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Mammals are colonized by large numbers of microorganisms, including trillions of bacteria, most of which live in the intestinal tract. These indigenous microorganisms that inhabit the body of humans and animals are referred collectively to as the microbiota. Accumulating evidence indicates that the microbiota regulates the development and/or function of different types of immune cells in the intestine. For example, the microbiota drives homeostatic, pathogenic, and regulatory T cell immune responses that contribute to tissue homeostasis, but also can promote disease. The gut microbes also facilitate IgA responses, which in turn regulate the composition and function of the gut microbiota. Thus, the reciprocal regulation of the gut microbiota and the host immune system may influence the balance between homeostasis and disease in the intestine.

The gut microbiota

Vertebrates are colonized by a large number of commensal microorganisms, including bacteria, fungi, and viruses, that are referred collectively to as the microbiota. In humans, >100 trillion bacteria colonize the skin and mucosal surfaces, including the oral cavity and the intestine. By far, most indigenous bacteria reside in the distal intestine. Millions of years of coevolution between the host and microbes have led to a symbiotic relationship in which the microbiota contribute to many host physiological processes and the host, in turn, provides hospitable and nutritious niches for microbial survival (1). In the intestine, the microbiota contributes to the development of specific organ structures, induction of immunity, and metabolism of nutrients, such as carbohydrates and certain vitamins. Alternatively, the gut microbiota can also cause disease or increase the risk for disease development in genetically susceptible individuals (2).

In this review, we provide an overview of the current understanding of the role of the microbiota in the development of gut-specific immunity with an emphasis in the regulation of lymphoid function.

Microbiota-dependent development of intestinal steady-state Th17 cells

Th17 cells are a selective lineage of CD4+ Th cells that are critical for host defense and play a role in the development of autoimmune disease by producing the proinflammatory cytokines IL-17A, IL-17F, and IL-22 (3). Recent studies have revealed that the presence of intestinal Th17 cells is dramatically reduced in antibiotic-treated or germ-free animals (4, 5). Additionally, a specific species of Clastridia-related bacteria, called segmented filamentous bacteria (SFB), has been found to promote the generation of Th17 cells (4, 6, 7). Mounting evidence indicates that lamina propria (LP) mononuclear phagocytes, including dendritic cells (DCs) and macrophages, sense the gut microbiota and promote Th17 cell development in the intestine (Fig. 1). Colonic CD70high CD11c+ LP DCs express purinergic P2X and P2Y receptors and promote Th17 development in the presence of commensal microbe-generated ATP (5). This subset of DCs expresses Th17 drivers such as IL-6 and the integrin molecules, integrin αv and β8, which contribute to the activation of the latent form of TGF-β in response to ATP (5). However, SFB monocolonization does not increase luminal ATP levels following activation of the CD70highCD11c+ LP DC subset (7). SFB adhesion to the epithelium induces serum amyloid A production, which promotes IL-6 and IL-23 production by CD11c+ LP DCs in the ileum (7). Thus, SFB and other commensals appear to promote Th17 cell development through different mechanisms (Fig. 1). Another key molecule that is induced by the gut microbiota is the cytokine IL-1β (8). Impaired IL-1β signaling leads to blunted development of Th17 cells, but not of Th1 cells in the small intestine (8). The gut microbiota constitutively primes CD11b+CD11c− LP macrophages to induce pro–IL-1β, although the specific commensals that regulate pro–IL-1β in LP phagocytes and the mechanism involved remain to be identified (8, 9). Because resident macrophages and DCs are hyporesponsive to

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Abbreviations used in this article: DC, dendritic cell; EAE, experimental autoimmune encephalomyelitis; GF, germ-free; IEL, intraepithelial lymphocyte; ILC, innate lymphoid cell; ILF, isolated lymphoid follicle; iNKT, invariant NKT; LP, lamina propria; LTi, lymphoid tissue inducer; RA, retinoid acid; RALDH, retinoic acid dehydrogenase; RORγt, retinoic acid orphan receptor γt; SFB, segmented filamentous bacteria; Treg, regulatory T cell.

