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Host–microbiota interactions in *Caenorhabditis elegans* and their significance

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As a useful genetic model, *C. elegans* can facilitate investigation of the genetic underpinnings of host–microbiota interactions. However, decades of feeding it with *Escherichia coli* left a gap in our understanding of its interactions with microbes, hindering such use. This is changing, with recent studies characterizing the gut microbiota of worms in their natural habitats, comparing them to those in their environment, and evaluating the significance of gut and environmental commensals. This work defined a shared core gut microbiota significantly influenced by host genetics, and unraveled bacterial contributions to life history traits. Establishing *C. elegans* as a new model of host–microbiota interactions will benefit from existing knowledge about bacterial modulation of worm physiology, and could draw mechanistic insights from characterized interactions between parasitic nematodes and their symbionts.

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Introduction

In the trinity of multicellular genetic model organisms—*Mus musculus*, *Drosophila melanogaster*, and *Caenorhabditis elegans*, the latter is the latest to lend its genetic tractability to studying host–microbiota interactions. This reflects the growing interest in microbiotas, particularly those of the gut, which emerge as universal factors shaping host traits—from development, to physiology, immunity, even behavior, and potentially provide a route for manipulating host functions to promote well-being. What was lost in time could be compensated by the advantages that *C. elegans* offers, in particular for elucidating the role of genetic factors in shaping the gut microbiota. Pivotal among these advantages is the ability to work with self-fertilizing genetically homogenous populations, which better than sexually-reproducing organisms, can help average out inter-individual variation to discern gene effects. We are not there yet, but this review summarizes our current understanding of the interactions of *C. elegans* with environmental and food microbes and with its gut commensals, focusing on the new trove of information provided by the recent characterization of the *C. elegans* gut microbiota [1••,2••,3••].

Food with a twist

C. elegans and other nematodes have been grown in the lab for decades on monoxenic cultures, mostly of auxotrophic *Escherichia coli* strains. This was convenient for various reasons, including the suitability of the thin bacterial lawns for microscopy, and reproducible worm development. However, as it is now clear, this created a gap in our understanding of *C. elegans* biology, overlooking the vast interactions that this bacterivorous organism normally has with microbes in its environment and in its gut, and impeding our understanding of how microbe-derived signals affect host metabolism and physiology.

Standard food *E. coli* does not appreciably colonize *C. elegans* (with the exception of old worms [4]). That *C. elegans* can develop and reproduce on *E. coli*, without a gut microbiota to speak of, might thus suggest that unlike other animals, worm fitness is independent of a microbiota. However, the full picture is more complex: axenic media can sustain worm growth, but development is slow and fecundity low [5]; furthermore, worms raised on heat-lysed, or antibiotic-killed bacteria arrest at larval stages (Berg *et al.*, personal communication). A simple interpretation of these observations, one that is further supported by studies described below, is that the fitness of *C. elegans* depends on live intact bacteria, even if it's only the non-colonizing *E. coli*.

Recent data indicates that *E. coli* provides cues that affect worm development and physiology. Different strains of *E. coli* differently affect levels and patterns of fat storage in the worm, reportedly through activation of host signaling [6,7]. Different *E. coli* strains and mutants can further modulate worm life history traits, including lifespan, development, or timing of reproduction [8–10,11•]; and such effects depend on specific worm genes, attesting to gene–diet interactions [12]. Progress has been made in identifying *E. coli* metabolites that are responsible for modulating *C. elegans* life history traits. Thus, it was found that disruption of *E. coli* folate synthesis (vitamin B9),

