REVIEW ARTICLE

The impact of a helminth-modified microbiome on host immunity

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Intestinal helminths have well-characterized modulatory effects on mammalian immune pathways. Ongoing helminth infection has been associated with both the suppression of allergies and an altered susceptibility to microbial infections. Enteric helminths share a niche with the intestinal microbiota, and the presence of helminths alters the microbiota composition and the metabolic signature of the host. Recent studies have demonstrated that the helminth-modified intestinal microbiome has the capacity to modify host immune responses even in the absence of live helminth infection. This article discusses the mechanisms by which helminths modify the intestinal microbiome of mammals, and reviews the evidence for a helminth-modified microbiome directly influencing host immunity during infectious and inflammatory diseases. Understanding the multifaceted mechanisms that underpin helminth immunomodulation will pave the way for novel therapies to combat infectious and inflammatory diseases.

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INTRODUCTION

Helminths are multicellular parasitic worms that remain a global health concern; billions of people are currently infected worldwide. These parasites can mount long-lasting infections, often spanning years, which has been attributed to their ability to manipulate mammalian immune responses and thereby avoid immune-mediated expulsion.¹

Modulation of mammalian immune responses by helminths not only promotes their own persistence, but can additionally affect host immunity to concurrent infections and responses to bystander antigens. For example, helminth infection has been associated with impaired immunity to coinfection with various microbial parasites, bacteria, and viruses, both in human populations^{2–6} and in mouse infection models.^{7–15} Given that chronic helminth infections are predominantly restricted to regions of poor sanitation where people have a high exposure to microbial pathogens,¹⁶ understanding how helminth infection modulates host responses to microbial coinfection is critical. In parallel, live helminth infection has been associated with a reduced prevalence of allergic disease in human populations,¹⁷ and suppression of allergic airway inflammation in mouse disease models.^{18–21} Understanding how helminths modulate host immunity is therefore of global importance, as triggering the immune pathways helminths target has the potential for exploitation in the treatment of allergic conditions, which are a growing burden on the healthcare system in industrialized countries.²²

Helminth infection typically elicits a type 2 immune response, characterized by the production of IL-4, IL-5, IL-9, and IL-13 from type 2 innate lymphoid cells (ILC2) and T helper 2 (Th2) cells, and the recruitment of eosinophils, mast cells, basophils, and alternatively activated macrophages.²³ Type 2 effector mechanisms are essential for immune-mediated helminth expulsion, yet are often ineffective, largely due to concurrent regulatory responses induced by helminth infection. For example, helminths

release a variety of so-called excretory-secretory (ES) products, which include immunomodulatory proteins, glycoproteins, and miRNAs.^{24,25} Helminth ES products have been reported to modulate the activity of multiple immune cell types, and can directly induce regulatory immune cells, such as Foxp3⁺ regulatory T cells (Tregs).^{1,26} Production of ES material by helminths likely underpins the longevity of helminths in their host, as well as modulating host susceptibility to inflammatory and infectious diseases.²⁷

Intestine-dwelling helminths are not alone in the gut. Mammalian intestines harbor a vast array of mutualistic and commensal microbes, collectively termed the microbiota, which includes species of bacteria, viruses, and fungi. Helminth infection not only affects the composition of microbiota species, but as a result, infection alters the array of products derived from the microbiota. In this article, we define the ‘intestinal microbiome’ as the microbiota species themselves, their genes and products, as well as the products in their surrounding intestinal environment. Several recent studies have investigated how shifts in the intestinal microbiome during helminth infection contribute to the immunomodulatory effects of helminth infection. Below, we discuss the mechanisms by which helminths alter the microbiome, and review the evidence for a helminth-modulated microbiome directly affecting host immunity during infectious or inflammatory disease conditions.

