fat inflammation, whereas HF diet enriched with n-6 or n-3 fatty (FA) did not. The authors highlighted an increase of H_2S-producing bacteria in response to HF diet with saturated FA only, and an association between *Bilophila* and the gut permeability.

Mice born from a mother fed a diet depleted in n-3 polyunsaturated FA, and maintained on this type of diet for several months, exhibit a decrease in caecal tissue and content weights, suggesting a lower caecal fermentation [70]. This is associated with a decrease of body weight and the development of hepatic steatosis, as compared to mice fed a standard diet [70]. A second similar experiment showed that mice fed with a diet depleted in n-3 PUFA exhibit a higher amount of bifidobacteria and a lower level of *Lactobacillus* spp. and *Bacteroides-Prevotella* in their caecal content, compared to mice fed with a standard diet [71]. In response to diet, the gut microbiota is able to modulate host physiology through the production of bioactive metabolites from lipids. The implication of the gut microbiota in the production of PUFA-derived metabolites has been demonstrated by a higher level of these metabolites in the colonic content of conventionalized mice upon a low-fat diet, compared to germ-free mice, despite a similar PUFA proportions. Additionally, a western diet significantly decreases the levels of PUFA-derived metabolites in conventionalized mice. Interestingly, in a cohort of obese women, some of these PUFA-derived bacterial metabolites are positively correlated with specific fecal bacteria (*Bifidobacterium* spp., *Eubacterium ventriosum* and *Lactobacillus* spp.) and inversely correlated with serum cholesterol (total, LDL, HDL) [72]. One recent systematic review

aimed to summarize the results of available studies in humans on dietary fat intake (quantity and quality), the intestinal microbiota composition and related cardiometabolic health outcomes [73]. They conclude that HF and high SFA diets can exert unfavorable effects on the gut microbiota and are associated with an unhealthy metabolic state. Also, high MUFA diets may negatively affect gut microbiota whereas PUFA do not seem to negatively affect the gut microbiota or metabolic health outcomes. However, data are not consistent and most randomized controlled trials and observational studies showed risks of bias.

2.5 Impact of protein on gut microbiota in obesity

Dietary proteins and amino acids are important substrates for microbial fermentation in the gut, where they also serve as an important nitrogen source for the microbiota [74]. Recent findings reported that microbial protein fermentation could also alter the gut microbiota [74]. Indeed, substantial amounts of even easily digestible proteins can escape assimilation in healthy humans [75]. These proteins are used as substrate by bacteria, resulting in the release of peptides and amino acids and the apparition of secondary metabolites including ammonia, short or branched-chain fatty acids, hydrogen sulfide, phenolic or indolic compounds [76]. Many microbial species could contribute to the proteolytic fermentation and this process is limited to the distal colon where metabolic products accumulate [76]. It has been demonstrated that a high-protein diet could quickly modified the gut microbiota composition and rapidly enhanced the synthesis of secondary metabolites in both in vitro and clinical models [26, 77]. Microbial activity mirrored differences between plant- and animal-based diets, reflecting differences between carbohydrate and protein fermentation [26]. The impact of a high-protein diet on the gut microbiota composition, according to different sources of protein, has been previously studied in a randomized, double-blind, parallel trial performed in overweight participants [78]. This trial demonstrated that 3-weeks of consumption of high-protein diet did not alter the fecal microbiota composition but altered bacterial metabolite production. Interestingly, some of these effects depend of the source of proteins. For instance, both casein and soy as protein source induced the decrease of fecal butyrate and an increase of amino acids-derived metabolites, confirming a shift from carbohydrates to protein fermentation by the gut microbes [78]. Finally, the relative fecal concentrations of branched-chain amino acids (BCAA) were higher in the casein group, compared to soy protein and the placebo. Interestingly, the authors highlighted positive correlations between amino acids degradation and the abundance of some bacterial genera (such as O*scillospira, Butyricimonas* or *Odoribacter*). In humans, a high-protein and low-carbohydrate diet resulted in increased proportions of branched-chain fatty acids (BCFA) and concentrations of phenylacetic acid and N-nitroso compounds [79]. This was associated with decreased concentrations of butyrate and a reduction of *Roseburia/Eubacterium rectale* group of bacteria. Glutamate was also associated with deleterious effects on organism [80]. Indeed, serum glutamate concentrations decreased in obese individuals and was negatively correlated with the abundance of *Bacteroides thetaiotaomicron*, glutamate-fermenting bacteria. Gavage with *Bacteroides thetaiotaomicron* in mice reduced the diet-induced body weight gain and the plasma glutamate concentrations. Very interestingly, weight-loss intervention such as bariatric surgery also improved metabolic alterations, partially reverted the decreased abundance of *Bacteroides thetaiotaomicron* and regulated glutamate concentrations [80].

