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Review Article

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Gut Microbial Metabolites on Host Immune Responses in Health and Disease

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ABSTRACT

Intestinal microorganisms interact with various immune cells and are involved in gut homeostasis and immune regulation. Although many studies have discussed the roles of the microorganisms themselves, interest in the effector function of their metabolites is increasing. The metabolic processes of these molecules provide important clues to the existence and function of gut microbes. The interrelationship between metabolites and T lymphocytes in particular plays a significant role in adaptive immune functions. Our current review focuses on 3 groups of metabolites: short-chain fatty acids, bile acids metabolites, and polyamines. We collated the findings of several studies on the transformation and production of these metabolites by gut microbes and explained their immunological roles. Specifically, we summarized the reports on changes in mucosal immune homeostasis represented by the Tregs and Th17 cells balance. The relationship between specific metabolites and diseases was also analyzed through latest studies. Thus, this review highlights microbial metabolites as the hidden treasure having potential diagnostic markers and therapeutic targets through a comprehensive understanding of the gut-immune interaction.

Keywords: Microbiota; Short-chain fatty acid; Bile acids; Polyamines; Immunomodulation

INTRODUCTION

Many microorganisms inhabit the intestine, and their critical role in maintaining immune homeostasis is well established. Microbial dysbiosis and associated alterations in microbiome-derived metabolites are often associated with dysregulated immune responses (1). Microbial metabolites are mainly synthesized or transformed by a complex network of interactions between dietary components and the host microbiota. The nutritional components consumed largely shape the intestinal niche and regulate the immune response via various microbial metabolites. Hence, improving current understanding regarding the synthesis of metabolites and their effects on the adaptive immune compartment, especially

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Conflict of Interest
The authors declare no potential conflicts of interest.

Abbreviations
BA, bile acid; CA, cholic acid; CDCA, chenodeoxycholic acid; CNS, central nervous system; DC, dendritic cell; DCA, deoxycholic acid; DSS, dextran sodium sulfate; EAE, experimental autoimmune encephalomyelitis; EAP, experimental autoimmune prostatitis; EAU, experimental autoimmune uveitis; FXR, farnesoid X receptor; TGR5, Takeda G-protein receptor 5; GPBAR1, G protein-coupled bile acid receptor 1; GPR, G-protein coupled receptor; mitoROS, mitochondrial reactive oxygen species; HCC, hepatocellular carcinoma; HDAC, histone deactylase; HIF, hypoxia-inducible factor; HSDH, hydroxysteroid dehydrogenases; IBD, inflammatory bowel disease; ILC, innate lymphoid cell; LCA, lithocholic acid; LN, lymph node; MCA, muricholic acid; NAFLD, non-alcoholic fatty liver disease; ODC, ornithine decarboxylase; PSC, primary sclerosing cholangitis; PXR, pregnane X receptor; RA, rheumatoid arthritis; RORγt, RAR-related orphan receptor gamma; SCFA, short-chain fatty acid; SLE, systemic lupus erythematosus; TLCA, tauro-lithocholic acid; T-βMCA, tauro-β-muricholic acid; UDCA, ursodeoxycholic acid; VDR, vitamin D receptor.

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on the function and differentiation of T cells (known to be widely distributed in the intestinal tract), can be highly beneficial for developing better therapeutics. In this review, we specifically discussed 3 categories of metabolites: 1) those produced by the gut microbiota from dietary components, 2) those produced by the host and modified by the gut bacteria, and 3) those synthesized *de novo* by the gut bacteria. We analyzed the latest research trends by selecting short-chain fatty acids (SCFAs), bile acids (BAs), and polyamines as representative metabolites of each group. We reviewed the representative metabolites and described the role of the microbiota in their synthesis. We then discussed the roles of these molecules in immune regulation, focusing on the function of the Tregs/Th17 cells. Finally, we summarized our perspective along with known facts regarding how these metabolites promote diseases by triggering changes such as that in the Tregs/Th17 balance. A comprehensive understanding of the gut bacteria-immune connection through bacterial derivatives is critical for finding novel drug targets and therapeutics against immunological disorders.

GUT MICROBIOTA-DERIVED METABOLITES

SCFAs

SCFAs are fatty acids with fewer than 6 carbon atoms. They are mainly produced through bacterial fermentation of dietary fibers in the colon and primarily constitute acetate, propionate, and butyrate. The conversion of dietary fibers to SCFAs involves several reactions mediated by various microbial enzymes (**Fig. 1**). Hence, the abundance of SCFAs is highly influenced by the host diet and gut microbiota composition (2). A growing body of evidence shows that SCFAs play an important role in health and onset of disease (3). Although production and absorption of SCFAs mainly proceed in gut, their systemic circulation makes it not only important to maintain intestinal homeostasis but also regulate various physiological processes of the host. These include energy expenditure, adipocyte metabolism, and especially immunological homeostasis (4-6). SCFAs regulate various immunological diseases, such as allergies, colitis, type 1 diabetes, cirrhosis, pathological bone loss, and even preeclampsia, by enhancing Tregs function, regulating the Tregs/Th17 balance, and inducing the migration of Tregs into pathological sites (7-11).

Role of the microbiota in SCFA metabolism

Anaerobic bacteria in colon mediate starch to SCFA conversion through specific enzymes, making them resistant to digestion and absorption in the small intestine (12). Acetate, a major SCFA, is produced by most enteric bacteria (including *Akkermansia muciniphila*, *Bacteroides* spp., *Bifidobacterium* spp., *Prevotella* spp., *Ruminococcus* spp., *Blautia hydrogenotrophica*, *Clostridium* spp., and *Streptococcus* spp.) from pyruvate using acetyl-CoA. The process takes place via the Wood-Ljungdahl pathway, which involves reduction of CO_2 to formate or CO (13). Propionate is synthesized through 3 different pathways: the succinate, acrylate, and propanediol pathways, which require distinct microbes. The succinate pathway is activated by *Bacteroides* spp., *Phascolarctobacterium succinatutens*, *Dialister* spp., *Veillonella* spp., *Megasphaera elsdenii*, and *Coprococcus catus*. The propanediol pathway involves *Salmonella* spp., *Roseburia inulinivorans*, and *Ruminococcus obeum* (14). The synthesis of butyrate involves the fusion of 2 molecules of acetyl-CoA, followed by reduction to butyryl-CoA, which is finally converted to butyrate via 2 different pathways mediated by different types of gut microbiota: 1) the phosphotransacetylase/butyrate kinase route utilized by *Coprococcus comes* and *Coprococcus eutactus*, and 2) the butyryl-CoA:acetate CoA-transferase route utilized by *Anaerostipes* spp., *C. catus*, *Eubacterium rectale*, *Eubacterium hallii*, *Faecalibacterium prausnitzii*, and *Roseburia* spp. (2).