HELMINTHS MODIFY THE BACTERIAL INTESTINAL MICROBIOTA

The bacterial microbiota provide several functions that are vital for the health of mammals. Their presence is required for the development of normal gut architecture,²⁸ for stimulating immune development and for maintaining normal immune homeostasis.²⁹ Compositional differences within the microbiota

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Fig. 1 Parameters modified during helminth infection which may contribute to intestinal microbiota modification. Helminths may alter the microbiota composition directly, through the antimicrobial activity of their ES products,^{55–57} as well as indirectly, through altering host production of anti-microbial peptides (AMPs).^{15,48,62–64} Intestinal mucus can provide a niche and energy source for certain microbiota species, and the presence of helminths can affect host mucus in several ways: through affecting mucus-producing goblet cell proliferation,¹⁰⁰ and through altering mucin composition, decoration, and degradation.^{65,101,102} In addition, the availability of intestinal nutrients may be affected during helminth colonization, as compromised epithelial glucose absorption has been reported in the presence of helminths.⁵⁸ Furthermore, helminths and helminth-derived products can regulate host recognition of microbes through influencing host pattern-recognition receptor signalling, such as through altering the expression patterns of TLRs,^{2,103–105} and through modulating the responsiveness of immune cells to TLR ligands.¹⁰⁶ Helminths may also affect microbiota composition through interference with the production of microbe-specific IgA in the intestine.² ES excretory-secretory, AMP anti-microbial peptide, TLR toll-like receptor, Ig immunoglobulin

have also been shown to fine-tune steady-state immune cell differentiation, for example, specific microbiota species have been associated with the differentiation of mucosal Th17 cells^{30–32} and Tregs.^{32–35} Compositional differences within the bacterial microbiota of individuals have been associated with differing levels of susceptibility to immune-driven diseases, such as allergies and inflammatory bowel disease (IBD).^{36,37} The bacterial microbiota also provide protection from colonization with pathogenic microbes, either directly, by producing toxins or competing for nutrients and space, or indirectly, by promoting intestinal barrier function.^{38,39} Further, members of the bacterial microbiota are able to metabolize dietary components that mammalian enzymes are incapable of digesting.⁴⁰

Helminth infection disrupts the composition of the microbiota within their mammalian hosts, as has been reported in several different animal-helminth systems (recently reviewed in ref.⁴¹). Species within the bacterial family Lactobacillaceae, which are capable of inducing host regulatory responses,⁴² have been widely reported to increase in abundance during helminth infection, irrespective of helminth or host species.^{43–50} Further studies have demonstrated that the presence of *Lactobacilli* species can promote the persistence of helminth infection, providing evidence for a mutualistic relationship between helminths and *Lactobacilli* species.^{43,45,51} Aside from the commonly described upregulation of Lactobacillaceae family members, reported helminth-elicited microbiota taxonomical changes vary greatly between studies. Such variation likely arises from a

number of factors, not least the species and infection intensity of the colonizing helminth, and their host species. The life cycle, size, and niche of helminths within their mammalian host vary drastically between helminth species, and will have a profound impact on their interaction with the microbiota population of the host. Further, the site at which the microbiota is sampled (for example fecal or intestinal sections), and the sampling time-point relative to helminth exposure will affect the recorded impact on microbiota composition, since helminth-elicited taxonomical shifts vary over the course of infection in mice.^{43,47,52} In addition, baseline differences in microbiota composition between individuals, that could result from a multitude of factors including host diet,^{53,54} will contribute to the impact of helminth infection on microbiota populations.

Enteric helminths may affect the structure of intestinal microbial communities through multiple parallel routes (Fig. 1). Helminths may modify microbiota composition through the direct antimicrobial activity of their ES products, which has been predicted or demonstrated for components of the ES material of several helminth species.^{55–57} In addition, the presence of helminths can alter both nutrient and niche availability in the intestine. For example, epithelial glucose absorption has been reported to be impaired during helminth infection,⁵⁸ which likely favor microbiota species that ferment sugars. Intestinal mucus plays a major role in controlling microbiota populations,²⁹ and changes in mucus dynamics during helminth infection could also favor the growth of select microbial species. For example, mucus-colonizing

Mucispirillum species⁵⁹ are increased in abundance in *Trichuris muris*-infected mice and *Trichuris suis*-infected pigs,^{47,52,60} and helminth-induced mucus production has been associated with a bloom of Clostridial species.⁶¹ Finally, helminth infection may modify both innate and adaptive host immune responses that can promote clearance of intestinal microbes.

