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PERSPECTIVE

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C. elegans: A biosensor for host–microbe interactions

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Microbes are an integral part of life on this planet. Microbes and their hosts influence each other in an endless dance that shapes how the meta-organism interacts with its environment. Although great advances have been made in microbiome research over the past 20 years, the mechanisms by which both hosts and their microbes interact with each other and the environment are still not well understood. The nematode *Caenorhabditis elegans* has been widely used as a model organism to study a remarkable number of human-like processes. Recent evidence shows that the worm is a powerful tool to investigate in fine detail the complexity that exists in microbe–host interactions. By combining the large array of genetic tools available for both organisms together with deep phenotyping approaches, it has been possible to uncover key effectors in the complex relationship between microbes and their hosts. In this perspective, we survey the literature for insightful discoveries in the microbiome field using the worm as a model. We discuss the latest conceptual and technological advances in the field and highlight the strengths that make *C. elegans* a valuable biosensor tool for the study of microbe–host interactions.

Microbes are a major force in nature, and they have shaped this planet since the origin of life[1]. Animals and plants have been in close contact with microorganisms for billions of years; these relationships have affected the biological functions of the species involved and ultimately influenced their evolutionary trajectories[2–4]. The shared history between microbes and hosts has led to the acquisition of dependence between two biological systems that range across several taxonomic levels[2,4]. The wide range of potential interactions between a host and its microbes challenges our understanding of what an organism or a biological function is in the context of the microbiome[5–7] while defying the very same notion that all animals need a microbiome[8].

Nevertheless, microbial communities are key drivers of a wide range of biological functions and can affect many processes such as nutrition and immunity[9]. Yet, we are still far from achieving a complete understanding of the intricate relationship between the host and its microbiota. The inherent complexity of this problem can be tackled from different angles by using a wide array of tools including theoretical approaches[10–12], classical in vitro studies[13,14] and animal models[15,16]. The latter offer the possibility of establishing causality links, allowing robust interpretations of the real influence of one system on the other. An increasing number of animal models are currently being used to study microbe–host interactions. In particular, the bacterivore nematode *Caenorhabditis elegans* has emerged as a suitable model offering strong advantages that outweigh its limitations[17–19].

In this perspective, we discuss what makes *C. elegans* a supreme model for the study of microbe–host interactions, with a focus on methodologies and insightful discoveries from studies that have used the worm as a biosensor of microbial activity over the past 20 years.

The worm and its microbiota: parallels to humans

From an evolutionary point of view, *C. elegans* is a suitable model for the identification of the molecular processes involved in pathogenic and commensal interactions because these processes are often conserved in other organisms of interest, including humans[20–22]. At the level of the gut, there are basic morphological similarities between the intestinal cellular structure in humans and worms. In addition to presenting functional similarities in the extraction and absorption of nutrients and the ability to host live microbes, the gut of the worm is a perfectly adequate small but physiologically relevant organ for the analysis of host–microbe interactions.

In the wild, *C. elegans* harbors a rich and diverse microbiome that is relatively stable across geography. Like mammals and other animals, the microbiota of *C. elegans* is composed of major phyla such as Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria[23–25], with the latter, mostly from the *Enterobacteriaceae* genus, often the most dominant. Likewise, studies have shown great intraspecies variations in intestinal microbiota according to the environment as well as the host's genetics[19,25,26]. For example, Gammaproteobacteria such as the human pathogen *Pseudomonas aeruginosa* exploit monosaccharides from the intestinal mucin layer to successfully colonize *C. elegans*[27]. Whether other commensal, pathobionts and/or pathogenic microbes exploit this mechanism for worm colonization remains to be studied. Historically, the most commonly used bacteria in the context of *C. elegans* work in the laboratory setting has been mono-colonization with the enterobacteria *Escherichia coli*[28,29], an important representative of human gut commensal microbes.

