npj | biofilms and microbiomes

Review

Published in partnership with Nanyang Technological University

https://doi.org/10.1038/s41522-024-00610-9

Unlocking gut-liver-brain axis communication metabolites: energy metabolism, immunity and barriers

Xiaoge Sun[1,2], Manish Shukla[2], Wei Wang[1] ✉ & Shengli Li[1] ✉

The interaction between the gut-microbiota-derived metabolites and brain has long been recognized in both health and disease. The liver, as the primary metabolic organ for nutrients in animals or humans, plays an indispensable role in signal transduction. Therefore, in recent years, Researcher have proposed the Gut-Liver-Brain Axis (GLBA) as a supplement to the Gut-Brain Axis. The GLBA plays a crucial role in numerous physiological and pathological mechanisms through a complex interplay of signaling pathways. However, gaps remain in our knowledge regarding the developmental and functional influences of the GLBA communication pathway. The gut microbial metabolites serve as communication agents between these three distant organs, functioning prominently within the GLBA. In this review, we provide a comprehensive overview of the current understanding of the GLBA, focusing on signaling molecules role in animal and human health and disease. In this review paper elucidate its mechanisms of communication, explore its implications for immune, and energy metabolism in animal and human, and highlight future research directions. Understanding the intricate communication pathways of the GLBA holds promise for creating innovative treatment approaches for a wide range of immune and metabolic conditions.

The Gut-Brain Axis has been well defined over the past decades, it present that the Gut–Brain axis offers a two-way regulatory communication pathway utilizing metabolites, hormonal, and immunological channels[1]. Dysfunction of this axis can lead to pathophysiological outcomes. The gut plays a vital role in absorbing nutrients, vitamins, minerals, and water, and also functions as an excretory route for substances eliminated in bile. Upon digestion, the liver is the primary organ to encounter the diverse array of small molecules. Here, the delivery of nutrients is sensed from the intestine, and this information is not only relayed to other organs but also utilized to prompt adaptations in liver function, enhancing the efficient processing of nutrients[2]. The regulation of liver function in response to nutrients absorbed from the intestine includes endocrine and nervous system mechanisms, as well as direct effects of substances on both liver parenchymal and non-parenchymal cells[3]. Present evidence indicates that alterations in liver hydration in reaction to nutrients and hormones constitute an autonomous and robust signal that aids in adjusting metabolic liver function and gene expression to variations in intestinal absorption[2]. Therefore, the concept of the Gut-Liver-Brain Axis (GLBA) has been emerged and gained considerable attention in recent years, as researchers strive to unravel the intricate connections between the gut, liver, and brain. This axis represents a dynamic communication connection that integrates signals from the gastrointestinal and metabolic systems with the central nervous system (CNS), impacting a broad range of physiological processes, such as immune responses, metabolic and neurodevelopmental pathways. At the core of this communication network are signaling molecules, which serve as crucial mediators of inter-organ communication.

Microbial metabolites, produced by the trillions of microorganisms inhabiting the gut, have been demonstrated to regulate immune response, regulate neurotransmitter synthesis, and influence neural development[4]. The bidirectional interaction of microbial and host metabolites manipulates processes including the regulation of the nervous system[5], anti-pathogens[6], nutrient metabolism[7], neurological behavior[8] and immune regulation[9]. It has been suggested that the microbiota has a broader impact on the regulation of systemic immunity, attributed to the translocation of microbial products from the luminal side of the mucosa into the circulation[10,11]. Previous studies have emphasized that changes in the makeup of gut bacterial populations are associated with various inflammatory and metabolic diseases in host, such as obesity, inflammatory bowel disease (IBD), and fatty

[1]State Key Laboratory of Animal Nutrition and Feeding, College of Animal Science and Technology, China Agricultural University, Beijing, 100193, P. R. China. [2]Department of Neurosurgery, College of Medicine, The Pennsylvania State University, Hershey, PA, 17033, USA. ✉e-mail: wei.wang@cau.edu.cn; Shenglicau@163.com

liver disease[12–14]. Numerous comprehensive reviews have detailed how the innate immune system recognizes commensal bacteria and the way individual consortia or species influence specific aspects of both innate and adaptive immune responses, and the immune system[15–17]. Consequently the immune system influences the profile of the microbiota. Communication between gut-microbes and the host immune process occurs via a diverse range of signaling routes involving various types of molecules. A recent article offers a unique perspective on tissue-specific immune cell adaptation mediated by both the liver and central nervous system, which regulates the levels of gut pT_{reg} cells and prevents gut inflammation[18]. This study underscores the critical role of the GLBA neural arc in defining the immunoregulatory niche and fine-tuning immune responses in the intestine. These pathways extend beyond the immune framework and encompass microbial metabolites, inflammatory cytokines, and neurotransmitters. These immune-related signaling pathways, together with immediate chemical crosstalk between the gut-microbe and host, impact various organs including the gut, liver, and brain. These intricate interplays collectively form what is defined as the GLBA. This axis is characterized as a complex, bidirectional chemical communication network between specific host cellular process and various microbiotas[19].

While numerous studies have illuminated the knotty and essential role of gut flora and gut-derived metabolites in the pathological and physiological conditions of their hosts, numerous aspects remain undiscovered. The application of advanced omics technologies in the context of gut microbiota research has unveiled fresh perspectives, uncovering crucial connections between specific gut-derived metabolites and the health of animals or humans. This review emphasizes the importance of comprehensively understanding the crosstalk between host-microbiota metabolic, immune-inflammatory, liver-energy metabolic and GLBA. This axes, which physiologically link the gut, liver, and brain, are pivotal for advancing therapeutic strategies targeted towards modifying the gut flora to tackle diseases and enhance the overall health of animals and humans.

Communication signaling metabolites: gut SCFAs

SCFAs and energy metabolism

Recent studies indicate that an average human male body harbors around 3.8×10^{13} individual microorganisms[20], the gut microbiota of mice contains approximately 1×10^{13} to 1×10^{14} microbes[21], and the rumen microbiota of cows contains approximately 1×10^{11} to 1×10^{12} microbes per gram of rumen content[22]. Together, the host and its gut flora produce various small molecules through the metabolism of xenobiotics and food. Many of these molecules play crucial roles in facilitating communication between host cells and their gut microbial symbionts[14]. Indeed, roughly 10% of metabolites have been approximated to be present in circulatory system are estimate to originate from gut microbes[23].

Short-chain fatty acids (SCFAs) are synthesized in the large bowel, particularly in the rumen of ruminants, by the bacterial breakdown of dietary starch and fiber, such as acetate, propionate, and butyrate, are key metabolites formed through the digestion of dietary fiber by gut bacteria (Table 1)[5,24]. Additionally SCFAs, including valerate, formate, and caproate, are produced in smaller quantities[25]. Colonocytes quickly absorb SCFAs, primarily through active transportation facilitated by monocarboxylate transporters (MCTs) (Fig. 1). MCT1 mediates SCFA transport in a proton-coupled, electroneutral fashion, whereas SCFA anion transport is facilitated by the electrogenic, sodium-dependent MCT1[26]. SCFAs are additionally taken up from the intestinal lumen via swapping with (Cl^{-})[27] and $(HCO3^{-})$[28]. Following absorption, SCFAs participate the mitochondrial citric acid cycle to produce ATP and cellular energy[29]. SCFAs provide as energy substrates for hepatocytes. Furthermore, acetate serves as a precursor for fatty acid synthesis in the liver[30,31]. Propionate is recognized as a substrate for generating glucose in the liver, particularly in ruminants[32], while gluconeogenesis from propionate is quantitatively less significant in the human liver[30]. In fact, the majority of acetate, propionate, and butyrate produced in the gut (64%, 91%, and 98%, respectively) remains within the gut, with only a fraction reaching the systemic circulation and peripheral tissues of the host[33]. Other origins of plasma acetate comprise endogenous synthesis from amino acid metabolism and fatty acid oxidation[34,35]. Dairy cow milk fatty acids also serve as an origin of butyrate, since part of the triacylglyceride mixture in milk includes butyrate, which is subsequently secreted in mammals through gastric lipase[36]. SCFAs have been associated with the progression of diabetes and obesity[37,38]. A prior study documented elevated cecal SCFA levels, which led to increased hepatic lipogenesis in mice exposed to subtherapeutic doses of antibiotics during early life[39]. SCFA levels are recognized by free fatty acid receptors (FFARs), which are specific G-protein-coupled receptors (GPCRs) and play roles in lipid homeostasis and glucose processing. A prior study has demonstrated that dietary addition of

Table 1 | Sources of metabolites and their role in immune development

Metabolites	Involved Bacteria	Immune development
Acetate	most of the enteric bacteria, e.g., *Akkermansia muciniphila*, *Bacteroides spp*., *Bifidobacterium spp*., *Prevotella spp*., *Ruminococcus spp*[155,156] (Producer)	Suppressing neutrophil and macrophage pro-inflammatory cytokine production[157]
Propionate	*Bacteroides spp*., *Phascolarctobacterium succinatutens*, *Dialister spp*., *Veillonella spp*., *Bacteroides spp*., *Phascolarctobacterium succinatutens*, *Dialister spp*., *Veillonella spp*[155,158] (Producer)	Reduced production of pro-inflammatory cytokines such as IL-6 and IL-12; suppresses dendritic cell maturation[159]
Butyrate	*Coprococcus comes, Coprococcus eutactus, Anaerostipes spp., Coprococcus catus, Eubacterium rectale, Eubacterium hallii, Faecalibacterium prausnitzii, Roseburia spp*[156,160] (Producer)	The most potent anti-inflammatory SCFA; inhibits the production of pro-inflammatory cytokines (TNF-α, IL-6) by acting as an HDAC (histone deacetylase) inhibitor[161,162]
Bile Acids	*Clostridium and Eubacterium*[70] (Convert primary bile acids to secondary bile acids)	.Regulating the differentiation of Treg cells and Th17 cells[80]; exhibits anti-inflammatory properties by activating TGR5 (BA receptor)[85,86]
Polyamine (such as Spermine)	*Bifidobacterium animalis subsp. lactis LKM512*[93] (Producer)	Suppress M1 macrophage activation by downregulating ornithine decarboxylase expression and inhibiting the generation of inflammatory cytokines[92,93]
Tryptophan	*Clostridium sporogenes, Ruminococcus gnavus*[103] *(Metabolize tryptophan)*	Reduce the hyperinflammation by an immunosuppressive effect
LPS	*Gram-negative bacteria: such as Bacteroides fragilis and Escherichia coli*	induced pro-inflammatory signaling