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intestinal inflammation. Certain subsets of commensal microbiota, such as *Clostridium*, and TGF-β role in the gut. IL-23, IL-12, IL-1β pathogenic ILCs. SFB promote the differentiation of Th17 cells in the gut. Steady-state Th17 cells produce IL-17, IL-22, and IL-10 and may play a homeostatic function of TCR γδ T cells. In turn, TCR γδ+ ILCs negatively regulate the differentiation and/or function of RORγt+ ILCs. The microbiota stabilizes the expression of RORγt+ in ILCs through induction of IL-7. The absence of microbiota-induced IL-7 signaling or the presence of IL-12 and IL-15 facilitates the conversion of RORγt+ ILCs into RORγt+ IFN-γ-producing pathogenic ILCs. SFB promote the differentiation of Th17 cells in the gut. Steady-state Th17 cells produce IL-17, IL-22, and IL-10 and may play a homeostatic role in the gut. IL-23, IL-12, IL-1β, and TGF-β3 induce conversion of homeostatic Th17 cells toward pathogenic, IFN-γ-producing Th17 cells that facilitate intestinal inflammation. Certain subsets of commensal microbiota, such as *Clostridium clusters XIVa and IV* and *B. fragilis*, promote the development and functional maturation of Foxp3+Helios– inducible Tregs. Foxp3+ induced Tregs suppress the expansion of Th17 cells as well as their conversion into IFN-γ-producing Th17 cells.

microbial stimulation (9), it is possible that commensal microbes induce pro–IL-1β in LP macrophages/DCs by an indirect mechanism that may involve epithelial or stromal cells. Because MyD88-deficient mice exhibit reduced pro–IL-1β expression in CD11b+CD11c– LP macrophages and reduced Th17 cell development (8), it is likely that commensals induce pro–IL-1β via stimulation of TLRs or members of the IL-1/IL-18 receptor family, which are upstream of MyD88. Another aspect that remains unclear is the signal that leads to the processing of pro–IL-1β into the mature IL-1β. One possibility is that ATP and serum amyloid A, which are known to activate the NLRP3 inflammasome, may regulate the processing of pro–IL-1β into mature IL-1β via caspase-1 (10). However, there is no conclusive evidence as yet that caspase-1 or the inflammasome regulates the development of intestinal Th17 cells.

Although the microbiota promotes the development of steady-state Th17 cells in the gut, it is unclear whether resident Th17 cells exhibit specificity for microbial Ags. So far, the body of evidence does not support an Ag-specific role for steady-state Th17 cells in the intestine. For example, development of the gut Th17 cells is normally observed in TCR transgenic mice in the absence of cognate Ag (11). Furthermore, i.p. administration of rIL-1β injection into germ-free (GF) mice promotes the development of intestinal Th17 development in the absence of commensal microbes (8). These results suggest that the induction of Th17 cells in response to commensal stimulation is not likely due to the expansion of commensal-specific Th17 cells. Instead, microbiota-driven Th17 cells may merely reflect bystander expansion of multiple repertoires of Th17 cells or alternatively of populations of Th17 cells with skewed TCRs that home to the intestine. Because SFB-induced Th17 cells contribute to the pathogenesis of autoimmune disease outside of the gut, such as arthritis in K/BxN mice and experimental autoimmune encephalomyelitis (EAE) (12, 13), steady-state Th17 cells appear capable of recognizing self-Ags or promoting the pathogenic activity of autoreactive T cells.

**Homeostatic versus pathogenic Th17 cells**

Although Th17 cells have been shown to promote pathology in inflammatory disease models (12, 13), they are numerous under steady-state conditions and presumably exert a beneficial role in the host. Indeed, Th17 cells are protective against infection with *Citrobacter rodentium*, a mouse enteric pathogen that models infection with pathogenic *Escherichia coli* in humans. Mice reared under specific pathogen-free conditions, but lacking SFB, exhibit higher susceptibility to *Citrobacter rodentium* than do specific pathogen-free mice colonized with SFB (7). However, the interpretation of these experiments is difficult because the differences could be explained by commensals...
other than SFB or unrelated host factors. Monoclonization of GF mice with SFB induces Th17 cells in the gut but does not promote Salmonella clearance (14). Thus, the role of steady-state Th17 cells in host defense in the gut remains unclear. Additionally, intestinal Th17 cells can promote the pathogenesis of autoimmune diseases under certain conditions (12, 13). However, the involvement of steady-state Th17 cells in intestinal inflammation is controversial. In humans, the production of Th17-related cytokines is elevated in the intestinal mucosa of patients with inflammatory bowel disease (15). However, monoclonization of mice with SFB did not promote intestinal inflammation in the adaptive T cell transfer colitis model (16). Notably, cocolonization of mice with SFB and other commensals induced severe colitis in the T cell transfer model, whereas inflammation was mild or moderate in mice colonized with commensals other than SFB (16). These results suggest that SFB-induced Th17 cells are not harmful in mice, but they can promote inflammation or be converted into pathogenic T cells under inflammatory conditions or in the presence of other commensals (Fig. 1).