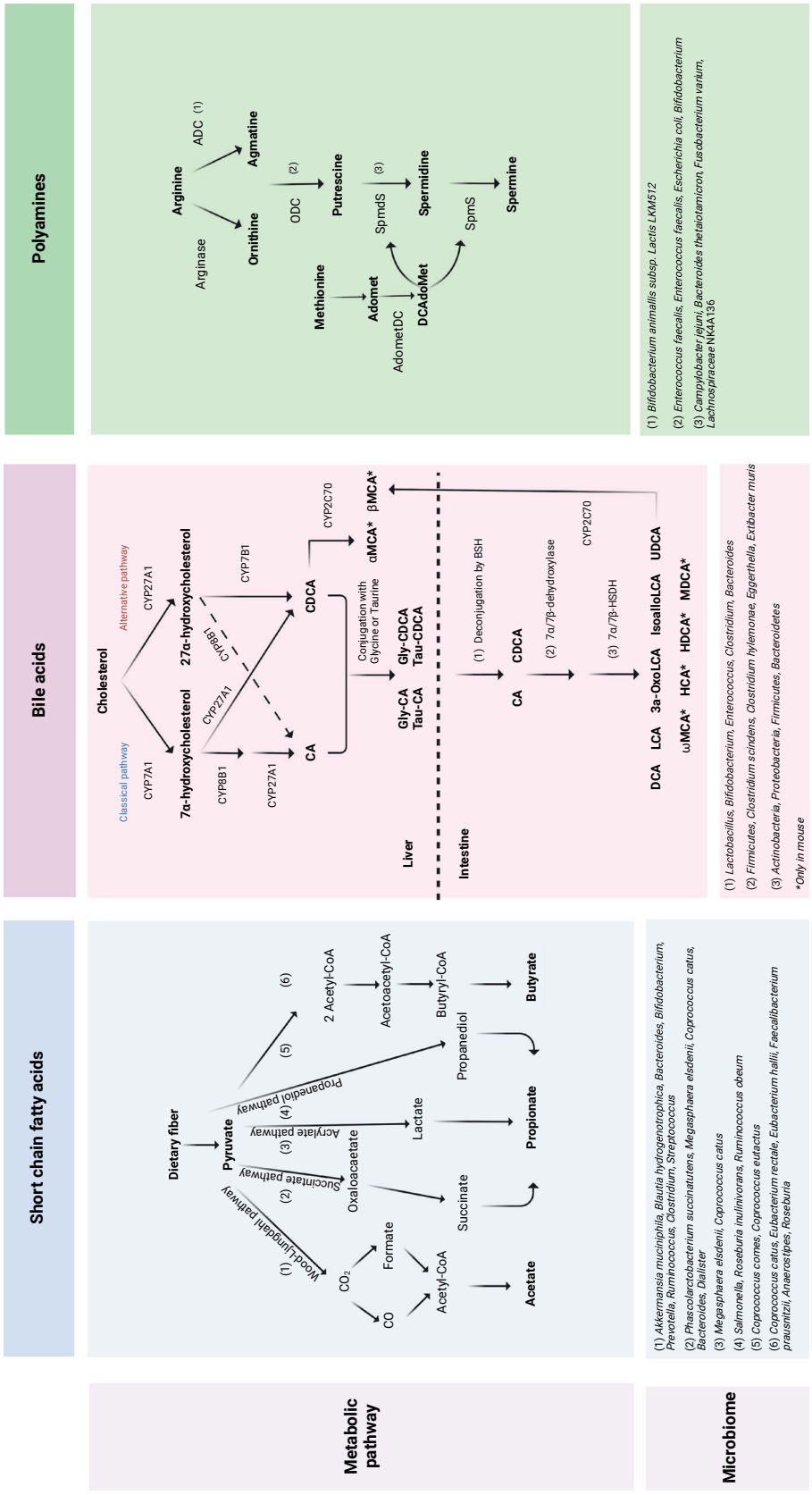

Figure 1. The biosynthetic pathways of SCFAs, BAs and polyamines along with the microorganisms involved are presented. Acetate, propionate and butyrate, the 3 main components of SCFAs, are produced by microbial fermentation of dietary fiber. Acetate is produced from pyruvate through Wood-Ljungdahl pathway which mediates reduction from CO_2 to CO and subsequently converts acetyl-CoA and acetate. Propionate is synthesized through 3 different pathways: pyruvate is converted to succinate and lactate which finally forms propionate; propionate is generated via the propanediol pathway without passing through pyruvate; lactate from rumen microbial fermentation is converted to propionate through the acrylate pathway. Butyrate is synthesized by the formation of 2 molecules of acetyl-CoA, acetoacetyl-CoA, which is further converted to butyryl-CoA. In BA metabolism, cholesterol is converted to primary BAs, CA and CDCA, and conjugated with glycine or taurine in liver. After being secreted to the intestine, primary BAs are deconjugated through BSH produced by bacteria, such as *Lactobacillus* and *Bifidobacterium*. In the subsequent step, 7α/7β-dehydroxylation occurs and the product is oxidized and epimerized by 7α/7β-HSDH. In the polyamine biosynthetic pathway, Putrescine is generated by the decarboxylation of ornithine catalyzed by the enzyme ODC. The synthesis of spermidine and spermine is mediated by the enzyme AdoMetDC, and the transferase enzymes SpmdS and SpmS.
CYP7A1, cholesterol 7 alpha-hydroxylase; CYP27A1, sterol 27-hydroxylase; CYP8B1, sterol 12-alpha-hydroxylase; CYP7B1, 25-hydroxycholesterol 7-alpha-hydroxylase; BSH, bile salt hydrolase; ADC, arginine decarboxylase; AdoMet, S-adenosyl-methionine; DCAdoMet, decarboxylation product of S-adenosyl-methionine; AdoMetDC, adenosyl-methionine decarboxylase; SpmdS, Spermidine synthase.