Several parameters that likely have downstream effects on microbiota composition are dependent on the type 2 immune response induced during helminth infection. For example, changes in host expression of antimicrobial peptides (AMPs) during *T. muris* and *Nippostrongylus brasiliensis* infection are associated with the induction of Th2 responses in resistant mice.^{62,63} During *T. muris* infection, changes in expression of the AMP Ang4, as well as altered mucin expression patterns depend on signaling through IL-4Rα.^{64,65} The initiation of a type 2 response, even in the absence of live helminth infection, can be sufficient to modulate intestinal microbiota populations: administering mice IL-25, an initiating factor for type 2 immunity,⁶⁶ can alter AMP expression levels and reduce the abundance of SFB, which replicates phenotypes seen in *N. brasiliensis*-infected mice.⁴⁸ The effects of a type 2 response on AMP expression and mucus likely reflect the need for the host to stimulate tissue repair pathways as a result of damage caused during helminth infection.⁶⁷ This is exemplified in the case of idiopathic chronic diarrhea in captive monkeys where *Trichuris trichuria*-induced IL-4 was associated with repair of helminth-induced epithelial damage, and was accompanied with altered mucosal attachment of bacteria and microbiota composition.⁶⁸ Additionally, helminth infection has been reported to cause shifts in microbiota populations independently of IL-4 and IL-13 signaling, as microbiota taxonomical changes have been reported to occur in IL-4Rα-deficient *Heligmosomoides polygyrus*-infected mice.⁴⁶

METABOLIC CONSEQUENCES OF HELMINTH INFECTION

Helminth infection has been widely reported to modify the metabolic capacity of their mammalian hosts (Table 1). Helminth-elicited metabolic shifts are likely a combined result of altered host, bacterial, and helminth production of metabolites, as well as altered patterns of metabolite utilization, excretion, and absorption during helminth infection. Type 2 immune responses, such as those induced during helminth infection,²³ can alter host metabolic function,⁶⁹ as well as modifying bacterial microbiota populations, as discussed above.

The bacterial microbiota are major producers and utilizers of intestinal metabolites.⁴⁰ Microbiota-derived metabolites have been shown to influence immune system development systemically and at a tissue level, and can fine-tune the immune response after the system has matured.⁷⁰ While mammals lack the enzymes required to break down dietary fibers such as cellulose, certain microbiota species in the intestine can digest these carbohydrates through anaerobic fermentation. As a result, short-chain fatty acids (SCFAs) are released, a group of abundant metabolites (including acetate, butyrate, and propionate) that have been shown to influence multiple facets of immunity. Helminths themselves also both use and produce metabolites,⁷¹ and several helminth species are able to produce acetate.^{19,72}

SCFAs can promote a regulatory immune response through stimulating the differentiation and suppressive capacity of Foxp3⁺ Tregs in the intestine.^{73–75} Further, SCFAs can contribute to intestinal barrier function through stimulating mucus production, and can inhibit the release of inflammatory cytokines through the inhibition of NF-κB.⁷⁶ In line with these effects on host immunity, a diet high in dietary fibers has been shown to dampen allergic airway inflammation and enhance tolerance to food antigens in mice.^{77–79} SCFA levels can influence susceptibility to bacterial infection, as microbial acetate production has been shown to

protect against *E. coli* infection, likely through promoting barrier function.⁸⁰

