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HIGHLIGHTS

REVIEW

Non-zero-sum microbiome immune system interactions

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Fundamental asymmetries between the host and its microbiome in enzymatic activities and nutrient storage capabilities have promoted mutualistic adaptations on both sides. As a result, the enteric immune system has evolved so as not to cause a zero-sum sterilization of non-self, but rather achieve a non-zero-sum self-reinforcing cooperation with its evolutionary partner the microbiome. In this review, we attempt to integrate the accumulated knowledge of immune—microbiome interactions into an evolutionary framework and trace the pattern of positive immune—microbiome feedback loops across epithelial, enteric nervous system, innate, and adaptive immune circuits. Indeed, the immune system requires commensal signals for its development and function, and reciprocally protects the microbiome from nutrient shortage and pathogen outgrowth. In turn, a healthy microbiome is the result of immune system curatorship as well as microbial ecology. The paradigms of host–microbiome asymmetry and the cooperative nature of their interactions identified in the gut are applicable across all tissues influenced by microbial activities. Incorporation of immune system influences into models of microbiome ecology will be a step forward toward defining what constitutes a healthy human microbiome and guide discoveries of novel host–microbiome mutualistic adaptations that may be harnessed for the promotion of human health.

Keywords: enteric nervous system · gut-brain axis · immune system · microbiome · mutualism

Introduction

The host–microbiome mutualistic networks are fundamentally asymmetric in their interactions. The collective genomes of microbiome members harbor at least two orders of magnitude more genes than the human genome. The latest estimates of the size of microbial genomic space based on the analysis of 2182 gut microbiome metagenomes put it at 22,254,436 non-redundant consensus genes, although about half of which are unique to a single sample [1]. In contrast, the size of the human genome is estimated to be 42,611 genes and only about half of them are protein-coding [2]. Therefore, the enzymatic capacity of the microbiome is much greater than the host. Furthermore, while the genome of the host is stable throughout its life, the collective genome of microbiome adapts in response to external factors (e.g., diet change) and evolves under the influence of both positive [3] and negative [4] selections. The host-microbiome genetic asymmetry has provided powerful evolutionary incentives for the host to harness the enzymatic potential of the microbiome to access otherwise unavailable small molecules and energy sources. In addition to the genetic host–microbiome asymmetry, the unique positioning of the microbiome at the interface between the host and environment creates additional evolutionary forces for the host to develop the capability to curate the microbiome's composition, both through positive reinforcement by supporting the beneficial members as well as through negative pressure by deselecting parasitic and pathogenic members of the microbiome. To achieve

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this goal, the host mucosal immune system employs a highly efficient, layered defense strategy featuring passive measures, such as the mucus barrier that creates a bacteria-free zone separating the enteric epithelium from the microbiota [5–7], as well as active measures, such as the production of antimicrobial peptides (AMPs) and secretory IgA antibodies. The limited resources of the mucosal immune system are deployed in a coordinated and timely manner, notably through the involvement of intestinal epithelial cells (IECs), myeloid cells, innate lymphoid cells (ILCs), and the enteric nervous system (ENS), together with adaptive immune cells. For instance, in mice upon infection by pathogens, the ENS affects the development of IECs [8], activates ILCs [9,10], and simultaneously engages damage-control transcriptional programs in macrophages [11].

There is also an opposite direction of the asymmetric host–microbiome partnership: the host is capable of storing energy, whereas the microbiome is unable to do so. Taking advantage of this asymmetry, the host supports the beneficial members of the microbiome by supplying dietary polysaccharides or secreting sugar- and lipid-decorated proteins into the lumen. In times of nutrient scarcity, the host uses its reserves to support the beneficial members of microbiome, for example, by fucosylation of the epithelium, thus protecting the commensals from starvation [12]. Such support of metabolically beneficial commensals indirectly leads to protection of the host from pathogenic infections through their occupation of the limited ecological niches—a concept known as colonization resistance [13].

At the fundamental level, the host–microbiome mutualism is based on cooperative behavior between two entities in which the actions of one depend on those of the other with the overall goal being homeostasis. Mathematically, given that an interaction between two entities has a defined goal and follows logical rules, such an interaction can be analyzed and an optimal strategy for each participant as well as important characteristics, such as boundary conditions where the interaction breaks down, may be calculated. The framework for the analysis of strategic interactions is termed "game theory" [14]. The theory was first developed from considerations of simplified strategic interactions namely zero-sum games (e.g., poker) in which the sum of wins and losses of all players equals zero or in other words described strictly competitive interactions. Later the theory was expanded onto non-zero-sum interactions such as cooperation and it became clear that any kind of strategic interaction could be represented as a "game" and viewed in a framework of the theory [15]. The nature of immune system–microbiome interactions is not a zero-sum sterilization of non-self, but can be viewed as a non-zero-sum cooperation between interdependent evolutionary partners [16]. The non-zero-sum interaction with the microbiome mediates robustness and tunability in the immune network. This self-reinforcing mutualistic host–microbiome coevolution is well captured by the concept of the microbiome as an extra organ of the human body [17]. A baseline understanding of their interdependent interactions also provides insights into how its collapse influences disease risk and what are potential targets for future lifestyle, drug, probiotic, prebiotic, and live biotherapeutic interventions. Herein, we summarize recent progress toward deciphering the principles of microbiome–immune bidirectional interdependent interactions in the intestine. As causality studies are predominantly only possible in animal models, unless stated otherwise research reviewed herein was performed in mice.

The innate immune system as the regulator of gut barrier function and immune homeostasis

During the past decade, there have been significant advances in our understanding of the gut microbiome and immune system bidirectional interactions. Molecular and cellular investigations have identified numerous cell types and molecules critical for microbial recognition and circuitry of signaling cascades to mount homeostatic and inflammatory immune responses. In particular, IECs, ENS, myeloid cells, and ILCs have been revealed to play critical roles as force multipliers to handle the otherwise uneven host-microbiome standoff (Fig. 1–3).

Intestinal epithelial cells

Despite their non-hematopoietic origin, IECs constitute a major part of the mucosal innate immune system in the context of both health and disease. A single cell layer of IECs forms the border that separates the host from the microbiome and the environment. Therefore, IECs need to simultaneously fulfill roles of a physical barrier guarding self from non-self as well as a conduit facilitating the bidirectional interaction between the host's immune system and the microbiome. Despite the single-cell layer organization, intestinal epithelium is functionally subdivided into distinct biogeographical niches spanning from the tip of villi to the bottom of the crypts. The bottom of the crypts serves as a niche for $LGR5^+$ intestinal stem cells (ISCs), early progenies of ISCs, as well as Paneth cells that secrete AMPs into the lumen, preventing most bacteria from reaching the ISCs niche [18]. The villus body fulfills the absorptive, sensory, and secretory roles.

The epithelial layer is maintained by the proliferative activity of ISCs, which differentiate into six major IEC types. The absorptive lineage progenitors develop into enterocytes and microfold (M) cells, while the progenitors of the secretory lineage give rise to Paneth cells, goblet cells, enteroendocrine cells, and tuft cells [19, 20]. The enterocytes absorb nutrients and serve as a physical barrier. Enteroendocrine cells sense distinct dietary components, regulate intestinal motility, and modulate feeding behavior through the gut–brain axis [21]. Tuft cells detect parasite-associated metabolites and elicit a type 2 immune response [22–25]. Secretions from goblet cells form the mucus barrier precluding most bacteria from direct contact with the epithelium [26]. Located in Peyer's patches, M cells sample luminal antigens, helping promote IgA responses and thus curating the microbiome composition [27, 28]. The number of M cells is tightly regulated

by gut-innervating nociceptor sensory neurons and is reduced upon sensing by the neurons of *Salmonella typhimurium* that uses M cells as entry points for mucosal infection [8].