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BA metabolites

BA, a component of bile, produced by hepatocytes through the oxidation of cholesterol in the liver, acts as a detergent and supports the digestion of lipid components from food in the intestine (15). In humans, BAs are categorized into 2 groups: primary and secondary (**Fig. 1**). Primary BAs consist of cholic acid (CA) and chenodeoxycholic acid (CDCA). In the classical pathway, 7α-hydroxylase (CYP7A1) is involved in production of primary BA, while in the alternative pathway, 27-hydroxylase (CYP27A1) takes part in producing primary BA from cholesterol (16). Mice produce α-muricholic acid (MCA) and β-MCA—primary BAs exclusive to them— from CDCA and ursodeoxycholic acid (UDCA) using the CYP2C70 (17). Primary BAs are conjugated with the amino acid glycine or taurine in the liver by amino acid N-acetyltransferase, and the liver secretes approximately 200–600 mg BAs per day in humans (18). The secreted BAs are stored in the gallbladder and passed through the duodenum after meals. Approximately 95% of the secreted BAs are reabsorbed in the terminal ileum and re-enter the liver via the enterohepatic circulation. About 15% of the conjugated BAs not reabsorbed in the terminal ileum enter the colon, where they are subjected to microbiota-mediated deconjugation and biotransformation into secondary BAs (19). This "gateway reaction" is carried out by bile salt hydrolase produced by the gut bacteria (20). Deconjugated CAs and CDCAs are further transformed into secondary BAs, such as deoxycholic acid (DCA) and lithocholic acid (LCA), respectively, by 7α-dehydroxylase. These BAs are involved in various physiological and pathological reactions, such as metabolism, inflammation, and immunity.

Role of the microbiota in BA metabolism

Microbiota plays a pivotal role in the conversion of primary BAs to secondary BAs in intestine. These secondary BAs recirculate to liver and regulate the synthesis of primary BAs by inhibiting transcription of enzymes like CYP7A1, CYP8B1 (21,22). Although deconjugated BAs, mainly DCA, are considered toxic to some susceptible microbiota (as they can disrupt the bacterial membrane), certain microbes are resistant to BA toxicity and are involved in their metabolism (20). As mentioned, bile salt hydrolase, which deconjugates primary BAs, is produced by bacteria, including *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, *Clostridium* spp., and *Bacteroides* spp. (20). The subsequent BA metabolism is also mediated mainly by the gut microbiota. For instance, the oxidation and epimerization of hydroxyl groups (C3, C7, and C12) along with 7α/7β-dehydroxylation by the gut microbiota are major steps in BA metabolism. 7α- and 7β-hydroxysteroid dehydrogenases (7α/β-HSDHs) are the key enzymes involved in BA epimerization, which decreases the toxicity of CDCA. *Clostridium absonum* has both 7α- and 7β-HSDHs and converts CDCA to UDCA (23). Dehydroxylation of primary BA by 7α/7β-dehydroxylase is an essential step in the production of secondary BA. In *Clostridium scindens*, the BA-inducible operon contains 8 genes involved in 7α-dehydroxylase synthesis (24). 3α-dehydrogenation mediated by 3α-HSDH is an important step in the 7α-hydroxylation pathway. *Clostridium perfringens*, *Peptostreptococcus productus*, and *Eggerthella lenta* are typical bacteria producing 3α-HSDH (25). Furthermore, the *Actinobacteria* and *Firmicutes* phyla enable LCA to 3-oxoLCA conversion via the action of 3α-HSDH (26). 3-oxoLCA can be further converted to isoalloLCA by the *Bacteroidetes* spp. (27). Multiple microorganisms act synergistically to generate BA metabolites, and bio-transformed BAs influence the gut bacterial pool. For example, Aguirre et al. (28) demonstrated that 7α-dehydroxylated secondary BAs inhibit *Clostridium difficile* and showed possibility of biomarkers for *C. difficile*-resistant bowel environment. This complex relationship between the microbiota and BAs shapes the homeostatic balance in gut microenvironment (29).

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Polyamines

Polyamines are cationic aliphatic amines that are multifunctional and ubiquitous, present in eukaryotic as well as prokaryotic organisms. Owing to their ionic characteristics, they interact with nucleic acids, ATP, acidic phospholipids, and specific types of proteins (30). Putrescine, spermidine, and spermine are the 3 major polyamines produced by mammalian cells. Polyamines play a crucial role in many fundamental biological functions, such as gene regulation, stress resistance, cell growth, survival, proliferation, and differentiation in health and disease (31-33). Intracellular polyamine levels are tightly regulated by various biosynthetic and salvage mechanisms (30). Putrescine can be synthesized from ornithine via ornithine decarboxylase (ODC) or alternatively from arginine via arginine decarboxylase to produce the intermediate agmatine, which is then converted to putrescine. Putrescine is converted into higher polyamines, such as spermidine and spermine, which are organic compounds composed of repeating amino groups, through a process called aminopropylation. The addition of aminopropyl groups to putrescine is catalyzed by spermidine synthase and spermine synthase in the presence of the aminopropyl donor decarboxylated S-adenosylmethionine (30,34).

Role of the microbiota in polyamine metabolism

Gut microbiota is the primary contributor of polyamine production in the intestine (35). This is a complicated process involving amino acid precursors as well as other intermediates, processed via various biosynthetic and degradation mechanisms along with specific transport systems (36). Sugiyama et al. (37) reported the role of dominant human-gut bacteria in producing polyamine from novel polyamine biosynthetic proteins and transporters. Another study has identified arginine decarboxylation as the dominant pathway for polyamine biosynthesis among common human gut microbiota species (38). *Enterococcus faecalis*, a prominent gut microorganism, metabolizes agmatine to putrescine via the agmatine deaminase pathway and has developed pH resistance to colonize the intestinal niche (39). Numerous bacteria can synthesize spermidine despite lacking orthologs of the polyamine biosynthetic enzymes, i.e., S-adenosyl-methionine decarboxylase and spermidine synthase. One example is *Campylobacter jejuni*, a human gut microbe that synthesizes spermidine via an alternative carboxyspermidine pathway (40). An isotope-labeling study suggested that multiple bacterial species produce putrescine through various cellular intermediates and enzymatic pathways (41). A novel hybrid system that monitors putrescine production demonstrated synergism between *Bifidobacterium* spp., *E. faecalis,* and *Escherichia coli*, both *in vitro* and *in vivo* (42). The synergistic supplementation of arginine with *Bifidobacterium animalis* subsp. *lactis* LKM512 in mice increased polyamine putrescine levels. Moreover, it enhanced the expression of polyamine biosynthetic genes, such as those encoding arginine decarboxylase, agmatinase, agmatine deiminase, and N-carbamoyl-putrescine amidase (43). Another study also reported that the administration of LKM512 in Crj:CD-1 mice increased longevity by augmenting intestinal polyamine levels (44). Further, *B. animalis* subsp. *lactis* and arginine significantly increased polyamine concentration in the feces and serum (45). Metagenomic analysis of ovariectomized mice by Chevalier et al. (46) suggested that exposure to warmth increased the abundance of polyamine-producing genera, *A. muciniphila*, *Bacteroides*, and *Alitsipes*, and reduced the expansion of polyamine-degrading genera, *Muribaculaceae* and *Lachnospirae*. This is correlated with higher polyamine levels in the feces and cecum. A recent study involving the transplantation of *Parabacteroides distasonis* to mice reversed triptolide-induced testicular dysfunction by increasing spermine and putrescine levels in the testis and cecum through the upregulation of HSP70s (47). Dietary supplementation with guar gum enhances the proliferation of *Bifidobacteria*, and its associated synthesis of putrescine and

