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Adaptive immune education by gut microbiota antigens

Qing Zhao and Charles O. Elson

Department of Medicine, The University of Alabama at Birmingham, Birmingham, AL, USA

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Correspondence: Dr Charles O. Elson, Department of Medicine, The University of Alabama at Birmingham, SHEL 607, 1825 University Boulevard, Birmingham, AL 35294, USA. Email: coelson@uabmc.edu
Senior author: Charles O. Elson

Summary

Host–microbiota mutualism has been established during long-term co-evolution. A diverse and rich gut microbiota plays an essential role in the development and maturation of the host immune system. Education of the adaptive immune compartment by gut microbiota antigens is important in establishing immune balance. In particular, a critical time frame immediately after birth provides a 'window of opportunity' for the development of lymphoid structures, differentiation and maturation of T and B cells and, most importantly, establishment of immune tolerance to gut commensals. Depending on the colonization niche, antigen type and metabolic property of different gut microbes, CD4 T-cell responses vary greatly, which results in differentiation into distinct subsets. As a consequence, certain bacteria elicit effector-like immune responses by promoting the production of pro-inflammatory cytokines such as interferon-γ and interleukin-17A, whereas other bacteria favour the generation of regulatory CD4 T cells and provide help with gut homeostasis. The microbiota have profound effects on B cells also. Gut microbial exposure leads to a continuous diversification of B-cell repertoire and the production of T-dependent and -independent antibodies, especially IgA. These combined effects of the gut microbes provide an elegant educational process to the adaptive immune network. Contrariwise, failure of this process results in a reduced homeostasis with the gut microbiota, and an increased susceptibility to various immune disorders, both inside and outside the gut. With more definitive microbial–immune relations waiting to be discovered, modulation of the host gut microbiota has a promising future for disease intervention.

Keywords: Microbiota; T cell; B cell; immune homeostasis; autoimmunity.

Introduction

When we think about the function of biological organs today, it is impossible to neglect the critical role of microbiota, especially the microbiota inhabiting the gastrointestinal tract, due to its enormous size, its diversity and, most importantly, its effects on the biological functions of the host. There are about $3{\cdot}8 \times 10^{13}$ bacteria, belonging to up to 1000 species,[1,2] colonizing the gut of a healthy human adult, plus a variety of fungi, viruses and archaea bacteria, which have been less studied.[3,4] Homeostasis between the host and its microbiota is the result of long-term co-evolution: gut microbiota relies on the host environment and nutrients for its survival, and in return provides the host with essential metabolites that promote a proper functioning of multiple organ systems. Generally, in a healthy adult gut, Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria and Verrucomicrobia are the five dominant bacterial phyla, with the first two being the most relatively abundant.[5] Descending from the duodenum to the distal colon, due to physiological and immunological differences along the intestine, the number and diversity of bacteria increase, and the predominant bacterial families change.[6] The continuous mutual selection between the host and the microbes during evolution has resulted in a set of host-specific microbiota. For instance, although the phyla are similar between human and mouse gut microbiota, there are significant differences in the bacterial species in different hosts.[7,8] The full maturation of the host immune system is dependent on their natural harbouring of host-specific microbiota, because colonization of germ-free (GF) mice with

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human or rat microbiota fails to induce an effective immune response and fails to provide protection against enteric infection.[8] Segmented filamentous bacteria (SFB, also known as *Candidatus Savagella*),[9] which are potent inducers of the murine adaptive immune response including gut T helper type 17 (Th17) cell differentiation[10–12] and IgA production,[13,14] are genetically different in mice and rats.[15] And interestingly, although it has been intensively studied in mouse models, a species that is genetically related to SFB has not been identified as yet in humans.[16]