LPS lipopolysaccharide

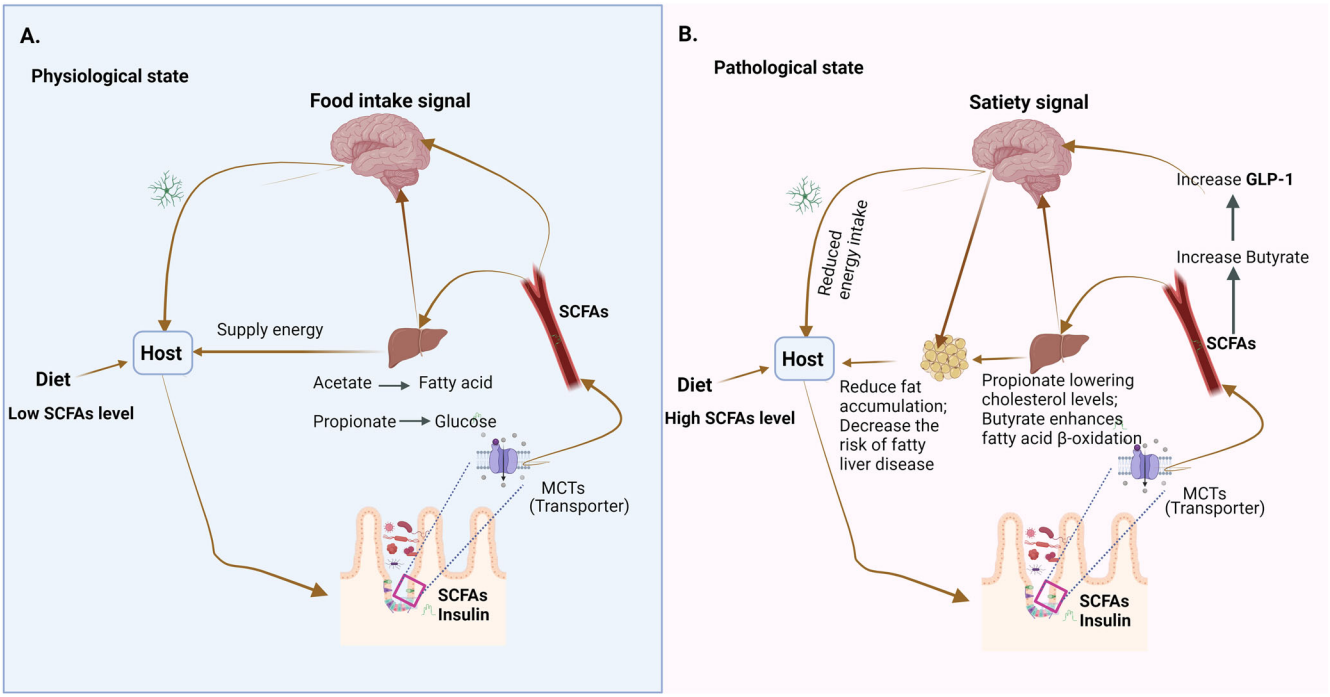

Fig. 1 | Effect of the short-chain fatty acids (SCFAs) on the metabolism. Short-chain fatty acids (SCFAs)'s metabolism and function pathways with the physiological state in Panel **A** and the pathological state in Panel **B**. SCFAs) formed through intestinal food fermentation, activate monocarboxylate transporter (MCT) proteins, facilitating entry into the bloodstream, thereby increasing systemic levels of SCFAs, glucagon-like peptide-1 (GLP-1), and insulin. In the liver, SCFAs regulate lipid and energy metabolism. Butyrate, a specific SCFA, notably enhances GLP-1 secretion, signaling satiety and stimulating insulin release after meals. This mechanism supports feelings of fullness and contributes to weight management by regulating appetite and metabolic processes. The term 'host' refers to both animals and humans; golden arrow indicates the direction of metabolite movement, while the black arrow represents activation, promotion, or increase.

acetate, propionate, butyrate, or their mixture suppresses weight gain caused by high-fat diet feeding through modulation of FFAR2 and FFAR3 expression[40]. This process ultimately decreases body weight by boosting triglyceride breakdown and promoting the breakdown of free fatty acids in adipose tissue. Furthermore, the microbial production of SCFAs, particularly butyrate, increases Glucagon-like peptide-1 (GLP-1) levels. This influences diabetes and obesity by acting as a signal of satiety and stimulating insulin secretion when released in the gut after eating, leading to increased feelings of fullness and reduced energy intake (Fig. 1)[41–43]. A recent study has verified a Gastric Inhibitory Polypeptide Receptor (GIPR) antagonist linked to GLP-1 analogues facilitates weight reduction and enhances metabolic indicators in obese male mice and cynomolgus monkeys[44]. Propionate production holds particular significance in human health, as it promotes satiety, inhibits liver lipogenesis, reduces cholesterol levels, and exhibits anticarcinogenic properties[4]. In a recent review, the available evidence suggesting that SCFAs also facilitate metabolic communication between the gut flora and skeletal muscle, which SCFAs boost fatty acid absorb and oxidation while inhibiting fat deposition in skeletal muscle[45].

SCFAs and immunity

SCFAs act as inhibitors of histone deacetylases (HDACs), regulating the proliferation of both hematopoietic and non-hematopoietic cell lineages, thereby impacting their roles in host immune response (Fig. 2)[46]. When HDACs are inhibited by SCFAs, they facilitate the development of immune tolerance and foster anti-inflammatory characteristics crucial for maintaining physiological balance. This underscores the microbiome's ability to influence host physiology through epigenetic signaling[47]. Exposure of peripheral blood mononuclear cells (PBMCs) and neutrophils to SCFAs, akin to being exposed to broad-spectrum HDAC modulators, leading to pro-inflammatory cytokine tumor necrosis factor (TNF) downregulation and nuclear factor-κB (NF-κB) inactivation[48,49]. Macrophages exhibit a comparable response to acetate and butyrate[50]. In contrast, SCFAs such as butyrate and propionate impede cell growth and foster the generation of tolerogenic in dendritic cells (DCs)[51]. Cumulatively, these findings highlight the role of SCFA-mediated HDAC inhibition in pro-inflammatory innate immunity by influencing NF-κB activity.

In an in vivo study, SCFAs have the ability to influence peripheral T cells, specifically regulatory T (T_{reg}) cells, by inhibiting HDACs, thereby altering their function and frequency[52]. In animal studies, suppression of HDAC9 resulted in heightened expression of forkhead box P3 (FOXP3), a pivotal T cell transcription factor, along with increased T_{reg} cell numbers. This augmentation boosted the inhibitory capacity of T_{reg} cells in normal physiological settings and enhanced their ability to mitigate colitis in mice[53]. Maternal consumption of diets enriched with SCFA transmitted the inhibitory influence to offspring[54], underscoring the epigenetic influence of SCFAs on immune system development and disease protection. In therapeutic contexts, HDAC inhibitors have demonstrated efficacy in various animal models of inflammation, such as lipopolysaccharide (LPS)-stimulated cytokine secretion from DCs, resulting in decreased levels of interleukin (IL)-6, IL-1β, TNF-α, and interferon (IFN)-γ, attributed to Nf-κB impairment (Fig. 2)[55]. In addition, SCFAs serve to bolster mucosal immune responses through fortifying the epithelial cells lining the mucosal layer[56]. These studies have also elucidated additional mechanisms through which SCFAs modulate host immunity, such as their interaction with GPCRs. For instance, GPR43 is crucial for SCFA-mediated neutrophil chemotaxis and for the proliferation and immunosuppressive activity of T_{reg} cells. GPR109A mitigates the development of colitis by enhancing the secretion of anti-inflammatory factors by monocytes and also prompting the differentiation of T_{reg} cells differentiation[57]. A recent review elucidated the molecular mechanisms by which butyrate attenuates inflammatory responses IBD, involving HDAC inhibitor activity, activation of PPARγ, and GPRs receptors. It emphasizing the importance of butyrate transporters in its absorption by colonocytes for these effects at the colonic level[58].

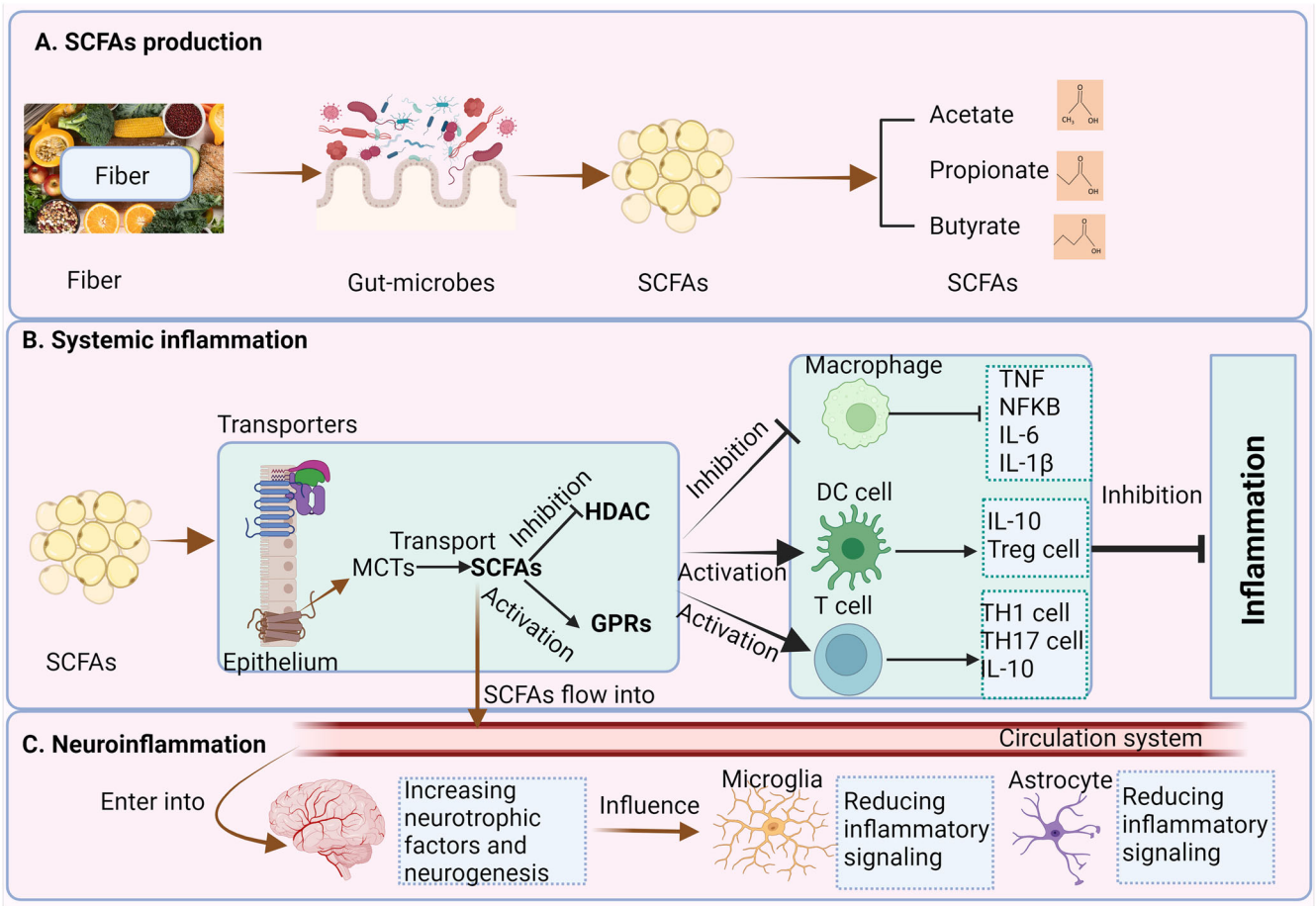

Fig. 2 | Effect of the Short-chain fatty acids (SCFAs) on immune response. SCFAs are crucial products of gut microbiota fermentation of indigestible polysaccharides shown in the Panel **A**, pivotal for gut-brain communication and brain function. SCFAs, primarily absorbed by colonocytes via H^+ dependent monocarboxylate transporters (MCTs), exert dual effects. In the periphery, they mitigate systemic inflammation by fostering T regulatory cell (T_{reg}) differentiation and modulating interleukin secretion shown in the Panel **B**. Within the central nervous system (CNS), SCFAs alleviate neuroinflammation by influencing glial cell morphology and function, enhancing neurotrophic factors, promoting neurogenesis, supporting serotonin synthesis, and maintaining neuronal homeostasis shown in the Panel **C**. This integrated role underscores SCFAs' impact on systemic and neuroinflammatory processes, essential for overall health and brain function. The term 'host' refers to both animals and humans.; golden arrow indicates the direction of metabolite movement, while the black arrow represents activation, promotion, or increase; the horizontal T arrow means inhibiting.

There is growing evidence that SCFAs entering the CNS possess neuroactive properties. While the exact mechanisms by which SCFAs affect the CNS are still not well understood, numerous animal studies have demonstrated that they have a broad impact on critical neurological and behavioral processes[26,59–61]. A diverse microbes support the upkeep and efficacy of microglia, while also aiding in their maturation in homeostatic conditions[62]. Moreover, previous study documented that the systemic inflammation may contribute significantly to neuroinflammation[63]. Remarkably, in a prior investigation involving germ-free mice, which commonly have immature microglia, the addition of SCFAs promoted the development of these microglia to a morphology akin to that found in control or specific pathogen-free mice[64], which probably engages FFAR's pathway[65]. Moreover, a SCFA mixture decreased the levels of cytokines released by THP-1 cells, and SCFAs such as formate and valerate particularly inhibited the phagocytic activity of activated THP-1 cells[66]. Studies have shown that treating microglia primary cultures with acetate reduces inflammatory signaling by decreasing the expression of IL-1β, IL-6, and TNF-α, and NF-κB[67]. Likewise, acetate has been found to modulate inflammatory cytokines and signaling pathways in astrocyte primary cultures[68]. Clearly, further study is required to uncover the precise process by which SCFAs could impact on neuroinflammation.

