REVIEW ARTICLE

Long-distance relationships - regulation of systemic host defense against infections by the gut microbiota

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Despite compartmentalization within the lumen of the gastrointestinal tract, the gut microbiota has a far-reaching influence on immune cell development and function throughout the body. This long-distance relationship is crucial for immune homeostasis, including effective host defense against invading pathogens that cause systemic infections. Herein, we review new insights into how commensal microbes that are spatially restricted to the gut lumen can engage in long-distance relationships with innate and adaptive immune cells at systemic sites to fortify host defenses against infections. In addition, we explore the consequences of intestinal dysbiosis on impaired host defense and immune-mediated pathology during infections, including emerging evidence linking dysbiosis with aberrant systemic inflammation and immune-mediated organ damage in sepsis. As such, therapeutic modification of the gut microbiota is an emerging target for interventions to prevent and/or treat systemic infections and sepsis by harnessing the long-distance relationships between gut microbes and systemic immunity.

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THE INTESTINAL MICROBIOTA AND HOST DEFENSE AGAINST INFECTIONS

From birth, the intestinal microbiota educates and regulates the development and function of our immune system[1]. The crosstalk between commensal microbes and the immune system is crucial in establishing and maintaining immune homeostasis, and preventing immune-mediated disorders such as autoimmunity, allergies, and chronic inflammatory diseases[2,3]. However, in addition to maintaining immune homeostasis and self-tolerance, the microbiota and its shaping of immunity are also critical for protection of the host against infections.

The most direct example of host protection conferred by the gut microbiota is through colonization resistance against mucosal pathogens like *Clostridium difficile*. Extensive mechanistic and clinical evidence has demonstrated that disruption of the intestinal microbiota by antibiotics plays a causal role in *C. difficile* infection of the gut, whereas restoration of a diverse intestinal microbiota through fecal transplant or microbial consortia therapy can be curative[4–6]. A diverse gut microbiota aides the host in resisting pathogen colonization through various mechanisms including inter-microbial competition for nutrients, metabolic competition, and direct antagonism/killing strategies[7], as well as fortification of mucosal barrier integrity[8,9] and local mucosal immune defenses[10]. In this way, gut commensals protect the host against mucosal infection, as well as secondary systemic infections that can occur as a result of overgrowth and translocation of intestinal pathogens into the circulation and distal organs[7,11–15].

However, in addition to its locally protective role against mucosal pathogens, the gut microbiota also exerts a crucial influence on the shaping of systemic host defense in the bloodstream and extra-intestinal organs. Germ-free (GF) and antibiotic-conditioned SPF mice display increased susceptibility to a wide variety of infection models including bloodstream infections, bacterial pneumonia, intra-abdominal sepsis, endotoxemia, as well as viral infections like influenza A, Lymphocytic Choriomeningitis Virus (LCMV), and others[16–24]. The observed defects in systemic host defense in GF and antibiotic-conditioned mice can be remedied by repopulating the gut with commensal microbes. Herein, we will review how commensal microbes that are spatially restricted to the gut lumen can engage in long-distance relationships with extra-intestinal immune cells to fortify host defense against systemic infections. We will also explore the consequences of intestinal dysbiosis on extra-intestinal host defense and susceptibility to systemic infections, and opportunities for mechanism-guided microbial-immunotherapy to bolster immune defense against severe infections and sepsis.

MECHANISMS OF LONG-DISTANCE COMMUNICATION BETWEEN GUT MICROBES AND EXTRA-INTESTINAL IMMUNE CELLS

The vast spatial separation between immune cells in extra-intestinal sites and commensal microbes in the lumen of the gut necessitates the use of long-distance mechanisms of communication to enact functional regulation of systemic host defense. Various organ-specific axes of communication have been well described (e.g., gut-brain axis, gut-liver axis, gut-lung axis) and have been the subject of recent focused reviews[25–29]. Here, we aim to provide a summary of the general mechanisms by which bacteria compartmentalized in the gut lumen can communicate

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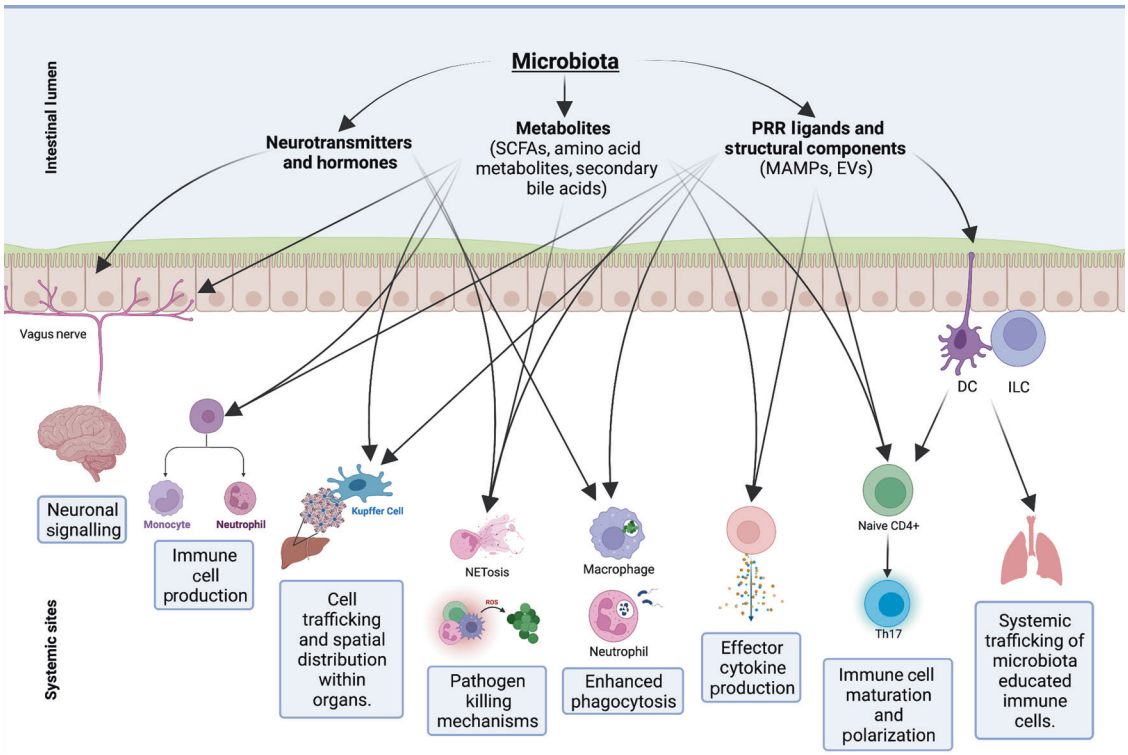

