Highlights

- Gut microbiota communicates with its mammalian host via microbial signalling metabolites
- Disease phenotypes can be modulated by microbiome intervention
- Microbial signalling metabolites impact signalling networks involved in disease
- Designing microbiome-inspired drugs is a promising strategy
The microbiome and its pharmacological targets: therapeutic avenues in cardiometabolic diseases

Author names and affiliations

Ana Luisa Neves¹#, Julien Chilloux¹#, Magali Sarafian¹, Mohd Badrin Abdul Rahim¹, Claire L. Boulangé¹,², Marc-Emmanuel Dumas¹

¹ Division of Computational and Systems Medicine, Department of Surgery and Cancer, Imperial College London, Exhibition Road, London SW7 2AZ, United Kingdom

² Current address: Metabometrix Ltd, Bio-incubator, Prince Consort Road, South Kensington, London SW7 2BP UK

#: These authors contributed equally to this review.

Corresponding author

Dr Marc-Emmanuel Dumas m.dumas@imperial.ac.uk
Abstract

Consisting of trillions of non-pathogenic bacteria living in a symbiotic relationship with their mammalian host, the gut microbiota has emerged in the last decades as one of the key drivers for cardiometabolic diseases (CMD). By degrading dietary substrates, the gut microbiota produces several metabolites that bind human pharmacological targets, impact subsequent signalling networks and in fine modulate host’s metabolism. In this review, we revisit the pharmacological relevance of four classes of gut microbial metabolites in CMD: short-chain fatty acids, bile acids, methylamines and indoles. Unravelling the signalling mechanisms of the microbial-mammalian metabolic axis adds one more layer of complexity to the physiopathology of CMD and opens new avenues for the development of microbiota-based pharmacological therapies.

Keywords

Cardiovascular diseases, Type 2 diabetes, Obesity, Gut microbiome, Microbial metabolism, signalling, G protein-coupled receptor, nuclear receptor.

Chemical compounds studied in this article

Introduction

Cardiometabolic diseases (CMD) present a complex array of interrelated risk factors affecting more than 1 billion people with a dramatic impact on mortality, morbidity and quality of life [1]. These factors (including impaired glucose tolerance, dyslipidemia, arterial hypertension, insulin resistance and central obesity) are epidemiologically clustered - the presence of three of five of these symptoms corresponding to the “metabolic syndrome” clinical diagnosis [1]. Although many pharmacological mechanisms have been suggested, the underlying causes of CMD and its potential therapeutic avenues remain to be fully explored. With the advent of high-throughput methodologies (metagenomics, metabolomics), the gut microbiome emerged as one of the key drivers for CMD [2]. The gut ecosystem, as well as its individual members, were shown to contribute to the host metabolism [3]*. A lower bacterial gene count (LGC) is associated to adiposity, insulin resistance and dyslipidemia [4]** and dietary intervention can improve both bacterial gene richness and clinical metabolic outcomes [5]**. Patients with type 2 diabetes (T2D) also show specific compositional and functional changes in their metagenomes [6]**.

With the increasing number of clinical studies reporting associations between the composition of the gut microbiota and CMD outcomes, one question arises - how are these changes in microbial ecology translated into pharmacological messages to the mammalian host? Consisting of trillions of non-pathogenic bacteria living in a symbiotic relationship with their host, gut microbiota produces several signalling molecules (e.g.: LPS, peptidoglycans, but also metabolites) that bind host proteins and impact signalling networks, therefore playing a central role as chemical messengers in the microbial-mammalian crosstalk [7]. The identification of the pharmacological targets and signalling pathways of these metabolites is key to a better understanding the molecular crosstalk supporting the microbial-mammalian metabolic axis – and provides a suitable framework for the discovery of the mechanistic basis of these associations. In this context, fine mapping of the microbial signalling metabolome and its host molecular targets opens up novel pharmacological avenues for microbiome interventions.
The microbiome interacts with its host through microbial metabolites

In this review, we shall present four classes of gut microbial metabolites impacting host molecular mechanisms relevant to CMD: short-chain fatty acids, bile acids, methylamines and indoles.