Communication signaling metabolites: Bile acids

Bile acids and metabolism

Bile acid (BA), produced in the liver and metabolized by intestine bacteria, serve as bactericidal agents that preventing microbial proliferation and gut dysbiosis. BA synthesis occurs through two primary signaling process, the classical and the alternative pathway, which are present in both humans and animals. The liver houses all the enzymes necessary for the classical BA biosynthesis process, while other tissues, such as adrenal glands, macrophages, and the brain, possess different enzymes for metabolizing cholesterol into oxysterols and BAs[69]. Following hepatic process, BAs are retained in the gallbladder and released into the gut upon nutrient ingestion, facilitating the uptake of dietary vitamins and lipids (Fig. 3). In gut, 7α-dehydroxylation is a critical microbial process that converts primary bile acids (such as cholic acid) into secondary bile acids (such as deoxycholic acid). *Clostridium* and *Eubacterium* species are primarily involved in this reaction (Table 1)[70]. Approximately 95% of gut BAs undergo reabsorption and enter the portal vein via enterohepatic circulation, ultimately returning to the liver for recycling[71]. BAs activate both the membrane Takeda G protein-coupled receptor 5 (TGR5), and the nuclear farnesoid X receptor (FXR)[72]. In the liver, FXR simulation by BAs results in feedback inhibition of cholesterol 7alpha-hydroxylase (CYP7A1) gene transcription, while in the gut, FXR triggers the secretion of fibroblast growth factor 19/15 (FGF19/15)[73]. FGF19

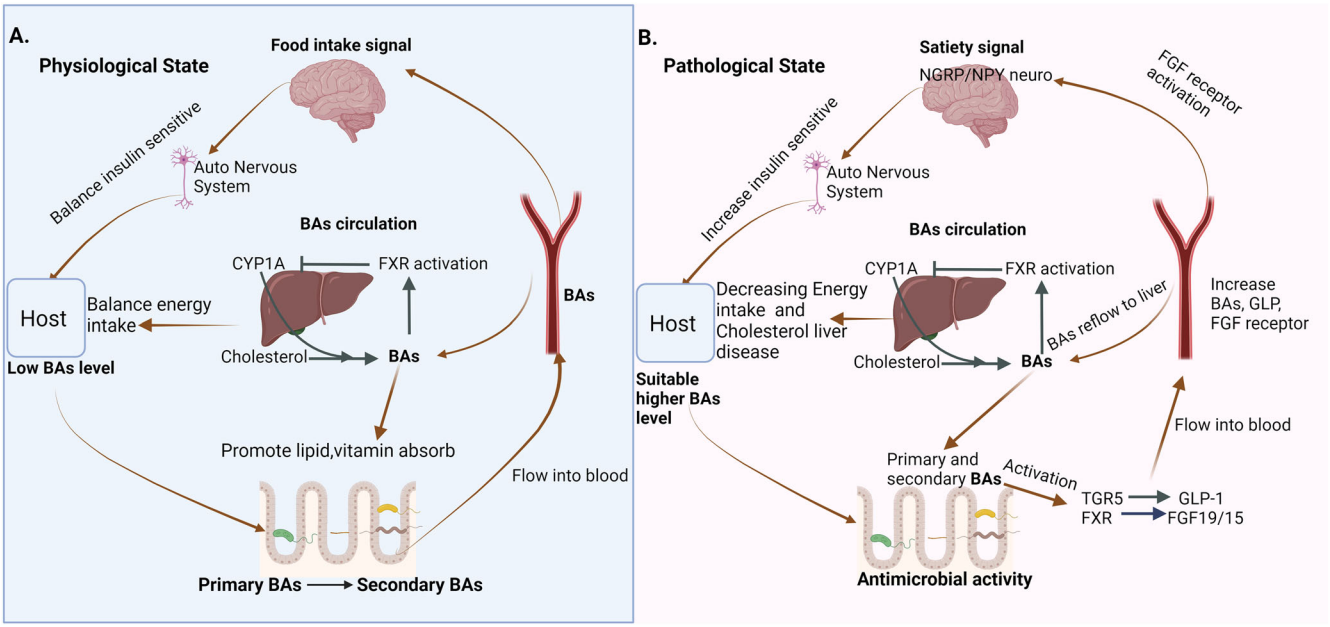

Fig. 3 | Effect of the bile acids (BAs) on the metabolism. BAs, synthesized in the liver and metabolized by gut bacteria, influence energy metabolism with the physiological state in the Panel **A** and the pathological state in the Panel **B**. Stored in the gallbladder, BAs are released post-nutrient intake to aid in absorbing dietary vitamins and lipids. BAs activate Takeda G protein-coupled receptor 5 (TGR5) on cell membranes and nuclear farnesoid X receptor (FXR). FXR activation in the intestine stimulates fibroblast growth factor 19/15 (FGF19/15) secretion and inhibits cholesterol 7alpha-hydroxylase (CYP7A1) gene transcription, crucial for BA synthesis. TGR5 activation promotes glucagon-like peptide-1 (GLP-1) secretion from intestinal L-cells, impacting insulin sensitivity and energy balance. The term 'host' refers to both animals and humans.; golden arrow indicates the direction of metabolite movement, while the black arrow represents activation, promotion, or increase; the horizontal T arrow means inhibiting.

then acts via the portal circulation to suppress CYP7A1, thereby regulating BA synthesis. BAs from the intestine stimulate the secretion of FGF19/15, which activates FGF receptors in hypothalamic AGRP/NPY neurons. Subsequent intracellular signaling of FGF receptors inhibits AGRP/NPY neurons, potentially improving glucose tolerance through modulation by the autonomic nervous system[74]. Furthermore, activation of TGR5 by BAs activates the secretion of GLP-1 from gut L-cells, influencing insulin sensitivity and energy intake[75]. Previous studies shown that treatment with BA blend or a TGR5-targeted BA mimic (INT-777), whether administered peripherally or centrally, resulted in decreased appetite in wild-type mice. Conversely, deletion of TGR5 specifically in neurons or agouti-related peptide neurons throughout the body led to a notable increase in food consumption[76]. It demonstrated that post-meal BAs can penetrate the BBB and trigger a negative-response mechanism regulating satiety during normal feeding through TGR5[77]. These data delineate a signaling pathway whereby BAs elicit immediate effects during the transition from fasting to feeding, promoting the onset of satiety, and reveal a function of physiological feedback driven by BAs within the CNS.

Bile acids and immunity

Recently studies have utilized serum metabolomics, fecal metagenomics, and proteomics to identify microbial determinants that predict vary responses to anti-cytokine and anti-integrin therapies in patients with IBD. They found that the elevated level of serum BAs such as ursodeoxycholic acid (UDCA), and glycodeoxycholic acid (GDCA) was predictive of early improvement in IBD host receiving anti-cytokine therapies[78,79]. Studies have indicated that derivatives of deoxycholic acid (DCA) and lithocholic acid (LCA) serve as crucial communicating metabolites in regulating the differentiation of T_{reg} cells and Th17 cells, thereby influencing the modulation of intestinal inflammation (Fig. 4)[80,81]. For example, 3-oxo-LCA inhibits Th17 cell differentiation by directly interacting with RORγt, a transcription factor crucial for Th17 cell development. Conversely, isoallo-LCA enhances the generation of T_{reg} cells by stimulating mitochondrial ROS production, consequently elevating the levels of FOXP3, a key transcriptional regulator of T_{reg} cell development (Fig. 4)[82]. IsoDCA, another derivative of DCA, boosted FOXP3 expression by suppressing the immunostimulatory functions of DCs, consequently fostering the proliferation of peripheral T_{reg} cells in the colon[81]. DCA was found to induce macrophage polarization towards the M1 phenotype, potentially via TLR2 transactivation mediated by the M2 muscarinic acetylcholine receptor. This led to heightened production of proinflammatory cytokines[83]. In response to BA-induced cytotoxicity, CD4 effector T cells (T_{eff}) display anti-inflammatory characteristics, relying on the constitutive androstane receptor (CAR) and the multidrug resistance protein 1 (MDR1)-IL10 axis[84]. A study elucidation highlights the role of the nuclear xenobiotic receptor CAR in regulating MDR1 release, thereby promoting the upregulation of detoxifying enzymes and drug transporters in T_{eff} cells within the small intestine lamina propria, alongside the essential anti-inflammatory cytokine IL-10[84]. TGR5 acting as a BA receptor, exhibits anti-inflammatory properties upon activation and promotes a tolerogenic state in different systems to mitigate chronic inflammation[85–87]. Additionally, TGR5 agonists have been found to reduce immune cells migration into the CNS[88]. In the gastrointestinal tract, TGR5 deficiency exacerbates liver damage, leading to hepatic inflammation and disease[89].

Communication signaling metabolites: gut bioactive metabolites

Despite the presence of gut SCFAs, intestinal cells also generate a diverse array of signaling molecules, such as dopamine, serotonin, gamma-aminobutyric acid (GABA), trimethylamines, and vitamins. These molecules play crucial roles in metabolism and signaling, influencing host homeostasis, including the integrity of the blood-brain barrier (BBB) and brain function. A previous study indicated that a high-salt diet triggers a TH17 immune reaction in the gut, causing a rise in circulating plasma IL-17[90]. Subsequently, IL-17 influences brain vascular endothelial cells, suppressing their nitric oxide (NO) synthesis, which ultimately leads to decreased cerebral perfusion and cognitive dysfunction. The gut, housing numerous enteroendocrine cells (EECs), stands as the body's largest secretory organ. Its symbiotic relationship with gut microbiota is pivotal, as

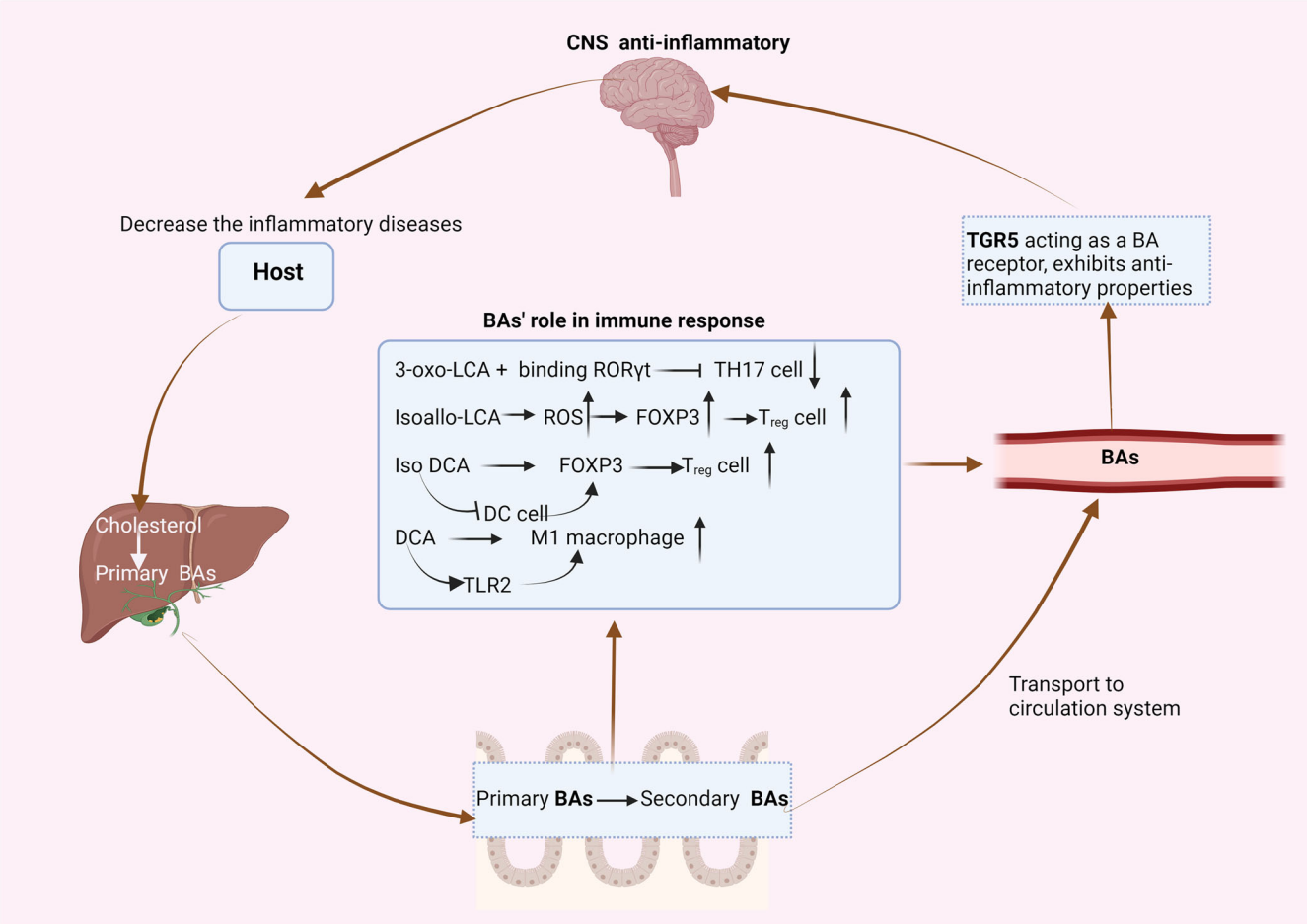

Fig. 4 | Bile acids (BAs) modulate host immunity in various ways. 3-oxo-lithocholic acid (3-oxo-LCA) inhibits Th17 cell differentiation by directly targeting RORγt, crucial for Th17 development. Isoallo-lithocholic acid (isoallo-LCA) boosts T_{reg} cell generation via mitochondrial ROS, elevating FOXP3 levels, vital for T_{reg} function. Iso-deoxycholic acid (IsoDCA), a deoxycholic acid (DCA) derivative, enhances FOXP3 expression by curbing dendritic cell (DC) immunostimulatory functions, fostering peripheral T_{reg} cell proliferation in the colon. DCA drives macrophage polarization towards the M1 phenotype, potentially via M2 muscarinic acetylcholine receptor mediated TLR2 transactivation. Takeda G protein-coupled receptor 5 (TGR5), a BA receptor, exhibits anti-inflammatory effects and promotes tolerance to combat chronic inflammation across diverse systems. The term 'host' refers to both animals and humans.; golden arrow indicates the direction of metabolite movement, while the black arrow represents activation, promotion, or increase; the horizontal T arrow means inhibiting.

microbiota and their metabolites serve as stimuli for EECs, orchestrating the release of gut peptides and hormones that, in turn, modulate diverse signaling pathways[91].