spermidine in the cecum (48). Similarly, pectin-fed gnotobiotic rats produce putrescine and spermidine, mediated by *Bacteroides thetaiotaomicron* and *Fusobacterium varium* (49). In addition, research has shown that changes in polyamine levels, such as increased spermidine, can also impact the composition and function of the gut microbiome in obese mice. Spermidine exerts a microbiota-dependent anti-obesity effect through expanding *Lachnospiraceae* NK4A136, resulting in improved gut barrier function (50).

Effect of metabolites on immune regulation

SCFAs are involved in the regulation of various immune cells (**Fig. 2**). At mucosal sites, microbe-associated molecular patterns are sensed and recognized by pattern recognition receptors such as TLRs on innate immune cells. SCFAs promote the production of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, by activating NF-κB as part of the TLR response in epithelial cells (51). In addition, a recent study showed that butyrate enhances the antimicrobial function of macrophages by inhibiting histone deacetylase 3 (HDAC3) activity, which modulates the metabolic states of macrophages and increases innate lymphoid cell 3 (ILC3)-mediated host defense as well as antimicrobial peptide production (52). In adaptive immunity, although SCFAs were initially recognized as immune-suppressive molecules that promote Tregs generation (53-55), the immunomodulatory properties of SCFAs are not only skewed toward tolerance but also toward boosting immunity against various types of microbes. This includes extracellular as well as intracellular bacteria, viruses, parasites and fungal infection (56-58). SCFAs have an impact on the development and function of both $CD4^+$ and $CD8^+$ T lymphocytes, however the processes differ significantly. *In vitro* treatment of CTLs and chimeric antigen receptor T cells with butyrate elevated the production of effector molecules, such as CD25, IFN-γ, and TNF-α together. Moreover, it significantly enhanced their anti-tumor activity in syngeneic murine melanoma and pancreatic cancer models by increasing mTOR and inhibiting class I HDAC activities (59). Furthermore, SCFAs upregulate IL-22 production in ILCs via G-protein coupled receptor 41 (GPR41) and inhibit HDACs, which mediate the upregulation of aryl hydrocarbon receptor and hypoxia-inducible factor-1α (HIF-1α). Finally, SCFA-mediated upregulation of HIF-1α and changes in the *IL22* promoter locus enhance IL-22 production through ILCs and $CD4^+$ T cells (60). Butyrate and propionate are sufficient to dampen antibody production by modulating essential steps in the intrinsic function of B cells. These include class-switch recombination, somatic hypermutation, and plasma cell differentiation by inhibiting HDAC3, indicating the potential immunomodulatory role of SCFAs in B cell function. However, further studies are necessary to elucidate their mode of action (61).

BAs modulate the host immune system via multiple mechanisms (**Fig. 2**). Firstly, their toxicity directly affects cellular and microbial viability (62), depending on their concentration, hydrophobicity, and conjugation status (63,64). Notably, taurine-conjugated BA is more hydrophilic and less toxic than glycine-conjugated BA (65). Secondly, nuclear and transmembrane BA receptors are the principal mediators of immune regulation by BAs (66). Although the nuclear farnesoid X receptor (FXR) was initially considered as an orphan receptor, a line of studies has shown it to be specific for BAs, including CDCA, CA, LCA, and DCA, for the modulation of many biological functions (67-69). FXR is also distributed across diverse tissues, such as the liver, intestine, and adrenal glands, and is known to be highly expressed in innate immune cells to regulate inflammation in murine colitis (70). Pregnane X receptor (PXR) is another orphan nuclear BA receptor for catatoxic compounds (71). PXR is activated by secondary BAs, such as LCA and DCA, to act as a cellular LCA sensor for the homeostatic concentration of toxic BAs at the transcriptional

