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The microbial-mammalian metabolic axis, a critical symbiotic relationship

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Abstract

Purpose of review—The microbial-mammalian symbiosis plays a critical role in metabolic health. Microbial metabolites emerge as key messengers in the complex communication between the gut microbiota and their host. These chemical signals are mainly derived from nutritional precursors, which also are in turn also able to modify gut microbiota population. Recent advances in the characterization of the gut microbiome and the mechanisms involved in this symbiosis allow the development of nutritional interventions. This review covers the latest findings on the microbial-mammalian metabolic axis as a critical symbiotic relationship particularly relevant to clinical nutrition.

Recent findings—The modulation of host metabolism by metabolites derived from the gut microbiota highlights the importance of gut microbiota in disease prevention and causation. The composition of microbial populations in our gut ecosystem is a critical pathophysiological factor, mainly regulated by diet, but also by the host's characteristics (e.g. genetics, circadian clock, immune system, age). Tailored interventions, including dietary changes, the use of antibiotics, prebiotic and probiotic supplementation and faecal transplantation are promising strategies to manipulate microbial ecology.

Summary—The microbiota is now considered as an easily reachable target to prevent and treat related diseases. Recent findings in both mechanisms of its interactions with host metabolism and in strategies to modify gut microbiota will allow us to develop more effective treatments especially in metabolic diseases.

Keywords

Microbiota; signalling metabolites; host metabolism; dietary intervention

Introduction

Humans have evolved as part of a critical symbiotic relationship with their gut microbes. The gut ecosystem harbours thousands of microbial species and millions of genes,

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integrating a number of co-evolved microbial metabolic reactions encoded in the gut metagenome complementing endogenous metabolic processes encoded in the mammalian genome. High-throughput technologies such as metagenomics and metabolomics provide novel insights into this complex ecosystem, which is now recognized to have a key impact in the development and progression of diseases such as cardiometabolic disorders, irritable bowel syndrome and cancer.

The human gut provides commensal microbiota with a specific biotope with an almost constant supply of diet- and host-derived substrates for bacterial fermentation, thus providing key nutrients and energetic needs for the bacterial community and its human host [1]. Beneficial cross-feeding in this symbiotic relationship is best exemplified by *i*) the bacterial breakdown of otherwise indigestible polysaccharides and fibres into monosaccharides and short-chain fatty acids [1], and *ii*) the rapid fucosylation of the host intestinal epithelium to sustain bacterial populations during sickness [2]. However, the range of metabolites produced by gut microbiota goes beyond simple metabolism and also include microbial metabolites that act as chemical messengers, binding human target proteins and thereby impacting signalling pathways and metabolic and inflammation-related processes in the host [3**,4].

In this review, we briefly present the ecological structure of the microbiome and address selected examples of how nutrients are converted by the gut microbiota into chemical signals with a strong impact on host physiology and behaviour. We also revisit recent progress in novel tools to remodel the gut bacterial community (e.g. dietary interventions, use of antibiotics, prebiotics and probiotics, faecal transplantation) and its relevance as personalised approaches targeting key features of the microbial-mammalian metabolic axis.

The gut microbiome architecture

The gut microbiome is a highly complex ecosystem. Every person presents a unique combination of microbial species making everyone’s microbiome unique. Several thousand species have been reported and result in combinations of more than 10 million individual bacterial genes which have been catalogued [5**]. The gut ecology can be divided into core species that are present in pretty much everyone of us and rare species which are only observed in a small proportion of the population. Moreover, enteric bacterial populations tend to converge towards three distinct community types, called enterotypes [6,7]. This particular architecture of the gut microbiome is not binary, but corresponds to a continuous distribution along a spectrum. These enterotypes are not related to gender, age and geography, and are dominated by one phylum: *Bacteroides*, *Prevotella* or *Ruminococcaceae*.

Variations related to the microbiome architecture are manifold. Microbial gene richness is variable in human populations and has been tied to metabolic health: people with a high microbial gene count are healthier than people with a low microbial gene count who tend to have metabolic syndrome [8**]. This is also the case for Irritable Bowel Syndrome where patients with IBS have a lower ecological diversity than healthy controls [9,10]. Obesity is associated with an imbalance between two major phyla, *Bacteroidetes* and *Firmicutes*, which is observed in both animal model and human populations [11].

