Review

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EMBO reports

Local and systemic effects of microbiome-derived metabolites

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Abstract

Commensal microbes form distinct ecosystems within their mammalian hosts, collectively termed microbiomes. These indigenous microbial communities broadly expand the genomic and functional repertoire of their host and contribute to the formation of a "meta-organism." Importantly, microbiomes exert numerous biochemical reactions synthesizing or modifying multiple bioactive small molecules termed metabolites, which impact their host's physiology in a variety of contexts. Identifying and understanding molecular mechanisms of metabolite–host interactions, and how their disrupted signaling can contribute to diseases, may enable their therapeutic application, a modality termed "postbiotic" therapy. In this review, we highlight key examples of effects of bioactive microbe-associated metabolites on local, systemic, and immune environments, and discuss how these may impact mammalian physiology and associated disorders. We outline the challenges and perspectives in understanding the potential activity and function of this plethora of microbially associated small molecules as well as possibilities to harness them toward the promotion of personalized precision therapeutic interventions.

Keywords commensals; immune; metabolites; microbiome; postbiotic
Subject Categories Metabolism; Microbiology, Virology & Host Pathogen Interaction; Signal Transduction
DOI 10.15252/embr.202255664 | Received 28 June 2022 | Revised 10 August 2022 | Accepted 16 August 2022 | Published online 29 August 2022
EMBO Reports (2022) 23: e55664

Introduction

Commensal microorganism consortia, collectively termed the microbiome, inhabit multiple mucosal sites of their mammalian host, and significantly contribute to the "holobiont" in cell numbers and genome size (Tierney *et al*, 2019). The microbiome carries out multiple roles, such as outcompeting pathogens in their habitat, providing signals of homeostatic or perturbed surrounding conditions, and producing, modulating, and degrading a wide range of small soluble bioactive molecules (herein referred to as metabolites, see Table 1), which feature multiple effects on the host. Microbial metabolism often involves the utilization of components not accessible to host metabolic enzymes, such as complex carbohydrates, but can also compete with host metabolic systems for substrates. Microbial products and processes are highly interconnected with the host's own metabolic function in contributing to the host's physiology and homeostasis (Thaiss *et al*, 2016b), complementing the host in degrading complex molecules (Cani *et al*, 2019), sensing different conditions in their environment, and in the regulation of commensal communities (Krautkramer *et al*, 2021). The microbial-produced metabolite repertoire is dependent on host genetic and ecological diversity (Costello *et al*, 2012; Goodrich *et al*, 2014), geographic location (Hehemann *et al*, 2010), age (Yatsunenko *et al*, 2012; Sato *et al*, 2021), diet (Kolodziejczyk *et al*, 2019; Alexander & Turnbaugh, 2020), and other lifestyle-related factors (Bajaj, 2019). Certain classes of bacterial metabolites, including short-chain fatty acids (SCFAs) and bile acids are mostly linked to beneficial effects on their host's health (Koh & Bäckhed, 2020). Different end-products of microbial tryptophan metabolism can have either a beneficial or harmful impact (Agus *et al*, 2018; Paeslack *et al*, 2022). Others, such as some amino acid derivates or trimethylamine-oxide (TMAO) are largely associated with noxious effects contributing to disease pathogenesis (Agus *et al*, 2021). Insights into the mechanism of action and modulation of these microbial products may enable their integration as therapeutics (Chaluvadi *et al*, 2016), a modality recently termed postbiotic treatment (Aguilar-Toalá *et al*, 2018). A recent consensus statement by the International Scientific Association of Probiotics and Prebiotics (ISAPP) proposed to integrate supplementation with inactivated microorganisms (Salminen *et al*, 2021) into this term. However, this inclusive, industry-backed definition remains highly controversial (Aguilar-Toalá *et al*, 2021), with many microbiome researchers relating to "postbiotic" therapy only in the context of a well-defined and evidence-based small molecule intervention (Cullin *et al*, 2021; Vrzáčková *et al*, 2021; Box 1).

In this review, we aim to exemplify major mechanisms of action of microbially modulated metabolites, impacting host physiology and disease both locally at their site of production and following systemic distribution. Rather than focusing on the description of metabolite classes and their impact on selected organs (addressed in

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Table 1. Different classes of microbial products, disease contexts, and organismal platforms of conducted studies.

Category	Molecule	Source(s)	Platforms of study	Disease context
Short chain fatty acids (SCFAs)	Butyrate, propionate, acetate	Carbohydrates (diet)	*In vitro*, rodents, human: microbial transfer, metabolite supplementation	Intestinal inflammation, metabolic syndrome, adiposity, hypertension, atherosclerosis, ischemic stroke, chronic kidney disease, type-1 Diabetes mellitus
Carboxylic acid intermediates	Lactate, succinate	Carbohydrates (diet)	*In vitro*, rodents, human: microbial transfer	Metabolic syndrome, intestinal epithelial regeneration, bacterial vaginosis
Amino acids and derivatives	Branched-chain amino acids (BCAAs), niacin/ nicotinamide, 5-aminovaleric acid, dimethylglycine, acetylglycine	Amino acids (diet and microbial de-novo synthesis)	*In vitro*, rodents, human: observational	Adiposity, cardiovascular events, amyotrophic lateral sclerosis (ALS), intestinal inflammation and carcinogenesis, atherosclerosis, myocardial infarction, stroke
	Taurine	Primary bile acids (host metabolism)	*In vitro*, rodents	Intestinal inflammation
	Trimethylamine-oxide (TMAO)	Host metabolism of microbial trimethylamine (TMA)	*In vitro*, rodents, human: observational	Metabolic syndrome, type-2 Diabetes mellitus, liver steatosis, atherosclerosis, myocardial infarction, ischemic stroke, thrombosis
Pattern receptor recognition (PRR) ligands	Lipopolysaccharide (LPS), peptidoglycan, lipoteichoic acid (LTA), polysaccharide A, bacterial DNA, secreted microbial proteins	Structural components of microbes	*In vitro*, rodents, human: observational	Intestinal inflammation, infection and carcinogenesis, adiposity, liver steatosis, inflammation and fibrosis, acute liver failure, thrombosis, metabolic syndrome, type-1 Diabetes mellitus
Tryptophan metabolites	Indole-3-propionic acid (I3PA), indole-3-aldehyde (IAId), indoxylsulfate (IS), tryptamine	Amino acids (diet)	*In vitro*, rodents, human: observational	Intestinal inflammation, fungal infection, hypertension, chronic kidney disease, type-1 Diabetes mellitus, atopic dermatitis
Flavonoids	Quercetin, apigenin, naringenin	Polyphenols (diet)	*In vitro*, rodents	Adiposity, intestinal inflammation and infection
Secondary bile acids	lithocholic acid (LCA), deoxycholic acid (DCA) & derivatives	Primary bile acids (host metabolism)	*In vitro*, rodents, human: observational	Liver steatosis, inflammation and fibrosis, metabolic syndrome, adiposity, colon cancer, malabsorption and micro-nutrient deficiency, *C. difficile* infection
Other classes	Tetrahydrobiopterin (BH4), folate, sphingolipids, amyloids	Microbial de-novo synthesis, amino acids (diet)	*In vitro*, rodents	Metabolic syndrome, intestinal inflammation, Parkinson's disease, autism spectrum disorder (ASD)

ALS, amyotrophic lateral sclerosis; ASD, autism spectrum disorder; BCAAs, branched-chain amino acids; BH4, tetrahydrobiopterin; DCA, deoxycholic acid; I3PA, indole-3-propionic acid; IAId, indole-3-aldehyde; IS, indoxylsulfate; LCA, lithocholic acid; LPS, lipopolysaccharide; LTA, lipoteichoic acid; SCFA, short chain fatty acids; TMA, trimethylamine, TMAO, trimethylamine-oxide.

Box 1. In need of answers

Will consensus be reached on a clear definition and classification of therapeutic products derived from microbes or targeting microbial metabolism?
Is the role of certain microbial metabolites in health and disease correlative or causative?
Are the current analytical pipelines for microbiomes and their metabolites reflecting the *in vivo* conditions and can they be reproduced across studies?
What are the translational limitations of microbial metabolite focused studies in animal models to the human setting?
What host factors contribute to beneficial or deleterious effects of microbial metabolites?
Are personalized approaches to make use of the effects of microbial metabolites for health benefits superior to resource-saving one-for-all strategies?

excellent reviews (Wahlström *et al*, 2016; Borghi *et al*, 2020; van der Hee & Wells, 2021)), we illuminate the differential roles played by key microbial metabolites in their local environment of production, as compared to remote effects mediated by metabolite influx into the host's systemic circulation.

Effects of microbial metabolites on their local environment

As metabolically active organisms, microbes and their immediate neighboring host tissues have co-evolved to take advantage of each other's unique metabolic capabilities. Metabolites secreted and modulated by both constituents of the "holobiont" are used in various fashions, ranging from energy sources, sensing of nutrients,

directing physiologic responses or preventing the expansion of malicious microorganisms (Fig 1). At times, detrimental processes such as invasive pathogen infections or neoplasia may "hijack" metabolites and their signaling pathways in conferring a competitive advantage to themselves. Key examples of local metabolite functions are depicted below.