IECs perceive the microbiome composition directly via innate immune receptors as well as indirectly via recognition of microbiome-associated metabolites. Microbial recognition by IECs via innate immune receptors is vital for maintaining mucosal health. Indeed, IEC-specific deletion of elements of TLR signaling such as MyD88 [29], NEMO [30], and TRAF6 [31], as well as whole-body knock-out of NOD2 [32, 33], the DNA sensor AIM2 [34], or components of the NLRP3- or NLRP6-dependent inflammasome [26, 35-37] lead to either spontaneous severe pancolitis [30], spontaneous activation of small intestinal adaptive immune cells [29], or enhanced susceptibility in models of intestinal injury [26, 31-37]. Mechanistically, the absence of innate immune signaling results in decreased Paneth cell numbers and consequently lower luminal concentration of AMPs as well as reduced mucin production by goblet cells, allowing more bacteria to come into direct contact with the epithelium and promote mucosal inflammation.

In addition to fortification of the mucosal barrier through the secretion of AMPs and mucin, IECs serve as non-classical antigen presenting cells of microbial components. IECs in the small intestine take up luminal antigens [38–40], process [41] and present them via MHC class II (MHC-II) to T cells [42, 43]. In the crypt niche, $LGR5^+$ ISCs also express MHC-II and present luminal antigen to $CD4^+$ T cells, which reciprocally regulate differentiation rates of ISCs. $CD4^+$ T cell-derived proinflammatory cytokines such as IFN-γ, IL-17A, and IL-13 promote active differentiation of ISCs, whereas regulatory IL-10 attenuates differentiation and promotes self-renewal [44]. Therefore, renewal of damaged IECs is accelerated upon detection of pathogen infection, whereas ISCs prioritize conservation of resources under homeostatic conditions. In the villus niche, MHC-II-mediated interactions between mature enterocytes and intraepithelial $IL\text{-}10^+$ $CD4^+$ T cells regulate intestinal permeability diurnally to adapt barrier properties to fluctuating luminal antigenic load [45]. Diurnal nutrient intake, and consequently fluctuating microbiome composition, leads to dramatic differences in antigenic load at different times of the day [46, 47]. The mechanisms regulating intestinal permeability compensate for the antigenic fluctuations, preventing the mucosal sensory system from overloading at high antigen tide and maximizing its sensitivity at low tide. In addition to adapting regenerative or barrier properties of the epithelium, antigen sampling by IECs contributes to selecting inflammatory microbes to be targeted by humoral and cellular immune responses and thus actively curates the microbiome composition. Indeed, enterocytes sample antigens of mucosa-attaching bacteria such as segmented filamentous bacteria (SFB) by employing clathrin-independent, dynamin-dependent cell division control protein 42 (CDC42) mediated endocytosis [40]. Such microbial adhesion-triggered endocytosis (MATE) results in the induction of an SFB antigen-specific mucosal Th17 response [40], suggesting a mucosa-cleansing role of MATE. M cells, a specialized type of absorptive IECs, sample luminal antigens and simultaneously help to mediate the maturation of naïve B cells into IgA-producing plasma cells [27] targeting inflammatory disease-causing bacteria [48] as well as the induction of luminal pathogen-specific Th1, Th17, and Th22 responses [49]. Similar to M cell-mediated induction of cellular responses, goblet cells mediate goblet cell-associated antigen passage (GAP), which supplies luminal antigens to tolerogenic $CD103^+$ DCs in the lamina propria, thereby inducing differentiation of regulatory T (Treg) cells in the steadystate [50]. Successful clearance of pathogens requires a swift transition from a tolerant state of the immune system to an inflammatory one. In agreement with this paradigm, tolerogenic GAPs are inhibited during a *Salmonella* infection, thus allowing an inflammatory response to develop [51].

Complementary to the direct methods of microbiome perception, IECs sense the microbiome by detecting microbiome metabolites. In the colon, strictly anaerobic commensal bacteria digest dietary fiber to produce short-chain fatty acids (SCFAs) as byproducts. SCFAs are sensed by IECs via GPR41, GPR43, GPR109A, and PPARγ [52, 53]. SCFAs can reinforce the epithelial barrier by modulating the mucus layer, epithelial cell survival, as well as expression of tight junction proteins [53]. SCFAs are also utilized by colonocytes as an energy source via the pathway of mitochondrial fatty acid β-oxidation. This is an oxygen-consuming process that reduces the amount of oxygen emanating from the epithelium into the lumen of the colon, thereby supporting the niche for anaerobic bacteria [54–57]. SCFA-mediated PPARγ-signaling further limits the bioavailability of luminal oxygen and contributes to providing colonization resistance to pathogens [52]. In the absence of SCFAs producers due to antibiotic or dietary interventions, colonocyte metabolism shifts toward glycolysis, a process characterized by low oxygen consumption as well as activation of nitric oxide synthase. This results in luminal accumulation of oxygen and nitrate, thereby creating niches for facultative anaerobic pathogens such as *Escherichia coli* [55, 58] and *Citrobacter rodentium* [59]. Similar to regulation of oxygen metabolism by SCFAs in colonocytes, L-lactate has recently been reported to promote lipid storage while conversely acetate is shown to trigger lipid oxidation via the AMPK/PGC-1α/PPARα pathway in enterocytes in the small intestine [60]. Enterocytes are not the only cell type sensitive to lactate. Small intestinal $CX3CR1^+$ mononuclear cells express the lactate G-protein-coupled receptor GPR31. GPR31 signaling promotes dendrite protrusion and enhances uptake of luminal antigens by monocytes [61]. Small intestinal $LGR5^+$ ISCs express another lactate receptor GPR81; signaling through this receptor has been shown to stimulate ISCs expansion [62]. Concordantly, pre-feeding of mice with lactate protected them from chemotherapy- and radiation-mediated mucosal damage [62]. Metabolite sensing mechanisms are also utilized by tuft cells, which detect parasite- and microbiome-derived succinate via the Sucnr1 receptor and initiate type 2 immune responses [22, 24, 25].

IECs employ additional strategies to actively assist commensals in competition with pathogens over an ecological niche in the intestine to reinforce colonization resistance [13]. The components of the mucus barrier secreted into the lumen by goblet cells