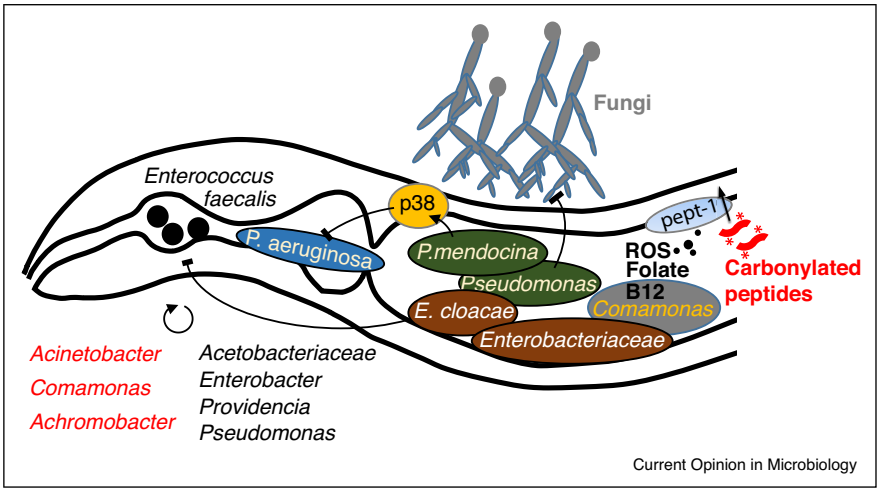
extended worm lifespan [11•,13]. In addition, certain folate derivatives (but not others) provided a signal to promote germ cell proliferation, which depended on the worm folate receptor homolog *folr-1* [14]. Reactive oxygen species (ROS) produced by *E. coli* were also shown to modulate worm life history traits, with bacterial mutations that increase ROS production found to activate host mitochondrial stress response, which delayed development, whereas mutations that increased ROS detoxification prevented this [15]. Interestingly, effects depended on an intestinal peptide transporter, encoded by *pept-1*, suggesting that ROS might act indirectly, perhaps through carbonylated peptides, their common and stable byproducts (Figure 1). Corroborating the role of bacterial ROS in modulating worm life history (directly or indirectly), worms fed with *Bacillus subtilis* show a dramatic lifespan extension compared to worms raised on *E. coli* (up to twofold, without any active colonization), which was found to depend on bacterial production of nitric oxide (also a ROS), and on worm stress-protective signaling pathways [16–19]. These reports, and additional ones, describing the effects of food-derived olfactory signals on reproduction and longevity [10,20], suggest that worms respond to bacteria-derived signals to modulate physiology long before they could sense changes in nutrient-dependent metabolic fluxes.

Stepping out to nature

Initial investigations of *C. elegans* responses to bacteria in the wild simply focused on soil bacteria. Such studies showed that feeding worms with certain soil bacteria accelerated the rate of development, while feeding with others, slowed it down; furthermore, worms altered their feeding behavior, showing a preference for bacteria that accelerated their development, that is increased their fitness [21]. Additional studies of one of these isolates, a *Comamonas* species subsequently identified as *Comamonas aquatica*, showed that acceleration of worm development (which came with a trade-off of reduced fecundity and shortened lifespan) depended on bacterial synthesis of vitamin B12, used by enzymes involved in methionine synthesis and in growth, but also for enzymes involved in synthesis of *S*-adenosyl methionine, a methyl donor used in various regulatory pathways [22•,23•,24•]. Other soil isolates were examined for their effects on lifespan, again showing differential effects, on lifespan and on overall fitness [25]. These were accompanied by differential gene expression patterns, with significant enrichment for genes involved in metabolism and innate immunity, suggesting involvement of these processes in worm–microbe interactions.

With the growing interest in *C. elegans* natural history and ecology, a recent study surveyed the environmental microbiotas in habitats from which *C. elegans* has been isolated, that is decaying vegetation and fallen fruit [26•]. In all habitats, members of the *Enterobactericieae* family were the most abundant, and slightly less so members of other *Gammaproteobacteria* families, including *Xanthmondaceae* and *Pseudomonadaceae*, as well as some *Alphaproteobacteria*, *Firmicutes* and *Bacteriodetes*. However, large proliferating *C. elegans* populations were associated specifically with habitats enriched in *Enterobacteriaceae* or *Acetobacteriaceae* (*Alphaprotebacteria*) species. Whereas *Enterobaceteriaceae* are also abundant inside worm guts (see below), *Acetobacteriaceae* are not, suggesting either that they can support *C. elegans* growth without colonization, similar to food *E. coli*, or that they function as

Figure 1



C. elegans and its commensals—interactions and contributions. Summarized are interactions and contributions identified for *C. elegans* commensals, as well as nutrients and metabolite mediators (mostly identified in *E. coli* but potentially relevant for interactions with commensals). Also listed are environmental commensals (black) and gut commensals (red), which positively affect worm proliferation.