Intestinal barrier function

Microbes inhabit large mucosal surfaces within their host. While commensals contribute to host barrier function in preventing colonization and translocation of exogenous pathogens, the large commensal biomass itself must be regulated by the host barrier in preventing harmful microbial invasion. The microbiome also provides crucial stimuli to the host to maintain the function of this important barrier. For example, tight junctions (TJ) and their cytoskeleton anchors constitute an important component of the intestinal epithelial barrier. Upregulation of their production can be induced by various gut bacteria-induced metabolites in mouse models, such as SCFAs (Wang *et al*, 2020), products of tryptophan-degradation, like indole-3-propionic acid (I3PA; Venkatesh *et al*, 2014), the flavonoid quercetin (Suzuki & Hara, 2009; Carrasco-Pozo *et al*, 2013), and amino acids (Grosheva *et al*, 2020). Metabolite-induced fortification of gut barrier function can increase intestinal resistance to several noxious events modeled in rodents, such as inflammation (Wang *et al*, 2020) or drug-induced injury (Singh *et al*, 2017). Bacterial toll-like receptor (TLR)-ligands activate Nod-like receptor pyrin domain-containing protein 6 (NLRP6) inflammasomes in "sentinel" goblet cells (senGCs) in lower crypts of the colon. This triggers mucus secretion and luminal expulsion of senGCs, both fortifying the mucus layer to prevent bacteria from breaching the intestinal barrier (Birchenough *et al*, 2016). The entry of microbes into the systemic circulation is also limited by the gut vascular barrier (GVB; Spadoni *et al*, 2015). Bile acids that are agonists of the farnesoid X receptor (FXR) have a stabilizing effect on the GVB in mouse models of liver injury (Sorribas *et al*, 2019). Bile acid deconjugation through gut microbes generally impacts the bile acid pools toward FXR agonists in mice and humans (Tremaroli *et al*, 2015; Parséus *et al*, 2017; Quinn *et al*, 2020) and therefore could play a role in maintaining the GVB. A combinatorial impact of multiple, yet uncharacterized barrier-strengthening and disrupting metabolites (Grosheva *et al*, 2020) likely contributes to differences in barrier function observed in different clinical and pathological contexts and merits future mechanistic studies.

Energy source

Microbial metabolites may also serve as sources of energy for their surrounding tissue. For example, as a result of co-evolution with their neighboring microbiome, intestinal epithelial cells (IECs) have adapted to harness nutrients in a variety of metabolic processes, such as oxidation, lipogenesis or the generation of ketone bodies, and amino acids (Bugaut, 1987; Bergman, 1990). SCFAs generated through microbial carbohydrate fermentation are utilized by IECs as energy sources (den Besten *et al*, 2013a). Additionally, a study in rats found vasoactive intestinal peptide (VIP) inducing epithelial gluconeogenesis, while propionate led to an increase of VIP-expressing neurons in the gut submucosal plexus (De Vadder *et al*, 2015). SCFAs are also able to engage in epithelial lipid metabolism. Acetate can be transformed into the metabolic intermediate Acetyl-CoA in IECs. This leads to activation of the anti-lipogenic master regulator AMP-activated protein kinase (AMPK) and therefore to increased fatty acid oxidation and downregulated lipid production. As a consequence, fewer lipids are shuttled to the lymph and systemically available as chylomicrons (Araújo *et al*, 2020). Acetyl-CoA derived from L-lactate of microbial origin features an opposite effect on lipid metabolism in IECs. Its transformation to Malonyl-CoA results in intracellular lipogenesis and decreased oxidation of lipids. Surprisingly, this leads to lower secretion of lipids from IECs despite an increased storage (Araújo *et al*, 2020). However, lipogenesis triggered by microbial metabolites can also have undesirable outcomes in downstream organs. Exposure to bile acids that act as FXR-agonists leads to IEC-production of ceramides, lipid molecules consisting of a sphingosine and fatty acid, contributing to hepatic lipogenesis in mice (Jiang *et al*, 2015). The beneficiary effect of the antidiabetic drug metformin depleting *B. fragilis* recently reported in a human cohort of Type-2-diabetics (Sun *et al*, 2018) could be a result of disruptions of microbial folate and methionine metabolism (Induri *et al*, 2022). Through this mechanism, the ability of *Bacteroides* to transform bile acids that fuel ceramide production is abrogated (Sun *et al*, 2018).

Microbially modulated bile acids can also alter the response of the endocrine pancreas to incretins released from intestinal L-cells in response to dietary signals. Mouse models found bile acids deconjugated by *Clostridium* and *Bacteroides* to bind the membrane G protein-coupled bile acid receptor 1 (TGR5) on L-cells, inducing the release of insulinotropic glucagon-like peptide 1 (GLP-1; Pathak *et al*, 2018), possibly through inhibition of local glycolysis (Trabelsi *et al*, 2015). In contrast, bile acid engagement with the nuclear receptor FXR in L-cells leads to a downregulation of SCFA-receptors, thereby abrogating their positive effects on GLP-1 release (Ducastel *et al*, 2020).

Intestinal motility

Both commensals, their dietary exposures (Dey *et al*, 2015), and microbial metabolite repertoires are involved in gut motility and the control of luminal content. SCFAs are able to trigger the release of the hormone peptide YY (PYY) from L-cells. As a late postprandial signal, PYY in murine *ex vivo* mucosa led to an inhibition of chloride driving fluid secretion into the gut lumen. It also interacts with both layers of the enteric smooth muscle as well as neurons belonging to the vagal afferent system leading to an antisecretory response and inhibition of gastro-intestinal motility *in vivo* (Tough *et al*, 2011). SCFAs can also induce pro-contractile responses. Neurons located in the rat intestinal myenteric plexus bind butyrate through monocarboxylate transporter 2 (MCT2) receptors, resulting in propulsive contractions (Soret *et al*, 2010). The same effect is observed upon acetylcholine release triggered from IECs upon exposure to propionate (Yajima *et al*, 2011). SCFAs are also capable to act on central nervous sensory and sympathetic ganglia in mice through transcriptional regulation, modulating gastrointestinal motility through a gut–brain circuit (Muller *et al*, 2020). A different bacterial metabolite, tryptamine derived from tryptophan by *R. gnavus* and *C. sporogenes*, exerts pro-contractile signals (Bhattarai *et al*, 2018). Upon binding serotonin-receptors, adenylate cyclase activation leads to luminal secretion of Cl^- and $HCO3^-$ ions as well as water, leading to a shortened colonic transit time in humanized mice (Bhattarai *et al*, 2018).

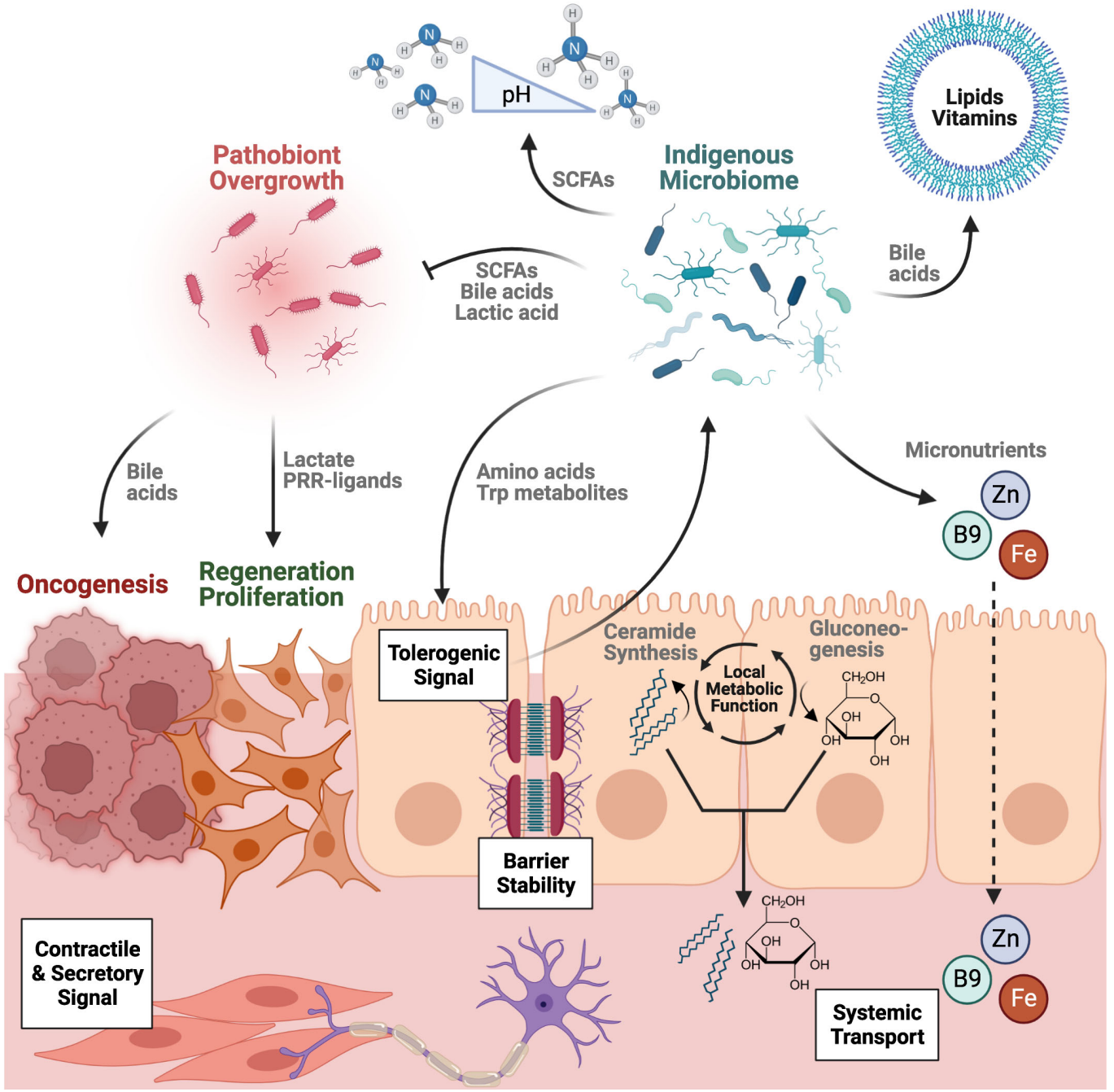

Figure 1. Molecules of microbial origin interact with the local environment at their site of production.