Like mammals, *C. elegans* acquires through the oral route an active gut microbiota that serves many roles beyond providing nutritional sustenance[24]. The view that bacteria serve as nutrients only for worms but not for mammals is also a misconception. As found in worms, microbes from the environment are often present in the distal gut of mammals[30]. Similarly to worms, bacterial contents are constantly released into the mammalian gut, as one-third of the bacterial cells are damaged with impaired membrane polarity, and approximately one-fourth have severely compromised membrane integrity[31]. Hence, several bacterial products, such as lipopolysaccharides[32], gut-commensal proteins[21] and a wide range of metabolites that are either unique to bacteria or co-metabolites of unknown

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origin, can be found in the host bloodstream. As seen in mammals, a vast literature shows that bacteria supplement the worm host with metabolites that regulate many physiological and metabolic traits or regulate the effects of drugs or nutrients, through mechanisms that are independent of the macronutrient content of bacteria[24,25,29,33–38]. Therefore, the recent focus on host–commensal interactions in the worm gut builds on past findings in which *C. elegans* has been an instrumental workhorse to study microbial pathogenesis[39–42].

As new resources become available (e.g., CeMbio[43]), a larger array of bacterial species can now be used to form complex communities in the worm gut that cover the major phyla and mimic the gut microbial environment of other organisms[2,10,43]. The utilization of a phylogenetically and metabolically diverse microbial community can make a suitable model to study functional aspects of the gut microbiome that are also present in humans[9,33,44,45]. Work in humans and other organisms including *C. elegans* suggests that studying the functional capability of the microbiome along with its phylogenetic composition is a good proxy to link microbial community composition to its regulatory effects on the host[5,26,46,47]. Given these results, there is a need to characterize the microbiome with high precision to fully capture the mechanisms by which it modulates host molecular and physiological phenotypes.

Using worm phenotypes as readouts of bacterial activity

Several reports published over the past 20 years and using *C. elegans* as a model organism have provided remarkable insights into host–microbe interactions (Fig. 1). For example, several studies using nematode development as a phenotypic readout have shown that the worm's microbiota is essential for the supply of micronutrients, such as vitamins B2[48], B6[29], B9[29,49] and B12[50,51], iron[21,31,52] and molybdenum[36], as well as reactive oxygen species[31,53]. The *C. elegans* model has also identified other metabolites at the host–microbe interface that regulate adult physiological traits. In particular, analyses of adult survival and longevity phenotypes have identified the production of nitric oxide[22,54,55] by the Firmicutes *Bacillus subtilis* and colanic acid[30,56,57], methylglyoxal[58], folate[49,59] and agmatine[28] from the Proteobacteria *E. coli* as key molecules regulating host aging. Moreover, perturbation of bacterial respiration through coenzyme Q biosynthesis impairment leads to modulation of *C. elegans* lifespan[60,61]. Using host lipid metabolism as a phenotypic readout, *C. elegans* studies have also identified microbial metabolites that regulate host lipid metabolism through NR5A-Hedgehog signalling[62]. In addition, *C. elegans* has been used as a biosensor to conduct studies on probiotics[63]. In 2020, using a *C. elegans* synucleinopathy model, Goya and colleagues found that the *B. subtilis* PXN21 strain inhibits, delays and reverses α-synuclein aggregation causing Parkinson's disease through alterations in the sphingolipid metabolism pathway of the host[64]. In addition, Urrutia and colleagues found that bacterial production of γ-aminobutyric acid and lactate conferred 40% of neuroprotection in another *C. elegans* model of neurodegeneration[65]. By revealing important links between bacteria and brain pathologies, these studies also offer further mechanistic insights into how the gut microbiota regulates the motor deficits and neuroinflammation observed in a mouse model of Parkinson's disease[66].

However, the mechanistic basis of the microbiota–brain signaling and its physiological relevance remain largely unknown. Using *C. elegans* olfactory responses (e.g., attractions to odors) as a phenotypic readout, a study has shown that commensal gut bacteria alter olfactory behavior through the production of the neuromodulator tyramine[67]. In particular, production of this metabolite by commensal *Providencia* bacteria bypasses the requirement for host tyramine biosynthesis and manipulates a host sensory decision, thus promoting fitness of both the host and the microorganism[67]. Likewise, the ability of *C. elegans* to 'read' and recognize bacterial small RNAs induces a transgenerational response, leading to appropriate behavioral changes in their progeny for pathogen avoidance[41]. Furthermore, the use of *C. elegans* as a biosensor has highlighted the fundamental role of microbiota in host defense against pathogens[68–71], a mechanism known as colonization resistance[2]. In particular, using worm survival as a physiological readout, *C. elegans* studies allowed the identification of microbiota-produced cyclic lipopeptides that confer resistance against intestinal colonization by the human pathogen *P. aeruginosa* and by natural pathogens such as *Bacillus thuringiensis*[68].

