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Review Article

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Microbial Components and Effector Molecules in T Helper Cell Differentiation and Function

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ABSTRACT

The mammalian intestines harbor trillions of commensal microorganisms composed of thousands of species that are collectively called gut microbiota. Among the microbiota, bacteria are the predominant microorganism, with viruses, protozoa, and fungi (mycobiota) making up a relatively smaller population. The microbial communities play fundamental roles in the maturation and orchestration of the immune landscape in health and disease. Primarily, the gut microbiota modulates the immune system to maintain homeostasis and plays a crucial role in regulating the pathogenesis and pathophysiology of inflammatory, neuronal, and metabolic disorders. The microbiota modulates the host immune system through direct interactions with immune cells or indirect mechanisms such as producing short-chain acids and diverse metabolites. Numerous researchers have put extensive efforts into investigating the role of microbes in immune regulation, discovering novel immunomodulatory microbial species, identifying key effector molecules, and demonstrating how microbes and their key effector molecules mechanistically impact the host immune system. Consequently, recent studies suggest that several microbial species and their immunomodulatory molecules have therapeutic applicability in preclinical settings of multiple disorders. Nonetheless, it is still unclear why and how a handful of microorganisms and their key molecules affect the host immunity in diverse diseases. This review mainly discusses the role of microbes and their metabolites in T helper cell differentiation, immunomodulatory function, and their modes of action.

Keywords: Microbiota; Microbial component; Host microbial interactions; Mucosal immunity; Adaptive immunity

INTRODUCTION

The human body consists of trillions of microorganisms with complex communities that interact with the host to provide beneficial effects in a wide range of host physiologies, including digestion, behavior, as well as immune maturation in healthy and diseased conditions (1-3). Commensal microorganisms are predominantly composed of bacteria with relatively smaller numbers of other organisms, such as fungi, viruses, and protozoa (2). Previous studies have defined the general role of bacteria in modulating immune responses, but the effects of different species are relatively less understood (1,2). Since commensal

commercial or financial relationships that could be construed as a potential conflict of interest.

Abbreviations

3-oxoLCA, 3-oxolithocholic acid; AhR, aryl hydrocarbon receptor; ALDH, aldehyde dehydrogenase; BA, bile acid; Bcl6, B cell lymphoma 6; CFTR, cystic fibrosis transmembrane conductance regulator; CSGG, cell surface β-glucan/galactan; DC, dendritic cell; FR4, folate receptor 4; Gadd45, growth arrest and DNA-damage-inducible 45α; GC, germinal center; GPCR, G protein-coupled receptor; HBV, hepatitis B virus; HDAC, histone deacetylase; IBD, inflammatory bowel disease; ICOS, inducible costimulatory; IDO, indoleamine-2,3-dioxygenases; IEC, intestinal epithelial cell; LBP, live biotherapeutic products; MGCP, mannan/β-1,6-glucan-containing polysaccharides; nTreg, natural Treg; OMV, outer membrane vesicle; PP, Peyer's patch; PRR, pattern recognition receptor; PSA, polysaccharide A; pTreg, peripheral Treg; RA, retinoic acid; SCFA, short-chain fatty acid; SFB, segmented filamentous bacteria; SIV, simian immunodeficiency virus; Tfh, T follicular helper; Tfr, T follicular regulatory; TNBS, 2,4,6-trinitrobenzenesulfonic acid solution; VDR, vitamin D receptor.

Author Contributions

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microorganisms play crucial roles in modulating the host immune system, targeting gut microorganisms has been considered as a potential therapeutic strategy against diverse clinically relevant disorders, including autoimmune diseases, cancers, and metabolic and neuronal disorders.

The composition and diversity of commensal microbes will most significantly affect the host's gut immunity. The intestines harbor the most significant number of immune cells in our body and retain a unique immune landscape with a tolerogenic microenvironment under homeostatic conditions. However, dysbiosis caused by antibiotic treatment, the intake of junk foods, or other environmental factors induces detrimental pro-inflammatory immune responses, mediating various immune disorders. The immune system is comprised of innate and adaptive immunity with complex networks. Innate myeloid lineage cells recognize microbes or microbial molecules in the lumen and mediate the induction and activation of adaptive immunity by causing the differentiation of CD4 T cells. In this process, microbes and microbe-derived molecules may confer the differentiation of CD4 T cells into particular subsets, exert significant effects on maintaining homeostasis, and regulate deleterious inflammatory responses in health and disease (4). Since CD4 T cells play key roles in orchestrating adaptive immune responses and maintaining homeostasis in health and disease (**Fig. 1**) (5), in this review, we primarily focus on the interaction of the microbiota and CD4 T cell-mediated immunity.

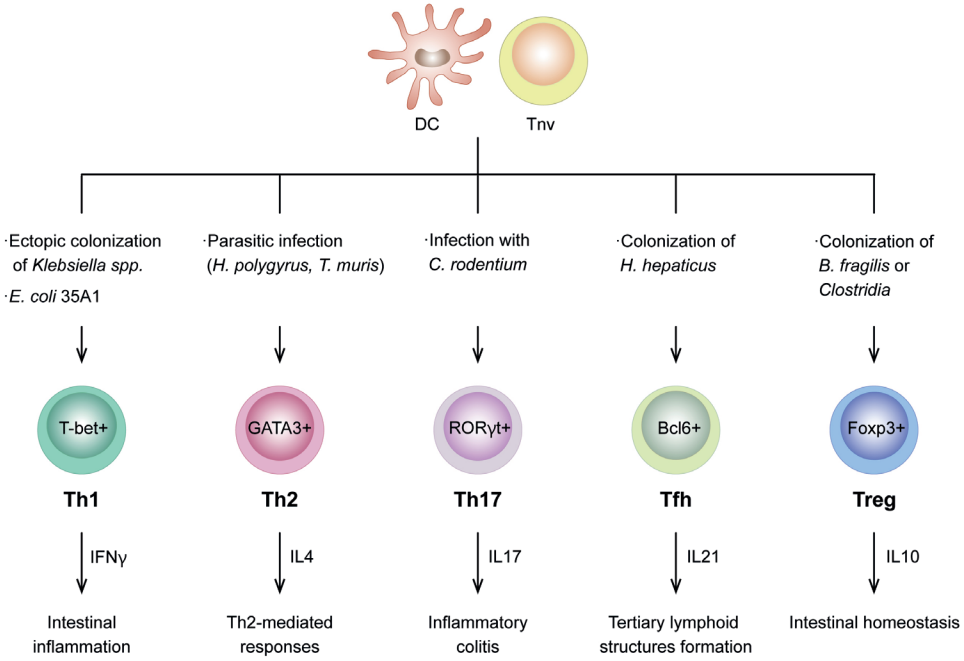

Figure 1. The differentiation and function of CD4 T cell subsets in intestinal health and disease.
Naïve CD4 T cells are activated and differentiate into distinct CD4 T cell subsets after interacting with Ag-loaded DCs. Various factors, such as types of Ags, TCR strengths, and cytokine combinations, are involved in developing CD4 T cell lineages. Therefore, the invasion of the pathogen can change the surrounding environment and induce specific subsets of CD4 T cells. For instance, intestinal colonization of Klebsiella species enhances the accumulation of Th1 cells and results in inflammation. *E. coli* 35A1 strain also can promote the generation of Th1 cells. Parasitic infections caused by *H. polygvrus* or *T. muris* drive the Th2 cell differentiation and boost Th2-mediated immune responses. Infection with *C.rodentium* induces the development of Th17 cells and then causes inflammatory colitis. Colonization of *H. hepaticus* facilitates bacteria-specific Tfh cell generation and leads to the formation of tertiary lymphoid structures, consequently inhibiting colorectal cancer. Unlike other effector CD4 T cells, Tregs have an immunoregulatory role. Thus, the differentiation of Tregs induced by *B. fragilis* or *Clostridia* suppresses inflammation and maintains mucosal homeostasis.