Short-chain fatty acids

Fermentation of otherwise indigestible dietary fibre by gut bacteria produces mostly short-chain fatty acids (SCFA) (e.g. formate, acetate, propionate, butyrate, isobutyrate, valerate, isovalerate), which can act either as substrates and/or signalling molecules [8] (Figure 1).

Butyrate is the primary substrate and energy source used by colonocytes [9]. Once inside the cell, butyrate is converted to acetyl-CoA by β-oxidation and enters the tricarboxylic acid cycle (TCA cycle) for energy production [8], which leads to an inhibition of autophagy [10].

While propionate is largely metabolised in the liver, acetate is the main SCFA in plasma [11]. After crossing the blood brain barrier, acetate has shown to suppress appetite and induce hypothalamic neuronal activation, thus modifying acetyl-CoA carboxylase activation and expression of neuropeptides responsible for appetite suppression [12]*. SCFA also trigger the production of glucagon-like peptide-1 (GLP-1), an gut hormones with anorexigenic properties [13]* [14] [15].

SCFAs also act as ligands for G protein-coupled receptors, therefore activating subsequent signalling pathways: activation of FFAR2 and FFAR3 by SCFA results in the inhibition of cAMP production via interaction with Gαi or Gαi/q, respectively [16].

FFAR2 activation by SCFAs seems to have a role as a sensor for excessive dietary energy, as its activation suppresses insulin sensitivity and fat accumulation in adipose tissue and increases insulin sensitivity in liver and muscle, thus regulating energy balance [17]*. Moreover, FFAR2 activation is also able to modulate immune responses [18] Conversely, FFAR3 activation increases leptin secretion, a hormone that acts as a signal of satiety [19]. Butyrate and propionate promote intestinal gluconeogenesis - which has beneficial effects in glucose homeostasis - by complementary
mechanisms: the first by activating intestinal gluconeogenesis gene expression and the second through FFAR3-dependent gut-brain axis [20]*.

Butyrate is a ligand for HCAR2 (also known as GPR109A), a G protein-coupled receptor with anti-inflammatory activity [21] [22]. The activation of HCAR2 by nicotinic acid, a known agonist for this receptor, reduces the production of TNF-α, IL-6 and monocyte chemoattractant protein-1 in monocytes [21]. The identification of butyrate as a HCAR2 agonist highlights its potential as a modulator of chronic low-grade inflammatory status, one of the central hallmarks of CMD.

Methylamines

Methylamines are metabolites produced from choline by the gut microbiota [18]. Choline is degraded into trimethylamine (TMA), which is after detoxified by the hepatic flavin-containing monooxygenase enzyme 3 (FMO3) into trimethylamine-N-oxide (TMAO), and demethylated into dimethylamine (DMA) and methylamine [for review see ref. 18]. Although the bacterial origin of TMA was recognised more than two decades ago [18], the members of the microbiota able to perform this conversion and the genes involved were only recently identified [23] [24]*. The bacterial genes CutC and CutD regulate the degradation of choline and are responsible for the regulation of the bioavailability of the circulating choline [23] [24]*. However, the recent Romano et al. study shows that at least one bacterial species could produce TMA in absence of the CutC gene [24] which suggests the existence of an alternative biosynthetic pathway. Although these genes were unknown at the time, we had previously shown that an increase in TMA and TMAO associated with a decrease in circulating choline and phosphatidylcholine played a role in the development of NAFLD and insulin resistance in high-fat diet fed mice [25], choline being a precursor of phosphatidylcholine and VLDL synthesis involved in lipid export from the liver; reducing dietary choline alters gut microbiota and leads to the development of non-alcoholic fatty liver disease [for a review, see ref. 18].
TMAO was also proposed as a marker of cardiovascular disease: high plasma TMAO is associated with cardiovascular disease in humans and in animal models. The association between TMAO and CVD was then further validated [26]* and confirmed in another cohort [27]. The inhibition of FMO3 in an atherosclerosis mouse model led to a decrease of circulating TMAO and an increase of TMA and has a protective effect on atherosclerosis [28]*. This FMO3 deletion also reduces plasma lipids, ketone bodies, glucose, insulin and hepatic lipids. This study suggests that rather than considering TMAO as an atherosclerosis precursor, direct roles of FMO3 in the prevention/development of cardiovascular diseases should be investigated. Further investigations in mice confirmed that FMO3 deletion is beneficial for atherosclerosis and that FMO3 expression is increased in obese/insulin resistant subjects [29]*.

