REVIEW ARTICLE

Gut microbiota-derived metabolites in the regulation of host immune responses and immune-related inflammatory diseases

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The gut microbiota has a critical role in the maintenance of immune homeostasis. Alterations in the intestinal microbiota and gut microbiota-derived metabolites have been recognized in many immune-related inflammatory disorders. These metabolites can be produced by gut microbiota from dietary components or by the host and can be modified by gut bacteria or synthesized *de novo* by gut bacteria. Gut microbiota-derived metabolites influence a plethora of immune cell responses, including T cells, B cells, dendritic cells, and macrophages. Some of these metabolites are involved in the pathogenesis of immune-related inflammatory diseases, such as inflammatory bowel diseases, diabetes, rheumatoid arthritis, and systemic lupus erythematosus. Here, we review the role of microbiota-derived metabolites in regulating the functions of different immune cells and the pathogenesis of chronic immune-related inflammatory diseases.

Keywords: gut microbiota; metabolites; T cells; B cells; autoimmune diseases

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INTRODUCTION

The intestine harbors diverse and dynamic microbial communities, which have a critical role in human health and diseases. Many immune-related inflammatory disorders, such as inflammatory bowel diseases (IBDs),[1,2] diabetes,[3] rheumatoid arthritis (RA),[4–6] and systemic lupus erythematosus (SLE),[7,8] have been associated with altered gut microbiota. The crosstalk between gut microbiota and the immune system is intricate and is partially dependent on gut microbial metabolites.[9] Both diet and gut microbiota species contribute to the production of various metabolites,[10] which act locally in the intestine and remotely exert their diverse effects on other organs. It is well-recognized that microbial metabolites have important roles in regulating immune responses and chronic immune-related inflammatory diseases through different mechanisms, including activation of metabolic-specific receptors.[11] More importantly, supplementation with some specific microbial metabolites,[12–14] their receptor agonists,[15,16] or a specific diet[17] has been shown to regulate disease severity in mice and humans. For example, gut microbiota-derived short-chain fatty acids (SCFAs) have been the focus of intense research due to their profound effect on almost all types of immune cells and their potential for treating various chronic inflammatory diseases.[18,19] In this review, we first introduce the key microbial metabolites that regulate immune responses, summarize the effect of these metabolites on immune cells, and discuss the relationship between microbial metabolites and chronic immune-mediated diseases. This review aims to provide a systematic understanding of microbiota-derived metabolites in immune cells and immune-related inflammatory diseases.

GUT MICROBIOTA REGULATION OF IMMUNE RESPONSES

The host and gut microbiota have co-evolved to form a mutualistic relationship. The gut microbiota and host immunity interact in a complex, dynamic, and context-dependent manner. The role of intestinal microbiota in the development of the immune system and immune responses has been well established.[20,21] Germ-free mice lack all microbial colonization, and therefore, their immune responses are "innocent" to the molecules of pathogens as well as beneficial gut microbiota. There are numerous immune deficits in germ-free mice, including impaired development of gut-associated lymphoid tissues (GALT) and systemic immune systems with decreased cellularity of GALT, mesenteric lymph nodes, and spleen.[22,23] Both T and B cell responses are impaired in germ-free mice in response to antigen stimulation from challenge with foreign antigens or pathogens.[21,24] Germ-free mice have fewer and smaller germinal centers within the spleen, fewer antibody-producing cells,[21] and fewer IgG and IgM antibodies.[24] Their T cells produce fewer cytokines in response to antigen challenge than conventionally colonized mice.[24] Furthermore, the production of intestinal IgA, which is the most abundant antibody isotype in the host and provides the first line of immune protection at the mucosal surface,[25,26] is nearly absent in germ-free mice.[27] Reconstitution with gut microbiota normalizes the development of immune systems and immune responses,[27,28] suggesting a crucial role of the microbiota in regulating the development and function of the immune system. Accumulating evidence indicates that not all gut bacteria function in the same way to regulate immune responses. Different gut bacteria differentially control the development of various components of the immune system. While segmented filamentous bacteria (SFB) promote Th17 cell development in the

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intestines, a cluster of Clostridia induces Treg cells.[29,30] Functionally distinct Th17 cell populations are present in the intestines and are primarily determined by distinct bacteria. SFB-induced Th17 cells are homeostatic, while Citrobacter-induced Th17 cells are pro-inflammatory.[31] Thus, it is essential to understand the molecular basis of such microbiota–host interactions, which could provide novel targets that shape immune function in treating various immune-related inflammatory diseases.

GUT MICROBIOTA-DERIVED METABOLITES

The gut microbiota does not merely evade the immune system in the intestinal tract. In addition to well-recognized TLR ligands, including LPS, flagellins, and dsDNAs,[32] which are beyond the scope of this review, gut microbiota-derived metabolites continuously regulate immune cells both locally and systemically. However, our understanding of these interactions is just beginning as most gut microbiota-derived metabolites are still unidentified, and many of their functions are yet to be defined.[10] A relatively small but diverse range of gut microbiota-derived metabolites has been identified and functionally studied in the last decade. Depending on their origin and synthesis, these gut microbial metabolites can be broadly divided into three groups: (1) metabolites produced by gut bacteria from dietary components, (2) metabolites produced by the host and modified by gut bacteria, and (3) metabolites synthesized *de novo* by gut bacteria (Fig. 1 and Table 1).

Metabolites produced by gut bacteria from dietary components

Short-chain fatty acids. Undigested carbohydrates can be fermented to SCFAs by gut microbiota, which express carbohydrate-active enzymes. SCFAs, referring to fatty acids with fewer than six carbons, principally include acetate, propionate, and butyrate, which exist in a 3:1:1 ratio in the gut.[33] SCFAs reach a concentration of ~100 mM in the intestinal lumen,[34] depending on dietary fiber and the gut microbial composition. Acetate production is mainly formed from acetyl-CoA by enteric bacteria or by acetogens through the Wood–Ljungdahl pathway.[35,36] The phylum *Bacteroidetes* primarily produces propionate through the succinate pathway or acrylate pathway by *Lachnospiraceae* and *Negativicutes*.[37] Alternatively, propionate production can also occur through the propanediol pathway by *Roseburia inulinivorans* and *Ruminococcus obeum*.[37] Butyrate is primarily produced by several species in the phylum *Firmicutes*, which express active CoA-transferase.[38] After being absorbed in the colon, SCFAs are either utilized locally to provide colonocytes with energy or transported into the blood, where they are distributed to other organs for metabolism and consumption through the portal vein.[34] SCFAs enter the cells in two primary ways: passive diffuse and carrier-mediated transportation via SMCT1 (SLC5A8) and MCT1 (SLC16A1).[39] SCFAs regulate the function of different immune cells by inhibiting histone deacetylase (HDAC)[40] and/or activating G protein-coupled receptors (GPRs),[41–43] which include GPR41, GPR43, and GPR109a.

