Received: 10 April 2024 | Accepted: 8 June 2024

DOI: 10.1002/ame2.12464

REVIEW

Role of short-chain fatty acids in host physiology

Mingyue Liu[1] | Yubo Lu[2] | Guoyu Xue[1] | Le Han[3] | Hanbing Jia[4] | Zi Wang[4] | Jia Zhang[5] | Peng Liu[6] | Chaojuan Yang[7] | Yingjie Zhou[8]

[1]Stem Cell Storage Center, Hebei Reproductive Health Hospital, Hebei Women and Children's Health Hospital, Hebei Research Institute For Reproductive Health, Shijiazhuang, China

[2]School of Electronic Information and Electrical Engineering, Shanghai Jiao Tong University, Shanghai, China

[3]Prevention Health Section, Hebei Reproductive Health Hospital, Hebei Women and Children's Health Hospital, Hebei Research Institute For Reproductive Health, Shijiazhuang, China

[4]Department of Medical Imaging, Hebei Reproductive Health Hospital, Hebei Women and Children's Health Hospital, Hebei Research Institute For Reproductive Health, Shijiazhuang, China

[5]Department of Obstetrical, Hebei Reproductive Health Hospital, Hebei Women and Children's Health Hospital, Hebei Research Institute For Reproductive Health, Shijiazhuang, China

[6]Department of Clinical Laboratory, Hebei Reproductive Health Hospital, Hebei Women and Children's Health Hospital, Hebei Research Institute For Reproductive Health, Shijiazhuang, China

[7]Key Laboratory of Biomechanics and Mechanobiology (Beihang University), Ministry of Education, Beijing Advanced Innovation Center for Biomedical Engineering, School of Engineering Medicine, Beihang University, Beijing, China

[8]Department of Obstetrics and Gynecology, Hebei Reproductive Health Hospital, Hebei Women and Children's Health Hospital, Hebei Research Institute For Reproductive Health, Shijiazhuang, China

Correspondence
Chaojuan Yang, Key Laboratory of Biomechanics and Mechanobiology (Beihang University), Ministry of Education, Beijing Advanced Innovation Center for Biomedical Engineering, School of Engineering Medicine, Beihang University, Beijing 100191, China.
Email: chaojuany@buaa.edu.cn

Yingjie Zhou, Department of Obstetrics and Gynecology, Hebei Reproductive Health Hospital, Hebei Women and Children,s Health Hospital, Hebei Research Institute For Reproductive Health, No. 639 Lianmeng Road, Xinhua District, Shijiazhuang 050000, China.
Email: yingjiehero@163.com

Funding information
Hebei Medical Science Research Project, Grant/Award Number: 20242002; National Natural Science Foundation of China, Grant/Award Number: 82001145; S&T Program of Hebei, Grant/Award Number: 21377722D

Abstract

Short-chain fatty acids (SCFAs) are major metabolites produced by the gut microbiota through the fermentation of dietary fiber, and they have garnered significant attention due to their close association with host health. As important mediators between the gut microbiota and the host, SCFAs serve as energy substrates for intestinal epithelial cells and maintain homeostasis in host immune and energy metabolism by influencing host epigenetics, activating G protein-coupled receptors, and inhibiting pathogenic microbial infections. This review provides a comprehensive summary of SCFAs synthesis and metabolism and offering an overview of the latest research progress on their roles in protecting gut health, enhancing energy metabolism, mitigating diseases such as cancer, obesity, and diabetes, modulating the gut-brain axis and gut-lung axis, and promoting bone health.

KEYWORDS
gut microbiota, host, interaction relationship, short-chain fatty acids

Mingyue Liu and Yubo Lu contributed equally to this paper.

1 | INTRODUCTION

The human microbiota refers to the collection of microorganisms that reside on or within our bodies, acquired through vertical transmission and established from birth. Among the microbial communities in the human body, the gut microbiota is the most diverse. The dynamic interaction between the gut microbiota and the host is crucial for host health, as they have coevolved over time. The host provides a relatively stable growth environment for the gut microbiota, and the gut microbiota provides a wide range of functions for the host, including the digestion of complex dietary nutrients, maintenance of intestinal barrier integrity, modulation of the immune system, and improvement of host metabolism.[1] Increasing evidence suggests that an imbalance in the gut microbiota can lead to the development of various diseases. The production of harmful or beneficial metabolites by the gut microbiota associated with disease progression or alleviation is one of the important mechanisms by which it influences overall health or disease.[2] The abundance and availability of these metabolites depend on the composition of the gut microbiota, while dietary behaviors and habits are key factors in modulating the gut microbiota composition and driving microbial metabolism. The types and quantities of short-chain fatty acids (SCFAs) produced in the gut are influenced by fermentation substrates, gut microbial communities, and host physiological status. Studies have shown that feeding mice a high-fat diet induces obesity, leading to significant changes in the composition and quantity of gut microbial communities compared to those of mice fed a normal diet, as well as a decrease in the production of SCFAs in their feces. However, cohousing obese mice with mice on a normal diet resulted in an increase in SCFA production compared to that in individually housed obese mice.[3] These findings suggest a direct link between the production of SCFAs in the gut and the gut microbiota ecosystem, and indicate that the metabolic products of the gut microbiota play a crucial role as key mediators of the impact of the gut microbiota on the host based on dietary habits. SCFAs, as major metabolites, play important roles in regulating energy metabolism homeostasis and the immune system, among other functions.

2 | SYNTHESIS AND METABOLISM OF SCFAS

SCFAs are also known as volatile fatty acids and are a collective term for saturated organic fatty acids with one to six carbon atoms. The SCFAs generated through the metabolism of the gut microbiota are primarily composed of acetic acid, propionic acid, and butyric acid, with the majority existing in the form of salt ions.[4] The main bacterial groups involved in the production of SCFAs in the gut microbiota include *Ruminococcus*, *Akkermansia*, *Bifidobacterium*, *Lactobacillus*, *Succinivibrio*, *Roseburia*, *Clostridium*, and *Eubacterium*. The related metabolic pathways can be found in Table 1. Some gut bacteria can utilize lactate and acetate to synthesize butyrate, which effectively prevents the accumulation of lactate and stabilizes the gut environment. Researchers used *Escherichia coli* as a model and found through targeted gene deletions and overexpression that most bacteria in the gut contain the synthesis genes pta-ackA for SCFAs and the lactate synthesis gene ldh.

At the same time, it was discovered that some uncommon genes, including thioesterase genes (yciA, tesA, tesB, and menI), can promote the formation of acetate/butyrate. Metagenomic data

TABLE 1 Intestinal microbiota and metabolic pathways producing SCFAs.

SCFAs	Metabolic pathway	Bacterial strain	References
Acetic	Pyruvate Acetyl-CoA pathway	*Ackermann's bacteria*, *Bacteroides*, *Bifidobacterium*, *Prevotella*, *Ruminococcus*	[5,6]
	Wood Ljungdahl pathway	*Hydrophilic Bacillus*, *Clostridium*, *Streptococcus*	
	Succinate pathway	*Bacteroides*, *Succinate Flake Bacilli*, *Micrococcus*, *and Vibriococcus*	
Propionic	Succinate pathway	*Escherichia coli*, *Deinococcus defecalis*	[7,8]
	Acrylate pathway	*Salmonella*, *Roseburia inurinivorans*, *Roseburia hominis*, *Ruminococcus ovale*	
	Propylene Glycol pathway	*Veillonella*	
Butyric	Phosphate butyrylase/butyrate kinase pathway	*Coprococcus comes*, *Coprococcus eutactus*	[5,9]
	Butyl CoA Acetate CoA Transferase pathway	*Anaerobic bacteria*, *Coprococcus catus*, *Escherichia coli*, *Escherichia coli*, *Clostridium pullulatum*, *Roseburia hominis*	

analysis also indicated that butyrate can be synthesized from proteins through the lysine pathway, further illustrating that the gut microbiota can adapt to nutrient conversion to maintain the synthesis of essential metabolic products such as SCFAs.[10] The identification of these genes potentially involved in SCFA synthesis provides new insights and gene targets for the discovery of novel bacterial strains in the gut microbiota. Additionally, dietary fiber has a beneficial impact on the gut microbiota and its metabolic products. Researchers have shown that type IV resistant starch from corn selectively enriches *Eubacterium rectale* and increases butyrate production, while type IV resistant starch from cassava selectively enriches *Parabacteroides distasonis* and increases propionate levels. Subtle structural differences in dietary fiber may precisely regulate the gut microbiota, especially its metabolic activities.[11] In summary, to effectively and quantitatively increase the content of short-chain fatty acids in the body, on the one hand, microecological preparations of short-chain fatty acid-producing bacteria (Table 1) or fecal bacteria can be taken orally to increase the relative content of these strains in the body, while on the other hand, intake of dietary fiber, such as long-chain prebiotics and resistant starch, can be increased.