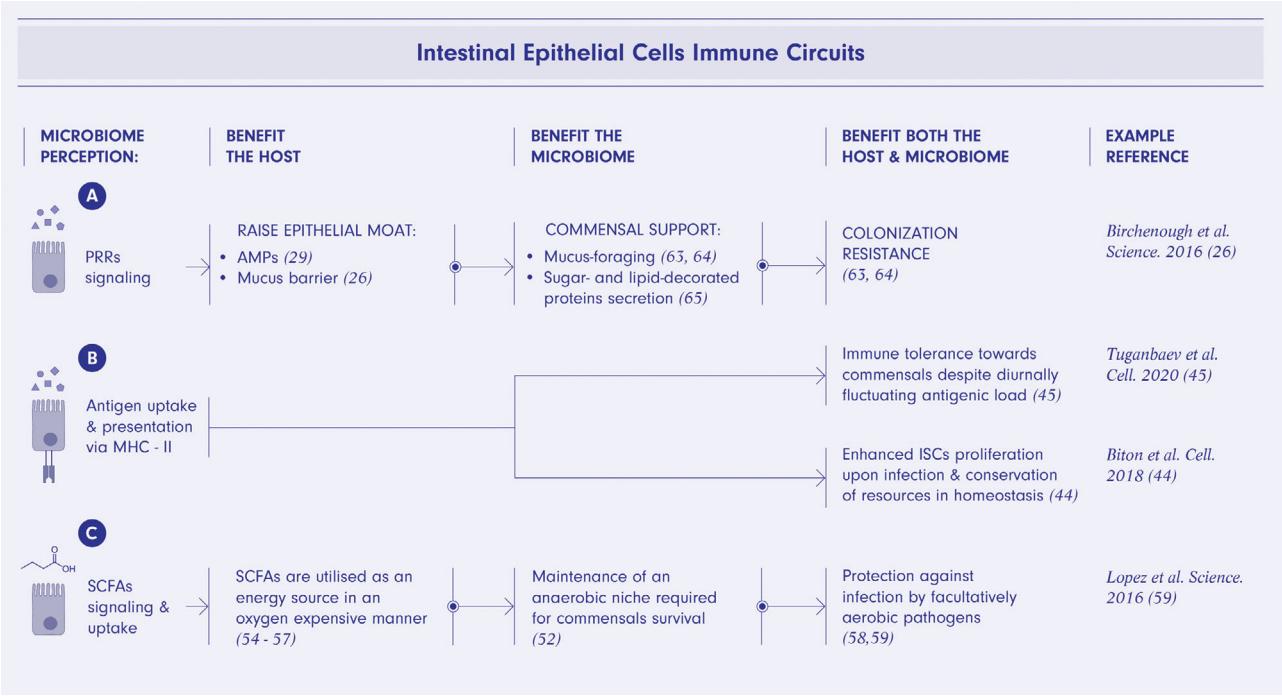

Figure 1. IECs immune programs are mutually beneficial for the host and microbiome. Perception of microbiome via pattern recognition receptors (PRRs) signaling promotes secretion of antimicrobial peptides (AMPs) and erection of a mucus barrier directly supporting beneficial mucus-foraging bacteria and indirectly via colonization resistance to pathogens of other commensal bacteria (**A**). Microbiome sensing via luminal antigen uptake informs diurnal adjustment of intestinal barrier properties maintaining immunological tolerance towards microbiome around the clock and calibrates proliferative activity of intestinal stem cells (ISCs) promoting host-microbiome homeostasis (**B**). Uptake of microbiome-derived short-chain fatty acids (SCFAs) promotes maintenance of an anaerobic environment required for homeostasis of commensal bacteria and protects against facultatively anaerobic pathogens (**C**). The figure was created using BioRender.com.

are decorated with sugars and lipids conferring a fitness advantage to commensals such as *Akkermansia muciniphila* [63] and *Ruminococcus gnavus* [64], which possess specialized enzymatic systems for harvesting these resources. Furthermore, given that the host possesses the ability to store energy in reserve while beneficial prokaryotic symbionts do not, the host enterocytes upregulate fucosyltransferase 2 (Fut2) and shed fucose into the lumen to sustain the commensals during periods of fasting and nutrient unavailability [65]. Concordantly, human milk oligosaccharides promote colonization of the newborn gut by beneficial commensals such as *Lactobacillus*, thereby developing colonization resistance to pathogens [66].

Already in invertebrates, the epithelium features some of the simplest and therefore probably the most evolutionary ancient innate immune programs that are composed of just two steps: perception and reaction. Representative examples include production of AMPs upon microbial sensing [37] (Fig. 1). In contrast, mammalian epithelial programs additionally include integration with the adaptive arm and therefore represent a more recent innovation in immune-microbiome co-evolution. Representative examples include the program regulating epithelial proliferation based on the microbiome composition [44] and the program adjusting epithelial permeability in response to diurnally fluctuating luminal antigenic load [45]. Importantly, programs at all levels of complexity pursue not the one-sided advantage for the host over the microbiome, but rather the collective benefits for the host and a diverse and stable microbiome (Fig. 1A-C).

Enteric nervous system

Recent advances in studies of the ENS have firmly established it as a critical component of the mucosal immune system in health and disease [67–69]. Structurally, the ENS network is composed of two main plexuses—the myenteric plexus (also termed Auerbach's plexus), located within the muscularis layer between the longitudinal and the circular muscles; and the submucosal plexus (also termed Meissner's plexus), located between the mucosa and the circular layer of muscles. The ENS innervates all layers of the intestinal tissue from the epithelial layer through the lamina propria, submucosa, muscularis, serosa, and the mesentery throughout the gastrointestinal tract. The total number of neurons in ENS is estimated to be on par with that of the spinal cord [69]. The diverse aspects of intestinal homeostasis such as gastric acid secretion, intestinal motility, barrier integrity, fluid and nutrient absorption, regulation of local blood flow, and interactions with the gut immune and endocrine systems are all collectively managed by reflex arcs of local ENS, reflex arcs that pass through extrinsic sympathetic and sensory ganglia, as well as reflexes that circle through the CNS [69]. The bidirectional

communication between the ENS and the CNS is established via three major routes: (1) parasympathetic vagal neurons that connect the ENS to the hindbrain, (2) sympathetic nerves that connect the ENS through the sympathetic visceral ganglia to the spinal cord, and (3) the pelvic pathways that connect the ENS directly with the spinal cord. Despite this interconnectivity, the ENS can manage the gastrointestinal functions even if the connection with the CNS is severely reduced (e.g., in the case of a vagotomy) [69]. In contrast, neuropathies involving failure of a part of the ENS, such as Hirschsprung disease [70] or Chagas disease [71], are potentially fatal.

A key player in ENS circuitry is the intrinsic sensory neuron (known as intrinsic primary afferent neurons, or IPANs) [72]. IPANs form ring-shaped networks encircling the gut while sending projections deep into the mucosa [72]. Interneurons on the other hand form linear networks spanning in the oral and anal directions along the length of intestine. Ascending chains of interneurons synapse onto excitatory motor neurons while descending interneurons interconnect with inhibitory motor neurons [72]. Located in the myenteric plexus, excitatory and inhibitory motor neurons form mesh-like networks interlaced by glial cells. In addition to classical subtyping of these ENS neurons based on morphology, electrochemical characteristics, neurotransmitters utilized for signal transduction and biogeographical location [73], recent single-cell transcriptomics has revealed additional layers of complexity [68, 74]. Further investigation into how spatial distribution as well as morphological, electrochemical, and transcriptomic profiles combine to form functional identity of neurons is required.

It has been shown that mucosal ENS circuitry promotes group 2 innate lymphoid cell (ILC2) activation in response to helminth infections [75]. An infection with the helminth parasite *Nippostrongylus brasiliensis* leads to a release of the neuropeptide neuromedin U by lamina propria cholinergic neurons, which in turn induces rapid ILC2-mediated responses, characterized by immediate and massive production of IL-5, IL-13, and amphiregulin (AREG) [75]. Similar to the ILC2-inducing reflex, neurons of the myenteric and submucosal plexuses in the colon react to *Salmonella typhimurium* infection by mounting an IL-18 response via the NLRP6- and Caspase 1/11-dependent inflammasome pathway. IL-18 then stimulates AMP production by goblet cells to sterilize the epithelium [76]. This pathway also induces pyroptosis of neurons, resulting in post-infection neuronal damage and thereby possibly promoting chronic irritable bowel syndrome. To prevent post-infection neuronal damage, sympathetic catecholaminergic neurons innervating the myenteric plexus rapidly respond to *Salmonella* infection by releasing norepinephrine, which stimulates local muscularis resident macrophages via the β2 adrenergic receptor (β2AR) [77]. In response, macrophages upregulate an M2-like tissue protective and regenerative transcriptional program shielding neurons from damage [11]. In the steady state, myenteric neurons also secrete colony stimulatory factor 1 (CSF1), and muscularis macrophages in turn secrete bone morphogenetic protein 2 (BMP2). BMP2R signaling in myenteric neurons adjusts the pattern of smooth muscle contraction [78]. Thus, enteric macrophages and neurons cooperate to manage intestinal motility, homeostasis, and damage control in the steady state and during infection. Whereas ENS regulates the commensal microbiome composition by adjusting intestinal peristalsis [78], the number and function of ENS neurons are affected by the commensal microbiome [79]. This is exemplified by the downregulation of expression of neuropeptides associated with neuro-immune crosstalk and ENS physiological function, such as neuromedin U, somatostatin, and Cocaine- and Amphetamine-Regulated Transcript Protein (CARTP), in germ-free (GF) or antibiotic-treated mice. Concordantly, the numbers of intestinal ENS neurons are reduced in animals lacking a microbiome. Mechanistically, the microbiome promotes maintenance of ENS neurons via suppression of NLRP6- and caspase-11-mediated neuronal death [79].