In addition to helping identify key mechanisms and metabolites involved in microbe–host interactions, the worm has also been a great model for revealing novel host mechanisms. Studies have notably uncovered the molecular processes used by the host to interpret the bacterial signals mediating various physiological functions. A groundbreaking study by Liu and colleagues identified the organismal pathways that survey and defend mitochondria against toxic by-products of several members of the microbiota[72]. Another study reported that the production of biofilm by *B. subtilis* can increase the life expectancy of the worms via the production of communication molecules involved in bacterial quorum sensing and nitric oxide. These molecules then trigger a dietary restriction–like response mediated by the Abnormal dauer formation protein 2 (DAF-2), DAF-16 and Heat shock factor protein 1 (HSF-1) signaling pathways that regulate lifespan[54,55]. In addition, several bacterial metabolites have been shown to affect host lifespan and healthspan by acting on mitochondrial function, activating the unfolded protein response, remodeling the host lipid response and interfering with insulin-like and dietary restriction–related pathways[73–75].

Over the years, the worm has therefore provided unique insights into health and disease phenotypes by elucidating key molecular mechanisms of host–microbe interactions.

An experimental pipeline to explore host–microbe interactions

Interactions in the host–microbe system are a two-way road, where each part is sensing and reacting to signals from its counterpart in a continuous loop. Being able to phenotypically and molecularly characterize how both microbes and host sense and respond to each other is therefore essential for capturing the mechanisms underlying their interaction. Molecular and synthetic biology tools are available to modify and study with great precision most layers of biological information from the worm host, its microbial community and the environment (Fig. 2). Thus, the worm and its microbiota provide an excellent system to study host–microbe interactions because each variable can be modified, while allowing deep phenotyping to measure the effects of these modifications on the host at scale[76].

The *C. elegans* host. This semi-transparent nematode has a short life cycle (~3 d) and lifespan (mean of ~18 d), which, together with its simple and cost-effective handling, allows the study of a wide range of processes and diseases that are evolutionarily conserved in humans[77]. The superpower of the worm model lies in its simple genetics and amenability to high-throughput screening. As fully reviewed by Nance. et al., 'the power of any genetic model organism is derived, in part, from the ease with which gene expression can be manipulated'[78]. Therefore, *C. elegans* is a great genetic model organism, owing to the wide range of molecular tools available to modify its genome, the cost effectiveness and simplicity associated with the generation of mutants and a fully supportive community of researchers who widely distribute their reagents. For example, thousands of genetically modified strains are readily available from the Caenorhabditis Genetic Center (https://cgc.umn.edu/) and the National BioResource Project laboratory (https://shigen.nig.ac.jp/c.elegans/top.xhtml). The variety of methods available for the creation of mutant strains is also very well documented, for both the knockout and knockdown of genes and the generation of transgenic lines[78–81].

