Trends in Parasitology

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Opinion

Helminth Microbiomes – A Hidden Treasure Trove?

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There is increasing attention on the complex interactions occurring between gastrointestinal parasitic helminths and the microbial flora (microbiota) inhabiting the host gut. However, little is known about the occurrence, structure, and function of microbial populations residing within parasite organs and tissues. In this article, we argue that an in-depth understanding of the interplay between parasites and their microbiomes may significantly enhance current knowledge of parasite biology and physiology, and may lead to the discovery of entirely novel, anthelmintic-independent interventions against parasites and parasitic diseases.

Gastrointestinal Helminths – Worm Guts within Host Guts

The gastrointestinal (GI) tract of vertebrates is inhabited by 10–100 trillion microorganisms, including bacteria, viruses, fungi, protists, and archaea, which are collectively known as the 'gut **microbiota**' (see Glossary) [1,2]. This complex ecosystem exerts a number of highly specialised functions that are essential to host physiology, including the absorption of nutrients, synthesis of essential organic compounds, development of adaptive immunity, and protection against pathogens [3–6]. In particular, amongst such pathogens are metazoan parasites (called 'the **macrobiota**', which includes parasitic nematodes such as roundworms, hookworms, and whipworms) that are traditionally considered detrimental to the vertebrate host as they can subtract nutrients, damage host tissues, and release toxic waste products (reviewed in [7]). These parasites live in close association with the vertebrate microbiota and, over the last few years, evidence has started to emerge of the existence of complex **mutualistic** relationships between these two players that might facilitate the long-term establishment of nematodes in the gut of the host [8–11]. Similar to their vertebrate hosts, parasitic nematodes have complete, tubular digestive systems responsible for nutrient uptake, processing, and absorption; yet, for most species of socioeconomically important parasites, and GI nematodes in particular, little is known about the occurrence, structure, and function of populations of resident gut microbes [12]. Nevertheless, critical evidence of the existence of essential **symbiotic** relationships between parasites and bacteria is provided by filarial nematodes, for example, *Onchocerca volvulus* (causing river blindness) and *Wuchereria bancrofti* and *Brugia malayi* (causing lymphatic filariasis) (reviewed in [13]), whose propagation and survival are dependent on a genus of bacteria, that is, *Wolbachia*, which has become the target of intense investigations aimed at developing novel filaricidal compounds [14–18]. This evidence supports the hypothesis, strongly corroborated by recent experimental findings [19,20], that the digestive system, as well as other organs and tissues of GI nematodes, may also harbour resident microbes with essential roles in parasite physiology and survival. Fully characterizing and understanding the structure and function of **helminth microbiomes**, and determining the role(s) they play in key aspects of parasite biology and host–parasite interactions, could not only have broad implications for future studies of the origin of parasitism itself, but might also lead to the discovery of radically new interventions against these worms.

Highlights

In spite of a plethora of evidence supporting key roles of resident bacteria for parasite fitness and survival (i.e., in filarial nematodes and whipworms), little is known of microbial populations inhabiting organs and tissues of gastrointestinal nematodes of major socioeconomic significance.

To date, one of the few well characterised examples is the symbiotic relationship between bacteria of the genus *Wolbachia* and filarial nematodes.

Notably, our understanding of this symbiosis has already been successfully exploited for therapeutic purposes.

The relentless advancement in sequencing techniques, together with the rise of novel microbiome editing tools provide unprecedented opportunities to investigate helminth microbiomes and exploit parasite–microbiome relationships for the development of novel strategies of parasite control.

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Here, we (i) summarize current knowledge of the origin, structure, and function of helminth microbiomes; (ii) identify some key knowledge gaps for future research in this field; and (iii) discuss the potential therapeutic advances that such knowledge could deliver, with a particular focus on the development of novel, helminth microbiome-based strategies for the control of infections by GI nematodes of major socioeconomic significance.