In addition to gut intrinsic neurons, the intestine is innervated by different classes of extrinsic neurons, which detect and convey the information within the gut to the extrinsic ganglia and the CNS. Extrinsic ganglia, such as the sensory nodose ganglion and dorsal root ganglion, and the sympathetic coeliac-superior mesenteric ganglia project neurons to the gut [80]. Complementary to the intrinsic ENS, gut-extrinsic neurons are also involved in control of the mucosal immune system. For instance, transient receptor potential cation channel subfamily V member 1 $(TRPV1)^+$ nociceptor neurons projected from the dorsal root ganglion respond to a *Salmonella typhimurium* infection by releasing a neuropeptide calcitonin gene-related peptide (CGRP) and thus suppressing the differentiation of ileum M cells to block further entry of *Salmonella* [8]. The reduction in M cell density also leads to an increase in mucosal colonization by SFB, which competes with *Salmonella* for mucosal ecological niches, resulting in further limitation of *Salmonella* infection [8]. While extrinsic neurons regulate infections, their homeostasis is supported by the commensal microbiome. Indeed, the commensal microbiome plays an important role in preventing aberrant activation of the sympathetic neurons in the coeliac-superior mesenteric ganglia [80]. In this preventive mechanism, nodose sensory neurons detect microbiome-derived SCFAs and transmit suppressive signals to sympathetic neurons [80]. Epithelial cell subsets, particularly enteroendocrine cells, have also been implicated in transmitting luminal input to the intrinsic and extrinsic ENS. Mechanistically, enteroendocrine cells may communicate with the ENS directly via synapse-like innervation [21] or via enteroendocrine hormone signaling in ENS neurons, as was recently predicted by a single cell survey of the mouse and human ENS [68]. This prediction was recently validated by the demonstration that glucagon-like peptide 1 (GLP-1) can activate gut sympathetic neurons [80]. Therefore, homeostatic communication in the intestine involves contributions by the gut microbiome, epithelium, ENS, CNS, and the immune system.

Epithelial and neuronal cells form the main sensory networks that perceive and interact with the microbiome. Similar to epithelial-microbiome interaction programs, the immune reflexes of the ENS, both intrinsic and extrinsic, as well as of all levels of complexity function not solely for the benefit of the host but instead promote and rely on the health of the commensal

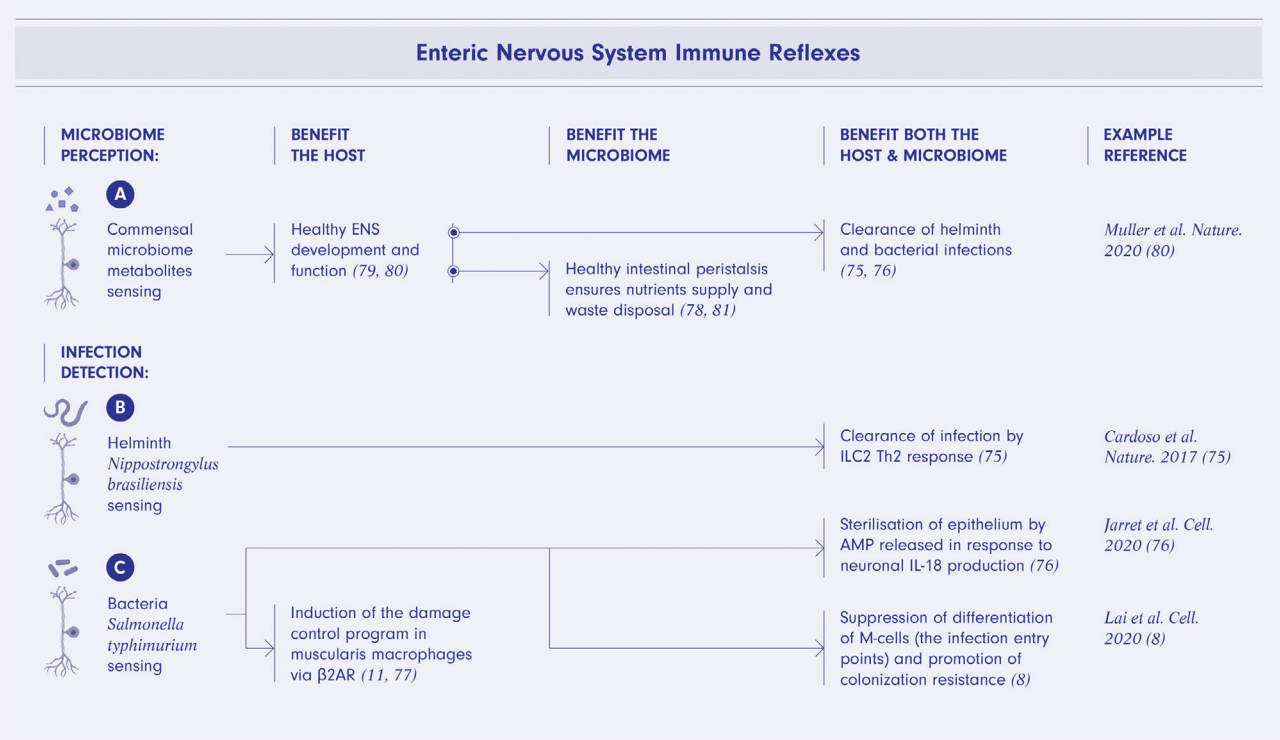

Figure 2. Enteric nervous system immune reflexes are mutually beneficial for the host and microbiome. Microbiome-derived metabolites are required for healthy ENS development and function including peristalsis supplying nutrients to and disposing of waste from the microbiome community as well as benefiting the host and ultimately promoting clearance of parasite and bacterial infections by ENS-immune reflexes (**A**). Sensing of *Nippostrongylus brasiliensis* infection by ENS neurons triggers innate lymphoid cells type 2 (ILC2) mediated Th2 immune response resulting in clearance of the helminth (**B**). Detection of *Salmonella typhimurium* infection by ENS leads to neuronal secretion of IL-18 and a release of antimicrobial peptides (AMPs) by epithelial cells sterilizing the epithelium as well as suppression of M-cells differentiation thus limiting infection entry points and the induction of neuronal damage control program in muscularis macrophages via β2AR (**C**). The figure was created using BioRender.com.

microbiome. At steady state, intestinal peristalsis–crucial for both the microbiome and the host's homeostasis–requires sensing of the microbiome by enteric neurons [81]. During an infection that displaces commensals out of their ecological niches, ENS reflexes stimulate innate and adaptive immune responses to cleanse the pathogen, freeing the ecological niches for commensals to recolonize [76]. Commensals in turn produce metabolites vital for ENS homeostasis [80]. The commensal microbiome also promotes damage control programs within the ENS and CNS [11, 77], making the host more resilient to infections, reflecting the fact that the host's health is in the microbiome's best interest. Thus, the ENS and microbiome non-zero-sum interactions counter infections and promote intestinal homeostasis (Fig. 2A-C).

