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Cohabitation in the intestine: interactions between helminth parasites, bacterial microbiota and host immunity

Lisa A. Reynolds[1], **B. Brett Finlay**[1,2], and **Rick M. Maizels**[3]

[1]Michael Smith Laboratories, University of British Columbia, Vancouver, BC, V6T 1Z4, Canada

[2]Department of Microbiology and Immunology, University of British Columbia, Vancouver, BC Canada; Department of Biochemistry and Molecular Biology, University of British Columbia, Vancouver, BC Canada.

[3]Centre for Immunity, Infection and Evolution, and Institute of Immunology and Infection Research, Ashworth Laboratories, University of Edinburgh, EH9 3JT

Abstract

Both intestinal helminth parasites and certain bacterial microbiota species have been credited with strong immunomodulatory effects. Recent studies have reported that the presence of helminth infection alters the composition of the bacterial intestinal microbiota, and conversely that the presence and composition of the bacterial microbiota affects helminth colonisation and persistence within mammalian hosts. This article reviews recent findings on these reciprocal relationships, in both human populations and mouse models at the level of potential mechanistic pathways, and the implications these bear for immunomodulatory effects on allergic and autoimmune disorders. Understanding the multidirectional complex interactions between intestinal microbes, helminth parasites and the host immune system will allow for a more holistic approach when using pro-, pre-, synbiotics, antibiotics and anthelmintics, and when designing treatments for autoimmune and allergic conditions.

Introduction

The mammalian immune system has evolved to cope with immense microbial presence, including some dangerous, some harmless, and some beneficial microbes (1), but also in conjunction with macrobionts such as helminth parasites (2). In each case host immunity has to make the correct judgement, whether to reject or accept the new species, and if the latter, how to control it. In parallel, incoming organisms have evolved to maximise their chances of acceptance, through immune evasion, mimicry and induction of host immunoregulatory pathways. Thus, while commensal bacteria and multicellular helminths occupy very different taxonomic space, they have both responded to evolutionary forces by developing similar strategies of modulating host immunity. Moreover, it is apparent that these different kingdoms of life have developed a surprising degree of dialogue with a common agenda of establishing a new homeostasis in the host intestinal tract (3, 4).

The parallel agendas of bacterial microbes and intestinal helminths include dampening or deceiving host immunity to permit their survival, even though bacteria and helminths need to suppress very different T helper (Th)1/17 and Th2-dominated effector mechanisms

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respectively. Common strategies include the induction of suppressive regulatory T cells (Tregs) by a range of bacteria including *Bacteroides fragilis* (5), *Bifidobacterium infantis* (6), *Clostridium* spp. (7-9) and *Lactobacillus* spp. (10-13) as well as by intestinal nematode parasites such as *Heligmosomoides polygyrus* (14) and *Strongyloides ratti* (15). Interestingly, activation of Tregs appears to be a widespread feature of both microbiota colonisation (16, 17) and helminth parasite infection (18) (Figure 1).

Expansion of Treg activity may underpin a further feature shared between many helminths and microbiota species: the systemic muting of the immune response so that reactivity to bystander antigens – such as allergens and autoantigens – is inhibited. The parallels were not immediately articulated and indeed separate models emerged of helminth (19) and microbial (20) mediated protection against allergy, before more recently coalescing. These similarities are illustrated by the fact that both *H. polygyrus* (21, 22) and *Lactobacillus* spp. (12) in the intestinal tract can block the development of allergic reactivity in the airways of mice, while heightened susceptibility to allergy development, in humans and in animal allergy models can result from either antibiotic or anthelmintic treatment (23-25). Likewise, both commensals (26, 27) and helminths (28) can ameliorate autoimmune and colitic disease. It will be interesting to follow these parallels as further systemic effects of intestinal colonisation come to light, including changes in metabolism, obesity and behavior (29-31).