The concentration of SCFAs varies along the length of the intestine, with the highest concentrations found in the cecum and proximal colon, while the content decreases in the distal colon. Under physiological conditions, the concentration of SCFAs in the colon is approximately 100 mmol/L, with a ratio of acetate to propionate to butyrate of 4:1.7:1. Approximately 95% of these SCFAs are rapidly absorbed by colon cells, while the remaining 5% are excreted in the feces. Decreases in SCFA concentration may be attributed to increased SCFAs absorption through the sodium-coupled monocarboxylate transporter SLC5A8 and the proton-coupled monocarboxylate transporter SLC16A1.[12] Butyrate is the preferred energy source for colonic cells and is locally consumed. The remaining butyrate salts flow into the portal vein. Propionate is metabolized in the liver and can serve as a substrate for gluconeogenesis after absorption from the colon. It also inhibits the activity of 3-hydroxy-3-methylglutaryl-CoA reductase, reducing cholesterol synthesis and therefore is present in peripheral circulation only at low concentrations. Acetate is the most abundant SCFA in the peripheral circulation. In peripheral blood, the concentration of acetate is approximately 100–150 μmol/L, that of propionate is approximately 4–5 μmol/L, and that of butyrate is approximately 1–3 μmol/L.[13]

3 | THE MECHANISM OF ACTION OF SCFAS

3.1 | SCFAs affect the epigenetics of hosts

SCFAs are important mediators between the gut microbiota and epigenetic states.[14] Epigenetics refers to changes in gene expression levels based on nongenetic sequence alterations, such as DNA methylation and chromatin remodeling. Histone modifications during chromatin remodeling are important mechanisms for regulating DNA replication, transcription, etc.[15] Acetylation of histones can affect the affinity between histones and double-stranded DNA, thereby altering the chromatin state (loose or condensed), subsequently influencing the binding of transcription factors and other regulatory proteins to chromatin, thus regulating gene expression. Acetyl groups are added to histone tails by histone acetyltransferases (HATs) and removed by histone deacetylases (HDACs).[16] Mutations in acetyltransferases can lead to arrested expression of normal genes (tumor suppressor genes), while mutations in deacetylases or some related proteins can result in the overactivation of proto-oncogenes, leading to tumor-producing diseases.[17] Numerous studies have shown that SCFAs can inhibit HDACs to varying degrees, with butyrate being the most effective inhibitor.[18,19] By inhibiting the activity of HDACs, SCFAs play important roles in suppressing cancer cell proliferation and differentiation,[20] regulating insulin secretion,[21] and maintaining immune homeostasis.[22] In addition to HDAC inhibition, recent research has revealed a new mechanism by which SCFAs influence host epigenetics. Specifically, SCFAs can activate acetyltransferase p300, inducing highly acetylated histones.

3.2 | Activation of G protein-coupled receptors

In addition to serving as an energy source and influencing histone acetylation, SCFAs also act as key signaling molecules, playing important roles in regulating various cellular physiological processes and functions.[23] G protein-coupled receptors (GPCRs) are a large class of membrane protein receptors. When they bind to their respective ligands, they can rapidly activate intracellular signaling pathways and trigger a series of cellular responses. GPCRs that serve as ligands for SCFAs include GPR43/FFAR2, GPR41/FFAR3, GPCR109A, and PSGR.[24] These GPCRs are widely expressed in cells such as white adipocytes, enteroendocrine cells, intestinal epithelial cells, pancreatic cells, immune cells, and peripheral neurons. They interact with SCFAs and play crucial roles in regulating intestinal hormone secretion, glucagon-like peptide-1, lipid synthesis and accumulation, anti-inflammatory effects, and stimulation of the peripheral nervous system.[25] One study has shown that when diabetic mice lacking the gene encoding the G protein-coupled receptor GPR43 or GPR109A were fed different concentrations of dietary fiber, the mice fed a high-fiber diet were significantly less likely to develop diabetic kidney disease.[26] In the mice that showed less proteinuria, but not in the absence of GPR43 or GPR109A, dietary fiber prevented diabetic nephropathy by regulating the gut microbiota, enriching SCFA-producing bacteria, and increasing SCFA production, and GPR43 and GPR109A are essential for protection against SCFA-mediated diabetic nephropathy. Other studies have shown that microbial-derived short-chain fatty acids (SCFAs) promote IL-22 production by CD4+ T cells and ILCs through G protein receptor 41 (GPR41) and the inhibition of histone deacetylase (HDAC). SCFAs upregulate the production of IL-22 by promoting the expression of aromatic hydrocarbon receptor (AhR) and hypoxia-inducing factor 1α (HIF1α),

thereby protecting the intestine from inflammatory damage and maintaining intestinal homeostasis.[16]

3.3 | Inhibition of pathogenic microbial infections

SCFAs not only help maintain the immune system and combat inflammation but also have the ability to inhibit pathogenic microbial infections and promote gut health. Researchers have found that SCFAs can acylate toxin factors of pathogenic bacteria. For example, butyrate can acylate specific lysine sites in the transcription regulatory factor HilA, thereby reducing the invasion and infectivity of *Salmonella enterica*.[27] It was found that feeding animals with rye bran could increase the content of short-chain fatty acids in their intestines, and the OD value of *Salmonella* in the experimental group with the high rye bran diet was significantly lower than that in the control group.[28] The colonic acidification and cellular acidification mediated by SCFAs can disrupt the environment favorable for the growth of drug-resistant pathogens, helping to eradicate drug-resistant pathogens such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* in the gut.[29] Furthermore, SCFAs can directly inhibit the growth and colonization of pathogenic microbes by perturbing the intracellular pH homeostasis of these microbes. For example, propionic acid produced by bacteria of the genus Bacteroides can disrupt the acid–base balance within *Salmonella enterica* cells, inhibiting *Salmonella enterica* infection in the intestinal tract of experimental mice.[30] In poultry, SCFAs have been reported to have broad-spectrum activity against gram-positive and gram-negative pathogens such as *Salmonella*, *Escherichia coli* and *Clostridium* and can moderately reduce the use of antibiotics.[31,32] SCFAs can also activate peroxisome proliferator-activated receptor-gamma in colonic cells, inducing β-oxidation of SCFAs and consuming oxygen, thereby reducing the oxygen content in the intestines and inhibiting the proliferation of aerobic pathogenic bacteria.[33]

4 | SCFAS AND HOST PHYSIOLOGY

4.1 | SCFAs and intestinal health

4.1.1 | Protecting the intestinal mucosal barrier

Metabolites derived from the gut microbiota have been shown to play a crucial role in communication between microbes and their hosts, with SCFAs receiving significant attention. SCFAs maintain intestinal integrity by regulating pH and mucin secretion, providing fuel for epithelial cells and impacting mucosal immune function.[34] Butyrate is the main and preferred metabolic substrate for colonocytes, providing 60%–70% of the energy required for proliferation and differentiation,[35] and in the intestinal epithelium, SCFAs, especially butyrate, regulate stem cell proliferation, the expression of antimicrobial molecules and tight junction proteins, and the production of cytokines and chemokines, thereby promoting intestinal mucosal health and integrity.[36] The intestinal mucosal barrier consists of absorptive intestinal epithelial cells (IECs), goblet cells secreting mucus, enteroendocrine cells secreting hormones, antimicrobial peptides, and Paneth cells secreting defensins and lectins. Adding SCFAs to cultured intestinal epithelial cell lines increases local oxygen consumption, stabilizes hypoxia-inducible factor, and improves intestinal epithelial barrier function.[37] Butyrate activates inflammasomes in IECs, promoting the production of the anti-inflammatory cytokine IL-18, which is involved in the production of mucins and antimicrobial peptides and controls the composition of the gut microbiota.[38,39] It also promotes crypt IEC differentiation by inhibiting stem cell proliferation, regulating the expression of tight junction proteins, and enhancing intestinal barrier function,[40] and in addition induces the expression of TGF-β in IECs, which indirectly induces B-cell class switching to produce IgA.[41] In summary, SCFAs play a crucial role in protecting the intestinal mucosal barrier.