Myeloid and innate lymphoid cells

The interaction between myeloid cells and the microbiome runs deep and starts before birth and continues throughout life. This is exemplified by the observation that antibiotic treatment of pregnant mice leads to a reduced number of neutrophils in their offspring, which could be prevented by microbial colonization of the pregnant mice [82]. Transitory colonization of pregnant female mice increases the number of ILC3s as well as F4/80$^+$CD11c$^+$ mononuclear cells in pups [83]. Furthermore, adult GF mice have a profound defect in myelopoiesis, characterized by a reduction of both yolk sac- and BM-derived myeloid progenitors [84]. These defects can be restored by microbial recolonization, suggesting that healthy myelopoiesis requires continuous microbiome interaction throughout life rather than solely during the developmental stage [84]. Mechanistically, it has been proposed that the microbiome stimulates myelopoiesis via TLR signaling [85] and by producing metabolites such as SCFAs [84, 86]. In addition to influencing myelopoiesis, the microbiome drives maturation of neutrophils [87] and basophils [88]. The microbiome also affects the tissue-specific adaptation of myeloid cells. The microglia of the brain of GF mice display an immature phenotype, which is phenocopied in SPF mice deficient for an SCFA receptor FFAR2 [89]. In the skin, the development of monocyte-derived DCs depends on the presence of a skin microbiome [90]. The functional polarization of lung-resident macrophages is modulated by the composition of the intestinal microbiome via prostaglandin E2 (PGE2) [91]. Similarly, the tolerogenic polarization of intestinal macrophages and DCs requires continuous SCFA-mediated signaling [92, 93].

In contrast to the myeloid arm of the innate immune system, ILCs develop normally in number in the absence of the microbiota [94]. Instead, the microbiome regulates the maturation

and tissue-specific adaptation of ILCs [95–97]. ILCs consist of cytotoxic NK cells and non-cytotoxic ILC1, ILC2, and ILC3 cells. ILC1s express the transcriptional factor T-bet and produce IFN-γ [98–100]. ILC2s are characterized by the expression of GATA3 and release IL-5 and IL-13 [101–103]. ILC3s express RORγt and secrete IL-22 [104]. IFN-γ expression by gut-derived meningeal NK cells is induced by the gut microbiota [105]. Intestinal IFN-γ^+ NK cells migrate into the meninges and drive homeostatic expression of TRAIL by astrocytes, which limits inflammation in the CNS by inducing T cell apoptosis [105]. ILC1 cells are directly involved in mucosal defense against opportunistic pathogens such as *Clostridioides difficile*, as loss of ILC1, but not other ILC subsets or conventional T and B cells, rendered mice highly susceptible to infection with this organism [106]. Furthermore, the loss of T-bet in Rag2-deficient mice led to a spontaneous colitis that was mediated by pathobionts including *Klebsiella pneumoniae*, *Proteus mirabilis* and *Helicobacter typhlonius* [107, 108], suggesting that ILC1s are required for the management of specific members of the intestinal microbiome. ILC2s work in close coordination with tuft and goblet cells, promoting intestinal barrier function against bacteria and parasites. Following pathogen clearance, ILC2s-mediated promotion of tuft and goblet cells expansion impairs future infections in a phenomenon termed concomitant immunity [25, 109]. Tuft cells sense parasites by detecting the helminth-derived metabolite succinate and respond by producing IL-25 [24, 25]. IL-25 in turn activates ILC2s to produce the type 2 cytokine IL-13, which helps to repel the infection and additionally stimulates tuft cells to promote feedforward production of IL-25 [109]. ILC2s express TLR1, 4, and 6 [110], and the transcriptional profile of ILC2 cells changes upon microbial colonization [111]. However, further studies will be needed to clarify the issue of ILC2 plasticity and its dependency on the microbiome.

ILC3s are indispensable in integration of signals from the microbiome, IECs, ENS, as well as both the innate and adaptive arms of the immune system in order to promote mucosal homeostasis. ILC3s reinforce the intestinal barrier, promote immunological tolerance to commensals, and bolster colonization resistance to pathogens. Stimulated by the microbiome, myeloid and epithelial cells produce IL-23 and IL-1β [112–114]. In response, ILC3s release IL-17 and IL-22 in the steady state, and IFN-γ and GM-CSF under inflammatory conditions [115]. Cytokine release from ILC3s is drastically reduced in GF mice [95, 96, 116]. In addition to indirectly receiving microbial signals via myeloid and epithelial cells, ILC3s are capable of sensing the microbiome directly via the aryl hydrocarbon receptor (AhR) [117–119]. Regardless of the mode of ILC3 activation, ILC3-derived IL-22 has a profound reinforcing effect on the intestinal mucosal barrier. IL-22 promotes ISC regeneration in the stem cell niche [120] and tight junction formation in the absorptive compartment of the epithelium [121]. IL-22 also stimulates the release of AMPs, production of mucus [29, 122, 123], as well as fucosylation of the apical surface of IECs [12, 65]. Concordantly, mice deficient in ILC3s [124] or AhR [125] exhibit enhanced colonization of mucosal surfaces by SFB. In addition to AhR and IL-23 signaling, IL-22 production by ILC3s is stimulated by PGE2 [126]. Accordingly, PGE2 blockade results in an intestinal barrier failure and a systemic translocation by commensal microbes [126]. Furthermore, the ILC3-mediated IL-22 response can also be initiated by the ENS. The glial-derived neurotrophic factor produced by enteric glial cells stimulates the RET tyrosine kinase receptor on ILC3s, resulting in the production of IL-22 [127]. Moreover, ILC3s express vasoactive intestinal peptide receptor 2 and react to VIP produced by the ENS [9, 10]. As food consumption is a strong stimulator for the production of VIP from the ENS, the function of ILC3s is dynamically controlled in a coordinated manner and has a circadian pattern [9, 10]. On the other hand, microbiota-stimulated ILC3s regulate the diurnal expression of the circadian transcription factor NFIL3 (also known as E4BP4) in IECs [128]. NFIL3 controls expression of a circadian lipid metabolic program and regulates lipid absorption in IECs [128]. In addition to their mucosal barrier reinforcing role via secretion of IL-17 and IL-22, ILC3s produce GM-CSF and IL-2, which contribute to the development of Treg cells and the maintenance of a tolerogenic state in the mucosal immune system [116, 129-131]. Moreover, the CCR6$^+$ subset of ILC3s is capable of antigen presentation to CD4 T cells [132] and iNKT cells [133]. MHC-II expression by ILC3s leads to the control of mucosal IgA responses, thereby contributing to editing the intestinal microbial composition and sustaining its diversity [134]. The activity of ILC3s is also controlled by CD4 T cells. Without CD4 T cells, ILC3s exhibit extensive and persistent Stat3 activation and IL-22 production, resulting in impaired host lipid metabolism by decreasing lipid transporter expression in the intestine [135]. Taken together, ILC populations interact with the microbiota and multiple host cells to contribute to mounting immune response against pathogens as well as shaping the mature commensal microbiome to help to maintain tissue homeostasis (Fig. 3A–E).

Bidirectional interactions between the adaptive immune system and the microbiome

It has long been known that the gut microbiome contributes both to the development and to set the tone of adaptive immune cells. This is exemplified by the overall diminished state of the adaptive immune system in GF mice, characterized by underdeveloped intestinal lymphoid tissue architecture [136], reductions in intraepithelial lymphocytes (IELs) [137], and in IgA-producing B cells [138]. In addition, recent studies have shown that the microbiome directs the functional maturation of T cells, such as Th17, Treg, follicular helper T (Tfh), and CD8 T cells, and determines the gut antibody repertoire [139–142]. The adaptive immune system in turn curates the composition of the microbiome, with the goal of sustaining maximal diversity thus promoting broad colonization resistance and preventing infections with pathogens. Therefore, the interaction between adaptive immune cells and the microbiome is bidirectional and mutualistic (Fig. 4).