In the past decade, many studies have focused on the interactions between the host immune system and the gut microbiota. The innate immune system rapidly responds to the gut microbiota in an antigen-nonspecific manner through the activation of pattern recognition receptors, and releases cytokines such as interferon-α, interleukin-18 (IL-18) and IL-22 to promote epithelial antimicrobial responses such as the production of antimicrobial peptides.[17] The recently defined innate lymphoid cells mimic the cytokine production of T cells in an antigen-nonspecific way.[18] Although mice lacking adaptive immunity survive well with their microbiota in a specific pathogen-free (SPF) environment, they have a greater vulnerability to opportunistic infections, such as *Pneumocystis carinii* pneumonia.[19] Similarly, HIV-infected individuals are very susceptible to infections due to their greatly decreased CD4 T cells.[20] Different from the innate immune system, the adaptive immune compartment recognizes specific microbial antigens through its highly mutated cell surface receptors[21] and depending on the type of bacteria it encounters, naive T cells can differentiate into either effector T cells to fight against the bacteria, or into regulatory T (Treg) cells to tolerate their presence and promote mutualism. Although it takes time for the adaptive immune system to differentiate and proliferate to respond to microbial antigens after the first encounter, some of the antigen-experienced memory cells survive long-term and provide a strong and timely response in a recall encounter.[22]

In this review, we will focus on the interactions between the host adaptive immune system and the gut microbiota, in particular how the adaptive immune compartment recognizes microbiota antigens and regulates microbiota composition to maintain gut homeostasis, and reciprocally how an abnormal composition of the microbiota or dysbiosis affects the host immune system and may result in mucosal or systemic immune disorders.

Early-life host–microbiota interactions and 'window of opportunity'

It is widely accepted that the first burst of microbial encounter occurs at the moment of birth.[23] Although evidence of prenatal microbiota in the placenta has emerged, the numbers and effects are small compared with microbial colonization after birth.[24–26] Several factors, including mode of delivery, breastfeeding,[23,27] antibiotics[28] and environmental exposure,[29,30] have been shown to greatly modulate the dominant bacteria of the neonate's early gut colonizers, which can exert long-term health effects in the offspring.[31] Therefore, restoring the gut microbiota of newborns delivered by caesarean section with exposure of maternal vaginal fluids or addition of probiotics into formula may lower disease susceptibility in childhood, and even into adulthood.[32] Besides microbial antigens,[33] breast milk contains a considerable amount of maternal antibodies that not only help to establish the microbial composition, but also dampen excessive follicular T-cell and germinal B-cell responses to gut microbes in neonatal mice.[34] Maternal IgA has been shown to provide protection of the newborn from epithelial translocation of opportunistic bacteria such as *Ochrobactrum anthropi*, and to provide long-term benefits by preventing intestinal inflammation.[35] The transition from breast milk/formula to solid food triggers the first major wave of the gut microbiota expansion,[36] and depending on the diet and lifestyles, the composition of the gut microbiota continues to change with age towards adulthood.[37]

The gut microbiota remains unstable during neonatal life, which creates a crucial 'window of opportunity' for the development of the host immune system. This process generally takes about 4–6 weeks in mice, and 2–3 years in children,[38–41] until the microbial community reaches a relatively stable status, which is then maintained into adulthood. Because of the close proximity between the enteric microbes and the gut mucosal barrier, the most dramatic impact that the microbiota brings to host immune development is on the mucosal compartment. Although cryptopatches, Peyer's patches (PPs) and mesenteric lymph nodes form prenatally,[42] postnatal microbial stimulation further promotes their development, including the formation of isolated lymphoid tissues from cryptopatches,[43] further recruitment of T and B cells into the lamina propria (LP) and PPs,[44] and T-cell differentiation and B-cell maturation (discussed below). Depending on the variations of gut microbial introduction and colonization postnatally, host immune development can differ dramatically and result in altered immune reactivity that could affect the host's susceptibility to diseases such as autoimmune and allergic diseases in later life. Insufficient microbial stimulation in neonatal mice results in increased IgE class switching of mucosal B cells and elevated serum IgE level in a CD4 T-cell-dependent manner, a process reversed by colonization with conventional gut microbiota immediately after birth, but not in adulthood.[45] Similarly, invariant natural killer T-cell accumulation is observed in GF mice, which is associated with increased susceptibility to inflammatory bowel disease compared with SPF mice. However, microbiota