Strategies of Acquisition and Maintenance of Helminth Microbiomes

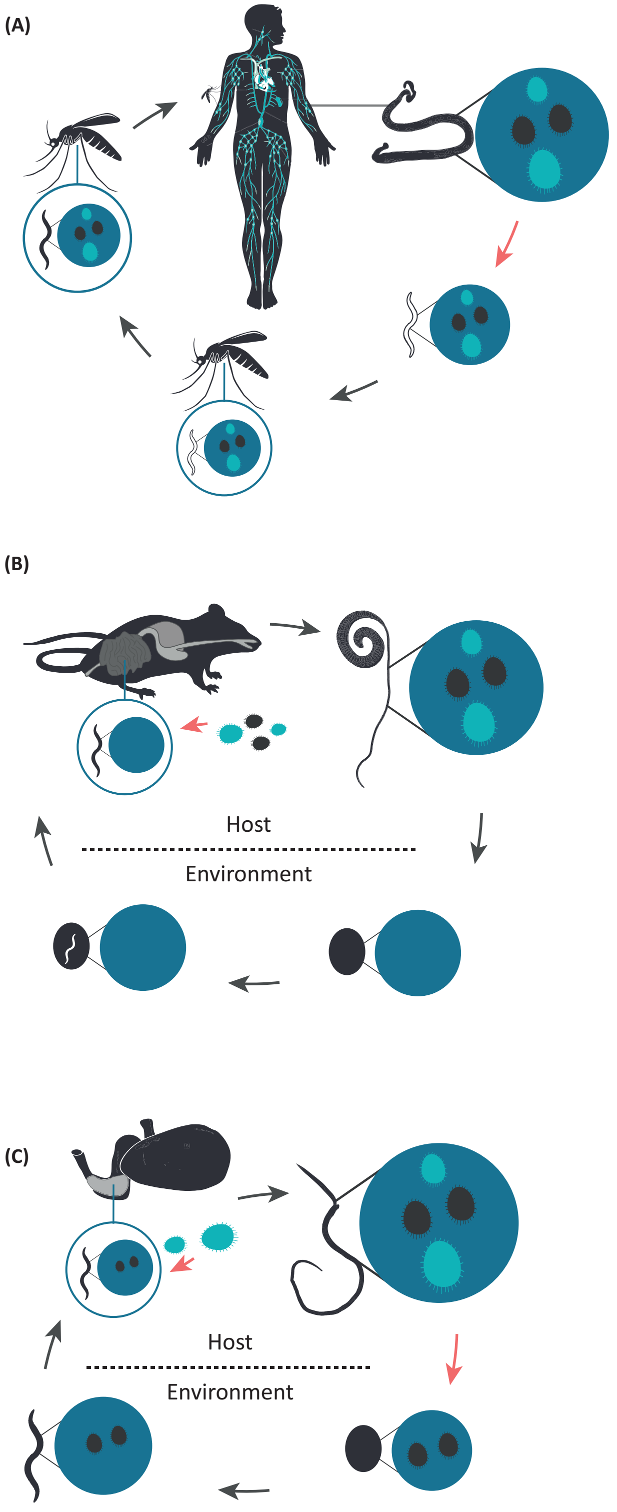
Investigations of the interactions between parasites and their resident bacteria rely on a thorough understanding of the dynamics of microbiome acquisition. Whilst for GI nematodes knowledge in this area is relatively limited, several investigations have documented the fine strategy via which bacteria of the genus *Wolbachia* are propagated through successive generations of filarial parasites (reviewed in [21]) (cf. Figure 1). In the filarial nematode *B. malayi*, these bacteria inhabit the lateral chords of both adult male and female worms, and the reproductive system of the latter sex, where they colonise the ovaries, oocytes, and early embryos within the uteri [22]. Upon egg fertilisation, populations of *Wolbachia* segregate asymmetrically in the developing embryo, which results in an uneven distribution of these bacteria in the tissues of the microfilariae [22]. In particular, the numbers of vertically transmitted *Wolbachia* remain stable (~70 per embryo [17]) throughout development of the new generation of filarial parasites into infective third-stage larvae (L3s) in the mosquito vector (reviewed in [21]). Upon L3-invasion of a susceptible vertebrate host, the number of *Wolbachia* bacteria rapidly increases in the hypodermal cord of developing worms, with a further expansion occurring in the reproductive tissues of sexually mature females (reviewed in [21]). Crucially, embryonic development is entirely dependent on *Wolbachia*, as treatment with tetracycline antibiotics results in a marked reduction of viable microfilariae (reviewed in [22]). To date, the **obligate relationship** between filarial nematodes and *Wolbachia* represents the only known example of a mutualistic association between parasitic nematodes and bacteria.