Given the relatively unexplored theme of bacterial-parasite interactions within the mammalian host, and the emerging therapeutic potential of both bacterial microbiota species (32) and parasitic helminths (33), it is now essential to understand the multilateral interactions between these organisms and the host immune system. In this Review, we discuss the experimental evidence regarding these relationships, and examine to what extent the reported immunomodulatory effects of helminths can be attributed to a modulation of microbiota composition or function.

Helminth infection modulates bacterial microbiota composition and function

Controlled laboratory animal experiments have clearly demonstrated that infection with helminth parasites results in substantial shifts in the intestinal microbiota species composition. Chronic *H. polygyrus* infection in the duodenum of mice results in an increased abundance of Lactobacillaceae and Enterobacteriaceae species in the small intestine (34-36). Similarly, a chronic infection with the mouse whipworm *Trichuris muris*, which colonises the cecum, leads to a reduced diversity of fecal bacterial species particularly within the Bacteroidetes phyla, as well as an increase in abundance of Lactobacillaceae family members (37, 38). Rats infected with the tapeworm *Hymenolepis diminuta* had an altered community structure compared to uninfected animals that involved around 20% of their total cecal bacterial microbiota, with a general shift in abundance from members of the class Bacilli to the class Clostridia in helminth-infected rats (39). Microbiota changes following helminth infection correlate with worm burdens (36, 40), but revert to normal following drug clearance of helminths, indicating that the continuing presence of parasites is required for sustained changes to the bacterial microbiota (38). In wild mice (*Apodemus*

flavicollis) around half of animals sampled were simultaneously infected with more than one helminth species, most commonly a combination of *H. polygyrus*, *Syphacia* spp. (pinworm) and *Hymenolepis* spp. (tapeworm) (41). Helminth infections correlated with heightened bacterial microbiota diversity, with the presence of each helminth being associated with specific shifts in microbiota species composition or abundance(41).

Very recent findings indicate helminth infection can also modify host metabolism, with onward implications for immune modulation. Thus, experimental *T. muris* infection in mice reduced a large number of metabolomic products as measured in the feces, including Vitamin D2/D3 derivatives, many fatty acids and related metabolites, glycerophospholipids, dietary plant-derived carbohydrates, and amino acid synthesis intermediates (38); hamsters infected with the human hookworm *Necator americanus* also showed extensively altered urinary metabolite levels that could be explained by changes in the intestinal microflora (42). Infection of pigs with the related porcine whipworm *Trichuris suis*, which also alters the composition of the colonic microbiota, is again accompanied by a metabolic shift, with infection resulting in reduced cofactors for carbohydrate metabolism and amino acid biosynthesis (40, 43). Such metabolomic alterations following helminth infection may result from microbiota compositional changes, altered intestinal absorption of dietary products, or from the direct production of metabolites by helminth parasites (38).

In human populations, studies on the influence of helminth infection on microbiota composition and function have only recently commenced. In a cohort of Zimbabwean children, those positive for *Schistosoma haematobium* infection were found to have a significantly higher fecal abundance of several operational taxonomic units (OTUs) from within the genus *Prevetella* (44). In these subjects, praziquantel-induced helminth clearance did not revert the microbiome composition, suggesting that childhood helminth exposure may have long-term effects on microbiota community structure (44). In a Malaysian population, the fecal microbiota of individuals colonised by at least one helminth parasite (*Trichuris* spp., *Ascaris* spp. or hookworms) harbored a more diverse community than those individuals free from helminth infection (45). However, less marked differences have emerged from a study of school-age children in Ecuador with similar helminths (46), or from 8 human volunteers experimentally infected with *N. americanus* (47).

It should be noted that populations with a high prevalence of helminth parasites are also very distinct in diet, lifestyle and host genetics from those in the major industrialised societies, and appear to carry markedly different sets of intestinal microbes (48). Interpretation of data is likely to be further confounded by variable infection intensities in natural helminth infections. These human studies are also restricted to fecal analyses, which do not accurately reflect local microbiota shifts that may occur, for example after infection with small intestine dwelling hookworms *(eg N. americanus)* and roundworm *(Ascaris lumbricoides*).