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CD4 T CELL DIFFERENTIATION

Previous studies have identified several microbial species and microbial molecules that can orchestrate the overall landscape of the immune system by driving particular CD4 T cell responses and inducing immunological homeostasis (6). Naïve CD4 T cells differentiate into five different subsets according to the different cytokine combinations required for the differentiation of each T cell subset, and each subsets have the unique cellular and functional features (7). Th1 cells express *T-bet* and *CXCR3* as their lineage-specifying signatures and produce IFN-γ to target infections caused by intracellular pathogens. Th2 cells can be identified by the expression of *GATA3* as a key regulator and are marked by CCR4 and CRTH2 on their surfaces. Th2 cells control helminth infections by inducing humoral immunity through IL-4, IL-5, and IL-13 production. In addition to Th1 and Th2 cells, transcription factors *RORγt* and *RORα* potentiate Th17 cell differentiation and lead to the upregulation of the CCR6 receptor on the cell surface. Th17 cells are implicated in wound healing and host defense mechanisms against the invasion of extracellular pathogens, especially fungal invasion.

Recent studies have demonstrated that T follicular helper (Tfh) cells are a distinct subset of CD4 T cells that play a critical helper role in mediating humoral immunity. Unlike other CD4 T cell subsets, the differentiation of Tfh cells undergo a multifaceted process in secondary lymphoid organs (8). At the initial stage of Tfh cell differentiation, naïve CD4 T cells are primed by Ag-loaded dendritic cells (DCs) and are concurrently regulated by co-receptor signaling and cytokines such as the inducible costimulatory (ICOS), IL-6, and IL-21 in the T cell zone. Activated naïve CD4 T cells start to express B cell lymphoma 6 (*Bcl6*) and the chemokine receptor *CXCR5*. *Bcl6*, a master transcription factor of Tfh cell, acts as a repressor that suppresses other CD4 T cell subsets lineage commitments. In the early stage of differentiation, Tfh cells migrate into the B cell zone in response to CXCR5 signaling by CXCL13. $Bcl6^{+}$ $CXCR5^{+}$ mature Tfh cells interact with B cells and promote further maturation of B cells to generate high-affinity Ag-specific Abs in the germinal center (GC).

Compared to effector T cells, Tregs are indispensable for maintaining immune equilibrium in the healthy state, especially within the intestinal microenvironments, and in regulating the onset and development of inflammatory or autoimmune disorders (9). Tregs are defined by the high expression of the master transcription factor *Foxp3* and have a high-affinity subunit of the IL-2 receptor CD25. Over the recent decades, numerous studies have identified that several numbers of microorganisms and microbiota-derived molecules orchestrate the immune landscapes by driving the differentiation of a particular CD4 T cell. Here, we discuss up-to-date evidence on how microbial species or microbial components control distinct differentiation of CD4 T cell subsets and modulate unique functions of individual T cell lineages.

Th1 CELL DIFFERENTIATION AND FUNCTION

Microorganism

Bacteria

Th1 cells are responsible for the induction of cell-mediated immune responses and the clearance of intracellular pathogens; however, excessive Th1 cell-mediated immune responses are deleterious, as observed in the pathogenesis and pathophysiology of multiple inflammatory disorders and autoimmune diseases (10). Healthy commensal microorganisms with complex communities limit the induction of Th1 cell differentiation and suppress

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inflammatory responses by promoting the development of regulatory immune cells such as Tregs. Some microorganisms with the potential to induce Th1 cell differentiation have been discovered. As such, *Klebsiella* species normally inhabits the oral cavity, but during gut microbial dysbiosis, *Klebsiella* species can strongly potentiate Th1 cell differentiation after ectopic colonization in the colon (**Fig. 1**) (11). *Klebsiella* species induce Th1 immunity through $CD11b^{-}CD103^{+}$ DCs in a TLR-dependent mechanism (**Fig. 2**, **Table 1**) (11). The potential roles of exopolysaccharide capsules and LPS in mediating the virulence of *Klebsiella* have been proposed, although the precise mechanism of those microbial molecules in the induction of Th1 immunity is unknown (12).