Fig. 1 Mechanisms of long-distance communication between the gut microbiota and systemic immune cells. Intestinal microbes communicate with immune cells in extra-intestinal organs through multiple mechanisms. Gut microbes produce small molecule metabolites, PRR ligands (MAMPs), extra-cellular vesicles, neurotransmitters, and hormones that can enter the lymph and circulation, travelling to distant organs where they impact immune cell development and function. In addition to soluble signals that act at distant sites, the gut microbiota also locally educates immune cells in the mucosa, including dendritic cells, ILCs, T cells, and others, that then egress from the gut and migrate to systemic sites to contribute to host defense. Lastly, long-distance communication by the gut microbiota can also be mediated via neuronal communication between the gut and distant organs including the brain. Microbiota-derived compounds are sensed by the enteric nervous system, and afferent signalling through the vagus nerve can enable coordinated systemic responses via the central nervous system.

with, and functionally regulate, immune cells in the bloodstream and distant organs (Fig. 1).

Perhaps the most well studied mechanism involves microbe-associated molecular pattern (MAMP) components, like LPS and peptidoglycan from bacteria or β-glucan from fungal colonizers, that access the circulation and bind to pattern recognition receptors (PRRs) on immune cells throughout the body (Fig. 1). Even in the absence of gut barrier pathology, low levels of MAMPs can be detected in the circulation of mice and humans that regulate myeloid and lymphoid cell production in the bone marrow and thymus, and impart regulatory influences on immune cell functions throughout the body, as discussed further below[30–32]. Although commensal-derived MAMPs and pathogen-derived PAMPs can act on the same PRRs, the immunological outputs may differ to prevent commensal-derived MAMPs from inducing pathological inflammation. For example, LPS from *Bacteroidales* colonizers has a hypoacetylated structure that supresses TLR4-mediated cytokine release from human mononuclear cells, in contrast to LPS from pathogenic *E. coli* that induced robust cytokine production[33].

Similar to long-distance MAMP signals, gut bacteria also produce a variety of immune-active small molecule metabolites that gain access to the bloodstream and communicate with systemic immune cells (Fig. 1). Short-chain fatty acids (SCFAs) have emerged as pleiotropic immunoregulatory mediators produced by intestinal microbes through fermentation of dietary fibre. SCFAs provide a crucial energy source for intestinal epithelial cells, and can modulate immune cell function epigenetically through inhibition of histone deacetylases (HDACs), as well as through activation of G-protein coupled receptors (GPR41, GPR43, GPR109a) expressed on immune cells[34]. As such, the transit of SCFAs to extra-intestinal tissues contributes to the regulation of systemic inflammation, directing leukocyte recruitment, anti-pathogen cell programming, and cytokine release[34]. In addition to SCFAs, gut microbes produce a range of other immune-regulatory metabolites from modification of dietary molecules (tryptophan metabolites, TMAO), host bile acids (secondary bile acid metabolites), as well as *de novo* bacterial metabolites (polyamines, vitamins, branched chain amino acids) that can facilitate long-distance regulation of systemic immune responses[34].

Signalling between the gut and extra-intestinal organs can also be accomplished through neuro-immune mechanisms that are tuned by gut microbes (Fig. 1). Intestinal bacteria can synthesize neurotransmitters like γ-aminobutyric acid (GABA), as well as modulate host production of a variety of neurotransmitters that can impact immune cell functions[25]. In addition, gut bacteria stimulate the release of neuroendocrine peptide hormones by enteroendocrine cells that can access the circulation and act at systemic sites[35,36]. Interestingly, gut bacteria can also communicate with distal organs via neuronal pathways. For example, autonomic nerve terminals in the intestinal mucosa have been found to sense bacterial metabolites and relay signals to the central nervous system[37,38]. Additional research is needed to understand how these neuronal mechanisms of long-distance microbiota-immune communication may impact host defense, but one would hypothesize an important contribution given the role of neural reflexes in the regulation of immune cell functions during infections and sepsis[39,40].