Helminth infections –resetting immune homeostasis and impact on microbiota

A characteristic feature of helminth infection is the elicitation of a Type-2 immune response, alongside a regulatory response, especially in the setting of chronic, asymptomatic infection

(2). Given the immune system's role in regulating and containing the intestinal microbiota population (1) it seems likely that disruption and rebalancing of immune homeostasis can result in functional shifts in microbiota populations. Interestingly, such changes to the set points can be observed through both innate and adaptive pathways (Figure 2).

A significant effect of helminths on innate interactions with the microbiota may be to alter the production of antimicrobial peptides in the intestinal tract. BALB/c mice, which mount a Th2-polarised immune response following *T. muris* infection, showed increased expression of the antimicrobial peptide angiogenin 4 in colonic goblet cells after *T. muris* infection (49). Furthermore, *H. polygyrus* infection increased expression levels of the antimicrobial C-type lectin RegIIIγ in the cecum of mice (50). Such alterations in antimicrobial peptide secretion leading to microbiota compositional shifts following helminth infection may be evoked by specific products released by helminths (termed excretory/secretory products or ES) acting on intestinal epithelial cells. Consistent with this is a report that the broad microbiota compositional changes caused by *H. polygyrus* infection in mice was independent of IL-4Rα signaling and Th2 induction (35).

An altered physical microenvironment elicited by helminth infection, including epithelial barrier disruption and the stimulation of mucus production, may also select for the outgrowth of specific species within the microbiota (43). Changes to the intestinal mucus layer include a switch from Muc2 to Muc5AC following *T. muris* infection (51), and more subtle changes to the glycosylation patterns of mucins (which impact upon viscosity) following infection of rats with the rodent helminth parasite *Nippostrongylus brasiliensis* (52). Most significantly, perhaps, the IL-13/IL-22-dependent hyperproliferation of goblet cells and over-production of mucus following helminth infection (53) is likely to substantially alter the ability of different bacterial species to remain in the intestinal tract.

Toll-like receptor (TLR) interactions are central to the maintenance of host-microbiota homeostasis (54), and interference with TLR or other pattern recognition receptor (PRR) signaling may be a mechanism by which the presence of helminths alters microbiota composition. There is evidence both that helminth infection can alter expression levels of TLRs (55, 56), and modulate downstream signaling following TLR stimulation (28, 57-59). Within the intestinal setting, infection of rats with the tapeworm *Hymenolepis diminuta* increases expression of TLR2 and TLR4 (60), while *H. polygyrus* infection induces TLR4 expression specifically on small intestinal lamina propria T cells (61), which may be stimulated through the increased exposure of host immune cells to microbiota ligands during helminth infection.

As well as altering TLR expression levels, it has been well documented that helminth ES products can modulate inflammatory responses from dendritic cells (DCs) and macrophages following stimulation with TLR ligands (62). For example, a fatty acid binding protein from the human and animal parasitic trematode *Fasciola hepatica* (Fh12) can suppress IL-12p35, TNF-α, IL-6 and IL-1β production from bone marrow-derived macrophages in response to lipopolysaccharide (LPS) stimulation (63) and the ES of *H. polygyrus* (HES) can suppress IL-12p70 and IL-10 production in response to CpG stimulation of bone-marrow derived dendritic cells (64). Interestingly, ES from the whipworm *T. suis* not only downregulates DC

TLR responses, but interacts with C-type lectin receptors (CLRs) though specific glycan moieties (65). The functional role of these modulatory responses in the intestinal setting is not yet clear, however these pathways may be important in situations where helminth infection promotes host tolerance against specific groups within the bacterial microbiota.

Modulation of microbiota populations through the adaptive, antigen-specific arm of the immune system can also take place. For example, microbiota-specific T cells are generated following epithelial barrier breach induced either by dextran sodium sulfate (DSS) administration, or by acute infection with the protozoan parasite *Toxoplasma gondii* (66). Intestinal helminths could likewise boost the T cell response to microbial antigens, although in other contexts certain helminth species effectively down-regulate the host T cell compartment (67) to establish a more tolerogenic environment.