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conventionalization of neonatal GF mice reduced the increase of invariant natural killer T cells in the gut and lung, whereas colonization in adulthood had no such beneficial effect.[46] This time-sensitive perturbation of invariant natural killer T-cell homeostasis was regulated by bacterial sphingolipids produced by *Bacteroides fragilis*.[47] Early-life exposure to antibiotics also has a potentially detrimental impact on the host due to the instability of gut microbiota and hence an altered differentiation of immune cells.[48] Gut microbiota disruption introduced by early-life antibiotics can remain altered during adulthood even with normal environmental exposure.[49] Oral administration of antibiotics in adult mice ameliorated psoriasis severity, whereas neonatal exposure to antibiotics exaggerated psoriasis progression, an effect mediated by IL-22-producing T cells in the skin.[49] Neonatal antibiotic exposure in both mice and humans enhanced the sensitization to various allergens due to an altered gut microbiota, resulting in increased risk of childhood atopy, asthma and food allergies.[50–52] Treg cells play an important role for establishment of immune tolerance in this early life. Compared with adult mice, neonatal mice harbour a higher fraction of Treg cells in their gut CD4 compartment as well as a stronger suppressive function.[53] Maternal antibodies help to prevent the translocation of luminal antigens present in the dam.[35] As a consequence, effector CD4 cell functions are actively repressed before weaning.[53] However, at weaning, shifts in the gut microbiota are associated with induction of peripheral Treg cells (pTreg), and a change in thymic Treg (tTreg)/pTreg ratio.[54] There is a critical time window before weaning for the establishment of commensal-specific pTreg cells in mice via goblet-cell-associated passages, and disruption of these goblet-cell-associated passages during this critical time leads to an impaired control of gut homeostasis later in adulthood.[55]

As the host ages, the gut microbiota remains relatively stable with minor fluctuations. However, antibiotics and dietary changes can still bring compositional and functional changes to the gut microbiota.[37,56–58]

T cell–gut microbiota interactions

Conventionally, T-cell education refers to thymic selection, by which immature T cells with high self-reactivity are eliminated or converted to Treg cells to prevent autoimmunity.[59] More recent studies have included peripheral education by gut microbial antigens as a form of T-cell education, which also maintains homeostasis.[60,61] In addition to physical separation of the microbiota from the intestinal immune cells by the mucus, the epithelial layer, antimicrobial peptides and secretory antibodies, a major component maintaining gut homeostasis are Treg cells, including canonical Foxp3-expressing Treg cells,[62] IL-10-expressing Foxp3$^-$ Treg type 1 cells,[63] and the newly defined regulatory intraepithelial CD4$^+$ CD8$\alpha\alpha^+$ T cells.[64] Although Treg cells are present in the gut mucosa postnatally regardless of microbial colonization,[54] in adult mice, certain endogenous bacteria (Clostridium clusters IV, XIVa and XVIII),[65,66] bacterial products (*B. fragilis* polysaccharide),[67] or bacterial metabolites (short-chain fatty acids including acetate, butyrate and propionate),[68–70] can induce functional Treg cells in the colonic LP (Fig. 1) and provide protection to immune-related diseases locally or systemically.[71,72] Further analyses of transcription factors and T-cell receptor (TCR) repertoire suggest that gut Treg cells that are present before weaning are mainly of thymus origin (tTreg), because they express the tTreg-specific transcription factor Helios and surface marker Neuropilin-1.[73–75] In contrast, Treg cells induced by microbiota colonization express low levels of Helios,[54] and they may use a different TCR repertoire,[60,61] indicating that they are a result of pTreg induction instead of expansion of tTreg cells. Induction of pTreg cells was shown to occur primarily in the mesenteric lymph nodes with robust Foxp3$^+$ cell proliferation.[54] As stated earlier, gut Treg cells are required to help establish oral tolerance to food antigens as well as to the enteric microbiota. Co-transfer of Treg cells with CD45RB^{hi} T cells abrogates colitis in immunodeficient mice.[76] It has also been suggested that conversion from Th17 cells into Treg cells in late-phase colitis helps to resolve inflammation.[77] MyD88-Stat3-dependent sensing of gut microbiota in Treg cells is indispensable for the induction of intestinal IgA and the restraint of pro-inflammatory T-cell responses in the gut.[78] Using the CBir1 flagellin TCR transgenic mouse model, of which > 85% CD4 T cells recognize the epitope expressed on the flagellin of the *Lachnospiraceae* family of Clostridiales, Treg cells provide tolerance to commensal bacteria by promoting the survival of antigen-specific IgA$^+$ B cells,[79] because depletion of Treg cells with anti-CD25 resulted in the loss of intestinal IgA B cells. Similarly, using adoptive transfer models, it was shown that failure of pTreg induction for selected microbiota antigens results in T effector cell differentiation and increased susceptibility to intestinal inflammation.[80] Nonetheless, Treg cells can accomplish their suppressive function both in antigen-specific and bystander ways through the secretion of anti-inflammatory cytokines transforming growth factor-β and IL-10,[81] and the induction of IgA, either directly or through the promotion of T follicular helper (Tfh) cells[78,82] and T follicular regulatory cells,[78,83] to maintain gut homeostasis.