The intestinal tract harbors abundant levels of polyamines, sourced from both dietary intake and the endogenous synthesis by host and microbial cells. Polyamines are essential for cellular process in host, and disrupted concentrations of ornithine decarboxylase and polyamines are associated with cellular expansion abnormalities when concentrations are low and resulting in toxicity and cancer development at high concentrations[47]. Spermine can suppress M1 macrophage activation by downregulating ornithine decarboxylase expression and inhibiting the generation of inflammatory cytokines, without affecting the production of anti-inflammatory IL-10 and transforming growth factor-β (TGFβ)[92]. Combining arginine with *Bifidobacterium animalis subsp. lactis* LKM512 increased circulating and colonic polyamine levels, which were associated with lower concentrations of IL-6 and TNF in the colon[93]. Collectively, it hypothesis that dietary manipulation and supplementation with beneficial bacteria could potentially modulate colonic polyamine metabolism, thereby promoting host health.

Polysaccharide A (PSA) is synthesized and secreted by *Bacteroides fragilis*, which primarily inhabiting the surface colonic mucosa. PSA plays a critical role in the development and effective colonization of *Bacteroides fragilis*, facilitating communication with other microbiota and the host[94]. PSA has the ability to activate macrophages, influencing the secretion of cytokines through various molecular signaling networks, such as NF-κB, mitogen-activated protein kinases (MAPKs), and Toll-like receptors (TLRs)[95]. Research conducted on an animal model demonstrated that PSA extracted from Tinospora cordifolia could enhance NO production[96]. This upregulation promotes the formation of NO boosts microbicidal capabilities of macrophages. The study also suggested that TCPs could boost the expression of inflammatory such as TNF-α, IFN-γ, and IL-12 by triggering macrophages through the TLR4 signaling pathway, thereby demonstrating an anti-tumoral response[96]. In animal models of abscess formation and colitis, PSA demonstrates its anti-inflammatory properties by stimulating IL-10 generation in activated CD4 + T cells[97]. In neuroinflammation, the effects of PSA on T_{reg} cells rely on the upregulation of CD39 production, enabling the translocation of T_{reg} cells to the CNS[98]. The absence of CD39 in T_{reg} cells was correlated with a failure to inhibit experimental colitis, while elevated CD39 production in patients with IBD was linked to condition improvement[99]. Taken together, these studies suggest that PSA could serve as a promising immunomodulatory microbial-associated molecular pattern (MAMP) for treating autoimmune diseases in humans.

Vitamins are essential organic nutrients vital for regular cellular function. Certain commensal bacterial species possess the ability to synthesize key vitamins, particularly those from the vitamin B and vitamin K groups. This microbial synthesis has been suggested as a significant source of

these vitamins[100]. Specifically, the invariant major histocompatibility complex class I–related protein presents vitamin intermediates from the B12 synthesis pathway to mucosa-associated invariant T cells. These T cells which produce IFN-γ and IL-17, and are triggered by microbial metabolites originating from the B12 metabolic pathway[101]. These findings suggest that metabolites derived from vitamin metabolic processes of commensal bacteria, rather than just the end product vitamins, may represent a previously overlooked class of molecules that modulate immune cells response or serve as signals for immune cells to detect commensal bacteria.

The body requires 20 essential amino acids, which must be obtained from the diet and absorbed through specialized transport proteins in the gut. Amino acids play multiple roles in the body, they are essential for protein creation, act as precursors in metabolic processes (glutamine in the citric acid cycle), and function as signaling molecules for cell-to-cell communication (like the neurotransmitter glycine)[102]. Additionally, certain members of the human gut microbiota, such as *Clostridium sporogenes* and *Ruminococcus gnavus*, can decarboxylate tryptophan to produce the neurotransmitter tryptamine[103]. Recent studies have demonstrated that amino acid metabolism and signaling processes are essential in controlling pathogen infections and regulating inflammatory response by the stimulation of innate and adaptive immune reaction[104]. This study also highlights how certain amino acids affect immunity. For instance, the availability of tryptophan, regulated by the Indoleamine 2,3-dioxygenase-1 (IDO1), as pathways that regulate immune response and influence inflammation and adaptive immunity. Furthermore, amino acids such as glutamine, serine, cysteine, methionine, and phenylalanine are also implicated in pathogen evolution and in maintaining equilibrium of immune response. Generally, a surplus of amino acids and hyperactivation of mTOR seem to create an environment favorable for virus infection, while amino acid deprivation and GCN2 activation limit viral enter[104]. However, the pathway by which commensal bacteria influence host amino acid process across different compartments remain unknown. Further functional analyses are needed to comprehend how disruptions in amino acid balance influenced by commensal bacteria affect the immune system.

Endotoxins are bacterial components that become toxic to animals upon release, with LPS being the most abundant. The primary source of endotoxin in healthy humans is gut-resident Gram-negative bacteria, such as *Bacteroides fragilis* and *Escherichia coli*[105]. Limited amount of endotoxins are believed to cross the intestinal wall, with most being removed by the liver; however, small yet significant levels of LPS are detectable in the blood of most humans. LPS can serve as a potential activator of monocytes, binding to TLR4 to initiate downstream activation of NF-κB and Interferon Regulatory Factor (IRF) transcription factors, leading to the production of inflammatory cytokines and chemokines[106]. Generally, gut dysfunction and increased intestinal permeability, often referred to as a leaky gut, can permit LPS to enter the gut wall, promoting local expression and elevated LPS levels in the bloodstream then activate the peripheral innate immune system.

In understanding the collective impact of gut-derived metabolites on the immune system involves recognizing that the initial detection of infection is orchestrated by innate pattern recognition receptors (PRRs). These receptors encompass TLRs, NOD-like receptors, RIG-I-like receptors, and C-type lectin receptors[107]. They detect microorganism-associated molecular patterns (MAMPs) of microorganism, such as formyl peptides, lipopolysaccharide, and peptidoglycan. Triggering PRR signaling pathways induces the generation of antimicrobial peptides (AMPs), chemokines, and cytokines[108]. Any disturbances or modifications in these signaling processes may significantly contribute to the development of various diseases.

Metabolites and barriers

First barrier: gut mucosa and epithelial barrier

The gut mucosa lining serves as the initial cellular barrier, separating the host from intestinal microorganisms and facilitating symbiotic interactions with beneficial microbes[109]. This barrier includes occluding junctions within the gut epithelium, antimicrobial peptides, secretory IgA, and a mucin-based gel layer that prevents direct contact between larger particles and gut microbes (Fig. 5)[110]. Situated beneath the mucus layer, the gut epithelial barrier acts as a semi-permeable physical and biochemical barrier. It facilitates a harmonious balance of interaction and spatial separation between gut bacteria and the host. Epithelial cells possess the ability to detect enteric bacteria and their metabolites by utilizing PRR, notably nucleotide-binding domain leucine-rich repeat-containing proteins and TLRs. Upon activation, these receptors govern the inflammatory response and influence epithelial barrier function via diverse intracellular signal transduction pathways. Among these pathways, the MYD88/NF-κB signaling pathway has garnered significant interest, as it was confirmed to modulate intestinal tight junction integrity following the interaction of bacterial membrane component LPS with TLR4[111]. SCFAs, such as butyrate, significantly contribute to maintaining gut epithelial barrier integrity and supporting host immunity. Butyrate has been shown to enhance barrier function by increasing transepithelial electrical resistance (TEER), reducing permeability to molecules like 4 kDa FITC-dextran and insulin, although higher doses can induce apoptosis[112]. Butyrate has also been reported to promote tight junction assembly by increasing AMP-activated protein kinase[113]. In animal gut epithelial cells, SCFAs have been shown promote barrier integrity through increasing claudin 1 protein expression (rat and piglet) or upregulating the expression of Muc2, Ocln and TJP1 (also known as Zo1) genes (in mice)[114]. Similar to SCFAs, tryptophan metabolites or indole derivatives have been shown to increase the expression of occludin, ZO-1 and claudins, resulting in improved barrier function.

Second barrier: gut vascular barrier

Beyond the mucosal layer, the gut vascular barrier consists of endothelial cells that form a secondary line of defense against the dissemination of microorganisms, toxins, proteins, bacterial metabolites, and cytokines into the host circulation and distant organs from the gut. Gut microbe-derived metabolites play crucial roles in regulating vascular endothelium and possess anti-inflammatory effects. For instance, SCFAs have been shown that mitigate TNF-α and LPS-induced endothelial activation by suppressing the synthesis of proinflammatory cytokines such as IL-6 and IL-8[115]. Additionally, BAs derivatives regulate gut vascular barrier permeability via the FXR receptor[116]. Indoles, from tryptophan metabolism contribute to overall vascular homeostasis and protect against endotoxin translocation into the peripheral circulation[117]. Additionally, hydrogen sulfide governs endothelial homeostasis, and its dysregulation is implicated in the underlying mechanisms of endothelial disorder across various pathological conditions[118]. Thus, the breach of the gut vascular barrier is likely crucial to GLBA pathophysiology. Certain gut luminal composition, such as live pathogenic and commensal microbiota, crosses the intestine barrier and enters into the circulation system. In this process, intestine cytokines, metabolites, bacterial PAMPs, and diet-derived HDL and other small-moleculars, is transfered to the liver through the portal blood. While some of these substances undergo initial processing during transit, the liver ultimately metabolizes and detoxifies them. In advanced chronic liver disease, hepatic encephalopathy stands out as a prevalent and severe complication—a neuropsychiatric syndrome arising from the systemic buildup of gut-derived neurotoxins, notably ammonia, in individuals with compromised liver function[119]. Utilizing rifaximin, a nonabsorbable antimicrobial agent highly concentrated in the gastrointestinal tract, has proven effective in sustaining remission from hepatic encephalopathy in patients experiencing recurrent overt disease[119,120]. This underscores a robust connection between the intestine bacteria and liver disease, particularly those affecting the brain, emphasizing the intricate interplay along the GLBA. Moreover, the association between the intestine bacteria and brain function gains conviction from the occurrence of microbial dysbiosis and intestine inflammation in neurological disease, which are also linked to immune system imbalances.

