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Review Article

Regulation of intestinal inflammation through interaction of intestinal environmental factors and innate immune cells

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The mammalian gastrointestinal tract, the site of nutrient digestion and absorption, harbors a dense microbial community. The intestinal immune system can distinguish between symbiotic bacteria and pathogens, and activates pro-inflammatory responses against pathogenic bacteria for host defense while remaining unresponsive to the beneficial microbes and dietary antigens. Abnormal activity of innate immunity, which directs the development of adaptive immunity, causes the onset and/or progression of several inflammatory diseases. Thus, activity of innate immunity is finely regulated in the gut. Inflammatory bowel disease is a chronic inflammatory disorder caused by alteration of several factors, such as host genetics, commensal bacteria and diet-derived compounds and metabolites. In intestinal mucosa, multiple innate immune cells have been identified and some populations play a crucial role in the maintenance of gut homeostasis by preventing inadequate adaptive immune responses while others are implicated in the pathogenesis of inflammatory bowel disease by driving Th1 and Th17 responses. In addition, recent studies demonstrated that dietary components and their metabolites produced by commensal bacteria contribute to the generation of a unique intestinal environment and further regulation of a variety of immune responses. Accordingly, alterations of intestinal microbial composition and perturbation of metabolites can trigger intestinal inflammation by inducing inadequate innate/adaptive immune responses.

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Introduction

The gastrointestinal tract is composed of complex microenvironments containing intestinal microbes and dietary components, with a finely regulated immunosurveillance system. Most of the microbial community in the intestine, known as commensal microbiota, has co-evolved with the host immune system to form a symbiotic relationship. Microbiota plays a crucial role in maintaining gut homeostasis through enhancement of epithelial barrier integrity, development of host immune systems, and nutritional metabolism. Breakdown of the microbial community structures, termed dysbiosis, increases the risk of pathogen invasion, overgrowth of pathobionts, and inflammatory diseases such as inflammatory bowel disease (IBD) characterized by two main clinical forms, Crohn's disease (CD) and ulcerative colitis (UC). Accordingly, several studies have identified differences in the composition of commensal microbiota between healthy individuals and patients with IBD[1-3].

To date, several studies have reported a significantly higher concordance rate for CD (42-58%) in monozygotic twins than for UC (6-17%), indicating that genetic factors contribute significantly more to CD compared with UC[4, 5]. Genome-wide association studies recently identified 163 distinct susceptibility loci to IBD, which can be divided into several pathways such as autophagy, maintenance of epithelial integrity, immune tolerance, interleukin (IL)-23/Th17 axis, T/B cell regulation, and antigen presentation[6, 7]. Most loci had an impact on both CD and UC, while some loci were specific for either CD or UC. Among these gene products, NOD2 is well studied[8]. The NOD2 ligand, the core component of a peptidoglycan muramyl dipeptide, induces autophagy, which controls bacterial killing and antigen presentation that are associated with ATG16L1, which is also linked to CD susceptibility[9]. In addition, NOD2 signaling may mediate immune tolerance by inhibiting Toll-like receptor (TLR)-dependent NF-κB signaling[10] and inducing the production of IL-10, an anti-inflammatory cytokine[11, 12]. Interestingly, IBD patients with *NOD2* or *ATG16L1* mutations showed altered composition of intestinal microbes characterized by decreased levels of *Bacteroidetes* and *Firmicutes*[13]. This suggests that the host genetic alteration-dependent perturbation of intestinal microbiota composition mediates the pathogenesis of IBD. In addition to genetic factors, specific environmental factors might play an important role in the pathogenesis of IBD because the rate of CD and UC concordance is not 100% in monozygotic twins. Recently, several studies demonstrated that dietary compounds and dietary metabolites are essential environmental factors that influence the development and maintenance of the gut immune systems[14-16].