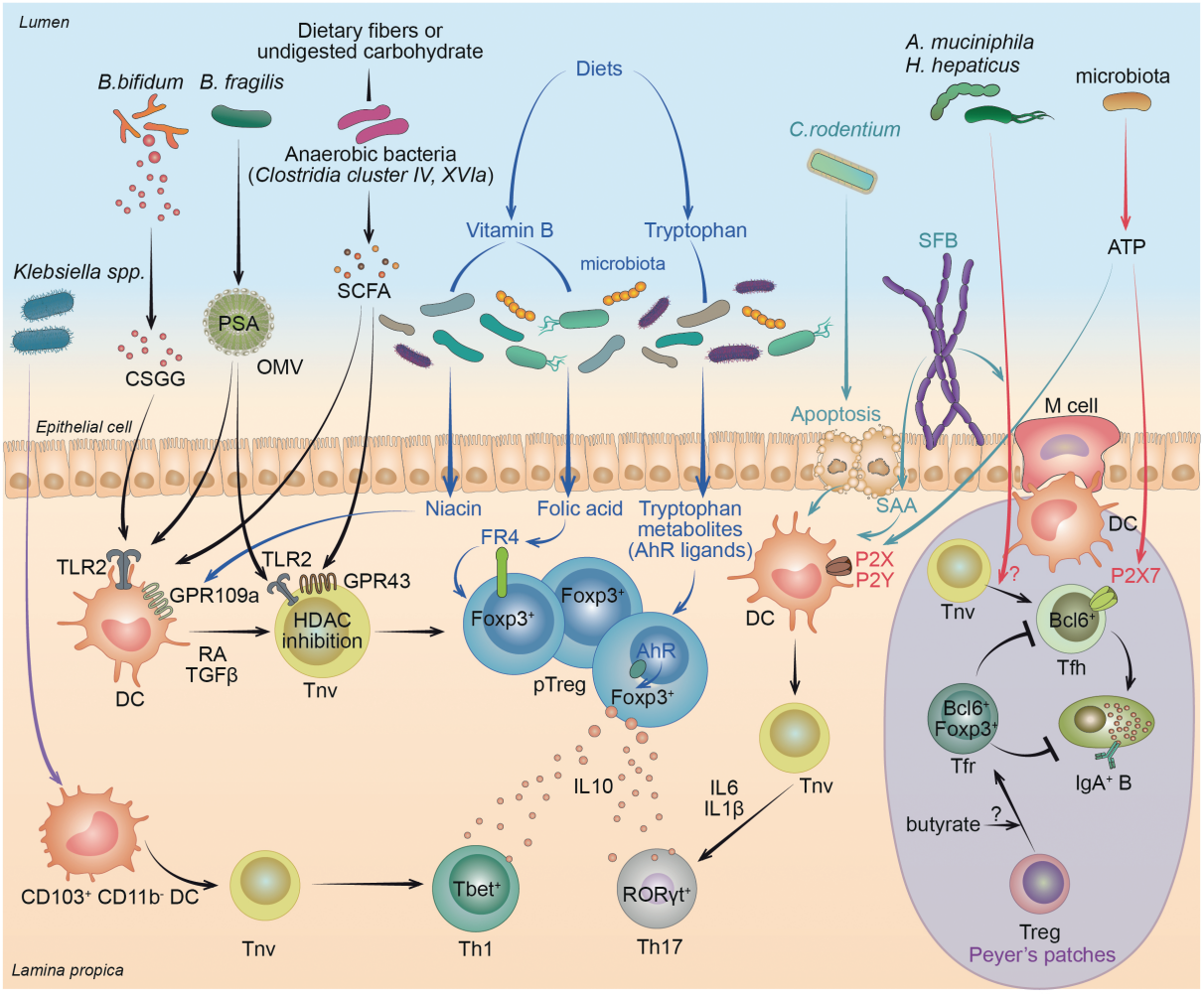

Figure 2. Microbial components and effector molecules play a key role in the development of CD4 T cell subsets.
Microbial species with Th1 cell inducing potential are poorly defined, while ectopic colonization of orally derived *Klebsiella* spp. in the colon are capable of facilitating pro-inflammatory Th1 cell response through $CD103^{+}CD11b^{-}$ DCs. *C. rodentium* infection triggers apoptosis of epithelial cells that consequently strongly drives induction of Th17 cells in the intestine. SFB adhering to the small intestine epithelial barrier promotes the generation of Th17 cells in a manner dependent on SAA production from the epithelial cells. Differentiation of Tfh cells in PP is driven by specific microbes such as *A. muciniphila*, *H. hepaticus* and SFB. Furthermore, microbiota-derived ATP confers differentiation of not only Tfh cell but also Th17 cells through a P2 receptor-dependent mechanism. On the other hand, several microbial components with immunoregulatory potential have been identified. CSGG and PSA are respectively derived from *B. bifidum* and *B. fragilis*, and both molecules drive Treg differentiation through DCs by a TLR2-dependent mechanism. The microbiota is capable of utilizing diet components and secreting diverse metabolites. Microbiota-associated metabolites are implicated in the differentiation and function of Tregs. SCFAs facilitate the generation of Tregs by inhibiting HDAC activity through GPR109a and GPR43 mediated signaling in DCs and naïve T cells, respectively. In addition, niacin intensifies the development of Tregs in a GPR109a-dependent manner. Folic acid reinforces the survival of Tregs through the FR4 receptor. Tryptophan-derived metabolites confer hypomethylation of the *Foxp3* region and promote the differentiation of Tregs. In the PP, butyrate can drive the conversion of Tregs into Tfr cells, but the underlying mechanism is unknown.

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Table 1. T effector cells-inducing bacteria and their effector molecules

Cell types	Immunomodulatory bacterial molecules	Related bacteria species and diets	Mode of action	References
Th1 cells	Unidentified	*Klebsiella* spp.	Through: $CD11b^{-}CD103^{+}$ DCS via TLR dependent mechanism	(11,12)
	Unknown	*Bilophila wadsworthia*	Unknown	(14)
Th2 cells	Peptidoglycan, lipoteichoic acid, second immunoglobulin-binding protein (Sbi)	*Staphylococcus aureus*	Activates keratinocytes to produce IL-33 through TLR2-TLR6 heterodimer	(30,32)
Th17 cells	Unknown	Segmented filamentous bacteria	Induce secretion of SAA protein from epithelial cells that sequentially activates DCs to produce Th17 driving cytokines	(46-48)
	Unknown	*Prevotella nigrescens*	Through Ag presenting cells via TLR2 dependent mechanism	(51,52)
	Potential implication of toxin A and B as well as surface layer proteins	*Clostridium difficle*	Activates Ag presenting cells via TLR4 dependent signaling	(55,56)
Tfh cells	Microbiota-derived extracellular ATP	Microbiota derived (species unidentified)	Through P2X7 on Tfh cell	(86)
	Unknown	*Akkermansia muciniphila*	Unknown	(78)

Additionally, other bacteria are well documented for their abilities to regulate Th1 immunity. A recent study suggested potent roles of *Akkermansia muciniphila* in driving Th1 immune responses, which confers beneficial effects on enhancing anti-tumor immunity in cancer patient (13). In addition, *Bilophila wadsworthia*, which is a human commensal bacteria species with sulfite-reducing capability, expands in the setting of dysbiosis induced by a high-fat diet (14,15). This alteration of microorganism communities leads to enhanced inflammatory Th1 immune response in the intestines and promotes the development of colitis in IL-10 deficient mice (**Table 1**) (14,15). Also, nine distinct strains of bacteria isolated from Crohn's disease patients enhanced Th1 cells in the intestines, including a particular *Escherichia coli* strain, the *E. coli* 35A1. *E. coli* 35A1 could induce a strong intestinal Th1 cell response that exacerbated intestinal inflammation (**Fig. 1**) (16). Furthermore, a previous study demonstrated that a bacteria consortium composed of 11 human commensal bacterial strains upregulated Th1 cells in the intestines along with increased Th17 cell differentiation and facilitated antitumor immunity (17). Despite the identification Th1 cell-inducing bacterial species, the underlying molecular mechanism remains elusive.

Fungi

Gut bacteria have been highlighted to study the cross-talk between the microbiota and the immune system, yet the role of other commensal microorganisms and their underlying mechanisms are largely unexplored. Fungal communities are the second most studied type of commensal microorganism, and similar to bacteria, mycobiota also exert significant effects to modulate the immune system (2). Accumulating evidence in both humans and mice demonstrated that the Th1 response appears to be closely implicated in a defensive mechanism against fungal infections. Mice that are compromised for Th1 responses are highly susceptible to *Candidiasis* or *Aspergillosis*, especially caused by infections with *Candida albicans* or *Aspergillus fumigatus*, respectively (18,19). Despite evidence suggesting the association of fungal species with the immune system, the particular fungal species that induce the differentiation of specific CD4 T cells are unknown. Interestingly, numerous studies have demonstrated the role of fungal cell wall β-glucan in driving inflammatory responses mediated by Th1 cells, and the preclinical efficacy of β-glucan in cancer therapy based on Th1-inducing properties (20). Additionally, although the number is relatively less, some studies have suggested an immunosuppressive potential of β-glucan (21). Zymosan is a cell surface particulate of yeast *Saccharomyces cerevisiae*, which is broadly used in studying the role of β-glucan in the immune system. Zymosan is composed dominantly of β-1,3-glucan, along with relatively less amount of β-1,6-glucan, mannan, protein, and ash (22).

Interestingly, β-1,3-glucan from zymosan is capable of potentiating Th1 immune responses and upregulating IFN-γ expression in CD4 T cells (23).

Other minor types of microorganisms

The role of the other microorganisms, such as protozoa and viruses, in inducing Th1 immune response has been suggested in the setting of infections by *Toxoplasma gondii* or Hantaviruses (24,25). However, the role of microorganisms other than bacteria and fungi is largely unexplored, and the comprehensive effects of those microorganisms in the homeostatic healthy condition remain elusive. Further studies should be conducted to assess if and how commensal protozoa and viruses can regulate Th1 immunity.

Microbial metabolites

Short-chain fatty acid (SCFA)

SCFAs are free fatty acids composed of less than 6 carbons for their structural feature and are produced by gut microorganisms as a fermentation product of fibers in the gut. SCFAs confer significant impacts on diverse human physiologies, including the modulation of the immune system (26). Butyrate, a major SCFA with 4 carbons, is produced from multiple species of bacteria and is critical in maintaining homeostasis of the gut microenvironment by inducing the differentiation of immunoregulatory cells and enhancing the integrity of epithelial barrier functions (26). Recent studies have suggested that, although butyrate induces immunoregulatory cells, butyrate is also capable of promoting the expression of T-bet and IFN-γ in the same CD4 T cells simultaneously (27). However, the clinical relevance of the increased Th1-associated signatures is controversial, and further studies are required to understand butyrate's precise role in inflammatory disease settings.

Th2 CELL DIFFERENTIATION AND FUNCTION

Microorganism

Bacteria

In healthy states, Th2 immunity contributes to the maintenance of mucosal homeostasis by preventing helminth infections and by exerting beneficial effects on epithelial barrier functions through producing Th2 cell-associated immune mediators (28). Gut microbiota play a key role in orchestrating the immune system to induce adequate immune responses (1). Disruption of commensal microorganisms by antibiotics leads to an aberrant immunoglobulin response with elevated concentrations of systemic IgE, which is implicated with increased susceptibility to allergic diseases (29). These shreds of evidence suggest that commensal microorganism represses Th2 immunity during healthy conditions. However, disease conditions can also trigger Th2 immunity. For instance, during atopic dermatitis, cell surface lipoproteins of *Staphylococcus aureus* such as peptidoglycan and lipoteichoic acid induce Th2 immune responses, which activate the differentiation of Th2 cells (**Table 1**) (30-32). Yet beyond such examples, the particular bacterial species that induce Th2 immune responses in other healthy and diseased models remains largely unknown.