4.1.2 | Regulating intestinal immunity

Immunosuppression

The intestinal immune system must maintain a delicate balance between tolerance of commensal organisms and immunity against pathogens, maintaining low reactivity toward commensals in the steady state. Therefore, immunosuppressive mechanisms are essential for intestinal homeostasis.[42] SCFAs, particularly butyrate, act as HDAC inhibitors (Figure 1), suppressing the production of proinflammatory mediators (such as TNF-α, IL-6, and neutrophil chemokine-2) mediated by macrophages, neutrophils, and mast

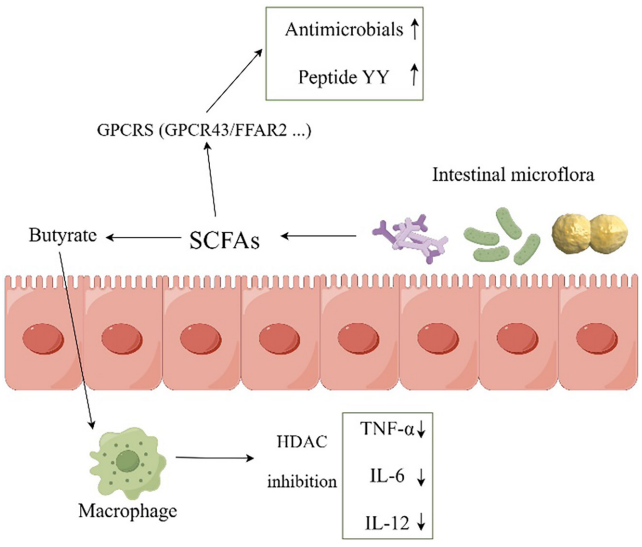

FIGURE 1 SCFAs produced by the intestinal flora inhibit HADC and activate GPCRs. Intestinal flora metabolizes dietary fiber to form short-chain fatty acids, which can activate GPCRS (GCPR43/FFAR2) and further regulate intestinal secretion of antimicrobial peptide YY. Butyric acid, one of the short-chain fatty acids is an inhibitor of HDAC, and can inhibit macrophages and reduce the production of TNF-α, IL-6, and IL-12.

cells both in vivo and in vitro, thereby reducing their phagocytic capacity and cytotoxicity.[43,44] Butyrate induces apoptosis in macrophages and neutrophils, reducing the number of proinflammatory M1 macrophages and neutrophils in the body.[45] Dendritic cells are involved in driving the inflammatory T-cell response in the intestine, and butyrate decreases the activity of costimulatory molecules on dendritic cells, reducing their activation and inhibiting the production of Th1 cell cytokines (such as TNF-α, IL-1β, and IL-8).[17] By inhibiting HDAC activity, butyrate blocks the G1 phase of the cell cycle, suppresses T-cell cycle progression, and inhibits the proliferation of CD4+ and CD8+ T cells.[46] It also inhibits the signal transducer and activator of transcription 1 (STAT1) and STAT5 signaling pathways in activated CD4+ T cells and suppresses the production of Th1 and Th17 cell cytokines. These findings suggest that SCFAs, especially butyrate, exert immunosuppressive effects on the intestinal immune system by modulating immune cells. However, further research is still needed to determine the underlying mechanisms involved.

Immune activation

If the host is in a state of fighting against pathogens, SCFAs activate the immune response and promote the secretion and expression of anti-inflammatory factors to alleviate inflammation. In vitro, SCFAs can directly increase the generation of Foxp3+ cells in mice and humans, increase the population of pTregs in the colonic lamina propria of mice, promote pTreg differentiation, and reduce the severity of experimental colitis.[47] Butyrate increases the number of anti-inflammatory M2 macrophages by inhibiting HDAC[48] and indirectly exerts anti-inflammatory effects by inducing pTregs and producing Th2 cell cytokines (such as IL-10 and IL-5).[49] Colitis is an inflammatory bowel disease induced by multiple factors, and its incidence is increasing annually. SCFAs, especially butyrate, can alleviate colitis in mice. By activating GPR41/FFA3 receptors on innate lymphoid cells (ILCs) and CD4+ T cells, butyrate promotes the expression of hypoxia-inducible factor 1α (HIF1α). HIF1α binds to the HRE region of the IL-22 promoter, and butyrate induces histone acetylation in the HRE region of the IL-22 promoter by inhibiting HDAC, thereby enhancing IL-22 expression and alleviating colitis in mice.[16] SCFAs bind to GPR43/FFA2 receptors on effector T cells, activate the STAT3 and mTOR pathways, upregulate the expression of the transcription factor Blimp-1, and promote the production of IL-10 by Th1 cells, thereby alleviating colitis in mice.[50] SCFAs also bind to GPR43/FFA2 receptors on intestinal epithelial cells, activate the mTOR and STAT3 pathways, and stimulate the expression of antimicrobial peptides such as RegIIIγ and certain defensins (Figure 1).[51] Hexokinase 2 (HK2) in intestinal epithelial cells is upregulated during colitis in mice and in patients with inflammatory bowel disease. Butyrate inhibits the expression of HDAC8, which inhibits HK2 expression, reduces mitochondrial respiration, and alleviates colitis in mice.[52] The intestine is a unique immune site where microbiota-host interactions occur. The intestinal immune system needs to tolerate self-antigens and harmless nonself antigens, such as the commensal gut microbiota, while also maintaining its ability to recognize pathogenic microorganisms and induce strong proinflammatory responses. SCFAs have various regulatory effects on intestinal immunity.

4.2 | SCFAs and cancer

Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer-related death. Chronic inflammation is a recognized risk factor for CRC. Numerous clinical studies have suggested that short-chain fatty acids (SCFAs) can regulate intestinal immune homeostasis, alleviate chronic inflammation, and have a protective effect on the occurrence and development of CRC.[53] Researchers have found through systematic reviews and meta-analyses that concentrations of acetate, propionate, and butyrate are significantly lower in individuals at high risk of CRC than in healthy individuals, and individuals with lower SCFA levels have a greater incidence of CRC. This suggests that fecal SCFAs can serve as potential noninvasive biomarkers for predicting CRC.[54] *Holdemanella biformis*, found in the human intestinal tract, can inhibit the growth of tumor cell lines or patient tumor samples in vitro by releasing SCFAs, and its abundance is decreased in fecal samples of patients with advanced adenoma.[55] In a mouse model of colorectal cancer, SCFAs (butyrate and propionate) act as HDAC inhibitors, overcoming inflammatory reactions by inhibiting the activation of nuclear factor-kappa B (NF-κB) and the production of proinflammatory mediators, thus alleviating CRC. Additionally, supplementation with butyrate-producing probiotics, such as *Faecalibacterium prausnitzii*, can inhibit the Wnt/β-catenin protein signaling pathway and inhibit tumor cell proliferation by activating GPR43/FFAR2.[56] Loss of GPR43/FFAR2 leads to increased intestinal permeability in mice with colorectal cancer, decreased expression of E-cadherin, significantly increased spontaneous colon tumors, increased bacterial burden in colon tumors, increased secretion of IL-27 by dendritic cells, and increased depletion/death of T cells. Targeting IL-27 with antibodies can inhibit colon tumor formation.[26] Furthermore, GPR43/FFAR2 is critically important for butyrate salt-induced inhibition of HDAC expression and induction of inflammation-inhibiting genes by hypermethylation, suggesting that GPR43/FFAR2 is an epigenetic tumor suppressor. SCFAs such as butyrate salt activate the GPR43/FFAR2 receptor and regulate colonic inflammation and may represent a potential strategy for treating colorectal cancer.

Butyrate salts can enhance the antitumor cytotoxicity of CD8+ T cells in mice by inducing the expression of inhibitor of differentiation 2 (ID2) and promoting the IL-12 signaling pathway, thereby enhancing the anticancer efficacy of the chemotherapeutic drug oxaliplatin.[57] SCFAs (and propionate) can significantly enhance the antitumor activity of cytotoxic T lymphocytes (CTLs)

and chimeric antigen receptor (CAR) T cells through metabolic and epigenetic reprogramming, showing potential for adoptive T-cell immunotherapy in human cancer.[58] On the other hand, the traditional 'butyrate paradox' suggests that the effects of butyrate depend on its concentration: low butyrate doses promote tumor development, while high butyrate doses inhibit tumor development. However, recent research has shown that the production of butyrate by *Bilophila wadsworthia* induces colorectal tumor formation, and inhibiting the synthesis of butyrate in the bacteria suppresses its protumorigenic effect.[59] Therefore, the impact of SCFAs on host physiological health needs to be analyzed on a case-by-case basis.