Helminth infection has repeatedly been reported to affect host carbohydrate metabolism (Table 1), in studies which either described predicted effects based on the detection of specific microbiota species,^{44,60,81–83} or in studies that directly measured end-products of carbohydrate metabolism.^{19,47,60,84–86} While carbohydrate metabolism and concentrations of SCFAs have been reported to be elevated during infections of mice with *H. polygyrus*¹⁹ and goats with *Haemonchus contortus*,⁸³ a reduced activity of these metabolic pathways has been reported during *Ascaris* infection in humans⁸² and *T. suis* infection in pigs.⁶⁰ The differential helminth-elicited effects on carbohydrate metabolism may reflect different immune evasion strategies between helminth species. For example, dietary fermentable carbohydrates resulted in elevated cecal SCFA levels and accelerated the expulsion of *T. suis* in pigs,⁸⁷ therefore *Trichuris* species may have evolved strategies to downregulate carbohydrate metabolism. In contrast, other helminth species might benefit from SCFA production through the induction of a regulatory immune response,^{73–75} which helps to prevent their own expulsion. The identification of key microbial metabolites that are affected during helminth infection (and characterization of their effect on immune responses) will likely provide a greater insight into the mechanisms by which helminth colonization affects immunity than associations between helminth infection and the presence of (potentially redundant) specific microbial taxa.

A HELMINTH-MODIFIED MICROBIOME DIRECTLY AFFECTS HOST IMMUNITY

The regulatory immune response that is established during helminth infection has the potential to ameliorate allergic disease,^{19,21,75,77,78} while a helminth-elicited tolerogenic environment could render the host more susceptible to microbial coinfections.^{7,9,13,14,88–90} Since intestinal helminths and the bacterial microbiota have a shared agenda of avoiding their own expulsion from the mammalian intestinal tract and have therefore each evolved mechanisms to modulate host immunity, several recent studies have examined the extent to which the immunomodulatory effects of helminth infection can be attributed to changes in the intestinal microbiome (Fig. 2). Transfer of a helminth-modified microbiota alone, in the absence of live helminth infection, has been shown to reduce airway inflammation in recipient mice in a mouse model of allergic asthma, suggesting that one of the mechanisms by which helminth can mediate allergic inflammation is through modifying the microbiome.¹⁹ Further, while infection with *H. polygyrus* reduced the severity of allergic lung inflammation in mice, protection was lost when *H. polygyrus*-infected mice were treated with antibiotics, indicating that an intact microbiota was required for protection from airway inflammation in this experimental system.¹⁹ A helminth-modified microbiota may also play a role in protecting from respiratory syncytial virus (RSV) infection: a pathogen which has been associated with an increased risk for allergic asthma development.⁹¹ In a mouse model, coinfection with *H. polygyrus* ameliorated RSV-induced lung pathology and reduced viral loads, and this was dependent on the presence of the microbiota, as helminth-mediated protection from RSV was lost in germ-free mice.¹⁰

In the intestinal tract, the bacterial microbiota can provide colonization resistance, therefore a loss of beneficial microbiota members has the potential to contribute to infectious disease.³⁹ Since helminths alter the microbiota composition,⁴¹ helminth colonization may protect against bacterial-driven intestinal inflammation by promoting the expansion of protective members of the microbiota that inhibit outgrowth of inflammatory bacteria. For example, a helminth-induced bloom of Clostridiales species

