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Gut Microbiota and Host Metabolism: A Biochemical Perspective

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Abstract

The gut contains a huge and complex population of microorganisms, the gut microbiota, which have a powerful biochemical effect on host metabolism. In this review, the authors discuss the possible mechanistic pathways of gut microbes that interact with host metabolic pathways, particularly key microbial metabolic products such as short-chain fatty acids (SCFAs), bile acid derivatives, branched-chain amino acid catabolites, tryptophan metabolites, and trimethylamine N-oxide (TMAO). This bidirectional dialogue between the microbiota and host tissues, such as the liver, adipose tissue, intestinal epithelium and central nervous system, is explored. Dysbiosis-related metabolic diseases including obesity, type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), and metabolic syndrome are given special attention. Insurgencies in the treatment of Dysbiosis with prebiotics, probiotics, symbiotic, fecal microbiota transplantation (FMT) and precision nutrition are discussed critically. Overall, a full picture of host–microbiota metabolic crosstalk could provide new opportunities for disease markers and targets.

Keywords: Gut microbiota, host metabolism, SCFAs, dysbiosis, bile acids, TMAO, metabolic syndrome, microbiome–liver axis

1. Introduction

The gut microbiota, which includes bacteria, archaea, fungi, viruses and protozoa, is estimated to colonise the human gastrointestinal tract with 1013-1014 microorganisms. This microbial ecosystem harbours over 150 times as many genes as the human genome and has a truly extraordinary metabolic potential – a 'second genome' as it is sometimes called. Gut microbiota is not a mere commensal passenger, but an active player in host physiology, with an array of functions that include nutrient digestion, immune modulation and neuroendocrine signaling. Biochemically, the gut microbiota breaks down substrates that are indigestible by host enzymes, such as complex polysaccharides,

resistant starches and polyphenols from plants, into a multitude of bioactive metabolites. These metabolites are transferred to the systemic circulation and regulate metabolic pathways in virtually all the major organ systems such as liver, adipose tissue, skeletal muscle, pancreas and brain.

Host genetics, diet, age, antibiotic use and the environment all influence the composition of gut microbiota. An imbalance in the normal microbial community, known as dysbiosis, is now known to play a role in a variety of metabolic disorders. It is therefore important to understand the biochemical mechanism of action of the microbiota on host metabolism, to develop new diagnostic and therapeutic strategies [1]. This review aims to give an integrative biochemical viewpoint on the metabolic interactions between host and microbiota, highlighting the main classes of metabolites produced by the microorganisms, metabolic axes in the organs, diseases association and therapeutic frontiers.

2. Composition and Ecology of the Gut Microbiota

2.1 Phylogenetic Overview

In the adult human gut, the predominant bacterial phyla in the microbiota are Firmicutes, 50–80% and Bacteroidetes, 20–40%, and Proteobacteria, Actinobacteria, Verrucomicrobia and Fusobacteria are present in smaller amounts. Bacteroides, Prevotella, Ruminococcus, Faecalibacterium, Lactobacillus, Bifidobacterium, Akkermansia and Clostridium are key genera. Methanobrevibacter smithii is an important archaeon for disposing hydrogen, which increases the efficiency of the fermentation of polysaccharides by cross-feeding with saccharolytic bacteria. The individual microbiome is very consistent over time and very different among individuals, but healthy individuals share some common factors to constitute the 'core microbiome'. High throughput 16S rRNA gene sequencing and metagenomics have dramatically changed the capacity to characterise microbial communities and correlate these with host metabolic phenotypes [2].

2.2 Enterotypes and Functional Redundancy

The notion of ‘enterotypes', that is, discrete and robust community states characterized by the relative abundance of dominant genera (Bacteroides, Prevotella or Ruminococcus), reflects a certain ecological organization in the microbiome. However, there is functional redundancy, which is the ability of taxonomically different microorganisms to catalyze the same metabolic reactions, therefore community structure does not necessarily imply metabolic function. Combining metagenomic and metatranscriptomic data shows that functional gene content and active gene expression

predict metabolic outcome of the host more strongly than just the phylogenetic composition does[3].

2.3 Developmental and Environmental Determinants

Important changes of microbiota occur from birth to adult life. Delivery mode (vaginal or cesarean), breastfeeding and early antibiotic exposure have an impact on initial colonization. The adult microbiome becomes stable around 3-5 years and changes little with age after that, except in the elderly, when it becomes less diverse with more Proteobacteria. The single biggest factor which affects the microbiome is diet: long-term dietary patterns have a stronger impact than short-term changes, and plant-rich, high-fiber diets correlate with increased diversity and abundance of the bacteria that produce butyrate[4].