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Factors affecting the gut microbial ecology

Gut microbiota composition is complex and multifactorial. Individual composition is influenced by environmental and genetic factors in a polygenic model [12,13**]. Not surprisingly, abundance in Gram-positive organisms mapped with several inflammation-related genes such as cytokine *Il22*, *Irak3*, a kinase regulating the MyD88-dependent *Toll*-like receptor (TLR) pathways [12]. The expression of *Irak4*, another kinase involved in TLR pathway correlates with abundance of beneficial *Roseburia* ssp in a study of the genetic determinants of the microbiome, whereas *Akkermansia municiphila* mapped with lipopolysaccharide-binding protein (*Lbp*) and *Bpi*, an antibiotic secreted protein targeting Gram-negative bacteria [14*].

Diet is an environmental factor that critically reshapes the microbial ecology and therefore the microbial-mammalian symbiotic relationship. Diet drives the functional convergence of microbiomes across various species and habitats [15]. High fat diet (HFD) rapidly alters the gut microbiome [16*] and long-term dietary patterns associated with the distribution of enterotypes: carbohydrate diets are linked with the *Prevotella* enterotype whereas animal protein and fats are linked with the *Bacteroides* enterotype [17].

The host circadian clock influences gut microbial ecology through feeding and diurnal rhythms; long-distance travel and jetlag result in the disruption of this molecular clock and feeding rhythms thereby inducing dysbiosis which promotes impaired glucose tolerance [18**]. In fact, travel influences the microbiome even in absence of jetlag, as local diets exert a key influence on gut motility and the microbiome, even in absence of disruptions of the circadian clock [19**].

Age is a major factor related to microbiome architecture, starting with the ecological dichotomy observed between C-section and natural births. The maturation of the microbiome in the first few years has a therefore critical impact on a person's health. For instance, antibiotics knock down gut bacteria and destabilise microbial ecology. There is an early life developmental window in which the microbiome can be disrupted by low-dose penicillin treatment, resulting in long-term metabolic programming [20**]. However, this perturbation provides an opportunity for the microbial ecology to evolve towards different equilibria, and therefore microbiome compositions and functions. In some cases, antibiotic therapy also results in the development of abnormal microbial ecologies such as opportunistic *C. difficile* infections. Likewise, gut microbiota composition in the elderly populations correlates with frailty, co-morbidity, nutritional status and inflammation [21].

Surprisingly, dietary supplements such as artificial sweeteners have a direct impact on the gut microbial ecology and gene function, which then promote impaired glucose tolerance [22**]. Anti-diabetic drug metformin also has a spectacular impact on the microbiome in animals and in humans [23**].

Also, diet heavily influences the production of microbial metabolites by the gut microbiota. This review will address, in particular, the impact of three microbial metabolite families involved in the microbial-mammalian metabolic axis and in human health (short-chain fatty acids (SCFA), methylamines and indoles).

Microbial metabolites from dietary fibre fermentation impact host metabolism

Consumption of dietary products rich in fibre has proven benefits for the human health, either improving insulin sensitivity or inflammatory parameters [24]. Interestingly, in both cases, gut microbial metabolism has been postulated as the link mediating these effects [24,25]. As many plant-derived carbohydrates are partially or totally resistant to human digestion in small intestine, they progress into the colon were they can undergo bacterial transformation. As a result, carbohydrate fermentation and bacterial cross-feeding produce a range of SCFAs (e.g. acetate, butyrate, propionate) [24].

Acetate may be produced by many enteric species including *Blautia hydrogenotrophica* [1]. Propionate is mostly produced through the succinate pathway, either by *Bacteroidetes spp* producing propionate from carbohydrates and by *Firmicutes spp* using lactate or succinate as substrates [1]. Propionate can also be produced from lactate by *Firmicutes spp*. (acrylate pathway) or from deoxyhexose sugars by *Firmicutes* and *Proteobacteria* spp., through the propanediol pathway [1].

SCFAs are involved in several beneficial processes for human health. Butyrate, propionate and acetate prevent both diet-induced obesity and insulin resistance [3**]; butyrate and propionate promote intestinal gluconeogenesis with a beneficial effect in the host's glucose homeostasis [26**]. Propionate upregulates the release of appetite-suppressing gut hormones, such as GLP-1 and PYY, in both rats and mice [27*]; in overweight humans, propionate has also shown to prevent weight gain [28*]. Acetate has anorexigenic properties, by altering the hypothalamic expression of neuropeptides involved in appetite suppression[29**] and regulates inflammation [30].