Microbial tryptophan catabolites. As an essential aromatic amino acid, tryptophan is supplied mostly from dietary protein. Tryptophan absorption primarily occurs in the small intestine for protein synthesis, whereas a variety of bacteria in the colon can directly degrade tryptophan into several metabolites, including indole, indole ethanol (IE), indolepropionic acid (IPA), indole lactic acid (ILA), indoleacetic acid (IAA), indolealdehyde (IAld), indoleacrylic acid (IA), skatole, and tryptamine.[44] The types and levels of microbial tryptophan metabolites are primarily influenced by the gut microbiota, which possesses different catalytic enzymes for tryptophan metabolism. Tryptophan is converted into indole by numerous bacterial species (such as *Escherichia coli*[45] and *Proteus vulgaris*[46]) using tryptophanase.[47] Additionally, various other bacterial species produce several tryptophan metabolites through different metabolic pathways. For example, *Clostridium sporogenes* and *Rominococcus gnavus* can produce tryptamine by decarboxylation of tryptophan.[48] *Clostridium sporogenes* and *Peptostreptococcus* spp. produce IA.[49,50] *Clostridium* spp., such as *Clostridium botulinum*, *Clostridium caloritolerans*, and *Clostridium sporogenes*, can convert tryptophan into IPA.[49] Gut microbiota-derived tryptophan catabolites regulate intestinal immune responses locally and systemically affect host physiology through the bloodstream, where they activate the pregnane X receptor (PXR)[51] and/or aryl hydrocarbon receptor (AhR).[52,53]

Trimethylamine-N-oxide. Trimethylamine (TMA) is a gut microbiota metabolite derived from carnitine, choline, or choline-containing compounds in the diet.[54] The formation of TMA depends on the balance and diversity of the gut microbiota. The sulfate-reducing bacteria *Desulfovibrio alaskensis* and *Desulfovibrio desulfuricans*, which possess the choline-utilization gene cluster (*Cut*), can convert choline to TMA in the gut,[55] whereas the genera *Acinetobacter* and *Serratia*, encoding *CntA* and *CntB*, can generate TMA from L-carnitine.[56,57] Furthermore, another gene pair, *YeaW/YeaX*, with homology to *CntA/B*, also contributes to

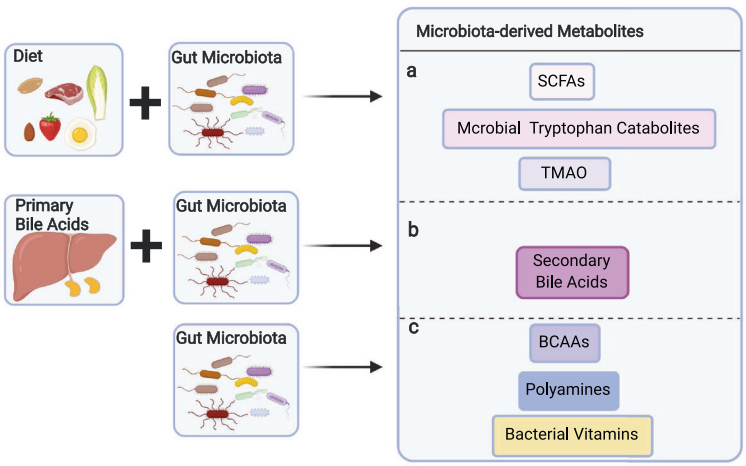

Fig. 1 Production of gut microbiota-derived metabolites. Gut microbiota-derived metabolites can be produced by gut microbiota from dietary components (**a**), by the host and modified by gut bacteria (**b**), and synthesized *de novo* by gut bacteria (**c**). *BCAAs* branched-chain amino acids, *SCFAs* short-chain fatty acids, *TMAO* trimethylamine-*N*-oxide

Table 1. The characteristics and functions of the major gut microbiota-derived metabolites

Groups of microbial metabolites	Representatives of metabolites		Receptors	Functions	
	Metabolites	Examples			
Produced by gut bacteria from dietary components	SCFAs	Acetate Propionate Butyrate	GPR41[42] GPR43[43] GPR109a[41]	T cells	Regulation of $CD4^+$ T cell differentiation and cytokines production[42,43,93–97,104,105,109,145,146] Induction of memory $CD8^+$ T cell responses[110–113]
				B cell	Regulation of cell activation and antibody production[122,123,126,129,130]
				DCs	Suppression of maturation and modulation of cytokines/chemokines production[140,141,143,144]
				Macrophages	Enhancement of antimicrobial function and modulation of cytokines production[135,150,151]
	Microbial tryptophan catabolites	Indole IPA IAA	PXR[51] AhR[52]	T cell	Induction of Treg cell but inhibition of Th17 development[102,103,106] Induction of $CD4^+$ $CD8^+$ IELs[119]
	TMAO	TMAO	TAARs[59] PERK[60]	Macrophages	Induction of M1 polarization[154]
Produced by the host and modified by gut microbiota	Secondary bile acids	DCA LCA	FXR[65] PXR[67] VDR[69] CAR[70] TGR5[71]	T cells	Induction of Treg differentiation and $ROR\gamma^+$ Treg cell development, but suppression of Th17 differentiation[99,100] Regulation of hepatic NKT cell accumulation[114]
				Macrophages	Induction of Kupffer cells[152] Inhibition of LPS-induced proinflammatory cytokines in macrophages[71,153]
Synthesized *de novo* by gut microbiota	BCAAs	Leucine Isoleucine Valine	unknown	T cells	Maintenance of Treg cells[74]
				Macrophages	Suppression of LPS-induced cytokines[155]
	Polyamines	Spermine Spermidine putrescine	NMDA[81] CaR[82]	T cells	Suppression of IFN-γ production[107]
				DCs	Modulation cell activation and phenotypes[148]
	Bacterial vitamins	Ascorbate 6-FP 5-OP-RU	MR1[117,118]	T cells	Suppression of $CD4^+$ effector T cell[88] Regulation of MAIT cell activation[117,118]