The other main T-cell subset that has been studied the most regarding microbiota education comprises Th17 cells. The CD4$^+$ Th17 subset is characterized by expression of master transcription factor Rorγt, and the production of cytokines including IL-17F, IL-17A, IL-21 and IL-22.[84] Th17 cells are considered to be pathogenic

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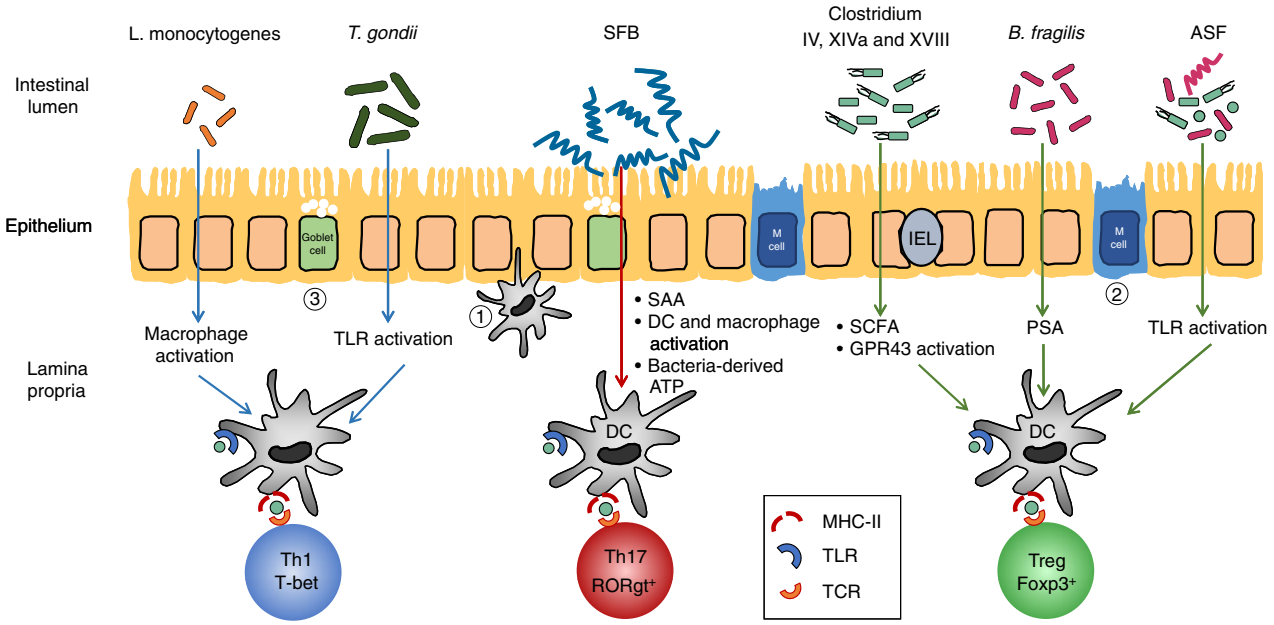