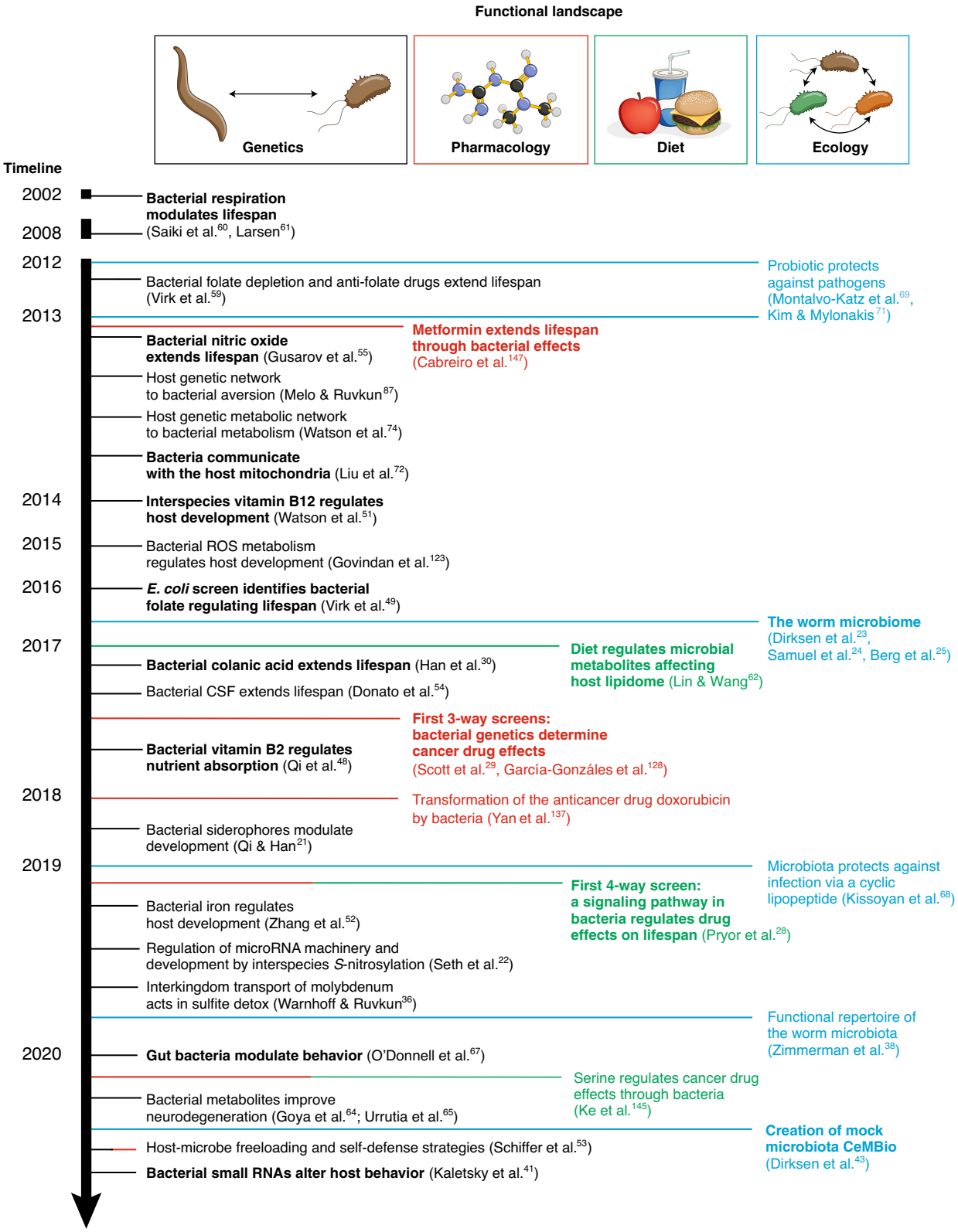

Fig. 1 | Timeline of publications providing remarkable insights into *C. elegans*–microbe interactions. Each publication entry has been classed (by position and color) according to the main functional landscape explored in the work. Worm as a biosensor has revealed links between: host and/or microbial genetics (black), drugs–microbe and host (red), nutrition–microbe and host (green) and microbe–microbe host relationships (blue). Selected publications have been highlighted in bold. CSF, competence sporulation stimulating factor; ROS, reactive oxygen species.

Precisely regulating the expression of host genes is essential for causally linking the influence of an environmental cue with a phenotype. In particular, unbiased forward (e.g., random mutagenesis[82–85]) and reverse genetic screens[79,86] have been powerful tools for linking a genotype to a phenotype. For example, in the context of host–microbe interactions, an RNAi-based approach

