The microbial-mammalian metabolic axis: a critical symbiotic relationship

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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 in turn are 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 microbiome 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
dietary intervention, host metabolism, microbiota, signalling metabolites

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, 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-derived 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 the bacterial breakdown of otherwise indigestible polysaccharides and fibres into monosaccharides and short-chain fatty acids (SCFAs) [1], and 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 includes 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 personalized approaches targeting key features of the microbial-mammalian metabolic axis.

**THE GUT MICROBIOOME 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 (IBS) in which 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].

**FACTORS AFFECTING THE GUT MICROBIOTIC 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 and 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 spp. in a study of the genetic determinants of the microbiome, whereas Akkermansia muciniphila is mapped with lipopolysaccharide-binding protein (Lbp) and bactericidal permeability-increasing protein (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 jet lag 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 the absence of jet lag, as local diets exert a key influence on gut motility and the microbiome, even in the 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 therefore has a critical impact on a person’s health. For instance, antibiotics knock down gut bacteria and destabilize 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 different microbiome compositions and functions. In some cases, antibiotic therapy also results in the development of abnormal microbial ecologies such as opportunistic Clostridium 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]. Antidiabetic 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 (SCFAs, 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 where 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 or by Firmicutes spp. using lactate or succinate as substrates [1]. Propionate can also be produced from lactate by Firmicutes spp. (via the 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 (IGN) with a beneficial effect in the host’s glucose homeostasis [26]. Propionate upregulates the release of appetite-suppressing gut hormones, such as GLP-1 (glucagon-like peptide-1) and PYY (peptide YY), 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 has been 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–Eubacterium 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-monoxygenase 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 mice [38*] and to be associated with inflammation in both mice and humans [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 and prevents hypercholesterolaemia and atherosclerosis [40*,41*]. This role played by FMO3 in cholesterol metabolism was also recently extended to endoplasmic reticulum (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 METABOLIZED 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 diabetes [44,45] whereas 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 differ different aspects of the host’s health. Tryptophan-nase-containing gut bacteria (e.g. *Escherichia coli*) metabolize tryptophan directly into indole [48*], that is subsequently sulphated into indoxylsulphate in the liver. Various clostridial species (e.g. *Clostridium 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. HFDs promote leaky intestinal barrier allowing translocation of bacteria and bacterial components such as lipopolysaccharide (LPS), providing a crucial link between gut microbiota and metabolic disorders (e.g. HFD-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**]. Proinflammatory 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. [53**] implemented a mathematical approach modelling the metabolism of key members of the microbiome of these patients and predicted the impact of the microbiome on faecal and circulating SCFAs and amino acids during this weight loss programme.

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 faecal metagenomes and used it to design personalized diets. These tailored dietary interventions were able to modify the gut microbiota and to increase populations of bacteria previously reported as beneficial.

Reshaping the gut microbial ecosystem with the utilization of functional food ingredients 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 normalize 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 randomized studies showed an improved inflammatory status, glucose sensitivity and an influence on satiety on overweight patients [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 out 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 one thousand times lower than the trillions of endogenous gut microbes and prebiotic administration temporarily influence the microbiome therefore not having a lasting effect on microbial ecology [62**]. Although 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 nonalcoholic fatty liver disease [64]. The FMT approach has been trialled for metabolic syndrome in human clinical studies [65] but has never been confirmed since that time.

FMTs 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 influences interactions with the host. Recent discoveries have shown that some metabolites produced by gut act as signalling molecules on the host and by this mechanism could directly modulate host metabolism. These discoveries help the development of specific strategies to modify gut microbiota that will allow us to develop more effective treatments of metabolic diseases.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

The microbial-mammalian metabolic axis Chilloux et al.


This article confirms previously described positive associations between Akkermansia muciniphila and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. Gut 2016; 65:426–436.


This article presents the first genetic analysis of the microbiome using 16 ribosomal DNA (rDNA) sequencing of the United Kingdom twins registry, thereby defining heritability for each taxon.