4.3 | SCFAs and obesity

SCFAs play an important role in regulating host energy metabolism through interactions with GPCRs on intestinal endocrine cells, pancreatic cells, and adipocytes. A high-fat high-fructose diet (HFFD) can reduce the weight of cecal chyme and the concentration of SCFAs in rats. There was a negative correlation between SCFA concentrations and rat abdominal circumference and the Lee index, indicating the potential role of SCFAs in the incidence of obesity and metabolic diseases.[4] Butyrate and propionate stimulate intestinal enteroendocrine L cells to promote the secretion of GLP-1 and the appetite-regulating hormone PYY. GLP-1 and PYY can exert a gut-mediated insulinotropic effect (enhancing insulin secretion), reduce food intake, and inhibit gastric emptying.[60] However, recent studies have shown that double knockout of GLP-1 and PYY receptor genes does not eliminate the effects of a high-fat diet and weight loss surgery on mice. The mechanisms underlying obesity, metabolic disease occurrence, and improvement may involve more complex pathways.[61] In addition to gastrointestinal hormones, growth hormone (GH) is a pulsatile hormone secreted from the pituitary gland that controls energy metabolism homeostasis by stimulating fat breakdown and protein preservation. In rat pituitary tumor cell lines, butyrate can promote GH secretion induced by basal hormones and GH-releasing hormone, improving lipolysis and oxidative metabolism.[62]

In addition, in vitro experiments have shown that butyrate can activate lysine-specific demethylase 1 (LSD1) through the transporter MCT1 and the decomposing enzyme ACSM3. Normal expression of LSD1 can restore the impaired thermogenic cycle in antibiotic-treated mice, promoting energy storage in white adipose tissue and energy burning in brown and beige adipose tissue, thus reducing diet-induced obesity.[63] SCFAs can stimulate various organs and tissues in the body to produce large amounts of hormones and neural signals, which inhibit short-term appetite and energy intake. Acetate can directly regulate appetite in the central nervous system.[64] Propionate and butyrate can also serve as intestinal gluconeogenic substrates, exerting beneficial metabolic effects.[65]

4.4 | SCFAs and diabetes

A decrease in the intestinal SCFA concentration is associated with various chronic autoimmune and inflammatory diseases. SCFAs have beneficial anti-inflammatory effects and contribute to maintaining a stable intestinal environment, which may be an important mechanism for alleviating type 1 diabetes (T1D).[66] In newly diagnosed pediatric patients with T1D, there is a reduction in SCFAs produced by the gut microbiota, accompanied by changes in the microbiota-mediated IgA immune response. In nonobese diabetic (NOD) model mice, acetate and butyrate levels in blood and feces are negatively correlated with key indicators of T1D. Long-term acetate treatment can reduce the binding of bacteria to IgA, inhibit the formation of germinal center B cells, and alleviate pancreatic inflammation in NOD mice. Additionally, acetate significantly reduces the frequency of self-reactive T cells in lymphoid tissues through its effects on B cells, while butyrate exerts protective effects by increasing the quantity and function of Treg cells. Even in situations where immune tolerance is disrupted, feeding NOD mice a high-fiber diet rich in SCFAs can still alleviate T1D-related symptoms.[67] Human studies have shown that dietary supplementation with SCFA-based supplements (acetate- and butyrate-modified high-amylose maize-resistant starch) increases SCFA levels in feces and plasma, effectively controls blood glucose levels, and leads to the detection of predominant metabolic producers, such as long bifidobacteria and adolescent bifidobacteria, in the gut microbiota. Furthermore, there is an increase in blood B and T cells, a significant decrease in proinflammatory marker levels, and an improvement in immune status.[66] Although SCFAs inhibit T1D in NOD mice, further research is needed to determine whether SCFAs play a role in other animal models and in human diabetes and whether their effects on the immune system are indirect results of inhibiting autoimmune reactions or the primary mechanism of T1D protection.

Unlike T1D, poor dietary habits and obesity are key factors in the development of type 2 diabetes (T2D). A prospective cohort study involving 8750 adult participants revealed that a southern dietary pattern characterized by the consumption of high-fat, fried foods, eggs, organ meats, processed meats, and sugary beverages showed the strongest positive correlation with T2D.[68] On the other hand, a randomized clinical study using a diet rich in dietary fiber and fecal shotgun metagenomics analysis revealed that dietary fiber promoted SCFA production, leading to greater improvement in participants' hemoglobin A1c levels, partially due to increased production of GLP-1. The targeted restoration of these SCFA producers through ecological interventions may provide a new approach for managing T2D.[69] Individuals with an obesity-prone (OP) phenotype exhibit distinct gut microbiota compositions with significantly reduced levels of SCFAs but increased levels of propionate. Propionate specifically induces high methylation at the cg26345888 site, inhibiting the expression of the target gene DAB1. DAB1 is closely associated with clinical vitamin D deficiency, which further impacts the occurrence and progression of diabetes.[70] Therefore, the gut microbiota

and SCFAs may serve as targets for the clinical treatment and prevention of diabetes.

4.5 | SCFAs and the gut-brain axis

The gut-brain axis refers to the bidirectional signaling mechanism between the gastrointestinal tract and the central nervous system. Through a complex neural-humoral pathway, signals originating from the gastrointestinal tract can regulate brain function, and signals from the brain can alter the sensation, motility, and secretion of the intestines.[71] Due to the neuroactivity of SCFAs and their impact on other gut-brain signaling pathways, including the immune and endocrine systems, SCFAs may directly or indirectly participate in the microbiota-gut-brain axis.[72]

The interaction between the central nervous system and cytokines affects neural processes, thereby influencing the function of neural circuits involved in regulating emotions, among others.[73] Microglia are tissue macrophages in the central nervous system and are key innate immune cells in the brain. Their characteristics and functions are influenced by the gut microbiota. Dysregulation of microglia has been reported in a range of psychiatric disorders, including major depression, schizophrenia, autism, and obsessive-compulsive disorder.[74] SCFAs may regulate the differentiation and maturation of immune cells (neutrophils, dendritic cells, macrophages, monocytes, and T cells), affect systemic inflammatory responses, influence the structure and functional integrity of microglia, and activate microglial cell activities related to neuroinflammation through HDAC inhibition and activation of G protein-coupled receptors.[75] In germ-free mice, metabolic genes of immature microglia exhibit epigenetic imprints resulting from the enrichment of acetylation and methylation marks (H3K4me3 and H3K9ac). This leads to phenotypic and functional defects such as changes in metabolic pathways, increased mitochondrial quantity and quality, and impaired respiratory chain complex II function. Acetate can be taken up by microglia, and supplementation with acetate can reverse defects in gene expression, cell morphology, metabolic features, mitochondria, and other aspects in germ-free mice.[76]

SCFAs can also exert their effects on the gut-brain axis by regulating the secretion of intestinal hormones. SCFAs activate G protein-coupled receptors and stimulate enteroendocrine L cells to release glucagon-like peptide 1 (GLP-1) and peptide YY (PYY), and this process may, in turn, activate a signaling cascade that affects brain circuits through systemic circulation or the vagus nerve pathway.[77] In mice, GLP-1 is involved in improving learning and memory,[78] promoting neuroprotection and neuroplasticity in the hippocampus,[79] and reducing beta-amyloid plaques and microglial activation in an Alzheimer's disease animal model. Knockout of the PYY gene exacerbates depressive and anxiety-related behaviors in mice,[80] while in another study, it exacerbated depressive-related behaviors rather than anxiety.[81] Enhanced Y2 receptor knockout enhances the ability of mice to cope with stress, while increased receptor stimulation increases depressive and anxiety-related behaviors.[82] Other metabolic hormones that affect brain function and are influenced by SCFAs include insulin, leptin, and ghrelin (growth hormone-releasing peptide). Insulin can act on the central nervous system to regulate behavior and systemic metabolism. In different mouse models of Alzheimer's disease, a high-fat diet can promote the deposition of amyloid proteins and amyloid pathology in the mouse brain by causing insulin resistance,[83] while improving brain insulin resistance may provide a new approach for the prevention and treatment of metabolic and cognitive diseases.[84] Disruption of leptin signaling is associated with Alzheimer's disease, depression, bipolar disorder, and schizophrenia.[85] Ghrelin is a major appetite-stimulating hormone that acts as a neuropeptide in the central nervous system. Ghrelin regulates stress, depression, and anxiety and enhances learning and memory abilities through the hypothalamic–pituitary–adrenal (HPA) axis, the serotonin system, and the sympathetic nervous system.[86] However, further research is needed to elucidate the interaction between SCFAs and leptin and ghrelin.

In conclusion, the effects of SCFAs are not limited to the intestines. They may directly or indirectly influence brain function through immune and endocrine pathways. However, more research is needed to uncover the underlying principles and precise mechanisms of microbiota-gut-brain axis signaling in both healthy and diseased states.