Bile acids

The gut microbiota contributes also to the structural diversity of circulating bile acids - indeed, primary bile acids (cholic acid and chenodeoxycholic acid) synthesised by the liver are conjugated with taurine or glycine and during enterohepatic circulation primary bile acids are deconjugated, hydroxylated, oxidized and epimerized by gut enzymes to form secondary bile acids [30]. The enterohepatic circulation of these secondary bile acids generate tertiary bile acids. The bile acids and their precursors oxysterols are versatile molecules with i) bacteriostatic [31], ii) emulsifying and iii) signalling properties. Bile acids have a beneficial effect in CMD by improving insulin sensitivity, hyperglycemia and dyslipidemia. Bariatric surgery studies also demonstrated that microbiome interventions increased circulating bile acids, which appeared to be critical for body weight loss and glucose homeostasis [32]** [33].

Bile acids regulate glucose homeostasis via several pathways, i.e., activation of Farnesoid X Receptor (FXR or NR1H4), Gαi protein-dependent receptor and the TGR5 receptor (or GP-BAR1, or M-BAR) (Figure 2) [34]. Activation of FXR by bile acids downregulates fatty acid and triglyceride synthesis in the liver and decreases circulating triglycerides and VLDL production (Figure 2) [34]. Bile acids also
increase energy expenditure through cAMP-mediated synthesis of thyroid hormone [34]. In vitro experiments also show that deoxycholic acid is a stronger TGR5 agonist [34] and it is a greater antimicrobial agent compared to cholic acid [31]. However, the potential beneficial effects of deoxycholic acid are offset by the fact that it can cause obesity [35] and trigger hepatocellular carcinoma through the senescence secretome [36]*.

Bile acids modified by the gut microbiota, such as deoxycholic acid and lithocholic acid, are also able to activate alternative pathways through interactions with EGFR/FAS [37] and PXR/Vitamin D receptor respectively [38]. For instance, a mouse study highlighted the ability of the gut to reduce bile acid pool size, particularly of the primary bile acid tauro-beta-muricholic acid (TβMCA) and to modulate Fibroblast Growth Factor 15 (FGF15, in human FGF19), which is involved in the inhibition of bile acid synthesis [39]*. However, key outcomes of modified bile acid pool by the gut are still unclear. In addition, the major bile acids differ between mice and humans, and thus the relevance of these findings to humans is contentious.

**Indoles**

The gut microbiome also heavily influences metabolism of aromatic amino-acids, degrading tryptophan into a series indoles with signalling properties. Tryptophan is an aromatic amino acid that can be directly converted to indole through the activity of bacterial tryptophanase (present in *Bacteroides thetaiotaomicron, Proteus vulgaris* and *Escherichia coli*, amongst others) [40]. Indole is later sulphated into 3-indoxylsulphate in the liver [40]. Conversely, *Clostridium sp.* and *Lactobacillus sp.* are able to deaminate tryptophan, producing indole-3-pyruvate indole-3-lactate, indole-3-acetate and 3-methylindole [41].

3-indoxylsulphate induces nuclear translocation of Aryl Hydrocarbon Receptor (AhR) [42]*. AhR agonists enter the cell by diffusion and bind to the cytosolic inactive AhR complex, comprised by heat shock protein 90 (hsp90), HBB X-associated protein 2 (XAP2) and protein 23 (p23) [43,44]. Upon binding, the bound complex is translocated into the nucleus, resulting in the recognition of
xenobiotic responsive elements (XRE) and transcription of genes coding for detoxification enzymes (CYP1A1, CYP1A2 and CYP2S1)[43]. AhR was also shown to mediate inflammatory signalling through non-canonical pathways, activating NF-KB and AP-1 independently of AhR nuclear translocation [45].