The intestinal microbiota metabolism of L-carnitine, a trimethylamine present in red meat, also produces a metabolite associated with harmful effects on health, the trimethylamine-N-oxide (TMAO) [81, 82]. This metabolite contributed to the development of atherosclerosis in mice and was associated with a higher risk of cardiovascular disease in humans.

2.6 Impact of phytochemicals on gut microbiota in obesity

Phenolic compounds, usually called polyphenols and present in fruits, vegetables, grains, and other plants, can be degraded by the gut bacteria into various metabolites. In addition, polyphenols and their metabolites can modulate gut microbiota. Approximately 8000 structures of polyphenols have been identified and have been subclassified into four main groups: flavonoids (including eight subgroups), phenolic acids (such as curcumin), stilbenoids (such as resveratrol), and lignans [83]. Studies have reported that only few polyphenols can be absorbed in the small intestine. The remaining (90–95%) non-absorbed polyphenols reach the colon in high concentrations (up to mM range), where they are metabolized, often through deglycation and hydrolysis, by microbial enzymes into metabolites that can be absorbed [28]. Thus, the gut microbiota can regulate the health effects of polyphenols, namely by allowing their metabolism into bioactive compounds available for host [84]. Polyphenols have been extensively studied over the past decade because of their strong antioxidant and anti-inflammatory properties [83]. They currently interest the research community because of their potential role in reducing obesity [85]. For an up-to-date review on plant polyphenols and their effects on gut microbiota and/or obesity in preclinical studies, see Carrera et al. [83] Plant polyphenols can therefore meet the criteria of prebiotics, although far more studies in the target host are required [63]. The traditional Mediterranean diet is characterized by a high phenolic-rich foods intake. One of the mechanisms involved in weight loss in which polyphenols may have a role is a prebiotic effect for gut microbiota [86]. Some polyphenols were reported to

decrease fecal SCFAs in obese rats and, consequently, prevent weight gain in association with the changes in the bacterial composition of the gut microbiota by increasing *Faecalibacterium* spp., *Lactobacillus* spp., and *Bacteroidetes* phylum proliferation [87]. In addition, the potential prebiotic effect of proanthocyanidin on *A. muciniphila* has been described by Anhê et al. [88]. This last study promotes the consumption phytochemical-rich fruits as a safe and easily implementable nutritional strategy to trigger the expansion of *A. muciniphila* and other potentially beneficial bacteria in the gut microbiota to alleviate several detrimental features of the metabolic syndrome.

3 Microbial co-metabolites as molecular drivers of the effect of nutrients in the management of obesity

Several data strongly support the hypothesis that some gut-related metabolites, as well as components released or secreted by gut microbes, could link the gut microbial changes and could be part of the beneficial effects observed upon manipulation of the gut microbiota. In this section, we will concentrate on the current hypothesis of a beneficial role potentially driven by the bacterial components or metabolites in the management of metabolic syndrome and obesity.