More recently, bacterial extracellular vesicles (EVs) were identified that instruct differential host responses dependent on

the source microbe (Fig. 1)[41]. As with LPS, the immunogenicity of microbiota-derived EVs differs between microbial taxa, with EVs from pathogenic bacteria associated with pro-inflammatory responses compared to anti-inflammatory responses initiated by commensal EVs[41]. For example, EVs from a commensal strain of *E. coli* enhanced production of mucosal cytokines important for host defense[42]. While much of what we know about microbiota-derived EVs is based on investigations of their local effects in the gut, recent findings showed that there is also systemic regulation of host immunity, with microbiota-derived EVs priming neutrophils for inflammatory responses to secondary stimuli[43].

Lastly, gut microbes preside over the local education of immune cells in the mucosa that then recirculate to other body compartments to participate in systemic host defense (Fig. 1). Notably, it is well established that mucosal antigen-presenting cells (APCs) can carry microbiota antigens to distant organs to direct peripheral T cell function[44]. Dendritic cells (DC) migrate from the gut to the thymus to help shape the T cell receptor repertoire of microbiota-reactive T-cells, and to peripheral lymph nodes to shape the effector, regulatory, and memory T cell pools[45–47]. As described further below, intestinal microbiota-imprinting of peripheral $CD4^+$ T cells with reactivity to intestinal microbiota may support a systemic monitoring system for a rapid memory response to disseminated gut pathobionts[48].

Collectively, these mechanisms help expand the host-microbe interface beyond the local environment of the gut to enable a long-distance relationship between gut commensal and systemic immunity. In the next section, we will explore how these communication mechanisms are utilized to modulate the development, polarization, and functions of various immune cell populations involved in systemic host defense against infections.

SHAPING SYSTEMIC HOST DEFENSE THROUGH MICROBIOTA-IMMUNE INTERACTIONS

The contribution of gut microbes towards shaping extra-intestinal host defense encompasses all major immune effector cells of the innate and adaptive immune systems. Below, we will focus our discussion on the primary effector cell populations involved in anti-pathogen host defense within the bloodstream as the key compartment for invasion and dissemination of systemic infections (Fig. 2). Organ-specific microbiota-immune axes between the gut and brain, lung, liver, and other key organs are beyond the scope of the current review but have been recently summarized[25–28].

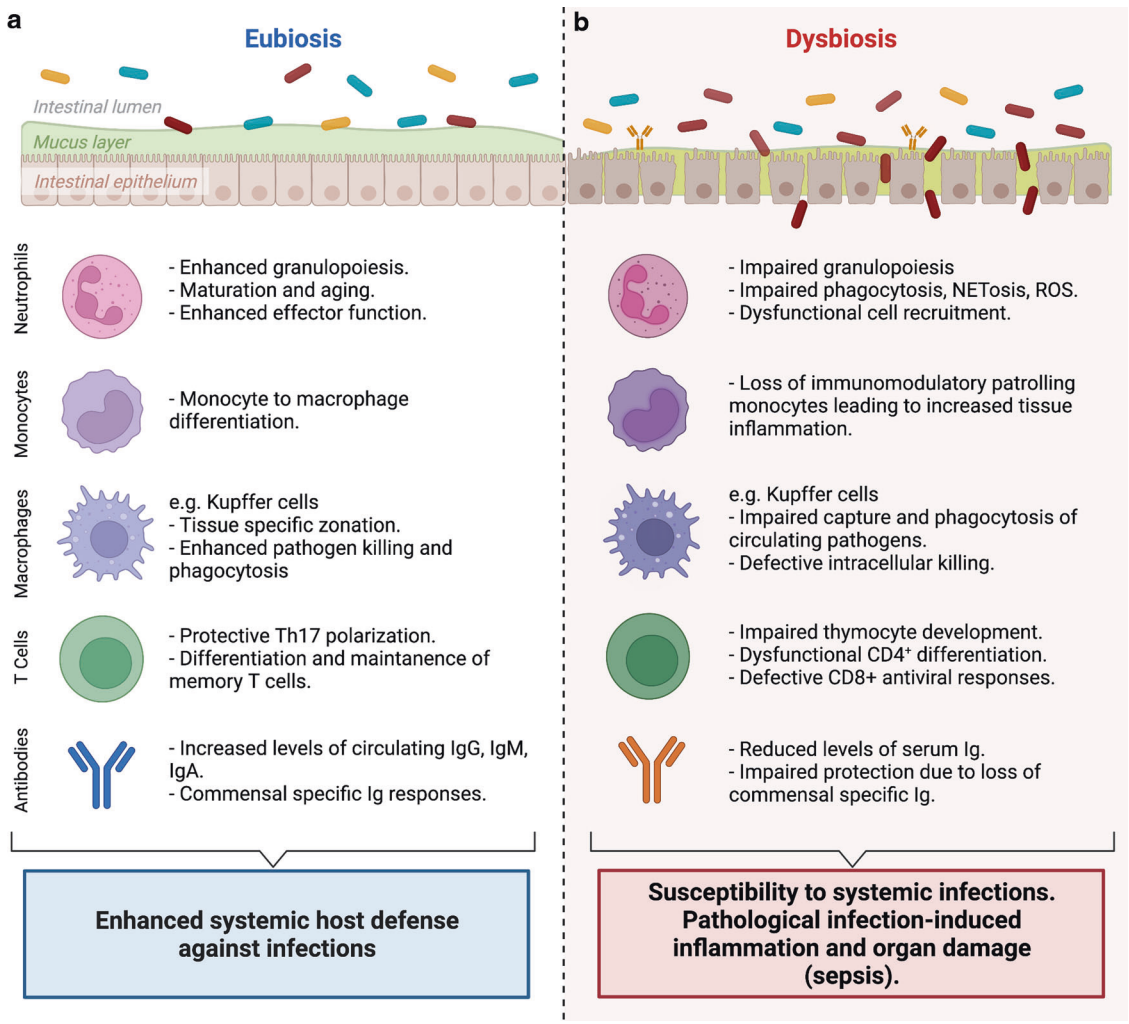

Fig. 2 Gut microbiota control of systemic host defense against infection and the pathological consequences of dysbiosis. a During eubiosis, homeostatic communication between the gut microbiota and systemic immune cell populations maintains key mechanisms of systemic host defense against infections. **b** In contrast, intestinal dysbiosis results in a breakdown of microbiota-dependent mechanisms of systemic host defense and impaired clearance of pathogens, as well as aberrant immune cell functions that contribute to immune-mediated organ damage in sepsis.