3. Key Microbial Metabolites and Their Biochemical Actions

3.1 Short-Chain Fatty Acids (SCFAs)

Short-chain fatty acids primarily acetate (C2), propionate (C3), and butyrate (C4) are produced by anaerobic fermentation of dietary fiber by colonic bacteria, predominantly Firmicutes (Lachnospiraceae, Ruminococcaceae) and Bacteroidetes. The total luminal SCFA concentration ranges from 50–150 mM in the proximal colon, decreasing distally as substrate is depleted.

3.1.1 Butyrate

Butyrate is the preferred energy substrate for colonocytes, supplying approximately 70% of their energy via mitochondrial beta-oxidation, generating acetyl-CoA that enters the TCA cycle. Beyond bioenergetics, butyrate exerts epigenetic regulatory effects: it is a potent inhibitor of class I and II histone deacetylases (HDACs), thereby promoting histone acetylation and enhancing expression of genes involved in cellular differentiation, tight junction integrity, and anti-inflammatory signaling. Butyrate-mediated HDAC inhibition activates peroxisome proliferator-activated receptor gamma (PPARγ) in colonocytes, stimulating beta-oxidation and suppressing expression of pro-inflammatory cytokines (TNF-α, IL-6).

Systemically, butyrate reaches the portal circulation in low concentrations (~10 μM) and influences hepatic lipid and glucose metabolism. It stimulates gluconeogenesis from propionate in hepatocytes and promotes intestinal gluconeogenesis via a portal nerve-mediated reflex that reduces hepatic glucose output and improves insulin sensitivity. Butyrate also activates free fatty acid receptors GPR41 (FFAR3) and GPR43 (FFAR2) on enteroendocrine L-cells, stimulating secretion of peptide YY (PYY) and glucagon-like peptide-1 (GLP-1), which suppress appetite and enhance insulin secretion respectively [5].

3.1.2 Propionate

Propionate is primarily produced by Bacteroidetes via the succinate pathway and by some Firmicutes via the acrylate pathway. It is efficiently extracted by the liver (~90% first-pass), where it serves as a gluconeogenic precursor via propionyl-CoA carboxylase and methylmalonyl-CoA mutase, ultimately entering the TCA cycle as succinyl-CoA. Propionate inhibits hepatic lipogenesis by reducing cytoplasmic acetyl-CoA availability and suppressing fatty acid synthase (FAS) expression via downregulation of SREBP-1c. It also activates GPR43 and inhibits histone acetylation in hepatocytes, modulating inflammatory gene expression [6].

3.1.3 Acetate

Acetate is the most abundant circulating SCFA and exerts systemic effects. It crosses the blood-brain barrier and suppresses appetite through central hypothalamic mechanisms involving GABA-ergic signaling. Peripherally, acetate is incorporated into acetyl-CoA in multiple tissues, contributing to lipid and cholesterol synthesis. Its role in peripheral energy homeostasis is complex; while it can serve as a lipogenic substrate in adipocytes, acetate receptor GPR43 activation in adipose tissue inhibits lipolysis and reduces circulating free fatty acids, thereby lowering lipotoxic stress in peripheral tissues [7].

Table 1. Major SCFAs: Biochemical Properties and Metabolic Functions

SCFA	Primary Producers	Main Metabolic Site	Key Receptors	Major Metabolic Effect
Butyrate (C4)	Lachnospiraceae, Ruminococcaceae	Colonocytes, Liver	GPR41, GPR43, HDAC inhibition	Colonocyte energy, anti-inflammatory, gut barrier
Propionate (C3)	Bacteroidetes, some Firmicutes	Liver (~90% extracted)	GPR41, GPR43	Hepatic gluconeogenesis, anti-lipogenic
Acetate (C2)	Bacteroidetes, Bifidobacterium	Peripheral tissues, CNS	GPR43, GPR41	Appetite suppression, acetyl-CoA substrate