Parasite

Infections with helminth strongly drive Th2-mediated immune response (33). Chronic infections by *Heligmosoides polygyrus* or *Trichuris muris* confer the generation of Th2 cells by promoting the production of Th2-associated cytokines such as IL-4, IL-25, and IL-33 (**Fig. 1**) (34-36). Although it still remains controversial and ambiguous, recent studies suggest a

potential function of helminths as adjuvants that can induce Th2 immunity against non-parasitic Ags (37,38). In this respect, *Nippostrongylus brasiliensis* can promote the differentiation of Th2 cells by producing IL-2 and IL-4, which drive Th2 cell differentiation in an autocrine mechanism (38). Also, several molecules derived from particular parasitic species are identified to induce Th2 cell differentiation. For instance, glycans derived from *Schistosoma mansoni* (39,40) and RNase Omega-1 from *Schistosoma mansoni* eggs, as well as other lipids and lipoproteins (41-43) potentiate Th2 cell differentiation.

Fungi

Previous studies suggest that in the setting of cystic fibrosis, *A. fumigatus* is capable of activating Th2 immunity through CD4 T cells in mice deficient with cystic fibrosis transmembrane conductance regulator (CFTR) (44). In general, Th2 immunity is detrimental to anti-fungal immunity since Th2 immunity suppresses protective Th1 immune responses against fungal infection (45).

Th17 CELL DIFFERENTIATION AND FUNCTION

Microorganism

Bacteria

Numerous studies have demonstrated that many bacterial species with Th17-inducing capacities have detrimental roles in multiple inflammatory and autoimmune disorders (8). Segmented filamentous bacteria (SFB) is a representative bacterium for Th17-inducing function that inhabits particularly within the terminal ileum of the small intestine (46). The indigenous strain of SFB adheres to epithelial cells and triggers the secretion of serum amyloid A proteins (SAAs), which facilitates the differentiation of Th17 cells with inflammatory potential through the production of Th17-driving cytokines from lamina propria DCs (**Fig. 2**, **Table 1**) (46-48). Additionally, similar to SFB, human commensal bacteria with adherent-invasive potential, *Bifidobacterium adolescentis* and *E. coli*, potentiate the differentiation of Th17 cells and play a harmful role in settings of autoimmune diseases. The underlying mechanism, however, remains unknown (49,50).

Prevotella copri is often enriched in fecal contents from patients with rheumatoid arthritis, of which the pathophysiology is closely associated with Th17 cells (51). This observation was recapitulated in a murine system of experimental autoimmune arthritis, during which *Prevotella nigrescens* was found to induce Th17 cell differentiation through a TLR2-mediated induction of Th17-driving cytokines (**Table 1**) (51,52). Gut bacteria can also cause other Th17 mediated disorders. Infection with *Citobacter rodentium* induces the development of inflammatory colitis by triggering robust differentiation of Th17 cells (**Fig. 1**), a relatively moderate Th1 response, the upregulation of TGF-β and IL-23 cytokines, and the apoptosis of epithelial cells (**Fig. 2**) (53,54). A similar response was observed in the setting of *Clostridium difficle* infection, which resulted in robust type 3 immune responses and an augmented Th17 cell immunity through inflammasome activation in response to *C. difficle* toxins A and B (55,56). In this process, DCs played a key role in sensing the immunostimulatory microbial molecules through damage-associated molecular patterns or pathogen-associated molecular patterns (**Table 1**) (55,56). Additionally, in the context of immune dysregulation, *Helicobacter hepaticus* also elicits inflammatory colitis by enhancing the production of Th17 cell-inducing cytokines from activated innate immune cells (57,58). However, in the steady state, *H. hepaticus* can also contribute to the induction of intestinal Treg differentiation (57,58). Bacteria-derived

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molecules are also capable of inducing Th17 responses. Curdlan, a highly purified β-1,3-glucan from the soil bacteria *Alcaligenes faecalis* var. *myxogenes*, plays a detrimental role in experimental autoimmune disease settings by inducing the differentiation of Th17 cells (59).

Fungi

Multiple preclinical and clinical studies have demonstrated the key roles of Th17 cells in controlling mucosal fungal infections in the setting of diverse animal models (2). Among the various fungal species, predominant studies that aim to understand the role of the fungal community in immune modulation have focused on *C. albican*, a dominant species in the gastrointestinal tract, which is known to induce Th17 cell differentiation during health and disease (60). In the intestines, *C. albican* stimulates the immune system through diverse polysaccharide components of their cell wall, including β-glucan, mannan, and chitin, which are recognized by mononuclear phagocytes that express CX_3CR1-via multiple pattern recognition receptor (PRR) families (2,61). In addition to intestinal commensal fungi, *Malassezia* can potentiate the induction of Th17 cells with increased expression of Th17 signature cytokines that aggravate skin inflammation (62).

Mycobacterium tuberculosis causes public health problem (63), and several mechanisms of *M. tuberculosis*-mediated immune modulation have been demonstrated. However, the mechanism by which *M. tuberculosis* modulates the immune system is not fully understood, particularly at the latent or active stages of *M. tuberculosis* infection (64). *M. tuberculosis* exerts Th17 cell differentiation through DCs by an *M. tuberculosis*-derived β-glucan and Dectin-1 dependent axis (65). Furthermore, a previous study has demonstrated that β-glucan of zymosan triggers the onset of experimental autoimmune encephalomyelitis by facilitating the differentiation of Th17 cells (66).

Other microorganisms

Previous studies showing Th17 inducing microorganisms have been dominantly focused on either bacteria or fungi, which are the first and second most abundant microorganisms among the commensal microbiota. Interestingly, a few studies have proposed the potential of enteric parasites of the *Giardia* species, such as *Giardia muris* and *Giardia lamblia*, to induce Th17-associated immune responses, but the precise cellular source of IL-17A during *Giardia* infections are unclear (67). Also, the roles of other parasitic species during Th17-meidated immune responses are not fully understood.

The association of Th17 immunity and virus is largely unknown, with only a few pieces of evidence suggesting the protective role of Th17 cells against infections by influenza virus or herpes simplex virus. Infection of *Il17* gene-deficient mice with such viruses showed elevated susceptibility and mortality (68,69). Additionally, the role of Th17 cells have also been examined in infectious conditions by hepatitis B virus (HBV). The HBV surface Ag, HBsAg, stimulates the production of IL-23 from myeloid dendritic cells and macrophages, which elicits Th17 cell differentiation and potentially contributes to liver damage in individuals infected by HBV (70,71). Although several studies have suggested the potential association of the virus and Th17 immune responses, the precise and comprehensive role of the virus in Th17 immunity is largely unexplored.

Microbial metabolites

ATP

ATP is a microbiota-derived metabolite capable of stimulating the differentiation of Th17 cells (**Fig. 2**). During *in-vitro* settings, a previous study showed that multiple genera

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of bacterial species secrete ATP (72), and a consistent result was observed *in vivo*; mice absent with commensal microbiota were observed to have decreased levels of luminal ATP accompanied with compromised Th17 cell populations in the gut, as compared to mice with normal commensal flora (73). ATP produced from bacteria drives Th17 cell differentiation by stimulating a unique subset of lamina propria DCs marked by $CD70^{high}CD11c^{low}$ (73). These DCs have the ATP receptor P2X and P2Y, which leads to the production of Th17 cell driving cytokines such as IL-6, IL-23 and TGF-β activating integrin αV and β8 (73). Interestingly, treatment of lymphopenic mice with ATP exacerbates the pathophysiology of experimental colitis by enhancing the differentiation of Th17 cells in the colonic lamina propria (73). In addition, in the experimental obesity settings, ATP skews the microenvironment favorably to Th17 cells with high levels of IL-1β and IL-6 (74).