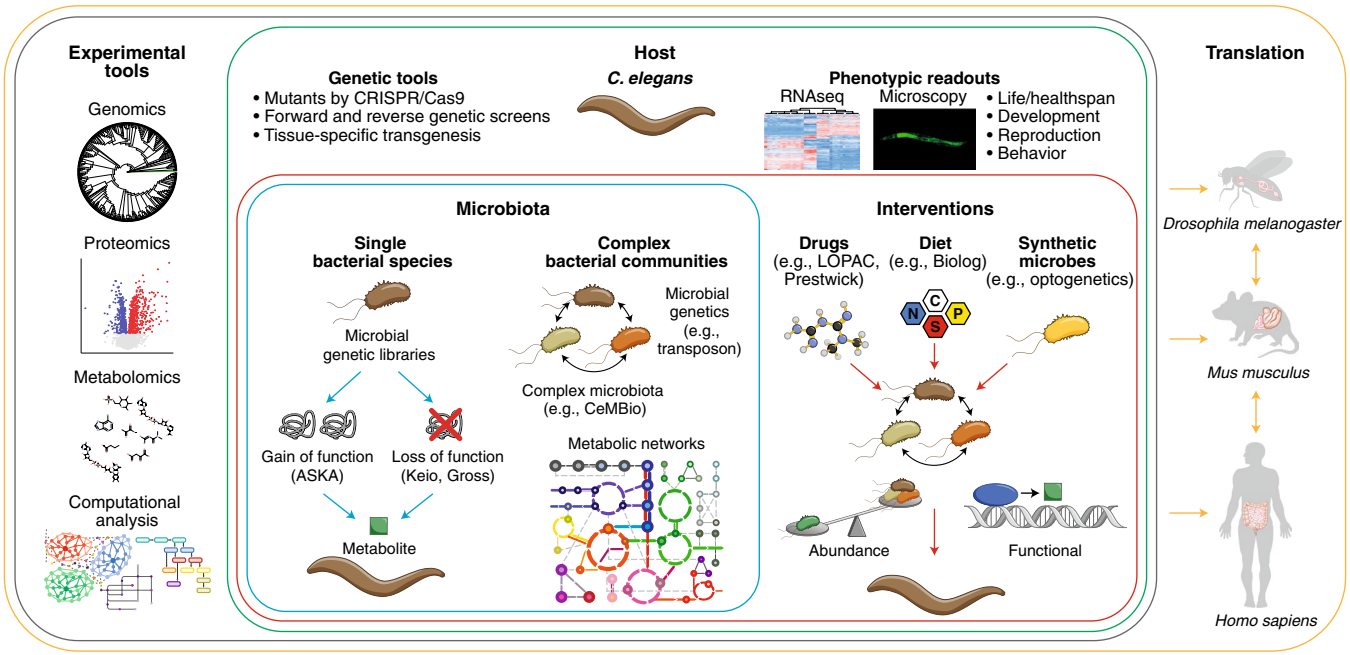

Fig. 2 | An experimental pipeline to explore host–microbe interactions. A modular, scalable, layered and flexible workflow to explore the complex landscape of host–microbe interactions. Multiple experimental options exist for *C. elegans* molecular or phenotypic readouts, including the use of large mutant libraries for host genetics (green). High-throughput screening of single or complex microbial communities and metabolic network modeling tools are available for worm–microbiota studies (blue). Drug and dietary interventions can be incorporated to study the influence of environmental cues on host–microbe interactions (red). Multi-omics and computational analyses can be applied to individual or combined entities of the worm–microbe model for in-depth molecular characterization (black). The evolutionarily conserved nature of the worm–microbe model allows testing and further validation of findings in more complex models (orange). ASKA, a complete set of E. coli K -12 ORF archive; LOPAC, library of pharmacologically active compounds.

has provided remarkable insights into the host mechanisms regulating microbial aversion[87]. The transparent nature of the worms allied to the simple generation of transgenic fluorescent reporter lines permits the study of how microbes regulate worm gene expression profiles in a spatial (tissue-specific), temporal and quantitative manner[88]. The combination of these unique features and molecular techniques has been used to identify microbial signaling and metabolic pathways, including the respective metabolites involved, regulating host lipid metabolism[28]. Furthermore, the combination of these approaches with forward and reverse genetic methods has been instrumental in identifying the host genetic networks that underlie lipid metabolism regulation mediated by bacterial vitamin B12[51]. Overall, these tools allow researchers to modify and study with precision the contribution of host genetics in determining a molecular or physiological phenotype driven by microbes.