Gut immunity protects the host from pathogenic organisms by inducing inflammatory responses while beneficial antigens from commensal bacteria and dietary compounds are immunologically ignored, because inadequate and continuous inflammatory responses are linked to the development of intestinal inflammation. It was commonly assumed that a disruption in the balance between Th1 and Th2 responses caused intestinal inflammation. However, the use of blocking antibodies to a pro-inflammatory cytokine, interferon (IFN)-γ showed limited clinical effectiveness in both a mouse colitis model and IBD patients. In contrast, treatment with blocking antibodies to IL-12p40, which neutralizes IL-12 and IL-23, showed considerable efficiency in active CD. The discovery of a third population of helper T cells, Th17 cells, has resolved this discrepancy. Th17 cells are induced by IL-23, and express transcription factor RORγt, a master regulator that induces production of a pathogenic cytokine IL-17. Abnormal Th17 activation is implicated in the pathogenesis of CD. The number of Th1/Th17 cells was increased in the intestinal lamina propria of patients with IBD compared with healthy individuals, suggesting the Th1/Th17 pathway contributes to the development of IBD[17]. At steady state, the number and activity of effector T cells are tightly regulated by $Foxp3^+$ regulatory T (T_{reg}) cells because excessive Th1/Th17 responses can cause intestinal inflammation. The transcription factor Foxp3 is a master regulator of T_{reg} cells. Indeed, loss-of-function mutations in *FOXP3* causes IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome)[18]. Thus, $Foxp3^+$ T_{reg} cells are responsible for suppression of inflammatory responses.

In the intestine, the activity of innate immune cells such as dendritic cells (DCs) and macrophages is tightly regulated by several pathways because excessive or inadequate initiation of innate immunity results in intestinal inflammation by driving inadequate Th1/Th17 responses.

In this review, we describe the unique subsets of innate immune cells residing in the intestinal lamina propria and then focus on the crosstalk among host immune cells, commensal microbiota and dietary components that contribute to maintenance of gut homeostasis.

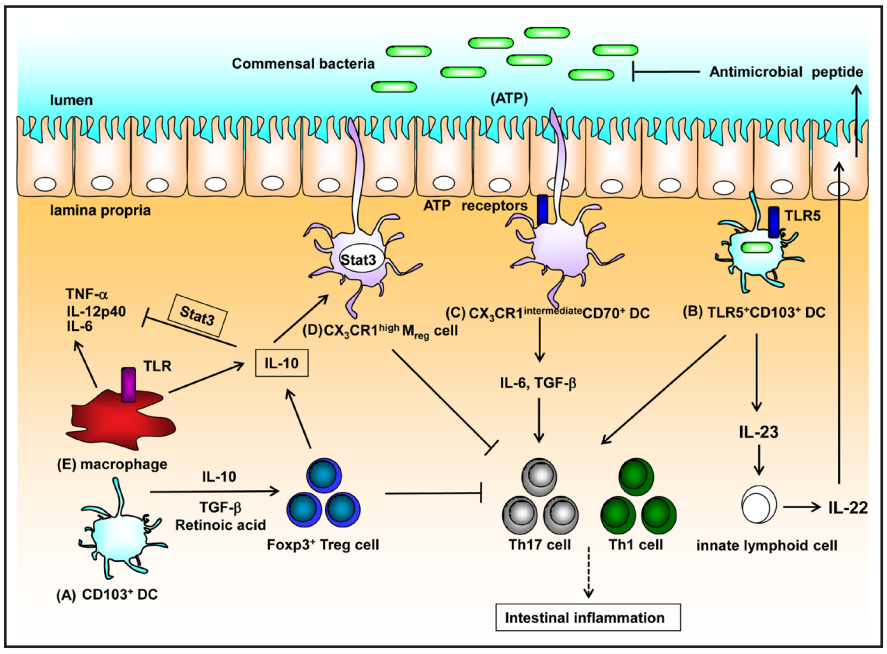

Fig. 1 Regulation of gut homeostasis by innate immune cells

(A) CD103$^+$ DCs facilitate the differentiation of Foxp3$^+$ T_{reg} cells through the production of retinoic acid and TGF-β. (B) TLR5-activated CD103$^+$CD11c$^+$ DCs polarize Th1/Th17 cells and show flagellin-dependent IL-23 production, leading to the induction of IL-22 followed by antimicrobial peptide expression in intestinal epithelial cells. (C) $CX_3CR1^{intermediate}$ CD70$^+$CD11b$^+$ DCs express a series of ATP receptors that induce Th17 cell development. (D) M_{reg} cells present in the lamina propria suppress CD4$^+$ T cell proliferation by a cell-cell contact-dependent mechanism. (E) Intestinal macrophages produce large amounts of IL-10 and inhibit the production of pro-inflammatory cytokines including IL-12 and TNF-α produced by activated intestinal myeloid cells against microbiota by an IL-10/Stat3 signal-dependent mechanism.

Innate immune cells and gut homeostasis

Several subsets of intestinal mononuclear phagocytes have been identified that maintain gut homeostasis by enhancing or suppressing T cell responses[19-22]. In particular, $CX_3CR1^+CD11b^+CD11c^+$ cells and CD103$^+$ DCs have been well characterized in the murine intestinal lamina propria[23-25](Fig. 1). Both CD103$^+$ DCs and CX_3CR1^+ cells are heterogeneous populations. In addition, the human counterparts to murine intestinal macrophages, CD103$^+$ DCs and $CX_3CR1^{intermediate}$CD70$^+$ DCs, were recently identified.