3.2 Bile Acid Metabolism

Primary bile acids cholic acid (CA) and chenodeoxycholic acid (CDCA) are synthesized in hepatocytes from cholesterol via the classical (microsomal) and alternative (mitochondrial) pathways, conjugated with glycine or taurine, and secreted into bile. The gut microbiota profoundly modifies the bile acid pool through two major biotransformations: deconjugation by bile salt hydrolases (BSH), widely expressed across Lactobacillus, Bifidobacterium, Clostridium, and Bacteroides; and 7α-dehydroxylation by

specialized Clostridium and Eubacterium species, converting primary bile acids into secondary bile acids deoxycholic acid (DCA) from CA, and lithocholic acid (LCA) from CDCA. Bile acids act as signaling molecules that activate two main receptors: the farnesoid X receptor (FXR), a nuclear receptor central to hepatic lipid and glucose homeostasis; and the Takeda G-protein receptor 5 (TGR5, also known as GPBAR1), a membrane receptor expressed on enteroendocrine L-cells and macrophages. FXR activation in the intestine stimulates fibroblast growth factor 19 (FGF19) secretion, which travels via the portal vein to the liver to suppress de novo lipogenesis, reduce bile acid synthesis through negative feedback on CYP7A1, and improve glycemic control by modulating hepatic glycogen synthesis. TGR5 activation by secondary bile acids (particularly LCA and DCA) stimulates GLP-1 secretion from L-cells and promotes energy expenditure by inducing thyroid hormone deiodinase type 2 (D2) activity in brown adipocytes, increasing intracellular T3 and thermogenesis.

Dysbiosis reduces BSH activity and 7α-dehydroxylation capacity, shifting the bile acid pool toward conjugated primary bile acids. This impairs FXR signaling, disrupts lipid absorption and cholesterol homeostasis, and alters GLP-1 secretion, contributing to metabolic dysfunction. Elevated DCA levels, conversely, are associated with hepatocyte apoptosis and promotion of hepatocellular carcinoma in animal models [8].

3.3 Amino Acid-Derived Metabolites

3.3.1 Tryptophan Metabolites

Tryptophan, an essential aromatic amino acid, is catabolized by the gut microbiota through multiple pathways generating metabolites with distinct biological activities. The indole pathway, mediated by bacterial tryptophanase (tnaA gene, expressed by E. coli, Clostridium, Bacteroides), produces indole and its derivatives (indole-3-acetic acid [IAA], indole-3-propionic acid [IPA], indole-3-aldehyde [IAld]), which are potent ligands for the aryl hydrocarbon receptor (AhR) and pregnane X receptor (PXR). AhR activation by microbial indoles in intestinal epithelial cells and Th17 lymphocytes stimulates IL-22 production, promoting epithelial barrier repair, antimicrobial peptide secretion, and mucosal immunity. IPA is a particularly potent antioxidant that scavenges hydroxyl radicals and has neuroprotective properties; it also activates intestinal PXR to downregulate TNF-α-mediated inflammatory signaling. The serotonin pathway is also microbially regulated: enterochromaffin cells produce >90% of the body's serotonin from tryptophan via tryptophan hydroxylase 1 (TPH1), and colonization by spore-forming Clostridia promotes TPH1 expression. Serotonin modulates GI motility, platelet aggregation, and central neurotransmission via the gut-brain axis. The competing kynurenine pathway, regulated by host indoleamine 2,3-dioxygenase (IDO) and

tryptophan 2,3-dioxygenase (TDO), is upregulated by inflammation and produces neuroactive metabolites including quinolinic acid (excitotoxic) and kynurenic acid (neuroprotective), with implications for depression and neuroinflammatory conditions [9].

3.3.2 BCAA Metabolism and Imidazole Propionate

Branched-chain amino acids (BCAAs leucine, isoleucine, valine) are catabolized by gut bacteria, particularly Prevotella copri and Bacteroides vulgatus, generating intermediates that enter the host circulation. Elevated circulating BCAAs are among the strongest metabolic predictors of insulin resistance and type 2 diabetes. Mechanistically, chronic BCAA excess activates the mTORC1/S6K1 signaling cascade in skeletal muscle, promoting inhibitory serine phosphorylation of IRS-1 and uncoupling insulin receptor signaling from downstream PI3K/Akt activation, thereby blunting glucose transporter GLUT4 translocation. Imidazole propionate, a microbially-derived histidine catabolite produced by species including Streptococcus mutans and Eggerthella lenta, directly impairs insulin signaling through a distinct mechanism: it activates the p38γ MAPK – mTORC1 axis, promoting inhibitory phosphorylation of IRS-1 at Ser1101 independently of BCAA pathways. Fecal imidazole propionate levels are elevated in type 2 diabetic patients, suggesting it may be a clinically relevant mediator of microbiota-driven insulin resistance [10].