C. elegans provides an excellent opportunity to perform microbiota studies at a scale only outcompeted by in vitro unicellular high-throughput screening[17]. Several worm phenotypes can be monitored in a high-throughput manner, including survival readouts upon challenge with pathogens or xenobiotic compounds[20,39,40,68,89–93], measurements of adult lifespan[30,32,54,55,57,64,70], arrested development[21,22,32,36], impaired fertility[54,55,69,94,95], resistance to stress[55,70] and altered behavior[96,97]. The measurement of such phenotypes in a high-throughput manner allows the study of individual or communities of microorganisms that colonize the worm intestine and regulate several traits of host physiology. Recently, the model has experienced a giant leap in its high-throughput capacity with the use of state-of-the art deep phenotyping[76]. This technological advance has been possible through the development of a new set of hardware and software tools allowing the manipulation, recording and imaging of worms grown in hundreds of conditions in parallel. These tools include flow cytometry–like stations such as COPAS[98] to measure worm physical variables including axial length and optical density; the 'WorMotel' developed by Fang-Yen[99] and the Lifespan Machine by Fontana[100] to measure lifespan; diverse tracking platforms developed by the Brown[96,101], Nollen[102], Kerr[103], Driscoll[104] and Goodman[105] laboratories, which can assess motor-related phenotypical variables including behavior; fully automated workstations as developed by Pincus[106] or Lu[97], to monitor long-term behavior and healthspan; and many other tools[107–110]. With these technologies, worms can be phenotypically characterized with a high degree of reproducibility by using often-affordable imaging systems[111]. Fluorescence imaging can also be performed in a high-throughput manner, taking advantage of the transparent nature of *C. elegans* and further extending the screening capabilities of the worm as a biosensor. Fluorescence imaging can provide information at different scales, from studying protein dynamics in whole animals[108,112] to uncovering processes in particular specific cell lineages[113]. Hence, by using worm molecular or physiological phenotypes as readouts of bacterial activity, it is possible to capture in fine detail at the host level several molecular mechanisms that are involved in these complex host–microbe interactions. As a consequence, these high-throughput phenotyping approaches generate a large amount of complex phenotypic data that requires the use of computational tools for proper analysis and extraction of meaningful information. Therefore, machine learning and deep learning algorithms are now being used in addition to commonly used statistical techniques (e.g., PCA or correlation[114]) to uncover hidden features and trait prediction[115] from complex datasets.

Thus, *C. elegans* provides unique opportunities as a model organism for studying host–microbe interactions, including a unique set of tools to study in depth the vast and uncharted functional landscape of this relationship.

The microbes. A major problem of current microbiome research is that an excessive amount of the available data establishing causation between microbiota physiology and host function was drawn

simply from correlation data. One potential solution to this problem is the creation of synthetic communities to dissect causality in complex host–microbiota interactions. To increase the likelihood of success, one should consider creating a simplified microbial community that represents both phylogenetically and functionally the complex microbiome of interest, taking also into consideration the model organism that will host the community. Finally, and most importantly, one should consider whether the mock community and their host are adequate models to address the scientific question at hand. The groups of Félix, Samuel, Schulenburg and Shapira[23–25] have importantly contributed to this more effective approach. As a result of their in-depth meta-analysis of the natural microbiome of *C. elegans*, they have created CeMbio[43], a simplified natural worm microbiota mock community. Key features of CeMbio include a set of easily culturable bacterial strains that colonize the worm gut and distinctly affect *C. elegans* physiological traits and life trajectories. These strains have fully sequenced genomes, diagnostic PCR primers and well-characterized metabolic network models.

Approaches combining computer modeling of metabolic pathways and experimental characterization of bacterial physiology allow researchers to study not only the impact of bacterial functional diversity but also the role of the environment on host functions. Zimmermann and colleagues have led this integrative approach, bringing together the use of phenomic microarray (Biolog) technology[116] to assess metabolic competences of selected bacteria with metagenomics and computer modeling to reconstruct metabolic networks at the community level and study ecological interactions between members of the community[117]. Their work has shown that host physiology and fitness is dependent on the nutritional landscape for microbe–microbe interactions[117].