1)Murine intestinal innate immune cells

(i) CD103$^+$ DCs

Intestinal CD103$^+$ DCs possess a variety of functions including induction of gut immune tolerance by facilitating the differentiation of Foxp3$^+$ T_{reg} cells through the production of retinoic acid and TGF-β[21, 26, 27](Fig. 1A). Toll-like receptor (TLR)5-activated CD103$^+$CD11c$^+$ DCs induce Th1/Th17 cells[28](Fig. 1B). Moreover, CD103$^+$ DCs show flagellin-dependent IL-23 production, leading to the induction of IL-22 by innate lymphoid cells followed by antimicrobial peptide expression in intestinal epithelial cells[29](Fig. 1B). Furthermore, CD103$^+$ DCs stimulate CD4$^+$ and CD8$^+$ T cell proliferation[30, 31] and strongly induce cytotoxic T lymphocytes[30]. Thus, CD103$^+$ DCs mediate multiple responses by inducing intestinal immune tolerance to intestinal antigens while promoting protective immune responses through the induction of effector T cell activation and antimicrobial defense.

(ii) $CX_3CR1^{intermediate}$CD70$^+$CD11b$^+$ DCs

CX_3CR1^+ mononuclear cells have been identified as a major population in the intestinal lamina propria using CX_3CR1-GFP transgenic mice[32]. To date, several subsets of CX_3CR1^+ cell have been characterized in the colonic lamina propria, such as $CD11c^-CX_3CR1^+$, $CD11c^+CX_3CR1^+CD68^+F4/80^+$, and $CD11c^+CX_3CR1^+CD68^-F4/80^-$ cells[25]. Furthermore, CX_3CR1^+ cells can drive Th17 development[33, 34]. In particular, $CX_3CR1^{intermediate}$CD70$^+$CD11b$^+$ DCs express a series of ATP receptors that induce Th17 cell development[33](Fig. 1C).

CX_3CR1^+ intestinal innate immune cells do not always induce pro-inflammatory responses. IL-10 produced by CX_3CR1^+ macrophage in a CX_3CL1-dependent manner expands Foxp3$^+$ T_{reg} cells[35]. Furthermore, CX_3CR1^+ macrophages can capture soluble dietary antigens and transfer them to CD103$^+$ DCs via a Connexin-43-dependent mechanism, leading to the development of Foxp3$^+$ T_{reg} cells and oral tolerance[36]. In addition, CX_3CR1^+ macrophages limit Th17 cell-dependent intestinal inflammation by controlling bacterial clearance[37]. Antigen cross-presentation by CX_3CR1^+ cells in the small intestinal lamina propria is responsible for the differentiation of IL-10, IL-13, and IL-9-expressing CD8$^+$

T cells that suppress antigen-specific activation of $CD4^+$ T cells, leading to inhibition of intestinal inflammation[38].

(iii) CX_3CR1^{high} regulatory myeloid cells

The $CX_3CR1^{high}CD11b^+CD11c^+$ subset, named regulatory myeloid (M_{reg}) cells, possesses a negative regulatory function[39](Fig. 1D). M_{reg} cells present in the lamina propria suppress $CD4^+$ T cell proliferation by a cell-cell contact-dependent mechanism, and contribute to the prevention of intestinal inflammation. M_{reg} cells preferentially associate with $CD4^+$ T cells via highly expressed adhesion molecules such as ICAM-1 and VCAM-1, but do not activate $CD4^+$ T cells owing to the IL-10/Stat3-dependent suppression of CD80/CD86 expression. Mice with Stat3 mutations specifically in myeloid cells (*LysM-cre*; *Stat3flox/flox*) spontaneously develop colitis and show defective M_{reg} cell function. Administration of wild-type M_{reg} cells to Stat3 mutant mice ameliorated intestinal inflammation, indicating that the dysfunction of M_{reg} cells is involved in the pathogenesis of intestinal inflammation.

(iv) Macrophages

Intestinal $CD11b^+CD11c^-$ macrophages produce large amounts of IL-10 in response to microbiota[40-42]. Intestinal macrophage-derived IL-10 inhibits the production of pro-inflammatory cytokines including IL-12 and tumor necrosis factor (TNF)-α produced by activated intestinal myeloid cells against microbiota by an IL-10/Stat3 signal-dependent mechanism (Fig. 1E). In addition, IL-10 produced by intestinal macrophages prevents intestinal inflammation by maintaining the persistence of Foxp3 expression in T_{reg} cells[43]. Accordingly, IL-10-deficient mice and *LysM-cre*; $Stat3^{flox/flox}$ mice spontaneously develop enteric inflammation accompanied by enhanced effector T cell activity[40, 44].