3.4 Trimethylamine N-Oxide (TMAO)

Trimethylamine N-oxide is produced through a two-step pathway: gut bacteria (primarily Gammaproteobacteria, Firmicutes, and Actinobacteria) metabolize dietary precursors choline, phosphatidylcholine, L-carnitine, and betaine to trimethylamine (TMA) via enzymes encoded by the cutC/D, cntA/B, and yeaW/X gene clusters. TMA is absorbed and oxidized to TMAO in the liver by flavin-containing monooxygenase 3 (FMO3). TMAO promotes atherosclerosis through multiple mechanisms: it impairs reverse cholesterol transport by suppressing hepatic bile acid synthesis (CYP7A1, CYP27A1) and reducing hepatic cholesterol efflux transporter (ABCA1, ABCG1) expression; it enhances macrophage foam cell formation by upregulating scavenger receptors CD36 and SR-A1 while inhibiting reverse cholesterol transport; and it promotes platelet hyperreactivity and thrombosis through enhanced intracellular Ca^{2+} release. Circulating TMAO levels independently predict major adverse cardiovascular events in prospective clinical studies. TMAO also induces endoplasmic reticulum stress in hepatocytes, promoting hepatic lipid accumulation and inflammation relevant to NAFLD pathogenesis [11].

3.5 Lipopolysaccharide (LPS) and Metabolic Endotoxemia

Lipopolysaccharide, the outer membrane component of Gram-negative bacteria, is a potent activator of innate immune signaling through TLR4/CD14/MD-2 receptor complexes. In healthy conditions, intestinal tight junction proteins (claudin-1, occludin, ZO-1) limit LPS translocation. High-fat diets increase intestinal permeability and promote translocation of LPS into the portal circulation, establishing a state of 'metabolic endotoxemia' (plasma LPS 2–3× above fasting baseline). Portal LPS activates Kupffer cell TLR4 signaling, triggering NF-κB-mediated hepatic inflammation, JNK-mediated inhibition of insulin signaling, and promotion of steatohepatitis. Systemic low-grade LPS signaling in adipose tissue activates inflammatory macrophages (M1 polarization), generating a cytokine milieu (TNF-α, IL-1β, IL-6) that promotes systemic insulin resistance [12].

4. Microbiota–Host Metabolic Axes

4.1 The Gut–Liver Axis

The liver occupies a privileged anatomical position as the primary recipient of portal blood, making it the first solid organ exposed to gut-derived metabolites, microbial products, and translocated bacteria. The hepatic microbiome is normally negligible, but dysbiosis-associated portal LPS influx activates Kupffer cell TLR4–NF-κB signaling, driving hepatic inflammation. Simultaneously, altered SCFA profiles reduce hepatic PPAR-α-mediated fatty acid oxidation while increased LPS promotes de novo lipogenesis via LXR and SREBP-1c, creating a biochemical environment conducive to non-alcoholic fatty liver disease (NAFLD) progression.

Gut-derived secondary bile acids regulate hepatic cholesterol and triglyceride metabolism through FXR. FXR activation suppresses CYP7A1 (rate-limiting enzyme in bile acid synthesis), reduces VLDL secretion via apolipoprotein C-II downregulation, and promotes insulin sensitivity by enhancing hepatic glycogen synthesis and suppressing gluconeogenic gene expression (PEPCK, G6Pase). Dysbiosis-associated reduction in secondary bile acid production impairs FXR signaling and contributes to hepatic dyslipidemia [13].

4.2 The Gut–Adipose Tissue Axis

The gut microbiota influences adipose tissue mass and function through multiple biochemical mechanisms. Germ-free mice have dramatically reduced adipose tissue despite comparable caloric intake, implicating microbial factors in fat storage regulation. Key mechanisms include: suppression of fasting-induced adipose factor (FIAF/Angptl4) by microbiota, which enhances lipoprotein lipase (LPL) activity and promotes triglyceride storage in adipocytes; SCFA-mediated GPR43 activation in adipocytes, which inhibits adenylyl cyclase and reduces cAMP-dependent lipolysis; and microbially-influenced

modulation of endocannabinoid tone in adipocytes, which promotes lipogenesis through CB1 receptor signaling. Akkermansia muciniphila, a mucin-degrading Verrucomicrobia species, has emerged as a keystone organism linking gut integrity to metabolic health. Its abundance inversely correlates with obesity, type 2 diabetes, and cardiometabolic risk markers. A. muciniphila-derived outer membrane protein Amuc_1100 activates TLR2 in adipocytes and macrophages, promoting anti-inflammatory signaling and improving insulin sensitivity. In mouse models, A. muciniphila supplementation reduces adipose tissue inflammation and improves glucose homeostasis even in the absence of viable bacteria [14].