4.6 | SCFAs and the gut-lung axis

With the discovery of the role of the gut microbiota and its metabolites in initiating immune responses against allergic and infectious reactions in the airways, the concept of the gut-lung axis has received great attention. SCFAs have been found to be key signaling molecules that play important roles in inflammation and protective immune responses in the gut and lungs. SCFAs have a protective effect on individuals with airway inflammation by upregulating the fatty acid β-oxidation pathway in colonic epithelial cells and promoting the accumulation of thymus-derived peripheral Treg cells associated with allergic airway diseases.[87] High levels of SCFAs, particularly acetate and butyrate in feces, stimulate dendritic cell differentiation and proliferation, allowing the lungs to have high phagocytic capacity and inhibiting the effector function of Th2 cells, which is associated with reduced atopic sensitization and decreased risk of asthma later in life.[88]

SCFAs from the gut microbiota reach the lungs through the circulation and affect bone marrow hematopoietic precursors, thereby reducing lung inflammation. Therefore, SCFAs may influence the host immune response to viral infections.[89] Acetate supplementation can regulate the type I interferon response in lung epithelial cells by activating the GPR43/FFAR2 receptor, enhancing the defense of the lung against secondary pneumococcal infection, and effectively preventing recurrent infections caused by influenza virus and RSV. Butyrate can inhibit viral infection by regulating the expression of SARS-CoV-2-related genes and enhancing antiviral immunity in rats, and a lack of butyrate negatively impacts antiviral immune

function.[90] Researchers have also found that SCFAs can induce the secretion of IgA and neutralizing antibodies (NAbs) that prevent SARS-CoV-2 infection by enhancing the intracellular synthesis of ATP, acetyl-CoA, and plasmablast-derived lipids. They also regulate immune responses.[91] SCFAs are absorbed in the intestinal mucosa and tend to adhere to immune cell receptors in the respiratory tract, thereby enhancing antiviral responses in the lungs through the modulation of mucosal immunity. These studies contribute to a deeper understanding of the role of the gut-lung axis in antiviral infections and the development of novel antiviral therapeutic approaches.

4.7 | SCFAs and bone health

SCFAs impact local and systemic immune function, and their role as important mediators links the gut microbiota to bone health.[92] Skeletal muscle, the largest organ in the human body, contains a significant number of SCFA receptors (such as GPR41 and GPR43). SCFAs participate in glucose, lipid, and protein metabolism in skeletal muscle, affecting muscle mass and function and playing a crucial role in endurance exercise performance.[93] SCFAs are important regulators of osteoclast metabolism and bone mass. Treatment with SCFAs or a high-fiber diet significantly increases bone mass in mice and effectively prevents bone loss in postmenopausal or inflammation-induced models. Propionate and butyrate induce metabolic reprogramming in osteoclasts, enhancing glycolysis at the cost of oxidative phosphorylation, which downregulates key osteoclast genes (TRAF6 and NFATc1), inhibiting osteoclast differentiation and bone resorption.[94] A decrease in fecal butyrate levels has been observed in patients with rheumatoid arthritis and in mouse models of arthritis. Supplementation with butyrate can promote the production of the microbial metabolite indole-3-acetic acid, which activates the aryl hydrocarbon receptor on regulatory B cells (Bregs) capable of secreting IL-10. This enhances the immunosuppressive function of Bregs and alleviates arthritis in mice.[95]

5 | PROSPECTS

The growing understanding of host-microbiota interactions emphasizes the crucial role of microbiota-derived metabolites, such as short-chain fatty acids (SCFAs), in maintaining metabolic and

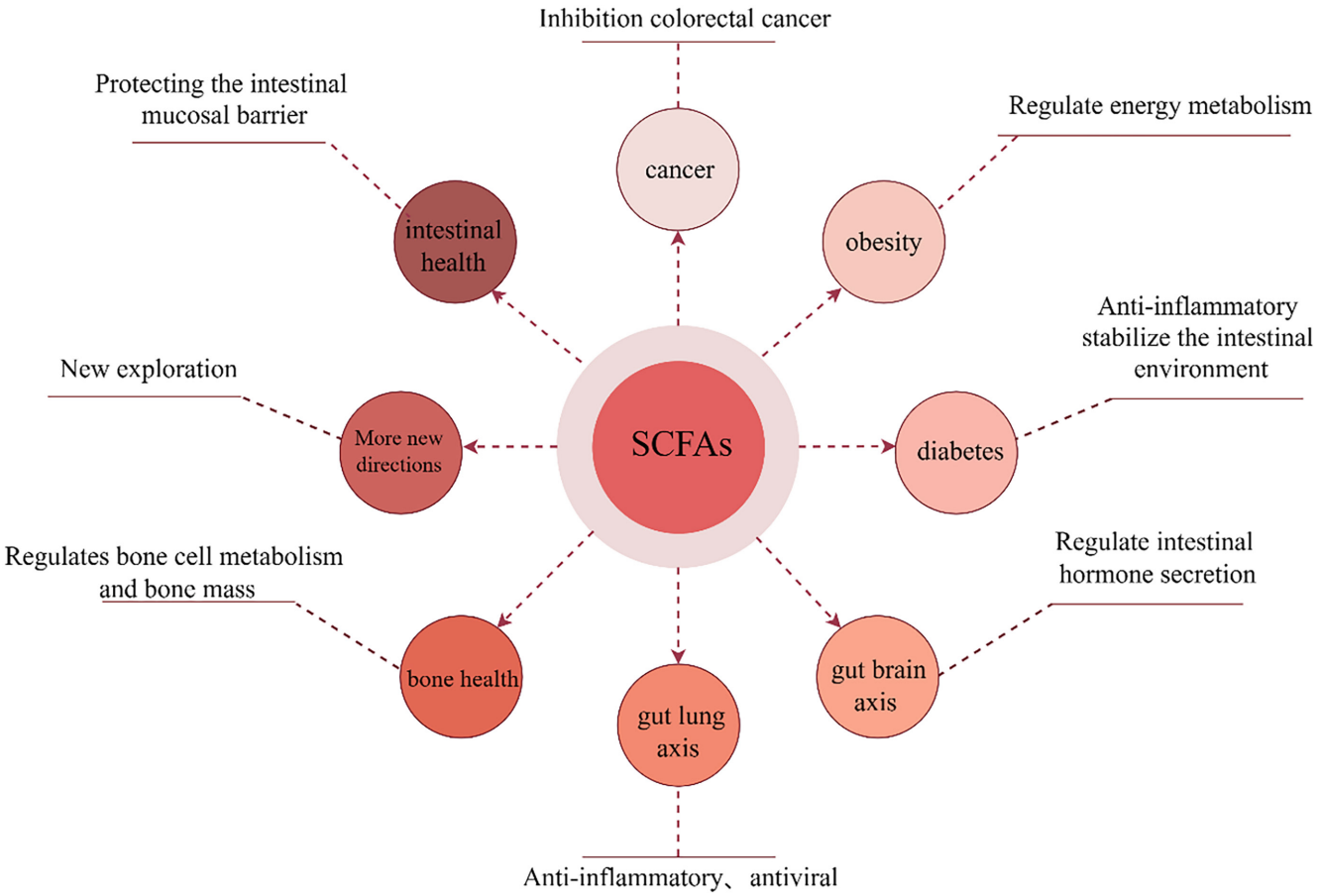

FIGURE 2 Mechanisms by which SCFAs are associated with different hosts conditions. SCFAs protect the intestinal mucosa barrier to promote intestinal health; SCFAs can inhibition colorectal cancer; SCFAs regulate energy metabolism to inhibit obesity; SCFAs can alleviate diabetes by being anti-inflammatory and stabilizing the intestinal environment; SCFAs regulate intestinal hormone secretion and stabilize the gut-brain axis; SCFAs regulate the gut-brain axis by anti-inflammatory and antiviral action; SCFAs regulate bone cell metabolism and bone mass to protect bone health thus offering promising avenues for future research.

immune homeostasis in the body (Figure 2). SCFAs exert their effects by influencing host epigenetics, activating G protein-coupled receptors, and inhibiting pathogenic microbial infections, playing important roles in mitigating diseases such as colitis, cancer, obesity, and diabetes. SCFAs are involved in immune regulation and systemic circulation, influencing brain, lung, and bone health. However, most of the research findings are based on mouse models and single cell lines, and more studies based on human principles are needed in the future.

The concentration of SCFAs largely depends on the intake of dietary fiber in our diet and the ability of the gut microbiota to ferment these fibers. Therefore, increasing the endogenous production of SCFAs through dietary interventions and cultivating a healthy gut microbiota would be effective approaches for improving overall health. When therapeutically supplementing SCFAs, personalized intervention plans may be necessary based on the characteristics of the target population. Furthermore, increasing evidence suggests that SCFA concentrations in the body are in a dynamic balance, and both excessively high and low SCFA concentrations may have adverse effects on human health. It has been reported in mouse studies that the contents of butyrate in the intestines of mice fed a high-fiber diet significantly increase.[96] Compared with those of mice fed a low-fiber diet, the results showed increased colonization of pathogenic bacteria, decreased body weight and increased mortality. Excessive acetic acid activates the parasympathetic nervous system to increase hunger hormones, while increasing insulin secretion stimulated by glucose, triggering obesity.[97] Real-time monitoring and maintenance of the dynamic balance of SCFA biosynthesis is highly important for understanding the physiological functions of SCFAs.