Tfh CELL DIFFERENTIATION AND FUNCTION

Microorganism

Bacteria

Bacteria-targeting IgA is one of the essential arms of mucosal immunity that fine-tunes microbial diversity and maintains intestinal surveillance. The production of IgA relies on two distinct pathways: T cell-independent and T cell-dependent responses. T cell-dependent IgA is mostly mediated by bacteria located near the mucosal epithelial surface, and Tfh cells help regulate the class switching of IgA in the Peyer's patch (PP) (29). PP resident Th17 cells are also converted into Tfh cells to underpin the generation of high-affinity IgA under the homeostatic conditions (75).

As with other $CD4^+$ T cell lineages, Tfh cells mutually communicate with the intestinal microbiota. Environmental factors such as commensals, pathogens, and bacterial-derived molecules influence the development and function of Tfh cells. At the same time, Tfh cells can affect the microbiota's composition, diversity, and function. A previous study identified that T cell-intrinsic innate adaptor MyD88 signaling, which is a downstream signaling pathway of TLRs activated by engagement with divers microbial molecules, was required for intestinal GC Tfh cell differentiation and GC-mediated IgA responses against symbionts. MyD88-dependent dysregulation of GC reactions resulted in altered bacterial diversity (76). These findings describe microbiota-derived factors that can intensify Tfh cell generation in a MyD88-dependent manner, leading to enhanced Tfh-mediated IgA production, which consequently regulates microbial community composition (76).

Several reports have illustrated specific members of bacteria, which are closely linked to Tfh cell-mediated humoral immune responses. For instance, the *Anaeroplasma* genus is able to amplify mucosal IgA levels by upregulating TGF-β expression in PP Tfh cells (77). Additionally, colonization with *A. muciniphila* induces Tfh cell accumulation, especially within the PP, concurrent with Ag-specific IgG production under steady-state conditions (**Fig. 2**, **Table 1**) (78). Furthermore, Overacre-Delgoffe et al. (79) demonstrated that *H. hepaticus* promotes the generation and infiltration of Ag-specific Tfh cells, which in turn facilitates the formation of ectopic lymphoid follicles near colon cancers (**Figs. 1** and **2**). These microbiota-induced Tfh cells are sufficient to fight off cancer, shedding new light on a novel therapeutic implications of microbiota (79).

Interestingly, the microbiota can modulate the onset of systemic immune reactions by regulating the abundance of Tfh cells in the PP. In an experimental model of human inflammatory arthritis, commensal SFB in *K/BxN* mice interacts with DCs to accelerate Tfh cell differentiation by suppressing IL-2 availability from CD4 T cells within the PP (**Fig. 2**) (80). In this manner, SFB-triggered Tfh cells can migrate from the PP to extraintestinal lymphoid organs, which aggravates the progression of autoantibody-mediated arthritis (80).

Other microorganisms

Viruses and parasites can shift naïve CD4 T cells toward Tfh cell fate commitment. Given that Ab-mediated humoral immune responses effectively targeting viruses are fundamental for eradicating infectious diseases, a deep comprehension of virus-specific Tfh cell generation will contribute to new insights for the development of novel vaccination and treatment strategies. Different lineages of T cells are required for eliminating viruses based on the duration of the infection. Virus-specific cytotoxic CD8 T cells and memory CD8 T cells are important in getting rid of acute infections, while Ag-specific CD4 T cells, especially Tfh cells, have a central role in chronic infections (81). Virus-specific CD4 T cells are endowed with differentiation potential toward $CXCR5^+$ Tfh-like cell fate, concurrent with attenuated Th1 cell differentiation, under infections such as lymphocytic choriomeningitis virus clone 13, HIV, and simian immunodeficiency virus (SIV) (82,83).

The properties of virus-specific Tfh cells are two-sided, and therefore they have both protective and pathogenic functions during HIV and SIV infections in a context-dependent manner. Even though less is known about the exact mechanisms underlying virus-specific Tfh-like cell generation during infections, several factors may be involved in this shift towards Tfh cells, including type I interferon signaling, IL-6 family receptor-related signaling, and histone demethylase UTX (81,84). Besides this, it has been revealed that the induction of IL-4-producing Tfh cells is mediated by helminth infections such as *Nippostrongylus brasiliensis*, *Heligmosomoides polygyrus*, and *Schistosoma mansoni* (85).

Microbial metabolites

ATP

One of the well-known Tfh-inducing components is ATP, which is released by the microbiota and regulates Tfh cell differentiation in the gut. Microbial extracellular ATP restrains the proportion of Tfh cells in the PP by controlling the ATP receptor P2X7 activity. This ATP/P2X7 axis in Tfh cells is associated with metabolic homeostasis and microbiota composition (**Fig. 2**, **Table 1**) (86). Mice deficient for *P2rx7* cannot sense ATP and thereby exhibit dysbiosis, aberrant IgA secretion, and modified glucose metabolism (86).

Treg DIFFERENTIATION AND FUNCTION

Microorganism

Bacteria

The gut is continuously exposed to tremendous environmental cues, including microorganisms, food, allergens, and self-Ags. Therefore, the host immunity is inevitably required to distinguish between detrimental pathogens and non-harmful Ags to both protect from diseases and maintain homeostasis. Tregs have an imperative role in sustaining immune homeostasis by inducing tolerance and repressing immune responsiveness to persistently encountered Ags at mucosal sites. Dysfunction of Tregs thus leads to a collapse

of tolerance, causing formidable disorders varying from autoimmunity and catastrophic inflammations (6,87).

Tregs consist of 2 major subpopulations, natural Tregs (nTregs) and peripheral Treg (pTreg) cells, based on their site of origin (9). The development of nTregs occurs in the thymus to suppress hyperactivation of immune responses against self-Ags, whereas pTregs stem from the periphery in response to commensal microbiota and dietary Ags (9). A growing body of literature has established that gut microbiota shapes the expansion, maturation, and function of extrathymic Tregs (1,6). Considering that Tregs fail to accumulate in the colon of germ-free mice, it is evident that peripheral education of Tregs by the microbiota is of paramount importance in gut health (88). Accordingly, there has been a great deal of interest in elucidating individual species and commensal communities that can induce the proliferation, generation, and function of Tregs for therapeutic applications.

The first investigation into the impact of microbiota on Tregs discovered that *Bacteroides fragilis*-derived polysaccharide A (PSA) promotes the accumulation of intestinal IL-10-producing Tregs (**Fig. 1**), whose regulatory ability is enough to ameliorate both experimental autoimmune and colonic inflammation models induced by 2,4,6-trinitrobenzenesulfonic acid solution (TNBS) or *H. hepaticus* (**Fig. 2**, **Table 2**) (89-91). PSA, a capsular polysaccharide, acts as a microbe-associated molecular pattern recognized by PRRs, which is necessary for host immune functions (92). Intriguingly, PSA directs host immune responses toward inducing mucosal tolerance to commensals, but not eliciting inflammatory responses to pathogens (92). PSA-induced intestinal tolerance is mediated through TLR2, a receptor for PSA, which is expressed on various immune cells (92). Interaction between PSA and CD4 T cells directly drives Treg lineage commitment and creates an IL-10 enriched environment that restrains Th17 cell development in a manner that requires TLR2 signaling (93). In addition to the direct effect of PSA, Treg differentiation is also induced by PSA-imprinted DCs, which exert a regulatory characteristic in a TLR2-dependent manner (91). Given that gram-negative symbionts usually communicate with the host via delivery of outer membrane vesicles (OMVs), *B. fragilis* adopts a similar strategy for their commensalism (87). *B. fragilis* secretes PSA packed in OMVs and transports them to intestinal DCs, which consequently upregulates the expression of OMV-specific genes, particularly growth arrest and DNA-damage-inducible 45α (*Gadd45α*) (94). Recently, it was proposed that host genetic factors are closely linked to *B. fragilis*-mediated protective regulation (95). The generation of Tregs induced by *B. fragilis* relies on a noncanonical autophagy pathway of DCs through *ATG16L1* and *NOD2* genes. Mice and humans with DCs that are defective in *ATG16L1* genes have improper development of IL-10^+ Tregs in response to OMVs, and thus they are more susceptible to mucosal inflammation (95). This finding suggests an intimate relationship between the host genome and microbiota in etiologies, particularly inflammatory bowel disease (IBD) (95).