BCAAs branched-chain amino acids, *CaR* calcium-sensing receptor, *CAR* constitutive androstane receptor, *DCA* deoxycholate, *FXR* farnesoid X receptor, *GPR* G protein-coupled receptor, *IPA* indolepropionic acid, *IAA* indoleacetic acid, *LCA* lithocholic acid, *MR1* MHC-related molecule 1, *NMDA* *N*-methyl-D-aspartate receptors, *PERK* protein kinase R-like endoplasmic reticulum kinase, *PXR* pregnane X receptor, *SCFAs* short-chain fatty acids, *TAARs* trace amine-associated receptors, *TGR5* G protein-coupled bile acid receptor 1, *TMAO* trimethylamine-*N*-oxide, *6-FP* 6-FP 6-formylpterin, *VDR* vitamin D receptor, *5-OP-RU* 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil.

the production of TMA.[32] TMA can be absorbed in the intestine and then transferred to the liver, where it is oxidized to trimethylamine-*N*-oxide (TMAO) by flavin monooxygenases (FMOs).[58] TMA, but not TMAO, selectively activates human trace amine-associated receptors (TAARs).[59] It has been revealed recently that TMAO directly binds and activates protein kinase R-like endoplasmic reticulum kinase (PERK), a key sensor of intracellular stress.[60]

Metabolites produced by the host and modified by gut bacteria

Secondary bile acids. Primary bile acids, including cholate (CA) and chenodeoxycholate (CDCA), are synthesized by hepatocytes.[61] After conjugation with glycine or taurine, which promotes the surfactant function of bile acids, the conjugated bile acids enter the intestinal lumen, where they promote digestion, transport, and absorption of nutrients.[61,62] Most of the conjugated bile acids are absorbed in the small intestine and transported back to the liver. Approximately 5% of bile acids are converted into secondary bile acids by a limited number of microbiota species (e.g., *Firmicutes* species, notably *Clostridium scindens*) in the cecum and colon.[63] Among secondary bile acids, deoxycholate (DCA) and lithocholic acid (LCA) are the two major types that are generated through 7a-dehydroxylation of CA and CDCA, respectively.[63,64] In addition to directly affecting bacteria, bile acids activate cells by binding to nuclear hormone receptors, including farnesoid X receptor (FXR),[65,66] PXR,[67,68] vitamin D receptor (VDR),[69] and constitutive androstane receptor (CAR),[70] as well as a cell-surface receptor, G protein-coupled bile acid receptor 1 (GPBAR1, also called TGR5).[71]

Metabolites synthesized *de novo* by gut bacteria

Branched-chain amino acids. Among nine essential amino acids, leucine, isoleucine, and valine are branched-chain amino acids (BCAAs) having an aliphatic side chain with a branch.[72] Although diet is the primary source of BCAAs in humans, BCAAs can also be synthesized by gut microbiota.[73] Upon bacterial invasion, there is a markedly increased demand for synthesis substrates, including BCAAs, for immune responses and functions. In addition to enhancing protein synthesis and providing energy via catabolism, BCAAs regulate cell functions by activating the mTOR pathway.[74]

Polyamines. Polyamines, mainly spermine, spermidine, and putrescine, are widely distributed polycationic molecules in almost all living cells and are essential for biological functions.[75] The polyamines in the intestinal lumen originate either from the diet or are synthesized *de novo* by host cells and intestinal microbiota.[76] Dietary protein is the primary source of polyamines in the intestinal tract,[77] and the majority of polyamine absorption occurs in the small intestine. The intestinal microbiota, such as *Bacteroides* spp. and *Fusobacterium* spp., are considered primary producers of polyamines in the lower parts of the intestine.[78,79] In

addition, diet can modulate microbial polyamine production. Specifically, dietary fiber increases SCFA production and lowers luminal pH, both of which activate intestinal bacteria to produce polyamines.[80] Polyamines serve as ligands for various types of receptors, such as *N*-methyl-D-aspartate receptors (NMDA)[81] and calcium-sensing receptor (CaR).[82]

Bacterial vitamins. Vitamins, essential nutrients for bacteria and host metabolism, are obtained from the diet or synthesized by gut microbiota. While dietary vitamins are absorbed in the small intestine,[83] gut microbiota-derived vitamins are primarily utilized in the colon.[84] For example, vitamin K2 (menaquinone) and vitamin B family members are the major vitamins produced by gut flora.[85] Gut bacterial species, including *Lactic acid bacteria* and *Bacteroides*, produce vitamin K2.[86,87] However, diet is the sole source of vitamin K1 (phylloquinone). Various gut bacteria produce vitamin B, including vitamin B1 (thiamine), B2 (riboflavin), B3 (nicotinic acid), B5 (pantothenic acid), B6 (pyridoxine), B7 (biotin), B9 (folates), and B12 (cobalamin). For instance, vitamin B2 is synthesized by several bacterial species in the phyla *Bacteroidetes*, *Fusobacteria*, *Proteobacteria*, and *Firmicutes*, while the synthesis of vitamin B12 occurs in the phylum *Fusobacteria* but rarely in *Actinobacteria* and *Proteobacteria*.[84] It has also been recently found that gut microbiota can produce vitamin C (ascorbate).[88]

GUT MICROBIOTA-DERIVED METABOLITE REGULATION OF HOST IMMUNE RESPONSES

Accumulating evidence indicates that gut microbiota-derived metabolites regulate the development and function of multiple types of immune cells, including both adaptive and innate cells. Due to space limitations, we will mainly focus on their effects on major populations of immune cells, i.e., T cells, B cells, dendritic cells (DCs), and macrophages (Table 1 and Figs. 2, 3).