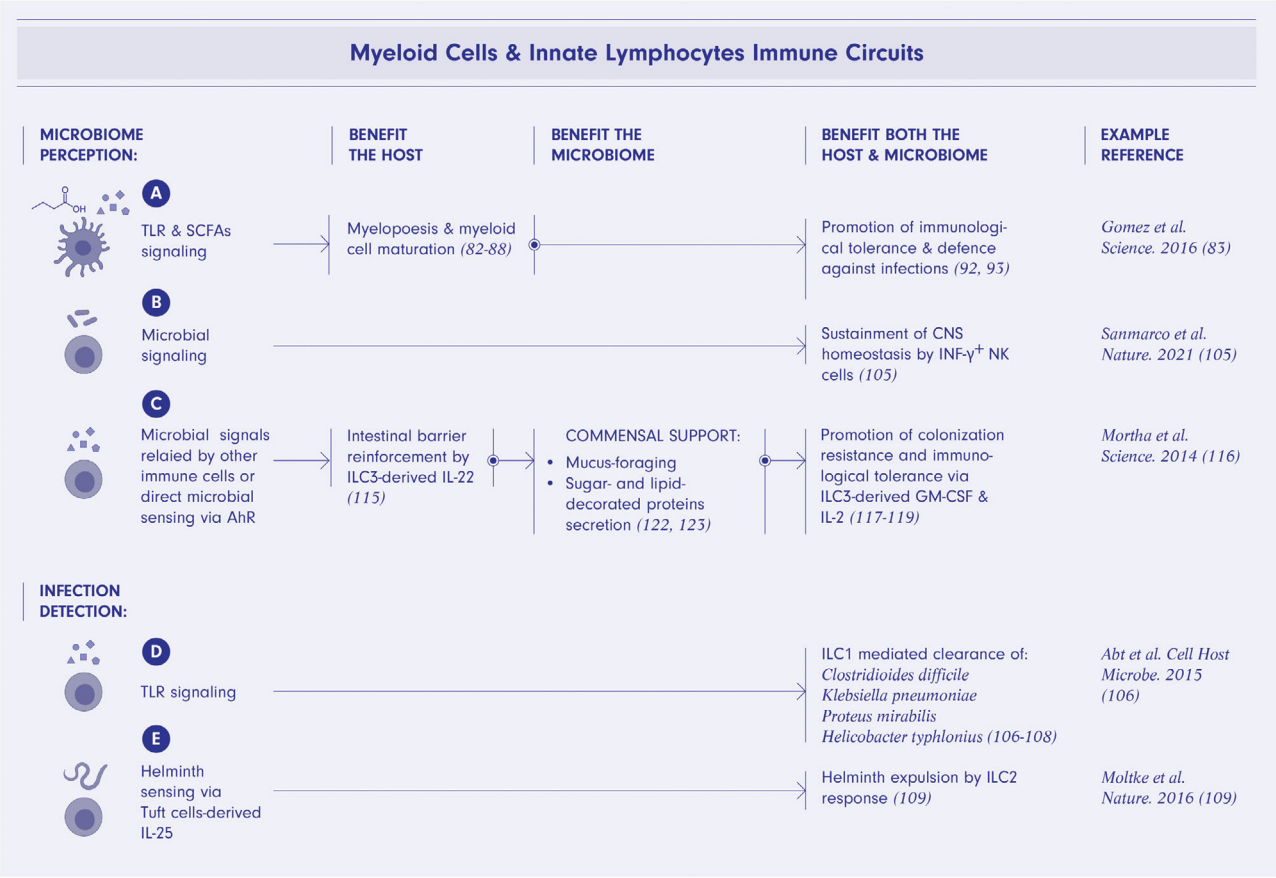

Figure 3. Mutually beneficial myeloid and innate lymphocytes -microbiome interactions. Microbiome perception via TLRs and short-chain fatty acids (SCFAs) signaling promote myelopoiesis and myeloid cell maturation ultimately supporting immunological tolerance to commensal microbes and defense against infections (**A**). Microbial signaling in NK cells promotes CNS homeostasis (**B**). Microbial signals relayed by other immune cells or direct microbial sensing via aryl hydrocarbon receptor (AhR) leads to production of IL-22, GM-CSF and IL-2 by innate lymphoid cells type 3 (ILC3) thus promoting colonization resistance and immunological tolerance as well as to secretion of mucus supporting mucus-foraging commensals (**C**). TLR signaling in ILC1 triggers a bacterial infection clearing Th1 immune response benefiting commensal microbes as well as the host (**D**). Helminth sensing via Tuft cells-derived IL-25 by ILC2 leads to parasite expulsion by a Th2 immune response (**E**). The figure was created using BioRender.com.

B cells

B cells are curators of a healthy and diverse intestinal microbiome [143, 144]. Intestinal B lineage plasma cells produce several grams of a diverse array of secretory IgA per day [144, 145]. Although less effective as compared with IgA^+ B cell responses, IgG1 responses specific to commensal species, such as *Akkermansia muciniphila*, can also be induced in the intestine [146]. In contrast to the T cell-dependent IgG1 response, IgA-producing cells develop in both T cell-dependent and -independent ways. The diversity of the IgA repertoire, and antigen recognition possibilities, are increased by somatic hypermutation in germinal centers in a T cell-dependent manner. The high diversity of the IgA repertoire helps to sustain high diversity of the microbial composition (Fig. 4A). Therefore, it has been considered that T cell-dependent pathway is mostly responsible for the microbiome curatorship[144]. However, recent studies provide evidence that T cells do not substantially modulate the specificity of IgA [147, 148]. As IgA-producing cells in tissues other than the small intestine are severely reduced in the absence of the microbiota and T cells, T cells are likely required more for the generation of extraintestinal IgA-producing cell populations [148]. In any case, IgA-producing cells in the intestinal and extraintestinal tissues typically show microbiota-reactive and polyreactive specificities [148]. It has been shown that microbial exposures at the intestinal mucosa generate polyreactive but oligoclonal responses, different from the diverse IgG repertoire responses to systemic microbial exposures [149]. Moreover, priming thresholds differ depending on exposure routes; a higher dose exposure is needed to shape the mucosal IgA repertoire than that of systemic IgG [149]. As intestinal IgA induced by luminal microbes is predominantly specific to cell-surface antigens [149], a broad, but distinct, subset of microbiota is bound by IgA antibodies *in vivo*. In particular, Enterobacteriaceae as well as mucus-resident bacteria are heavily coated with IgA [48, 150]. IgA binds to commensal species and promotes their growth [144, 145]. On the other hand, IgA also induces agglutination, enchained growth, neutralization, and immune exclusion of microbes. Although it remains unclear what