Table 1. Metabolic consequences of helminth infection

Host species	Helminth species	Days post infection	Site sampled	Analytical method	Metabolic shifts predicted/measured during helminth infection	Citation
Human (<i>n</i> = 447) rural Uganda	<i>Schistosoma mansoni</i>	Unknown	Urine	¹ H-NMR spectroscopy and metabolite identities determined using in-house reference data	Several reported shifts, including: acetate ↑ in children, acetate ↓ in adults	86
Human (<i>n</i> = 51) rural Malaysia	various (<i>Ascaris</i> species, <i>Trichuris</i> species and/or hookworm)	Unknown	Feces	16S rRNA sequencing to identify OTUs, metagenomes inferred by PICRUSt, functional annotation using KEGG database	Amino acid metabolism ↑, carbohydrate metabolism ↓ (associated with <i>Ascaris</i>)	82
Pig	<i>Trichuris suis</i>	21	Colon	(1) Metagenomic DNA extraction and sequencing, ORF predicted using FragGeneScan, functional annotation using Pfam, COG and KEGG databases (2) volatile organic compounds analyzed by GS-MS, metabolite identities determined using NIST software and mass spectral library	(1) Carbohydrate metabolism ↓, amino acid metabolism ↓ (2) oleic acid ↑, 2,6-dimethyl-4-heptanone (butyrate metabolite) ↓, 2-methyl-2-butenal (carbohydrate metabolite) ↓	60
Pig	<i>Trichuris suis</i>	53	Colon	Metagenomic DNA extraction and sequencing, ORF predicted using FragGeneScan, functional annotation using Pfam and KEGG databases	Amino acid metabolism ↑	107
Pig	<i>Ascaris suum</i>	56	Colon	Targeted metabolomics (GC-MS), metabolite identities confirmed by comparison with SCFA standards	SCFA (propionate, butyrate) ↑	19
Mouse strain: <i>MMRI</i>	<i>Schistosoma mansoni</i>	49	Urine	¹ H-NMR spectroscopy	Several reported shifts, including: SCFAs (acetate, propionate, butyrate) ↓	85
Mouse, strain: <i>C57BL/6</i>	<i>Trichuris muris</i>	41	Feces	Untargeted metabolomics (GC-MS and LC-MS), putative metabolite identification using PUTMEDID_LCMS workflows	Various, including: various amino acids ↑, Vitamin D2/D3 derivatives ↓, fatty acids (and related metabolites) ↓, glycerophospholipids ↓, dietary plant carbohydrate breakdown products ↓	52
Mouse wild: <i>Apodemus flavicollis</i>	Various (<i>Heligmosomoides polygyrus</i> , <i>Mastophorus muris</i> , <i>Syphacia</i> species, and/or <i>Hymenolepis</i> species)	Unknown	Multiple stomach and intestinal sites	16S rRNA sequencing to identify OTUs, metagenomes inferred by PICRUSt, functional annotation using COG database	Specifically associated with <i>H. polygyrus</i> colonization: carbohydrate transport and metabolism ↑ in the cecum	44
Mouse strain: <i>C57BL/6</i>	<i>Heligmosomoides polygyrus</i>	28	Cecum	Targeted metabolomics (GC-MS), metabolite identities confirmed by comparison with SCFA standards	SCFAs ↑ (acetate, propionate, butyrate)	19
Mouse, strain: <i>C57BL/6</i>	<i>Heligmosomoides polygyrus</i>	14	Duodenum and jejunum	Untargeted metabolomics (UPLC-FMMS), putative identities assigned using Metlin database	Shifts in several metabolite features (putative identities)	9
Syrian Hamster strain: <i>SLAC</i>	<i>Necator americanus</i>	35	Urine and serum	¹ H-NMR spectroscopy	Various reported shifts, including ↓ acetate in serum	84
Goat	<i>Haemonchus contortus</i>	50	Abomasum	16S rRNA sequencing to identify OTUs, metagenomes inferred by PICRUSt, functional annotation using KEGG database	Carbohydrate metabolism ↑, Amino acid metabolism ↑, Lipid metabolism ↑	83

This table details studies that have either predicted (based on bacterial metagenomes) or directly measured shifts in metabolites during helminth infection. Several of the studies presented here report shifts in a vast array of directly identified or predicted metabolites that extend beyond those that we have space to report; individual references should be referred to for further details. ¹H-NMR proton nuclear magnetic resonance, SCFA short-chain fatty acid, ORF open reading frame, PICRUSt phylogenetic investigation of communities by reconstruction of unobserved states, KEGG Kyoto Encyclopedia of Genes and Genomes, COG clusters of orthologous groups of proteins, GC-MS gas chromatography-mass spectrometry, LC-MS liquid chromatography-mass spectrometry, UPLC-FMMS ultra-high-performance liquid chromatography-Fourier transform mass spectrometry