Although initially described as a xenobiotic receptor, AHR is currently considered a physiological modulator of energy metabolism, as its activation is associated with both obesity and type 2 diabetes [46]. Serum levels of 3-indoxylsulphate are associated with several deleterious cardiac outcomes, including left ventricular cardiac fibrosis [47]* but the underlying molecular mechanism remains unclear. By modulating inflammation via AHR, 3-indoxylsulphate is potentially regulating a core feature of CMD, which might partially explain these clinical associations [48].

Another indolic compound, indole-3-propionate, was also shown to play a role in two important mechanisms in CMD – intestinal integrity and inflammation. When the intestinal barrier becomes compromised, the access of both dietary antigen and pathogens is facilitated, eventually leading to innate immune activation, increased cytokine production and insulin resistance [48]. PXR activation improves inflammatory tone in intestinal bowel syndrome contexts [49]. Playing a central role in intestinal integrity via Pregnane X Receptor (PXR) modulation, indole-3-propionate may also play a beneficial role in CMD [50]*.

Through the previous examples (Figure 3), we have shown how the gut microbial signalling metabolome can modulate CMD development and progression.

**Microbiome interventions**

Manipulating gut microbiota emerges, therefore, as a promising therapeutic tool to reduce CMD prevalence but this concept has been challenged by the difficulty of identifying rational targets.
Promotion of beneficial bacteria growth: prebiotic supplementation

Nutritional interventions have proved to be a practical and easy way to modify gut bacterial ecosystem; healthy eating having beneficial outcomes for both the microbiome and its host. The growth of beneficial species can be directly promoted by the supplementation with prebiotics, substrates used as energy sources (i.e.: fructosyl-oligosaccharides, inulin (long-chain fructosyl-oligosaccharide), and galactosyl-oligosaccharides) promoting the growth of beneficial bacteria. This concept was supported by the finding that supplementation with oligo-fructants type fibres in high-fat-diet fed mice promoted and increased *Bifidobacteria* and *Lactobacilli* leading to an improvement of glucose tolerance, a reduction of endotoxemia and normalisation of the low-grade inflammatory status [51]. Dietary supplementations with prebiotics in mouse models was also associated with reduced appetite, modification of lipid metabolism in rodents [52]. In particular, galacto-oligosaccharides supplementation in healthy mice down-regulates the activity of lipogenic enzymes fatty acid synthase (FAS) and the microsomal triglyceride transfer proteins (MTTP), the latter being involved in VLDL synthesis [53].

Modulation of GLP-1 signalling is one of the possible routes through which prebiotics participate in the control of obesity and associated disorders. Treatment with the prebiotic oligofructose increases the total number of GLP-1 expressing cells in the colon of male Wistar rats [54]. Interestingly, butyrate stimulates the production of GLP-1 in intestinal cells [13], highlighting that gut microbial modulation with prebiotics promotes the growth of butyrate-producing bacteria, thus increasing GLP-1 production. In general the beneficial effects of prebiotic and probiotics have been attributed to the increased SCFA production [51].

Transferring beneficial bacteria: probiotic interventions and fecal microbiota transplantations

A different approach is the utilisation of probiotic bacteria as dietary supplements with the aim of improving human health. Treatment of high-fat diet-fed mice with the probiotic VSL#3 showed to
increase the levels of butyrate, and to suppress body weight gain and insulin resistance in various mouse models [13]*. In humans, the administration of the probiotics *Lactobacillus acidophilus* La5 and *Bifidobacterium lactis* Bb12 significantly improved glucose homeostasis and increased total antioxidant status [55]. Probiotic bacteria also modulate the enterohepatic circulation and bile acids production [52]. A potential future probiotic treatment could also involve *Akkermansia muciniphila*, a bacteria able to reverse high-fat diet induced metabolic disorders in mice [56]**. The association between *Akkermansia muciniphila* and a healthier metabolic status has been recently validated in human study [57]*.

Prebiotics and probiotics have also been used concomitantly in clinical trials – the synbiotic approach. As an example, the administration of a synbiotic shake, containing *Lactobacillus acidophilus*, *Bifidobacterium bifidum* and oligofrutose significantly increased HDL cholesterol, but no significant decrease was observed either in total cholesterol or triglycerides [58].