Figure 1. Microbiota induction of intestinal regulatory T (Treg)/ effector T (Teff) cell differentiation. Commensal bacteria such as Clostridium cluster IV, XIVa and XVIII, *Bacteroides fragilis* and altered Schaedler flora (ASF) promote the differentiation and expansion of Treg cells in the gut through various mechanisms, whereas microbially derived ATP and epithelium-adhering bacteria such as segmented filamentous bacteria (SFB) stimulate the induction of intestinal Th17 cells. Antigen-specific Th1 cell differentiation can be promoted by intracellular pathogens such as *Listeria monocytogenes* and *Toxoplasma gondii*. Microbiota antigens are sampled via (1) transepithelial dendrites of dendritic cells (DC), (2) transcytosis through microfold cells (M cell), or (3) goblet cell-associated antigen passages (GAP) and then induce T-cell differentiation in the mesenteric lymph nodes or *de novo* in the lamina propria. Teff cells and Treg cells are both plastic and can convert into each other and into other T-cell subsets under certain conditions.

because of their ubiquitous presence in a variety of inflammatory disorders. However, more recent studies have revealed a Th17 homeostatic role in the gut.[85] In SPF mice, Th17 cells are among the most abundant effector CD4 T cells in the healthy gut LP. Unlike the gene expression signature of pathogenic Th17 cells isolated from an inflammatory milieu, homeostatic Th17 cells have a significantly lower level of pro-inflammatory transcripts including *Tnf*, *Ifng* and *Il23a*, and an up-regulated expression of anti-inflammatory genes, such as *Ctla4*, *Icos* and *Il22*.[86] The majority of Th17 cells in the murine intestinal LP are reactive against microbiota antigens, in particular to SFB.[87,88] GF mice or mice provided from the Jackson Laboratory (Bar Harbor, ME), which do not harbour SFB, have low numbers of Th17 cells in their gut LP.[10,11] Unlike other commensals that are mainly present in the mucus layer or intestinal lumen, SFB attach and penetrate into the epithelium of terminal ileum.[11,16] It is postulated that this unique property results in the induction of Th17 cells. In agreement with this hypothesis, epithelial cell adhesive bacteria *Citrobacter rodentium*, *Escherichia coli* O157, and a mixture of 20 bacterial strains isolated from human gut with properties of epithelial adherence were shown to induce gut Th17 cells in mice.[89] Although it is still not entirely clear where and how the induction of Th17 cells happens, several groups have shown that this process primarily happens *de novo* in the small intestine and requires MHC-II expressing intestinal dendritic cells and macrophages.[88,90] Innate lymphoid 3 cells are also suggested to participate in the induction of SFB-specific Th17 cells through secretion of IL-22.[91] SFB-specific Th17 cells are found in the peripheral lymphoid organs beyond the intestine, which could potentially contribute to the vulnerability to some autoimmune diseases in genetically susceptible hosts.[92,93] In addition to previously proposed molecular mimicry and bystander activation theories as to the mechanism for microbiota-reactive T cells to trigger autoimmunity,[94,95] a recent study in a lung autoimmune mouse model showed that SFB selectively expanded Th17 cells that expressed dual TCR, one of which recognized SFB peptide and the other directed at a self-antigen.[96]

Compared with the induction of intestinal Treg and Th17 cells, much less is known about the role of specific commensal microbiota on Th1 and Th2 cell differentiation. Reduced abundance and diversity of Bacteroidetes were associated with a decreased Th1 response in infants delivered by caesarean section.[97] Colonization of GF mice with the polysaccharide-expressing bacteria *B. fragilis* corrected an imbalance between Th1 and Th2 cells.[98] *Listeria monocytogenes*[99] and *Toxoplasma gondii*[100] infections drove an antigen-specific Th1 response in the host.