Circulating Neutrophils

Neutrophils in the bloodstream are rapidly deployed to sites of infection where they contribute a powerful payload of anti-pathogen effector mechanisms that are essential to the containment and eradication of pathogens. As such, effective neutrophil responses are dependent on their continuous supply in the bloodstream (primarily through granulopoiesis in the bone marrow), recruitment to sites of infection, and regulation of their arsenal of pathogen killing mechanisms. Emerging evidence has revealed that signals emanating from the gut microbiota are amongst the most influential modulators of neutrophil production and function during infection (Fig. 2).

For many years, it has been appreciated that germ-free and antibiotic-conditioned animals displayed suppressed myelopoiesis in the bone marrow, resulting in relative neutropenia and monocyte defects that contribute to impaired pathogen clearance and death in experimental models of infections[21,30,31,49]. Bone marrow myelopoiesis is rescued in GF and antibiotic-conditioned mice by reconstituting the gut with microbes[30] and can be partially reversed by gastrointestinal administration of non-viable microbes (heat killed *E. coli* or autoclaved cecal contents) in a manner that is dependent on PRR signaling via MyD88[21]. Furthermore, experiments using transient (~48–72 h) gut colonization with auxotrophic *E. coli* demonstrated that myelopoiesis is dynamically regulated via continuous input from gut-derived signals, rather than long-term imprinting[30]. Specifically, granulopoiesis at steady-state is controlled through a feedback circuit involving TLR-mediated recognition of microbiota products by innate lymphoid cells (ILCs) in the gut mucosa, which produce IL-17 that stimulates production of G-CSF, culminating in augmented granulopoiesis in the bone marrow[21,50,51]. This microbiota-dependent mechanism of granulopoiesis is negatively regulated by homeostatic migration of neutrophils back to tissues (possibly the gut) which inhibits the IL-17/G-CSF axis[52]. Collectively, these findings implicate the gut microbiota as a key controller of the circulating pool of phagocytes available to respond to invading pathogens.

In addition to their supply in the bloodstream, the gut microbiota also fine-tunes the anti-pathogen functionality of neutrophils. Neutrophils from germ-free or microbiota-depleted mice display marked functional impairment, including defects in migration, phagocytosis, and production of anti-microbial molecules like myeloperoxidase and ROS, culminating in impaired capacity to kill pathogens[53,54]. PRR-dependent priming of neutrophils by gut microbiota-derived peptidoglycan was found to enhance phagocytosis and killing of *S. pneumoniae* and *S. aureus* ex vivo and improve survival during in vivo infection[22]. Similar functional priming has been observed in response to gut-microbe derived SCFA[55]. Zhang et al. reported that the gut microbiota induces a specific functional program of neutrophil aging in vivo, whereby neutrophils undergo phenotypic and functional maturation characterized by upregulation of CXCR4 and downregulation of L-selectin, enhanced phagocytic capacity, inflammatory cytokine production, and neutrophil extracellular trap formation[56]. Microbiota-induced neutrophil aging was dependent on gut-derived TLR ligands in the circulation that directly stimulated neutrophils in a MyD88-dependent manner[56]. Lastly, there is emerging evidence that the gut microbiota may contribute to the orchestration of neutrophil-mediated host defense thought the regulation of cell trafficking to sites of infection. In germ-free zebrafish, the absence of intestinal microbiota was associated with aberrant neutrophil trafficking towards sites of injury[57]. In mice, germ-free status was associated with marked impairment of neutrophil recruitment to the inflamed peritoneum[54], as well as defective neutrophil trafficking to the lungs in a model of bacterial pneumonia[58]. Taken together, the cumulative evidence demonstrates that long-distance communication between intestinal commensals and neutrophils in the bone marrow and circulation is critical for the orchestration of effective host defense against systemic infections.

Macrophages and monocytes

Well-defined axes of communication exist between the gut microbiota and tissue resident macrophages in the gut[59,60], brain[61,62], lung[63], spleen[64], liver[16,65,66], and other organs. Among these, the impact of the gut microbiota on systemic host defense against infection is perhaps best exemplified by the unique intravascular macrophages of the liver (Kupffer cells, KC) (Fig. 2). Their unique residence within the vascular lumen of liver sinusoids positions these cells as defenders of the bloodstream, displaying a remarkable capacity to rapidly detect, capture, and engulf pathogens circulating in the blood as they pass through the liver. KC are continuously bathed in gut-derived signals reaching the liver via the portal veinous drainage of the GI tract. Studies in KC-depleted mice reveal the crucial role of these intravascular macrophages in preventing dissemination of microbes in the systemic circulation during infection, as well as preventing steady-state dissemination of gut commensals that translocate into the portal blood[16,67,68].