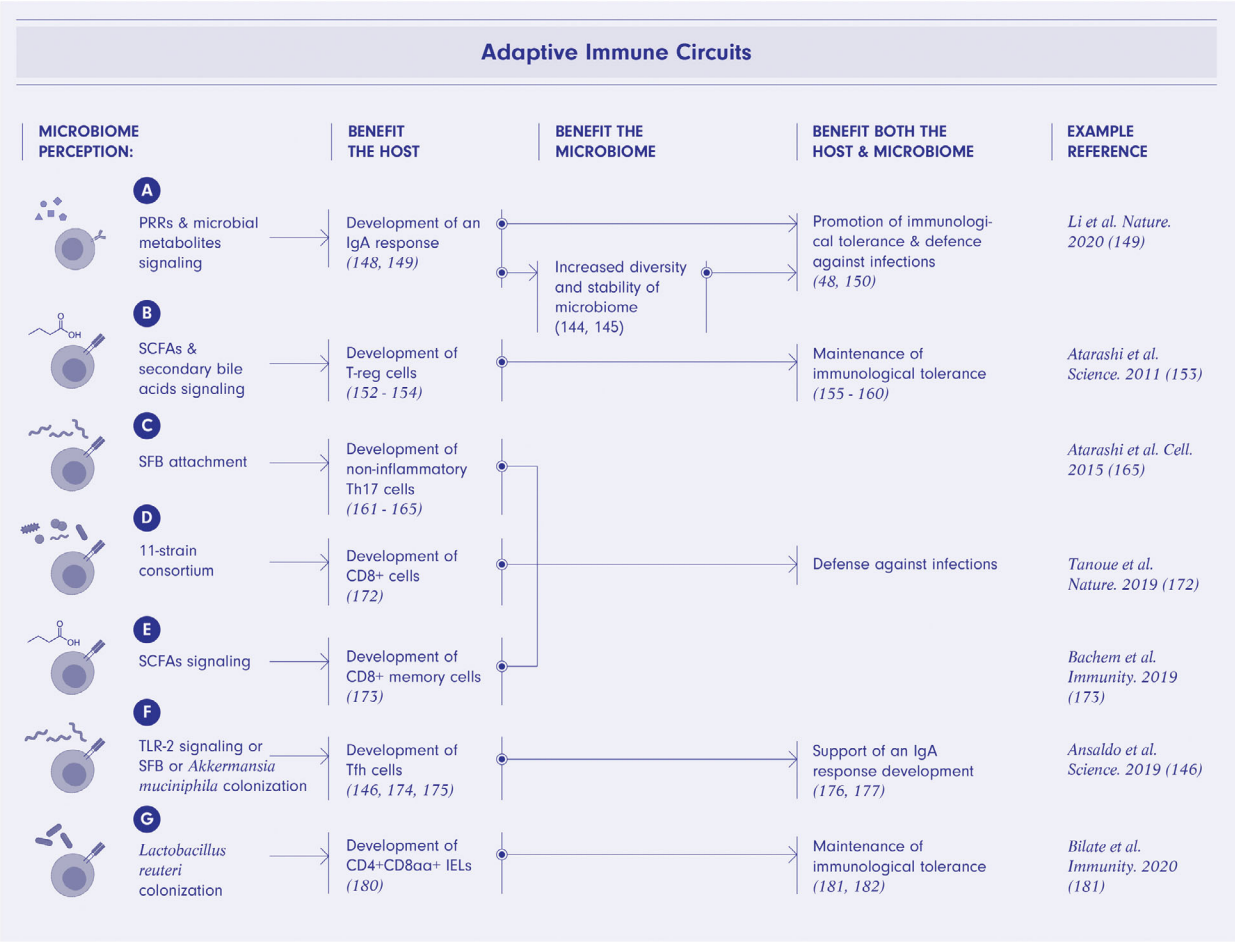

Figure 4. T and B cell-microbiome mutually beneficial interactions. Microbial sensing via pattern recognition receptors signaling and microbial metabolites signaling promotes an IgA humoral response curating microbiome diversity, promoting immunological tolerance, and providing defense against infections (**A**). Short-chain fatty acids (SCFAs) and secondary bile acids signaling promote differentiation of T regulatory cells ultimately bolstering immunological tolerance toward microbiome (**B**). Specific bacterial species such as segmented filamentous bacteria (SFB) or the 11-strain consortium and SCFA signaling result in differentiation of Th17 (**C**), $CD8^+$, (**D**) and memory $CD8^+$ cells (**E**) respectively and provide defense of the host and microbiome from infections. TLR2 signaling or SFB or *Akkermansia muciniphila* colonization promotes the differentiation of Tfh cells that support development of an IgA response thus curating microbiome composition and benefiting the host and microbiome (**F**). *Lactobacillus reuteri* colonization promotes differentiation of tolerogenic $CD4^+CD8\alpha\alpha^+$ intraepithelial lymphocytes (IELs) thus enhancing immunological tolerance towards microbiome (**G**). The figure was created using BioRender.com.

factors determine whether the IgA-coating enhances or diminishes the fitness of microbes in the intestine, accumulating evidence indicates that IgA-coating leads to alterations in microbial gene expression, motility, and/or spatial localization.

While microbes are required for induction of IgA, it appears that the opposite is true for IgE. IgE is elevated in the sera of GF mice and decreases upon colonization with commensal microbes [142]. GF mice begin to produce IgE shortly after weaning age to high levels and maintain these levels unless colonized with microbes within the first week of life.

T cells

Both circulating and tissue-specific populations of CD4 T cells are influenced by the intestinal microbiome. This is exemplified by the observation that a significant proportion of circulating CD4 T cells are specific to intestinal microbes in the steady state [151]. Among gut-resident CD4 T cells, several subsets depend on the presence of specific members of the microbiome. For instance, a subset of Treg cells depends on the metabolic activity of specific members of the gut microbiota [152–154]. In particular, microbes that ferment dietary fiber into SCFAs promote the development of Treg cells [153, 155-157]. In addition, microbiome-derived specific secondary bile acids can modulate the function and differentiation of Treg cells [158–160]. For example, isoallolithocholic acid (isoalloLCA) and isodeoxycholic acid (isoDCA) enhance the differentiation of naïve T cells into Treg cells [158, 159]. Mechanistically, vitamin D receptor and Nuclear Receptor Subfamily 1 Group H Member 4 [NR1H4, also known as Farnesoid X Receptor (FXR)] are implicated in recognition of secondary bile acids and regulation of gene expression in