Faecal microbiota transplantation (FMT) was suggested as a strategy to transfer an ecologically stable bacterial community with beneficial properties. Studies on animal models demonstrated that murine microbiomes could be transplanted to impact body weight and that the architecture of the microbiome in obese mice matches the observations in obese patients [59] [60]*. However, the effect of microbiome transplantations can be mitigated by environmental influences such as co-housing for animal models [60]*.

Vrieze et al. showed that transplanting patients with metabolic syndrome with intestinal content from lean donors resulted in an improvement of both insulin sensitivity and levels of butyrate-producing intestinal microbiota (*Roseburia intestinalis* and *Eubacterium hallii*). Hence, it can be speculated that this untargeted approach might be considered as a potential therapeutic strategy for glucose impairment disorders in humans [61].
Knocking down undesired bacteria: antibiotherapy and phage therapy

A more targeted approach would be to modify the gut microbiota through the specific modulation of bacteria known to be associated with cardiometabolic outcomes. Antibiotic therapy has been recently proposed as a therapeutic tool to help restore altered gut bacterial ecosystem in obese humans. Vancomycin, an antibiotic with anti-Gram negative activity, promoted a large reduction in *Firmicutes, Bacteroidetes* and *Proteobacteria* in a diet-induced obesity model [62]*. These changes were accompanied by a reduction in body weight gain and improved inflammatory and metabolic outcomes [62]*. However, antibiotic use has important clinical limitations, since it is a non-selective approach that may compromise gut microbial ecosystem and select resistant strains, eventually leading to multiple drug resistance. Vancomycin was also associated with a simplification of gut bacteria bio-diversity and the opportunistic overgrowth of pathogenic bacteria such as *Clostridium difficile* causing infections and diarrhoea [63], echoing other findings on bacterial gene count.

Phage therapy is another alternative strategy to selectively eliminate undesired bacteria. Bacteriophages – or “phages” – are obligate intracellular viruses that replicate inside bacteria, using their biosynthetic machinery. In *Clostridium difficile* infection, phage therapy has reduced total bacterial number and toxin production, without any negative impact of commensal flora [64]*. With the potential of phages to be genetically modified and converted into precise tools to target specific bacteria – and therefore, specific metabolites and signalling pathways – phage therapy surges now as a potentially powerful tool for gut microbiota modulation. However, the cost and the challenges of phage manufacturing techniques have slowed down the development of phage based therapy [65], as well as ethical considerations regarding the use of genetically-modified organisms as a potential cure for disease.

Conclusions

Metabolomic approaches allowed the identification and monitoring of microbial metabolites as potential risk markers for CMD. However, the gut microbiota is a dynamic ecological community
deeply affected by external stimuli, and the causality of these correlations must be interpreted cautiously. A more complete understanding of the targets and pathways of these metabolites is therefore crucial, placing the study of the pharmacology of the microbial-mammalian interaction as one of the most relevant areas of future research in CMD. The microbial metabolites addressed exemplify the broad scope of the interaction between the gut microbiota and its mammalian host, and their potential to influence key mechanisms of CMD (e.g. glucose homeostasis, lipid homeostasis, inflammation, gut barrier integrity). Revisiting the pharmacology of these four classes of metabolites reveals the tip of the iceberg of the mammalian-microbial pharmacological interaction – and suggests how potentially powerful could be the plethora of metabolites that have been identified, but whose targets and signaling pathways remain to be fully understood. The modification of the gut microbiota, its metabolites and pharmacological targets arises therefore as a promising therapeutic avenue. As novel and powerful analytical methods provide a clearer understanding complexity of this interaction, specific interventions might be designed for personalized healthcare approaches.