Recent evidence has uncovered important contributions of the gut microbiota to the anatomical localization and antimicrobial actions of KC. Recently, Gola et al. reported that the spatial distribution of KC to the periportal regions of the liver is dependent on tonic input from gut microbial signals, rather than developmental imprinting in early life[65]. MyD88-dependent signaling from gut microbial MAMPs to liver sinusoidal endothelial cells induced the establishment of chemokine gradients in the liver that guided KC to reside in periportal regions. This spatial zonation in colonized mice was critical for effective clearance of intravascular pathogens in a model of *Listeria monocytogenes* infection, compared to the uniform distribution of cells that occurs in the absence of gut microbial input[65]. Beyond spatial regulation, the gut microbiota also provides crucial input to KC to enhance their ability to phagocytize circulating pathogens and perform intracellular killing. Using intravital imaging of the liver, it was observed that KC in GF mice displayed defects in the capture, phagocytosis, and killing of circulating *S. aureus* and *E. coli*, contributing to an enhanced susceptibility of GF mice to disseminated bloodstream infections[16]. The compartmentalized shuttling of high concentrations of D-lactate from the gut to the liver via the portal vein was found to control pathogen uptake and killing by KC, and pathogen clearance in GF mice was restored by repopulating the gut with D-lactate producing bacteria[16]. In addition to pathogen killing, others have reported that microbial signals may also regulate KC density within the liver[66]. The exact mechanisms by which gut-derived mediators regulate KC anti-pathogen activities remain to be elucidated, but these findings uncover an important mechanism of long-distance communication mediated by bacterial metabolites that are crucial for macrophage host defense against systemic infections that enter the bloodstream.

Circulating monocytes contribute to the acute response against pathogens through recruitment to sites of infection, where they phagocytose and kill pathogens, regulate local inflammation, and also participate in shaping tissue immunity through their differentiation into resident macrophages[69]. In a groundbreaking study of 500 healthy humans, gut microbiota composition and function were shown to modulate cytokine production by peripheral blood mononuclear cells in responses to ex vivo stimulation with microbial products[70]. In mice, the absence of an intestinal microbiota results in aberrant programming of inflammatory monocytes, as shown recently that splenic monocyte homeostasis was dependent on MAMPs produced by an intact gut microbiota[64]. Kolypetri et al. reported that antibiotic-treated mice harbour an altered splenic monocyte pool with impaired inflammatory cytokine production following LPS challenge which

could be rescued through treatment with PRR ligands such as muramyl-dipeptide (MDP)[64]. Differentiation of monocytes into tissue macrophages is also regulated by the intestinal microbiota and may contribute to anti-pathogen defense. For example, the SCFA butyrate directs enhanced and long-lived anti-bacterial activity in human macrophages that differentiate from CD14 + monocytes[71]. Interestingly, microbiota-programming of monocytes likely differs between mice and humans. Ang et al., show that human monocytes stimulated with SCFA acetate experienced inflammatory re-programming, resulting in reduced expression of inflammatory cytokines such as GM-CSF, IL-1β and ICAM-1, whereas mouse monocytes responded to acetate with enhanced inflammatory cytokine production via distinct signalling pathways[72]. In mice fed high fiber diets, microbiota-derived SCFA promoted generation of non-classical Ly6C$^-$ monocytes that differentiated into alternatively activated macrophages and helped blunt excessive inflammation in response to influenza A infection[73]. Overall, pleiotropic modulation of monocytes is emerging as an important mechanism by which the gut microbiota shapes both acute anti-pathogen responses as well as the landscape of macrophage-mediated tissue immunity.

Innate lymphoid cells (ILCs)

NK cells and other innate lymphoid cells (ILCs) are intimately tied to the gut microbiota through its role in directing the development and programming of ILCs in vivo[74,75]. ILCs primarily reside at mucosal sites including the gastrointestinal tract, and make well described contributions to host defenses in the gut. However, microbiota-educated ILCs also participate in systemic host defense against infections both directly and indirectly. Mucosal ILC3 in the intestine produce IL-17 in response to gut microbes, which regulates G-CSF production and granulopoiesis in the bone marrow[21]. This ILC3-mediated response to gut commensals was critical for effective neutrophil-mediated host defense against pneumonia in neonatal mice[21]. Their powerful ability to modulate the function of other immune cells represents an important indirect contribution of microbiota-responsive ILCs to systemic host defense against infections.

More directly, microbiota-ILC interactions can impact pathogen clearance at extra-intestinal sites of infection. NK cell-mediated protection against viral infections is markedly impaired in germ free mice[75]. The gut microbiota was shown to be critical for effective NK cell priming and antiviral activity, however this was not an NK cell-intrinsic effect but was instead mediated by microbiota-educated mononuclear cells[75]. In addition to antiviral immunity, collaborations between the microbiota and ILCs can impact host defense against bacterial infections. Gray et al. reported that exposure of neonatal mice to intestinal commensals induced trafficking of ILC3 to the lungs, where they were key to effectively combatting pneumonia pathogens[76]. Through an intestinal dendritic cell intermediary, gut microbes induced upregulation of the lung homing chemokine receptor CCR4 on ILCs, leading to their selective recruitment to the lungs of colonized neonatal mice. Microbiota-directed homing of ILC3s to the lungs and production of IL-22 was crucial for survival in a neonatal model of *S. pneumonia* infection[76]. Collectively, the influence of intestinal microbes on ILC biology provides the host with multiple important direct and indirect benefits for enhanced defense against bacterial and viral infections at systemic sites.