Members of another group of helminth parasites, the digenean trematodes, are known to harbour populations of *Neorickettsia* **endosymbionts** which share numerous genetic similarities with *Wolbachia* (reviewed in [23]). *Neorickettsia* inhabit a range of environments suitable for the development of the infective stages of digenean parasites and their intermediate hosts (e.g., aquatic molluscs), thus lending credit to the hypothesis that a proportion of these bacteria are horizontally transmitted (reviewed in [23,24]). Nevertheless, in *Plagiorchis elegans*, a common GI helminth of a range of fishes, birds, and mammals (including humans) [25], *Neorickettsia* is predominantly transmitted vertically across generations of parasites [26]. However, unlike *Wolbachia* in filarial nematodes, transmission of *Neorickettsia* in *P. elegans* also occurs through the asexual stages of this parasite [27]. Furthermore, since transmission rates of *Neorickettsia* from adult *P. elegans* to the offspring vary from 11% to 91% [27], it has been suggested that the life cycle of this flatworm is not dependent on their neorickettsial endosymbionts, but rather that *Neorickettsia* utilises *P. elegans* as a vehicle for transmission to vertebrate hosts [28].

For GI nematodes, experimental evidence of microbiome acquisition strategies is available for two species, namely *Haemonchus contortus*, an abomasal roundworm of small ruminants [19], and *Trichuris muris*, a large intestinal whipworm of rodents [20] (cf. Figure 1). For the former, a recent study [19] localised selected genera of bacteria (i.e., *Weissella* and *Leuconostoc*) to the gut of adult worms and to the uterus of sexually mature females by fluorescence *in situ* hybridization (FISH) and transmission electron microscopy; using DNA fingerprinting, the same genera could be identified in eggs laid by these females and, following larval culture, their L3 offspring [19]. Notably, these microorganisms could not be identified in the faecal matter on which larval culture was performed, thus providing evidence of maternal transmission of these

Glossary

Core microbiome: the group of microbes consistently found within a host microbiome, which demonstrate a persistent association and provide a critical function within the habitat in which they are detected.
Endosymbiont: any organism that lives within the body or cells of another organism in a symbiotic relationship with the host body or cell, often but not always to mutual benefit.
Helminth microbiome: the collective microbiome of parasitic helminths.
Macrobiota: collective term used to describe the macroorganisms (e.g., helminths) that live in a particular niche, on or in a living being, and are large enough to be seen with the naked eye.
Microbiome editing: targeted manipulation of microbiota through the use of technology and/or other microbiota.
Microbiota: collective term used to describe the microorganisms that live in a particular niche, on or in a living being, and exhibit a symbiotic relationship with the host.
Mutualism: a symbiosis which is beneficial to both organisms involved.
Obligate relationship: a relationship in which one or both of the symbionts depend entirely on their partner for survival.
Symbiosis: a relationship between two or more organisms that live closely together.



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bacteria [19]. Other bacterial genera (i.e., *Lactococcus* and *Streptococcus*) could be identified in the distal uterus of sexually mature females of *H. contortus* [19]. Nevertheless, these bacteria were not detected in newly deposited eggs and developed L3s. Since these bacteria occur in the rumen of the host [29], the authors hypothesized that female worms acquired them by ingesting ruminal fluid [19]. Whilst the roles that species of *Lactococcus* and *Streptococcus* might play in the fundamental biology of *H. contortus* is presently unknown, these data suggest that this parasite might employ a 'hybrid' microbiome acquisition strategy, with some 'core' endosymbionts (i.e., *Weissella* and *Leuconostoc*), which may play essential roles in parasite fitness and survival, being vertically transmitted, and others (i.e., *Lactococcus* and *Streptococcus*) being acquired from the host to underpin a certain level of microbiome plasticity and capacity for environmental adaptation.