Fig. 2 A helminth-modified microbiome directly affects host immunity. The activity of a helminth-modified microbiome has been recently demonstrated in various mouse model systems. Transferring the fecal microbiota (FMT) from helminth-infected mice to non-helminth infected recipient mice can reduce levels of induced allergic airway inflammation in recipient mice, through the transfer of bacteria enriched in the production of short-chain fatty acids which likely contribute to Treg induction.¹⁹ A helminth-modified microbiome has been associated with impaired immunity to enteric bacterial infection, as FMT from helminth-infected mice resulted in elevated Treg frequencies and IL-10 levels in the gut-associated lymphoid tissue of recipient mice, alongside exacerbated *Citrobacter*-induced inflammation.⁹⁰ In comparative studies of metabolites extracted from the small intestines of naïve or helminth infected mice, helminth-modified intestinal metabolites promoted the virulence of enteric infectious bacteria compared with metabolites from naïve mice.⁹ Finally, helminth infection can promote immunity to respiratory viral infection in mice through the induction of lung type I interferon, which was dependent on the helminth-modified microbiome, as protection from respiratory viral infection was lost in helminth-infected germ-free mice.¹⁰ FMT fecal microbiota transfer, SCFA short-chain fatty acids, Treg T regulatory cell, IFN interferon

blocked a bloom of pro-inflammatory *Bacteroides vulgatus* and ameliorated disease in a mouse model of IBD.⁶¹ However, the ability of a helminth-modified microbiota to protect from intestinal inflammation likely depends on the bacterial species that are driving inflammation. Supporting this, during a mouse model of *Citrobacter rodentium*-driven colitis, a helminth-modified microbiome exacerbated, rather than protected from, intestinal inflammation.⁹⁰ Transfer of a *H. polygyrus*-modified microbiota in the absence of live helminth infection was sufficient to enhance colitis pathology initiated by *C. rodentium* infection.⁹⁰ Together, these findings indicate that the helminth-modified microbiota can drive immunomodulation independently of live helminth infection in several scenarios, establishing an additional route by which helminth colonization causes host immunomodulation. The outcomes on disease development after exposure to a helminth-modified microbiota are heavily context-dependent.

MECHANISMS BY WHICH A HELMINTH-MODIFIED MICROBIOME AFFECTS HOST IMMUNITY

Direct effects of intestinal metabolites on pathogens
Helminths alter the composition and abundance of metabolites in the intestine (Table 1), which may directly affect the growth and/or virulence of enteric pathogenic bacteria.⁹² While metabolites extracted from the intestine of naïve mice have been shown to

inhibit the invasive capacity of *Salmonella enterica* serovar Typhimurium,⁹³ metabolites from *H. polygyrus*-infected mice were unable to suppress *S. Typhimurium* invasion of epithelial cells. A loss of metabolite-mediated inhibition of bacterial invasion may contribute to the increased intestinal colonization of *S. Typhimurium* seen during helminth infection.⁹

Induction of regulatory immune responses by microbiota-produced metabolites

Helminth suppression of allergic airway inflammation can be mediated, at least in part, by a helminth-modified microbiota that is enriched in the capacity for SCFA production.¹⁹ Evidencing this, *H. polygyrus*-infected mice showed a bloom in SCFA-fermenting Clostridial species and a corresponding increase in cecal SCFA levels, and transfer of a *H. polygyrus*-modified microbiota resulted in elevated SCFA levels in recipient mice.¹⁹ Antibiotic treatment of *H. polygyrus*-infected mice entirely abolished SCFA production and reverted the suppressive effects of helminth infection on airway inflammation.¹⁹ Further, the effects of helminth infection on allergic inflammation were dependent on expression of GPR41, a major SCFA receptor.^{19,77} A helminth-modified microbiota with a high capacity for SCFA production likely contributes to the amelioration of allergic airway inflammation through the induction of Tregs.^{21,75,78} In support of this, helminth-infected mice exhibited GPR41-dependent increases in IL-10 and TGF- β levels in