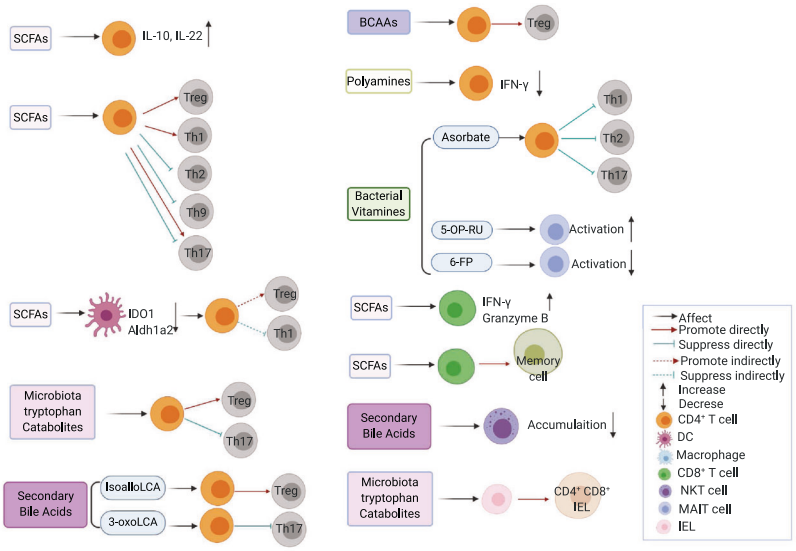

Fig. 2 Effects of gut microbiota-derived metabolites on T cells. Microbiota-derived metabolites differentially modulate T cell functions. *Aldh1a2* retinal dehydrogenase aldehyde dehydrogenase 1A2, *BCAAs* branched-chain amino acids, *DC* dendritic cell, *IEL* intraepithelial lymphocyte, *IDO1* indoleamine 2,3-dioxygenase 1, *LCA* lithocholic acid, *NKT* natural killer T cells, *MAIT* mucosal-associated invariant T cell, *SCFAs* short-chain fatty acids, *5-OP-RU* 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil, *6-FP* 6-formylpterin

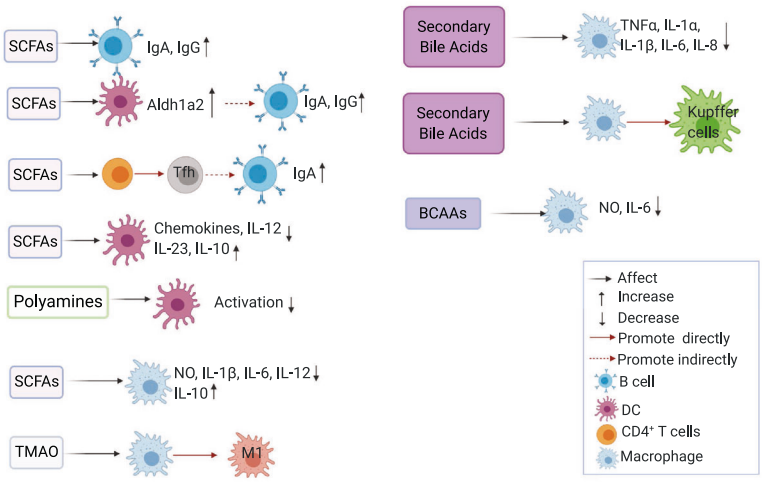

Fig. 3 Effects of gut microbiota-derived metabolites on B cells, macrophages, and dendritic cells. Microbiota-derived metabolites regulate various types of immune cells. *Aldh1a2* retinal dehydrogenase aldehyde dehydrogenase 1A2, *BCAAs* branched-chain amino acids, *DC* dendritic cell, *DCA* deoxycholate, *SCFAs* short-chain fatty acids, *TMAO* trimethylamine-*N*-oxide

T cells

T cells, the major mediators in regulating immune responses, are divided into two populations, TCRαβ and TCRγδ T cells.[89] Among TCRαβ T cells, there are $CD4^+$ T cells, $CD8^+$ T cells, natural killer T cells (NKT cells), intraepithelial lymphocytes (IELs), and other innate TCRα-expressing T cells, i.e., mucosal-associated invariant T (MAIT) cells.[90–92] In this section, we will summarize the effects of gut microbiota-derived metabolites on T cells (Table 1 and Fig. 2).

$CD4^+$ T cells. The role of microbiota-derived metabolites in regulating $CD4^+$ T cells is an area of intensive investigation. Given that Treg cells are essential for limiting immune responses, various types of metabolites have been investigated for their effects on Treg cells. SCFAs have been found to promote colonic Treg differentiation by inhibiting HDAC expression and activity in a GPR43-dependent manner[93] or by enhancing histone acetylation in the conserved noncoding sequence region (CNS) 1 of the *Foxp3* locus in a GPR43-independent manner.[94,95] However, SCFAs did not induce Treg cells under Th1 and Th17 polarization conditions with a high anti-CD3 activation level, whereas Foxp3 expression was upregulated under low T cell activation conditions.[96] Furthermore, butyrate failed to generate Treg cells in the absence of TGFβ.[97] Therefore, SCFAs affect Treg cells in a context-dependent manner. Secondary bile acids are known to affect innate immunity,[16,71,98] but their effects on adaptive immune responses have been poorly investigated until recently. It has been shown that isoalloLCA, an LCA derivative, promoted Treg differentiation via histone modification of CNS3 of the *Foxp3* locus and production of mitochondrial reactive oxygen species.[99] Furthermore, dominant intestinal bile acids along with their potent secondary bile acids induced $ROR\gamma^+$ Treg cells, which are critical in maintaining intestinal immune homeostasis, in a VDR-dependent manner.[100] AhR, a transcription factor widely expressed in immune cells, has a crucial role in regulating immune responses, including $CD4^+$ T cells.[101] AhR ligands, including bacterial tryptophan catabolites, modulate $CD4^+$ T cell responses. It has been reported that indoles and indole derivatives promoted Treg differentiation both in vitro and in vivo in an AhR-dependent manner.[102,103] Amino acids are essential for activated T cells with high metabolic demands. The maintenance of Treg cells was regulated by BCAAs, which activated mTOR through the transporter SLC3A2.[74]