Other initial researches have shown that consortia of *Clostridium* cluster IV and XIVa are powerful inducers of colonic Tregs in humans and mice (**Figs. 1** and **2**, **Table 2**) (88,96). In these studies, colonization with a mix of 46 strains of mouse-derived *Clostridia* induces the expansion of Tregs within the colon of gnotobiotic mice. This mixture of *Clostridia* makes intestinal epithelial cells (IECs) not only produce more TGF-β in the surrounding niche, but also enhance indoleamine-2,3-dioxygenases (IDO) expression, paving the way for stimulating Treg differentiation. The boost in *Clostridia*-mediated Tregs alleviates systemic Ab responses as well as mucosal inflammation (88). As with the murine *Clostridium* consortia, 17 selected strains of human-derived *Clostridia* can also guard mice against experimental colitis via an

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Table 2. Treg-inducing bacteria and effector molecules

Bacterial factors	Related bacteria species and diets	Mode of action	References
Polysaccharide A	*Bacteroides fragilis*	· Directly through TLR2 expressed on Treg · Indirectly through DC sensing *B. fragilis*-derived PSA in OMV in a TLR2-dependent manner. · Associated with autophagy-related genes expressed in DC, such as *Gadd45α*, *Atg16l1*, and *Nod2*	(89-95)
Possibly via Flagellin	*Roseburia hominis*	· Through a TLR5-related manner	(110)
Unidentified	*Helicobacter hepaticus*	· Through a c-Maf-dependent manner	(119)
SCFA	*Clostridia* clusters IV, XIVa and XVIII (46 strains from mouse and 17 strains from human)	· Through the stimulation of colonic IECs to produce TGF-β and upregulation of IDO and Treg-inducing markers	(88,96,97)
	Anaerobic bacteria (mainly *Clostridia*-butyrate/propionate- *Bacterodies* and *Firmicutes*)	· Suppression of HDAC and acetylation of histone within Foxp3 locus regions that result in stabilization of Foxp3	(124,125)
		· Through GPR43 expressed on Tregs	(123)
Propionate	*Bacteria consortium* (IRT5)	· Induction of CD11c$^+$ DCs which express high levels of TGF-β, IDO, and Cox2 · Through GPR43 expressed on DC and CD4 T cells	(98,99)
CSGG	*Bifidobacterium bifidum* PRI1	· Conversion of CD11c$^+$ DC into regulatory DC in a TLR2-dependent manner and creating niche enriched with IL-10 and TGF-β	(101)
Unknown	*Bifidobacterium infactis* 35624	· Unknown	(102,103)
Unknown	*Clostridium ramosum*	· Unknown	(107)
Unknown	*Clostridium butyricum*	· Expansion of IL-10$^+$F4/80$^+$CD11b$^+$ macrophage via TLR2/Myd88 signaling · Induction of TGF-β secreted by DC via TLR2-ERK-AP1 and autocrine TGF-β-Smad signaling	(104,105)
Indole metabolites (indole acetic acid, indole propionic acid)	*Bacterodies thetaiotaomicro*	· Through activation of AhR which results in hypomethylation within Foxp3 promoter	(112)
Levan exopolysaccharide	*Lactobacillus reuteri* 100-23	· Unknown	(114)
Oxytocin	*Lactobacillus reuteri* ATCC 6475	· Unknown	(115)
Unknown	*Lactobacillus reuteri* (strain DSM 17983 and RC-14)	· Unknown	(116)
Unknown	*Lactobacillus murinus*	· Through upregulation of IL-10 and TGF-β expressed in DC and macrophage	(117)
Unknown	*Lactobacillus rhanmnosus* GG	· Through increase in mesenteric CD103$^+$CD11c$^+$ DCs	(118)

abundance of colonic pTregs expressing high levels of *RORγt*, IL-10, CTLA4, and ICOS (96). An underlying molecular pathway has been suggested where the regulatory ability of these *Clostridia* strains depends on SCFA, mainly butyrate and acetate (97).

The bacteria consortium, IRT5, is a well-characterized mixture of beneficial bacteria which elicit strong immunosuppressive capacity in a synergistic manner. Kwon and his colleagues (98) pinpointed that IRT5, which is composed of *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus reuteri*, *Bifidobacterium bifidum*, and *Streptococcus thermophilus*, directly promotes the generation, function, and migration of Treg by augmenting CD11c$^+$ regulatory DCs that exhibit increased levels of TGF-β, IDO, and Cox2 (**Table 2**). A wide variety of research has identified that IRT5 could alleviate various preclinical models of immune diseases, including IBD, atopic dermatitis, rheumatoid arthritis, multiple sclerosis, and skin allergy, suggesting its promising therapeutic potential in clinical fields (98-100). Propionate, mainly produced from *L. reuteri*, is proposed to be a key effector metabolite by which IRT5 systemically regulates aberrant inflammation beyond the gut (99). Propionate produced by *L. reuteri* of IRT5 acts directly on CD4$^+$ T cells as well as indirectly on CD11c$^+$ DCs through its receptor GPR43, which enhances pTreg accumulation and leads to the prophylactic effects of IRT5 (99).

Furthermore, a recent study has suggested that a single bacterium alone can induce Tregs. *B. bifidum* PRI1 isolated from the feces of a breastfed baby could induce Tregs mainly in the colon to control the progression of intestinal inflammation (101). Of note, cell surface β-glucan/galactan (CSGG) polysaccharides, a neutral component of *B. bifidum* cell surface, function

as critical effector molecules that engenders the *de novo* generation of RORγt^{+}Nrp1^{-}Helios^{-} pTreg within the colon in a DC-dependent fashion (**Fig. 1**, **Table 2**). CD11c^{+} DCs recognize CSGG through TLR2 and converts their phenotype to skew towards a regulatory manner (101). This provides an immunoregulatory niche in favor of the peripheral development of Tregs that express a TCR specific for *B. bifidum,* other commensals, and dietary Ags (101). Similarly, *Bifidobacterium infantis* 35624 expands Treg populations and protects against systemic infections and colitis (**Table 2**) (102,103).

Clostridia species have also been widely defined as beneficial symbionts for the treatment or prevention of immune-related diseases. *Clostridium butyricum*, belonging to the *Clostridium* cluster I, indirectly facilitates the conversion of naïve CD4^{+} T cells into Tregs through interactions with mucosal APCs (**Table 2**). One of the mechanisms of *C. butyricum* is an accumulation of IL-10-secreting F4/80^{+}CD11b^{+} macrophages via the TLR2/MyD88 pathway (104). *C. butyricum* also stimulates vigorous TGF-β production from DCs in a manner that is concurrent with TLR2-ERK-AP1 and autocrine TGF-β-Smad signaling (105). *C. butyricum* can also alter microbial compositions, increasing the prevalence of *Bifidobacterium, Lactococcus*, and *Lactobacillus* genera (106). Another bacterium, *Clostridium ramosum*, intensifies the expansion of RORγt^{+} Helios^{-} Tregs within the colonic lamina propria (**Table 2**) (107). Additionally, *Clostridium leptum* has been shown to induce Tregs in the spleen and mediastinal lymph nodes (108).

The *Roseburia* genus, a member of *Clostridia*, are flagellated gram-positive bacteria that produce SCFAs and are less abundant in IBD patients (109). Colonization of *Roseburia hominis* increases the size of the colonic Treg pool in a TLR5-dependent fashion, possibly suggesting *R. hominis*-derived flagellin is associated with Treg induction (**Table 2**) (110). Recent studies also propose that *Roseburia intestinalis* potentiates the development of extrathymic Treg (111).