4.3 The Gut–Brain Axis

The bidirectional gut–brain axis encompasses neural (vagus nerve), endocrine (gut hormones, HPA axis), immune (cytokines), and metabolic (microbial metabolites) communication pathways. Gut microbiota influence central appetite regulation through multiple mechanisms: SCFA-stimulated GLP-1 and PYY secretion from enteroendocrine L-cells activates hypothalamic neurons suppressing food intake; acetate crosses the blood-brain barrier and directly suppresses hypothalamic NPY/AgRP neurons; and gut-derived serotonin modulates vagal afferent signaling that regulates satiety perception. Microbially produced neurotransmitter precursors and modulators include: tryptophan (serotonin precursor), tyrosine (dopamine/norepinephrine precursor), GABA (produced by Lactobacillus and Bifidobacterium), and acetylcholine precursors. Germ-free rodents exhibit abnormal stress responses and anxiety-like behavior, altered hippocampal neurogenesis, and impaired serotonin turnover, suggesting that developmental microbiome colonization programs the HPA axis and limbic system. In adult life, Lactobacillus rhamnosus supplementation reduces stress-induced corticosterone release via vagus-dependent pathways and modulates GABA receptor expression in cortical regions [15].

4.4 The Gut–Pancreas Axis

Microbially-stimulated GLP-1 and GIP secretion from enteroendocrine cells is the primary mechanism by which gut microbiota influence pancreatic function. GLP-1 stimulates glucose-dependent insulin secretion from beta cells, promotes beta-cell proliferation, and inhibits glucagon secretion from alpha cells. GLP-1 also reduces hepatic glucose output and promotes satiety via the vagus nerve. The microbiota also influences pancreatic islet development; germ-free mice have morphologically abnormal islets with reduced beta-cell mass that are corrected by SCFA supplementation or normal colonization, suggesting microbially-derived SCFAs promote pancreatic beta-cell development and function through GPR41-mediated signaling.

5. Dysbiosis and Metabolic Disease

5.1 Obesity

The association between gut microbiota composition and obesity has been extensively studied in both animal models and human cohorts. Landmark studies demonstrated that germ-free mice are protected from diet-induced obesity and that transplantation of microbiota from obese mice or humans to germ-free recipients increases adiposity relative to lean donor transfers, establishing a causal role for the microbiome in fat mass regulation. Obese individuals typically exhibit reduced microbial diversity, decreased Bacteroidetes:Firmicutes ratio (though this is less consistent than originally reported), and depletion of butyrate producers such as Faecalibacterium prausnitzii and Roseburia intestinalis. Biochemically, the obese microbiome has enhanced capacity for energy harvest from complex carbohydrates, producing more SCFAs per unit substrate — an adaptation that initially appears metabolically beneficial but, under caloric surplus conditions, contributes to excess energy extraction. The obese microbiome also impairs gut barrier function, increasing LPS translocation and metabolic endotoxemia, and shifts bile acid metabolism to favor secondary bile acid profiles that reduce FXR activation and impair energy expenditure[10].

5.2 Type 2 Diabetes Mellitus

Multiple large-scale metagenomic studies have identified consistent alterations in the gut microbiome of patients with type 2 diabetes (T2D). Key features include depletion of butyrate-producing Roseburia intestinalis and Faecalibacterium prausnitzii, enrichment of Lactobacillus gasseri, and elevated proportions of Clostridiales and Proteobacteria. The gut microbiome of T2D patients exhibits reduced capacity for biosynthesis of essential vitamins (B12, biotin) and altered amino acid metabolism with overproduction of BCAAs and imidazole propionate. Mechanistically, T2D-associated dysbiosis impairs insulin signaling through: (1) TMAO-mediated ER stress and hepatic lipid accumulation; (2) BCAA and imidazole propionate-mediated IRS-1 inhibitory phosphorylation; (3) Reduced GLP-1 secretion due to impaired SCFA production and altered bile acid signaling; (4) Chronic low-grade inflammation from metabolic endotoxemia activating JNK and IKKβ pathways that phosphorylate IRS-1 serine residues, disrupting the insulin receptor cascade [7].