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Colon-resident *Helicobacter* spp. have dual roles for T-cell responses, including pTreg induction at homeostasis, and driving differentiation of Foxp3 to effector T cells during colitis.[101] The microbiota has effects on Tfh cell number and function, and conversely Tfh in turn can modulate the microbiota. Compared with SPF mice, GF mice have a substantial reduction of Tfh cells in the PPs.[102] Programmed cell death-1-deficient mice, which lack Tfh cells, showed a significant reduction of anaerobic bacteria in the gut.[103] Also, Tfh cells are able to sense bacterial ATP through the receptor P2X7, and in turn shape gut microbiota composition.[104] SFB promotes PPs Tfh cell differentiation and dissemination into systemic sites, leading to an increased production of autoantibodies and worsened arthritis.[93]

B-cell–gut microbiota interactions

T-cell-dependent and -independent B cells complete the other half of the adaptive immune system via production of antibodies that protect the host against microbial invasions.[105] T-cell-dependent B-cell production of antibodies has been linked to microbial antigen exposure. Although B cells are present in the gut-associated lymphoid tissues, including PPs and mesenteric lymph nodes, before birth,[42] microbiota antigens and microbial metabolites, such as short-chain fatty acids, strongly promote plasma cell differentiation in both mucosal and systemic sites.[106] IgA serves as the major form of secretory antibody present at the mucosal surface and so plays a critical role in maintaining gut homeostasis.[107] Potential mechanisms include binding and prevention of uptake of microbial antigens in the lumen,[79] bacterial disruption and agglutination,[108,109] enchaining of growing bacteria,[110] and neutralization of pathogenic bacterial toxins.[111,112] Multiple mechanisms have been advanced to explain the establishment of mutualism between secretory IgA and gut microbiota. Secretory IgA can induce members of the microbiota such as *Bacteroides thetaiotaomicron* to downregulate the expression of pro-inflammatory surface epitopes.[113] Coating of some luminal bacteria by secretory IgA guides bacterial entry into the PPs, where a germinal centre response is induced and a positive loop of antigen-specific IgA production is established.[114] Microbial antigen recognition mediated by different MHC repertoires also contributes to altered IgA repertoires, which in turn modulates microbiota composition in the gut.[115]

Due to physical proximity, the gut microbiota greatly influence the production of intestinal IgA.[13] Lack of intestinal microbial stimulation results in fewer numbers of IgA^+ plasma cells in the gut and reduced abundance of IgA.[14,116,117] This is possibly because of a compromised development of isolated lymphoid tissues – a major site for T-cell-independent IgA production.[118] SFB potently promotes T-cell-independent IgA production through stimulation of postnatal development of isolated lymphoid tissues and tertiary lymphoid tissue in the gut.[13,14] A fraction of anti-microbial IgA in the gut is polyreactive and generated from this high-capacity low-affinity pathway.[119–121] However, the majority of intestinal IgA is T-cell-dependent, particularly that directed at bacterial protein antigens, and is part of a low-capacity and high-affinity pathway. This T-dependent IgA mainly occurs in the PPs by B cells interacting with antigen-loaded dendritic cells in a CCR6-dependent manner.[122,123] Bacteria such as SFB and *Mucispirillum* sp. able to adhere to epithelial cells are potent inducers of T-cell-dependent IgA,[120] probably by enhanced uptake of their antigens into dendritic cells. IgA-producing B cells home to the intestinal LP, where IgA is produced and then transported across the epithelium into the gut lumen through polymeric immunoglobulin receptor expressed on the basolateral side of epithelial cells.[124] Polymeric immunoglobulin receptor deficiency leads to the abrogation of IgA and IgM transcytosis, resulting in increased serum IgG antibodies against gut commensals and pathogens,[125] demonstrating the important role of secretory antibodies in limiting systemic exposure to microbiota antigens.