3.1 A key role for short chain fatty acids?

Studies assessing the effect of diet interventions on the microbiota composition and activity have mostly focused on DF, which well known as important dietary substrates for bacterial fermentation. The resulting production of SCFA as metabolites allowed to establish for the first time a molecular link between bacterial activity towards nutrients, and host physiology [7, 89]. Consistently, emerging data conducted on mice have shown that SCFA supplementation alleviated stress-induced increase in intestinal permeability as well as selective and enduring alterations induced by repeated psychosocial stress supporting their mediational role in the microbiota–gut–brain axis crosstalk and future research into microbiota-targeted therapies for stress-related disorders [7, 90]. SCFA are mainly produced in the colon by bacterial fermentation of carbohydrates that escaped digestion in the small intestine. The majority of SCFA (up to 95%) are rapidly absorbed by the colonocytes resulting in decreasing concentrations from the proximal to distal colon. Only a minor fraction of SCFA (about 5%) is excreted in faeces [91]. The fraction that is not consumed by the colonocytes is transported across the basolateral membrane and reaches the liver via the portal bloodstream. SCFAs have been shown to affect the host through multiple mechanisms including the regulation of histone acetylation and methylation, G protein coupled receptors (GPCRs), facilitating the secretion of various hormones (e.g. GLP-1 and PYY) and neurochemicals (e.g. serotonin) and the induction of vagus nerve signaling [89, 92]. Although an increase in fecal SCFA has also been correlated with obesity, increasing evidence supports a beneficial role for SCFA in adipose tissue, skeletal muscle and liver substrate metabolism and function, thereby contributing to improved insulin sensitivity (for review, see [93]). For instance, 6 months of acetate injections in obese rats improved the expression of glucose transporter glut4 and activated AMPK protein by increasing the AMP/ATP ratio in abdominal muscles [94]. Surprisingly, SCFA-mediated activation of GPR43 seemed to suppress insulin signaling only in adipocytes, but not in the liver and skeletal muscles, leading to an inhibition of fat accumulation [95]. These data suggest an important role of SCFA in glucose metabolism and control. However, human SCFA intervention studies are still needed to confirm the role of SCFA in glucose homeostasis and insulin sensitivity. Acetate is used by the liver as a precursor for the synthesis of long-chain fatty acids and cholesterol. A recent study in obese individuals showed an inverse association between serum acetate levels and visceral adipose tissue and suggest that colonic acetate only slightly contributes to hepatic lipogenesis in individuals following a Western-type diet [96]. In mice, it was shown that acetate derived from colonic fermentation of fermentable carbohydrates crosses the blood–brain barrier and directly suppresses appetite through central hypothalamic mechanisms [97]. Propionic acid is often the second most predominant SCFA and has received much attention for its potential roles in the reduction of lipogenesis, cholesterol synthesis inhibition, and more recently for its activation of G protein-coupled receptors (GPR) 41 and GPR43, release of satiety hormones and other metabolic and anti-inflammatory effects [91]. Indeed, it has been demonstrated that addition of a mixture of SCFA enriched in propionate, in a HF diet, decreased the liver triglycerides content and reduced the mRNA levels of markers involved in lipid metabolism (Fasn, Scd-1, Acly and, Acacb) [98]. Butyrate also had a beneficial impact on insulin sensitivity in HF diet mice and increased fatty acid oxidation in skeletal muscles [99]. Overall, the relationships between the microbiota composition, intestinal SCFA levels and obesity are far from being elucidated.

Besides those well-known SCFA, lactate and succinate are intermediates in the fermentation process of carbohydrates. In healthy conditions, they are further metabolized to acetate or butyrate and propionate, respectively and do not substantially accumulate in the colonic lumen [91]. Recent evidence suggests that succinate acts as a signal for inflammation [100]. Interestingly, prebiotic (inulin-type fructan) supplementation in diet-induced obese mice increased the caecal content of succinate [101]. The authors demonstrated that addition of succinate into the diet activated the intestinal gluconeogenesis and lead to an improvement of both glucose tolerance and insulin

sensitivity, associated with a reduced body weight gain and a decreased hepatic glucose production. Moreover, colonization of conventional mice with the succinate-producer *Prevotella copri* exhibited the same beneficial effects than those observed with succinate supplementation. From the experimental data, performed both in humans and mans, SCFA appears in most cases as interesting nutrients in the control of host energy metabolism. However, some controversies exist, including the fact that several studies have positively related the fecal amount of SCFA and obesity (see in the previous sections). Measuring SCFA content in the faeces does not necessarily reflect their potential effect in the upper part of the gut and their distribution in host tissues. More accurate methodologies, including the use of isotope-labelled SCFA and fiber substrates, will be very useful to unravel their real contribution as energy substrates and regulators in host tissues [102].