5.3 Non-Alcoholic Fatty Liver Disease (NAFLD)

The gut–liver axis is a central mechanistic framework for NAFLD pathogenesis. Dysbiosis increases intestinal permeability, elevating portal LPS and other microbial products that activate hepatic Kupffer cell TLR4 signaling. NF-κB activation induces hepatic inflammatory cytokine production (TNF-α, IL-1β, IL-6), which promotes hepatocyte

steatosis through inhibition of PPAR-α-mediated fatty acid oxidation and activation of SREBP-1c-driven de novo lipogenesis. Simultaneously, gut-derived ethanol (produced by Klebsiella pneumoniae in some individuals) induces hepatic oxidative stress and acetaldehyde formation, mimicking alcoholic liver injury mechanisms. TMAO accumulation in NAFLD promotes hepatocyte ER stress, activating the unfolded protein response (UPR) and triggering NLRP3 inflammasome activation — a key step in progression from simple steatosis to non-alcoholic steatohepatitis (NASH). Dysbiosis-associated reduction in FXR activation (due to impaired secondary bile acid production) removes an important hepatoprotective brake on lipogenesis and inflammation. Conversely, restoration of normal microbiome composition through interventions such as FMT or A. muciniphila supplementation consistently reduces hepatic steatosis and inflammation in preclinical models [11].

5.4 Metabolic Syndrome

Metabolic syndrome the clustering of abdominal obesity, dyslipidemia, hypertension, and insulin resistance shares microbiome features with each of its component conditions. A characteristic 'metabolic syndrome microbiome' displays reduced alpha-diversity, decreased F. prausnitzii and Akkermansia muciniphila abundance, increased Ruminococcus gnavus and Blautia, and altered SCFA/bile acid profiles. The shared microbial underpinning of metabolic syndrome components suggests that dysbiosis may be an upstream driver rather than a mere correlate, acting through the interlocking mechanisms of impaired SCFA signaling, elevated TMAO, metabolic endotoxemia, and altered bile acid-FXR-FGF19 signaling [14].

Table 2. Microbiota-Derived Metabolites in Metabolic Disease

Metabolite/Factor	Disease Association	Key Biochemical Mechanism	Therapeutic Target?
Butyrate (↓)	Obesity, T2D, IBD, NAFLD	Reduced HDAC inhibition, impaired GLP-1 secretion, barrier dysfunction	Yes (butyrate-producing probiotics)
TMAO (↑)	CVD, NAFLD, T2D	Impairs RCT, macrophage foam cells, ER stress, platelet activation	Yes (FMO3 inhibitors, DMB)
Secondary bile acids	Obesity, T2D,	Reduced FXR and TGR5	Yes (bile acid

Metabolite/Factor	Disease Association	Key Biochemical Mechanism	Therapeutic Target?
(↓)	NAFLD	activation, impaired energy expenditure	analogs, BSH probiotics)
LPS / metabolic endotoxemia (↑)	Obesity, T2D, NASH, MetS	TLR4-NF-κB hepatic/adipose inflammation, IRS-1 serine phosphorylation	Yes (prebiotics, gut barrier restoration)
BCAA catabolites (↑)	Insulin resistance, T2D	mTORC1/S6K1 activation, IRS-1 Ser307 phosphorylation, GLUT4 impairment	Yes (dietary BCAA restriction)
Imidazole propionate (↑)	T2D, insulin resistance	p38γ/mTORC1-mediated IRS-1 Ser1101 phosphorylation	Under investigation
Indole / IPA (↓)	IBD, gut dysbiosis, neurological	Reduced AhR/PXR activation, impaired IL-22, barrier repair, antioxidant	Yes (tryptophan-rich diet)

6. Therapeutic Strategies Targeting the Gut Microbiome

6.1 Dietary Interventions and Prebiotics

Diet influences the composition and metabolic activity of gut microbiome the most, and is the easiest to modify. Eating a lot of high fibre foods is consistently associated with growth of bacteria that produce SCFA (Bifidobacterium, Roseburia, Faecalibacterium prausnitzii) and more SCFA in the faeces. The prebiotic fibers such as inulin-type fructans (ITF), galactooligosaccharides (GOS), resistant starch and arabinoxylan selectively stimulate the growth of beneficial microorganisms due to the fact that they are fermentation substrates that cannot be utilized by competitive microorganisms. RCTs show that the ITF supplementation increases Bifidobacterium content, increases butyrate content in the colon, reduces metabolic endotoxemia and enhances glycemic control in overweight populations. A high intake of plant polyphenols, monounsaturated fatty acids and dietary fibers is linked to a microbiome profile that is marked by a large number of SCFA producers and Akkermansia muciniphila, while also having a low

number of pro-inflammatory Proteobacteria. Because of their low bioavailability at the small intestine, plant polyphenols like flavonoids, phenolic acids and stilbenes are biotransformed by the colon flora, with the generation of metabolites like equol (from daidzein) by Lactobacillus/Clostridium and urolithin A (from ellagitannins) by Gordonibacter urolithinfaciens, showing metabolic protection and anti-inflammatory activity[16].