Although studied for several decades, the role of gut microbiota in IgA induction was intensely investigated in the past few years. The application of flow cytometry with 16S rDNA sequencing, a technology referred as IgA-Seq, has enabled the identification of IgA-bound versus IgA-unbound bacteria isolated from the gut. The IgA-bound bacteria vary according to the study and the composition of the microbiota at different laboratories. The bacterial surface antigens bound by IgA in this approach are largely carbohydrates.[121] Enrichment of *E. coli* and other *Enterobacteriaceae* was identified with high IgA coating in patients with Crohn's disease-associated spondyloarthritis and diet-dependent enteropathy, respectively.[126,127] Another study showed that colonization of GF mice with IgA-coated bacteria from patients with inflammatory bowel disease, exacerbated dextran sulphate sodium-induced colitis.[128] However, the characterization of all IgA-coated gut bacteria as 'pathobionts' is not warranted given the complexity of the microbiota and of bacteria–host interactions within the gut.

Gut IgA repertoires are highly diverse and distinct to individuals, which is even true in bacterial mono-colonized mice.[129] Using a reversible microbial colonization system *in vivo*, the production of antigen-specific IgA did not require persistent bacterial colonization, and once an antigen-specific B-cell response was established in the gut, the magnitude of that IgA response was long-lived unless new microbial species were encountered.[117] As mice age, their IgA repertoires become more complex with new B-cell clones continuously generated against new microbiota antigens; however, B-cell clones induced in early life are also maintained, indicating a long-lived memory B-cell

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response.[116] SPF mice have a much greater diversity of gut IgA repertoires than bacterial mono-colonized mice or GF mice.[129] These IgA-switched memory B cells recirculate between multiple lymphoid tissues inside and outside the gut, and can differentiate to plasma cells in the mammary glands, which contributes to antibody production in the breast milk that helps protect and establish the microbiota in offspring gut.[129]

In addition to intestinal IgA, IgM and some IgG subclasses also bind gut microbiota, the majority of which are elicited through the T-cell-independent pathway.[34,130] In mouse, B1 cells serve as the major source for polyclonal low-affinity anti-commensal IgM responses as a primitive natural antibody response.[130] However, in contrast to mice, humans have more abundant IgM^+ plasma cells in the gut, which secrete IgM antibodies that help retain a diverse community of commensals in the mucus layer in synergy with IgA.[131] Surprisingly, a considerable amount of IgG2b and IgG3 has been identified in the secretory compartment in the gut as well. The generation of these antibodies is dependent on Toll-like receptor signalling through B cells but independent of T-cell help, in that TCR-$\beta\delta^{-/-}$ mice have levels comparable to those of wild-type mice.[34] The IgD isotype is rare compared with other antibody isotypes, but recently it was shown that IgD class switch recombination happens preferentially in mucosal sites and is dependent on a diversified gut microbiota.[132]

Gut microbiota-adaptive immunity interplay in immunological disorders, and potential therapeutic applications of microbiota modulation in disease interventions

Immune recognition of gut microbiota is shown to trigger multiple inflammatory disorders. For example, both mucosal and serum antibodies targeting gut commensal antigens are elevated in individuals with Crohn's disease and those with ulcerative colitis.[133–136] Infiltrating T cells in the gut of Crohn's disease patients react to luminal microbial antigens and produce pro-inflammatory cytokines including tumour necrosis factor-α, interferon-γ and IL-17A.[137–139] Studies from our group and others have shown that flagellin of gut commensal bacteria, specifically bacteria belonging to *Lachnospiraceae* family of the Clostridiales, serve as immunodominant antigens in both experimental mouse colitis and in Crohn's patients.[134,140] CD4 T cells reactive to these flagellins can be activated during enteric pathogenic infections and form memory cells that persists in the host,[141] then serve as a potential reservoir for pathogenic effector cells or regulatory cells when they are reactivated later. Adoptive transfer of naive CD4 cells from CBir1 TCR transgenic mice into immunodeficient mice induces severe colitis, which is dependent on the colonization of CBir1 flagellin-expressing bacteria in the gut of the recipient mice.[142] *Lachnospiraceae* A4, which has flagellins similar to CBir1, was shown to induce transforming growth factor-β production in dendritic cells and so inhibit Th2 cell differentiation.[143] In agreement with this, CBir1 TCR transgenic CD4 T cells isolated from inflamed colon of adoptive recipients have a strong profile of interferon-γ and IL-17A expression, indicating that this colitis is mainly driven by flagellin-reactive Th1 and Th17 cells.[142]