T cell mediated host defense

The shaping of T cell immunity by gut microbes has been identified as an important aspect of host defense against a wide range of bacterial, fungal, and viral infections. Multiple mechanisms have been identified that mediate microbiota-T cell cross-talk, including direct and indirect modulation of T cell development, polarization, memory formation/maintenance, and effector regulation (Fig. 2)[77].

The shaping of T cell-mediated host defense by the microbiota begins during thymic development, where commensal microbes help shape diversity and specificities of T cell receptors in a manner that may protect against future infection by related pathogens. The impact of intestinal microbes on thymic T cell development is illustrated by the stark reduction in thymic cellularity and T cell output in germ-free and antibiotic-conditioned SPF mice[47,78,79]. Gnotobiotic mouse models have revealed that gut colonization leads to the production of microbiota-specific T cells in the thymus that provide protection against future infections by pathobionts and commensal-related pathogens[47]. In these mice, gut bacterial antigens were delivered to the thymus by CX3CR1$^+$ dendritic cells where they induced positive selection of CD4$^+$ T cells that then trafficked to peripheral tissues[47]. Additional mechanisms of microbiota-thymic communication have been identified that help shape the developing T cell repertoire, including regulation of autoimmune regulator (AIRE) expression in medullary thymic epithelial cells (mTEC), thus influencing the deletion of auto-reactive thymocytes and induction of thymic regulatory T cells (Treg)[80–82]. Further work is needed to better understand how this long-distance communication between gut microbes and the thymus impacts host defense, and the implications of intestinal dysbiosis during early life development on susceptibility to infections in later life.

Gut microbes also help shape systemic effector and memory T cell responses. Shaping of T cell polarization and effector responses by gut microbes is exemplified by the influence of segmented filamentous bacteria (SFB) on CD4$^+$ T cell polarization towards Th17 phenotype, which was originally shown to improve host resistance against *C. rodentium* infection in the murine gut[83]. More recently, intestinal SFB has also been found to promote systemic Th17 mediated responses against extraintestinal pathogens. Mice harbouring SFB in the gut had augmented Th17 responses in extraintestinal organs including the lungs, and were more resistant to pneumonia caused by diverse pathogens including MRSA and *Aspergillus fumigatus*[84,85]. In addition to SFB, intestinal fungi including *C. albicans* can influence T cell polarization towards Th17 phenotype in the spleen and peripheral lymph nodes[86]. Priming of systemic Th17 effector T cells by *C. albicans* yielded improved host defense against systemic candidemia, as well as augmented host defense against a heterologous pathogen *S. aureus*, indicating that T cell activation and polarization by intestinal *Candida* is not an antigen-specific response[86]. In addition to Th17-mediated immunity, specific mechanisms linking gut microbes to the polarization and effector functions of other CD4$^+$ T cell subsets have also been established[87–91]. Together, these studies support a key role for the gut microbiota in fortifying host defense by promoting effector CD4$^+$ T cell polarization in the systemic compartment.

Akin to CD4$^+$ T cells, CD8$^+$ T cells rely on signals and metabolites from the microbiota for optimal function in response to intracellular infections[92]. Germ free and antibiotic-conditioned SPF mice display reduced CD8$^+$ numbers, cytotoxicity, cytokine production, and enhanced susceptibility to infection by a variety of different viral pathogens including Influenza A virus, LCMV, flavivirus infections, and others[17,93,94]. In mice infected with Influenza A virus, defects in virus-specific CD8$^+$ T cell responses could be restored by intra-rectal administration of TLR ligands, suggesting PRR-dependent communication from gut microbes contributes to the regulation of effector CD8$^+$ responses[17]. In addition to TLR ligands, evidence from high-fat diet fed mice revealed that gut derived SCFA played a critical role in effective expansion and function of CD8$^+$ T cells during influenza through selective regulation of cellular metabolism[73]. Others have shown that SCFA like butyrate promote transition of extraintestinal CD8$^+$ T cells into memory cells and the maintenance of these specific memory cells in response to viral infection[95,96]. Taken together, the cumulative evidence supports the existence of multiple direct

and indirect mechanisms of communication between gut microbes and systemic T cells that is critical for effective $CD4^+$ and $CD8^+$ T cell-mediated host defense against extracellular and intracellular pathogens.

Microbiota regulation of antibody-mediated host defense

At mucosal surfaces, the interplay between gut microbes and secretory immunoglobulins is paramount in maintaining host-microbial homeostasis[97]. Within the systemic circulation, antibody responses are also heavily modulated by gut commensals in a manner that bolsters humoral immunity against invading pathogens. Germ-free and antibiotic-treated mice show marked reductions of serum IgA[98,99] and IgG[100] and an increase in IgE which is associated with predisposition to allergies[101]. Effects of antibiotic-driven IgA depletion are likewise observed in humans[18]. Correspondingly, probiotics and high dietary fiber increase IgG and IgA levels and suppress IgE[87,102]. Bacteria-produced SCFAs promote B cell maturation into germinal center B cells and plasma cells in secondary lymphoid tissues[102]. In addition to regulating Ig production, the gut microbiota also shapes the repertoire of protective antibody specificities in the systemic circulation. Commensal-specific IgG, IgA, and IgM can be detected in the circulation of microbiota colonized hosts[100,103,104]. These anti-commensal antibodies contribute to protection against cross-reactive invading pathogens, as well as against infection caused by translocated gut pathobionts. Transfer of commensal specific Ig from naïve SPF mice to GF animals improves their resistance against systemic bacterial infections[105]. Gut microbiota-induced systemic IgG specific for bacterial lipoprotein renders colonized mice more resistant to bloodstream infections by *E. coli* and *Salmonella enterica*[100]. In addition, microbiota-specific IgA in the blood has also been shown to improve survival in models of *Pseudomonas* pneumonia and polymicrobial sepsis[18,103]. Like bacterial colonizers, gut fungi also elicit a systemic protective anti-fungal IgG response. Intestinal *Candida* drive the production of anti-fungal IgG that protects against systemic infection by *C. albicans* and the emerging pathogen *C. auris*[106].