Considering the above-mentioned effects, it is relevant to understand the relative contribution of diet and microbiota composition to SCFA production. Dietary carbohydrate intake as shown to impact the faecal levels of SCFA, but the effect on butyrate was not proportional to the variation of total SCFA, suggesting that specific microbial groups (e.g. butyrate-producing *Roseburia - E.rectale* groups) may have a higher dependence on diet [24,31].

Microbial conversion of dietary choline into methylamines impacts insulin resistance and atherosclerosis

Methylamines are metabolites produced by gut microbiota from the degradation of choline in trimethylamine (TMA) [3**]. The estimated daily choline intake in adults is of 222-415 mg, mainly obtained from meat products but also from dairy products, egg, grains grain-based products and seafood [32*]. The bacterial species degrading choline into TMA were predicted *in silico* [33]. An *in vitro* screening of 79 human intestinal isolates validated that *CutC and CutD* expressing species were TMA producers, as well as *Edwardsiella tarda* despite the absence of Cut cluster, this latter finding having been met with scepticism [34**]. TMA diffuses through the host's bloodstream to the portal vein and is detoxified into TMA-*N*-oxide (TMAO) by the hepatic flavin-monooxygenase 3 (FMO3).

Raised TMAO plasma concentration was associated with cardiovascular risk in several studies [35]. Furthermore, TMAO dietary supplementation enhanced heart failure in an *in*

vivo model [36]. A recent study proposed the use of 3,3-dimethyl-1-butanol (a structural analogue of choline) as an inhibitor of TMA production by gut microbiota [37**]. This analogue is also able to reduce plasma TMAO levels in mice and *in fine* reduce atherosclerosis phenotype. [37**]. Oral TMAO was also suggested to promote impaired glucose tolerance in mouse [38*] and to be associated with inflammation in both mouse and human [38*,39*].

Finally, the FMO3 enzyme has been shown to play a central role in cardiovascular diseases. Indeed, the knockdown of FMO3 improves glucose tolerance, prevents hypercholesterolemia and atherosclerosis [40*,41*]. This role played by FMO3 in cholesterol metabolism was also recently extended to ER stress and inflammation [42*]. Altogether these studies suggest to consider the role of the TMA -> (FMO3) -> TMAO reaction as a whole process rather than TMAO's role alone.

Tryptophan is metabolised into a range of indole-containing derivatives

Tryptophan is an essential amino acid particularly abundant in egg white, red meat, poultry, fish, cheese, peanuts and also in some seeds [43]. According to the World Health Organization, the daily recommended dose of tryptophan for an adult human is 4 mg/kg of body weight [43]. Apart from its role in protein biosynthesis, tryptophan is also a biochemical precursor of serotonin and niacin. Recent studies have pointed out a novel potential role for tryptophan in metabolic outcomes: in humans, tryptophan levels are associated with an increased risk of type 2 [44,45] while in rats, interestingly, its supplementation decreases fat deposition and enhances both protein synthesis and fatty acid oxidation [46*]. A recent study in a fish model also points out a possible role on the improvement of the intestinal barrier integrity and immune function [47].

Tryptophan can also enter a complex network of bacterial-based metabolic reactions, producing a range of gut bacterial metabolites that lately impact different aspects of the host's health. Tryptophanase-containing gut bacteria (e.g. *Escherichia coli*) metabolise tryptophan directly into indole [48*], that is subsequently sulphated into indoxylsulphate in the liver. Various clostridial species (e.g.: *C. sporogenes*) produce indole-3-propionate (IPA) and other indole-containing intermediate molecules, including indole-3-pyruvate and indole-3-acetate[3**]. In a study comparing gnotobiotic with germ-free mice, IPA production was demonstrated to be completely dependent on the gut microbiota [48*]. By playing a role on the maintenance of the intestinal barrier integrity through Pregnane X Receptor (PXR) [49**], IPA contributes to a key beneficial aspect for host-microbe symbiosis. High fat diets promote leaky intestinal barrier allowing translocation of bacteria and bacterial components such as lipopolyssacharide (LPS), providing a crucial link between gut microbiota and metabolic disorders (e.g. high-fat diet-induced inflammation) [50].

Conversely, indoxylsulphate has been associated with deleterious effects, including cardiac fibrosis and cardiomyocyte hypertrophy [3**]. Indoxylsulphate is an aryl hydrocarbon receptor (AhR) agonist that induces several outcomes of endothelial dysfunction *in vitro*, including inhibited proliferation, cell migration and reduced nitric oxide production [51**].

Pro-inflammatory pathways, as well as oxidative stress, are also thought to be stimulated by this compound[51**].