2)Human intestinal innate immune cells

(i) $CD103^+$ DCs

Human $CD103^+$ DCs induce gut homing receptors such as CCR9 and integrin α4β7 on T cells, which function is similar to that of murine $CD103^+$ DCs[31]. In addition, transcription factor IRF4-expressing $CD103^+CD141^-SIRPα^{high}$ DCs have been identified in the human small intestine[45], which are equivalent to murine $CD103^+CD11b^+$ DCs that enhance effector T cell differentiation.

(ii) $CD14^+CD163^{low}$ cells

$HLA\text{-}DR^{high}CD14^+CD163^{low}$ cells were recently characterized. In the human intestinal mucosa, $HLA\text{-}DR^{high}Lin^-$ cells are divided into $CD14^+CD163^{low}$, $CD14^+CD163^{high}$, $CD14^-CD11c^{low}$, and $CD14^-CD11c^{high}$ subsets. $CD14^+CD163^{low}$ cells induce Th17 differentiation by high expression of IL-6, IL-23p19, TNF-α and IL-1β via TLR2, TLR4, and TLR5 signal pathways, even in the steady state. In addition, $CD14^+CD163^{low}$ cells express both macrophage- and DC-217 related markers as for murine $CX_3CR1^{intermediate}CD70^+CD11b^+$ DCs, suggesting $CD14^+CD163^{low}$ cells are the putative equivalents of $CX_3CR1^{intermediat}CD70^+CD11b^+$ cells inducing Th17 cells. Furthermore, Th17 cell-inducing activity of $CD14^+CD163^{low}$ cells is increased in the intestinal mucosa of patients with CD, suggesting that $CD14^+CD163^{low}$ cells might play a crucial role in the pathogenesis of CD.

(iii) Macrophages

Murine studies indicate that intestinal macrophages are involved in protecting the host from invading pathogens as well as regulating excessive immune responses to commensal bacteria by producing IL-10. Interestingly, numbers of $CD14^+$ macrophages are increased in patients with CD and produce greater amounts of colitogenic cytokines including IL-6, IL-23 and TNF-α against microbiota compared with healthy individuals[46]. Furthermore, human intestinal $CD14^+$ macrophage-derived IL-23 may enhance colitogenic IL-17 and IFN-γ-producing T cell differentiation, suggesting that abnormal innate immune responses by macrophages play a major role in the pathogenesis of IBD[46-49].

Commensal bacteria and gut homeostasis

The mammalian gastrointestinal tract is exposed to numerous members of the microbial community. Recent findings have shown that intestinal microbiota influence both nutrient metabolism and the development of host immunity[50-52](Fig. 2). In turn, host immune responses induced by commensal bacteria are responsible for the maintenance of a healthy microbial community. Alterations in the composition of commensal microbiota are linked to metabolic and inflammatory disorders such as IBD, obesity, type 2 diabetes mellitus, and allergy[53-56].

Pattern recognition receptors (PRRs) such as TLRs and NOD-like receptors (NLRs) sense microbial components, termed pathogen-associated molecular patterns, during infection and activate inflammatory responses that eliminate of pathogenic microorganisms. Although PRR ligands are also produced by microbial symbionts even in the steady state, microbiota-derived PRR ligands usually do not drive inflammatory responses but rather contribute to diverse aspects of immune system development and promote