This article assesses the genetics and environmental components of the variance related to gut microbiota-host interaction.


This article characterizes the monitoring of the effect of dietary changes on the microbiome using 16S rDNA sequencing and mass spectrometric analysis of SCFAs and bile acids in a cross-over design.


This article focuses on diurnal oscillations of the gut microbial ecology, mostly driven by host circadian rhythms.


This article highlights the effect of dietary change related to travel on the gut microbial ecology, in absence of disruption of the circadian clock.


This article demonstrates that early life low-dose antibiotics have a lasting effect on the development of the associated microbiota.


This article puts a paradoxical finding under the spotlight: sweeteners shift the microbial environment towards an impairment of host glucose tolerance.


This study reports an effect of metformin treatment on the microbiome of type 2 diabetic patients. Appropriate correction for metformin treatment resulted in the identification of a unified signature of type 2 diabetes with a depletion of butyrate-producing species.


This study extends the work of Psichas et al. [27] by demonstrating that propionate stimulates the production of GLP-1 and PYY from human colonic cells, but also prevents actual weight gain in overweight adult humans.


This article highlights the novel properties of acetate as a neuroactive compound involved in safety and appetite regulation. The article demonstrates that this effect is mediated by acetate-induced expression of anorexigenic neuropeptides.


This article is a complete analysis of choline sources and consumption by the European population.


This article screened for the first time which bacterial isolates are able to produce TMA from choline.


This study proposes a therapeutic approach for TMAO-related atherosclerosis. The aim of this study was to reduce circulating TMAO by inhibiting choline degradation in TMA using a choline analog.


This article shows the role of TMAO in the development of insulin resistance in mice fed a HFD.


This study highlights a positive correlation between TMAO and inflammation on 217 patients cohort.


This study shows that FMO3 is necessary for the development of diabetes in mouse and that FMO3 is increased in the livers of insulin-resistant patients.


This study shows, using animal model, that modification of FMO3 activity could be a potent target to regulate glucose and lipid homeostasis.
Metabolic endotoxemia initiates obesity


The potential beneficial role of Gut microorganisms as promising

48. Hubbard TD, Murray IA, Perdew GH. Indole and tryptophan metabolism:
endogenous and dietary routes to Ah receptor activation. Drug Metab Dispos 2015; 43:1522–1535.

This review focuses on the role of specific tryptophan metabolites as AHR ligands, as well as the impact of this agonism on inflammation and gastrointestinal system.


This article provides evidence supporting the role that IPA has beneficial properties for both host barrier function and immune status, through PXR agonism.


In this review, the authors address the role of uremic toxins from tryptophan metabolism as AHR ligands, and the consequences of this interaction on cardiovascular complication in the context of chronic kidney disease.


By using a metabolic reconstruction of a selected group of gut bacteria reflecting metabolite levels in blood and faeces, this article describes the impact of the host’s diet on bacterial metabolism.


By using a validated algorithm for accurate prediction of personalized postprandial responses, this study points out the relevance of personalized diets on the modification of postprandial glycemic levels and, lately, its metabolic consequences.


This review summarizes the extensive studies on the fructo-oligosaccharides and galacto-oligosaccharides on obesity and inflammation and discuss the effects of new generations of prebiotics on human intestinal health.


The article summarized the mechanisms by which the prebiotics impact host physiology and review the main studies investigating the role of prebiotics on obesity and the metabolic syndrome.


This review surveys pharmaceutical, surgical and nutritional intervention effects on type 2 diabetes patients and discuss the relevance of using prebiotics, probiotics and faecal transplants in the management of type 2 diabetes.


This article gives new insights about the prebiotics concept, current limitations and highlight the importance of better understanding of the functional features of the microbiota in order to strengthen the prebiotic effects on human health.


This article compares the impact of probiotics, antibiotics and microbial transplants on the modulation of the gut microbiota and present their therapeutic potentials on human health.


This review highlights the evidences that faecal transplant is efficient to combat not only Clostridium difficile infection but also ulcerative colitis, irritable bowel diseases and the metabolic syndrome.