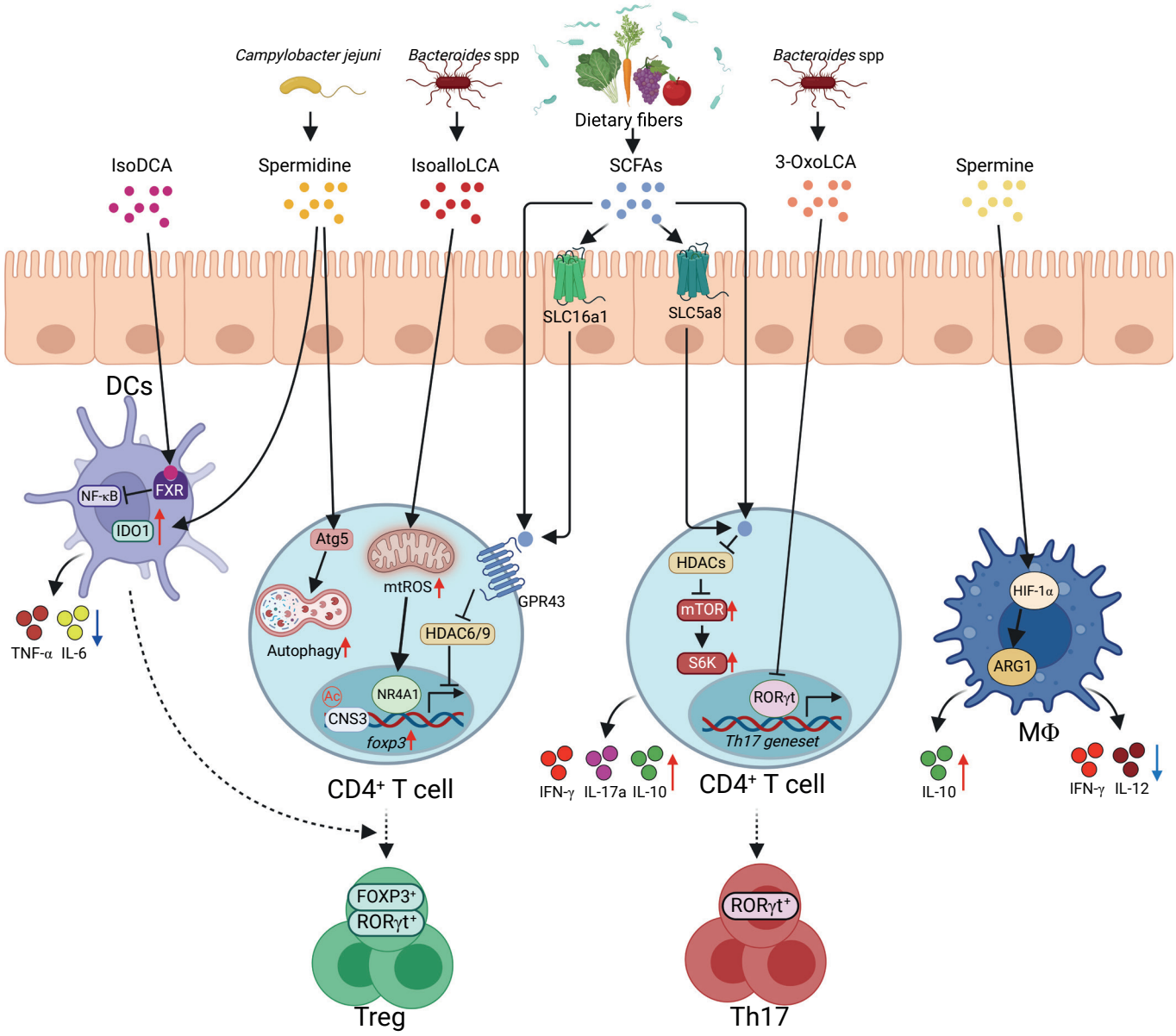

Figure 2. Metabolite-mediated expansion of Treg and Th17 cells in the intestinal niche is depicted. SCFAs, converted from dietary fiber, pass from gut epithelium to laminal propria through passive diffusion and via transporters (SLC16a1, SLC5a8). Naïve T cells capture SCFAs through GPR43, which mediates inhibition of HDAC6/9 and the subsequent acetylation of the foxp3 promoter region, finally differentiating into Tregs. SCFAs also induce Th17 cell differentiation in inflammatory conditions such as *Citrobacter rodentium* infection. SCFAs directly inhibit HDAC3 without passing through GPR41 and GPR43, which subsequently increases mTOR activity and finally induces RORγt expression. IsoalloLCA promotes production of mitoROS and induces the acetylation of CNS3 region of FOXP3 promoter, resulting in the upregulation of FOXP3 transcription. IsoDCA acts on FXR on DC to repress pro-inflammatory activity and upregulate anti-inflammatory transcription factors like SOCS1 and IkBα which increases Tregs differentiation. The 3-oxoLCA directly interacts with RORγt to interfere in its transcriptional activity, resulting in the inhibition of Th17 cell differentiation. The polyamine spermidine directs the autophagy-mediated differentiation of Treg cells, thereby establishing a regulatory environment in the gut. Spermidine induces IDO1-dependent immunosuppressive phenotype in DCs and thus can promote the expansion of Treg cells. Spermine exhibits an anti-inflammatory effect by means of macrophage-mediated IL-10 production and suppression of IL-12 and IFN-γ production.
SLC16a1, monocarboxylate transporter 1; SLC5a8, sodium-coupled monocarboxylate transporter 1; RORγt, RAR-related orphan receptor gamma; SOCS1, suppressor of cytokine signaling 1; CNS3, conserved non-coding sequence 3; Atg5, autophagy protein 5; IDO1, indoleamine 2,3-dioxygenase 1.

level (72). G protein-coupled bile acid receptor 1 (GPBAR1), also known as Takeda G-protein receptor 5 (TGR5), is a representative surface BA receptor expressed in intestine, liver, gallbladder, and adipose tissue (73), involved in immune regulation (74), BA homeostasis (75), energy expenditure, and glucose metabolism (76). Sphingosine-1-phosphate receptor

2, a transmembrane receptor for conjugated BA, is a well-known BA receptor involved in various biological functions (77). BAs directly modulate immune response via these receptors (70). Conventionally, FXR is mainly expressed in the liver as well as intestine and is known to regulate the metabolism of BAs, glucose, and lipids. Recently, FXR has been shown to be expressed in various cell types and implicated in the progress of several inflammatory diseases including inflammatory bowel disease (IBD) (78,79). Gadaleta et al. (80) reported that the FXR agonist, INT-747, alleviates symptoms of dextran sodium sulfate (DSS)-induced colitis (weight loss, rectal bleeding, and change in colon length) and protects against DSS-induced intestinal barrier permeability in mouse. Moreover, treatment with INT-747 significantly reduced the production of IFN-γ, IL-17, and TNF-α by human PBMCs and lamina propria mononuclear cells, stimulated by LPS and antibodies (anti-CD2, anti-CD28) respectively, from patients with IBD. In rodent hepatitis model, Mencarelli et al. (81) demonstrated that FXR acts directly on NKT cells in the liver and reduces production of osteopontin, an immunoregulatory cytokine, resulting in the attenuation of liver injury by hepatitis. GPBAR1 responds to various BAs, irrespective of the conjugation status, but mainly binds to deconjugated secondary BA. GPBAR1 is expressed in most tissues, including the intestine, liver, and biliary tract. Analogous to other BA receptors, GPBAR1 is also observed in various immune cells, such as monocytes, macrophages, DCs, and NK cells (70,81). Tauro-lithocholic acid (TLCA), a GPBAR1 agonist, promotes macrophage activation to encourage biliary epithelial cell proliferation following a liver injury (82). Additionally, macrophages can be reprogrammed from pro-inflammatory to anti-inflammatory phenotypes by TLCA (83). GPBAR1 also functions as a gatekeeper for liver NKT cell activation to suppress the differentiation of NKT cell into a type I NKT cell in murine immune-mediated hepatitis (84). Furthermore, GPBAR1 is critical for maintaining the integrity of intestinal barriers together with the suppression of M1-like macrophage and enhancement of M2-like macrophage in murine colitis (85,86). DCA is known to attenuate NF-κB-related pro-inflammatory cytokines in dendritic cells (DCs) to mitigate murine autoimmune uveitis (87). In the hepatic system, BAs inhibit LPS-induced cytokine expression in Kupffer cells via GPBAR1-cAMP dependent pathways, indicating their protective role in murine cholestatic liver disease (88). Recent studies have elucidated the pivotal roles of BAs in the development and function of T cells. BAs, specifically CDCA, DCA, and α-MCA, inhibit T-cell activation by perturbing the intracellular calcium concentration, eventually leading to deactivation of the NFAT signaling pathway in murine hepatitis B virus infection (89). Similarly, LCA inhibits Th1 cell activation via vitamin D receptor (VDR) signaling (90). Oral supplementation of BAs ameliorated IL-23-mediated psoriasiform dermatitis by inhibiting IL-17A production by T cells and decreasing CCL20 dependent chemo-trafficking of T cells in skin lesions (91). As BAs are directly secreted into the intestinal lumen, they show profound effects on the mucosal immune system. Recent studies have observed that BA metabolites produced by specific microbiota are involved in mucosal immunity via modulation of the Tregs/Th17 balance (26,92-94).