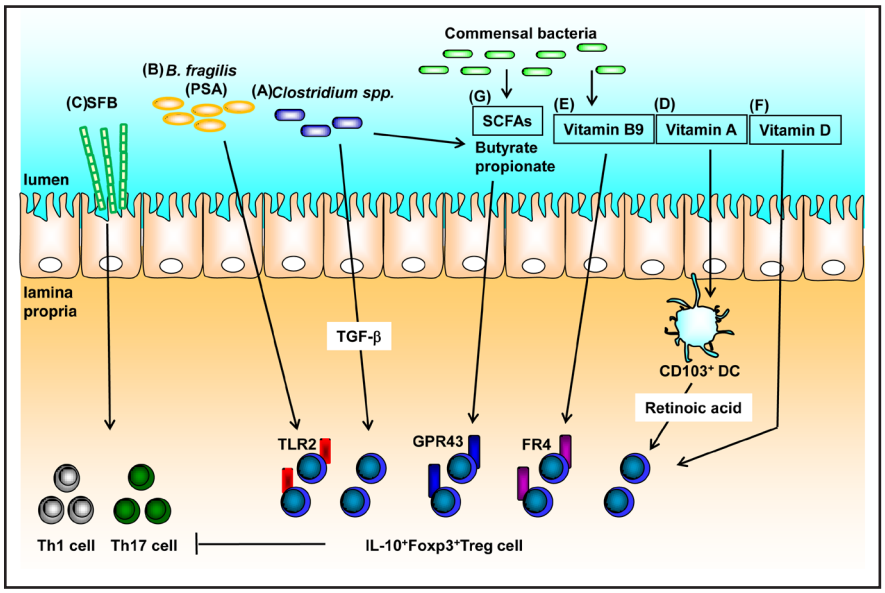

Fig. 2 The development of gut immunity by microbiota and dietary components

(A) *Clostridium* species induces the development of Foxp3$^+$ T_{reg} cells in the colon. (B) *B. fragilis*-derived PSA binds to TLR2 on CD4$^+$ T cells is involved in the induction of IL-10-producing Foxp3$^+$ T_{reg} cells. (C) SFB mediates Th17 development in the small intestine. (D) Vitamin A is metabolized into retinoic acid by intestinal CD103$^+$ DCs and retinoic acid mediates the induction of Foxp3$^+$ T_{reg} cells. (E) Vitamin B9 promotes survival of gut Foxp3$^+$ T_{reg} cells via folate receptor 4 (FR4). (F) 1,25-dihydroxyvitamin D (1,25(OH)$_2$D3), an active form of vitamin D, promotes development of Foxp3$^+$ T_{reg} cells. (G) SCFAs, specifically butyrate and propionate acting through GPR43, influence the accumulation of Foxp3$^+$ T_{reg} cells and promotion of their suppressive activity.

immune functions. For instance, a lack of microbiota in a mouse model of intestinal injury results in more severe disease, and administration of TLR ligands such as lipopolysaccharide and lipoteichoic acid ameliorates the intestinal injury. This suggests that interactions between commensal bacteria and TLRs are essential for protection against gut injury and maintenance of gut epithelial cell homeostasis[57]. Moreover, the lack of specific PRRs such as TLR2, TLR4, TLR5, and TLR9 can result in an altered composition of intestinal microbiota and disturbed epithelial barrier functions leading to translocation of commensals to systemic organs[58-60]. In addition to TLRs, NLRs influence the maturation and regeneration of intestinal epithelial cells by inducing IL-18 and IL-1β via activation of the inflammasome. For instance, NLRP6 deficiency results in decreased secretion of IL-18 and increased susceptibility to dextran sodium sulfate (DSS)-induced colitis, which is associated with altered colonic microbiota characterized by enrichment of Prevotella and TM7 species[61]. In addition, disease susceptibility in NLRP6-deficient mice can be transferred to wild-type mice through colitogenic microbiota.

Recently, specific members of the commensal microbiota have been shown to generate anti-inflammatory Foxp3$^+$ T_{reg} cells or inflammatory Th17 cells in the intestine. For instance, *Clostridium* species belonging to cluster XIVa and IV induce the development of Foxp3$^+$ T_{reg} cells in the colon[62](Fig. 2A). In addition, *Bacteroides fragilis* protected mice from experimental colitis via the induction of IL-10-producing T_{reg} cells[63] (Fig. 2B). The beneficial effect of *B. fragilis* depends upon the expression of polysaccharide A that binds to TLR2 on CD4$^+$ T cells[64]. Meanwhile, segmented filamentous bacteria (SFB)[65] mediate Th17 cell induction in the small intestine (Fig. 2C). Mice colonized with SFB were resistant to infection with *Citrobacter rodentium*, indicating Th17 cell initiation by SFB is responsible for protective immune responses[65]. SFB was previously shown to induce IgA production in the small intestine[66]. Moreover, SFB induces Th1 and Treg cells in Peyer's patches[67], indicating SFB might coordinate an intestinal adaptive immune system by multiple mechanisms. In addition to its protective role during infection, SFB monocolonization of K/BxN mice triggered autoimmune arthritis through Th17 cell accumulation[68], and enhanced experimental autoimmune encephalomyelitis (EAE) via the induction of Th17 cells and autoantibody-producing B cells in the central nervous system[69, 70]. Thus, Th17 cell differentiation by SFB colonization is connected to the development of autoimmune diseases while contributing to mucosal protection against pathogens.