3.2 Amino acid-derived metabolites

Other bacterial metabolites, namely produced upon microbial metabolism of amino acids, could be of interest in the management of obesity-associated liver complications. For instance, branched-chain amino acids (BCAA) [103] have been proposed as harmful metabolites since the serum metabolome of insulin-resistant individuals is characterized by increased levels of BCAA. In addition, some driver species, such as *Prevotella copri*, can induce insulin resistance concomitantly with an increase levels of BCAA in the serum of mice. Besides SCFA, the gut microbiota can produce branched-chain fatty acids (BCFA) from the degradation of branched-chain amino acids, and phenylacetate, benzoate, p-cresol, and indole from aromatic amino acids [91]. The BCFA isobutyrate, 2-methylbutyrate and isovalerate are produced by bacterial fermentation of valine, isoleucine and leucine, respectively. Similar to other protein fermentation metabolites, faecal BCFA concentrations are reduced after prebiotic intake [91]. Little is known regarding potential effects of BCFA and faecal BCFA are considered only as markers for bacterial protein fermentation rather than markers of colonic health [91].

Recently, imidazole-propionate was identified as a microbially produced histidine-derived metabolite that is present at higher concentrations in subjects with versus without type 2 diabetes. Imidazole-propionate treatment impairs glucose tolerance in mice and inhibits insulin signaling at the level of IRS through activation of the p38g/p62/mTORC1 pathway at the cellular level. Furthermore, increased activation of p62 and mTORC1 in liver from subjects with type 2 diabetes, suggesting that imidazole-propionate may contribute to the pathogenesis of type 2 diabetes [104]. Interestingly, the authors showed that, among 42 bacterial strains owing an authentic form of urocanate reductases able to produce imidazole-propionate from urocanate, 67% of these strains were more abundant in subjects with T2D. Among these strains, *Streptococcus mutans* and *Eggerthella lenta* were those largely more abundant in T2D patients. Another elegant study suggested a direct role for microbial degradation of phenylalanine into phenylacetic acid in non-diabetic obese patients with steatosis [105]. The authors demonstrated that phenylacetic acid positively correlates with a low microbial gene richness and hepatic steatosis. Moreover, they corroborated the role of this metabolite by showing that 24-h of treatment with phenylacetic acid on human hepatocytes, as well its chronic supplementation in mice, induce liver steatosis and BCAA metabolism in both models. This study confirms that the crosstalk between diet and microbiome could influence the host physiology, and in this case, led to the synthesis of metabolites exhibiting deleterious effects on the host metabolism.

The phenolic compounds phenol, p-cresol and indole are the major metabolites of bacterial fermentation of tyrosine, phenylalanine and tryptophan [91]. These metabolites are largely and rapidly excreted in urine after sulfate or glucuronide conjugation in the mucosa or the liver [106]. In obese individuals, urinary p-cresol and phenol levels at baseline were considerably higher than those reported in normal-weight and decreased upon weight loss [107]. Of particular interest in the context of obesity, the production of indole may contribute to the secretion of GLP-1 by intestinal enteroendocrine cells [14]. Our team has recently shown that the indole metabolite decreases the mRNA expression of pro-inflammatory mediators (IL-1β, Ccl2 and Cd14) in precision cut-liver slices from Ob/Ob mice, a model of NAFLD associated with chronic liver inflammation [108]. In vivo, we have demonstrated that indole reduced the hepatic expression of genes involved in inflammation and macrophage activation as well as plasmatic concentration of aminotransferases reflecting hepatic damage in Ob/Ob mice (unpublished data). These findings was consistent with previous data demonstrating the beneficial impact of indole exposure, produced by *Escherichia coli*, on both inflammation and epithelial cell barrier properties in intestinal epithelial cells [109].