Bacterial species belonging to *Bacteroides*, including *Bacteroides thetaiotaomicron* and *Bacteroides caccae*, can boost the development of colonic CD103^{+}Nrp1^{-} pTreg (**Table 2**) (107,112). Although the detailed mechanism of *B. caccae* remains elusive, it is reported that *B. thetaiotaomicron*-derived indole metabolites activate aryl hydrocarbon receptor (AhR) signaling that instigates the hypomethylation of CpG sites within the Foxp3 promotor in Tregs under dextran sulfate sodium colitis conditions (113).

Similar to *Clostridia* and *Bacteroides* genera, *Lactobacillus* is also well known as immunosuppressive bacteria that are capable of potently inducing Treg populations. By a way of illustration, *L. reuteri* performs a regulatory function in a wide variety of disorders, with particular strain-specific differences. For instance, *L. reuteri* 100-23 enlarges the splenic Treg population through their production of levan exopolysaccharide (**Table 2**) (114). Oral administration of *L. reuteri* ATCC 6475 to mice boosts plasma levels of oxytocin, and it increases the abundance of Tregs accompanied with advanced wound repair (**Table 2**) (115). In addition to these strains, *L. reuteri* DSM 17983 and *L. reuteri* RC-14 are also reported to exert influence on Treg induction (**Table 2**) (116). As another example, *L. murinus* stimulates the accumulation and development of Tregs via upregulating TGF-β and IL-10 expression in Ag-presenting cells like DCs and macrophages within lamina propria (**Table 2**) (117). Gastric treatment of *L. rhamnosus* GG confers resistance to OVA-induced allergic airway inflammation, dependent upon the expansion of both mesenteric CD103^{+}CD11c^{+} DCs and intestinal CCR9^{+} Tregs (**Table 2**) (118). Of interest, pathobiont as well as symbionts are able to drive mucosal tolerance so as to inhibit the onset of severe inflammation. In an effort to maintain intestinal homeostasis, Ag-specific RORγt^{+} Tregs are developed within colonic lamina propria in

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response to *H. hepaticus* in a mechanism dependent on the transcription factor c-Maf (**Table 2**) (119). If the mucosal immune balance is uncontrolled and broken, *H. hepaticus* preferentially promotes the generation of pro-inflammatory Th17 cell rather than that of Treg (119).

Fungi

Various studies have addressed that fungi can elicit tolerance in the gut, even though fungi are conventionally characterized to mount pro-inflammatory reactions to protect and defend our body against invaders. More specifically, *Aspergillus fumigatus* is a powerful mediator of human Tregs that efficiently restrain fungus-specific memory CD4 T cells to balance mucosal homeostasis against this fungal threat (120). Beside this, recent compelling research pinpointed that yeast *Saccharomyces cerevisiae*-derived mannan/β-1,6-glucan-containing polysaccharides (MGCP), promotes *de novo* generation of Tregs and consequently suppresses deleterious IFN-γ-producing Th1 cell development. Structural specificities of β-glucan, notably, were indispensable for their immunomodulatory ability that induces Treg, and indeed elimination of β-1,6-glucan from the MGCP confers compromised regulatory potential which is coincident with a diminished abundance of Treg pools (23). The differentiation of MGCP-induced Treg depends on Dectin1-Cox2 signaling in $CD8^{-}CD11b^{+}$ DCs (23).

Metabolites

SCFA

Symbiont anaerobic microbiota, such as the *Clostridia* genus, produces SCFAs by fermentation of undigested carbohydrates, primarily in the large intestines (29). A growing body of literature has elucidated that SCFAs, including butyrate, acetate, and propionate, are a predominant driver of Tregs and regulate the equilibrium of the intestinal environment. The cellular and molecular mechanism whereby SCFAs regulate Treg population underlies both stimulation of their receptor G protein-coupled receptor (GPCR) and inhibition of histone deacetylases (HDACs) (**Fig. 2**, **Table 2**) (121). Microbiota-derived SCFAs augment the proliferation and generation of colonic Tregs, whose function is sufficient to protect against colitis, and these SCFA-induced Tregs are required for GPCR43 signaling on Treg (122). Along with GPCR43, butyrate is also sensed by GPCR109a expressed on APCs such as DCs and macrophages. This butyrate-mediated GPCR109a signaling endows mucosal APCs with regulatory features to promote the differentiation of naïve CD4 T cells into Tregs (123). SCFAs intriguingly modulate epigenetic programs of Tregs in the colon. SCFAs, especially butyrate and propionate, induce the peripheral development of Tregs by inhibiting HDACs activity that accelerates histone acetylation in the promoter and CNS1 region of the *Foxp3* gene locus (124,125). In particular, acetate administration in pregnant mice mitigates the progression of allergic airway disease in adults and fetuses, possibly through HDAC9 inhibition, indicating that this Treg-mediated resistance is maternally transferred to offspring (126).

Vitamin

1. Folic acid (vitamin B9)

Vitamins influence a broad range of host immune responses, particularly the differentiation, proliferation, maturation, and function of Tregs. Vitamin B cannot be synthesized *de novo* in humans, and therefore, it entirely comes from commensal microbiota or the diet. Folic acid, namely vitamin B9, is derived from environmental factors and is absorbed largely through the gut (127). Certain commensal bacteria, such as *Lactobacilli*, *Bifidobacteria*, and *Clostridia*, are known as folic acid-producing genera (128).

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Table 3. Treg-inducing bacterial molecules

Immunomodulatory bacterial molecules	Associated bacteria species	Mode of action	References
Folic acid (vitamin B9)	*Bacteroides fragilis*, *Prevotella copri*, *Clostridium difficile*, *Lactobacillus plantarum*, *Lactobacillus delbrueckii* ssp., *bulgaricus*, *Lactobacillus reuteri*, *Streptococcus thermophilus*, *Bifidobacterium*, *pseudocatenulatum*, *adolescentis*, *Fusobacterium varium*, *Salmonella enterica*	· Through a FR4 receptor-dependent fashion · Upregulation of anti-apoptotic genes such as Bcl2 and Bcl-xL in Tregs	(129-131)
Niacin (vitamin B3)	Diet: *Bacteroides fragilis*, *Prevotella copri*, *Ruminococcus lactaris*, *Clostridium difficile*, *Bifidobacterium infantis*, *Helicobacter pylori*, *Fusobacterium varium*	· Through GPR109a expressed on DCs and macrophages	(123)
Vitamin D3	Unknown	· Through the induction of VDR binding into Foxp3 locus that leads to the augmentation of Foxp3 expression in response to 1,25-dihyroxyvitamin D3	(135)
Tryptophan metabolites (AhR ligands)	*L. reuteri*, *Lactobacillus*, *Clostridium*, *Bacteroides*, *Firmicutes* (*Ruminococcus* genus)	· Through activity of AhR ligands	(136,137)
Butyrate	Commensals	· Through GPR109a on DC and macrophages	(123)

Folic acid signaling specifically regulates the maintenance of Tregs because folate receptor 4 (FR4), a subtype of the folic acid receptor, is highly and constitutively expressed on Tregs compared to other CD4 T cell subsets (**Fig. 2**, **Table 3**) (129). Indeed, blocking folic acid using an anti-FR4 neutralizing Ab or methotrexate leads to a decrease in Tregs, coincident with an improved antitumor effect (129). Folic acid-deficient Tregs fail to properly survive and suppress TNBS-induced colitis due to diminished expression of anti-apoptotic genes such as Bcl-2 and Bcl-xL (130), although naïve CD4 T cells are normally converted to Tregs in the absence of folic acid (131). Collectively, folic acid is a survival factor of Tregs though it is dispensable for its differentiation.

2. Niacin (vitamin B3)

In contrast to other types of vitamin B, vitamin B3, noted as niacin, nicotinamide, or nicotinic acid, can be supplied from tryptophan in the mammalian liver or obtained from the diet (127). Commensal microbiota, *B. fragilis*, *Ruminococcus lactaris*, and others possess a unique synthesis pathway of niacin and can provide it to the host (132). Niacin enhances Treg generation by activating its receptor GPR109a on colonic DCs and macrophages, consequently suppressing colonic inflammation and cancer (**Fig. 2**, **Table 3**) (123).