The indigenous microbiome secretes amino acids and tryptophan metabolites maintaining its own stability through tolerogenic signals received from the host's epithelium. Other commensal factors such as bile acids, lactic acid, or short chain fatty acids (SCFAs) can counteract the overgrowth of pathobionts. Besides supplying micronutrients including vitamin B9, iron, and zinc directly to the host, the microbiome also modifies the absorption of dietary components in the gastrointestinal tract: conjugated bile acids increase the solubility of lipids, while lactic acid contributes to maintain pH levels preventing the absorption of toxic ammonia. Bacterial products such as SCFAs, flavonoids, tryptophan metabolites, amino acids, and toll-like receptor (TLR)-ligands contribute to fortify the intestinal barrier, preventing bacteria from dislocating into deeper mucosal layers. Intestinal epithelial cells (IECs) utilize SCFAs as their main metabolic precursors for the harvest of nutrients. They also utilize SCFAs and bile acids in the regulation of metabolic circuits resulting in the production and systemic deployment of glucose or ceramides. SCFAs or tryptamine can promote intestinal motility activating feedback-loops involving the epithelium, local neurons, and smooth muscles. While lactate and TLR-agonists can progress regenerative processes of the epithelium after injury, bile acids have the potential to drive proliferative signals facilitating tumor development. SCFA, short chain fatty acid; TLR, toll-like receptor; Trp, tryptophan. (Created with BioRender.com).

Intestinal digestion and absorption

Microbial metabolites may modify the digestion and absorption of dietary compounds. Bile acids are responsible for the emulsification of hydrophobic fat droplets into micelles and therefore heavily influence the digestion and absorption of lipids and fat-soluble vitamins (A, D, E, K). Microbial deconjugation of bile acids tends to reduce their emulsifying potential (Swann *et al*, 2011). However, most of the absorption of dietary lipids and vitamins takes place in the small intestine (Iqbal & Hussain, 2009), while bacterial deconjugation through bile salt hydrolases is commonly found in the large intestine (Guzior & Quinn, 2021). This geographical distinction can drastically change after surgical creation of blind loops or the congenital occurrence of large diverticula in the small intestine. These regions of blind loops, isolated from the regular gut transit, can undergo an overgrowth of anaerobic bacteria capable of bile salt deconjugation. The consequential impaired emulsification can eventually lead to lipid maldigestion causing diarrhea and a deficiency of a number of vitamins due to malabsorption (Quigley *et al*, 2020). Furthermore, microbial-derived products also feature a regulatory impact on intestinal lipid absorption and digestion, as these processes were found defective in germ-free mice. As such, bacterial metabolites may trigger the release of enzymes involved in digestion and transepithelial shuttling of lipids (Martinez-Guryn *et al*, 2018) and the maturation of lymphatic vessels draining lipids absorbed in the intestine (Suh *et al*, 2019). The production of SCFAs from colonic microbial fermentation results in local acidification, which may augment absorption. One example is the shift from ammonia (NH_3) toward the less diffusable cationic ammonium (NH_4^+) under acidic conditions. This principle has been applied for more than half a century in the treatment of hepatic encephalopathy, in which ammonia cannot be detoxified due to poor liver function. Lactulose, a nonabsorbable disaccharide, contributes to acidic conditions upon microbial digestion in the colon and trapping of ammonia (Agostini *et al*, 1972).

Gut commensals are also capable of producing micronutrients. Though these compounds maintain numerous host metabolic, cellular, and immune functions, only few insights exist about the systemic impact of their bacterial synthesis (Biesalski, 2016). A defective gut bacterial production of folic acid was recently suggested to be linked to the development of Parkinson's disease (PD) in a human study cohort (Rosario *et al*, 2021), in line with previous findings of lowered systemic folate levels in patients with PD (dos Santos *et al*, 2009) and PD-like symptoms in mouse models of folic acid deficiency (Duan *et al*, 2002). The microbial generation of SCFAs through carbohydrate fermentation may impact the intestinal bioavailability and absorption of certain trace elements. The supplementation of dietary fiber leads to an increase of trans-epithelial iron transport in the cecum in a rat model of anemia (Lobo *et al*, 2014), while improving the bioavailability of zinc in another study (Scholz-Ahrens & Schrezenmeir, 2002). Nevertheless, the impact of metabolites of microbial origin in determining the bioavailability of trace elements merits further studies, especially in the human setting (Coudray *et al*, 1997).

Protection against pathogens and pathobionts

Microbial metabolites are involved in the reaction against the overgrowth and invasion of potentially noxious organisms while allowing indigenous commensals to harbor their niches. For example, intestinal infection with *C. difficile* is often triggered by a disruption of eubiotic communities through broad-spectrum antibiotic treatment. *C. scindens* was found to counteract the blossom of this pathobiont through deconjugation of the bile acid cholic acid (Buffie *et al*, 2015). The augmentation of a healthy intestinal microbial community through fecal microbial transplantation (FMT) is effective as treatment of therapy-resistant *C. difficile* infection. Metabolites derived from the transplanted microbiome, such as the bile acids deoxycholic acid (DCA) and lithocholic acid (LCA), and the SCFAs propionate and butyrate may contribute to this beneficial effect (Seekatz *et al*, 2018).

Microbial communities can induce tolerogenic signals in their host, thereby enabling the persistence of microbes with beneficial effects and preventing the overgrowth of pathogenic strains. Tryptophan metabolites produced by lactobacilli lead to Il-22 release upon aryl hydrocarbon receptor (AHR) signaling from intestinal immune cells, counteracting *Candida* colonization through an amplified antifungal immune response (De Luca *et al*, 2010; Zelante *et al*, 2013). Vice versa, Il-22 secretion also serves to maintain a community rich in bacterial AHR-ligand producers: Defective Il-22 signaling in mice led to dysbiosis concomitant with low AHR-ligand production and colitis susceptibility, while in humans, lower gut microbial AHR activation and a single nucleotide polymorphism linked to impaired Il-22 function were associated with inflammatory bowel disease (Lamas *et al*, 2016). A similar effect was observed upon gut microbial taurine production in mice inducing epithelial NLRP6 inflammasome activation and Il-18 secretion. Subsequently, the release of antimicrobial peptides (AMPs) counteracted an overgrowth of bacteria that lead to an inflammatory reaction and sustained the commensal taurine producers (Levy *et al*, 2015).

Beyond the gut, lactic acid produced in the vaginal mucosal surface by resident lactobacilli (most effectively by the *crispatus* species) is present in its protonated form at pH levels < 3.9. In this state, it exerts direct antimicrobial effects protective of bacterial overgrowth (Tachedjian *et al*, 2017), coupled with virucidal effects on HIV and HSV-2 (Conti *et al*, 2009; Aldunate *et al*, 2013). A recent first-in-human clinical trial suggested that restoration of the vaginal microbiome with vaginal microbiome transplantation (VMT) successfully reestablishes lactic acid-producing communities and reverses the overgrowth of anaerobes, collectively improving intractable and recurrent bacterial vaginosis and its associated symptoms (Lev-Sagie *et al*, 2019). The contribution of metabolite shifts to this effect merit further studies.

Epithelial cell replenishment

Epithelial cells are frequently replaced through differentiation and proliferation of intestinal stem cells. This enables intestinal regeneration after injury, but, when excessive and unregulated, also increases susceptibility toward colorectal cancer development. Bacterial-produced lactate is involved in a number of proliferative processes in the intestinal epithelium. It interacts with Paneth cells through the receptor GPR81, leading to epithelial expansion and maintenance of intestinal stem cells (ISCs) in mice through Wnt/β-catenin signals (Lee *et al*, 2018). Recognition of bacterial components through specialized pattern recognition receptors (PRRs) plays an important role in all phases of gut epithelial regeneration after injury: In mouse models of chemical colitis it was involved in initial epithelial restitution (Fukata *et al*, 2006; Normand *et al*, 2011), proliferation (Hsu *et al*, 2010; Zaki *et al*, 2010), and eventually

differentiation (Podolsky *et al*, 2009; Round *et al*, 2011). Mice subjected to starvation exert a hyperproliferation of IECs upon refeeding triggered by lactate as a metabolite derived from *Lactobacillus murinus* (Okada *et al*, 2013). Additionally, chronic inflammatory or premalignant conditions may trigger proliferative signals from microbial metabolites that can induce oncogenic pathways. For example, intestinal adenoma-prone Apc^{Min} mouse exposure to deoxycholic acid, a product of bacterial bile acid deconjugation, may trigger the intestinal adenoma–carcinoma pathway concomitant with activation of the inflammatory Il6-STAT3 axis (Wang *et al*, 2019). Sensing of bacterial components through TLR2 and nucleotide binding and oligomerization domain 2 (NOD2) induces the expression of major histocompatibility complex (MHC) class II in ISCs. This contributed to immune surveillance of the intestinal epithelium and prevented the formation of tumors under premalignant conditions in mice (Beyaz *et al*, 2021).