An additional component aiding in containment of the intestinal microbiota is the production of mucosal immunoglobulin (Ig)A by lamina propria plasma cells, which is stimulated by the presence of the microbiota itself (68). Surprisingly, while robust parasite-specific IgA responses are elicited in helminth infections, these antibodies have only a limited role in protective anti-parasite immunity (69, 70). It is possible however, that helminth infection modulates the generation of microbe-specific IgA responses, as indeed is reported in the suppression of cholera toxin IgA antibodies in patients co-infected with helminths and *Vibrio cholerae* (71).

A fascinating study of the adaptive Th2 response that may modulate both microbial populations and host pathology concerns the treatment of spontaneous idiopathic chronic diarrhea amongst captive rhesus macaques. The experimental administration of *Trichuris trichiura* ova improved disease symptoms (measured by an increased fecal consistency and weight gain) in 4 out of 5 animals, despite the lack of establishment of a chronic infection with *T. trichiura* (72). In these animals, a higher frequency of IL-4-producing $CD4^+$ T cells was detected in colonic biopsies taken after, compared with before, helminth exposure (72). Additionally, following helminth exposure, the total load of several bacterial taxa detected in colon biopsies was reduced alongside a heightened diversity of bacterial species (72). A local colonic Th2 response induced by *T. trichiura* exposure may have promoted mucus production and epithelial turnover, sufficient to reduce the association of bacterial microbiota species with the colonic mucosa, recovering intestinal homeostasis (73).

Independently of these immunological pathways, there are of course likely to be direct interactions between helminths and microbes, as suggested by the identification of an antibacterial peptide from the pig roundworm *Ascaris suum* (74) and the finding that HES contains at least 8 lysozyme homologues with potential anti-microbial effects (75). Furthermore, the ES of *Trichuris suis* was found to contain antibiotic activity in vitro, although the active principle was not identified (76). The extent to which these effects functionally alter the microbial composition in situ remains to be tested.

Impact of helminths on infection with enteric bacterial pathogens

As well as impacting the composition and function of the commensal and symbiotic bacterial microbiota species, helminth infection can also alter the host response to infection with pathogenic bacterial species. *H. polygyrus* or *N. brasiliensis* co-infection in mice impairs clearance of *Salmonella enterica* serovar Typhimurium (*S.* Typhimurium) when compared to singly *S.* Typhimurium-infected mice, resulting in increased mortality, more pronounced edema of intestinal tissue, further epithelial erosions, and increased thickening of gut wall (50, 77). Similarly, mice infected with *H. polygyrus* prior to *Citrobacter rodentium* infection show higher bacterial colonisation levels, and greater *C. rodentium*-induced pathology than those singly infected, as measured by increased weight loss, epithelial cell hyperplasia, inflammatory cell infiltration, thickening of the gut wall, as well as a higher incidence of anal prolapse and mortality (78). In this experimental system, the effect of helminth co-infection was shown to be dependent on the Type-2 immune response induced by *H. polygyrus*, as co-infected STAT6-deficient mice did not show these measures of exaggerated disease severity (78). In part this may be due to a helminth-induced Type-2 response repressing effector IFN-γ responses towards *C. rodentium* (78), although multiple additional parallel mechanisms likely contribute to the exaggerated pathology in helminth co-infected mice.