In the field of biomedicine, bioavailability of short-chain fatty acids can be increased via advances in nanodelivery, analog development, and phytochemicals, and the effective application of synthetic biology, metatenomics, metabolic engineering, enzyme evolution, and machine learning methods will make it possible to construct intelligent biological systems for optimizing SCFAs concentration to protect human health.

AUTHOR CONTRIBUTIONS

Yingjie Zhou and Chaojuan Yang designed and supervised the manuscript. Mingyue Liu and Yubo Lu wrote the manuscript. Guoyu Xue and Le Han revised the manuscript. Hanbing Jia, Zi Wang, Jia Zhang, Peng Liu contributed to manuscript writing. All authors have read and approved the final manuscript.

ACKNOWLEDGEMENTS

Not applicable.

FUNDING INFORMATION

This work was supported by the Hebei Medical Science Research Project (20242002), S&T Program of Hebei (21377722D) and the National Natural Science Foundation of China (82001145).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICS STATEMENT

Not applicable.

ORCID

Chaojuan Yang https://orcid.org/0009-0004-3039-7560

REFERENCES

1. Yan Q, Zhai W, Yang C, et al. The relationship among physical activity, intestinal Flora, and cardiovascular disease. *Cardiovasc Ther*. 2021;2021:3364418. doi:10.1155/2021/3364418
2. Pant A, Maiti TK, Mahajan D, Das B. Human gut microbiota and drug metabolism. *Microb Ecol*. 2023;86(1):97-111. doi:10.1007/s00248-022-02081-x
3. Schwiertz A, Taras D, Schafer K, et al. Microbiota and SCFA in lean and overweight healthy subjects. *Obesity (Silver Spring)*. 2010;18(1):190-195. doi:10.1038/oby.2009.167
4. Sulistyowati E, Handayani D, Soeharto S, Rudijanto A. A high-fat and high-fructose diet lowers the cecal digesta's weight and short-chain fatty acid level of a Sprague-Dawley rat model. *Turk J Med Sci*. 2022;52(1):268-275. doi:10.3906/sag-1911-14
5. Louis P, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. *Nat Rev Microbiol*. 2014;12(10):661-672. doi:10.1038/nrmicro3344
6. Rey FE, Faith JJ, Bain J, et al. Dissecting the in vivo metabolic potential of two human gut acetogens. *J Biol Chem*. 2010;285(29):22082-22090. doi:10.1074/jbc.M110.117713
7. Louis P, Flint HJ. Formation of propionate and butyrate by the human colonic microbiota. *Environ Microbiol*. 2017;19(1):29-41. doi:10.1111/1462-2920.13589
8. Scheiman J, Luber JM, Chavkin TA, et al. Meta-omics analysis of elite athletes identifies a performance-enhancing microbe that functions via lactate metabolism. *Nat Med*. 2019;25(7):1104-1109. doi:10.1038/s41591-019-0485-4
9. Duncan SH, Barcenilla A, Stewart CS, Pryde SE, Flint HJ. Acetate utilization and butyryl coenzyme A (CoA):acetate-CoA transferase in butyrate-producing bacteria from the human large intestine. *Appl Environ Microbiol*. 2002;68(10):5186-5190. doi:10.1128/AEM.68.10.5186-5190.2002
10. Vital M, Howe AC, Tiedje JM. Revealing the bacterial butyrate synthesis pathways by analyzing (meta)genomic data. *MBio*. 2014;5(2):e00889. doi:10.1128/mBio.00889-14
11. Deehan EC, Yang C, Perez-Munoz ME, et al. Precision microbiome modulation with discrete dietary fiber structures directs short-chain fatty acid production. *Cell Host Microbe*. 2020;27(3):389-404.e6. doi:10.1016/j.chom.2020.01.006
12. Slizewska K, Wlodarczyk M, Sobczak M, et al. Comparison of the activity of fecal enzymes and concentration of SCFA in healthy and overweight children. *Nutrients*. 2023;15(4):987. doi:10.3390/nu15040987
13. Hu J, Kyrou I, Tan BK, et al. Short-chain fatty acid acetate stimulates adipogenesis and mitochondrial biogenesis via GPR43 in Brown adipocytes. *Endocrinology*. 2016;157(5):1881-1894. doi:10.1210/en.2015-1944
14. Dupraz L, Magniez A, Rolhion N, et al. Gut microbiota-derived short-chain fatty acids regulate IL-17 production by mouse and human intestinal gammadelta T cells. *Cell Rep*. 2021;36(1):109332. doi:10.1016/j.celrep.2021.109332
15. Zhang Y, Sun Z, Jia J, et al. Overview of histone modification. *Adv Exp Med Biol*. 2021;1283:1-16. doi:10.1007/978-981-15-8104-5_1