Moreover, 1 mM of p-cresol, another metabolite produced by gut microbes from aromatic amino acid tyrosine also prevented the LPS-induced up-regulation of two pro-inflammatory cytokines (Ccl2 and il-1β) in vitro in precision cut-liver slices from *ob/ob* mice, after 4 h of incubation [108]. However, this result was to consider with some caution since at higher concentrations and for a longer incubation (1.6 or 3.2 mM during 1 day), these metabolites appeared to be genotoxic for colonocytes by increasing DNA damage [110]. Similarly, to p-cresol, some other amino acids-derived metabolites have detrimental effects on the colonic epithelium when they are present or administered at high concentrations in preclinical models, such as ammonia or hydrogen sulfide [111].

It has been recently demonstrated that other gut microbiota-derived tryptophan bacterial metabolites - indole-3-acetate and tryptamine- were depleted in mice fed with a HF diet and were associated with positive outcomes [112]. indole-3-acetate and tryptamine attenuated the increase of fatty acid- and LPS-stimulated production of pro-inflammatory markers in macrophages. Additionally, in hepatocytes, indole-3-acetate reduced the lipogenesis induced by fatty acid preconditioning, by regulating Fasn (a key lipogenic enzyme) and Srebp1c (transcription factor regulating cholesterol/bile acid biosynthesis) [112]. These effects were abrogated in the presence of an aryl-hydrocarbon receptor (AhR) antagonist, suggesting that gut microbiota could influence inflammatory responses in the liver through metabolites engaging host receptors (AhR).

Altogether, the gut microbiota could influence inflammatory tone of the liver through the release of gut microbiota-derived tryptophan metabolites via the portal vein.

3.3 Bile acids and bacterial-derived lipid mediators

Bile acids (BA) are signaling molecules that coordinately regulate metabolism and inflammation via the receptors FXR and TGR5, as recently reviewed [15]. BA are first synthesized from cholesterol in hepatocytes, then conjugated to glycine or taurine and secreted into the biliary tract to reach the intestines. The intestinal microbiota transforms primary BA into secondary BA by deconjugation and/or reduction. Reabsorbed BA (95%) can return into the liver and a small amount of BA escaping hepatic capture reach the peripheral tissues via the systematic circulation. Obesity and NAFLD are associated with gut dysbiosis and changes of BA pool concentration and composition [15, 113]. BA have been identified as signaling molecules impacting glucose, lipid and energy homeostasis, and inflammation. Few studies have investigated the impact of gut microbiota modulation by prebiotics or probiotics on BA turnover. The administration of gut guar gum, a fermentable dietary fiber, reduces hepatic steatosis but enhances hepatic inflammation and fibrosis in a mouse model of NAFLD [114]. This is corroborated with increased plasma total BA suggesting that the up-regulation of BA by guar gum could worsen features of NAFLD. Interestingly, resistant starch, another dietary fiber improves insulin sensitivity and in parallel, restores the caecal BA profile in both conventional and germ-free mice fed with a western diet. Those data, suggest that the metabolic benefits of resistant starch related to bile acid homeostasis occurs independently of gut microbiota [115]. Rats fed with high-fructose diet and receiving Lactobacillus casei during two weeks exhibit a lower expression of TGR-5 receptor in the liver, associated with increased abundances of *Bifidobacterium* and *Lactobacillus* and decreased *Clostridium coccoides-E. rectale* and *Clostridium scindens* in microbiota, compared to rats untreated with the probiotic [116]. Interestingly, *C. scindens* exhibits a high 7alpha-dehydroxylating activity, suggesting that decrease of *C. scindens* by probiotics limits the conversion of primary BA and reduce secondary BA synthesis in the intestine.