Acknowledgements

A.L.N. is funded by the Portuguese Foundation for Science and Technology (FCT, SFRH/BD/52036/2012), J.C. by EU-FP7 METACARDIS (HEALTH-F4-2012-305312), M.S. is funded by Nestlé (RDLS015375), M.B.A.R. is funded by the Malaysian Government Agency (MARA, 330400647241), C.L.B. is funded by Metabometrix Ltd. M.-E.D. is supported by grants from the EU (Metacardis under agreement HEALTH-F4-2012-305312, Neuron II under agreement 291840) and the MRC (MR/M501797/1).
Figure 1. Role of butyrate in colonocytes metabolism and schematic overview of receptors activation by short-chain fatty acids (SCFA). (A) Butyrate produced from microbial fermentation of dietary fibre is transported into the colonocytes where is metabolised as major source of energy via TCA cycle. Butyrate also promotes hyperacetylation of histone protein by acting as HDAC inhibitor. SCFA bind to Free-Fatty Acid Receptors, causing the dissociation of the heterotrimeric G-protein complex into Gαi (FFAR3) (C) or Gαi/q (FFAR2) and Gβγ subunits. Gαi inhibits adenylate cyclase (AC) activity and decreases intracellular cAMP levels, with a resulting reduction in protein kinase A (PKA) activity. The inhibition of PKA activity leads to a decreased phosphorylation of CREB, therefore regulating the transcription of downstream genes. Gqα pathway activates phospholipase-Cβ (PLC-β) which catalyses the cleavage of phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol 1,4,5 triphosphate (IP3) and diacylglycerol (DAG). IP3 binds to IP3 receptors (IP3R) on the membrane of endoplasmic reticulum (ER) and increases the cytosolic Ca2+ concentration. Ca2+ and DAG also synergistically activate protein kinase C (PKC). Part of illustrations were designed using Servier Medical Art used under CC BY 3.0.

Figure 2. Bile acid signalling and regulation of cardiometabolic risk factors. Bile acid activation of the Farnesoid X Receptor (FXR) regulate lipid metabolism via activation of apolipoproteins A1, C II and C III (apo A1, apo C II and apo C III) and inhibition of Sterol Regulatory Element Binding Protein 1c (SREBP-1c). In addition, glucose homeostasis is regulate by various pathways including; FOXO1, Glucocorticoid Receptor (GR) and Hepatocyte nuclear factor 4 α (HFN4α) activated through FXR, Glucagon-Like Peptide-1 (GLP-1) by TGR5 receptor (or GP-BAR1, or M-BAR) and Glycogen Synthase (GS) by Gαi protein.

Figure 3. Synoptic chart of precursors, microbial-mammalian co-metabolites and respective targets and effects. Gut microbiota converts dietary and endogenous substrates into metabolites that act as chemical messengers and modulate CMD-related outcomes. AhR: Aryl hydrocarbon receptor; CA: Cholic acid; CDCA: Chenodeoxycholic acid; DCA: Deoxycholic acid; FFAR2: Free fatty acid receptor 2; FFAR3: Free fatty acid receptor 3; FXR: Farnesoid X receptor; LCA: lithocholic acid; PXR: Pregnane X receptor; TMA: trimethylamine; TMAO: trimethylamine-N-oxide.
References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as: * of special interest ** of outstanding interest


This article shows that diet influences bacterial metabolism as demonstrated by metabolic reconstruction of a selection of the most abundant bacteria in the human gut reflecting metabolite levels in feces and blood.


In this landmark article, investigators from the MetaHIT consortium introduced the concept of gene richness based on the observation that obese patients presented a lower gene count than healthy patients in a metagenomic study. Although there are already several phylogenetic diversity indices, using the total number of non-identical bacterial genes as a potential risk factor was equally surprising and succesful.


This study from the MicroObes consortium further examplified the concept of gene richness introduced in the previous reference, by demonstrating that dietary interventions, such as weight loss diet, can increase gene richness as volunteers become healthier, thus showing that the gene richness x obesity negative association can be therapeutically actioned.


This study develops a comprehensive metagenomic signature associated with type 2 diabetes in 145 Swedish post-menopausal women, suggesting both compositional and functional shifts in the metagenome of diabetics.


In this paper, new properties of short-chain fatty acid acetate as a neuroactive compound regulating appetite are exposed. This study shows that acetate induces anorectic neuropeptide expression profiles, thus complementing the existing functional repertoire of short-chain fatty acids which are already fuel metabolites, receptor agonists and histone deacetylation inhibitors.


This study suggests that probiotic-induced production of SCFAs improves glucose tolerance and lowers food intake through the excretion of the satiety hormone, GLP-1.