Effector $CD4^+$ T cells have an essential role in modulating immune-related inflammatory diseases. SCFAs were found to promote naïve $CD4^+$ T cell differentiation into Th1 cells through activation of the mTOR–S6K pathway, which was dependent on the inhibition of HDAC activity but not GPR41 and GPR43.[96,104] However, the effects of SCFAs on Th17 cells are context-dependent. Although SCFAs have been reported to induce Th17 differentiation,[96] butyrate has also been shown to inhibit T cell IL-17 expression through induction of T-bet, a key transcription factor for Th1 cells,[97] and by inhibiting the expression of the transcription factors retinoid-related orphan receptor (Ror)α and Rorγt.[104] In addition, SCFAs suppressed Th2 and Th9 differentiation.[97,105] It has been shown that an LCA derivative, 3-oxoLCA, suppressed Th17 cell differentiation by directly binding to Rorγt.[99] Indoles and indole derivatives, which are bacterial tryptophan catabolites, were found to suppress Th17 development through the AhR pathway.[102,103,106] Spermine, one type of polyamine, suppressed Th1 cytokine IFN-γ secretion by spleen cells,[107] suggesting that it might regulate T cell responses. Ascorbate, a novel microbial metabolite of bacterial vitamins, was reported to suppress T effector cells and inhibit T cell activation.[88]

IL-10 produced by effector T cells is an important self-regulatory mechanism for maintaining immune homeostasis.[108] It has been reported that SCFAs promoted IL-10 production in differentiated Th1 cells in a GPR43-dependent manner,[43] while SCFA induction of IL-10 during the differentiation of Th1 and Th17 cells was dependent on inhibiting HDAC activity.[96,104,109] IL-22, a member of the IL-10 family, is critical to host protection against intestinal inflammation. $CD4^+$ T cells are considered major sources of IL-22 during chronic intestinal inflammation. We recently identified SCFAs as important metabolites in inducing IL-22 in $CD4^+$ T cells through the GPR41 pathway and in inhibiting HDAC activity.[42]

$CD8^+$ T cells. The investigation into how gut microbiota-derived metabolites affect $CD8^+$ T cells, which are indispensable in mediating immune defenses against intracellular pathogens and tumor surveillance, is still in the early stage. It has been demonstrated that SCFAs regulate $CD8^+$ T cell functions.[110] Systemic acetate levels were increased following bacterial infection, and upregulated acetate production facilitated the rapid recall responses of memory $CD8^+$ T cells by promoting glycolysis.[110] A recent study reported that butyrate enhanced memory $CD8^+$ T cell responses, which were dependent on both GPR41 and GPR43.[111] In addition, GPR41 is critical in SCFA-mediated expansion of $CD8^+$ T cell functionality.[112] Conversely, butyrate suppressed IL-17 but promoted IFN-γ and granzyme B in $CD8^+$ T cells, which was due to the inhibition of HDAC activity but not by activating GPR41 and GPR43.[113] Collectively, SCFAs and their receptors are essential for modulating the functions of $CD8^+$ T cells.

Other T cells. There are only a few reports on how gut microbiota-derived metabolites regulate NKT cells, which can recognize a diverse repertoire of lipids presented by CD1d and participate in the regulation of immune responses. A recent study demonstrated that primary bile acids and secondary bile acids regulated hepatic NKT cell accumulation in opposing ways in liver tumors,[114] which was attributed to hepatic CXCR6 expression induced by primary bile acids but suppressed by secondary bile acids. Further investigation is needed to clarify the underlying mechanisms as well as whether bile acids affect NKT cells in other conditions.

Accumulating evidence indicates that gut microbiota-derived metabolites regulate MAIT cells, a subset of T cells restricted by MHC-related molecule 1 (MR1). MAIT cells can respond to diverse microbiota in an MR1-dependent manner.[115,116] The pyrimidine-based intermediate 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU), along with the vitamin B2 riboflavin biosynthetic pathway, are the most potent agonists for MAIT cells.[117] The vitamin B9 metabolite 6-formylpterin (6-FP) inhibits MAIT cell activation by competitively binding to MR1,[118] indicating that specific vitamin metabolites have important roles in activating MAIT cells.

IELs, which reside within the intestinal epithelium, are involved in immune protection against invading pathogens and microbiota. There is scant literature on how gut microbiota-derived metabolites regulate IELs. An elegant recent study revealed that the bacterial species *Lactobacillus reuteri* produced indole derivatives of dietary tryptophan to induce $CD4^+$ $CD8\alpha\alpha^+$ double-positive intraepithelial lymphocytes from interepithelial $CD4^+$ T cells in an AhR-dependent manner,[119] which underscores the delicate interplay between gut microbiota and the diet in the maintenance of intestinal homeostasis.

B cells

Among the microbial metabolites, SCFAs and microbial tryptophan catabolites have been shown to regulate B cell activation and antibody responses (Table 1 and Fig. 3).

B cell activation and antibody production depend on energy and metabolites from glycolysis and oxidative phosphorylation.[120,121] SCFAs directly enhanced cellular acetyl-CoA levels in B cells, leading to higher mitochondrial energy production, fatty acid synthesis, and mTOR-mediated glycolysis, which contributed to plasma cell differentiation and antibody production.[122]

Additionally, SCFAs regulated the expression of genes (i.e., *Aicda*, *Xbp1*, and *Prdm1*) associated with B cell differentiation via HDAC inhibition.[122] However, it has also been reported that SCFAs at lower doses directly impacted B cell-intrinsic functions to moderately enhance antibody production, while SCFAs at higher doses inhibited antibody production through regulation of AID and Blimp1 expression, class switching response (CSR), somatic hypermutation, and plasma cell differentiation,[123] suggesting that SCFAs at different doses differentially affect B cell responses. Intestinal IgA undergoes CSR and affinity maturation in germinal centers (GCs) with the help of T follicular helper cells and follicular DCs.[124,125] SCFAs can also regulate B cell IgA production through interactions with T cells and DCs. Dietary fiber promoted Tfh cell differentiation, which further promoted GC formation and IgA CSR.[122,126] Retinoic acid (RA), converted from a vitamin A metabolite by retinal dehydrogenase aldehyde dehydrogenase 1A2 (Aldh1A2) in DCs, maintained the development of B cells and intestinal IgA production.[127,128] SCFAs induced the expression of Aldh1A2 in DCs to promote intestinal IgA responses[126,129] and mucosal adjuvant activity of cholera toxin in a GPR43-dependent manner.[130] Given that IL-10 is a key cytokine for B cell differentiation and antibody maturation,[131,132] SCFAs also indirectly affected B cell functions through the induction of IL-10 in $CD4^+$ T cells,[43,133] DCs,[134,135] and macrophages.[134] Collectively, SCFAs regulate B cell activation and antibody production by directly acting on B cells or indirectly acting on other cell types.