6.2 Probiotics and Symbiotic

Probiotics", live microorganisms with a health promoting effect, are now starting to be utilised in the field of metabolic diseases. Commercial probiotics are mostly of the genera Lactobacillus (L. acidophilus, L. rhamnosus, L. reuteri) and Bifidobacterium. Modest yet significant effects of probiotics on fasting glucose, insulin resistance (HOMA-IR), LDL cholesterol and liver enzymes in T2D and NAFLD have been reported in meta-analyses. Mechanistic actions include upregulation of tight junction proteins, reduced metabolic endotoxemia, changed composition of the bile acid pool (via BSH activity) and local modulation of the immune system.

NGPs are important emerging beneficial taxa such as Akkermansia muciniphila, which has anti-insulin-resistance and anti-obesity properties; Faecalibacterium prausnitzii, which has anti-inflammatory bowel disease and anti-metabolic-syndrome properties; and Christensenella minuta, which has anti-obesity properties and is heritable. An A. muciniphila preparation is currently undergoing human clinical trials using pasteurized bacteria, with positive results in insulin resistant patients with regard to cardio metabolic markers; therefore, the possibility of using pasteurized (non-viable) probiotics with retained therapeutic activity exists. A more advanced approach to chronic modulation of the microbiome is the combination of both probiotics and prebiotics – these are called symbiotic [5].

6.3 Fecal Microbiota Transplantation (FMT)

Re-establishment of a healthy microbiome can be as broad as FMT (fecal microbiota transplantation) a healthy stool transferred to the recipient. FMT has been demonstrated to be effective in the treatment of recurrent C. difficile infection (>85% cure rate) and is under investigation for metabolic diseases. Pilot studies revealed that FMT of lean donors to metabolic syndrome patients resulted in peripheral insulin sensitivity for up to 6 months, engraftment of donor microbial taxa and increased levels of fecal butyrate. There are, however, differences in effect size and this is influenced by donor selection, initial composition of the recipient's microbiome, and host factors. The composition of the donor's microbiome is of fundamental importance, 'super-donors' with high microbiome diversity and presence of certain taxa, like Akkermansia muciniphila,

Prevotella copri, are more successful in treatment. The development of manufactured FMT products (oral capsule, lyophilized product) and consortium based therapies (defined mixtures of cultured organisms) will be attempted to standardize and scale FMT for use in the context of metabolic disease to reduce the safety concerns of transferring undefined stool[2].

6.4 Precision Nutrition and Personalized Microbiome Modulation

That diet glycemic responses vary greatly between individuals, depending, in part, on microbiome composition, has sparked interest in precision nutrition. The groundbreaking Weizmann Institute study (Zeevi *et al.,* 2015, Cell) showed that postprandial glucose responses to the same type of food were highly heterogeneous across different individuals, and a machine-learning algorithm based on microbiome data more accurately predicted personal glucose responses and suggested personal dietary interventions than traditional nutritional advice. This paradigm, which combines the use of microbiomics, continuous glucose monitoring, and AI analytics to generate personalized diet recommendations, is a cross-disciplinary approach.

Improved understanding of how the microbiome–metabolism axis is regulated and the ability to target it with pharmacological strategies, including: inhibitors of FMO3, which decrease the production of TMAO in the liver; inhibitors of the TMAO pathway, including inhibitors of bacterial TMA lyases such as 3,3-dimethyl-1-butanol (DMB); selective inhibitors of BSH, which shift the bile acid pool toward the FXR-activating primary bile acids; and engineered bacterial chassis to deliver metabolically active molecules, including bile acid-converting enzymes and enzymes to produce SCFA. Such targeted methods are still in their infancy but are the cutting edge of microbiome-related metabolic therapy[6].

7. Future Directions and Challenges

While the understanding of host–microbiota metabolic interactions has turned out to be impressive, there are still several challenges to address. First, it is still challenging to establish causality rather than correlation in human studies, requiring integration of the longitudinal cohort studies, Mendelian randomization and mechanistic animal studies. Second, taxonomy-based sequencing of the microbiome does not fully reflect its functional metabolic output, which can only be achieved by multi-omics approaches such as metagenomics, metatranscriptomics, metaproteomics and metabolomics to fully phenotype the microbiome.