This study show that SCFA-mediated activation of GPR43 inhibits insulin signalling in adipocytes and consequently reduces lipid storage in adipose tissue, promoting its metabolism in other tissues.


This article demonstrates that butyrate activates intestinal gluconeogenesis (IGN) by a cAMP mechanism, whilst propionate activates IGN through a gut-brain neural circuit involving FFAR3 receptor.


This paper identified confirmed that 7 out of 8 human gut isolates (out of 79 tested) were able to produce TMA from Choline as predicted from phylogenetics and based the presence of Cut
C gene [32], whereas the 8th isolate produced TMA but did not have Cut C. The article demonstrated that inoculation of germ-free mice with TMA-producing bacteria results in an increase in TMA abundance in cecum, increase TMAO in serum and reduce choline bioavailability.


This article further develops the role of TMAO in atherosclerosis by focussing on L-carnitine as a substrate for TMA synthesis and secondary TMAO formation in the liver.


This article suggests a direct role of TMAO-generating FMO3 enzyme on glucose and lipid homeostasis independently of TMAO metabolism. Increasing FMO3 activity would be able to prevent atherosclerosis even if this increases TMAO concentration.


This article suggests a link between TMAO-generating FMO3 enzyme and insulin resistance. Shows that FMO3 is increased in human livers from obese/insulin-resistant patients and that SNPs at the FMO3 locus significantly associated with blood glucose levels.


This landmark article shows that mice deficient for bile acid nuclear receptor FXR regain weight after stomach-stapling surgery and highlights bile acids as key microbial metabolites in the weight loss area.


Although bile acids have various beneficial properties, this study identified a carcinogenesis process involving gut bacterial bile acid product deoxy-cholic acid, through senescence-associated secretome.


This study demonstrates that, apart from regulating secondary bile acid metabolism, gut microbiota also reduce the synthesis of bile acids in the liver, by a mechanism involving the suppression of FXR expression in the ileum.


In this paper, the uremic solutes indoxylsulphate and indole-3-acetate were shown to upregulate the production of tissue factor, as well as several genes regulated by the aryl hydrocarbon receptor pathway. These results suggest a new toxicity mechanism for cardiovascular risk in chronic kidney disease patients.


This paper demonstrates that treatment with indoxylsulphate aggravates cardiac fibrosis and cardiomyocyte hypertrophy in a rat model. Interestingly, an enhancement of the oxidative stress was also observed, suggesting that this underlying mechanism might be involved.


This article provides new insights into the role of bacterial metabolites as signalling molecules, by showing that indole-3-acetate (IPA) has beneficial properties for host GI barrier function and immune tone through an agonism for xenobiotic receptor PXR.


This article shows that treatment with *Akkermansia muciniphila*, a mucin-degrading member of the gut microbiota inversely correlated with body weight, reversed high-fat diet-induced metabolic disorders such as body weight gain, insulin resistance and low-grade inflammation.


This study confirms the positive association between *Akkermansia muciniphila* and health as initially described in [56], and further expands the beneficial association with gene richness introduced [2] and its modification by dietary interventions [4].


This article demonstrates that the effects of gut microbiota transplantations on obesity can be modulated by environmental factors such as cage effects in the case of animal models.


This paper provides further evidences of the potential therapeutic applications of antimicrobial agents and highlights the importance of their specificity in the treatment of obesity


This experiment demonstrates the efficacy of phage therapy in limiting pathogenic bacteria *C. difficile* and highlights the limitations associated to lysogenic phages.

Figure 2
Dietary and endogenous substrates

- Choline
- Primary bile acids (CA, CDCA)
- Indigestible dietary fibre
- Tryptophan
- Other metabolites

Microbial-mammalian co-metabolites

- Methylamines (TMA, TMAO)
- Secondary (DCA, LCA) and tertiary bile acids
- SCFAs (acetate, propionate, butyrate)
- Indoles (3-indoxylsulphate, indole-3-propionate)

Targets

- FXR TGR5
- FFAR2, FFAR3
- AhR, PXR

Effects

- Atherosclerosis NAFLD
- Glucose homeostasis Lipid homeostasis
- Appetite regulation Glucose homeostasis
- Inflammation Intestinal barrier integrity