There are a few reports on the role of microbiota-derived tryptophan in B cells. Considering that microbial tryptophan catabolites (i.e., indole and its derivatives) can bind to AhR, which profoundly regulates B cell development,[136] differentiation,[137] cytokine production, and regulatory activity,[138] microbial tryptophan catabolites may act on B cells through AhR signaling. Interestingly, butyrate administration increased tryptophan-metabolizing bacteria in mice, promoting IL-10-producing regulatory B cells in an AhR-dependent manner,[139] indicating the complex network between microbial metabolites and the regulation of B cell function. However, it is still unknown whether and how microbiota-derived tryptophan directly regulates B cell IL-10 production as well as antibody production.

Dendritic cells

DCs, one of the major professional antigen-presenting cells, have a critical role in the interaction between innate and adaptive immune responses. Accumulating evidence demonstrates the role of gut microbiota-derived metabolites in regulating DC functions (Table 1 and Fig. 3).

SCFAs suppressed the maturation of DCs from mouse bone marrow stem cells[140–142] and their generation from human monocytes.[143] Mechanistically, SCFAs inhibited HDAC activity in DCs via the Na^+-coupled monocarboxylate transporter Slc5a8, thereby inhibiting the transcription factors associated with the maturation of DCs, namely, PU.1 and RelB.[140] In addition, SCFAs modulated the cytokines and chemokines secreted by DCs. It has been shown that SCFAs suppressed IL-12 production,[143] whereas they upregulated IL-23 and IL-10 production in DCs.[141,143] Furthermore, SCFAs decreased DC production of chemokines, i.e., CCL3, CCL4, CCL5, CXCL9, CXCL10, and CXCL11.[144] SCFAs also indirectly regulate T cell functions through modulation of DCs. SCFAs impaired the capacity of DCs to induce $CD4^+$ and $CD8^+$ T cell proliferation,[142,143] which was likely due to upregulated IL-10 in DCs.[143] Butyrate-treated DCs promoted Treg differentiation but inhibited Th1 differentiation by inducing DC expression of the immunosuppressive enzymes indoleamine 2,3-dioxygenase 1 (IDO1) and Aldh1a2 in a Slc5a8-dependent manner.[145] In addition, lung DCs purified from propionate-treated mice were ineffective at driving Th2 cell responses.[146] All these studies indicate that SCFA-treated DCs promote Treg cell function but inhibit effector T cell responses. DCs exposed to SCFAs are also involved in regulating humoral immune responses.[129,130] Our study showed that acetate induced B cell IgA responses in the presence of DCs, which was dependent on GPR43.[129] This effect was due to acetate induction of Aldh1a2 expression in DCs.[129] We further found that the administration of SCFAs facilitated cholera toxin mucosal adjuvanticity through DCs in a GPR43-dependent manner.[130] Therefore, SCFAs not only directly affect DC function but also regulate other adaptive cell functions through modulation of DCs.

Taurochenodeoxycholic acid (TCDCA), a taurine-conjugated form of the primary bile acid CDCA, induced monocytes to differentiate towards an IL-12 hypoproducing DC phenotype through TGR5 but not the FXR pathway.[147] In addition, FXR activation inhibited DC differentiation from monocytes and suppressed DC production of TNFα.[16] Given that secondary bile acids can also activate TGR5 and FXR, it can be speculated that these bacterial metabolites may also regulate DC functions.

Polyamine also regulates DC functions. The polyamine compound deoxyspergualin (DSG) suppresses shock protein-induced activation of DCs.[148] Putrescine, a polyamine molecule, affects the phenotype of DCs and reduces the capacity of DCs to activate T cells.[149] However, the underlying mechanisms are still unclear.

Macrophages

Macrophages can ingest and kill pathogens, produce proinflammatory and anti-inflammatory cytokines, and present antigens to T cells and are thus indispensable in maintaining immune responses. Increasing studies have indicated that gut microbiota-derived metabolites regulate macrophage function (Table 1 and Fig. 3).

SCFAs suppressed proinflammatory cytokines through inhibition of HDAC activity[135] but promoted anti-inflammatory IL-10 expression in macrophages.[150] In addition, butyrate inhibited HDAC3 to reduce the activation of mTOR and glycolysis, which contributed to the enhanced antimicrobial function of macrophages,[151] indicating that SCFAs promote the anti-inflammatory function of macrophages against infection and inflammation.

Bile acids also regulate macrophage functions. DCA, a secondary bile acid, induced Kupffer cells, which are specialized macrophages located in the liver, to generate reactive oxygen species.[152] Both primary and secondary bile acids inhibited LPS induction of proinflammatory cytokines in macrophages in a TGR5-dependent manner.[71,153] BAR501, a TGR5 agonist, promoted the M1 shift to M2 macrophages.[15] Foam cells, macrophages containing low-density lipoproteins (LDL), are involved in the pathogenesis of atherogenesis. INT-777, a TGR5-specific semisynthetic bile acid, inhibited macrophage foam cell formation by reducing the uptake of LDL.[98]

In addition, TMAO has been shown to induce M1 polarization,[154] and BCAAs were able to suppress LPS-induced NO and IL-6 and reduce the damage caused by H_2O_2 in macrophages in vitro.[155] It is unclear whether they also function in the regulation of macrophages in vivo, which will be crucial in dissecting their roles in macrophages in the real world.

GUT MICROBIOTA-DERIVED METABOLITE REGULATION OF IMMUNE-RELATED INFLAMMATORY DISEASES

Many chronic inflammatory diseases are immune-related disorders caused by dysregulated immune responses to autoantigens or environmental antigens. It has been established that the gut microbiota regulates the pathogenesis of various immune-related inflammatory diseases. In this section, we will discuss the effects of gut microbiota-derived metabolites on the regulation of the pathogenesis of these immune-related chronic inflammatory diseases, including IBD, diabetes, RA, and SLE (Fig. 4).