A clear strategy of microbiome acquisition from the mammalian host has been recently demonstrated for *T. muris* [20] (cf. Figure 1). The essential role that the host microbiome plays in the development and propagation of this parasite had already been demonstrated in a seminal study [30] which showed that parasite egg hatching in the large intestine of the mouse was dependent on the microbial flora within the host gut. Recently, a study by the same research group [20] demonstrated that, following egg hatching, *T. muris* acquires populations of bacteria that, together, form a 'core' nematode microbiome, which is markedly distinct from the microbiome inhabiting the environment in which the worms reside [20]. Although the *Trichuris* microbiome described predominantly comprised Firmicutes and Bacteroidetes, similar to the host microbiome, it was also rich in Proteobacteria. Proteobacteria constituted 9% of the entire *T. muris* microbiome – a 31-fold and 13-fold increase in relative proportions of this bacterial group compared with the microbiome of uninfected mice and *T. muris*-infected mice, respectively [20]. This process of selective microbiome acquisition was demonstrated to be independent of the initial host microbiome composition, and the administration of broad-spectrum antibiotics to adult *T. muris ex vivo* resulted in a marked decrease in parasite fitness and survival rates, thus providing cogent evidence for an essential role of the host-acquired microbiome for the successful completion of the whipworm life cycle. Whether *T. muris* acquires its own microbiome passively, or actively selects populations of bacteria with functional properties which are able to facilitate its survival in the vertebrate host, remains to be established (cf. [20]). Nevertheless, the observation that mono-colonisation of germ-free mice with a single species of bacterium, that is, *Bacteroides thetaiotaomicron*, resulted in successful egg hatching and establishment of chronic *T. muris* infection [20] provides a unique opportunity to design targeted experiments that can shed light on the precise mechanisms of acquisition of the *T. muris* microbiome. In turn, this knowledge will form the necessary basis to answer fundamental questions regarding helminth microbiome structure and function.

Figure 1. Proposed Helminth Microbiome Acquisition Strategies for *Brugia malayi, Trichuris muris*, and *Haemonchus contortus*. (A) *B. malayi* microfilariae acquire *Wolbachia* microorganisms via the female germ line, and populations of resident microbes expand throughout larval development through to infective third-stage larvae in the mosquito intermediate host. In adult male and female *B. malayi*, the bacteria localise to the lateral chords of both sexes and the female reproductive system, where they colonise the ovaries, oocytes, and early embryos within the uteri. (B) Unembryonated *T. muris* eggs are passed through murine faeces, and embryos develop inside the eggs. Upon ingestion by a susceptible host, the eggs hatch in the small intestine and release larvae that acquire selected populations of bacteria from the gut of their rodent hosts. Thereafter, the larvae mature and establish themselves as adult males and females in the colon. (C) Female *H. contortus* transfer selected populations of bacteria to the offspring via the germline. Eggs shed in the environment with the faeces of the ruminant host hatch and release first-stage larvae. Upon ingestion of the latter by a new ruminant host, the developing worms acquire further populations of bacteria from the rumen of the latter. Red arrows indicate helminth microbiome acquisition events. Empty blue circles indicate current lack of clear evidence of microbiome transfer.

Are Helminth Microbiomes Key to Parasite Fitness?

Studies of the structure and function of helminth microbiomes are in their infancy. Nevertheless, over the past decades, evidence has emerged about the functional association between the free-living nematode *Caenorhabditis elegans* and the bacteria inhabiting it [31,32]. Indeed, *C. elegans* is known to host a species-rich bacterial community, dominated by Proteobacteria, such as *Enterobacteriaceae* and members of the genera *Pseudomonas*, *Stenotrophomonas*, *Ochrobactrum*, and *Sphingomonas* [31,32]. Crucially, the relative proportions of bacterial populations forming the *C. elegans* microbiome vary according to the developmental stage of this nematode [32], thus suggesting that worm development relies on a range of bacterial functions that differ over time. In support of this hypothesis, worms experimentally colonised with a subset of bacterial isolates representing the *C. elegans* '**core**' **microbiome** displayed increased fitness and survival rates, and were maintained under stressful conditions of temperature and osmolarity, compared with worms colonised solely by *Escherichia coli* [32]. In addition, compared with *E. coli*-colonised *C. elegans*, worms fed with the soil bacterium *Comamonas* displayed accelerated development, which was attributed to the ability of this bacterial group to upregulate the expression of genes associated with the nematode moulting program [33]. The *C. elegans* microbiome has also been demonstrated to play important roles in worm defence against pathogens; indeed, *Pseudomonas* isolates detected amongst the worm resident populations of bacteria produce antimycotic compounds that prevent colonisation by fungal agents [32].