Feedback from bacterial microbiota to modulate helminth colonisation and persistence

The first striking example of how helminth parasites require the presence of the microbiota in order to successfully colonise mammals came from the observation that *T. muris* eggs, which after ingestion hatch in the large intestine of their hosts, fail to do so without signals from the bacterial microbiota (79). *T. muris* likely utilises the high density of microbes in the large intestine as an environmental cue, to trigger hatching in the correct location for its larvae to emerge. The requirement for the microbiota appears to be common amongst helminth parasites, as *H. polygyrus* is less able to form persistent infections in mice lacking a microbiota (germ-free), compared to conventionally raised mice (80-82). This is particularly striking, since germ-free mice are generally more susceptible to infections with bacterial or viral pathogens (83). Unlike *T. muris*, *H. polygyrus* eggs hatch in the external environment and infective larvae are ingested (84), thus additional mechanisms must underlie how the presence of the host microbiota benefits *H. polygyrus* survival within the host. It is possible that the failure of *H. polygyrus* to chronically infect germ-free mice results from morphological abnormalities along the intestinal tract of germ-free animals, such as an altered villous length (83), but additionally, recent evidence suggests that in conventionally raised mice, the composition of species within the microbiota can alter susceptibility to helminths (Figure 2).

Treating mice with a low dose antibiotic to modify the composition of their intestinal microbiota, without significantly reducing the total load of bacteria, is sufficient to alter susceptibility to infection with *H. polygyrus* (36). The abundance of *Lactobacillus* spp. in the duodenum was shown to positively correlate with *H. polygyrus* adult worms numbers 28

days post infection, and importantly, experimental administration of the single commensal species *Lactobacillus taiwanensis* was sufficient to prolong the persistence of an *H. polygyrus* infection (36). That a chronic *H. polygyrus* infection results in *Lactobacillus* spp. expansion, and that a *Lactobacillus* species is able to promote *H. polygyrus* infection, points to mutually beneficial relationships between helminths and select bacterial species within the mammalian host (36).

Similarly, the administration of both live, or dead *Lactobacillus casei* to mice was shown to enhance susceptibility to *T. muris* (85), and given that the abundance of Lactobacillaceae family members increases following *T. muris* infection, the possibility is raised that helminth species have evolved to select for the expansion of bacterial species that promote their own persistence (37, 38).

A Type-2 immune response is required for expulsion of helminths (84), thus the presence of certain bacterial species within the microbiota may aid helminth persistence through inhibiting Type-2 immunity. *L. casei* administration inhibited Th2 cytokine production in the mesenteric lymph nodes (MLN) and Peyer's patches (PP) of *T. muris* infected mice (85), and *L. taiwanensis* administration resulted in an increased frequency of Tregs in MLN and PP tissue (36), although whether these are the primary mechanisms by which these *Lactobacillus* spp. promote susceptibility to helminth infection remains to be determined. The presence of a specific pathogen free microbiota can stimulate the induction of RORγt$^+$ Tregs in the intestinal lamia propria, and mice generated to specifically lack RORγt$^+$ Tregs showed heightened frequencies of GATA3$^+$ (Foxp3$^-$) CD4$^+$ T cells in their small intestinal lamina propria, and were rendered more resistant to *H. polygyrus* infection (86).

If microbiota specific responses are generated following epithelial barrier breach (66) during helminth infection, it may reduce the capacity of the host immune system to respond to helminth antigens. Alongside this, microbiota compositional differences induced by helminths may lead to an altered metabolomic profile within the intestine, which has the potential to modulate the function of immune cells (87), conceivably reducing the capacity of the host to mount an effective parasite-clearing response.

Perhaps the most central mechanism through which the microbiota influence helminth infections is through the ubiquitous TLR signaling pathways. Certainly, mice lacking the TLR adaptor protein MyD88 are better able to control *H. polygyrus* and *T. muris* infections than MyD88-sufficient mice (88, 89). In both models, loss of MyD88 signaling resulted in greater Th2 cytokine release following helminth infection (88, 89). MyD88 mediates signaling through TLRs, but additionally mediates signaling of IL-1 family members including IL-1α, IL-1β and IL-18 (90), thus it is possible a lack of helminth chronicity in MyD88-deficient animals is due to a loss of either one, or a combination, of these signals. In the absence specifically of TLR4, *T. muris* failed to maintain a chronic infection (89), however loss of TLR4 alone did not affect *H. polygyrus* colonisation (88), raising the possibility that during *H. polygyrus* infection, redundant signaling through other TLRs or MyD88-dependent pathways maintains susceptibility to this parasite.