Systemic impacts of microbial products on the host

In addition to the aforementioned local mechanisms of metabolite activity, their distribution throughout the body by portal and

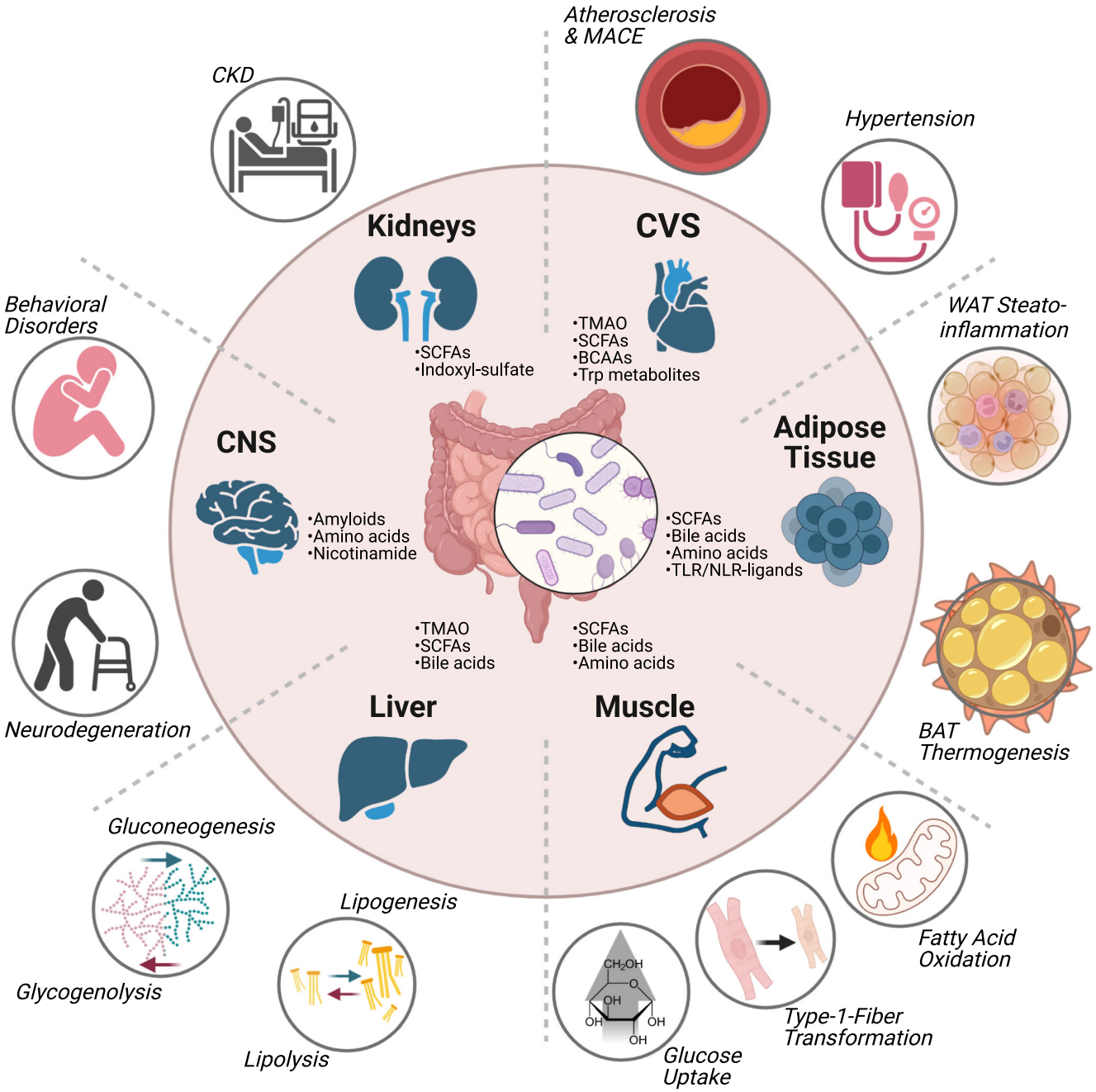

Figure 2.

Figure 2. Microbial metabolites systemically impact host physiology.

Numerous metabolic functions of the host are influenced by products of microbial origin. Short-chain fatty acids (SCFAs) can act as precursors for lipid or glucose production in the liver. SCFAs and bile acids may also induce hepatic pathways to degrade glucose and lipids. In muscle, SCFAs can increase the net uptake of glucose and induce the transformation to type-1 fibers capable of increased fatty acid oxidation. Additional improvements of muscle metabolism can be induced by bile acids or amino acids, such as a higher energy expenditure. Adipose tissue may respond to SCFAs or bile acids modulating the transformation of white adipose tissue (WAT) to brown adipose tissue (BAT) to enhance thermogenesis. Microbe-associated molecular patterns activating toll-like receptors (TLRs) and nucleotide binding and oligomerization domain receptors (NLRs) as well as microbiome-modulated amino acids may trigger steato-inflammation in adipose tissue. Amino acids of bacterial origin, particularly trimethylamine-oxide (TMAO) and branched-chain amino acids (BCAAs), are linked to the development of atherosclerosis, myocardial infarction or stroke. In patients suffering from chronic kidney disease (CKD), SCFAs may modulate disease progression, while an impaired degradation of the tryptophan metabolite indoxylsulfate (I3S) could aggravate uremic symptoms. In the central nervous system (CNS), microbial metabolic dysfunction resulting in a lack of nicotinamide in amyotrophic lateral sclerosis (ALS) or an excess of amyloids in Parkinson's disease (PD) contribute to neurodegeneration and worsening motor functions. Behavioral disorders, such as autism spectrum disorder (ASD) are accompanied by alterations of the microbial production of amino acids, such as 5-aminovaleric acid and taurine upon microbiome transfer to germ-free mice or tetrahydrobiopterin (BH4) in a mouse model of ASD. ASD, autism spectrum disorder; BAT, brown adipose tissue; BCAA, branched-chain amino acid; CKD, chronic kidney disease; CNS, central nervous system; CVS, cardiovascular system; MACE, major adverse cardiovascular event; NLR, nucleotide binding and oligomerization domain receptor; SCFA, short chain fatty acid; TLR, toll-like receptor; TMAO, trimethylamine-oxide; Trp, tryptophan; WAT: white adipose tissue. (Created with BioRender.com).

systemic circulation may result in interaction with a variety of remote organs and cells, where they may influence their host's systemic homeostasis and risk of disease (Fig 2, Table 1). In the below section, we exemplify some of these effects by focusing on metabolites impacting systemic features of host metabolism. In a separate section, immune-mediated effects will be discussed.

Glucose metabolism

Every cell in the mammalian body is capable of utilizing glucose as a source of energy. Systemically distributed microbial products act as metabolic precursors and in signaling cascades modifying their hosts' glucose metabolism. The potential of SCFAs to act as gluconeogenic substrates through incorporation into the tricarboxylic acid (TCA) cycle has already been mentioned in the previous local metabolic section. Systemically, radiolabeling suggests that propionate may also contribute to a net glucose synthesis (den Besten *et al*, 2013b). The intestinal metabolic capacity significantly contributes to energy homeostasis, with SCFAs converted to glucose in IECs inducing decreased bodyweight, improved insulin sensitivity, and ameliorated hepatic glycogenolysis in mice (De Vadder *et al*, 2014, 2016). Propionate interacting with periportal afferent neurons was suggested to drive this effect (De Vadder *et al*, 2014). SCFAs can act as precursors of two major energy sources of skeletal muscle, glucose and fatty acids. They are also involved in muscle cell uptake of glucose through an increase of intracellular transport (Yamashita *et al*, 2009). SCFAs can induce a switch toward the fatty-acid oxidizing type-I fiber, facilitating glucose clearance and increasing insulin sensitivity in mice (Gao *et al*, 2009).

Additionally, microbially deconjugated secondary bile acids have beneficial metabolic effects on skeletal muscles. In a mouse model, TGR5-triggered cAMP-dependent thyroid hormone-activated enzyme type 2 iodothyronine deiodinase (D2), thereby leading to a higher energy expenditure (Watanabe *et al*, 2006). Amino-acid derivatives undergo metabolic conversions through both host and microbial enzymes. Trimethylamine-oxide (TMAO) is generated in the liver from trimethylamine, which is produced by gut microbes from multiple precursors including choline, carnitine, and betaine (Chhibber-Goel *et al*, 2016). In rodents, TMAO may modulate glucose homeostasis via induction of the unfolded protein response (UPR), though the downstream results remain debated. Work by Dumas *et al* (2017) suggests that TMAO induces an improved insulin secretion and glucose tolerance in mouse models of metabolic dysfunction, while others (Chen *et al*, 2019b) argue that TMAO interacts with the UPR-effector PERK, thereby disrupting glucose tolerance. A study in non-diabetic humans did not find serum levels of TMAO to be associated with fasting glucose or insulin resistance, but suggested that it may constitute an independent predictor of meeting one of the prediabetes-defining criteria (Roy *et al*, 2020).