What is the difference between steady-state and pathogenic Th17 cells? There is evidence for plasticity of Th17 cells, which may ultimately influence disease susceptibility. For example, the ability of Th17 cells to produce the anti-inflammatory cytokine IL-10 (17), which is important for suppression of autoimmune diseases such as EAE (17), is context-dependent. The production of IL-10 by Th17 cells is induced when cells are differentiated and maintained with TGF-β1 and IL-6, whereas IL-10 is suppressed when the cells are stimulated with IL-23 (17). Importantly, Th17 cells stimulated by IL-23 and lacking expression of IL-10 are capable of inducing autoimmune disease in mice (17). Additionally, TGF-β3-induced Th17 cells are functionally different from TGF-β1-induced Th17 cells (18). Similar to IL-23–induced Th17 cells, TGF-β3–induced Th17 cells are pathogenic and promote EAE or colitis whereas TGF-β1–induced Th17 cells are not (18). Therefore, the capacity to produce IL-10 may explain the functional difference between steady-state homeostatic Th17 and pathogenic Th17 cells. Another example that reflects the plasticity of Th17 cells is that Th17 cells developed in vitro show a typical Th17 phenotype and produce IL-17 but not IFN-γ; however, when stimulated with IL-12 or IL-23, Th17 cells produce IFN-γ (19). This conversion of Th17 into IFN-γ–producing Th1-like cells is also observed in vivo (20, 21). In the course of colitis, Th17 cells can convert into IL-17/IFN-γ double-positive cells and IFN-γ–producing Th1-like cells (20, 21). In humans, IL-1β regulates the conversion of IL-17+IL-10+ Th17 cells into pathogenic IL-17+IFN-γ+ Th17 cells (22). Thus, although commensal-induced steady-state Th17 cells are not harmful and may be homeostatic, the intestinal inflammatory microenvironment, such as that found in the presence of IL-12, IL-23, IL-1β, or TGF-β3, promotes conversion of the resident Th17 cells to IFN-γ–producing pathogenic Th17 cells and may contribute to the progression of intestinal inflammation (Fig. 1).

Microbiota-dependent induction of regulatory T cells in the gut

Foxp3+ regulatory T cells (Tregs) are key suppressive cell types that regulate autoimmune inflammation in the body (23). In the gut, Tregs accumulate under steady-state conditions where they play an important role in the regulation of inflammation against microbial stimuli. Indeed, adoptive transfer of CD4+ T cells in the absence of Tregs, but not in their presence, elicits commensal-driven colitis (24). Furthermore, depletion of Tregs induces spontaneous colitis, which is abrogated when the mice are reared under GF conditions (25). Thus, Tregs are critical for the prevention of spontaneous inflammation against commensal microbes (Fig. 1). In antibiotic-treated mice or GF mice, Tregs remain detectable, but their numbers are significantly decreased in the intestinal LP, suggesting that the microbiota promotes the differentiation and/or maintenance of Tregs (26, 27). Colonization of GF mice with 46 strains of Clostridium (26), or with a mixture of eight defined commensals, called altered Schaedler flora, is sufficient to induce Tregs in the gut (26, 27). Furthermore, a human commensal bacterium, Bacteroides fragilis, can also induce Tregs in the mouse intestine (28). In the absence of the microbiota, the number of Foxp3+ Tregs is decreased in the colon, but not in the small intestine and lymph nodes (26, 29). Thus, Treg development is largely dependent on the microbiota in the colon, but not in the small intestine. A key mechanism by which the commensal microbiota induces Treg differentiation involves TGF-β (Fig. 1). Colonization of specific commensal microbes to the intestinal epithelium may induce activation of the latent form of TGF-β in epithelial cells (2). In addition to epithelial cell–derived TGF-β, certain subsets of LP mononuclear phagocytes are involved in the induction of Treg differentiation in the gut. For example, CD103+ expressing DC subsets (including CD103+CD11b+CD11c– LP DCs and CD103+CD11b–CD11c+ LP DCs) preferentially induce Treg differentiation from naive CD4+ T cells (30, 31). CD103+ LP DCs robustly express molecules that drive Treg differentiation, such as TGF-β and retinoic acid (RA) dehydrogenase (RALDH), a key enzyme in the synthesis of RA (32). RA acts as a potent inducer of Tregs in the presence of TGF-β (32). In addition to DC subsets, CD11b+CD11c– LP macrophages also express RALDH and are able to induce the differentiation of intestinal Tregs (33). In addition to Treg differentiation, RA acts on T cells to imprint gut-homing properties (34). Although the exact role of the microbiota in the generation of gut-specific DCs remains poorly understood, it is possible that commensals regulate the expression of RALDH in DCs to promote their ability to instruct gut-specific functions in T cells.