A further nexus of helminths, bacteria and TLR signaling has emerged from studies with mice treated with an antibiotic cocktail during infection with *Schistosoma mansoni*; while parasites establish in the mesenteric vasculature rather than the intestinal tract itself, they release eggs which traverse the mucosal epithelium to enter the lumen. Antibiotic treatment significantly reduced the consequent granulomatous pathology in the intestinal mucosa, a reaction previously shown to require MyD88 signaling (91) but also reduced egg egress into the feces; hence optimal transmission by *S. mansoni* appears to require co-stimulation by the microbiota in the intestine (92).

Immunomodulation during helminth infection – through parasites or microbes?

Both helminth parasites and the bacterial microbiota are widely credited with immunomodulatory abilities (28, 93), leading to the question of whether the anti-inflammatory effects of helminth infection are due, at least in part, to changes in the microbiota composition or function. Many soluble ES products released by helminths are able to ameliorate disease severity in mouse models of inflammation without the presence of active infection (28, 94-97); while it seems unlikely each of these helminth ES products operate solely through modifying the host microbiota, the degree to which they indeed modulate intestinal microbial biology has yet to be explored.

A key pathway contributing to the immunomodulatory abilities of helminth parasites, particularly in the context of suppression of allergic airway diseases, is the generation of Tregs (14, 21). Foxp3 expression in naïve $CD4^+$ T cells can be induced by exposure to HES, through a TGF-β-dependent pathway (14). A parallel induction of Tregs has been described for many microbiota species (5, 7, 8, 10, 12, 13), including a mixture of several *Clostridia* spp., which are able to stimulate TGF-β1 production from human and mouse intestinal epithelial cell lines (8). Metabolites generated by the microbiota can also affect T cell differentiation in the intestine-the short-chain fatty acids (SCFA) acetate, butyrate and propionate can potentiate Treg generation and IL-10 production from Tregs in the periphery (98-100), which is notable as increased circulating SCFA levels are protective in a mouse model of allergic airway disease (101). Interestingly, parasitic helminths are also known to generate acetate (102), opening the possibility of another common pathway shared by microbiota and helminths. Given that helminth infection shifts the bacterial microbiota composition, and both helminths and the bacterial microbiota can exploit host pathways to generate intestinal Tregs (Figure 1), it will be important to dissect the relative contributions of helminth product-elicited and microbiota-elicited Tregs during the dampening of allergic inflammation during helminth infection.

Conclusions

Microbes and helminths have co-evolved within the mammalian host, and examples of their mutualism and the synergistic pathways by which they cause host immunomodulation to promote their own survival are beginning to emerge (Figure 1). It is interesting to note that the distinction between symbiotic or commensal microbiota species and parasitic or pathogenic organisms plays through to important differences in their life strategies: to a

large extent, commensal microbiota species strive to condition their environment with minimal damage to the host, generally remaining at a safe distance, and are self-regulating in population. In contrast, most parasites and pathogenic bacteria need to breach or invade the mucosal barrier, deplete nutrients, and manipulate the host immune system in a more profound manner. The latter is a more difficult task, and perhaps this may explain why hundreds if not thousands of commensal and symbiotic bacterial species can colonize the human gastrointestinal tract, but the number of helminth organisms and pathogenic bacteria that can do so is limited. Notably, these few human-infective helminths and pathogenic bacteria each exert a strong effect on host immunity (28, 103), contrasting with the picture from the commensal and symbiotic microbiota population comprising of a large number of species each with small effects. An emerging field is the study of how pathogenic immunomodulatory agents including helminths, protozoan parasites, bacteria and viruses interact in a co-infection setting within the mammalian host, given that the global regions where these organisms are most prevalent often overlap (104).