16. Yang W, Yu T, Huang X, et al. Intestinal microbiota-derived short-chain fatty acids regulation of immune cell IL-22 production and gut immunity. *Nat Commun*. 2020;11(1):4457. doi:10.1038/s41467-020-18262-6
17. Sanchez HN, Moroney JB, Gan H, et al. B cell-intrinsic epigenetic modulation of antibody responses by dietary fiber-derived short-chain fatty acids. *Nat Commun*. 2020;11(1):60. doi:10.1038/s41467-019-13603-6
18. Hou H, Chen D, Zhang K, et al. Gut microbiota-derived short-chain fatty acids and colorectal cancer: ready for clinical translation? *Cancer Lett*. 2022;526:225-235. doi:10.1016/j.canlet.2021.11.027
19. Thomas SP, Denu JM. Short-chain fatty acids activate acetyltransferase p300. *elife*. 2021;10:e72171. doi:10.7554/eLife.72171
20. Gonzalez-Bosch C, Zunszain PA, Mann GE. Control of redox homeostasis by short-chain fatty acids: implications for the prevention and treatment of breast cancer. *Pathogens*. 2023;12(3):486. doi:10.3390/pathogens12030486
21. Chriett S, Dabek A, Wojtala M, Vidal H, Balcerczyk A, Pirola L. Prominent action of butyrate over beta-hydroxybutyrate as histone deacetylase inhibitor, transcriptional modulator and anti-inflammatory molecule. *Sci Rep*. 2019;9(1):742. doi:10.1038/s41598-018-36941-9
22. Wang J, Zhu N, Su X, Gao Y, Yang R. Gut-microbiota-derived metabolites maintain gut and systemic immune homeostasis. *Cells*. 2023;12(5):793. doi:10.3390/cells12050793
23. Liu P, Wang Y, Yang G, et al. The role of short-chain fatty acids in intestinal barrier function, inflammation, oxidative stress, and colonic carcinogenesis. *Pharmacol Res*. 2021;165:105420. doi:10.1016/j.phrs.2021.105420
24. Kimura I, Ichimura A, Ohue-Kitano R, Igarashi M. Free fatty acid receptors in health and disease. *Physiol Rev*. 2020;100(1):171-210. doi:10.1152/physrev.00041.2018
25. Milligan G, Barki N, Tobin AB. Chemogenetic approaches to explore the functions of free fatty acid receptor 2. *Trends Pharmacol Sci*. 2021;42(3):191-202. doi:10.1016/j.tips.2020.12.003
26. Lavoie S, Chun E, Bae S, et al. Expression of free fatty acid receptor 2 by dendritic cells prevents their expression of interleukin 27 and is required for maintenance of mucosal barrier and immune response against colorectal tumors in mice. *Gastroenterology*. 2020;158(5):1359-1372.e9. doi:10.1053/j.gastro.2019.12.027
27. Zhang ZJ, Pedicord VA, Peng T, Hang HC. Site-specific acylation of a bacterial virulence regulator attenuates infection. *Nat Chem Biol*. 2020;16(1):95-103. doi:10.1038/s41589-019-0392-5
28. Homann C, Eckey I, Chuppava B, et al. Rye and Rye bran as components of diets in piglet production-effects on salmonella prevalence. *Animals (Basel)*. 2023;13(14):2262. doi:10.3390/ani13142262
29. Sorbara MT, Dubin K, Littmann ER, et al. Inhibiting antibiotic-resistant Enterobacteriaceae by microbiota-mediated intracellular acidification. *J Exp Med*. 2019;216(1):84-98. doi:10.1084/jem.20181639
30. Dunkley KD, Callaway TR, Chalova VI, et al. Foodborne Salmonella ecology in the avian gastrointestinal tract. *Anaerobe*. 2009;15(1–2):26-35. doi:10.1016/j.anaerobe.2008.05.007
31. Szabo RT, Kovacs-Weber M, Zimboran A, Kovacs L, Erdelyi M. Effects of short- and medium-chain fatty acids on production, meat quality, and microbial attributes-a review. *Molecules*. 2023;28(13):4956. doi:10.3390/molecules28134956
32. Xue W, Yuan X, Ji Z, Li H, Yao Y. Nutritional ingredients and prevention of chronic diseases by fermented koumiss: a comprehensive review. *Front Nutr*. 2023;10:1270920. doi:10.3389/fnut.2023.1270920
33. Byndloss MX, Olsan EE, Rivera-Chavez F, et al. Microbiota-activated PPAR-gamma signaling inhibits dysbiotic Enterobacteriaceae expansion. *Science*. 2017;357(6351):570-575. doi:10.1126/science.aam9949
34. Martin-Gallausiaux C, Marinelli L, Blottiere HM, Larraufie P, Lapaque N. SCFA: mechanisms and functional importance in the gut. *Proc Nutr Soc*. 2021;80(1):37-49. doi:10.1017/S0029665120006916
35. Salvi PS, Cowles RA. Butyrate and the intestinal epithelium: modulation of proliferation and inflammation in homeostasis and disease. *Cells*. 2021;10(7):1775. doi:10.3390/cells10071775
36. Yu M, Han Y, Li J, Wang L. Magnetic N-doped carbon aerogel from sodium carboxymethyl cellulose/collagen composite aerogel for dye adsorption and electrochemical supercapacitor. *Int J Biol Macromol*. 2018;115:185-193. doi:10.1016/j.ijbiomac.2018.04.012
37. Zhao J, Hu J, Ma X. Sodium caprylate improves intestinal mucosal barrier function and antioxidant capacity by altering gut microbial metabolism. *Food Funct*. 2021;12(20):9750-9762. doi:10.1039/d1fo01975a
38. Tian P, Yang W, Guo X, et al. Early life gut microbiota sustains liver-resident natural killer cells maturation via the butyrate-IL-18 axis. *Nat Commun*. 2023;14(1):1710. doi:10.1038/s41467-023-37419-7
39. Beisner J, Filipe Rosa L, Kaden-Volynets V, Stolzer I, Gunther C, Bischoff SC. Prebiotic inulin and sodium butyrate attenuate obesity-induced intestinal barrier dysfunction by induction of antimicrobial peptides. *Front Immunol*. 2021;12:678360. doi:10.3389/fimmu.2021.678360
40. Korsten S, Vromans H, Garssen J, Willemsen LEM. Butyrate protects barrier integrity and suppresses immune activation in a Caco-2/PBMC Co-culture model while HDAC inhibition mimics butyrate in restoring cytokine-induced barrier disruption. *Nutrients*. 2023;15(12):2760. doi:10.3390/nu15122760
41. Huang J, Pearson JA, Peng J, et al. Gut microbial metabolites alter IgA immunity in type 1 diabetes. *JCI. Insight*. 2020;5(10):e135718. doi:10.1172/jci.insight.135718
42. Goncalves P, Araujo JR, Di Santo JP. A cross-talk between microbiota-derived short-chain fatty acids and the host mucosal immune system regulates intestinal homeostasis and inflammatory bowel disease. *Inflamm Bowel Dis*. 2018;24(3):558-572. doi:10.1093/ibd/izx029
43. Chang PV, Hao L, Offermanns S, Medzhitov R. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. *Proc Natl Acad Sci USA*. 2014;111(6):2247-2252. doi:10.1073/pnas.1322269111
44. Zhang H, Du M, Yang Q, Zhu MJ. Butyrate suppresses murine mast cell proliferation and cytokine production through inhibiting histone deacetylase. *J Nutr Biochem*. 2016;27:299-306. doi:10.1016/j.jnutbio.2015.09.020
45. Liang L, Liu L, Zhou W, et al. Gut microbiota-derived butyrate regulates gut mucus barrier repair by activating the macrophage/WNT/ERK signaling pathway. *Clin Sci (Lond)*. 2022;136(4):291-307. doi:10.1042/CS20210778
46. Schiweck C, Edwin Thanarajah S, Aichholzer M, et al. Regulation of CD4(+) and CD8(+) T cell biology by short-chain fatty acids and its relevance for autoimmune pathology. *Int J Mol Sci*. 2022;23(15):8272. doi:10.3390/ijms23158272
47. Yang J, Pei G, Sun X, et al. RhoB affects colitis through modulating cell signaling and intestinal microbiome. *Microbiome*. 2022;10(1):149. doi:10.1186/s40168-022-01347-3
48. Ji J, Shu D, Zheng M, et al. Microbial metabolite butyrate facilitates M2 macrophage polarization and function. *Sci Rep*. 2016;6:24838. doi:10.1038/srep24838
49. Wiechers C, Zou M, Galvez E, et al. The microbiota is dispensable for the early stages of peripheral regulatory T cell induction within mesenteric lymph nodes. *Cell Mol Immunol*. 2021;18(5):1211-1221. doi:10.1038/s41423-021-00647-2
50. Sun M, Wu W, Chen L, et al. Microbiota-derived short-chain fatty acids promote Th1 cell IL-10 production to maintain intestinal homeostasis. *Nat Commun*. 2018;9(1):3555. doi:10.1038/s41467-018-05901-2