Inflammatory bowel diseases

IBD, which mainly includes Crohn's disease and ulcerative colitis, is a group of chronic inflammatory intestine disorders. In addition to

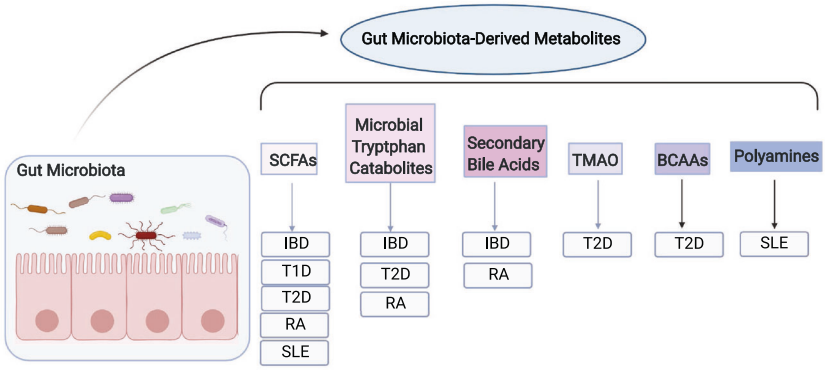

Fig. 4 Gut microbiota-derived metabolites and immune-related inflammatory diseases. Certain gut microbiota-derived metabolites regulate the pathogenesis of various immune-related chronic inflammatory diseases. *SCFAs* short-chain fatty acids, *TMAO* trimethylamine-*N*-oxide, *BCAAs* branched-chain amino acids, *IBD* inflammatory bowel diseases, *T1D* type-1 diabetes, *T2D* type-2 diabetes, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus

genetic factors, diet and intestinal microbiota have been implicated in the development of IBD. Fecal metabolomic studies demonstrated that bacterial metabolites were altered in patients with IBD, including decreased SCFAs,[156–158] secondary bile acids,[158] vitamin B,[158] TMA,[157] BCAAs,[157] and increased primary bile acids[158–160] and polyamines.[160] Furthermore, microbiota-derived metabolites, mainly SCFAs, bacterial tryptophan catabolites, and bile acids, have been found to regulate the pathogenesis of IBD.[43,100,161]

SCFAs have been reported to regulate intestinal inflammation in different experimental colitis models. Butyrate attenuated colitis severity in mice with transferred $CD4^{+}$ $CD45RB^{hi}$ T cells,[94] which is a T cell-dependent chronic colitis model. We and others further showed the beneficial effect of butyrate on T cell-induced colitis.[43,96,104] However, it is still controversial whether butyrate attenuates or worsens intestinal inflammation in dextran sulfate sodium (DSS)-induced colitis, an acute colitis model that causes epithelial injury, compromises barrier integrity, and subsequently induces inflammation. Maslowski et al.[162] and our group[43] found that administration of acetate or butyrate in drinking water attenuated DSS-induced colitis.[43,162] However, it has also been shown that butyrate did not affect colitis induced by DSS.[135] These differences might be attributed to the concentration of DSS used, the butyrate dose, the route by which butyrate was given, and the gut microbiota of the mice housed in different animal facilities. Indeed, the route of butyrate treatment has been shown to be crucial for its effect on colitis.[141] Butyrate given orally in drinking water exacerbated colitis, whereas butyrate given systemically by intraperitoneal injection decreased the severity of colitis in the DSS-induced model.[141] Interestingly, GPR43, the receptor of SCFAs, was decreased in CD patients,[163] indicating that GPR43 might be involved in the protection of IBD. In agreement with this argument, $GPR43^{-/-}$ mice and $GPR109a^{-/-}$ mice were more susceptible to colitis.[15,134] Several studies have reported that SCFA enemas demonstrated positive results in treating distal UC.[13,164,165] However, some other studies showed no significant beneficial effect of SCFA enemas on colitis severity compared with placebo in IBD patients.[166,167] Therefore, many questions on the effects and mechanisms of SCFAs on intestinal immune responses, especially in patients with IBD, require further investigation. More efforts are warranted to examine whether SCFAs only work among specific groups of IBD patients, as well as to examine the doses and route of treatment of SCFAs for IBD patients.

The association of tryptophan metabolites with IBD has been reported recently. Fecal tryptophan and a bacterial tryptophan metabolite, IAA, were decreased, while kynurenine, a host-derived tryptophan metabolite, was increased in both CD and UC patients.[168] Serum IPA, another bacterial tryptophan metabolite, was also reduced in patients with active UC.[169] Furthermore, serum tryptophan levels were associated with IBD.[161] These studies suggest that the dysregulation of tryptophan might be associated with IBD.[161] The expression of AhR, the receptor of bacterial tryptophan metabolites, in intestinal tissue was increased in patients with IBD.[170] Furthermore, reduced AhR activity was found in feces from IBD patients.[168] In experimental colitis, $AhR^{-/-}$ mice developed more severe intestinal inflammation induced by DSS[53] or *Citrobacter rodentium*,[171] whereas the administration of an AhR agonist attenuated intestinal inflammation induced by adoptive T cell transfer or chemicals.[170] Thus, the development of indole- or AhR-based therapies could be a potential approach for treating IBD.

Although the effects of primary bile acids and secondary bile acids on immune cells are not identical, a recent study showed that primary and secondary bile acid mixtures protected mice against DSS-induced colitis.[100] Bile acid receptors, including FXR, TGR5, and VDR, have been reported to regulate experimental colitis. INT-747, an FXR agonist, reduced chemical-induced colitis,[16] while $FXR^{-/-}$ mice developed more severe intestinal inflammation.[172] Furthermore, activation of TGR5 by BAR501 was protective in a trinitrobenzene sulfonic acid (TNBS)-induced model,[15] which is a T cell-mediated colitis model. Additionally, bile acids failed to protect $VDR^{-/-}$ mice from colitis development. Overall, these studies suggest that bile acids and their receptors are potentially involved in the pathogenesis of IBD, although their clinical effects remain to be defined.

Diabetes

Diabetes refers to a group of metabolic disorders with sustained high blood glucose caused by defects in insulin secretion, insulin efficiency, or both, which are mainly divided into two categories: type-1 diabetes and type-2 diabetes. In addition to the traditional major risk factors, i.e., genetics, age, sex, and lifestyle, the gut microbiota and their metabolites have been implicated in the development of diabetes.[3,173–175]

Type-1 diabetes. Type-1 diabetes is characterized by the destruction of insulin-producing pancreatic β cells, which is mediated by T cells. Studies on the relationship between gut microbiota-derived metabolites and type-1 diabetes are still in the early stage. It has been shown recently that treatment with a combined acetate- and butyrate-yielding diet protected against type-1 diabetes in nonobese diabetic mice,[176] demonstrating that the benefit of a high dietary fiber diet in type-1 diabetes might be attributed to SCFAs.