Yet, to functionally characterize the contribution of each microbe in maintaining the homeostasis of the community and their role in regulating host physiology, one needs to go deeper in the functional characterization of each microbial member. For this purpose, a wide range of technologies are available for bacterial modification, such as the random insertion of transposons in the genome[34,118–120] and the use of bacteriophages[35]. These techniques allow the creation of mutant libraries from several species, providing an opportunity to study and identify new genes regulating bacterial function. For example, such approaches have led to the identification of thousands of bacterial genes in Proteobacteria and Bacteroidetes that had no previously known function[121]. A major achievement was the construction of the Keio library, which contains a set of precisely defined monogenic deletions of all the nonessential genes of *E. coli* K-12 (3,985 genes out of a total of 4,288)[122]. These transposon and deletion bacterial libraries are now being used in mono-colonization experiments to causally link the effects of bacterial genes from a single species with a wide range of phenotypes from diverse hosts[51,123–127]. In *C. elegans* studies, the Keio library has been screened for *E. coli* genes involved in the regulation of lifespan[30,49], to show the dependence of host development on its microbiota for micronutrients (e.g., folate, iron and molybdenum[31,32,36]) and to infer the role of the microbiota in drug action[29,128] (e.g., fluoropyrimidines). *B. subtilis*, a human probiotic bacterium, is another commonly used bacterial strain for mono-association studies with *C. elegans*. The Gross laboratory has constructed two ordered, barcoded, antibiotic-resistance-marked single-gene deletion libraries, comprising 3,968 and 3,970 genes, respectively, allowing the genome-wide study of gene and pathway function in a Gram-positive bacterium[129]. To date, this resource has not been used in combination with a *C. elegans* host but may well provide an important tool to expand the possibilities of this microbiome model beyond its current potential. Although loss-of-function libraries are more widely used with *C. elegans*, gain-of-function libraries are also available. For example, the ASKA library, made up of single strains containing multicopy vectors overexpressing any gene of *E. coli*[37], was used with *C. elegans* and led to the identification of the bacterial metabolite methylglyoxal as a regulator of host lifespan[58].

New tools are also being implemented to study the gut environment in *C. elegans*. For example, RNAseq has been used to study the effects of the gut environment and host genetics on gene expression and metabolic pathways of *E. coli* within the gut of *C. elegans*[130]. The authors found that active metabolism of bioactive lipids in the gut may regulate host–microbial interactions. A similar observation was recently made in a mammalian model, where sphingolipids produced by the microbiota enter and regulate host lipid metabolism[131]. Interestingly, the authors observed an increase in aerotaxis-related genes expressed by bacteria growing in the gut compared to in vitro growth, suggesting that the gut of *C. elegans* may in fact be anaerobic. Although this is an interesting observation that could further expand the usefulness of this model, measurements of oxygen tension inside the worm gut are required. New synthetic biology reagents are being designed to expand the toolset to study microbes within the worm gut. This includes the development of bacterial biosensors capable of detecting molecules in the guts of worms[132], bioluminescent bacteria to evaluate bacterial survival in the gut[133] and the development of optogenetic tools in bacteria to control bacterial metabolism and indirectly regulate host physiology[57].

The environment. Recent research in humans shows that the environment dominates over host genetics in shaping the microbiota[134,135]. All the aforementioned tools provide a robust framework to capture the role of the microbiota on host physiology at the mechanistic level. The scalability of the current methods used in *C. elegans* allows the setup of systematic studies in which environmental perturbations can be added as important variables of investigation.

The inclusion of drugs as an additional factor produces a complex interaction landscape between microbes, drugs and host. For example, host physiology may be affected as a result of modified drug pharmacokinetics through direct microbial biotransformation[38,136–138], or by indirect effects resulting from the action of drugs on microbial community structure and function[13,14,38,139]. Levodopa, a medicine to treat Parkinson's disease, is used as a carbon source by bacterial taxa containing enzymes with tyrosine decarboxylase activity, resulting in reduced drug efficacy[140]. Studies in cancer research show that chemotherapy treatments often lead to intestinal disorders following an overall reduction in microbial abundance[141] or through increased drug toxicity after reactivation by microbial enzymes[142,143]. In addition, drugs can limit the biological functions of some taxa, arresting their growth and allowing other disease-associated taxa to outcompete. For example, colonization by *Clostridioides difficile* is prevented by colonization resistance properties of the fecal microbiota. Thus, weakening microbial colonization resistance by widespread use of antibiotics in the clinical setting is a major risk factor for *C. difficile*-associated morbidity[144]. *C. elegans* offers a reliable platform to investigate these complex relationships between host, microbes and drugs. Studies using the worm as a biosensor for host–microbe–drug interactions showed that doxorubicin, a commonly used anticancer drug, is metabolized by human gut bacteria such as *Klebsiella pneumoniae*, *E. coli* and *Raoultella planticola* among others[137]. Fluoropyrimidines (5-FU) are essential anticancer chemotherapy drugs for colorectal cancer, but their efficacy is highly variable between patients. To investigate the role of microbes in anticancer drug toxicity, our group in parallel with the Walhout and O'Rourke laboratories developed a three-way (microbe–drug–host) high-throughput screening method to explore the role of microbial genetics in mediating the effects of fluoropyrimidines on *C. elegans*[29,128,145] development, reproduction and survival. The relative contribution of each *E. coli* gene was obtained to perform a genome-wide systematic analysis of the pathways and