These two metabolites highlight the complex and subtle role of microbial metabolism of tryptophan - exemplifying how the same dietary substrate impacts the delicate balance of the host-microbial mammalian symbiosis, by undergoing different biosynthetic pathways.

Therapeutic interventions reshaping the gut microbiome ecology

Evidence from high-throughput technologies (e.g. metagenomics and metabolomics) supports the idea that the gut microbiota composition is a paramount aspect of the mammalian-microbial symbiotic relationship and, therefore, greatly affects human health and disease. Gene richness, a marker of metabolic health, is actionable by dietary interventions: gene count increases as obese patients follow a weight loss diet [52]. Moreover, Shoaie *et al* implemented a mathematical approach modelling the metabolism of key members of the microbiome of these patients and predicted the impact of the microbiome on fecal and circulating SCFAs and amino acids during this weight loss program [53**].

Postprandial glycemic responses are highly variable between two patients and this variability is associated with a range of dietary, clinical and metagenomic factors [54**]. Zeevi *et al*. developed a predictive model for postprandial glycemic responses based on anthropometric measurements dietary questionnaires and fecal metagenomes and used it to design personalised diets. These tailored dietary interventions were able to modify the gut microbiota and increase populations of bacteria previously reported as beneficial.

Reshaping the gut microbial ecosystem with the utilisation of functional food ingredient is a popular therapeutic strategy to improve host health. In particular, prebiotics are defined as fermented ingredients that beneficially affect the host by selectively stimulating the growth and/or the activity of colonic microbiota [55]. Prebiotics consist of oligosaccharides or short chain polysaccharides whose effect is mediated by the enhancement of beneficial microbes *Bifidobacteria* and *Lactobacilli* and the production of SCFAs [56**]. Prebiotics were also found to modulate systemic and hepatic inflammation *via* the secretion of glucagon-like-proteins (GLP1 and GLP2) [57*], and to lower calorie intake, improve glucose tolerance and glucose-induced insulin secretion and to normalise inflammation in overweight mice and humans. [58*,59**]. In humans, however, prebiotic studies vary in quality and outcomes depending on age, dietary habits and prebiotic doses [60]. Several clinical randomised studies showed an improved inflammatory status, glucose sensitivity and an influence on satiety on overweight subjects [56**].

Another approach to remodel the gut microbial ecology is the use of probiotics, usually a single microbial species that enhances intestinal balance by changing the composition and activity of gastrointestinal microbiota [55]. Probiotics turned to be efficient in improving lactose digestion, reducing diarrhoea, and bloating, restoring a symbiotic ecosystem after an antibiotic intervention, and enhancing glucose sensitivity in humans [55] but no clear effects of probiotics on obesity and metabolic outcomes were demonstrated in human studies [61].

However, oral probiotic doses are in general more than thousand time lower than the trillions of endogenous gut microbes and prebiotic administration influence temporary the microbiome therefore not having a lasting effect on microbial ecology [62*]. Whilst dietary and probiotic interventions impact the microbiome, faecal microbiota transplantation (FMT) allows the efficient transfer of an established microbial community together with its ecological properties. This approach has been highly successful and demonstrated that microbial communities could transfer disease phenotypes such as obesity [63], or non-alcoholic fatty liver disease [64]. The FMT approach has been trialled for metabolic syndrome in human clinical studies [65] but has never been confirmed since.

FMT have also reported efficiency in the reduction of the recurrence of *C. difficile* infection and held promising effects on ulcerative colitis and Crohn's diseases [66*]. A better understanding of the interplay between the prebiotics, probiotics, bacterial transplants and the gut microbiota is the prerequisite for optimising their uses in the treatment of inflammatory disorders and metabolic diseases.

Conclusion

The understanding of the importance of the microbiota in health and disease is now established. The interactions between gut microbiota and host can be described as a symbiotic balance. Research is now mainly focusing on the gut microbiota dynamics and how this influence interactions with the host. Recent discoveries have shown that some metabolites produced by gut act as signalling molecules on host and by this mechanism could directly modulate host metabolism. These discoveries help the development of specific strategies to modify gut microbiota which will allow us to develop more effective treatments of metabolic diseases.

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Key points

- the gut microbiome has a complex and modular architecture
- numerous genetic and environmental factors affect the microbiota ecology
- microbial mammalian metabolic axis is a symbiotic relationship
- dietary interventions and microbiota transplants are successful avenues for sustainable beneficial alterations of the microbiome
- deep characterization of the microbiome by metagenomics and metabolomics can predict health, and response to treatments