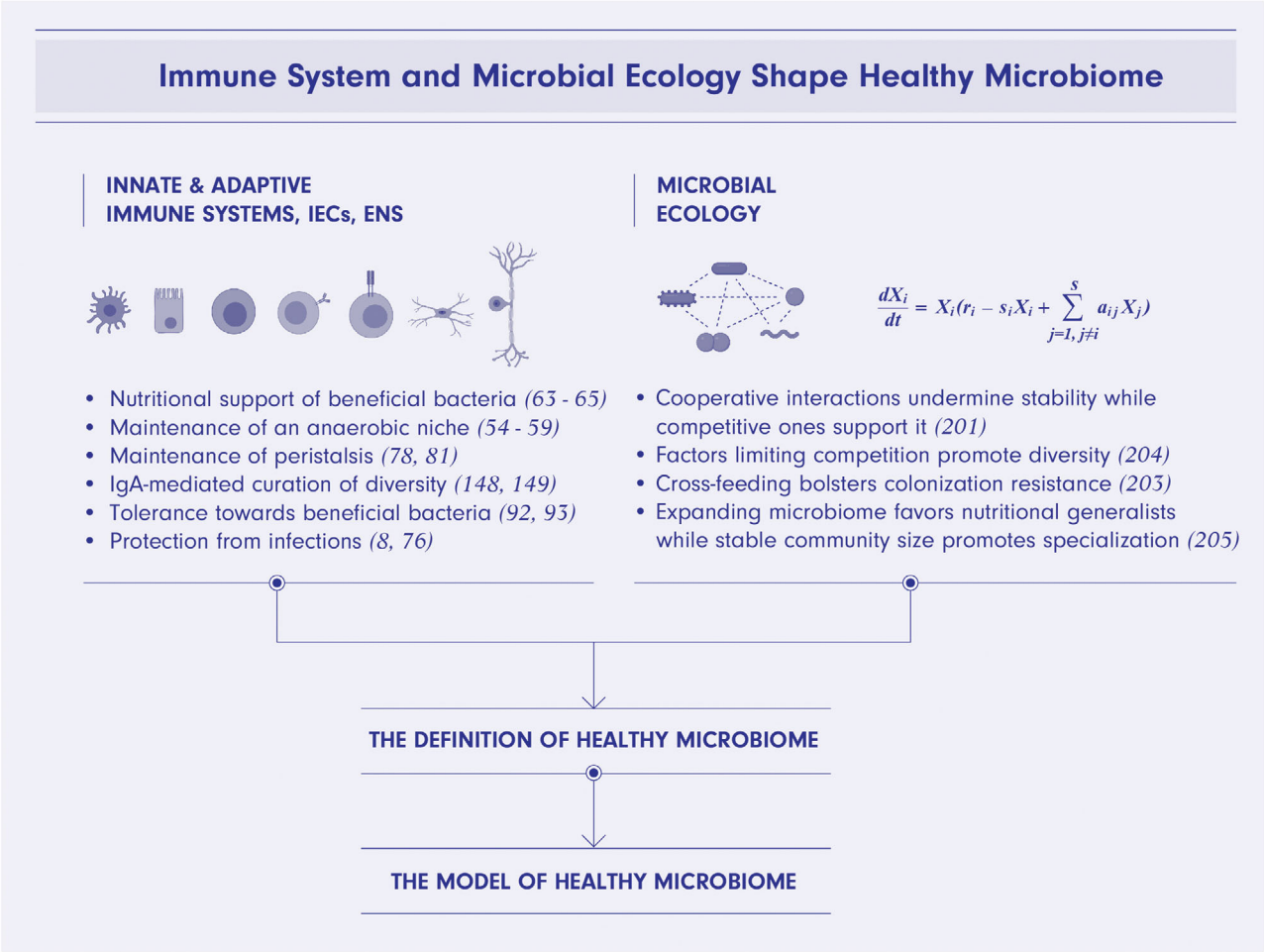

Figure 5. Immune system, IECs, ENS, and microbial ecology shape healthy microbiome. Integration of microbiome-curating programs of immune system, intestinal epithelial cells (IECs) and enteric nervous system (ENS) and microbial ecology will be a step forward toward defining and modeling healthy microbiome. IECs provide nutritional support and maintain an anaerobic niche for beneficial bacteria. ENS sustains peristalsis providing microbiome with a nutrients flow and disposing of waste products. B-cells secrete bacteria-targeting IgA antibodies curating microbiome composition with the overall effect of increased diversity and stability. Myeloid cells, T regulatory cells as well as other cell types establish the state of immunological tolerance towards commensal microbes. Cells of both innate as well as adaptive arms of immune system protect the host and microbiome from infections. Known patterns of healthy microbiome's ecology include dominance of competitive interactions over cooperative, high diversity supported by external factors, cross-feeding, and succession of nutrients utilization strategies from generalists in neonatal microbiome to mature communities dominated by specialists. The figure was created using BioRender.com.

antigen presenting cells and/or T cells for Treg cell differentiation [158, 160].

Similarly, lamina propria resident Th17 cells are induced by specific bacteria [161–165]. In particular, Th17 cells are induced by intestinal epithelial adhesive microbes, such as SFB [162–165], in a microbial antigen-dependent manner [40, 166]. Interestingly, the functional profile of Th17 cells depends on bacterial stimuli. Th17 cells induced by SFB or other commensals are non-inflammatory, while the opposite is true for the Th17 cells elicited by *Citrobacter rodentium* [167] or *Helicobacter hepaticus* in the condition of lacking IL-10 [168]. Homeostatic Th17 cell differentiation is promoted by IL-6 and TGF-β produced by microbiome-stimulated epithelial cells and gut resident DCs [162-165, 169]. On the other hand, it has been shown that IEC-derived serum amyloid A (SAA) proteins enhance differentiation of proinflammatory Th17 cells [170]. Epithelial cells express retinoic acid receptor β (RARβ), which activates vitamin A-dependent expression of SAA proteins by binding directly to the *Saa* promoter [171]. Mirroring the development of CD4 T cells, IFNγ-producing CD8 T cell differentiation is also promoted by specific commensal bacterial consortia [172]. Furthermore, the transition of antigen-activated CD8 T cells into memory cells depends on microbiome-derived SCFAs [173]. Another subset of T cells that depends on the microbiome is the Tfh cell, as its differentiation is impaired in GF mice but can be rescued by supplementation with TLR2 agonists [174] or colonization by SFB [175] or *A. muciniphila* [146]. In turn, Tfh cells indirectly influence the composition of the microbiome by participating in the induction of IgA-mediated (and perhaps also IgG1-mediated) microbiome selection [176, 177]. GF mice also feature an altered invariant natural killer T cell (iNKT)

compartment. The iNKT cells from GF mice are hyporesponsive and have weaker effector functions after antigenic stimulation [178]. The microbiota also affects the distribution of iNKT cells. Whereas the frequency of iNKT cells in GF mice is lower in spleen and liver, it is increased in the intestines. The iNKT tissue distribution is established in early life and affects host sensitivity to Th2-driven inflammation in later life [179]. Therefore, a time window exists within which the microbiota robustly affects the immune system. The development of $CD4^+CD8\alpha\alpha^+$ IELs is also affected by microbiota members, such as *Lactobacillus reuteri* [180]. The microbiota-driven expression of MHC-II and programmed death-ligand 1 (PD-L1) by IECs is required for the differentiation of CD4 T cells to become $CD4^+CD8\alpha\alpha^+$ IELs [181, 182].

The interactions of B and T cells with the microbiome provide perhaps the clearest example of non-zero-sum dynamics. These two compartments require microbial signals for development and activation and reciprocally promote microbiome homeostasis. In contrast to B cells, the contributions of the T cell compartment to microbiome homeostasis are indirect but broad. T cells cooperate with antigen-presenting epithelial cells, myeloid cells, and ILCs to protect the host from infections and promote IgA curatorship for microbiome diversity (Fig. 4B-G).

Conclusions

As the microbiome envelops all surfaces of the human body and mediates interactions with the environment, it is perhaps not surprising that it is involved in health and disease of virtually all organ systems. The microbiome participates in the maintenance of tissue homeostasis through its direct contact at the gastrointestinal [183, 184], respiratory [185], urogenital [186], and skin surfaces [187]. In addition, the microbiota produces a wide variety of molecules that can reach millimolar concentrations in the blood [188–192], thereby influencing remote organ systems such as the central and peripheral nervous systems [193], liver [194], adipose tissue [195, 196], skeletal muscles [197], and the cardiovascular system [198, 199]. Although the immune system no doubt serves as a major conduit of microbiome influences across multiple organs, major knowledge gaps still remain. The concept of microbiome-immune non-zero-sum interactions based on studies of host–microbiome interactions at the intestine is likely to be applicable across multiple organ systems and therefore may help guide formulation of hypotheses to be tested in future studies. Innate and adaptive immunological programs as well as IECs and ENS that evolved to support host-microbiome mutualism in the intestine may have counterparts in other organ systems that interact with microbiome directly and indirectly via immune system and microbiome-derived metabolites.

Another avenue of promising future research lies in utilizing the concept of immune system–microbiome mutualism to better define what constitutes a healthy microbiome (Fig. 5). Defining a healthy microbiome is a long-term goal of the field of microbiome research and will require to model the dynamics underpinning the seemingly endless compositional variability between individuals. Existing models of microbiome ecology successfully describe select aspects of bacteria-to-bacteria interactions by mapping limits of selfish behavior in a network [200], modeling an effect of the ratio of cooperative to competitive interactions on diversity and stability [201], applying game theory to metabolic interdependencies between microbes [15] and strategies of nutrients utilization [202], calculating an effect of cross-feeding on colonization resistance [203], studying the relationship between nutrients availability and diversity [204], and defining rules of assembly of infant microbiome [205]. However, by design these models are limited to bacteria-to-bacteria interactions. Studies reviewed herein and elsewhere demonstrate that a healthy microbiome is the result of active host immune system curatorship as well as the outcome of microbial ecology. Incorporation of microbiome-editing programs by innate and adaptive immune cells, IECs, as well as ENS will be an important step towards development of a model of healthy human microbiome (Fig. 5).

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Abbreviations: **AhR**: aryl hydrocarbon receptor · **AMP**: antimicrobial peptide · **ENS**: enteric nervous system · **IEC**: intestinal epithelial cell · **IEL**: intraepithelial lymphocyte · **ILC**: innate lymphoid cell · **ISC**: intestinal stem cell · **PGE2**: prostaglandin E2 · **SCFA**: short-chain fatty acid · **Tfh**: follicular helper T cells · **Treg**: regulatory T cell

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