Polyamines play a critical role in bacterial pathogenicity and biofilm formation (95). *Batrachochytrium dendrobatidis*, a pathogenic fungus that causes chytridiomycosis, uses spermidine and other polyamines to evade host immune surveillance (96). A recent study showed that polyamines facilitate the cellular attachment of coronaviruses and aid in viral replication, which is curbed upon the administration of DFMO, a polyamine synthesis inhibitor (97). Besides their role in microbial pathogenicity, polyamines also exhibit versatile roles in the activation of the immune response (**Fig. 2**). ODC in macrophages tempered antimicrobial M1 macrophage responses during *Helicobacter pylori* and *Citrobacter rodentium* infections in mice (98). Spermidine treatment improved the $CD8^+$ T cell response of aged

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mice to influenza vaccination and infection by mediating autophagy (99). The administration of multi-strain probiotics to dogs with IBD and colonic polyposis resulted in potential anti-proliferative and anti-inflammatory effects, accompanied by an increase in putrescine, spermine, and ODC levels (100). In the central nervous system (CNS), ODC expressing neurons play a key role in the recruitment of immune cells to the CNS (101). The addition of spermine to LPS-stimulated human PBMCs resulted in post-transcriptional and polyamine oxidase-independent suppression of the synthesis of pro-inflammatory cytokines TNF-α, IL-1, IL-6, MIP-1α, and MIP-1β (102). Spermine supplementation alleviated the inflammatory response by inducing IgM and anti-inflammatory cytokines (IL-10, TGF-β) but reducing pro-inflammatory cytokines (TNF-α, IL-1β, and IFN-γ) in piglets (103). Spermine administration also protected mice against the development of carrageenan-induced acute edema (102) and lethal sepsis by attenuating HMGB1-induced inflammatory markers (104). Spermidine supplementation established metabolic dormancy in IFN-DCs and reduced the production of pro-inflammatory cytokines *in vitro* and *in vivo*. The anti-inflammatory effects of spermidine are mediated by FOXO3 in DCs (105). In macrophages, the polyamine-eIF5A-hypusine axis controls OXPHOS-dependent alternative activation by modulating mitochondrial oxidative phosphorylation but not aerobic glycolysis-dependent classical activation (106). Spermidine-treated RAW 267.4 cells, belonging to a well-known macrophage cell line, decrease the production of TNF-α and IL-1β. The anti-inflammatory effects of spermidine were confirmed by the significant decrease in inflammation-associated migration of neutrophils and macrophages in zebrafish larvae (107). Furthermore, spermidine reverses B cell senescence caused by aging. B cells from aged mice exhibit loss of the hypusinated EIF5A-TFEB-autophagy axis due to reduced spermidine levels, which can be restored by exogenous supplementation (108). Thus, polyamines have versatile roles in the immune system in health and disease.

Role of metabolites in Tregs/Th17 cell-mediated immune regulation

The reciprocal regulation between Tregs and Th17 cells is crucial for maintaining host immune homeostasis, and this regulation is achieved through microbial metabolite-immune interaction (109). In colonic lumen, SCFAs are mainly transported into the lamina propria through passive diffusion or transporters, such as sodium-coupled monocarboxylate transporter 1 and monocarboxylate transporter 1. These are expressed mainly in the apical and basolateral membranes of colonocytes (110,111). In lamina propria, the SCFAs interact with their receptors, including GPR41, GPR43, and GPR109A (112). Although GRP41 and GPR43 are activated by all SCFAs, GPR109A is selectively activated by butyrate (113). SCFAs are expressed in various tissues and cell types, including adipose tissue, intestinal epithelial cells, and immune cells, indicating their immune-modulatory roles (114). Although there is still no detailed molecular mechanism of their immune-modulatory function, a line of studies has reported that SCFAs can modulate colonic Treg cells via GPR43, which mediates the inhibition of HDACs. This in turn loosens the intronic CNS region of the *Foxp3* locus leading to the upregulation of Foxp3 expression and Tregs differentiation in the colon (53-55). Furthermore, we have recently observed that probiotics-derived propionate in gut heightens not only the proportion but also effector function of Tregs during skin allergies (115). The physiological roles of SCFAs as HDAC inhibitors were demonstrated by supplementing the diet of germ-free mice with acetate, butyrate, and propionate, which increased histone acetylation leading to transcriptome changes in various tissues (116). At molecular level, the potential mechanism by which SCFAs inhibit HDAC activity involves competitive inhibition of the substrate from binding to the catalytic site of HDACs (117). A pioneering study regarding the effect of SCFAs on the polarization of $CD4^+$ T cells has demonstrated that SCFAs affect the differentiation of not only Tregs but also Th17 cells

(118). Interestingly, SCFAs do not act as Tregs cell inducers in certain Th polarization culture conditions with distinct cytokine milieu, but boost the polarization of $CD4^+$ T cells, especially into Th1/17 cells (118). Cancer patients undergoing anti-CTLA4 treatments showed a correlation between the worst clinical outcomes and high blood butyrate levels and Tregs cell proportion, in which butyrate indirectly dampens T cell-mediated anti-tumor immunity by inhibiting the anti-CTLA4-mediated upregulation of CD80/86 on DCs (119). Furthermore, HDAC inhibition by SCFAs leads to the generation of Th1, Th17, and IL-10-producing T cells through the acetylation of the p70 S6 kinase and phosphorylation of rS6, which is a crucial component of the mTOR pathway. In summary, SCFAs modulate T cell homeostasis by balancing effector and Tregs, depending on the immunological milieu.

Several recent studies have shown specific effects of BA metabolites on Tregs differentiation (27,92-94). IsoalloLCA increases the differentiation of Tregs through the production of mitochondrial ROS (mitoROS), which leads to increased expression of FOXP3 and Tregs differentiation independent of the microbiome composition (93). At the molecular level, isoalloLCA activates the nuclear hormone receptor NR4A1 to facilitate a permissive chromatin structure in the promoter region of the transcription factor FOXP3 (27). Together with isoalloLCA, isoDCA after microbial epimerization diminishes immunostimulatory properties of DCs via FXR. This promotes Foxp3 induction and Tregs differentiation in CNS1-dependent manner, indicating isoDCA-induced extrathymic differentiation of RAR-related orphan receptor gamma $(ROR\gamma t)^+$ Tregs cell (94). The 3-oxoLCA directly interacts with RORγt, which is a key Th17 cell-promoting transcription factor, to inhibit Th17 cell differentiation. Treatment of 3-oxoLCA ameliorated the severity of murine acute enteritis mouse model (93).