Autoimmune diseases that are outside the gut can be triggered by the enteric microbiota. It has been shown that *Prevotella copri* colonization activates autoreactive T cells in the gut and correlates with increased susceptibility of rheumatoid arthritis.[144,145] *Prevotella copri*-specific IgG and IgA were found in subgroups of individuals with new-onset rheumatoid arthritis but not in disease or healthy controls. Gut microbiota is also needed for the induction and acceleration of experimental autoimmune encephalomyelitis (EAE) in the relapsing–remitting mouse model, via activation of myelin oligodendrocyte glycoprotein-specific T cells and recruitment of autoantibody-producing B cells into the brain-draining lymph nodes.[146] Human studies found that *Akkermansia muciniphila* and *Acinetobacter calcoaceticus* were expanded in untreated multiple sclerosis (MS) patients, and colonization of germ-free myelin oligodendrocyte glycoprotein T-cell transgenic mice or wild-type mice with MS patient gut microbiota increased the incidence and disease severity of EAE, with a compromised Treg differentiation in the mesenteric lymph nodes.[147]

Gut dysbiosis is commonly associated with autoimmune disorders and metabolic syndromes in both mice and humans. Microbiome dysbiosis is defined as an altered gut microbiota composition together with a functional change in the microbial transcriptome, proteome or metabolome. However, a causal relationship between dysbiosis and the change of host immune response remains difficult to determine and awaits further definitive studies. Garrett *et al.*[148] provided the first solid evidence that a disrupted consortium of gut microbiota in T-bet-deficient $Rag^{-/-}$ mice could be transmitted to wild-type mice, and induce colitis in the latter. Studies have been performed to seek the relationship between dysbiosis and inflammatory bowel disease in humans as well. In a large cohort, an alteration of gut microbiota in treatment-naive new-onset Crohn's disease patients was identified; a set of taxa was identified with strong correlation with disease status, and antibiotic treatment further amplified the dysbiosis.[149] Similarly, dysbiosis is observed in patients with ulcerative colitis, with a reduction of *Roseburia hominis* and the anti-inflammatory bacteria *Faecalibacterium prausnitzii*[150] compared with healthy controls.[151]

Immune cells primed in the gut under the influence of an altered gut microbiota can contribute to the pathogenesis of systemic autoimmune diseases and can alter the

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outcome of cancer immunotherapy. Certain bacterial colonization, such as SFB in EAE and autoimmune arthritis, and *Prevotella copri* in murine autoimmune arthritis, are linked to increased disease susceptibility.[92,145,152] Gut microbiota was shown to participate in the modulation of anti-tumour immunotherapies as well, through the regulation of responses of different T-cell subsets.[153–156] Therefore, normalization of the gut microbiota of patients with inflammatory bowel disease or autoimmune diseases is increasingly suggested as an approach of disease intervention. So far, the treatment of *Clostridium difficile* infection with faecal microbiota transplantation has been remarkably effective.[157] However, the human gut microbiota is such a complex entity that it is under the influence of various factors, including host genetics, diet, environmental effects, antibiotics and competitions/interactions among members of the microbiota. With a small number of defined bacteria that are able to regulate the host immune responses, and countless unknown participants to be identified, further definitive evidence is required for a broader utilization of faecal microbiota transplantation and/or other proposed microbial modulation approaches such as probiotics and prebiotics in the treatment of dysbiosis-associated diseases.

Disclosures

The authors have no competing interests.

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