Adiposity

Historic observations in human subjects suggested a correlation between plasma SCFA levels and adipose tissue mass (Björntorp & Hood, 1966). In agreement, a study comparing gut microbial community structure in lean and obese twins (Turnbaugh *et al*, 2009), and another utilizing FMT from obese donors or those successfully reducing weight following bariatric surgery (Tremaroli *et al*, 2015) concluded that gut microbes from obese subjects harbor the capacity to harvest energy through enhanced carbohydrate fermentation and generation of SCFAs. FMT from lean and obese human twins into germ-free mice demonstrated a decline in adiposity in recipients of microbiomes from lean individuals, accompanied by an increased capacity to metabolize carbohydrates and higher propionate and butyrate levels (Ridaura *et al*, 2013). In contrast, human FMT from lean to obese subjects failed to alter SCFA levels (Mocanu *et al*, 2021) or induce sustainable metabolic improvements (Zhang *et al*, 2019). Other studies in mice suggested that higher SCFA availability may induce white adipose tissue (WAT) browning and an expansion of beige adipose tissue (BAT; Li *et al*, 2017, 2019; Weitkunat *et al*, 2017), potentially mediated by fatty acid oxidation (Gao *et al*, 2009), phosphorylation of AMPK, or reduction of PPARγ-signaling (den Besten *et al*, 2015; Gao *et al*, 2019). Besides a direct impact on adipose tissue, SCFAs can cross the blood–brain barrier (Li *et al*, 2019) and modulate neural circuits by releasing neuropeptide Y (NPY) that drives BAT activation and upregulation of thermogenesis (Li *et al*, 2018) in mouse models of obesity. Moreover, the release of the peptide hormone leptin from adipocytes, best known for its effects on satiety, is triggered by SCFAs (Xiong *et al*, 2004; Zaibi *et al*, 2010).

Additionally, microbially modulated bile acids may participate in regulation of adiposity (Tremaroli *et al*, 2015). The exposure of mice to cold temperatures led to changes in the gut microbiome and bile acid profile triggering lipolysis (Ziętak *et al*, 2016; Worthmann

et al, 2017). Switches in the microbial bile acid metabolic capacity can result in functional reprogramming of the adipose tissue (Li et al, 2013; Jiang et al, 2015; Pathak et al, 2018) enabling thermogenesis, lipolysis, and mitochondrial uncoupling (Broeders et al, 2015; Somm et al, 2017; Velazquez-Villegas et al, 2018). TMAO (originating from a bacterially produced precursor) may induce or aggravate hepatic steatosis (Chen et al, 2016; Tan et al, 2019; León-Mimila et al, 2021). A possible mechanism for this effect may involve microbial producers of TMA (the TMAO precursor) outcompeting the host for choline. The hepatic and visceral adipogenesis are a result of impaired DNA-methylation as well as decreased availability of phosphatidylcholine for lipoprotein synthesis (Romano et al, 2017).

In other contexts, dysbiosis in cigarette-smoking humans and smoke-exposed mice may increase the microbial conversion of the amino acid glycine into betaine and subsequently dimethylglycine (DMG), concurrently depleting acetylglycine (ACG). Upon smoking cessation, the dysbiosis in mice remained persistent, while the active smoking-related anorexigenic molecules dissipated, with a combination of increased DMG and depleted ACG contributing to the exacerbation of smoking cessation-related weight gain mediated through increased energy harvest. Interestingly, these metabolite effects may also be active upon supplementation to non-smoking obese mice (Fluhr et al, 2021). Another common and poorly understood obesity pattern in humans, involves recurring and gradually exacerbating cycles of obesity, also termed "yoyo" obesity. In mouse models of this obesity pattern, apigenin and naringenin, flavonoids modulated by the gut microbiome, are depleted upon induction of obesity, but fail to replenish upon successful dieting. Depletion of these flavonoids contributes to a susceptibility to excessive weight regain upon exposure to further bouts of obesity by impaired regulation of BAT decoupling of oxidation-phosphorylation, driving excessive net fat accumulation (Thaiss et al, 2016a).

Lipid metabolism

Hyperlipidemia, a component of the metabolic syndrome and a contributor to cardiovascular morbidity, may likewise be influenced by the microbiome (Zmora et al, 2018). Several metabolites may impact the metabolism of lipids at sites distant from their production. The liver, exposed to an array of metabolites originating from the gut through the portal vein, exerts a key role in lipid metabolism. The SCFAs butyrate and acetate supplemented to mice were shuttled from the gut and served as precursors for palmitate and cholesterol synthesis in the liver (den Besten et al, 2013b). Whether this function additionally contributes to obesity (Samuel et al, 2008) or fatty liver in humans (Chambers et al, 2019) remains debatable. This is due to the fact that numerous other studies found SCFAs potentially modulating lipid levels through several mechanisms including an activation of the master regulator AMPK/SREBP-1 axis (Gao et al, 2009; den Besten et al, 2015; Wu et al, 2019), increased β-oxidation of fatty acids (Gao et al, 2009; den Besten et al, 2015), and long-chain fatty acid (LCFA)-induced modulation of the ω6/ω3 ratio (Weitkunat et al, 2016). Sphingolipids (SL) produced by gut bacteria downregulate the host production of SLs in the liver (Johnson et al, 2020), a process linked to metabolic disorders such as insulin resistance and nonalcoholic steatohepatitis (Apostolopoulou et al, 2018).

Cardiovascular system

Cardiovascular disease (CVD) complications, including myocardial infarction (MI) or stroke, constitute a major source of morbidity and mortality in individuals suffering from the above features of the metabolic syndrome (Alberti et al, 2006; Roth et al, 2020). In the past decade, the microbiome and its metabolites were suggested to contribute to the pathogenesis of CVD. For example, gut microbiomes of omnivorous people harbored a higher capacity of processing L-carnitine compared to those of vegetarians and vegans, leading to increased systemic levels of TMAO (Koeth et al, 2013). Higher plasma L-carnitine and TMAO levels were identified as risk factors for coronary atherosclerosis and major cardiovascular events (Koeth et al, 2013; Senthong et al, 2016). Increased levels of TMAO were also associated with higher risk of stroke in the presence of hypertension or atrial fibrillation (Nie et al, 2018; Liang et al, 2019) A possible mechanistic explanation of this increased risk (Zhu et al, 2016) included a direct impact of TMAO on the activation of platelets, a critical step in the emergence of clot formation driving ischemic cardiovascular events. As such, FMT of gut microbial communities featuring enhanced capability of TMAO production to humanized mice induced a pro-thrombotic vascular dysfunction (Zhu et al, 2016). Structural components of bacteria can influence clot formation through PRR-interaction: Platelet TLR2 was found to mediate aggregation *in vitro* upon *S. pneumoniae* recognition (Keane et al, 2010), while in mice, LPS triggered platelet TLR4 expression (Aslam et al, 2006) resulting in adhesion and accumulation in the lung capillaries (Andonegui et al, 2005). Sensing bacterial signals through NOD-receptors on platelets induced MAPK and NO-signaling pathways eventually increasing clot formation in mesenteric vessels in a mouse model of thrombosis (Zhang et al, 2015). Branched-chain amino acids (BCAAs) were also linked to cardiovascular events like MI or stroke, although this effect may have been indirectly driven by impaired glucose metabolism (Tobias et al, 2018). Humans with acute ischemic stroke were found to harbor alterations of gut microbial communities associated with decreased SCFA production (Tan et al, 2021). In rats that developed similar dysbiotic traits upon ischemic stroke, replenishment of SCFA levels through FMT or direct butyrate supplementation led to improved neurological outcomes (Chen et al, 2019a). Another small study (Hayashi et al, 2021b) suggested that gut microbial community alterations were linked with an enhanced BCAA synthesis in people suffering from heart failure. Interestingly, tryptophan derivatives of bacterial and host origin may impact cardiovascular health in opposing manners. AHR-agonists of bacterial origin like indole-3-acetic acid (IAA) alleviated hypertension in mice (Wilck et al, 2017), while host production of kynurenines from tryptophan was associated with acute coronary events in a study cohort of elderly humans (Eussen et al, 2015). Microbial metabolites may also prevent atherosclerosis. A genome-wide association study suggested that microbially produced butyrate is negatively associated with atherosclerotic cardiovascular disease (Jie et al, 2017). Likewise, studies in rodents (Marques et al, 2017; Wang et al, 2017) and human diabetics (Roshanravan et al, 2017) pointed toward the potential role of SCFAs to attenuate high blood pressure as well as chronic injury of the heart and kidneys. However, these suggested microbiome-driven effects on blood pressure (Chen et al, 2020; Cook & Chappell, 2021) may also be indirectly driven by altered weight and glucose metabolism.