Third barrier: the blood brain barrier

There are a numerous reviews defining the function, anatomy, and modulation of BBB[121–124]. In current review, our focus is primarily on the effects of metabolites one the BBB. Only few of molecular can cross the BBB

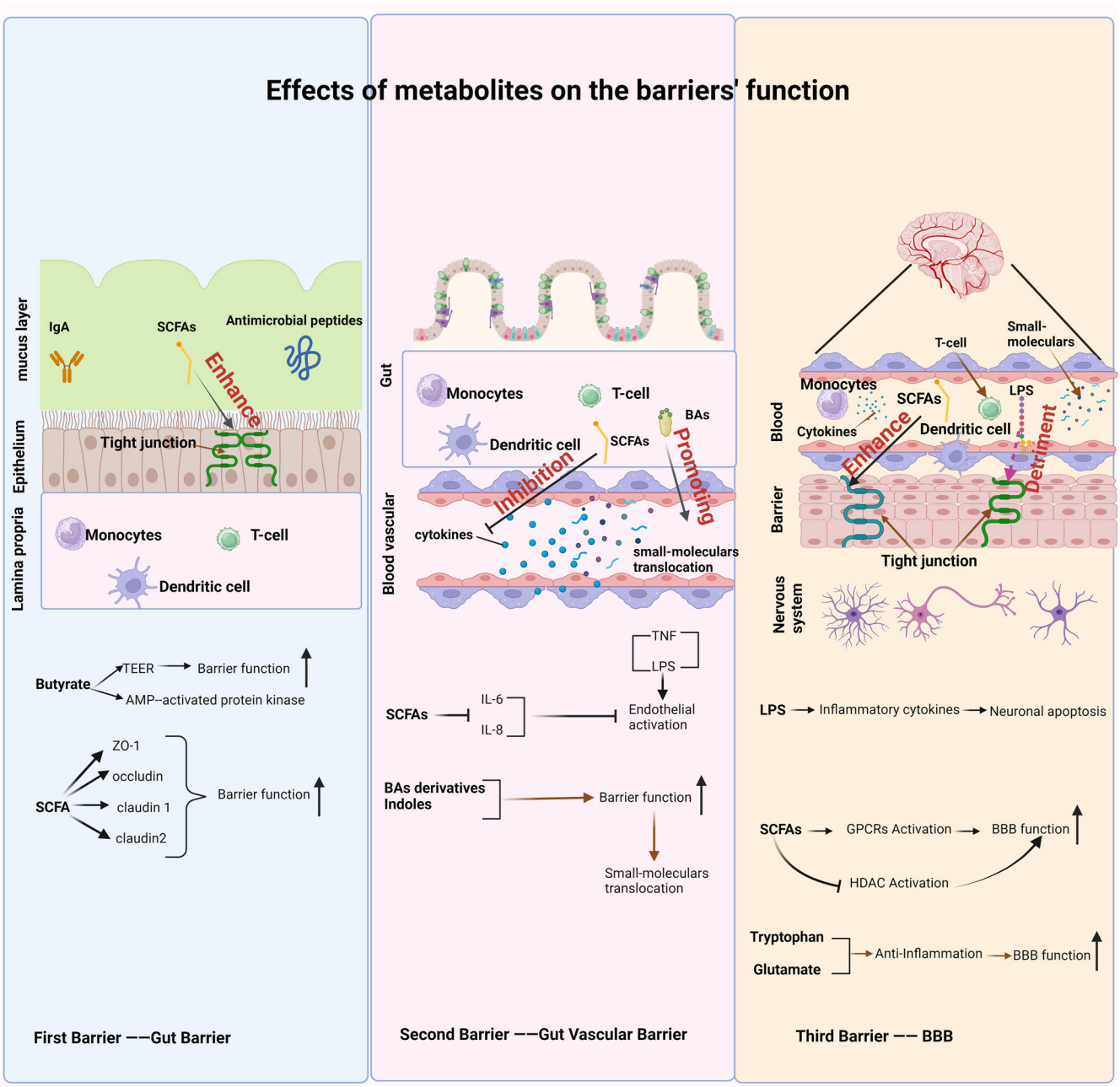

Fig. 5 | Effects of metabolites on the barriers. Metabolites such as butyrate bolster gut barrier function by enhancing trans-epithelial electrical resistance (TEER) through mechanisms like stimulating claudin 1 in gut epithelial cells (rats, piglets) or upregulating Muc2, Ocln, and TJP1 genes in mice. Short-chain fatty acids (SCFAs) uphold barrier integrity by mitigating TNF-α and LPS-induced endothelial activation, reducing IL-6 and IL-8. Bile acid (BA) derivatives modulate gut vascular barrier permeability via FXR. In the CNS, LPS activates TLR4 on microglia, prompting cytokine synthesis, affecting the blood-brain barrier (BBB) and neuronal apoptosis. SCFAs interact with GPCRs, safeguarding the BBB against oxidative stress in gut and brain endothelial cells. SCFAs inhibit HDAC, boosting brain-derived neurotrophic factor for neuronal health. The term 'host' refers to both animals and humans.; the dash arrow is used to represent detrimental, while the black arrow represents activation, promotion, or increase; the horizontal T arrow means inhibiting.

without transporters. The intact BBB prevents most blood substances from leakage into the brain, protecting the CNS from pathogens, toxins, ion dysregulation, and immune cells that could cause neuronal degeneration and dysfunction[125]. Increasing studies indicate that gut microorganism and their metabolites significantly impact on BBB integrity. Following dysfunction of the gut vascular barrier, gut microbes and their derived toxic metabolites can translocate into the circulation system, lead to an inflammatory reaction and compromising BBB integrity. The gastrointestinal tract has numerous bacteria that produce LPS, which is turn trigger gut immune cells to secret inflammatory cytokines. Previous studies suggest that LPS disrupts the BBB through the activation of microglia, which then impair endothelial cells[121]. Additionally, LPS impact on membrane transporters, the extracellular matrix, and the basal lamina. LPS also activates TLR4 on microglia, leading to the synthesis of chemokines and inflammatory cytokines in the CNS, and increase neuronal apoptosis, thereby impacting the BBB and CNS function[126].

SCFAs have been extensively shown to modulate the BBB, including the beneficial action of SCFAs on pan-barrier homeostasis[127,128] and as positive regulators of mitochondrial function[29,129]. Mitochondrial disorder has been well known in certain brain disorders[129]. SCFAs stimulate GPCRs on gut epithelial cells and brain endothelial cells, shielding the BBB from oxidative stress. SCFAs can traverse the BBB by the bloodstream to directly

Table 2 | Targeting metabolites and their therapeutic potentials for specific diseases

Targeted metabolite	Therapeutic potentials disease	Reference
SCFAs (acetate, butyrate, and propionate)	non-alcoholic fatty liver disease (NAFLD), insulin resistance, and type 2 diabetes	142
Butyrate	Inflammatory Bowel Disease (IBD)	139,140
Ursodeoxycholic acid (UDCA)	Cholestatic liver diseases; Non-Alcoholic Steatohepatitis (NASH); non-alcoholic fatty liver disease (NAFLD)	144
Arachidyl-amido cholanoic acid	NASH	145
Tauro-β-muricholic acid (T-βMCA), Glyco-ursodeoxycholic acid (GUDCA)	Obesity and NAFLD	149
Deoxycholic Acid (DCA), Lithocholic Acid (LCA)	Fatty liver disease	150
Omega-3 fatty acids	NAFLD	151
Tryptophan	IBD	153
Indoleamine 2,3-dioxygenase 1 (IDO1)	Colorectal cancer (CRC)	154

on influence its function. For example, germ-free mice fed with butyrate notably improved BBB function by upregulating tight junction proteins. In vitro studies also shown that butyrate and propionate could protect the BBB from LPS-induced disorder[65]. SCFAs also have been found in cerebrospinal fluid in appreciable concentrations, indicating that they can reach the brain. In addition, SCFAs can reach the interior of cells and suppress the activation of HDAC, which normally inhibits the transcription of brain-derived neurotrophic factor[126]. Overall, SCFAs play an important role in regulating various barriers supports the potential microbial signals to coordinate inter-barrier functions, facilitating communication along the GLBA.

Dietary intake, liver enzyme flavin monooxygenases (FMO) and microbial activity are the crucial factors in the synthesis of trimethylamine N-oxide (TMAO)[130]. The detection of TMAO in brains suggests its ability to cross the BBB[131]. Increased plasma concentrations of TMAO have been associated with a high risk of colorectal cancer and the progression of cardiovascular disease and atherosclerosis, primarily through impacts on cholesterol metabolism[132]. However, a study showed that physiologically relevant levels of the methylamine TMAO improved BBB integrity and inhibit it from inflammatory destruction by facilitating the tight junction regulator annexin A1[131]. However, the trimethylamine (TMAO precursor) has been verified to impair BBB function and disrupt tight junction integrity[130,131].

Blood BAs can cross the BBB and may exert direct effects through their receptors in the brain or indirectly via activation of intestinal receptors. This activation can lead to the expression of signaling molecules such as GLP-1 and fibroblast growth factor, influencing neuronal activity in various brain regions or through the vagus nerve[133]. The major primary BAs are chenodeoxycholic acid and cholic acid, which are mainly conjugated with the glycine or taurine[134]. Lots of intestine bacterial strains contribute to keep cholesterol balance via converting primary BAs into secondary BAs using dehydroxylation by dehydratase enzymes[135]. However, the specific mechanisms by which BAs affect the BBB remain unclear.

Similarly, the influence of amino acid metabolites on BBB integrity and function is not thoroughly understood. Tryptophan serves as a precursor to numerous microbial and host metabolites such as kynurenic acid, which exhibits anti-inflammatory properties in the gut and is regarded as neuroprotective[136]. In contrast, quinolinic acid, a neurotoxin and a modulator of the BBB, is implicated in the development of psychiatric disorders and neurodegenerative diseases[136]. Therefore, tryptophan and its derivatives, such as kynurenic acid and quinolinic acid, may playcritical roles in BBB protection and brain health. However, achieving a deeper understanding and exercising caution are essential in harnessing their therapeutic potential while mitigating the risks associated with potentially harmful effects.

Currently, some evidences verified the existence of hepatic barrier in the gut-liver-axis[137], but the structure and function of hepatic barriers are still unclear, as well as the effect of metabolites on the hepatic barrier are remain unknown. In the future, further research is needed to better understand the hepatic barrier and advance the development of GLBA.

Disease and therapeutic implications: targeting metabolites

Gut-liver-brain axis related metabolic and inflammatory disease

Mounting evidence suggest the dysbiosis of the microbial population plays a significant role in the onset of different inflammatory and liver diseases. It has been well documented that a leaky gut is associated with conditions like fatty liver and IBD in humans. In recent years, it has also been recognized that postpartum dairy cows usually experience a chronic low-grade inflammatory condition[138]. Additionally, these cows often experience intestinal disorders linked to high gut permeability, such as subacute ruminal acidosis, which elevate circulatory concentration of LPS and other inflammatory stimuli[138]. These molecules are considered driving factors in the development of common postpartum dysbiosis affecting energy and lipid metabolism in the liver, including fatty liver. The connections between gut dysbiosis, brain diseases, and liver diseases indicate that the pathophysiology of liver and inflammatory diseases is often associated with gastrointestinal issues. Over the past decades, numerous comprehensive reviews have covered GLBA related diseases. In this review, we focus on the potential therapeutic use of metabolites, based on research published in the last 10 years.

Modulate SCFAs production

SCFAs, previously noted for their roles in maintaining glucose homeostasis, food intake, energy metabolism and influence gut and brain barriers. Regulation of the SCFAs production were suggested to as one method to therapy GLBA related diseases. Decrease dietary fiber intake significantly reduces the presence of the immune-boosting *Faecalibacterium prausnitzii* and the production of the SCFA butyrate, both of which support digestive health[139]. For example, most research has focused on the effects of butyrate, suggesting its potential use as a prebiotic and/or probiotic treatment to support the management of IBD (Table 2)[140]. Importantly, higher diets rich in fiber diets have been observed to increase the variety and abundance of the intestine microbes, boost the abundance of beneficial taxa, and enhance butyrate production. Butyrate, known for its neuroprotective roles and improves neuronal plasticity[139]. In contrast, an animal-based diet high in fat and low in fiber reduced the composition of beneficial metabolites and enhanced bile-tolerant microorganisms[141]. In addition, studies provides strong evidence for the beneficial role of primary saccharolytic-derived microbial fermentation products—specifically the SCFA acetate, butyrate, and propionate—in the prevention of obesity, non-alcoholic fatty liver disease (NAFLD), insulin resistance, and type 2 diabetes mellitus (Table 2)[142].