Recent advances in our understanding of probiotics, live microorganisms that confer a health benefit, strongly suggest that these microorganisms can modulate gut homeostasis. Probiotics mainly consist of lactic acid bacteria such as *Lactobacillus* and *Bifidobacterium* species, which upon administration in proper amounts have proven beneficial in a variety of immunopathologies

including intestinal inflammation, atopic disease, and EAE in humans and mice[71-83]. It has been shown that probiotics elicit immunomodulatory effects through their actions on ep ithelial cells[84, 85] and microbiota[78] to maintain and improve host health. Furthermore, several probiotic effector molecules associated with the host immune system have been identified, including peptidoglycan, capsular saccharide, lipoprotein, and teichoic acid, which are bacterial cell wall components[86, 87]. In the context of intestinal inflammation, administration of probiotics inhibited the progression of inflammation via IL-10-producing or TGF-β-bearing regulatory T cells[88, 89]. *Bifidobacterium breve* was recently shown to induce IL-10-producing regulatory T (Tr1) cells in the colon via the TLR2-dependent activation of intestinal $CD103^+$ DCs, which contributed to the prevention of intestinal inflammation[90]. Probiotic mixture VSL#3 was reported to mediate the production of IL-10 by DCs, and inhibit the accumulation of Th1 cells through the suppression of IL-12 secretion and expression of co-stimulatory molecule CD80 by DCs[91]. Furthermore, administration of VSL#3 to mice during remission ameliorated the severity of Th1-mediated intestinal inflammation by inducing TGF-β-bearing T_{reg} cells[89]. Therefore, probiotic administration in IBD patients might become an effective therapeutic approach during clinical remission.

Nutritional components and gut homeostasis

Gut microbiota contribute to digestion associated with vitamin synthesis, generation of lipid mediators, and production of short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate, and lipid absorption. Accumulating evidences demonstrated that nutritional metabolites are influenced by microbial community structures and that dietary components contribute to shape microbiota architecture[54, 92]. Nutrients and their metabolites derived from commensal bacteria regulate the development of host immunity.

High dietary fiber consumption is linked to a low death rate from cancer, cardiovascular disease and respiratory diseases, while consuming a high-fat and low fruit and vegetable diet correlates with a high frequency of asthma[92-94]. In addition, high consumption of saturated fat changes the constitution of the intestinal microbial community by promoting alterations in bile acid composition. This was shown to increase the onset and incidence of colitis by excessive Th1 responses in IL-10-deficient mice, but not wild-type mice[95]. Collectively, abnormal connections among commensal bacteria, metabolites, and host immune cells are linked to increased morbidity of chronic inflammatory disorders such as IBD in genetically susceptible hosts.

1)G protein-coupled receptors

Many G protein-coupled receptors (GPCRs), which bind both dietary and bacterial metabolites, have been identified. The best-characterized GPCRs contributing to the maintenance of gut homeostasis are GPR43, a receptor for formate, acetate, propionate, and butyrate, and GPR109A, a receptor for butyrate and nicotinic acid. In a model of colitis, *Gpr43*-deficient mice developed exacerbated or unresolving inflammation, indicating that GPR43 binding to SCFAs is responsible for the induction of anti-inflammatory responses[96]. A lack of GPR109A caused decreased numbers of T_{reg} cells owing to the diminished anti-inflammatory properties of colonic macrophages and DCs. In addition, GPR109A mediates butyrate-dependent IL-18 production by colonic epithelial cells[97] and binds tryptophan metabolites such as nicotinic acid, which suppress inflammatory cytokine production by immune cells, endothelial cells and adipocytes[98, 99, 100].

2)Vitamins

Vitamins are divided into hydrophilic (vitamin B family and vitamin C) and hydrophobic (vitamin A, D, E, and K) groups. All vitamins are supplied by diet or commensal bacteria because host organisms cannot synthesize them in sufficient amounts.

Vitamin A is metabolized in tissue into retinol or retinoic acid (RA) by retinaldehyde dehydrogenase (RALDH). RA induces the expression of gut-homing captors such as α4β7 and chemokine receptor CCR9 on T and B cells[101, 102]. In addition, RA produced by $CD103^+$ DCs that highly express RALDH mediate the induction of $Foxp3^+$ T_{reg} cells by inhibiting development of Th17 cells[27, 103](Fig. 2D).