Although it was originally believed that systemic anti-commensal Ig responses were due solely to "leaking" of commensals and their antigens out of the gut during intestinal pathology[107], it is now established that mucosal colonization alone is sufficient to drive a systemic Ig response[108]. In fact, mucosal versus translocation exposure to commensals direct unique programs of Ig responses in the circulation, with systemic exposure eliciting a more broad IgG repertoire of anti-commensal antibodies in the blood[109]. Lastly, in addition to the specific repertoire of conventional B cell and Ig responses, the intestinal microbiota may also contribute to the generation of polyreactive natural antibodies (NAbs) by innate-like B-1 cells. Although debate exists as to whether NAbs are generated in response to microbiota antigens directly[110] or independently of exogenous antigen exposure in utero[111], polyreactive NAbs do bind to commensal microbes[112] and the repertoire of certain NAbs may be influenced by gut microbial composition[113]. These findings suggest at least a partial influence of select microbial species on NAb levels and repertoires, but many questions remain as to the exact mechanism and scope of this influence. These questions notwithstanding, research supporting the action of microbiota-induced NAbs in systemic host defense has been observed in experiments where natural antibodies transferred from conventional mice to germ free mice restored protection against *Klebsiella pneumoniae* lung infection[105].

INTESTINAL DYSBIOSIS AND PATHOLOGICAL SYSTEMIC HOST RESPONSE TO INFECTION

Many of the microbiota-immune connections noted above were discovered, in part, through the demonstration that these mechanisms of systemic host defense fail when the microbiota is disrupted by antibiotics or absent in GF mice[16–24]. Intestinal dysbiosis in both animals and humans has been linked to increased susceptibility to bacterial, viral, and fungal pathogens[20,21,114–117]. However, failure of microbiota-dependent host defense mechanisms is not the only consequence of intestinal dysbiosis during infection, as it is now appreciated that dysbiosis can also actively induce pathological systemic inflammation and immune-mediated organ damage in response to infection (ie. sepsis). For example, mouse models of pneumonia induced by a variety of pathogens have demonstrated that intestinal dysbiosis caused by pre-conditioning with antibiotics led to impaired pathogen clearance, but also exacerbated inflammation, multi-organ damage, and increased mortality[19,20,117,118]. Additionally, dysbiosis-induced defects in host defense in a model of post-surgical infection could be ameliorated with live (but not autoclaved) fecal microbiota transplantation from healthy littermates, mediated by restoration of butyrate levels and interferon regulator factor-3 signaling[119]. Further stark examples of how gut microbiota composition and diversity impact sepsis severity can be found in studies using "dirty" mice derived from pet shops or mice colonized with a wild/natural microbiome[120]. Mice harbouring a pet shop microbiome subjected to cecal ligation and puncture or endotoxin shock exhibited dramatically increased systemic inflammatory organ injury and mortality compared to conventional SPF mice[121]. In these animals, pathogen burden in the bloodstream was equivalent, suggesting that the exacerbated sepsis in dirty mice may be driven by a state of impaired disease tolerance mediated by pathologically altered systemic inflammation. Indeed, a role for the gut microbiota in mediating disease tolerance to infection has previously been demonstrated in gnotobiotic mice harbouring *E. coli* O21:H + that induced inflammasome-dependent resistance to muscle wasting during infection[122]. Overall, pathological alterations of gut microbiota composition appear to drive not only defects in host defense against pathogens, but may also actively participate in promoting a septic response to inflection mediated by dysregulated systemic inflammation and immune-mediated organ damage.

Observational studies of humans with sepsis and other hospitalized and critically ill patients have also reported extreme shifts in microbiota composition and diversity that have been linked with adverse outcomes, including increased infections, organ dysfunction, prolonged requirement for life support and hospitalization, and even mortality[15,123–132]. In particular, multiple studies have reported that the gut microbiota of patients with sepsis is depleted of anaerobic fermenters, with corresponding reductions in fecal SCFA levels[130,133–135]. Furthermore, the dysbiotic microbiome observed in septic patients is notably enriched with pathobionts of the Proteobacteria phylum as well as *Enterococcus* and *Staphylococcus*[123–126,132]. In addition to intestinal bacterial communities, Haak et al. recently reported the presence of multi-kingdom dysbiosis in critically ill septic patients including altered gut fungal ecology together with shifts in endogenous viruses[126]. This marked dysbiosis suffered by patients with sepsis and critical illness has been associated with worsening multi-organ dysfunction, as well as an increased risk of secondary (hospital-acquired) infections[123,125,127,128,131,132,136]. Furthermore, epidemiologic data generated from hospitalized patients revealed that individuals who sustained the greatest insult to their microbiota (ie. highest degree of dysbiosis) were at increased risk of being re-hospitalized with a recurrent bout of sepsis in the subsequent 90 days[137]. Together, these interesting hypothesis-generating observational data suggest that a pathologically altered gut microbiota may predispose to both a defective host response to infection, as well as exacerbation of disease severity through detrimental immune-mediated organ damage. This presents an exciting potential for therapeutic interventions targeting the microbiota for the prevention and treatment of systemic infections and sepsis.