BAs-targeting therapy

The metabolism of BAs in the gut-liver axis is primarily regulated by two key receptors: TGR5 and FXR. Stimulation of FXR suppress BA synthesis and uptake, increase BA secretion, thus mitigating the excessive buildup of BAs associated with hepatic disease[143]. Currently, the most commonly utilized FXR agonists are mainly BAs derivatives, and steroidal or nonsteroidal

compounds[133]. Ursodeoxycholic acid (UDCA), a key derivative of bile acids and an FXR agonist, is employed in the treatment of cholestatic liver diseases. It has also been considered as a potential therapy for Non-Alcoholic Steatohepatitis (NASH) and NAFLD[144]. However, the precise mechanisms by which UDCA mitigates primary biliary cirrhosis and hepatic BAs remains large gap knowledge, as UDCA does not directly impact TGR5 and FXR signaling pathways. Once entering the liver, UDCA undergoes extensive conversion into its conjugated forms, TUDCA and GUDCA, which have been suggested to be FXR antagonists. Additionally, TUDCA provide cytoprotection by effectively blocking ER stress, a key factor in NASH. Hence, additional research is needed to explore the therapeutic impact of UDCA on NASH.

Arachidyl-amido cholanoic acid (Aramchol), a novel fatty acid-BA conjugate targeting SCD1 in hepatic stellate cells, has shown potential in reducing fibrosis without worsening NASH in a phase IIb clinical trial and is now undergoing a phase III trial. Aramchol meglumine, a more soluble formulation, will be utilized in upcoming trials. Addionally, another promising compound, Amilo-5MER, has recently initiated its first human study[144].

In a phase III trial, obeticholic acid, a steroidal FXR agonist, has been effective in reducing fibrosis and key features of NASH, but it is associated with side effects like itching, altered cholesterol levels, and hepatotoxicity[145]. Similarly, EDP-305, another potent FXR agonist, has demonstrated reductions in hepatic ALT levels and lipid levels in a phase IIa trial but has similar side effects including pruritus, nausea, and headaches[146].

Targeting intestinal FXR shows promise for treating obesity[147] and NAFLD[148]. Natural FXR antagonists like T-βMCA and GUDCA are quickly hydrolyzed by BSHs, prompting the development of small molecule FXR inhibitors like GlyMCA, which resists BSH hydrolysis and improves metabolic conditions in mice[149]. Strategies to enrich gut-specific FXR antagonists include using Tempol, metformin, theabrownin, and caffeic acid phenethyl ester to reduce BSH activity, while ensuring these antagonists act only in the gut to avoid side effects like cholestasis and HCC.

TGR5, another BA receptor, regulates BA balance by the gut-liver axis. TGR5 agonists such as DCA, LCA, and semi-synthetic BAs like INT-767 and INT-777, activate cAMP, stimulate GLP-1 secretion, and improve hepatic glucose and lipid metabolism in fatty liver disease[150]. Omega-3 fatty acids, a type of N-3 PUFA, reduce liver fat and influence BA metabolism but did not show improvement in histological activity in NAFLD patients in a completed phase II clinical trial (NCT00681408)[151]. In contrast, dietary docosahexaenoic acid, another polyunsaturated fatty acid, demonstrates superior effects in attenuating blood lipid levels, mitigates liver damage, oxidative stress, and fibrosis formation in NAFLD compared to dietary eicosapentaenoic acid[152].

Targeting tryptophan metabolism application

The microbiota influences the levels of three primary tryptophan metabolites— kynurenine, serotonin, and indole derivatives—in the intestine, which are associated with intestinal inflammatory condition and IBD. Studies in animal and humans show that supplementation with xanthurenic or kynurenic acids can mitigate the severity of colitis by affecting intestinal epithelial cells and T cells, involving activation of the Aryl hydrocarbon Receptor (AhR) and the reconfiguration of cellular energy metabolism[153]. Hence, interventions targeting tryptophan metabolism can help repair dysfunctions within intrinsic metabolic pathways in IBD. The kynurenine pathway of tryptophan metabolism represents a particularly promising target for immunotherapy. Indoleamine 2,3-dioxygenase 1 (IDO1) which is frequently overexpressed in colorectal cancer (CRC), has been extensively studied. Phase I human trials have confirmed the safety and tolerability of orally administered small molecule inhibitors targeting IDO1[154].

Understanding the signaling pathways involved in GLBA communication provides opportunities for therapeutic intervention in various diseases. The new study also confirmed that targeting the GLBA neural arc may offer potential for developing treatments for inflammatory disease[18]. To concluded, targeted modulation of the gut microbial metabolite production and ameliorate metabolic and inflammatory disease, offer novel approaches for managing gastrointestinal and psychiatric disorders by restoring endogenous metabolism and immune balance.

Conclusion

In summary, metabolites play a crucial role in communication between the liver and brain by interacting with GPCRs on the host gut epithelium, the BBB, and with immune cells. They also regulate appetite and energy metabolism. The GLBA is essential for the maintaining metabolic homeostasis and relies on molecular communication signals between the CNS, the peripheral nervous system (PNS) and the gut, liver, and gut microbes. Peripheral signals such as gastric distension and activation of nutrient-sensitive gut receptors initiate hormone release, which modulates food intake and satiety. Despite ongoing research into its mechanisms, the GLBA's contributions to energy metabolism, immune function, and barrier integrity remain incompletely understood. Nevertheless, the influence of GLBA-associated metabolites on organ functions in both health and disease holds promise for future exploration and therapeutic strategies.

Data availability

No datasets were generated or analysed during the current study.

Received: 7 August 2024; Accepted: 14 November 2024;
Published online: 25 November 2024

References

1. Abou-El-Hassan, H. et al. Vγ1 and Vγ4 gamma-delta T cells play opposing roles in the immunopathology of traumatic brain injury in males. *Nat. Commun.* **14**, 4286 (2023).
2. Malaguarnera, G., Giordano, M., Nunnari, G., Bertino, G. & Malaguarnera, M. Gut microbiota in alcoholic liver disease: pathogenetic role and therapeutic perspectives. *World J. Gastroenterol.: WJG* **20**, 16639 (2014).
3. Zeuzem, S. Gut-liver axis. *Int. J. Colorectal Dis.* **15**, 59–82 (2000).
4. Sharon, G. et al. Specialized metabolites from the microbiome in health and disease. *Cell Metab.* **20**, 719–730 (2014).
5. Soret, R. et al. Short-chain fatty acids regulate the enteric neurons and control gastrointestinal motility in rats. *Gastroenterology* **138**, 1772–1782. e1774 (2010).
6. Clarke, T. B. et al. Recognition of peptidoglycan from the microbiota by Nod1 enhances systemic innate immunity. *Nat. Med.* **16**, 228–231 (2010).
7. Maurice, C. F., Haiser, H. J. & Turnbaugh, P. J. Xenobiotics shape the physiology and gene expression of the active human gut microbiome. *Cell* **152**, 39–50 (2013).
8. Hsiao, E. Y. et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell* **155**, 1451–1463 (2013).
9. Brestoff, J. R. & Artis, D. Commensal bacteria at the interface of host metabolism and the immune system. *Nat. Immunol.* **14**, 676–684 (2013).
10. Noverr, M. C. & Huffnagle, G. B. Does the microbiota regulate immune responses outside the gut? *Trends Microbiol* **12**, 562–568 (2004).
11. Macpherson, A. J. & Harris, N. L. Interactions between commensal intestinal bacteria and the immune system. *Nat. Rev. Immunol.* **4**, 478–485 (2004).
12. Flint, H. J., Scott, K. P., Louis, P. & Duncan, S. H. The role of the gut microbiota in nutrition and health. *Nat. Rev. Gastroenterol. Hepatol.* **9**, 577–589 (2012).
13. Kaw, A., Ahern, P., Griffin, N., Goodman, A. & Gordon, J. Human nutrition, the gut microbiome, and immune system: envisioning the future. *Nature* **474**, 327–336 (2011).
14. Nicholson, J. K. et al. Host-gut microbiota metabolic interactions. *Science* **336**, 1262–1267 (2012).

15. Zheng, D., Liwinski, T. & Elinav, E. Interaction between microbiota and immunity in health and disease. *Cell Res.* **30**, 492–506 (2020).
16. Leshem, A., Liwinski, T. & Elinav, E. Immune-microbiota interplay and colonization resistance in infection. *Mol. Cell* **78**, 597–613 (2020).
17. Ansaldo, E., Farley, T. K. & Belkaid, Y. Control of immunity by the microbiota. *Annu. Rev. Immunol.* **39**, 449–479 (2021).
18. Teratani, T. et al. The liver–brain–gut neural arc maintains the Treg cell niche in the gut. *Nature* **585**, 591–596 (2020).
19. Mulak, A. & Bonaz, B. Brain-gut-microbiota axis in Parkinson's disease. *World J. Gastroenterology: WJG* **21**, 10609 (2015).
20. Postler, T. S. & Ghosh, S. Understanding the holobiont: how microbial metabolites affect human health and shape the immune system. *Cell Metab.* **26**, 110–130 (2017).
21. Rosshart, S. P. et al. Wild mouse gut microbiota promotes host fitness and improves disease resistance. *Cell* **171**, 1015–1028. e1013 (2017).
22. Stewart, R. D. et al. Assembly of 913 microbial genomes from metagenomic sequencing of the cow rumen. *Nat. Commun.* **9**, 870 (2018).
23. Wikoff, W. R. et al. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. *Proc. Natl. Acad. Sci.* **106**, 3698–3703 (2009).
24. Hackmann, T. J., Ngugi, D. K., Firkins, J. L. & Tao, J. Genomes of rumen bacteria encode atypical pathways for fermenting hexoses to short-chain fatty acids. *Environ. Microbiol.* **19**, 4670–4683 (2017).
25. Macfarlane, S. & Macfarlane, G. T. Regulation of short-chain fatty acid production. *Proc. Nutr. Soc.* **62**, 67–72 (2003).
26. Dalile, B., Van Oudenhove, L., Vervliet, B. & Verbeke, K. The role of short-chain fatty acids in microbiota–gut–brain communication. *Nat. Rev. Gastroenterol. Hepatol.* **16**, 461–478 (2019).
27. Rajendran, V. & Binder, H. Apical membrane Cl-butyrate exchange: mechanism of short chain fatty acid stimulation of active chloride absorption in rat distal colon. *J. Membr. Biol.* **141**, 51–58 (1994).
28. Mascolo, N., Rajendran, V. M. & Binder, H. J. Mechanism of short-chain fatty acid uptake by apical membrane vesicles of rat distal colon. *Gastroenterology* **101**, 331–338 (1991).
29. Schönfeld, P. & Wojtczak, L. Short-and medium-chain fatty acids in energy metabolism: the cellular perspective. *J. Lipid Res.* **57**, 943–954 (2016).
30. Boets, E. et al. Systemic availability and metabolism of colonic-derived short-chain fatty acids in healthy subjects: a stable isotope study. *J. Physiol.* **595**, 541–555 (2017).
31. Hellerstein, M. et al. Measurement of de novo hepatic lipogenesis in humans using stable isotopes. *J. Clin. Investig.* **87**, 1841–1852 (1991).
32. Wiltrout, D. & Satter, L. Contribution of propionate to glucose synthesis in the lactating and nonlactating cow. *J. Dairy Sci.* **55**, 307–317 (1972).
33. Boets, E. et al. Quantification of in vivo colonic short chain fatty acid production from inulin. *Nutrients* **7**, 8916–8929 (2015).
34. Layden, B. T., Angueira, A. R., Brodsky, M., Durai, V. & Lowe, W. L. Jr Short chain fatty acids and their receptors: new metabolic targets. *Transl. Res.* **161**, 131–140 (2013).
35. Yamashita, H., Kaneyuki, T. & Tagawa, K. Production of acetate in the liver and its utilization in peripheral tissues. *Biochimica et. Biophysica Acta (BBA)-Mol. Cell Biol. Lipids* **1532**, 79–87 (2001).
36. Ren, Q. et al. New insights into the digestion and bioavailability of a high-melting-temperature solid triacylglycerol fraction in bovine milk fat. *Food Funct.* **12**, 5274–5286 (2021).
37. Portincasa, P. et al. Gut microbiota and short chain fatty acids: implications in glucose homeostasis. *Int. J. Mol. Sci.* **23**, 1105 (2022).
38. Fernandes, J., Su, W., Rahat-Rozenbloom, S., Wolever, T. & Comelli, E. Adiposity, gut microbiota and faecal short chain fatty acids are linked in adult humans. *Nutr. diabetes* **4**, e121–e121 (2014).
39. Cho, I. et al. Antibiotics in early life alter the murine colonic microbiome and adiposity. *Nature* **488**, 621–626 (2012).
40. Han, K. et al. Propionate functions as a feeding state–dependent regulatory metabolite to counter proinflammatory signaling linked to nutrient load and obesity. *J. Leukocyte Biol.* **115,** 738–749 (2024).
41. Martinez-Medina, M. et al. Western diet induces dysbiosis with increased E coli in CEABAC10 mice, alters host barrier function favouring AIEC colonisation. *Gut* **63**, 116–124 (2014).
42. Wichmann, A. et al. Microbial modulation of energy availability in the colon regulates intestinal transit. *Cell Host Microbe* **14**, 582–590 (2013).
43. Yadav, H., Lee, J.-H., Lloyd, J., Walter, P. & Rane, S. G. Beneficial metabolic effects of a probiotic via butyrate-induced GLP-1 hormone secretion. *J. Biol. Chem.* **288**, 25088–25097 (2013).
44. Véniant, M. M. et al. A GIPR antagonist conjugated to GLP-1 analogues promotes weight loss with improved metabolic parameters in preclinical and phase 1 settings. *Nat. Metabolism* 1–14 (2024).
45. Frampton, J., Murphy, K. G., Frost, G. & Chambers, E. S. Short-chain fatty acids as potential regulators of skeletal muscle metabolism and function. *Nat. Metab.* **2**, 840–848 (2020).
46. Fellows, R. et al. Microbiota derived short chain fatty acids promote histone crotonylation in the colon through histone deacetylases. *Nat. Commun.* **9**, 105 (2018).
47. Rooks, M. G. & Garrett, W. S. Gut microbiota, metabolites and host immunity. *Nat. Rev. Immunol.* **16**, 341–352 (2016).
48. Usami, M. et al. Butyrate and trichostatin A attenuate nuclear factor κB activation and tumor necrosis factor α secretion and increase prostaglandin E2 secretion in human peripheral blood mononuclear cells. *Nutr. Res.* **28**, 321–328 (2008).
49. Vinolo, M. A. et al. Suppressive effect of short-chain fatty acids on production of proinflammatory mediators by neutrophils. *J. Nutritional Biochem.* **22**, 849–855 (2011).
50. Chang, P. V., Hao, L., Offermanns, S. & Medzhitov, R. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. *Proc. Natl. Acad. Sci.* **111**, 2247–2252 (2014).
51. Thorburn, A. N., Macia, L. & Mackay, C. R. Diet, metabolites, and "western-lifestyle" inflammatory diseases. *Immunity* **40**, 833–842 (2014).
52. Park, J. et al. Short-chain fatty acids induce both effector and regulatory T cells by suppression of histone deacetylases and regulation of the mTOR–S6K pathway. *Mucosal Immunol.* **8**, 80–93 (2015).
53. Tao, R. et al. Deacetylase inhibition promotes the generation and function of regulatory T cells. *Nat. Med.* **13**, 1299–1307 (2007).
54. Thorburn, A. N. et al. Evidence that asthma is a developmental origin disease influenced by maternal diet and bacterial metabolites. *Nat. Commun.* **6**, 1–13 (2015).
55. Wang, L., De Zoeten, E. F., Greene, M. I. & Hancock, W. W. Immunomodulatory effects of deacetylase inhibitors: therapeutic targeting of FOXP3+ regulatory T cells. *Nat. Rev. Drug Discov.* **8**, 969–981 (2009).
56. Said, H. et al. FFA3 activation stimulates duodenal bicarbonate secretion and prevents NSAID-induced enteropathy via the GLP-2 pathway in rats. *Dig. Dis. Sci.* **62**, 1944–1952 (2017).
57. Duan, H., Wang, L., Huangfu, M. & Li, H. The impact of microbiota-derived short-chain fatty acids on macrophage activities in disease: Mechanisms and therapeutic potentials. *Biomed. Pharmacother.* **165,** 115276 (2023).
58. Yan, Q., Jia, S., Li, D. & Yang, J. The role and mechanism of action of microbiota-derived short-chain fatty acids in neutrophils: From the activation to becoming potential biomarkers. *Biomedicine Pharmacother.* **169**, 115821 (2023).
59. Fung, T. C., Olson, C. A. & Hsiao, E. Y. Interactions between the microbiota, immune and nervous systems in health and disease. *Nat. Neurosci.* **20**, 145–155 (2017).