The microbiota plays a role not only in development of Tregs, but also in the functional regulation of Tregs. It is known that the regulatory function of Tregs is mediated, in part, by the production of IL-10. A key role for IL-10 in the regulation of intestinal homeostasis is supported by the observation that IL-10 deficiency can lead to the development of colitis, which is triggered by the presence of commensals or enteric pathogens (35). Various cell types in the gut produce IL-10, including Foxp3+ Tregs (36), Foxp3–Tr1 cells (36, 37), CD11b+CD11c– LP macrophages (33), and regulatory B cells (38). The fact that conditional deletion of IL-10 in Foxp3+ Tregs triggers spontaneous colitis in mice (39) suggests that Treg-intrinsic production of IL-10 is critical for the prevention of inflammatory responses to commensals or pathogens present in the intestine. Although the mechanism by which commensals control IL-10 production by Tregs is largely unknown, certain microbes facilitate the production of IL-10 by Tregs through direct or indirect mechanisms. As we
described earlier, a human commensal bacterium *B. fragilis* induces Foxp3⁺ Tregs in mice (28). A key microbial molecule that is involved in the induction of Tregs by *B. fragilis* is polysaccharide A. *B. fragilis* polysaccharide A directly acts on Tregs to promote robust production of IL-10 by T cells that is TLR2-dependent (28). Thus, certain commensals have the ability to directly activate Tregs. Unraveling the mechanism by which commensals induce the production of IL-10 by Tregs may provide further mechanistic insight into the link between the microbiota and Treg function in the gut.

**The impact of the microbiota on intestinal B cell immunity**

The production of Ig is an adaptive immune response that is critical for the clearance of infectious microorganisms, vaccination, and development of autoimmune disease. IgA plays an important role in shaping the composition and function of the gut microbiota (40). Consistently, mice deficient in activation-induced cytidine deaminase that regulates Ig class switching recombination and therefore lack IgA contain an altered microbiota (41). Not only the quantity, but also the quality of IgA is important in the regulation of the gut microbiota. For example, G235 knock-in mutation in the activation-induced cytidine deaminase gene produces IgA with lower affinity for commensal microbes exhibits alteration in the composition of the gut microbiota (42). Mono-colonization of GF mice with the commensal *Bacteroides thetaiotaomicron* does not induce inflammatory responses in wild-type mice, but it triggers innate immune responses in Rag-2–deficient mice (43). Notably, implantation of IgA-producing hybridoma cells reactive with capsular polysaccharide of *B. thetaiotaomicron* into Rag-2–deficient mice affects gene expression in the bacterium and inhibits the innate immune response in the host (43). Thus, commensals and IgA can regulate each other, and this interaction promotes peaceful mutualism between host and the gut microbiota.