Systemic nonmetabolic effects

In addition to the above systemic metabolite-driven effects on host metabolism, microbial-modulated metabolites may modify a variety of other physiological and pathological processes in numerous cells and organs. For example, in the brain, a mouse model of amyotrophic lateral sclerosis (ALS) featured dysbiosis in the gut preceding the motor symptoms (Blacher *et al*, 2019). A decrease of *A. muciniphila* in ALS-bearing mice was accompanied by decreased systemic levels of nicotinamide, a metabolic disturbance that was also found in a cohort of ALS patients. *Akkermansia* or nicotinamide supplementation improved motor symptoms and triggered protective transcriptional neural pathways in the mouse ALS model, encouraging a future testing of this and other differentially abundant metabolites in human ALS clinical trials. Likewise, microbiome-associated metabolites may modify disease course in other central nervous system disorders. The aggregation of the amyloid protein alpha-synuclein (aSyn) is associated with several neurodegenerative disorders, including Parkinson's disease (PD). An amyloidogenic product secreted by *Enterobactericae* named "Curli" may increase the formation of aSyn-aggregates, while colonizing an aSyn-overexpressing mouse line with a Curli producing *E. coli* strain worsened the PD-like motor and intestinal impairments (Sampson *et al*, 2020). Other metabolite alterations correlated with autism spectrum disorder (ASD). 5-aminovaleric acid and taurine alleviated symptoms in an ASD mouse model and were suggested as candidates to modify behavioral patterns in ASD patients (Sharon *et al*, 2019). Altered bacterial tetrahydrobiopterin (BH4) synthesis was associated with behavioral disorders in a mouse ASD model, while targeted replenishment with BH4 improved ASD-like behavioral deficits (Buffington *et al*, 2021). These interesting observations merit further mechanistic validation in mice and humans. In the kidneys, the tryptophan derivate indoxylsulfate was found to accumulate in subjects suffering from chronic kidney disease (CKD), thereby contributing to uremic symptoms (Devlin *et al*, 2016). A probiotic intervention with a *Lactobacillus* strain increased renal SCFA levels, resulting in protective effects from fibrosis and chronic renal dysfunction after ischemia-reperfusion injury in mice. A subsequent administration of the probiotic to a cohort of CKD patients in a placebo-controlled study reduced the decline of kidney function over the period of observation (Zhu *et al*, 2021). Other examples of systemic metabolite-induced effects are reviewed elsewhere (Needham *et al*, 2020; Rossi *et al*, 2020; Schupack *et al*, 2022).

Microbial metabolites shaping host immunity

Metabolite impacts on the mammalian immune system can be both local and systemic and are central in shaping microbiome-host interactions and their physiological consequences. A variety of microbial recognition patterns of the host's innate and adaptive immune mechanisms are able to induce a myriad of host responses ranging from anti-microbial activity to maintenance of tolerance and commensalism (Fig 3). While microbial surface components and nucleic acids are central in innate immune system microbial recognition, their metabolites constitute important additional means of signaling with and modulation of both innate and adaptive immune cells.

Modulation of the innate immune system

The innate immune system is tasked with sensing of microbiome commensals, helping the host to differentiate between "friend and foe" signals, and directing responses to these signals that can range from tolerance to inflammation. Microbial-modulated metabolites are involved in these processes. IECs, increasingly considered an integral part of the mucosal immune system, serve as a critical communication hub, together with professional immune cells, in sensing and reacting to commensals and pathogens (Pott & Hornef, 2012; Soderholm & Pedicord, 2019). The most common specialized luminal receptors for the interaction with molecules of microbial origin are the G-protein coupled receptors (GPRs) 41, 43, and 109 sensing SCFAs, as well as TLRs recognizing a variety of bacterial surface structures (Zheng *et al*, 2022). Several other surface receptors such as Dectin-1 (Gantner *et al*, 2003), CD14 (Jiang *et al*, 2005), and CD36 (Hoebe *et al*, 2005) closely interact with TLRs in sensing components of putative pathogens. Additionally, intracellular detection and signaling is mediated by NOD-like receptors (NLRs) and multiprotein-complexes involving certain NLRs, termed inflammasomes. Collectively, integration of these diverse signals leads to tolerogenic versus inflammatory reactions (Rakoff-Nahoum *et al*, 2004; Macho Fernandez *et al*, 2011; Macia *et al*, 2015; Wang *et al*, 2020).

IEC crosstalk with bacterial metabolites is also essential for the secretion of AMPs. IEC-sensing of SCFAs (Zhao *et al*, 2018; Hayashi *et al*, 2021a) or the amino acid taurine activating NRLP6-inflammasomes (Levy *et al*, 2015) trigger the release of AMPs. This increases the resistance toward noxious toxin-producing *C. difficile* strains (Hayashi *et al*, 2021a) and attenuates the severity of experimentally induced colitis (Levy *et al*, 2015) in mice. Paneth cells can also independently respond with AMP-secretion upon microbial components sensed through TLRs on their surface or intracellularly through the NOD2 pattern recognition receptor (Ogura *et al*, 2003). This contributes to lower intestinal penetration of bacteria and decreases colonization with pathobionts (Vaishnava *et al*, 2008).

However, the recognition of bacterial components through TLRs on host cells can have detrimental outcomes in cases of chronic inflammation, such as ulcerative colitis (UC). As such, TLR4 is upregulated in colon tumors found in UC-patients as well as in a mouse model of inflammation-associated colon cancer (AOM-DSS; Fukata *et al*, 2007). The latter provides a potential mechanism linking TLR4 activation to the COX-PGE-EGFR pathway in promoting cancer (Fukata *et al*, 2007).

The innate immune system is also involved in responses to molecules of bacterial origin at sites remote from their production. Myeloid cells have emerged as critical hubs sensing and responding to bacterial signals. Innate lymphoid cells (ILCs) can be found in the subepithelial layers of organs harboring microbial communities. Their interaction with a variety of microbial products modulates their impact on innate immune response mechanisms. For example, SCFAs can influence type 3 innate lymphoid cells (ILC3s) through histone-deacetylase (HDAC)-inhibition (Yang *et al*, 2020), GPR43-binding (Chun *et al*, 2019) or triggering of neutrophils to induce inflammasome activation (Fachi *et al*, 2020). In mouse models, this resulted in a protective effect from gut inflammatory injury (Chun *et al*, 2019; Yang *et al*, 2020), and infection (Chun *et al*, 2019; Fachi *et al*, 2020). Moreover, ILC3s exert anti-inflammatory effects upon interaction with primary bile acids through TGR5 (Qi

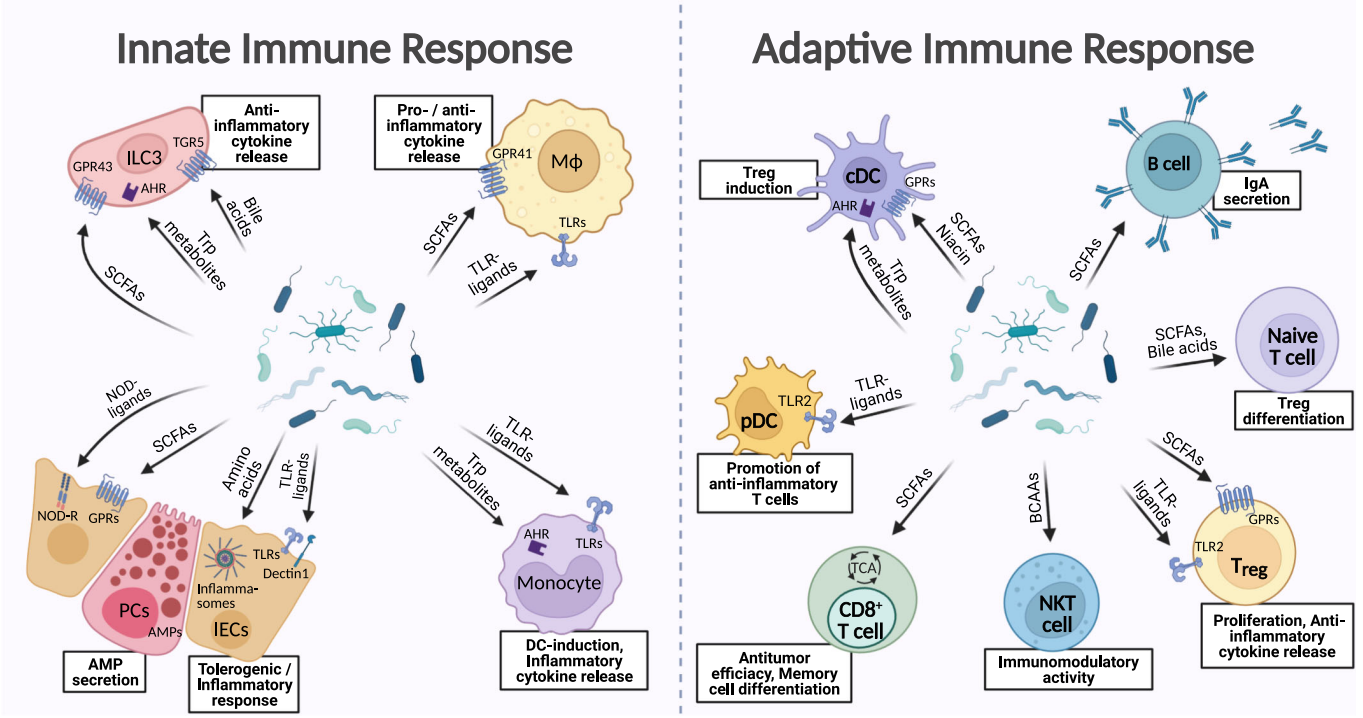

Figure 3. Microbiome-modulated metabolites modify the innate and adaptive immune response.