THERAPEUTIC IMPLICATIONS OF MICROBIOTA-IMMUNE INTERACTIONS IN SYSTEMIC INFECTIONS AND SEPSIS

Mouse models have shown that microbiota modulation can augment host defense and improve outcomes in response to a wide range of severe infections by therapeutic supplementation with immune-modulatory commensals[16], FMT[21,119], dietary modulation of microbial SCFA production[73], and administration of bacterial products and metabolites[16,56]. In humans, microbiota modifying therapeutics have been used very successfully to treat mucosal infections like *C. difficile* colitis[138], but the application of microbiota-based treatments for systemic infection and sepsis are in their infancy. As described above, widespread multi-taxa dysbiosis has been observed in septic humans, and the optimal approach to microbiota modulation has not been defined. Preliminary clinical trials of probiotics in adult patients with critical illness showed promising signals towards a reduction in systemic hospital-acquired infections[139], but a recent large randomized controlled trial of a *Lactobacillus rhamnosus* GG probiotic in this patient population failed to impact rates of secondary (hospital-acquired) infections or survival[140]. Case reports of FMT therapy in septic patients have been published, but limited data is available on the safety and efficacy of this approach[141]. Aside from restorative approaches like probiotics and FMT, other investigators have tested an opposing strategy of gut microbe depletion with antibiotics, a strategy called "selective digestive decontamination" (SDD) that is hypothetically combatting disease-associated pathobiont overgrowth in the gut[142]. This polarization of approaches to therapeutic microbiota modification (supplementation versus depletion) in sepsis and critical illness is perhaps the clearest indication that further research is needed to understand mechanisms of microbiota-host interactions to guide rationalized and targeted approaches to microbiota therapies that improve host defense and modulate pathological inflammation in sepsis.

Lastly, the use of microbial therapeutics in this sick and vulnerable patient population is not without risks. Recent high-profile publications of serious and deadly infections caused by FMT in vulnerable patients, as well as bloodstream dissemination of enterally administered probiotics in critically ill patients, reinforce the need to comprehensively understand the efficacy and safety of microbial therapeutics in these populations[143,144].

CONCLUSIONS

The cumulative evidence from mice and emerging evidence from humans supports an intimate and essential long-distance relationship between gut microbes and systemic immune responses that mediate host defense against infection. Breakdown of this relationship caused by intestinal dysbiosis has important consequences for the impairment of pathogen clearance as well as the induction of pathological immune dysregulation and sepsis. Furthermore, the therapeutic malleability of the gut microbiota makes this relationship an attractive target for intervention with microbiota-based immunotherapy to prevent and/or treat systemic infections and sepsis.

Although tremendous strides have been made in our understanding of the mechanisms underlying microbiota-immune communication in systemic host defense, much remains to be learned. Most notably, much of our understanding of these mechanisms is derived from inbred mouse models, whereas less is known about systemic microbiome-immune communication in humans. Emerging evidence from humans in both health and disease support an important connection between the gut microbiota and systemic immune function[70,145–147]. However, heterogeneity contributed by genetic diversity, environmental and dietary factors as well as co-morbidities and treatments are likely to make the impact of microbiota more nuanced in humans compared to highly controlled laboratory mouse models. Improvements in mouse models, including wild-microbiota and human-microbiota associated mice, may help by more effectively phenocopying human microbiota-immune responses including during infections and sepsis[148–150]. Nevertheless, further human translational research is crucial to understand how the microbiota, as well as microbiota-modulating therapeutics, impact immunity and host defense. Developing a comprehensive understanding of long-distance interactions between gut microbes and systemic immunity in humans will require integrating multi-omics profiling using systems-level analyses of immunity together with microbiota composition and function, and will also benefit from longitudinal study designs that sample the changing landscape of the microbiome and immune system throughout the course of infection and the impact of anti-microbial (and other) treatments. Defining these mechanisms in humans, and how they change in response to microbiome perturbations, will be key to developing effective microbiota-based therapies to treat infection and sepsis.

In addition, much remains to be learned about how other important biological inputs affect microbiome-immune communication that may also have important therapeutic implications. For example, sex-based differences in gut microbiota composition have been shown to impact systemic immunity in diseases like diabetes[151,152]. In mice, sexual dimorphism is associated with differences in protection against sepsis, yet the mechanisms underlying this remain unexplored including a potential role for sex-based differences in the microbiota[153]. Lastly, our understanding of microbiota-immune interactions to date has been very bacteria-centric, and yet there is emerging data that other kingdoms of commensal microbes have a powerful impact on systemic immunity and host defense. Gut fungi have been implicated in the regulation of host defense against infections caused by both fungal and bacterial pathogens, and it has been suggested that gut fungi may be important mediators of systemic trained immunity and resistance to heterologous infections[154]. Much remains to be learned about how commensal fungi, viruses, and protozoans, as well as cross-kingdoms interactions amongst gut microbes, contribute to the regulation of systemic host defense. Gaining a deeper understand of the breadth of communication between intestinal microorganisms and systemic immune mechanisms will undoubtedly pay dividends for the development of rationalized, precision-based therapies that harness long-distance microbiota-immune communication to prevent and treat infections and sepsis.

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J.S., I.S., M.B.G., and B.M. conceptualized, wrote, and edited the manuscript. All authors approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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