Type-2 diabetes. Type-2 diabetes is characterized by obesity and insulin resistance, which reduces the ability of cells to absorb and utilize glucose. Interestingly, the abundance of butyrate-producing bacteria was decreased in patients with type-2 diabetes.[3] Treatment with SCFAs increased insulin sensitivity in rats[177,178] and protected against diet-induced obesity and insulin resistance in mice.[179] Additionally, GPR43$^{-/-}$ mice exhibited obesity on a regular diet and reduced insulin sensitivity on a high-fat diet,[180] suggesting that SCFAs may be protective against the development of type-2 diabetes. However, whether SCFAs affect patients with type-2 diabetes remains to be investigated.

TMAO was increased in diabetic mice[181] and patients with type-2 diabetes.[182–184] Additionally, the TMAO-producing enzyme FMO3 was negatively correlated with insulin sensitivity in humans.[182] Dietary TMAO impaired glucose tolerance and increased high-fat-induced insulin resistance,[14] which could be mediated by TMAO directly binding to PERK, the endoplasmic reticulum stress kinase, which induces FoxO1 to drive metabolic diseases.[60] Interestingly, administration of 3,3′-diindolylmethane, which reduced TMAO, benefited insulin-resistant mice,[60] suggesting a potential therapeutic target for treating type-2 diabetes.

BCAAs and the bacterial tryptophan metabolite IPA have also been associated with type-2 diabetes. BCAA levels were associated with insulin resistance,[185–187] which has been considered a predictive biomarker of the development of type-2 diabetes. BCAAs aggravated obesity-associated insulin resistance,[188] and depletion of BCAAs in diets improved insulin sensitivity.[189] Furthermore, IPA was negatively associated with the incidence of diabetes.[190] Thus, BCAAs could promote whereas IPA could inhibit the pathogenesis of type-2 diabetes.

Rheumatoid arthritis

RA is an autoimmune disease that systemically affects joints and is caused by both genetic and environmental factors.[191] The link between gut microbiota, gut microbiota-derived metabolites, and RA has been established in recent decades.[139,162,192,193] A recent study demonstrated that SCFAs were positively associated with RA at the genetic, functional, and phenotypic levels.[192] Furthermore, butyrate in stool samples was decreased in RA patients.[139] Treatment with SCFAs attenuated disease severity in various RA mouse models, including collagen-induced arthritis (CIA),[193] K/BxN serum-transfer arthritis,[162] and antigen-induced arthritis.[139] Consistently, GPR43$^{-/-}$ mice developed more severe arthritis,[162] whereas an HDAC inhibitor reduced the severity of collagen-induced arthritis.[194] Overall, SCFAs and their receptors have a critical role in regulating the pathogenesis and progression of RA, and supplementation with SCFAs could benefit RA patients.

Abnormal bile metabolism has long been recognized in RA patients.[195] However, whether bile acids regulate the development of RA is still not completely understood. LCA, a secondary bile acid, exhibited anti-inflammatory effects in collagen-induced arthritis,[196] suggesting a potential role of bile acids in treating RA. The correlation between bacterial tryptophan catabolites and RA, however, remains unclear. A recent report demonstrated that indole-3-carbinol (I3C), a dietary indole derivative, reduced adjuvant-induced arthritis,[197] indicating that gut bacterial-derived indole and indole derivatives might be beneficial for RA treatment.

Systemic lupus erythematosus

SLE is an autoimmune disorder that occurs when the immune system mistakenly attacks the host's own tissues and organs. Many SLE patients have altered intestinal microbiota,[7,8] and the role of gut microbiota in the pathogenesis of SLE has also been implicated.[198,199] Furthermore, altered production of SCFAs was related to altered intestinal microbiota in patients with SLE.[200] It has been shown that both resistant starch and SCFAs suppress the development of TLR7-dependent systemic autoimmunity exacerbated by a *Lactobacillus* strain.[199] The benefit of SCFAs on murine SLE was also demonstrated.[123] However, it is still unknown whether SCFAs will benefit SLE patients, and more basic research and clinical investigations are needed to determine the potential role of SCFAs in treating SLE patients.

Given that polyamine synthesis reduced *S*-adenosylmethionine (SAM), a methyl donor, polyamines might have a role in autoimmune diseases, including SLE. Polyamine profiles in serum are different in SLE patients, with decreased levels of cadaverine and increased levels of *N1*-acetylcadaverine, spermidine, *N1*-acetylspermidine, and spermine.[201] It will be interesting to determine whether serum polyamine profiles could be biomarkers for the diagnosis of SLE in patients. Administration of difluoromethylornithine, an inhibitor of the first enzyme of polyamine synthesis, ornithine decarboxylase (ODC), reduced disease severity in a murine model of SLE.[202] Thus, targeting polyamine synthesis could be a potential therapeutic approach in treating SLE.

CONCLUDING REMARKS

The relationship between microbiota and host immune responses is complicated, and their interactions occur not only in the intestine but also elsewhere in the body. Gut microbiota-derived metabolites differentially regulate immune responses and the pathogenesis of various immune-related inflammatory diseases. Among these microbial metabolites, SCFAs and secondary bile acids in the regulation of immune cell responses have been relatively extensively investigated, but their potential clinical uses in the treatment of these immune-related chronic inflammatory diseases remain unclear. Regarding the other microbial metabolites mentioned in this review, it is necessary to investigate their effects on different immune cells and their potential roles in various immune-related chronic inflammatory diseases. As the effects of most gut microbiota-derived metabolites on immune cells are largely context-dependent, it is unknown whether they function differently under homeostatic and inflammatory conditions. Because the environments of mucosal and systemic tissues are dramatically different, it is also unclear whether they function differently at the mucosal surface and systemic tissues. Therefore, more studies are required under various conditions. As most gut microbiota-derived metabolites have not been identified and the functions of known metabolites are still not fully understood, more efforts are warranted to determine the microbial metabolite pathways that are important in human diseases. Understanding the interplay between gut microbiota-derived metabolites, the immune system, and diseases will help develop future therapeutics to treat various inflammatory diseases.

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ADDITIONAL INFORMATION

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