Evidence from investigations of *C. elegans*, employed as a model for nematode–microbiome interactions, points to a likely functional role of the microbiomes of parasitic helminths for worm physiology, development, and survival. However, the parasite microbiome itself may benefit from the protected and nutrient-rich environment that the worm host offers [34,35]. For instance, the Gammaproteobacteria *Photorhabdus* and *Xenorhabdus*, that inhabit the gut of the entomopathogenic nematodes *Heterorhabditis* and *Steinernema*, are released upon infection of the insect host by the infective juveniles; following their release, these bacteria actively replicate and kill the insect host, while converting the insect carcass into a source of nutrients to support nematode growth and development [36,37].

For parasitic nematodes of medical and veterinary importance, the mutualistic association between filarial nematodes and *Wolbachia* offers a key example of the fundamental functions that the helminth microbiome exerts in the biology of its worm host, and vice versa. Indeed, besides its known role in the development and survival of filarial embryos (reviewed in [21]), *Wolbachia* is essential for worm nutrition and metabolism. The bacterium synthesizes haem, riboflavin (vitamin B_2), and flavin adenine dinucleotide, which the parasite host is unable to synthesize and that have been inferred to play an important role in filarial reproduction and development, as well as nucleotides, which are required during oogenesis and embryogenesis [18,38,39]. In addition, members of the genus *Wolbachia* participate in pathways aimed at preventing apoptosis of filarial reproductive, embryonic, and somatic cells [17,40], likely by the direct targeting of the apoptotic signalling cascade [41–43]. Finally, in the filarial parasite of cattle, *Onchocerca ochengi*, *Wolbachia* has been demonstrated to play a key role in host immune evasion, specifically by attracting host neutrophils and, thus, averting a potentially lethal effector response by degranulating eosinophils [44].

Over the years, the fundamental roles that *Wolbachia* plays in pathways linked to reproduction, metabolism, and immune defence of filarial nematodes have been the subject of intense scrutiny, focusing on developing novel chemotherapeutics to disrupt this mutualistic relationship; some have been successful [15,17,21,45]. For instance, the administration of 4-week courses of doxycycline (belonging to the tetracycline family of antibiotics) and rifampicin have been deemed effective in reducing transmission of *O. volvulus* microfilariae to mosquito intermediate hosts and filarial embryogenesis, respectively (reviewed in [13]). Nevertheless, the length of drug administration required to achieve significant effects, along with the severe adverse reactions that tetracyclines can cause in children and pregnant women (e.g., permanent dental staining, teratogenic effects, and potentially fatal hepatotoxicity [46]), limit the use of these antibiotics in mass drug administration (MDA) programs in areas where filariases are endemic. Nonetheless, these findings raise the question as to whether a deep exploration of the microbiomes of other helminth parasites of major socioeconomic significance could hold promise for the identification of novel targets for the development of antibiotic-independent control strategies against the diseases caused by these worms.