Metabolite signaling contributes to a balance between tolerogenic and inflammatory immune reactions. Intestinal epithelial cells (IECs) sense short chain fatty acids (SCFAs); and other microbial metabolites through toll-like receptors (TLRs), nucleotide binding and oligomerization domain receptors (NLRs), inflammasomes and Dectin1, in inducing tolerance to commensals versus inflammatory responses against pathogens. The secretion of antimicrobial peptides (AMPs) from Paneth cells and IECs upon sensing of amino acids, SCFAs, and microbial-associated molecular patterns by TLRs- and NLRs contributes to protecting the gut from pathobiont bloom and invasion. Both monocytes and macrophages can recognize SCFAs, tryptophan metabolites, or TLR-ligands affecting the differentiation of surrounding dendritic cells (DCs) or triggering the release of either pro- or anti-inflammatory cytokines. In type 3 innate lymphoid cells 3 (ILC3s), recognition of SCFAs, bile acids, and aryl hydrocarbon receptor (AHR)-ligands through specialized cell surface receptors also leads to the promotion of anti-inflammatory cytokine patterns. Adaptive immune cells also interact with microbial metabolites. Classical dendritic cells (cDCs) recognize components of Gram-positive bacteria through TLR2, while plasmacytoid dendritic cells (pDCs) express AHR and G-protein coupled receptors (GPRs) interacting with tryptophan metabolites, SCFAs, and niacin. These antigen-presenting cell (APC)-signals modulate the activation of B and T cells. T cells also directly react to microbial signals in shaping their immunomodulatory phenotype: the differentiation of naïve T cells to regulatory T cells (Tregs) is reinforced by SCFAs and bile acids. Also, Tregs sense SCFAs and bacterial components through GPRs and TLR2 resulting in proliferation and the secretion of anti-inflammatory cytokines. SCFAs can lead to an immunoglobulin A (IgA)-class switch in B cells, so that secreted IgA in the intestinal lumen can counteract bacterial dissemination. Natural killer T (NKT) cells are polarized toward an immunomodulatory state counteracting inflammation in reaction to branched-chain amino acids (BCAAs). $CD8^+$ T cell sensing of SCFAs regulates their differentiation into memory cells and cytotoxic anti-tumor activity. AHR, aryl hydrocarbon receptor; AMP, antimicrobial peptide; BCAA, branched-chain amino acid; cDC, classical dendritic cell; DC, dendritic cell; GPR, G-protein coupled receptor; IEC, intestinal epithelial cell; IgA, immunoglobulin A; MΦ, macrophage; NKT, natural killer T cell; NLR, nucleotide binding and oligomerization domain receptor; NOD, nucleotide binding and oligomerization domain; PC, Paneth cell; pDC, plasmacytoid dendritic cell; SCFA, short chain fatty acid; TCA, tricarboxylic acid cycle; TGR5, G protein-coupled bile acid receptor 1; TLR, toll-like receptor; TMAO, trimethylamine-oxide; Treg, regulatory T cell; Trp, tryptophan. (Created with BioRender.com).

et al, 2019) as well as bacterial tryptophan derivatives binding AHR (Laurans *et al*, 2018; Hendrikx *et al*, 2019).

The liver serves as an immunologic "first-pass" gate keeper, by responding to an array of metabolites influxing from the gut through the portal vein. Kupffer cells, the tissue-resident macrophages in the liver, can respond to bacterial products while inducing distinct responses in their surrounding cell populations. Kupffer cell sensing of bacterial components through TLRs plays a role in triggering liver inflammation during liver steatosis (Henao-Mejia *et al*, 2012; Carpino *et al*, 2020) as well as in acute liver failure (Kolodziejczyk *et al*, 2020). On the other hand, the abrogation of bacterial signaling through TLR-ligands in germ-free animals may lead to an increased susceptibility to hepatic fibrosis (Mazagova *et al*, 2015).

Adipose tissue (AT) also contains macrophages exerting an important role in regulating local inflammation and lipid storage. Their inflammatory responses can be modified by certain molecules of microbial origin. SCFAs may cause AT-macrophages to abolish the secretion of various pro-inflammatory cytokines and chemokines (Al-Lahham *et al*, 2012; Ohira *et al*, 2013), including the adipokine resistin (Curat *et al*, 2006; Al-Lahham *et al*, 2010). Increased gut permeability during obesity is driven by dietary compounds, perturbations of gut microbial communities, and the local immune response of the host, leading to endotoxemia (Serino *et al*, 2012; Tilg *et al*, 2020). In the AT, this results in a TLR4-dependent recruitment of macrophages, triggering inflammation (Caesar *et al*, 2015). In addition, sensing of microbial patterns through TLR4 as well as NRLP3 in AT may trigger mitochondrial dysfunction upregulating fat storage processes, closely related to metabolic syndrome (Okla *et al*, 2018).

Modulation of the adaptive immune system

The adaptive immune response is an antigen-specific and memory-inducing immune reaction that evolved in vertebrates. Co-evolution with complex microbial communities contributes to proper development and function of the adaptive immune response (McFall-Ngai, 2007), while defective microbial colonization leads to an altered adaptive immunity, thereby triggering susceptibility toward infections (Mazmanian *et al*, 2005; Hall *et al*, 2008; Ivanov *et al*, 2009) and reduced efficiency of vaccinations (Korpe & Petri, 2012). Therefore, it is not surprising that microbial metabolites may shape functions of the adaptive immune system, in particular those involving several T cell subsets.

For example, SCFAs may impact intestinal T cell function by inducing their differentiation into anti-inflammatory regulatory T cells (Tregs), while preventing a shift toward the pro-inflammatory Th1/17 phenotype. This effect is mediated through HDAC-inhibition (Arpaia *et al*, 2013) and metabolic reprogramming toward fatty acid oxidation (Hao *et al*, 2021). Similarly, SCFAs signaling via GPRs may directly target intestinal Tregs, leading to their increase in number and proliferative capacity through HDAC-inhibition (Smith *et al*, 2013). To harness the local immunoregulatory potential of SCFAs, attempts of a postbiotic treatment were conducted in inflammatory bowel disease involving local administration of butyrate to patients suffering from ulcerous proctosigmoiditis (Scheppach *et al*, 1992; Scheppach & German-Austrian SCFA Study Group, 1996). However, only a few of the heterogeneous and rather small-scale studies were able to detect a decrease of inflammatory activity (Jamka *et al*, 2021).

The potential of SCFAs to facilitate an extrathymic development of anti-inflammatory Tregs (Arpaia *et al*, 2013) can promote delivering immuno-metabolic signals from gut microbes to distant effector organs. In mouse AT, butyrate leads to a Treg-triggered alleviation of steato-inflammation (Sato *et al*, 2020). In high-fat diet induced obesity, SCFA-triggered Tregs elicit weight loss and improve insulin sensitivity (Mandaliya *et al*, 2021). Inflammation in the course of pulmonary allergic hypersensitivity modeled in mice responds to increased SCFA levels leading to induction of higher numbers of Tregs (Trompette *et al*, 2014; Zaiss *et al*, 2015). In the pancreas, Tregs may alleviate the destruction of insulin-producing β-cells observed in the NOD1 mouse model of type-1 Diabetes mellitus (T1DM). This effect is dependent on gut microbial SCFAs and AHR-ligands, which, in turn induce pancreatic islet secretion of antimicrobial peptides (AMPs; Sun *et al*, 2015; Miani *et al*, 2018).

Importantly, SCFAs may also contribute to other adaptive immune effects. SCFAs may induce the inflammatory Th1/Th17 CD4 T cell phenotype in the setting of *C. rodentium* infection (Kim *et al*, 2013). Also, they may promote urethritis (Park *et al*, 2016), stimulate cytotoxic $CD8^+$ lymphocytes (Luu *et al*, 2018), possibly contributing to their anti-tumor effects, and impact B cell- and antibody-related responses. An activation of GPR41 and GPR109 in DCs stimulates B cells to an IgA-class switch and secretion of IgA into the gut lumen, thereby inhibiting bacterial dissemination into distant organs in the course of experimental colitis (Isobe *et al*, 2020).

Bile acids modified by gut commensals may also impact the differentiation and activity of T cells. Iso-desoxycholic acid induces anti-inflammatory $FoxP3^+/RoR\gamma t^+$ Tregs by blocking nuclear FXR-signaling in interacting DCs (Campbell *et al*, 2020). Both 3-oxo lithocholic acid (LCA) and iso-allo-LCA direct T cells toward an anti-inflammatory Treg phenotype while preventing Th17 differentiation (Hang *et al*, 2019). The mechanism by which both bile acids induce Tregs includes enhancement of mitochondrial function, resulting in transcription through histone acetylation at the promoter of FoxP3 (Hang *et al*, 2019).