In the intestine, T cells in the germinal center of gut-specific secondary lymphoid organs, such as Peyer’s patches, crypt patches, or isolated lymphoid follicles (ILFs), induce the generation of IgA⁺ B cells via TCR- and CD40L-dependent interactions (44). DCs in these lymphoid organs are required for the activation of follicular T cells to promote T cell–dependent and T cell–independent B cell activation (44). During T cell–dependent or –independent generation of IgA⁺ B cells, TGF-β and RA signaling are thought to be important for the induction of class switch recombination in B cells (45). It is known that LP DCs are capable of generating RA and activating the latent form of TGF-β through matrix metalloproteinases or integrin α₅β₃ (46, 47). Additionally, certain subsets of DCs in LP or lymphoid follicles express various factors such as TNF-α, inducible NO synthetase, BAFF, and proliferation-inducing ligand (APRIL) that promote the generation of IgA⁺ B cells (48). Various mechanisms have been proposed to explain the induction of IgA⁺ B cells by the intestinal microbiota. One mechanism involves a role for commensals in the formation of gut-specific lymphoid structures, which are essential for the generation of IgA⁺ B cells. Consistently, the generation and/or maturation of gut-specific lymphoid organs, such as Peyer’s patches and ILFs, are significantly decreased in GF mice or antibiotic-treated mice (49, 50). Furthermore, bacteria-derived molecules, including TLR ligands and NOD1 agonist, have been shown to be involved in the development of gut-specific lymphoid structures (50). Although experiments in gnotobiotic mice suggest that SFB induces IgA⁺ B cell development (51), the commensals species that stimulate the formation of lymphoid structures in the gut under steady-state conditions remain to be identified. It has become evident that bacteria recognition through MyD88 within follicular DCs is important for the generation of IgA⁺ B cells (52); however, the molecular link between the gut microbiota and activation of LP DCs remains poorly understood. Because LP DCs play a critical role in the development of IgA⁺ B cells (48), it is possible that the gut microbiota induces the expression of molecules such as RA, BAFF, an APRIL in LP DCs to trigger the development of IgA⁺ B cells.

**Microbiota-dependent regulation of innate lymphocyte development and function**

T and B lymphocytes play a major role in Ag-specific adaptive immune responses; however, some subsets of lymphocytes act as “innate” lymphocytes. Intraepithelial lymphocytes (IELs), including TCRβ⁺ T cells and TCRαβCD8αα T cells, are considered to be part of the innate lymphocyte family, although some of these cells also play a role in Ag-specific adaptive immunity (53). Although IELs express a skewed TCR repertoire and are activated through pattern recognition receptors (53), the Ag-specificity of these IELs is not fully understood. Given their close proximity to the intestinal lumen, IELs are thought to play a role in the regulation of immune responses against enteric pathogens and the commensal microbiota. However, a role for the gut microbiota in the development of IELs is still controversial. Several lines of studies have shown comparable or minimal differences in the number of IELs in GF mice and conventionally raised mice (54–56). The number of TCRαβCD8αα IELs and/or TCRβ⁺ IELs are comparable or modestly decreased in GF mice (54–56). In addition to the development of IELs, the gut microbiota may regulate the activation of TCRβ⁺ IELs. It is reported that production of the antimicrobial peptide RegIIIγ by TCRβ⁺ IELs is decreased in GF mice (57). Finally, microbiota-induced IL-1β and IL-23 can regulate the ability of IL-1R⁺ TCRβ⁺ T cells to produce IL-17 and to promote IL-17–mediated migration of neutrophils (58). RegIIIγ or IL-17 production by intraepithelial and/or lamina propria TCRβ⁺ innate-like T cells limits the penetration and dissemination of pathogens, including *Salmonella typhimurium* (57, 58). In addition to the protective role against pathogens, microbiota-induced RegIIIγ by γδIELs controls the composition of commensal bacteria (59). Thus, the gut microbiota and host IELs reciprocally regulate each other and control gut homeostasis.