Extending beyond the effect on helminth infections, signals from the microbiota have been shown to affect colonisation with bacterial, viral, and fungal pathogens (105). Defining the pathways by which these microbiota species manipulate host immunity will likely reveal novel therapeutic targets to aid the combat of infectious diseases. Further, given the ongoing clinical trials utilising helminths and helminth products (106), and the ability to modulate the microbiota function using pro-, pre-, and synbiotics, it will be important to define the contribution of the microbiota in mediating helminth immunomodulation, to allow for synergistic pathways to be targeted during the treatment of immune dysregulation.

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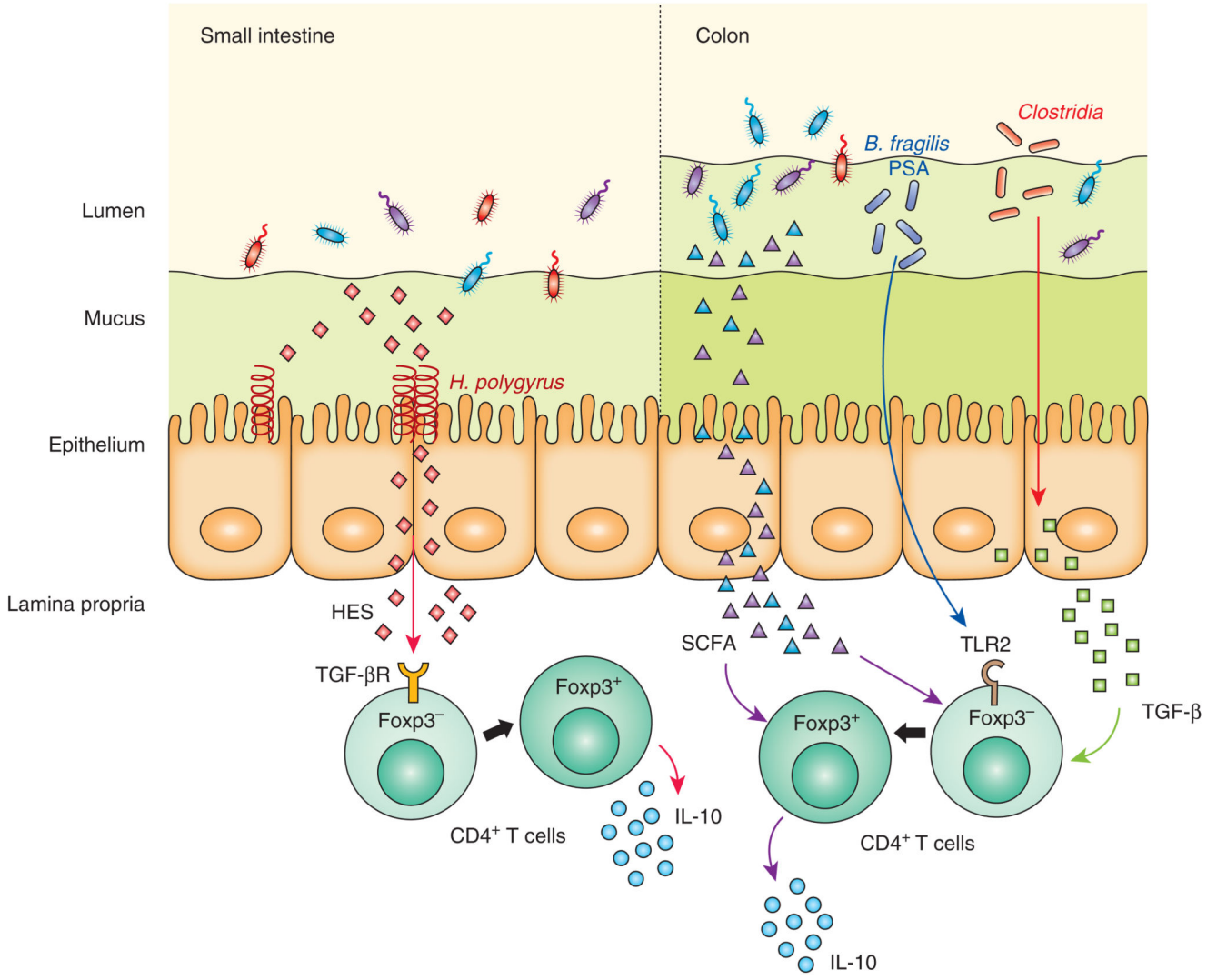