3. Vitamin D3

Vitamin D is usually derived from sunlight exposure and the diet, and recent literature reviews demonstrate that it is closely related to the microbiota. It has been suggested that vitamin D can modulate the microbiota community and skew it to increase *Akkermansia*, *Lactococcus*, *Faecalibacterium*, and *Ruminococcaeae* while decreasing overall *Firmicutes* (133).

Vitamin D is also sufficient for prompting the accumulation of Tregs (**Table 3**). Individuals treated with vitamin D exhibited an abundant population of Tregs compared to the placebo group (134). Vitamin D3 can also directly regulate the *Foxp3* expression to facilitate the generation of induced Treg *in vitro.* Several studies have revealed that activated vitamin D receptor (VDR), induced by 1,25-dihyroxyvitamin D3, binds to vitamin D response elements region in human *Foxp3* gene locus, and in turn, it enhances the *Foxp3* expression in human $CD25^-$ CD4 T cells in the presence of IL-2 (134,135).

Tryptophan-derived metabolites

Tryptophan, an essential amino acid mainly obtained from the diet, is catabolized by the host and commensal microbiota, and tryptophan metabolites serve as AhR ligands (136). The

activation of AhR modulates the commitment of CD4 T cell lineages, especially reciprocal development of Th17/Treg, in a ligand-specific manner (137). In the presence of TGF-β, AhR agonist induces the *in vitro* generation of functional human Tregs with upregulating *Smad1* and *Aiolos* expressions (138). AhR ligand indoles shift the Th17/Treg balance towards Tregs, and indoles-triggered Treg generation is sufficient to relieve mBSA-induced delayed-type hypersensitivity in mice (**Fig. 1**, **Table 3**). In addition to their immunoregulatory role, a recent study discovered that AhR activation could modulate the gut homing of Tregs under the homeostatic condition as well as during inflammation (139). They found that the interaction of AhR with Foxp3 directly promotes *GPR15* expression on Tregs, but interferes with RORγt binding to the Gpr15 locus, thereby enforcing homing of Tregs into colon.

The major metabolic pathway of tryptophan is the kynurenine pathway, and it begins with the degradation of tryptophan to kynurenine by the enzymatic activity of IDO. Kynurenine binds and activates AhR signaling, and this process is closely related to regulating the balance between Tregs and Th17 cells. In the host, kynurenine is synthesized by IDO-expressing cells, including $CD103^+$ DC, macrophage, and IEC (140,141). This accumulated kynurenine directs the induction of Tregs against that of Th17 cells, and indeed a decreased Th17/Treg ratio is correlated with defect in IDO1 activity among severe HIV patients (142).

Through metabolic pathways, intestinal microbiota also synthesizes tryptophan catabolites, such as indoles and indole derivates, consequently influencing the effect of AhR on mucosal immunity in the host (4). For example, *E. coli* and *Vibrio cholera* can produce indole and secrete it into blood (143), and the *Lactobacillus* genus is also known to generate indole-3-aldehyde and help host protection against mucosal inflammation (144). Furthermore, AhR ligands affect gut microbiota composition, with an increased abundance of *L. reuteri* and decreased amount of *Candidia albicans*, *Listeria monocytogenes*, and *C. rodentium* (144).

Bile acids (BAs)-derived metabolites

Recent studies have suggested additional indirect mechanisms of immune modulation by microorganisms instead of microbe-derived metabolite production. BAs are secreted into the gut lumen after being produced in the liver and have diverse biological activities on multiple hosts' physiologies (145). Several microorganisms play a role in converting human-derived BA into secondary BA and other derivatives with immunomodulatory potential and unique chemical structures (145). Recent studies have identified bacterial species responsible for producing BA derivatives 3-oxolithocholic acid (3-oxoLCA) and isolithocholic acid from the secondary BA lithocholic acid, and have demonstrated the suppressive role of 3-oxoLCA in the modulation of Th17 and Treg differentiations (146,147).

Retinoic acid (RA)-derived metabolites

RA is another well-understood immunomodulatory metabolite derived from vitamin A, and mediates the action of aldehyde dehydrogenase (ALDH) (87). Generally, RA is produced from several human cells, including intestinal mesenchymal cells, intestinal epithelial cells, macrophages, and DCs. However, a recent study has suggested direct evidence of epithelial cell-adhering SFB as a potential producer of RA through ALDH activity (6). However, unmet questions remain as to: 1) the potential of bacteria that can produce RA, 2) the particular species of microorganism with RA-producing capability, and 3) the comprehensive role and underlying mechanism by which different sources of RA (microbe-derived versus human-derived) orchestrates intestinal immunity.

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T FOLLICULAR REGULATORY (Tfr) CELL DIFFERENTIATION AND FUNCTION

The Tfr cells, which exhibits mixed features between Tfh and Tregs, are the specialized effector subpopulation of Tregs that precisely fine-tune Ab-mediated response by controlling Tfh and B cells (148). Tfr cells have been proposed to sustain the diversification and composition of the microbiota network by modulating IgA selection (148). Even though there is still ambiguity regarding an overt correlation between Tfr cells and microbiota, some environmental cues can program Tfr cell fate commitment. One research identified that commensal SFB reduces the expression of CTLA4 on Tfr cells by limiting TCR-Nur77 signaling and enhancing the glycolytic activity in autoimmune arthritic K/BxN mice (149). Besides this, butyrate intensifies the development of Tfr cells in a mechanism that facilitates histone acetylation in the promoter region of Tfr-related markers via inhibition of HDAC (**Fig. 2**). These butyrate-mediated Tfr cells ameliorate arthritis by controlling autoantibody production (150). Another SCFA, propionate, is also suggested to positively correlate with the circulating Tfr cell population in patients with clinically isolated syndrome and multiple sclerosis (151).

CONCLUSION

Advancements in understanding the critical role of microorganisms and microbial molecules behind immune modulation reveal the potential for novel therapeutic approaches for multiple diseases. The crucial role of diverse microorganisms in modulating the immune system in health and disease has been extensively examined over the recent decades. Microorganisms are significantly associated with the etiology and pathophysiology of multiple inflammatory autoimmune disorders by directly orchestrating the immune response or indirectly through producing diverse microbial bioactive molecules, including metabolites. Based on the significant immunomodulatory function in preclinical studies, the efficacy of those various microorganisms and their effector molecules have been extensively examined at the clinical level.

As such, by using a single species of bacteria or a bacterial consortium composed of multiple strains of microorganism, researchers have extensively studied the method of modifying the microbiota landscape to control CD4 T cell responses. However, the standard methodology of efficiently targeting microbiota intervention against diverse inflammatory or autoimmune diseases has not been established. This issue has been highlighted in developing microbiome-based therapeutics over the recent decades. Despite controversies, it has been revealed that building a microbial consortium using multiple species of microbes, including those with both immuno-stimulating and immuno-suppressive capabilities, might bring about an ‘immuno-balanced potential’.

The Food and Drug Administration recently approved the first fecal microbiota product to prevent the recurrence of *C. difficile* infection in individuals 18 years of age and older. As several live biotherapeutic products (LBP) are at phase 2 or 3 clinical trials, more LBP-based drugs are expected to become available. However, extensive studies are necessary to understand the comprehensive effects of the interaction between the microorganisms and the host immune system. Studies should focus on identifying relatively less abundant species of microorganism such as viruses, protozoa, and fungi that may have immunomodulatory

potentials. By doing so, we can establish comprehensive and precise underlying mechanisms by which microorganisms exert influence on the microbial landscape and functions of the immune system. Also, reciprocal interactions among the different microorganisms may affect each microbial species' immunomodulatory capacity and alter the immune cells' profile and immunological milieu. Further extensive investigations in the field of microorganism-immunology axis will contribute to demonstrating these unsolved issues and further expand our knowledge on how to develop and utilize microorganism-based therapeutics against various disorders.

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