Vitamin B9, also called folic acid, is derived from both diet and commensal bacteria. Deficiency of folic acid in the diet resulted in a marked reduction of gut $Foxp3^+$ T_{reg} cells expressing high levels of folate receptor 4[104, 105](Fig. 2E). The impaired survival of gut $Foxp3^+$ T_{reg} cells was associated with decreased expression of anti-apoptotic molecules such as Bcl-2 and Bcl-xL. Mice fed a folic acid-deficient diet exhibited higher susceptibility to intestinal inflammation, indicating that folic acid plays a crucial role in maintaining immunological homeostasis by promoting

survival of gut Foxp3$^+$ T_{reg} cells.

1,25-dihydroxyvitamin D (1,25(OH)$_2$D3), an active form of vitamin D, promotes development of Foxp3$^+$ Treg cells by inducing the binding of vitamin D receptor (VDR)-pregnane X receptor (PXR) complex to an enhancer in the *FOXP3* gene[106] but inhibits differentiation of Th1/Th17 cells (Fig. 2F). In addition, 1,25(OH)$_2$D3 indirectly suppresses Th1/Th17 responses by inhibiting DC maturation and production of pro-inflammatory cytokines including IL-12, IL-6, and IL-23[107, 108]. In humans, 1,25(OH)$_2$D3 activates human macrophage antimicrobial responses to infection[109]. Deficiency of vitamin D results in diminished numbers of CD8αα$^+$ intraepithelial lymphocytes owing to reduced proliferative capacity. Collectively, various vitamins and their metabolites regulate innate and adaptive immune responses, thereby mediating the maintenance of intestinal immune homeostasis.

3)Dietary lipids

Fatty acids generated by the digestion of dietary lipids mediate the regulation of intestinal immune responses. Lack of lipid mediator signaling pathways is associated with an imbalance in immune responses, leading to the development of inflammation, allergy, cancer, and metabolic syndrome[110-112]. Saturated fatty acids are thought to promote inflammatory responses whereas unsaturated fatty acids mediate both pro- and anti-inflammatory responses[113, 114].

ω-3 fatty acids, polyunsaturated fatty acids, are gut microbiota-independent metabolites and precursors of prostaglandins. ω-3 fatty acids exert an anti-inflammatory effect by inhibiting the expression of IL-1β, IL-6, and TNF-α in CD11c$^+$ macrophages via GPR120[115, 116].

Bile acids synthesized by commensal bacteria have been reported to maintain gut homeostasis through regulation of the host immune system. In macrophages and monocytes, bile acid signaling affects the induction of anti-inflammatory responses by inhibiting NF-κB activity and NF-κB-dependent transcription of *Il6*, *Tnf*, *Il1b*, and *Ifng* genes via the G protein-coupled bile acid receptor (GPBAR1) and nuclear receptors subfamily 1, group H, member4 (NR1H4, also known as FXR)[117-119]. Some patients with IBD show intestinal dysbiosis, which is associated with a decreased concentration of bile acid in the feces and periphery compared with healthy individuals[120]. This indicates that altered bile acid production by the commensal bacteria-host immune system axis might contribute to the development of IBD.

Another lipid mediator, sphingosine 1-phosphate (S1P), a metabolite obtained from diet, is essential for immune cell trafficking. S1P concentration is high in the blood and lymph because S1P receptor-expressing cells sense the S1P gradient and migrate towards high levels of S1P. In Peyer's patches, IgM$^+$ naive B cells highly express the type 1 S1P receptor ($S1P_1$). However, $S1P_1$ expression is downregulated during IgA class switching because decreased expression of $S1P_1$ allows newly generated IgA$^+$ B cells to reside in Peyer's patches during their differentiation into IgA$^+$ plasma cells[121]. In addition, S1P mediates the trafficking of peritoneal B cells and intraepithelial T lymphocytes into the intestine[122, 123]. In an ovalbumin-induced food allergy model, trafficking of pathogenic T cells, that produce high amounts of Th2 cytokines such as IL-4 and IL-5, into the colon and infiltration/proliferation of mast cells are dependent on S1P[124]. Regarding IgA responses, a recent study showed that dietary palmitic acid and its metabolites facilitate intestinal IgA production by plasma cells and increase the number of IgA-producing plasma cells in the colon by a serine palmitoyltransferase-dependent mechanism[125].

4)Short-chain fatty acids

The major metabolites produced by commensal bacteria-dependent fermentation of dietary fiber in the colon are SCFAs. The most abundant SCFA are butyrate, acetate, and propionate. To date, decreased dietary fiber is thought to be linked to poor intestinal homeostasis, leading to the development of allergies, asthma, and autoimmune disorders[16, 126]. Interestingly, these metabolites are distributed both in the gut and blood, bone marrow, and fetal environment[16]. Propionate has been reported to affect hematopoiesis, the generation of DC/macrophage precursors in bone marrow in a GPR41-dependent manner and the development of lung DCs that cannot drive Th2 responses, leading to protection against allergic inflammation in the lung[127].