Third, precision medicine approaches need to consider host genetic variation, which sets the context for a person-specific microbiome-host interaction, especially in innate immune receptor genes (TLR, NOD, NLRP3 loci), bile acid receptor genes (FXR,

TGR5), and metabolite transporter genes. Fourth, the virome and mycobiome are poorly studied compared to the bacteriome, and bacteriophages are known to have profound selective pressures on bacterial communities and fungal commensals metabolically interact with bacteria in ways that could have important impacts on host metabolism.

Fifth, little is known about the temporal dynamics of microbiome–host metabolic interactions across the life course – from early-life programming, to pregnancy, to aging. The microbiome seems to establish 'metabolic set points' in critical developmental periods and to have implications at the population level for metabolic disease prevention. The emerging field of circadian microbiology also shows that gut microbiome composition and function is a dynamic diurnal process, coordinated with host circadian rhythms and feeding schedules, and that disruption of circadian rhythms such as shift work, jet lag and irregular feeding, leads to dysregulated microbiome rhythmicity which is linked to metabolic dysfunction.

8. Conclusion

The gut microbiota forms a vital metabolic organ and is in constant communication with the host tissues in a complex chemical language of metabolites, immune signals and neuroendocrine mediators. The biochemical mechanisms discussed here – epigenetic and receptor-level regulation by SCFA, bile acid-FXR-TGR5 signaling, tryptophan catabolism via indole and kynurenine pathways, cardiac and vascular risk by TMAO, insulin resistance by BCAA, and metabolic endotoxemia by LPS – all demonstrate how microbial biochemistry is tightly integrated into basic mechanisms of host energy homeostasis, immune regulation, and organ function.

Whether it is Western dietary patterns, antibiotic use or other environmental perturbations, symbiosis impairs these biochemical interactions in such a way that leads to the entire spectrum of metabolic disease. In contrast, targeted nutrition, probiotic and pharmacological modulation of the gut microbiome provides a new and exciting avenue of metabolic therapy. Precision medicine for the microbiome is just around the corner as multi-omics technologies, machine learning and synthetic biology come together to allow matching interventions to an individual's unique microbiome and metabolic makeup.

Finally, complete biochemical understanding of the host–microbiota metabolic partnership will not only shed light on the mechanisms of common diseases, but also indicate that the microbiome was an unrecognized determinant of basic biochemistry of life.

References

1. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;444(7122):1027–31.
2. Sonnenburg JL, Bäckhed F. Diet–microbiota interactions as moderators of human metabolism. Nature. 2016;535(7610):56–64.
3. Cani PD, Bibiloni R, Knauf C, et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes. 2008;57(6):1470–81.
4. Postler TS, Ghosh S. Understanding the holobiont: how microbial metabolites affect human health and shape the immune system. Cell Metab. 2017;26(1):110–30.
5. Zhao L, Zhang F, Ding X, et al. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. Science. 2018;359(6380):1151–6.
6. Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med. 2013;19(5):576–85.
7. Plovier H, Everard A, Druart C, et al. A purified membrane protein from Akkermansia muciniphila or the pasteurized bacterium improves metabolism in obese and diabetic mice. Nat Med. 2017;23(1):107–13.
8. Zeevi D, Korem T, Zmora N, et al. Personalized nutrition by prediction of glycemic responses. Cell. 2015;163(5):1079–94.
9. Ridaura VK, Faith JJ, Rey FE, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science. 2013;341(6150):1241214.
10. Schroeder BO, Bäckhed F. Signals from the gut microbiota to distant organs in physiology and disease. Nat Med. 2016;22(10):1079–89.
11. Descamps HC, Herrmann B, Rastall R, Bruneau A, Grill JP, Guarner F. Gut microbiota and metabolic disorders: how prebiotic dietary fibers can act preventively and therapeutically. Front Nutr. 2022;9:901343.
12. Agus A, Clément K, Sokol H. Gut microbiota-derived metabolites as central regulators in metabolic disorders. Gut. 2021;70(6):1174–82.
13. Canfora EE, Jocken JW, Blaak EE. Short-chain fatty acids in control of body weight and insulin sensitivity. Nat Rev Endocrinol. 2015;11(10):577–91.
14. Wahlström A, Sayin SI, Marschall HU, Bäckhed F. Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. Cell Metab. 2016;24(1):41–50.
15. De Vadder F, Kovatcheva-Datchary P, Goncalves D, et al. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell. 2014;156(1–2):84–96.