A recent study showed that polyamine metabolism is a central determinant in the regulation of the helper T cell differentiation. T cell-specific depletion of ODC or deoxyhypusine hydroxylase promotes widespread epigenetic remodeling driven by alterations in histone acetylation and a re-wired tricarboxylic acid cycle. This leads to severe intestinal inflammation, implicating polyamine metabolism in the maintenance of Th lineage fidelity (120). Furthermore, polyamine metabolism is a decisive factor in Th17 pathogenicity, which is associated with arginine and downstream polyamine metabolism. Briefly, chemical and genetic perturbation of polyamine metabolism induces the transcriptome/epigenome of Th17 cell to move toward a Treg-like state, so as to inhibit Th17 but promote Treg differentiation (121). Along with pro-inflammatory function, polyamines can evoke an immune regulatory environment. Polyamines trigger an IDO1-dependent immunosuppressive property in DCs by activating IDO1-phosphorylating Src kinase (122). Spermidine potentiates the differentiation of both murine and human naïve $CD4^+$ T cells toward regulatory phenotypes and controls inflammation in the murine colitis model in an Atg5-dependent manner. This indicates the pivotal role of autophagy in immune regulation by spermidine (123).

Effect of microbial metabolites on diseases and clinical applications

Numerous bodies of evidence show that SCFAs play an important role in the maintenance of health as well as the development of disease (**Table 1**). Using multi-omics with a multi-organ model of ulcerative colitis *ex vivo*, Trapecar et al. (124) showed the paradoxical roles of microbiota-derived SCFAs in modulating the immune system. The SCFAs mitigated innate inflammation in the absence of $CD4^+$ T cells but exacerbated $CD4^+$ T cell-mediated acute inflammation through metabolic reprograming, leading to gut-barrier disruption and hepatic injury. Another multiomics-based study on patients with non-alcoholic fatty liver disease (NAFLD)-related cirrhosis, with or without hepatocellular carcinoma (HCC), revealed that

Table 1. List of the metabolites and their impacts under various disease conditions

Type of metabolite	Receptors/Molecular targets	Relevance to disease	Reference
SCFA	-	Increased in NAFLD-HCC patients compared to NAFLD only patients	(125)
		Decreased in IBD patients	(127,128)
		Decreased in type 1 diabetes patients	(162)
		Decreased in allergic infants	(163)
BA			
Primary			
CA	FXR, GGPBAR1, chimeric antigen receptor	Relatively increased in IBD, accelerate LN metastasis of tumor (taurine conjugated)	(138,164)
CDCA	FXR, GPBAR1, PXR, vascular endothelial growth factor	Relative increased in IBD patients, liver cancer, ameliorates Alzheimer's disease	(164,165)
Secondary			
DCA	FXR, PXR, VDR, TGR5	Decreased in IBD patients, uveitis (suppressive), accelerate LN metastasis of tumor (taurine conjugated)	(138,164,166)
LCA	FXR, PXR, VDR, TGR5	Decreased in IBD patients, psoriasis (suppressive), uveitis (suppressive), increased in coronary disease, breast cancer (suppressive)	(91,164,166-168)
UDCA	FXR, GPBAR1	NAFLD (improve disease status)	(169-172)
Derivatives of 2nd BA			
3-oxoLCA	PXR, VDR, RORγt	Decreased in IBD patients	(26,93)
IsoalloLCA	NR4A1	Decreased in IBD patients	(27)
IsoDCA	FXR	Unknown	(94)
IsoLCA	RORγt	Decreased in IBD patients	(26)
Polyamines			
Spermine	-	Increased level exerts anti-obesity effect	(50)
Spermidine and other polyamines	-	Pathogenic fungus uses the metabolites to evade host immune surveillance in chytridiomycosis	(96)
Putrescine, spermidine, ODC	-	Increase in levels associated with anti-inflammation with IBD and colonic polyposis	(100)
Spermine	-	Protect development of carrageenan-induced acute edema and lethal sepsis	(102,104)
Spermidine	Atg5-dependent manner	Controls inflammation in the murine colitis	(123)
Spermidine	AMPK, HIF-1α	Induces autophagy-mediated M2 polarization and ameliorate murine IBD	(148)
L-arginine	Arg1	Protection from colitis	(149)
Spermidine	Antioxidant activity	Alleviated the severity of murine EAE	(150)
Spermidine	Arg1	Reverses EAE progression	(151)
Spermidine, spermine, N1-acetylspermidine, N1-acetylcadaverine	-	Reduced plasma levels in SLE	(152)
Urinary polyamine, putrescine	-	Elevated levels to the activity and progression of RA	(154,155)

the higher SCFA-producing bacteria in NAFLD-HCC patients elicit the expansion of Tregs cells and attenuation of $CD8^+$ T cells compared to those in healthy controls (125). In a murine model of experimental autoimmune prostatitis (EAP), supplementation with propionate lowered the susceptibility to EAP induction and corrected the Th17/Tregs cell imbalance independent of the gut microbiome (126). Thus, SCFAs have shown their potent immune-regulatory functions not only in mucosal but also systemic immune system where they mainly modulate the Th17/Tregs cell balance.

Although there are plenty of pre-clinical studies regarding effects of SCFAs on immunological disorder, clinical trials of SCFAs on counterparts still need to be done. Representatively, clinical studies evaluating effects of SCFAs mixture on IBD patients showed improved clinical outcome in SCFAs-treated patients compared to placebo (127,128). Molecularly, SCFAs treatment inhibits nuclear translocation of NF-κB and macrophage and LPS-induced cytokine expression of lamina propria and peripheral blood macrophage (129).