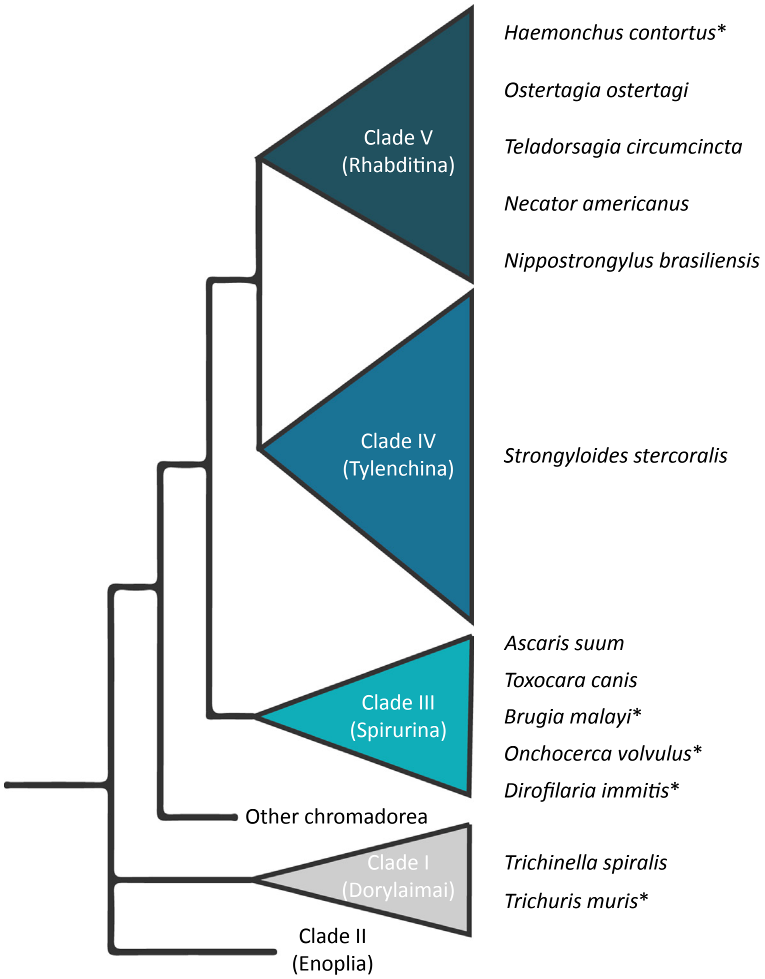

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Figure 2. Key Helminth Taxa to Be Investigated as Representatives of Their Taxonomic Clades. Asterisks (*) indicate taxa for which published data on parasite microbiome structure and/or function(s) are available. The figure was adapted from Parkinson *et al*. [60].

New Generation of Helminth Microbiome-Targeting Chemotherapeutics?

Globally, more than two billion people are at risk of infection by GI nematodes, mainly the hookworms *Ancylostoma duodenale* and *Necator americanus*, the whipworm *T. trichiura*, the roundworm *Ascaris lumbricoides*, and the threadworm, *Strongyloides stercoralis*. Collectively, these nematodes are responsible for more than 5.5 million disability-adjusted life years (DALYs) (reviewed in [47]). Moreover, GI nematodes inflict significant production losses in livestock due to the extensive morbidity and mortality associated with a range of diseases that they cause (reviewed in [48]). Complete reliance on anthelmintics for the control of these parasites (via MDA or targeted strategic worming programmes in humans and livestock) bears substantial risks, linked to the global threat of emerging anthelmintic resistance, as already observed in several GI nematodes of veterinary importance (reviewed in [49,50]). Yet, the discovery of alternative strategies for parasite control should be built on a thorough understanding of the fundamental biology of these pathogens, and of key mechanisms of interactions with their vertebrate hosts. A deeper knowledge of the structure and function of the microbiomes of parasitic helminths, and of mechanisms of microbiome acquisition and transmission, could lead to unprecedented discoveries in parasite physiology, pathology, and reproduction, and thus, to the development of completely novel control tools. Nevertheless, for such discoveries to be harnessed, fundamental information needs to be acquired. We propose that, in the first instance, the microbiomes of representative species of GI nematodes of considerable medical and veterinary significance (Figure 2) could be qualitatively characterized using high-throughput sequencing of the bacterial 16S rRNA gene (Box 1). The selection of specimens of a range of parasite species from different hosts and geographical locations would assist the determination of species-specific ‘core’ parasite microbiomes. Following the establishment of reference 16S rRNA databases for each key parasite species, shotgun metagenomic sequencing of their microbiomes would provide important information on the relative abundance of each ‘core’ microbial species, and clues about their functional potential. The latter, coupled to investigations of the proteomes and metabolomes of the microbial communities inhabiting these parasites, could

Box 1. Sequencing and Analysis of Helminth Microbiomes – A Need for Standardisation