51. Zhao Y, Chen F, Wu W, et al. GPR43 mediates microbiota metabolite SCFA regulation of antimicrobial peptide expression in intestinal epithelial cells via activation of mTOR and STAT3. *Mucosal Immunol*. 2018;11(3):752-762. doi:10.1038/mi.2017.118
52. Hinrichsen F, Hamm J, Westermann M, et al. Microbial regulation of hexokinase 2 links mitochondrial metabolism and cell death in colitis. *Cell Metab*. 2021;33(12):2355-2366.e8. doi:10.1016/j.cmet.2021.11.004
53. Moniri NH, Farah Q. Short-chain free-fatty acid G protein-coupled receptors in colon cancer. *Biochem Pharmacol*. 2021;186:114483. doi:10.1016/j.bcp.2021.114483
54. Alvandi E, Wong WKM, Joglekar MV, Spring KJ, Hardikar AA. Short-chain fatty acid concentrations in the incidence and risk-stratification of colorectal cancer: a systematic review and meta-analysis. *BMC Med*. 2022;20(1):323. doi:10.1186/s12916-022-02529-4
55. Zagato E, Pozzi C, Bertocchi A, et al. Endogenous murine microbiota member Faecalibaculum rodentium and its human homologue protect from intestinal tumour growth. *Nat Microbiol*. 2020;5(3):511-524. doi:10.1038/s41564-019-0649-5
56. Chen D, Jin D, Huang S, et al. Clostridium butyricum, a butyrate-producing probiotic, inhibits intestinal tumor development through modulating Wnt signaling and gut microbiota. *Cancer Lett*. 2020;469:456-467. doi:10.1016/j.canlet.2019.11.019
57. Zhang SL, Mao YQ, Zhang ZY, et al. Pectin supplement significantly enhanced the anti-PD-1 efficacy in tumor-bearing mice humanized with gut microbiota from patients with colorectal cancer. *Theranostics*. 2021;11(9):4155-4170. doi:10.7150/thno.54476
58. Luu M, Riester Z, Baldrich A, et al. Microbial short-chain fatty acids modulate CD8(+) T cell responses and improve adoptive immunotherapy for cancer. *Nat Commun*. 2021;12(1):4077. doi:10.1038/s41467-021-24331-1
59. Okumura S, Konishi Y, Narukawa M, et al. Gut bacteria identified in colorectal cancer patients promote tumourigenesis via butyrate secretion. *Nat Commun*. 2021;12(1):5674. doi:10.1038/s41467-021-25965-x
60. Fluitman KS, Wijdeveld M, Nieuwdorp M, IJzerman RG. Potential of butyrate to influence food intake in mice and men. *Gut*. 2018;67(7):1203-1204. doi:10.1136/gutjnl-2017-315543
61. Boland BB, Mumphrey MB, Hao Z, et al. Combined loss of GLP-1R and Y2R does not alter progression of high-fat diet-induced obesity or response to RYGB surgery in mice. *Mol Metab*. 2019;25:64-72. doi:10.1016/j.molmet.2019.05.004
62. Kubrak O, Koyama T, Ahrentlov N, et al. The gut hormone Allatostatin C/somatostatin regulates food intake and metabolic homeostasis under nutrient stress. *Nat Commun*. 2022;13(1):692. doi:10.1038/s41467-022-28268-x
63. Wang D, Liu CD, Li HF, et al. LSD1 mediates microbial metabolite butyrate-induced thermogenesis in brown and white adipose tissue. *Metabolism*. 2020;102:154011. doi:10.1016/j.metabol.2019.154011
64. Chambers ES, Morrison DJ, Frost G. Control of appetite and energy intake by SCFA: what are the potential underlying mechanisms? *Proc Nutr Soc*. 2015;74(3):328-336. doi:10.1017/S0029665114001657
65. De Vadder F, Plessier F, Gautier-Stein A, Mithieux G. Vasoactive intestinal peptide is a local mediator in a gut-brain neural axis activating intestinal gluconeogenesis. *Neurogastroenterol Motil*. 2015;27(3):443-448. doi:10.1111/nmo.12508
66. Bell KJ, Saad S, Tillett BJ, et al. Metabolite-based dietary supplementation in human type 1 diabetes is associated with microbiota and immune modulation. *Microbiome*. 2022;10(1):9. doi:10.1186/s40168-021-01193-9
67. Marino E, Richards JL, McLeod KH, et al. Gut microbial metabolites limit the frequency of autoimmune T cells and protect against type 1 diabetes. *Nat Immunol*. 2017;18(5):552-562. doi:10.1038/ni.3713
68. Tison SE, Shikany JM, Long DL, et al. Differences in the Association of Select Dietary Measures with Risk of incident type 2 diabetes. *Diabetes Care*. 2022;45(11):2602-2610. doi:10.2337/dc22-0217
69. Lancaster SM, Lee-McMullen B, Abbott CW, et al. Global, distinctive, and personal changes in molecular and microbial profiles by specific fibers in humans. *Cell Host Microbe*. 2022;30(6):848-862.e7. doi:10.1016/j.chom.2022.03.036
70. Guo W, Zhang Z, Li L, et al. Gut microbiota induces DNA methylation via SCFAs predisposing obesity-prone individuals to diabetes. *Pharmacol Res*. 2022;182:106355. doi:10.1016/j.phrs.2022.106355
71. Ju S, Shin Y, Han S, et al. The gut-brain Axis in schizophrenia: the implications of the gut microbiome and SCFA production. *Nutrients*. 2023;15(20):4391. doi:10.3390/nu15204391
72. Stilling RM, van de Wouw M, Clarke G, Stanton C, Dinan TG, Cryan JF. The neuropharmacology of butyrate: the bread and butter of the microbiota-gut-brain axis? *Neurochem Int*. 2016;99:110-132. doi:10.1016/j.neuint.2016.06.011
73. Margolis KG, Cryan JF, Mayer EA. The microbiota-gut-brain Axis: from motility to mood. *Gastroenterology*. 2021;160(5):1486-1501. doi:10.1053/j.gastro.2020.10.066
74. Lukens JR, Eyo UB. Microglia and neurodevelopmental disorders. *Annu Rev Neurosci*. 2022;45:425-445. doi:10.1146/annurev-neuro-110920-023056
75. Colosimo DA, Kohn JA, Luo PM, et al. Mapping interactions of microbial metabolites with human G-protein-coupled receptors. *Cell Host Microbe*. 2019;26(2):273-282.e7. doi:10.1016/j.chom.2019.07.002
76. Erny D, Dokalis N, Mezo C, et al. Microbiota-derived acetate enables the metabolic fitness of the brain innate immune system during health and disease. *Cell Metab*. 2021;33(11):2260-2276.e7. doi:10.1016/j.cmet.2021.10.010
77. Wessels AG. Influence of the gut microbiome on feed intake of farm animals. *Microorganisms*. 2022;10(7):1305. doi:10.3390/microorganisms10071305
78. Isacson R, Nielsen E, Dannaeus K, et al. The glucagon-like peptide 1 receptor agonist exendin-4 improves reference memory performance and decreases immobility in the forced swim test. *Eur J Pharmacol*. 2011;650(1):249-255. doi:10.1016/j.ejphar.2010.10.008
79. Verma MK, Goel R, Krishnadas N, Nemmani KVS. Targeting glucose-dependent insulinotropic polypeptide receptor for neurodegenerative disorders. *Expert Opin Ther Targets*. 2018;22(7):615-628. doi:10.1080/14728222.2018.1487952
80. Painsipp E, Herzog H, Holzer P. The gut-mood axis: a novel role of the gut hormone peptide YY on emotional-affective behaviour in mice. *BMC Pharmacol*. 2009;9(S2):A13. doi:10.1186/1471-2210-9-S2-A13
81. Painsipp E, Herzog H, Sperk G, Holzer P. Sex-dependent control of murine emotional-affective behaviour in health and colitis by peptide YY and neuropeptide Y. *Br J Pharmacol*. 2011;163(6):1302-1314. doi:10.1111/j.1476-5381.2011.01326.x
82. Kornhuber J, Zoicas I. Neuropeptide Y reduces social fear in male mice: involvement of Y1 and Y2 receptors in the dorsolateral septum and central amygdala. *Int J Mol Sci*. 2021;22(18):10142. doi:10.3390/ijms221810142
83. Wakabayashi T, Yamaguchi K, Matsui K, et al. Differential effects of diet- and genetically-induced brain insulin resistance on amyloid pathology in a mouse model of Alzheimer's disease. *Mol Neurodegener*. 2019;14(1):15. doi:10.1186/s13024-019-0315-7
84. Kullmann S, Kleinridders A, Small DM, et al. Central nervous pathways of insulin action in the control of metabolism and food intake. *Lancet Diabetes Endocrinol*. 2020;8(6):524-534. doi:10.1016/S2213-8587(20)30113-3

85. Kaneko K, Fu Y, Lin HY, et al. Gut-derived GIP activates central Rap1 to impair neural leptin sensitivity during overnutrition. *J Clin Invest*. 2019;129(9):3786-3791. doi:10.1172/JCI126107
86. Bali A, Jaggi AS. An integrative review on role and mechanisms of ghrelin in stress, anxiety and depression. *Curr Drug Targets*. 2016;17(5):495-507. doi:10.2174/1389450116666150518095650
87. Wu T, Li H, Su C, et al. Microbiota-derived short-chain fatty acids promote LAMTOR2-mediated immune responses in macrophages. *mSystems*. 2020;5(6):e00587-20. doi:10.1128/mSystems.00587-20
88. McLoughlin R, Berthon BS, Rogers GB, et al. Soluble fibre supplementation with and without a probiotic in adults with asthma: a 7-day randomised, double blind, three way cross-over trial. *EBioMedicine*. 2019;46:473-485. doi:10.1016/j.ebiom.2019.07.048
89. Brown JA, Sanidad KZ, Lucotti S, et al. Gut microbiota-derived metabolites confer protection against SARS-CoV-2 infection. *Gut Microbes*. 2022;14(1):2105609. doi:10.1080/19490976.2022.2105609
90. Li J, Richards EM, Handberg EM, Pepine CJ, Raizada MK. Butyrate regulates COVID-19-relevant genes in gut epithelial organoids from normotensive rats. *Hypertension*. 2021;77(2):e13-e16. doi:10.1161/HYPERTENSIONAHA.120.16647
91. Baradaran Ghavami S, Pourhamzeh M, Farmani M, et al. Cross-talk between immune system and microbiota in COVID-19. *Expert Rev Gastroenterol Hepatol*. 2021;15(11):1281-1294. doi:10.1080/17474124.2021.1991311
92. He J, Chu Y, Li J, et al. Intestinal butyrate-metabolizing species contribute to autoantibody production and bone erosion in rheumatoid arthritis. *Sci Adv*. 2022;8(6):eabm1511. doi:10.1126/sciadv.abm1511
93. Frampton J, Murphy KG, Frost G, Chambers ES. Short-chain fatty acids as potential regulators of skeletal muscle metabolism and function. *Nat Metab*. 2020;2(9):840-848. doi:10.1038/s42255-020-0188-7
94. Lucas S, Omata Y, Hofmann J, et al. Short-chain fatty acids regulate systemic bone mass and protect from pathological bone loss. *Nat Commun*. 2018;9(1):55. doi:10.1038/s41467-017-02490-4
95. Rosser EC, Piper CJM, Matei DE, et al. Microbiota-derived metabolites suppress arthritis by amplifying aryl-hydrocarbon receptor activation in regulatory B cells. *Cell Metab*. 2020;31(4):837-851.e10. doi:10.1016/j.cmet.2020.03.003
96. Serino M. SCFAs - the thin microbial metabolic line between good and bad. *Nat Rev Endocrinol*. 2019;15(6):318-319. doi:10.1038/s41574-019-0205-7
97. Perry RJ, Peng L, Barry NA, et al. Acetate mediates a microbiome-brain-beta-cell axis to promote metabolic syndrome. *Nature*. 2016;534(7606):213-217. doi:10.1038/nature18309

How to cite this article: Liu M, Lu Y, Xue G, et al. Role of short-chain fatty acids in host physiology. *Anim Models Exp Med*. 2024;7:641-652. doi:10.1002/ame2.12464