60. Sharon, G., Sampson, T. R., Geschwind, D. H. & Mazmanian, S. K. The central nervous system and the gut microbiome. *Cell* **167**, 915–932 (2016).
61. Dinan, T. G. & Cryan, J. F. Gut instincts: microbiota as a key regulator of brain development, ageing and neurodegeneration. *J. Physiol.* **595**, 489–503 (2017).
62. Mendes, M. S. & Majewska, A. K. An overview of microglia ontogeny and maturation in the homeostatic and pathological brain. *Eur. J. Neurosci.* **53**, 3525–3547 (2021).
63. Jiang, N. M., Cowan, M., Moonah, S. N. & Petri, W. A. The impact of systemic inflammation on neurodevelopment. *Trends Mol. Med.* **24**, 794–804 (2018).
64. Majumdar, A., Siva Venkatesh, I. P. & Basu, A. Short-chain fatty acids in the microbiota–gut–brain axis: role in neurodegenerative disorders and viral infections. *ACS Chem. Neurosci.* **14**, 1045–1062 (2023).
65. O'Riordan, K. J. et al. Short chain fatty acids: microbial metabolites for gut-brain axis signalling. *Mol. Cell. Endocrinol.* **546**, 111572 (2022).
66. Wenzel, T. J. R. (2020). Characterizing previously unrecognized effects of endogenous molecules on the phagocytic activity of glia, as well as their secretome. (University of British Columbia).
67. Soliman, M. L., Puig, K. L., Combs, C. K. & Rosenberger, T. A. Acetate reduces microglia inflammatory signaling in vitro. *J. Neurochem.* **123**, 555–567 (2012).
68. Soliman, M. L., Combs, C. K. & Rosenberger, T. A. Modulation of inflammatory cytokines and mitogen-activated protein kinases by acetate in primary astrocytes. *J. Neuroimmune Pharmacol.* **8**, 287–300 (2013).
69. Ferrell, J. M. & Chiang, J. Y. Bile acid receptors and signaling crosstalk in the liver, gut and brain. *Liver Res.* **5**, 105–118 (2021).
70. Ridlon, J. M., Harris, S. C., Bhowmik, S., Kang, D.-J. & Hylemon, P. B. Consequences of bile salt biotransformations by intestinal bacteria. *Gut microbes* **7**, 22–39 (2016).
71. Monteiro-Cardoso, V. F., Corlianò, M. & Singaraja, R. R. Bile acids: a communication channel in the gut-brain axis. *Neuromolecular Med* **23**, 99–117 (2021).
72. Ferrell, J. M., Pathak, P., Boehme, S., Gilliland, T. & Chiang, J. Y. Deficiency of both farnesoid X receptor and Takeda G protein–coupled receptor 5 exacerbated liver fibrosis in mice. *Hepatology* **70**, 955–970 (2019).
73. Chiang, J. Y. & Ferrell, J. M. Discovery of farnesoid X receptor and its role in bile acid metabolism. *Mol. Cell. Endocrinol.* **548**, 111618 (2022).
74. Liu, S. et al. A gut–brain axis regulating glucose metabolism mediated by bile acids and competitive fibroblast growth factor actions at the hypothalamus. *Mol. Metab.* **8**, 37–50 (2018).
75. Lun, W. et al. Mechanism of action of the bile acid receptor TGR5 in obesity. *Acta Pharmaceutica Sinica B.* **14**, 468–491 (2024).
76. Perino, A. et al. Central anorexigenic actions of bile acids are mediated by TGR5. *Nat. Metab.* **3**, 595–603 (2021).
77. Kawamata, Y. et al. AG protein-coupled receptor responsive to bile acids. *J. Biol. Chem.* **278**, 9435–9440 (2003).
78. Lee, J. W. J. et al. Multi-omics reveal microbial determinants impacting responses to biologic therapies in inflammatory bowel disease. *Cell Host Microbe* **29**, 1294–1304. e1294 (2021).
79. Cai, J., Sun, L. & Gonzalez, F. J. Gut microbiota-derived bile acids in intestinal immunity, inflammation, and tumorigenesis. *Cell Host Microbe* **30**, 289–300 (2022).
80. Hang, S. et al. Bile acid metabolites control TH17 and Treg cell differentiation. *Nature* **576**, 143–148 (2019).
81. Li, W. et al. A bacterial bile acid metabolite modulates Treg activity through the nuclear hormone receptor NR4A1. *Cell Host Microbe* **29**, 1366–1377.e1369 (2021).
82. Evangelakos, I., Heeren, J., Verkade, E. & Kuipers, F. Role of bile acids in inflammatory liver diseases. *Semin. Immunopathol* **43**, 577–590 (2021).
83. Wang, L. et al. Gut microbial bile acid metabolite skews macrophage polarization and contributes to high-fat diet-induced colonic inflammation. *Gut Microbes* **12**, 1819155 (2020).
84. Chen, M. L. et al. CAR directs T cell adaptation to bile acids in the small intestine. *Nature* **593**, 147–151 (2021).
85. Reich, M. et al. TGR5 is essential for bile acid-dependent cholangiocyte proliferation in vivo and in vitro. *Gut* **65**, 487–501 (2016).
86. Högenauer, K. et al. G-protein-coupled bile acid receptor 1 (GPBAR1, TGR5) agonists reduce the production of proinflammatory cytokines and stabilize the alternative macrophage phenotype. *J. Medicinal Chem.* **57**, 10343–10354 (2014).
87. Younossi, Z. M. et al. Current and future therapeutic regimens for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Hepatology* **68**, 361–371 (2018).
88. Ye, D., He, J. & He, X. The role of bile acid receptor TGR5 in regulating inflammatory signalling. *Scand. J. Immunol* **99,** e13361 (2024).
89. Shi, Y. et al. TGR5 regulates macrophage inflammation in nonalcoholic steatohepatitis by modulating NLRP3 inflammasome activation. *Front. Immunol.* **11**, 609060 (2021).
90. Faraco, G. et al. Dietary salt promotes neurovascular and cognitive dysfunction through a gut-initiated TH17 response. *Nat. Neurosci.* **21**, 240–249 (2018).
91. Fülling, C., Dinan, T. G. & Cryan, J. F. Gut microbe to brain signaling: what happens in vagus. *Neuron* **101**, 998–1002 (2019).
92. Ocaña, M. C., Martínez-Poveda, B., Quesada, A. R. & Medina, M. Á. Metabolism within the tumor microenvironment and its implication on cancer progression: An ongoing therapeutic target. *Medicinal Res. Rev.* **39**, 70–113 (2019).
93. Xiao, Y., Feng, Y., Zhao, J., Chen, W. & Lu, W. Achieving healthy aging through gut microbiota-directed dietary intervention: Focusing on microbial biomarkers and host mechanisms. *J. Adv. Res.* https://doi.org/10.1016/j.jare.2024.03.005 (2024).
94. Valguarnera, E. & Wardenburg, J. B. Good gone bad: one toxin away from disease for Bacteroides fragilis. *J. Mol. Biol.* **432**, 765–785 (2020).
95. Ma, N., Zhang, J., Reiter, R. J. & Ma, X. Melatonin mediates mucosal immune cells, microbial metabolism, and rhythm crosstalk: a therapeutic target to reduce intestinal inflammation. *Medicinal Res. Rev.* **40**, 606–632 (2020).
96. Sun, Y. et al. Polysaccharides confer benefits in immune regulation and multiple sclerosis by interacting with gut microbiota. *Food Res. Int.* **149**, 110675 (2021).
97. Surana, N. K. & Kasper, D. L. The yin yang of bacterial polysaccharides: lessons learned from B. fragilis PSA. *Immunol. Rev.* **245**, 13–26 (2012).
98. Miyauchi, E., Shimokawa, C., Steimle, A., Desai, M. S. & Ohno, H. The impact of the gut microbiome on extra-intestinal autoimmune diseases. *Nat. Rev. Immunol.* **23**, 9–23 (2023).
99. Gibson, D. J. et al. Heightened expression of CD39 by regulatory T lymphocytes is associated with therapeutic remission in inflammatory bowel disease. *Inflamm. Bowel Dis.* **21**, 2806–2814 (2015).
100. Amanzadeh, Z. & Amanzadeh, Z. The Need to Use Microorganisms and Their Biosynthesized Bioactive Metabolites for Biological and Medical Activities. In Bioactive Compounds-Biosynthesis, Characterization and Applications, (IntechOpen) (2021).
101. Crowther, M. D. & Sewell, A. K. The burgeoning role of MR1-restricted T-cells in infection, cancer and autoimmune disease. *Curr. Opin. Immunol.* **69**, 10–17 (2021).
102. Devignes, C.-S., Carmeliet, G. & Stegen, S. Amino acid metabolism in skeletal cells. *Bone Rep.* **17**, 101620 (2022).
103. Williams, B. B. et al. Discovery and characterization of gut microbiota decarboxylases that can produce the neurotransmitter tryptamine. *Cell Host Microbe* **16**, 495–503 (2014).