processes involved in the mediation of drug effects. These three independent studies show that microbes can bolster or suppress the effects of fluoropyrimidines through metabolic drug interconversion involving bacterial vitamin B6, vitamin B9 and ribonucleotide metabolism, and highlight the value of these approaches to unravel the mechanistic complexity of such interactions.

Nutrition is a key element at the interface between microbes and host dictating the fitness of the entire meta-organism. Given the immense complexity of nutrition[146], mapping the biological response of a host and its associated microbes to the different types of chemical components is a challenging task. Historically, the microbial nutritional landscape has often been studied with the well-established microbial phenotyping technology from Biolog[116]. This technology allows the investigation of hundreds of metabolites covering all major nutrient classes (e.g., sugars, fatty acids and amino acids) to study their role in regulating microbial growth phenotypes. Zimmermann and colleagues recently applied this technology to investigate how different microbes from the natural microbiome of *C. elegans* metabolize a diverse range of nutrients[117]. They showed that specific nutritional requirements by members of the worm's microbiota dictate the nature of their interaction (e.g., competitive or commensal) within a complex microbial community and their role in regulating worm physiology. Using the same technology, our laboratory developed a high-throughput four-way microbe–drug–nutrient–host screening approach to investigate how 337 dietary elements affect the efficacy of metformin on host physiology in a bacterial-dependent manner. Metformin is the most widely used drug for type 2 diabetes and a potential treatment for aging or age-related disease. Research spanning from worms to humans shows that metformin acts indirectly through the microbiota to regulate distinct host phenotypes and diseases[147–150]. Using a nutrient systems approach, we discovered that *E. coli* integrates signals from both metformin and the diet into a signaling cascade that affects the expression of the master nutrient regulator cAMP receptor protein CRP, which, in turn, indirectly regulates host physiology through modified arginine-derived metabolites[28]. Recently, a study by the O'Rourke laboratory investigating the role of amino acids in microbe–drug–host interactions revealed that dietary serine enhances fluoropyrimidine anticancer chemotherapy without altering pro-drug activation by *E. coli*[145]. Overall, the current use of *C. elegans* as a biosensor of bacterial activity is one of the ultimate state-of-the-art models to reveal novel mechanisms at the interface between drugs–nutrients–microbes and host physiology.

Future outlook

The vast complexity present in the human microbiome may be fully understood only with careful and systematic investigation of all the potential physical and biological constraints that exist in the gut. As an example, this model could be further extended to probe the effects of a wide variety of environmental conditions including new drugs/xenobiotics or pH fluctuations on host–microbe interactions and host physiology. As scalability of this system continuously grows from additional technological, biological and computational tools with seamless integration, new layers of complexity will be captured. Yet, despite the important contributions achieved by using this model, the microbiome *C. elegans* research field is still in its infancy. To conquer the vast unexplored complexity that exists in host–microbiome interactions, *C. elegans* research boundaries will have to be expanded to include larger microbial communities in complex but defined nutritional environments. The immense value of mimicking specific human microbiome conditions through the addition of further layers of complexity to this highly scalable system will permit the discovery of key principles in host–microbe interactions.

Past research on *C. elegans* as a model for the study of host–microbe interactions gives us hope. This work has permitted the discovery of many bacterial effectors influencing host physiology and the identification of the underlying host mechanisms. Some of the most exciting discoveries made by using worms to study complex phenotypic traits mediated by microbes have been extended to diverse host organisms[28,56], suggesting that the mechanisms are conserved across taxa. The quote 'You have evolved from worm to man, but much within you is still worm' by the German philosopher Friedrich Nietzsche has often been used to capture with simplicity the use of *C. elegans* as a valuable model organism for human disease processes. Once again, now in the study of complex host–microbe interactions, this simple model organism continues to enlighten and surprise us. Future work will lead to pioneering discoveries in one of the most extraordinary and complex problems that biology faces today.

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Competing interests

The authors declare no competing interests.

Additional information

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