Invariant NKT (iNKT) cells are another innate lymphocyte population that has been linked to gut homeostasis via the microbiota. Accumulation of iNKT cells in the gut is observed in GF mice, and increased iNKT cells promote susceptibility to colitis through upregulation of IL-4, IL-13, and IL-1β (60). Microbiota colonization can prevent Cxcl16 methylation, thereby reducing CXCL16 expression and preventing iNKT cell accumulation in the intestine. The microbiota-mediated reduction of Cxcl16 methylation is observed in neonatal, but not in adult, GF mice, suggesting that microbial exposure in early life is important for shaping the homeostatic development of the gut immune system (60). In addition to IELs and
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iNKT cells, NK-related cell types are considered to function as innate lymphocytes. These NK-related cell types are referred to as innate lymphoid cells (ILCs). Classical NK cells, which selectively produce IFN-γ, are considered as a type 1 ILC. Moreover, other ILC subsets, including IL-13–producing ILCs (ILC type 2 or nuocytes), IL-17–producing ILCs, and IL-22–producing ILCs, have been identified (61). Recent studies have revealed an important role for IL-22–producing ILCs in the regulation of gut immunity (62, 63). CD3−NKp46+ lymphocytes in mice and CD3−NKp44+ in humans were originally defined as a subset of IL-22–producing ILCs. These cells express the pan-NK cell marker NKp46 in mice (or NKp44 in humans), but they lack the expression of the NK cell marker NK1.1 and typical NK cell functions such as cytotoxic activity or IFN-γ production (62). Expression of the transcriptional factor RA orphan receptor (ROR)γt and production of IL-22 are two key features of the ILC subset (64-66). In addition to RORγtNKp46+ ILCs, other RORγt ILC subsets, which do not express NKp46, are present in the gut and play an important role in intestinal homeostasis (67). In the fetal intestine, RORγt-expressing CD3−CD4−/−CD127− cells, named lymphoid tissue inducer (LTI) cells, play a critical role in the generation of lymph nodes and Peyer’s patches. After birth, LTIi cells are also present in the intestinal LP as cell clusters called crypt patches, and they induce the development of ILCs (68). Recently, several studies have reported the presence of LTI-like cells in the adult intestine as a part of the IL-22–producing ILCs (69). LTIi-like ILCs include both CD3−CD4−RORγt−c-Kit−CD127− cells and CD3−CD4−RORγt−c-Kit+CD127+ cells (68). Thus, ILCs are heterogeneous and include multiple cell subsets of cells that need to be better defined.

A critical function of IL-22 is to promote antimicrobial peptide production by intestinal epithelial cells. IL-22 induces the expression of RegIIIβ and RegIIIγ, which are important for the regulation of the gut microbiota (59) (Fig. 1). Indeed, depletion of IL-22 or IL-22–producing ILCs causes intra- and extraintestinal overgrowth and/or dissemination of certain bacterial species, such as Alcaligenes xylosoxidans, that may increase the risk of subsequent intestinal damage and/or systemic inflammation (70).

The relationship between the development and function of ILCs and the gut microbiota is controversial. Some reports showed that the microbiota is required for the differentiation of RORγtNKp46+CD127+NK1.1− or RORγtNKp46+CD127+NK1.1+ ILCs (64, 65), whereas other studies concluded that the microbiota is dispensable but is nonetheless required for the production of IL-22 by NKp46+CD127+ NK1.1+ ILCs (64). In contrast, another study found that the microbiota is dispensable for the development of RORγt ILCs but suppresses the production of IL-22 by RORγt ILCs (71). In the latter study, GF mice exhibited an accelerated production of IL-22 by RORγt ILCs. The microbiota-dependent inhibition of IL-22 production by RORγt ILCs was mediated indirectly by intestinal epithelial cell–derived IL-25, which in turn activates IL-17R, a receptor for IL-25–expressing DCs in ILCs. Another recent finding has demonstrated that the gut microbiota stabilizes the expression of RORγt within NKp46+ ILCs (72). Commensals induce intestinal epithelial IL-17 production, which stabilizes the expression of RORγt and maintains the homeostatic phenotype of NKp46+ ILCs, such as IL-22 production (72). In contrast, the absence of the microbiota results in decreased IL-17 production and downregulation of RORγt gene expression in ILCs (72). As a consequence, ILCs are converted into IFN-γ–producing ILCs, which can promote intestinal inflammation (72). Thus, the gut microbiota can exert a homeostatic and pathogenic role in RORγt+ ILCs by regulating their development and function (Fig. 1).

Conclusions

There is clear evidence supporting a critical role for the microbiota in the development and functional regulation of the gut immune system. Additionally, intestinal immune cells may regulate, in turn, the composition and function of the microbiota. This flexible interaction between the host and the microbiota may determine, in part, the balance between peaceful mutualism and disease in the intestine. Mounting evidence suggests that different commensals play unique roles in the development and/or maintenance of intestinal immune populations. Furthermore, some members of the microbiota facilitate beneficial immune responses, such as the development of steady-state Th17 cells, induction or activation of Tregs, and the regulation of ILCs. Alternatively, some commensal populations referred to as “pathobionts” can promote harmful immune responses such as conversion of steady-state Th17 cells into pathogenic Th17 to elicit intestinal or systemic inflammation. Determining the genetic and functional differences between “beneficial commensals” and pathobionts may provide insight into mechanisms of disease. Collectively, the studies to date indicate that the link between the microbiota and the host immune systems is complex. Further work is needed to obtain a more comprehensive understanding of the relationship of host immune cells and microbes in the gut.

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