the lung during allergic airway inflammation.¹⁹ Microbial fermentation of dietary fibers may also modulate immunity during intestinal inflammation, since Treg expression of an additional SCFA receptor, GPR43, provided protection against a T cell transfer-induced mouse model of colitis.⁷⁴ In accordance with this, transfer of a helminth-modified microbiome boosted Treg frequencies and IL-10 expression in the mesenteric lymph nodes.⁹⁰ Tregs can contribute to effective immunity against *C. rodentium* through promoting Th17 induction,⁹⁴ but in the context of a helminth-modified microbiota transfer, induction of Tregs has been associated with susceptibility to *C. rodentium* infection.⁹⁰ Antibodies against CD25, and IL-10 neutralization, blocked the effects of a helminth-modified microbiota transfer on *C. rodentium* infection.⁹⁰ It will be important for future studies to characterize further potential mechanisms by which a helminth-modified microbiota can promote host regulatory responses.

Microbiota-dependent stimulation of innate responses
Helminth colonization can also induce changes in the innate immune pathways that affect host resistance to microbial pathogens. Microbiota-dependent shifts during *H. polygyrus* infection induced type I interferon production in the lung which was required for protection from RSV infection.¹⁰ Protection from RSV was lost in RAG^{−/−} and IL-4Rα^{−/−} mice, and in mice raised in germ-free conditions.¹⁰ Interestingly, protection against RSV infection in the lungs occurred after infection with irradiated *H. polygyrus* larvae, which were unable to develop into adult worms.¹⁰ Since *H. polygyrus* larval stages were sufficient to protect against viral infection, the authors proposed that the initial intestinal damage caused by larvae migrating into intestinal tissue and coincidental translocation of microbiota species into the tissue might evoke a systemic innate immune response, facilitating an antiviral response in the lungs.¹⁰

CONCLUSION AND OUTLOOK

Multiple mechanisms contribute to the modulation of host immunity during helminth infection. These include the products produced directly by helminths that have direct effects on host immune cells,²⁷ as well as the indirect effects on host immunity, through an altered composition and function of the intestinal microbiome during helminth infection. The pathways by which a helminth-modified microbiome affect host immunity have only recently begun to be explored, and it will be important to evaluate the extent to which a helminth-modified microbiome contributes to long-term host immunomodulation following clearance of live helminth infection.

The fact that antimicrobial molecules have been described within the ES products of helminths^{55–57} suggests that helminths have an incentive to control the microbial species with which they share a niche. This may have evolved to protect the host from microbial exposure during helminth infection, or as a helminth-driven strategy for modulating host immune responses.⁹⁵ While some aspects of anti-helminth host immunity are dependent on the microbiota,⁹⁶ it is also possible that helminths have evolved the ability to expand those microbiota species that benefit their own survival. The hatching of *T. muris* eggs in the ceca of mice is dependent on the presence of microbiota,⁹⁷ and supplementation with *Lactobacilli* species renders mice more susceptible to both *T. muris* and *H. polygyrus* infection.^{43,51} In addition, certain microbiota species could benefit from helminth infection, for example the abundance of *Lactobacilli* species is increased during chronic helminth infection.⁴³ This indicates the existence of a mutualistic relationship between helminths and certain microbiota species, which could be a result of a shared aim: regulating mucosal immune responses in order to persist in the intestinal environment.

Helminths, microbiota species and mammals share a long history of co-evolution, during which a complex web of intercommunication has evolved. When attempting to understand the mechanistic pathways by which helminths manipulate host disease states, it will be vital to consider the multi-directional relationships between the host, helminths, and the microbiota. These interconnected pathways have been starting to be explored in human studies,^{98,99} however the challenge remains to discern causal relationships, for which animal models are proving to be invaluable. Examining the effects of a helminth-modified microbiome paves the way for therapeutic treatment options using pre- or probiotics, or microbiome-derived products, which could be used alone or in combination with helminth-derived products for the prevention or treatment of allergic, infectious, or inflammatory diseases.

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T.P.B. and L.A.R. both discussed the article content, wrote and edited drafts of the article, and approved the final contents of the article.

ADDITIONAL INFORMATION

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