SCFAs produced by commensal bacteria maintain gut homeostasis by several mechanisms. High-fiber intake facilitates the expansion of commensal bacteria, preventing the access of pathogenic microorganisms to the gut epithelium. In addition to commensal bacteria, the mucus layer contributes to the promotion of immune tolerance by separating luminal bacteria and dietary antigens from epithelial cells and by delivering anti-inflammatory signals to DCs[128]. SCFAs also stimulate mucus production from

epithelial cells[129]. Furthermore, *Bacteroides thetaiotaomicron*, which produces acetate, facilitates goblet cell development and mucus secretion. Disrupted epithelial integrity permits the translocation of microorganisms and food antigens from the lumen to lamina propria causing inadequate immune responses. A recent study revealed that production of acetate by *Bifidobacterium longum* inhibited the translocation of *Escherichi coli* O157:H7 Shiga toxin by promoting intestinal epithelial integrity[130]. In addition, acetate facilitated the development of Th1 and Th17 cells during infection through direct inhibition of HDACs activity that regulates the mTOR pathway[131].

Recently, SCFAs were shown to play a critical role in promoting the generation and function of T_{reg} cells. SCFAs, especially butyrate and propionate acting through GPR43, affect the accumulation of $Foxp3^+$ T_{reg} cells and promotion of their suppressive activity through inhibition of HDAC activity[132, 133](Fig. 2G). In addition, butyrate produced by commensal bacteria such as Clostridia during starch fermentation, augments the generation of $Foxp3^+$ T_{reg} cells by enhancing H3 acetylation in the promoter and non-coding regions of the Foxp3 locus[132, 134]. Butyrate also downregulates the production of pro-inflammatory cytokines including IL-6, IL-12, TNF-α and nitric oxide from monocytes and macrophages through HDAC inhibition[135, 136]. Anti-inflammatory properties of HDAC inhibitors were shown to have potential therapeutic benefit for inflammatory diseases including IBD and autoimmune disorders. In addition, trichostatin-A, a broad HDAC inhibitor, promoted T_{reg} cell development and suppressive activity, indicating that HDAC inhibition potentiates anti-inflammatory reposes and immunological tolerance.

5)Amino acid

Tryptophan is an essential amino acid that mammals obtain from diet and intestinal microbiota-dependent tryptophan biosynthesis. Angiotensin I converting enzyme 2 (ACE2), an amino acid transporter, might regulate intestinal uptake of dietary tryptophan because serum levels of tryptophan are markedly reduced in ACE2-deficient mice[137]. Tryptophan absorbed by ACE2 activates mTOR pathways and subsequently induces production of antimicrobial peptides in gut epithelial cells. Lack of ACE2 in mice worsens DSS-induced colitis with dysbiosis, while administration of tryptophan and nicotinamide improves DSS-induced colitis in ACE2-deficient mice. This suggests that ACE2-dependent uptake of tryptophan in gut epithelial cells is critical for maintaining gut homeostasis through the regulation of antimicrobial peptide production and ecology of gut microbiota.

Tryptophan metabolites, such as kynurenin and 3-hydroxyanthranillic acid synthesized by indoleamine 2, 3-dioxygenase, are essential for DC-dependent generation of $Foxp3^+$ T_{reg} cells[138-140]. Another tryptophan metabolite, indole-3-aldehyde produced by lactobacilli, functions as an aryl hydrocarbon receptor (AhR) ligand and induces IL-22 production by group 3 innate lymphoid cells[141]. AhR-dependent IL-22 secretion contributes to balanced mucosal immune responses, and maintenance of the gut microbiota community that protects hosts against pathogens.

Conclusion

Recent advances have provided substantial insights into gut immune homeostasis associated with microbiota and dietary components; however, the mechanistic basis of IBD remains poorly understood. At the steady state, innate immunity plays a critical role in mediating gut homeostasis while dysbiosis influenced by alterations in dietary consumption can be a direct cause of chronic inflammation. In addition, correct Th1 and Th17 responses contribute to protection against pathogens during physiological conditions, whereas excessive activation of effector cells is responsible for intestinal inflammation. Thus, further studies to characterize the innate/adaptive immune systems implicated in gut homeostasis and intestinal inflammation may promote advances in diagnostic and therapeutic approaches for IBD.

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Conflict of interests

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