4 Which biomarkers can be proposed to link diet-microbiota-health in obesity?

Although controversies exist, the relative abundance of Firmicutes and Bacteroidetes (F:B ratio) in gut microbiota has been considered as a marker in the development of obesity. Emerging evidence has supported the use of other bacteria as biomarkers to characterize obesity status. To date, information available to relate microbiota or specific microbial species to dietary habits or nutrient intake was limited to dietary fibers. Some data showed that *Prevotella* species have been correlated with plant-rich diets, which are abundant in carbohydrates and fibers and also with improving CVD risk factor profile and glucose metabolism [117]. However, certain strains may exhibit pathobiontic properties which promoted metabolic syndrome and obesity. Therefore, there is a need for more studies in humans to ascertain a causal and potential disease-triggering role for *Prevotella* are needed in order to reveal the health- or disease modulating properties. Worth noting, the *Prevotella* to *Bacteroides* ratio was proposed to predict weight loss success in humans [118]. *Akkermansia* has attracted increasing attention in terms of its role in obesity. Emerging data demonstrated that the consumption of fruits (cherry, lingonberry, grape, mango) and vegetables (navy bean) increased the fecal abundance of *A. muciniphila* in obese mice [55, 57–60, 119, 120], probably due to the high levels of fibers and/or polyphenols in these foods [121, 122].

SCFAs can be proposed since it has been considered as a microbiota-related marker of obesity in humans because that colonic production of SCFAs correlated well with the BMIs and the levels of SCFAs are in accordance with the alteration of gut bacteria [39, 123]. Although SCFA are generally recognized as markers of carbohydrate fermentation in the colon and are therefore commonly considered as beneficial to health, a number of critical questions need to be answered before their concentrations can serve as biomarkers [91]. It should be noted that we have shown that prebiotic dietary fiber (inulin-type fructan) consumption decreases fecal SCFA concentration in obese women and that total SCFA, acetate and propionate, that are positively correlated with BMI, fasting insulinemia and homeostasis model assessment (HOMA)[124]. Recently, we proposed in the context of the FiberTAG project (Joint Programming Initiative "A Healthy Diet for a Healthy Life" 2017–2020 https://www.fibertag.eu/) to analyze volatile bacterial co-metabolites measured in breath to link health to microbial breakdown of nutrients or endogenous substrates

[125]. Indeed, selected ion flow tube-mass spectrometry (SIFT-MS) has been proposed as a powerful and sensitive analytical technique to rapidly quantify low levels of volatile metabolites – including SCFA – which could explain the biological effect of fermentable DF.

A toolbox called CASINO (Community And Systems-level INteractive Optimization) which comprises an optimization algorithm integrated with diet analysis was developed to predict the phenotypes and related dietary intake within the human gut microbiota [126]. Focusing on metabolic interactions between the diet, gut microbiota, and host metabolism, the predictive power of this toolbox was validated in a diet-intervention study of 45 obese and overweight individuals by using fecal and blood metabolomics data. Their prediction model suggested that the gut microbiota in "low gene count" (LGC) individuals may contribute to increased serum levels of many amino acids that have been found correlated with metabolic diseases such as type 2 diabetes. The "high gene count" (HGC) subjects, on the other hand, with their more gene-rich gut microbiome, has a higher capacity to produce SCFAs and may have a better conversion of amino acids, resulting in lower levels of these in the plasma. This kind of model could help in generating mechanistic insight into the contribution of individual species of the gut microbiome to the overall metabolism of the ecosystem and the host and may facilitate personalized interventions based on the microbiome.

5 Conclusion

The impact of nutrients that modulate the gut microbiota composition, or which are metabolized by the gut microbes into bioactive molecules, is largely described in vitro or in animal models. Those data available allow to point out key "co-metabolites" that influence gene expression in host tissues, which contributes to their effect in the control of appetite, adiposity, or metabolic disorders associated with obesity. If certain classes of co-metabolites are particularly studied nowadays, such as SCFA, bile acids, or indoles, we have to admit that it is really difficult to classify them as beneficial or harmful, since, following the biological context, or the model in which they are studied, controversies persist. There is a crucial need to develop methodologies and approaches allowing to deal with the complexity of the human physiology, including the dialogue between nutrition, the microbial ecosystem and human cells and organs. Moreover, a comprehensive view of how whole foods and dietary habits, rather than selective nutrients, modulate the gut microbiota is rarely taken into account. It would be interesting to get more data, like the ones reported by Han et al., describing the alterations of gut microbiota in obese rodents and humans induced by dietary intervention with various whole fruits and vegetables [127].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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