The most commonly used techniques for microbiome profiling include high-throughput sequencing of the bacterial 16S rRNA gene (often referred to as ‘16S rRNA sequencing’), and whole-genome sequencing of microbial communities (‘shotgun metagenome sequencing’) [53,54]. Whilst these techniques are highly suitable for the study of vertebrate microbiomes, their application to investigations of the microbiomes of helminth parasites, and GI nematodes in particular, will require careful considerations surrounding sample processing, as well as data analysis and interpretation. First, GI nematode specimens are usually directly harvested from vertebrate hosts (e.g., experimentally infected animals), or cultured in host faecal matter, which dramatically increases the risk of ‘contaminating’ microbial populations, for instance coating the outer nematode cuticle, in the parasite DNA of interest. In order to overcome this potential limitation, the cuticle of worms collected from infected hosts should be sterilized (e.g., using sodium hypochlorite) prior to microbial DNA extraction. In addition, in order to generate meaningful data on parasite microbiome structure and function, the determination of ‘core’ taxa, specific to a given parasite species and/or species group, will be necessary. Importantly, negative (‘no-DNA template’) samples must be processed alongside samples of interest, in order to ensure that sequences generated from microorganisms contaminating laboratory surfaces and equipment, glassware, and plasticware, as well as nucleic acid isolation and amplification and sequencing reagents [55,56], are correctly identified and subtracted from the final sequence dataset(s). Whilst existing high-throughput genome sequencing datasets generated from a range of GI nematodes (particularly as part of whole-genome sequencing projects; [57]) might include useful sequence information on the occurrence of resident microbial populations within parasite tissues (which, in such datasets, are traditionally considered ‘contaminant sequences’ and therefore discarded), the absence of adequate controls in these experiments largely prevents the retrospective use of these data in parasite microbiome-sequencing studies. Once microbial sequence data have been obtained and annotated [58], information on the localization of specific taxa of interest in parasite tissues can be obtained using microscopy techniques, including fluorescence *in situ* hybridization (FISH), immunofluorescence, and transmission electron microscopy (TEM) (reviewed in [59]). Whilst all of these techniques require highly specialized staff and are relatively costly and time consuming to use, they might provide useful insights into means of helminth microbiome acquisition and function.