Primary BAs are steroidal chemicals generated in the liver from cholesterol and released into the gut lumen after a meal, where they aid in the absorption of dietary fatty acids and vitamins (25). Once in the GI tract, these molecules are chemically transformed by the resident microbiota to generate a family of metabolites known as secondary BAs (25). Numerous studies have revealed that both primary and secondary BAs affect host physiopathology in health and disease (27,130-135) (**Table 1**). In murine psoriatic dermatitis, oral or intravenous administration of LCA ameliorated the symptoms of psoriasiform dermatitis by inhibiting IL-17a production and RORγt transcription in $CD3^+$ T cells cultured with IL-23 via FXR and GPBAR1 (91). Uveitis, commonly accompanied by autoimmune diseases, such as Behçet's disease, is also related to BA metabolites. Using metagenomic analysis, a specific dysbiosis disease was identified in the stools of patients with Behçet's disease, which is capable of exaggerating experimental autoimmune uveitis (EAU) in murine models (136). Treatment with DCA and LCA mitigates murine EAU by inhibiting the activation of $CD11c^+$ $MHCII^+$ DCs, which repress the induction of Th1 and Th17 cells through TGR5 signaling (87). BAs are considered a double-edged sword in tumor progression and immunity. In a mouse cancer model, both tauro-β-MCA (T-βMCA) and CDCA upregulated CXCL16 expression in liver sinusoidal endothelial cells to accumulate $CXCR6^+$ NKT cells in the liver, resulting in the inhibition of liver metastasis (137). However, BAs can also promote cancer progression by acting directly on tumor cells. Using comparative transcriptomics and metabolomics of primary and lymph node (LN)-metastatic tumors in mice, the specific accumulation of several bioactive BAs was observed in metastatic LNs. These BAs activate yes-associated protein in tumor cells via the nuclear VDR to intensify FAO signaling pathways leading to LN metastasis (138). In addition, natural FXR antagonists, T-βMCA and DCA, promote cancer stem cell proliferation together with the accumulation of DNA damage in Lgr5-expressing cancer stem cells, resulting in the progression of murine colorectal cancer (139). In summary, BAs play a pathophysiological role in various diseases. Thus, understanding their mode of action is important in order to uncover novel diagnostics and therapeutics for immune disorders, such as severe inflammatory diseases, autoimmune diseases, and cancer.

There are several clinical trials to use BAs in various disease, including liver and non-liver diseases regardless of its effect on immune system (13,140-144). UDCA was used in patients with primary sclerosing cholangitis (PSC) and improved liver function test in serum. But it didn't increase the survival rate and several serious adverse effects were reported (145). Mousa et al. (146) reported that BA profile score can be used as a biomarker to predict hepatic decompensation in PSC patients. Obeticholic acid, a semisynthetic derivative of CDCA, is an agonist of both FXR and GPBAR1. Initially, it was tried in primary biliary cholangitis for treatment and biomarkers for disease progression (147). Nowadays, it is also being attempted for use in non-alcoholic steatohepatitis (143).

Polyamines are essential for cell growth and proliferation as well as tissue regeneration. Increasing evidence indicates the pivotal role of these molecules in the physiopathogenesis of multiple diseases (**Table 1**). For instance, spermidine induces AMPK-, HIF-1α-, and autophagy-mediated M2 polarization, and spermidine-treated macrophages ameliorate murine IBD (148). Arginase 1 alters the microbiome and augments the degree of inflammation in IBD patients. A murine colitis model with Arg1 knockout mice, partially mimicking human IBD patients, showed necessity of L-arginine for protection from colitis, indicating L-arginine metabolism as a potential target for treatment of IBD (149). Furthermore, oral administration of spermidine effectively alleviated the severity of murine EAE, especially EAE-induced

optic neuritis, through its antioxidant activity (150). Spermidine also induces the inhibitory macrophages expressing arginase-1 (but not IL-1β, IL-12, and CD80), which reverses EAE progression in an Arg1-dependent manner (151). Patients with systemic lupus erythematosus (SLE) have specific alterations in the polyamine catabolism in serum, showing reduced plasma levels of spermidine, spermine, N1-acetylspermidine, and N1-acetylcadaverine but elevated cadaverine levels, which is associated with disease activity (152). This suggests that changes in polyamine patterns can act as potential biomarkers for assessing disease activity in SLE (152). Spermine can inhibit the binding of SLE-related anti-DNA antibodies in plasma to calf thymus DNA in a dose-dependent manner and can also displace the antibodies in preformed immune complexes (153). Elevated urinary polyamine levels can be linked to the activity and progression of rheumatoid arthritis (RA) (154). Higher putrescine levels are observed in the synovial fluid of RA patients compared to that of healthy controls (155). Daily supplementation of spermine significantly ameliorated cartilage and bone destruction in the synovial joints of rats with collagen-induced arthritis (156). Furthermore, the enhanced expression of polyamine-modulated factor 1-binding protein 1 and spermidine/spermine N1-acetyltransferase promotes the catabolism and recycling of polyamines. This leads to global DNA hypomethylation in the synovial fibroblasts of RA patients (157), indicating the polyamine recycling pathway as part of a novel epigenetic therapy for RA (158). Chemical inhibition of polyamine pathways has shown immune-modulatory function in various inflammatory disorders. For instance, methylthioadenosine, a spermine synthase inhibitor, ameliorates murine experimental autoimmune encephalomyelitis (EAE) by suppressing the production of IFN-γ, TNF-α, and inducible nitric oxide synthase but increasing the production of IL-10 in a dose-dependent manner (159,160). Simultaneous ablation of *de novo* synthesis and the salvage pathway by AMXT 1501 and DFMO confers protection against the development of EAE, which is substantiated by the reduction of IL-17$^+$ CD4$^+$ T cells mainly via arginine in the CNS (161). The complex integration of multiple mechanisms dictates the immune stimulatory or regulatory roles of the polyamines under homeostatic and pathological conditions.

CONCLUDING REMARKS

Gut microbiota intercommunicates with the mucosal immune system primarily through its metabolites to maintain immunological homeostasis. Among the various microbial metabolites, accumulating evidence has specially focused on the immune-modulatory function of SCFAs, BAs, and polyamines. The activities of SCFA and BA metabolites are mainly mediated through various receptors. However, polyamines, which are produced extracellularly and transported into cells, regulate the metabolic pathways in versatile immune populations to impact the host's health and disease status. These interactions may allow immune cells to integrate the nutritional supplementation from tissues with the optimal programing of their metabolic status. The benefits of targeting Tregs/Th17 balance can be ambiguous. Nonetheless, understanding the role of metabolomes, particularly in controlling Tregs or Th17 cell activity, is critical for regulating physiopathology in homeostatic and inflammatory circumstances through microbial metabolites. Understanding immune modulation via microbial metabolites can be important in this regard. In fact, specific metabolites and/or metabolic signatures could be utilized as biomarkers as well as potential therapeutic targets for developing innovative therapies against various intractable immune disorders. These include allergies, autoimmune diseases, and cancers. Thus, our review highlights the need for more research to decode the microbial metabolite-immune interactions and their physiopathological outcomes at a systematic level.

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