104. Tomé, D. Amino acid metabolism and signalling pathways: potential targets in the control of infection and immunity. *Nutr. Diabetes* **11**, 20 (2021).
105. Brown, G. C., Camacho, M. & Williams-Gray, C. H. The endotoxin hypothesis of Parkinson's disease. *Mov. Disord.* **38**, 1143–1155 (2023).
106. Rossol, M. et al. LPS-induced cytokine production in human monocytes and macrophages. *Critical Reviews™ in Immunology* **31,** 379–446 (2011).
107. Nielsen, A. E., Hantho, J. D. & Mancini, R. J. Synthetic agonists of NOD-like, RIG-I-like, and C-type lectin receptors for probing the inflammatory immune response. *Future Medicinal Chem.* **9**, 1345–1360 (2017).
108. Liu, C. H., Liu, H. & Ge, B. Innate immunity in tuberculosis: host defense vs pathogen evasion. *Cell. Mol. Immunol.* **14**, 963–975 (2017).
109. Martens, E. C., Neumann, M. & Desai, M. S. Interactions of commensal and pathogenic microorganisms with the intestinal mucosal barrier. *Nat. Rev. Microbiol.* **16**, 457–470 (2018).
110. Aburto, M. R. & Cryan, J. F. Gastrointestinal and brain barriers: unlocking gates of communication across the microbiota–gut–brain axis. *Nat. Rev. Gastroenterol. Hepatology* **21,** 222–247 (2024).
111. Huang, B. et al. Babao Dan alleviates gut immune and microbiota disorders while impacting the TLR4/MyD88/NF-κB pathway to attenuate 5-Fluorouracil-induced intestinal injury. *Biomedicine Pharmacother.* **166**, 115387 (2023).
112. Yan, H. & Ajuwon, K. M. Butyrate modifies intestinal barrier function in IPEC-J2 cells through a selective upregulation of tight junction proteins and activation of the Akt signaling pathway. *PloS one* **12,** e0179586 (2017).
113. Peng, L., Li, Z.-R., Green, R. S., Holzmanr, I. R. & Lin, J. Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. *J. Nutr.* **139**, 1619–1625 (2009).
114. Devriese, S. Treatment strategies for intestinal epithelial barrier dysfunction in inflammatory bowel disease. PhD thesis, Ghent University (2017).
115. Zheng, S. et al. Do short chain fatty acids and phenolic metabolites of the gut have synergistic anti-inflammatory effects?–New insights from a TNF-α-induced Caco-2 cell model. *Food Res. Int.* **139**, 109833 (2021).
116. Xiang, J. et al. Effect of different bile acids on the intestine through enterohepatic circulation based on FXR. *Gut Microbes* **13**, 1949095 (2021).
117. Cheng, C. K. & Huang, Y. The gut-cardiovascular connection: new era for cardiovascular therapy. *Med. Rev.* **1**, 23–46 (2021).
118. Sun, H.-J., Wu, Z.-Y., Nie, X.-W. & Bian, J.-S. Role of endothelial dysfunction in cardiovascular diseases: the link between inflammation and hydrogen sulfide. *Front. Pharmacol.* **10**, 493254 (2020).
119. Brescia, P. & Rescigno, M. The gut vascular barrier: a new player in the gut–liver–brain axis. *Trends Mol. Med.* **27**, 844–855 (2021).
120. Gasbarrini, A. et al. Update on the role of Rifaximin in digestive diseases. *J. Gastrointest. Liver Dis.* **32**, 92–109 (2023).
121. Galea, I. The blood–brain barrier in systemic infection and inflammation. *Cell. Mol. Immunol.* **18**, 2489–2501 (2021).
122. Kadry, H., Noorani, B. & Cucullo, L. A blood–brain barrier overview on structure, function, impairment, and biomarkers of integrity. *Fluids Barriers CNS* **17**, 1–24 (2020).
123. Wu, D. et al. The blood–brain barrier: structure, regulation, and drug delivery. *Signal Transduct. Target. Ther.* **8**, 217 (2023).
124. Segarra, M., Aburto, M. R. & Acker-Palmer, A. Blood–brain barrier dynamics to maintain brain homeostasis. *Trends Neurosci.* **44**, 393–405 (2021).
125. Knox, E. G., Aburto, M. R., Clarke, G., Cryan, J. F. & O'Driscoll, C. M. The blood-brain barrier in aging and neurodegeneration. *Mol. Psychiatry* **27**, 2659–2673 (2022).
126. Tang, W., Zhu, H., Feng, Y., Guo, R. & Wan, D. The impact of gut microbiota disorders on the blood–brain barrier. *Infection Drug Resistance* **13,** 3351–3363 (2020).
127. Valles-Colomer, M. et al. The neuroactive potential of the human gut microbiota in quality of life and depression. *Nat. Microbiol.* **4**, 623–632 (2019).
128. Radjabzadeh, D. et al. Gut microbiome-wide association study of depressive symptoms. *Nat. Commun.* **13**, 7128 (2022).
129. Rose, S. et al. Butyrate enhances mitochondrial function during oxidative stress in cell lines from boys with autism. *Transl. psychiatry* **8**, 42 (2018).
130. Praveenraj, S. S. et al. The role of a gut microbial-derived metabolite, trimethylamine N-oxide (TMAO), in neurological disorders. *Mol. Neurobiol.* **59**, 6684–6700 (2022).
131. Hoyles, L. et al. Regulation of blood–brain barrier integrity by microbiome-associated methylamines and cognition by trimethylamine N-oxide. *Microbiome* **9**, 1–21 (2021).
132. Gatarek, P. & Kaluzna-Czaplinska, J. Trimethylamine N-oxide (TMAO) in human health. *EXCLI J.* **20**, 301 (2021).
133. Yan, M. et al. Gut liver brain axis in diseases: the implications for therapeutic interventions. *Signal Transduct. Target. Ther.* **8**, 443 (2023).
134. Guzior, D. V. & Quinn, R. A. Microbial transformations of human bile acids. *Microbiome* **9**, 140 (2021).
135. Needham, B. D., Kaddurah-Daouk, R. & Mazmanian, S. K. Gut microbial molecules in behavioural and neurodegenerative conditions. *Nat. Rev. Neurosci.* **21**, 717–731 (2020).
136. Parker, A., Fonseca, S. & Carding, S. R. Gut microbes and metabolites as modulators of blood-brain barrier integrity and brain health. *Gut microbes* **11**, 135–157 (2020).
137. Wang, Y. & Liu, Y. Gut-liver-axis: Barrier function of liver sinusoidal endothelial cell. *J. Gastroenterol. Hepatol.* **36**, 2706–2714 (2021).
138. Ringseis, R., Gessner, D. K. & Eder, K. The gut–liver axis in the control of energy metabolism and food intake in animals. *Annu. Rev. Anim. Biosci.* **8**, 295–319 (2020).
139. Liu, L., Huh, J. R. & Shah, K. Microbiota and the gut-brain-axis: Implications for new therapeutic design in the CNS. *EBioMedicine* **77**, 103908 (2022).
140. Deleu, S., Machiels, K., Raes, J., Verbeke, K. & Vermeire, S. Short chain fatty acids and its producing organisms: An overlooked therapy for IBD? *EBioMedicine* **66**, 103293 (2021).
141. Sholl, J., Mailing, L. J. & Wood, T. R. Reframing nutritional microbiota studies to reflect an inherent metabolic flexibility of the human gut: a narrative review focusing on high-fat diets. *Mbio* **12**, 00579–00521 (2021).
142. Canfora, E. E., Meex, R. C., Venema, K. & Blaak, E. E. Gut microbial metabolites in obesity, NAFLD and T2DM. *Nat. Rev. Endocrinol.* **15**, 261–273 (2019).
143. Tully, D. C. et al. Discovery of tropifexor (LJN452), a highly potent non-bile acid FXR agonist for the treatment of cholestatic liver diseases and nonalcoholic steatohepatitis (NASH). ACS Publications (2017).
144. Jiao, T. Y., Ma, Y. D., Guo, X. Z., Ye, Y. F. & Xie, C. Bile acid and receptors: Biology and drug discovery for nonalcoholic fatty liver disease. *Acta Pharmacologica Sin.* **43**, 1103–1119 (2022).
145. Shah, R. A. & Kowdley, K. V. Obeticholic acid for the treatment of nonalcoholic steatohepatitis. *Expert Rev. Gastroenterol. Hepatol.* **14**, 311–321 (2020).
146. Ratziu, V. et al. EDP-305 in patients with NASH: A phase II double-blind placebo-controlled dose-ranging study. *J. Hepatol.* **76**, 506–517 (2022).
147. Li, F. et al. Microbiome remodelling leads to inhibition of intestinal farnesoid X receptor signalling and decreased obesity. *Nat. Commun.* **4**, 2384 (2013).
148. Sayin, S. I. et al. Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist. *Cell Metab.* **17**, 225–235 (2013).

149. Gonzalez, F. J., Jiang, C., Xie, C. & Patterson, A. D. Intestinal farnesoid X receptor signaling modulates metabolic disease. *Digestive Dis.* **35**, 178–184 (2017).
150. Pathak, P. et al. Farnesoid X receptor induces Takeda G-protein receptor 5 cross-talk to regulate bile acid synthesis and hepatic metabolism. *J. Biol. Chem.* **292**, 11055–11069 (2017).
151. Argo, C. K. et al. Effects of n-3 fish oil on metabolic and histological parameters in NASH: a double-blind, randomized, placebo-controlled trial. *J. Hepatol.* **62**, 190–197 (2015).
152. Jump, D. B., Depner, C. M., Tripathy, S. & Lytle, K. A. Potential for dietary ω-3 fatty acids to prevent nonalcoholic fatty liver disease and reduce the risk of primary liver cancer. *Adv. Nutr.* **6**, 694–702 (2015).
153. Michaudel, C. et al. Rewiring the altered tryptophan metabolism as a novel therapeutic strategy in inflammatory bowel diseases. *Gut* **72**, 1296–1307 (2023).
154. Santhanam, S., Alvarado, D. M. & Ciorba, M. A. Therapeutic targeting of inflammation and tryptophan metabolism in colon and gastrointestinal cancer. *Transl. Res.* **167**, 67–79 (2016).
155. Louis, P., Hold, G. L. & Flint, H. J. The gut microbiota, bacterial metabolites and colorectal cancer. *Nat. Rev. Microbiol.* **12**, 661–672 (2014).
156. Rey, F. E. et al. Dissecting the in vivo metabolic potential of two human gut acetogens. *J. Biol. Chem.* **285**, 22082–22090 (2010).
157. Fukuda, S. et al. Bifidobacteria can protect from enteropathogenic infection through production of acetate. *Nature* **469**, 543–547 (2011).
158. Scott, K. P., Martin, J. C., Campbell, G., Mayer, C.-D. & Flint, H. J. Whole-genome transcription profiling reveals genes up-regulated by growth on fucose in the human gut bacterium "Roseburia inulinivorans. *J. Bacteriol.* **188**, 4340–4349 (2006).
159. Smith, P. M. et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science* **341**, 569–573 (2013).
160. Duncan, S. H., Barcenilla, A., Stewart, C. S., Pryde, S. E. & Flint, H. J. Acetate utilization and butyryl coenzyme A (CoA): acetate-CoA transferase in butyrate-producing bacteria from the human large intestine. *Appl. Environ. Microbiol.* **68**, 5186–5190 (2002).
161. Furusawa, Y. et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* **504**, 446–450 (2013).
162. Arpaia, N. et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature* **504**, 451–455 (2013).

Acknowledgements

This study was funded by National Natural Science Foundation of China (32130100).

Author contributions

Conceptualization, X.S., M.S., S.L. and W.W.; software, X.S.; validation, S.L.; X.S.; writing—original draft preparation, X.S.; writing—review and editing, M.S.; visualization, X.S.; supervision, S.L.; project administration, W.W.; and funding acquisition, S.L. All authors have read and agreed to the published version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to Wei Wang or Shengli Li.