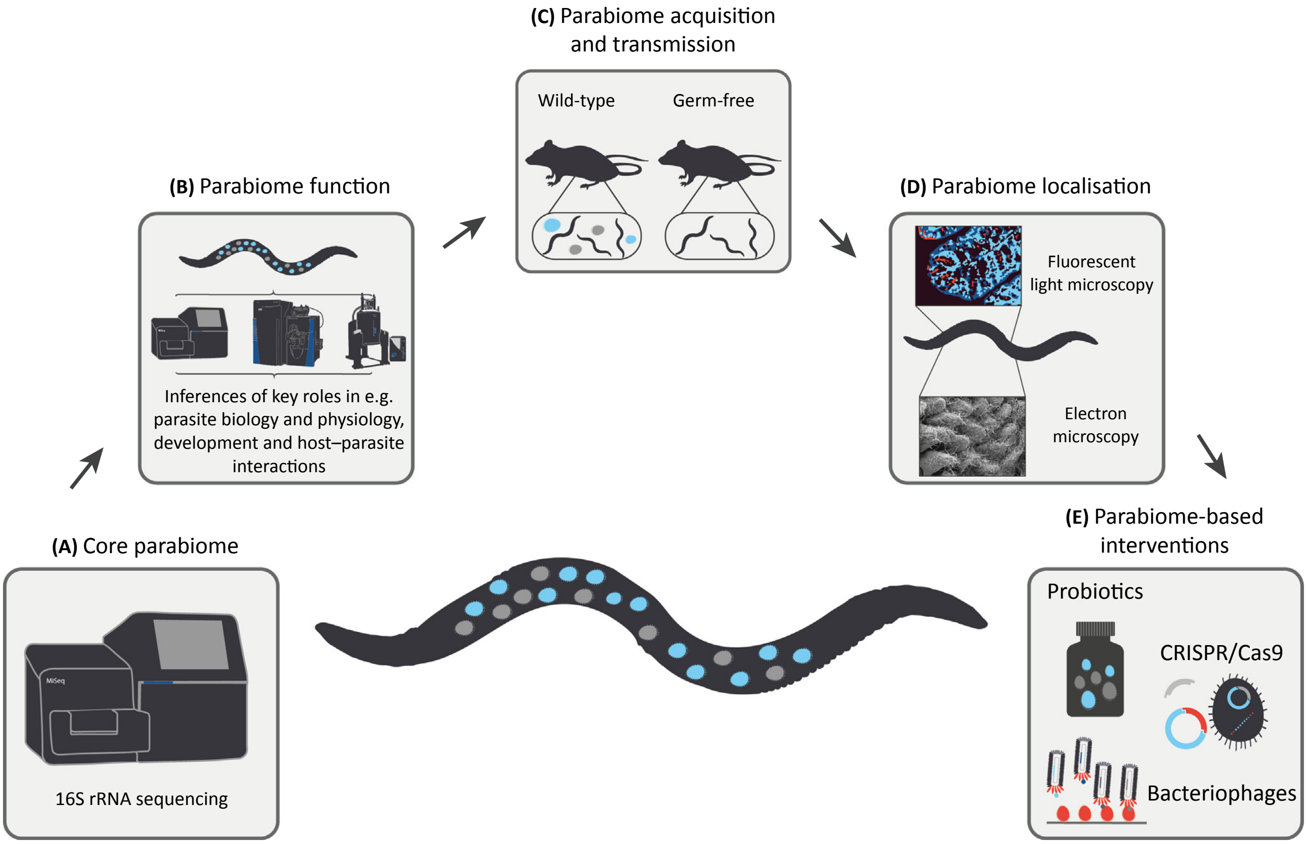

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Figure 3. Plan of Action for Efficient Investigations and Consequent Exploitation of Helminth Microbiomes. (A) Bacterial 16S rRNA gene sequencing of helminth microbiomes to establish core resident microbial species. (B) Shotgun metagenomic sequencing (i), proteomic (ii), and metabolomic (iii) analyses to establish microbial functions. (C) Experimentsin wild-type and germ-free mice to determine mechanisms of acquisition and transmission of helminth microbiomes. (D) Localization of core microbial populations through fluorescent light microscopy and electron microscopy. (E) Identification and targeting of key microbial species to decrease parasite fitness (based on the previously assessed parameters) via microbiome-editing techniques.

lead to a better understanding of the possible role(s) that the microbiomes of parasitic helminths play in the biology and physiology of individual worms.

Key information on the modes of transmission of helminth microbiomes could be acquired via experimental infections of vertebrate hosts with selected GI nematodes, followed by qualitative and quantitative comparative analyses of the host microbiomes and key parasite developmental stages. Furthermore, for selected GI nematodes (e.g., *Nippostrongylus brasiliensis*), experimental infections of germ-free or antibiotic-treated mice recolonised with fluorescently labelled bacteria might provide clues on host–parasite microbiome transfer using *in vivo* imaging (cf. [51]). Similar techniques could be used to localise species or groups of bacteria in parasite organs and tissues, thus providing additional clues on the functions of such microorganisms in worm biology. Together, this information would form a basis for experimentation, aimed at interfering with such functions that may potentially lead to the discovery of entirely novel, antibiotic-independent strategies for parasite control (Figure 3), for example, via cutting-edge **microbiome editing** techniques, including CRISPR/Cas9, engineered probiotics, and/or bactericidal bacteriophages (reviewed in [52]).

Concluding Remarks

In spite of substantial evidence that points towards key role(s) of microbial species inhabiting parasitic helminths in the fundamental biology of these pathogens and host–parasite interactions, for example, in filarial nematodes and, more recently, whipworms, current knowledge of the microbiomes of key parasites of major socioeconomic significance, such as GI nematodes of humans and livestock, is scarce and fragmented. Nonetheless, the relentless progress in microbiome investigation and sequencing technologies (Box 1), and novel high-throughput bioinformatics pipelines, provides us with unprecedented opportunities to thoroughly characterize the structures and functions of such microbial populations. At the core lie questions surrounding modes of helminth microbiome acquisition and propagation to successive generations of parasites, the localisation of endosymbiont microorganisms in the organs and tissues of parasites, the functions that helminth microbiomes (including bacteria, viruses, and fungi) play in parasite biology and physiology, and the effects that disrupting parasite–microbiome interactions may exert on parasite propagation and survival (see Outstanding Questions). In turn, the new knowledge can be expected to provide us with a plethora of opportunities to exploit parasite–microbiome associations to our advantage, for example, by applying cutting-edge microbiome-editing techniques as novel intervention strategies against parasitic nematodes and the diseases that they cause.

Outstanding Questions

Which microbial taxa form the core microbiomes of different helminth species?

How do helminths acquire their microbiomes?

Where do endosymbionts localise within the parasite host?

What are the functions of the microbiomes of parasitic helminths?

What role(s) do microbes other than bacteria (i.e., viruses and fungi) play in parasite biology and physiology?

Can helminth–microbiome relationships be exploited for the development of new strategies for parasite control?

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