While sensing of bacterial components by TLRs is mainly attributed to innate immune functions, it can also have an impact on inflammatory pathways driven by adaptive immune responses. Polysaccharide A (PSA), a component of the capsule of *B. fragilis*, induces a tolerogenic Treg phenotype through multiple mechanisms, including binding to TLR2 on plasmacytoid dendritic cells (pDCs; Dasgupta *et al*, 2014) or $FoxP3^+$ $CD4^+$ T cells (Round *et al*, 2011), as well as directly promoting the secretion of the anti-inflammatory cytokine Il-10 from T cells (Mazmanian *et al*, 2008). In the pancreas, microbial components interacting with different TLRs in mouse models can either exacerbate or alleviate autoimmune injury, a hallmark of T1DM. TLR2 may induce a microbiome-dependent inflammatory impairment, while TLR4 exerts a protective tolerogenic effect on pancreatic islets (Burrows *et al*, 2015).

Niacin, produced by commensal bacteria in the gut from nicotinamide adenine dinucleotide (NAD), can activate local DCs and macrophages by interacting with their membrane receptor GPR109a (Singh *et al*, 2014). This subsequently drives a differentiation of naïve T cells into Tregs (Singh *et al*, 2014). These effects reduce gut inflammation and the subsequent carcinogenesis induced in the azoxymethane-dextran sodium sulfate (AOM-DSS) mouse model (Singh *et al*, 2014). Bacterial tryptophan metabolites signaling through AHR in the gut can induce $CD4^+8^+$ double-positive intraepithelial lymphocytes (IEL; Cervantes-Barragan *et al*, 2017) as well as non-monocyte-derived DCs (Kinnebrew *et al*, 2012), both associated with reduced intestinal inflammation. In the skin epithelia, supplementation with the tryptophan derivate indole-3-aldehyde (IAId) results in reduced inflammation caused by a mouse model of atopic dermatitis (Yu *et al*, 2019). This bacterial metabolite is decreased in the skin of people suffering from this disease (Yu *et al*, 2019).

Other metabolites of bacterial origin induce effector T cells. Glycosphingolipids, generated from BCAAs, lead to the development of NKT-cells in the gut toward an immunomodulatory state capable of ameliorating colitis in mice (Oh *et al*, 2021). SCFA derivatives can be incorporated into the TCA of $CD8^+$ T cells to enhance their metabolic capacity through mitochondrial oxidative phosphorylation, eventually improving survival and leading to polarization toward memory cells upon activation through antigen encounter (Bachem *et al*, 2019). Harnessing this beneficial effect may enable to sustain T cell memory after vaccinations or enable *in vitro* induction of memory chimeric antigen receptor (CAR) T cells in optimizing cancer immunotherapy.

Challenges and perspectives in the study of microbiome-associated metabolites

As outlined in this review, metabolites derived from or modulated by microbial commensals impact their eukaryote host in a variety of local and systemic manners, which may affect host immunity, metabolism, and disease susceptibility. Disentangling the underlying mechanisms of these complex metabolite effects and harnessing

them as microbiome-targeted interventions remains complicated and elusive in most cases (Box 1).

Mechanistically studying metabolite impacts on host physiology and disease is complicated by multiple challenges. These include, among others, the lack of standardization of analytical pipelines, mainly those involving microbiome sequencing (Beresford-Jones *et al*, 2022), and difficulties in culturing of many commensals, resulting in over-reliance on their genomic characterization without sufficient evidence of causality (Cani, 2018). Moreover, functional analyses of bacterial metabolism, usually performed within the *in vitro* setting, does not account for metabolite impacts on the host and on neighboring microbes. Additionally, characterizing the "rules of engagement" of complex networks of microbial communities and their broad spectrum of metabolite secretomes necessitates the development of sophisticated computational tools and machine learning processes predicting the impact of metabolite consortia on distinct physiological responses.

Many approaches striving to determine metabolite causation and molecular mechanisms impacting disease processes heavily rely on rodent models. However, translational generalization of their findings to the human setting is impaired by the limited shared bacterial taxa (Chung *et al*, 2012), difficulties in reproducibility attributed to variations in microbial communities throughout animal vending and housing institutions (Beresford-Jones *et al*, 2022), constrains in colonization and function upon transfer of human bacteria into mice (Lundberg *et al*, 2020) and variable effects of microbial metabolites on host physiology across species (Koh & Bäckhed, 2020). Furthermore, in some cases, secretion of microbial metabolites and their downstream impact on the host are investigated using unphysiological doses and application routes, thereby reducing the potential to translate findings from animal studies into the human setting. In human studies, a major challenge includes a high inter-individual variability in microbiome composition and metabolite landscape, stemming from a multitude of environmental, immune, and genomic variations such as diet, ethnicity, and geography.

Regardless of these difficulties and challenges, the insight into the ubiquitous functions of microbially modulated metabolites has opened a new window of opportunity toward improving human health. In contrast to attempts to define a "core microbiome" by taxonomic similarity (Neu *et al*, 2021), the shared metabolite landscape of microbes and their host may allow a better functional classification of microbiome contributions in distinct clinical contexts (Beresford-Jones *et al*, 2022). Metabolites derived from or modified by commensals may play central roles in driving "personalized" interventions. Within the Personalized Nutrition Project, microbial features were harnessed to develop a prediction platform of glycemic responses (Zeevi *et al*, 2015). This outperformed common dietary approaches in an intervention targeting the postprandial glucose levels in healthy and (pre-)diabetic subjects (Zeevi *et al*, 2015; Ben-Yacov *et al*, 2021; Rein *et al*, 2022). A diet leading to the blossom of strains with the capacity of carbohydrate fermentation (Zeevi *et al*, 2015) as well as propionate production (Rein *et al*, 2022) was associated with metabolic improvements, corresponding to previous reports (Qin *et al*, 2012; Louis & Flint, 2017). However, a dietary pattern promoting strains from the *Alistipes* phylum and *Bacteriodetes* genus was found to have detrimental metabolic effects, contradicting prior studies which associated these microbial signatures with leanness (Turnbaugh *et al*, 2006, 2009). This underlines that personalized approaches focused on the interplay of diet and microbiome have the potential to guide future strategies in the prevention and treatment of metabolic disorders. Moreover, probiotic supplementation steadily increases in popularity, despite unequivocal results from studies with methodological quality issues, evidence of colonization resistance, and a lack of assessment of long-term adverse outcomes (Suez *et al*, 2019). Compounds secreted by probiotics play an important role in inhibiting the reconstitution of the gut microbiome after antibiotic therapy in susceptible subjects (Suez *et al*, 2018). The inter-individual variability in effects of probiotics adds a perspective of a personalized approach in refining their use, which is currently based on inconclusive evidence (McFarland, 2014). Eventually, postbiotic interventions can be tailored to balance disturbances in the metabolic function of the resident microbiome. A selective supplementation of metabolites, as demonstrated in preclinical models of weight gain after dieting and smoking cessation (Thaiss *et al*, 2016a; Fluhr *et al*, 2021), is expected to be increasingly researched also in the human setting, with an outlook to be incorporated into the precision medicine toolbox.

Acknowledgments

The authors thank the members of the Elinav lab, Weizmann Institute of Science, and members of the DKFZ microbiome and cancer division for insightful discussions. IS is supported by the Deutsche Forschungsgemeinschaft (SP 1902/1-1). EE is supported by the Leona M. and Harry B. Helmsley Charitable Trust; Adelis Foundation; Ben B. and Joyce E. Eisenberg Foundation; Estate of Bernard Bishin for the WIS-Clalit Program; Jeanne and Joseph Nissim Center for Life Sciences Research; Miel de Botton; The Vera Rosenberg Schwartz Research Fellow Chair; Swiss Society Institute for Cancer Prevention Research; Belle S. and Irving E. Meller Center for the Biology of Aging; Sagol Institute for Longevity Research; Sagol Weizmann-MIT Bridge Program; Norman E Alexander Family M Foundation Coronavirus Research Fund; Mike and Valeria Rosenbloom Foundation; Daniel Morris Trust; Isidore and Penny Myers Foundation; Vainboim Family; and by grants funded by the European Research Council; Israel Science Foundation; Israel Ministry of Science and Technology; Israel Ministry of Health; The German-Israeli Helmholtz International Research School: Cancer-TRAX (HIRS-0003); Helmholtz Association's Initiative and Networking Fund; Minerva Foundation; Garvan Institute; European Crohn's and Colitis Organization; Deutsch-Israelische Projektkooperation; IDSA Foundation; WIS-MIT grant; Emulate; Charlie Teo Foundation; Mark Foundation for Cancer Research, and Welcome Trust. EE is the incumbent of the Sir Marc and Lady Tania Feldmann Professorial Chair of immunology; a senior fellow, Canadian Institute of Advanced Research (CIFAR); and an international scholar, The Bill & Melinda Gates Foundation and Howard Hughes Medical Institute (HHMI). Open Access funding enabled and organized by Projekt DEAL.

Author contributions

Eran Elinav: Conceptualization; supervision; funding acquisition; writing – original draft; writing – review and editing. **Igor Spivak:** Conceptualization; data curation; writing – original draft; writing – review and editing. **Leviel Fluhr:** Conceptualization; data curation; writing – original draft; writing – review and editing.

Disclosure and competing interests statement

EE is a scientific founder of DayTwo and BiomX, and a paid consultant to Hello Inside and Aposense. The remaining authors declare no competing interests.

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