Figure 1. Parallel immunomodulatory strategies of helminths and bacteria in the intestinal tract-mechanisms of Treg induction

Both helminths and several bacterial microbiota species have been credited with host immunomodulatory capabilities, including the induction of Tregs. Various human and mouse helminth parasites stimulate Treg generation in the intestinal tract (18). In the case of the small intestinal mouse parasite *H. polygyrus*, *de novo* Foxp3 expression can be induced by its secretory products (HES), which is dependent on signaling through T cell TGF-βR (14). Short-chain fatty acids (SCFA), end products of bacteria-mediated fermentation of dietary fibers, can induce IL-10-producing Tregs in the colonic lamina propria (98-100). Particular species of bacteria, such as *B. fragilis,* or select *Clostridium* spp., can induce Tregs in the colonic lamina propria (5, 7, 8, 107). Treg induction by *B. fragilis* is dependent on the production of *B. fragilis* polysaccharide A (PSA) and the expression of T cell TLR2 (5, 107), and Treg induction by *Clostridium* spp. is though to be, at least in part, due to the stimulation of TGF-β secretion by intestinal epithelial cells (7, 8). Many additional bacterial microbiota species are capable of inducing Treg generation in the intestinal lamina propria

(17, 108), and it is likely a combination of signals from the microbiota and macrobionts such as helminth parasites together maintain a tolerogenic intestinal environment.

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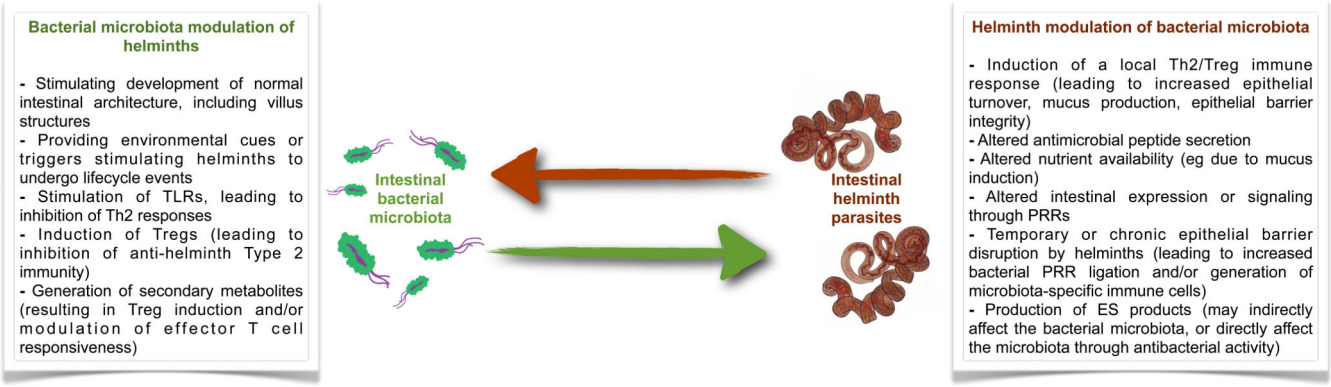

Figure 2. Proposed mechanisms by which intestinal helminths and bacterial microbiota bi-directionally influence persistence in the mammalian host

It has recently become clear that intestinal helminth parasites and members of the bacterial microbiota influence one another's ability to persist in the mammalian intestinal tract. The mechanisms by which they do so are likely multifactorial, site, and context dependent, and likely include direct as well as indirect effects on each other.