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Mechanisms of host seeking by parasitic nematodes

Spencer S. Gang, Elissa A. Hallem*

Department of Microbiology, Immunology, and Molecular Genetics and Molecular Biology Institute, University of California, Los Angeles, Los Angeles, CA 90095, United States

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ABSTRACT

The phylum Nematoda comprises a diverse group of roundworms that includes parasites of vertebrates, invertebrates, and plants. Human-parasitic nematodes infect more than one billion people worldwide and cause some of the most common neglected tropical diseases, particularly in low-resource countries [1]. Parasitic nematodes of livestock and crops result in billions of dollars in losses each year [1]. Many nematode infections are treatable with low-cost anthelmintic drugs, but repeated infections are common in endemic areas and drug resistance is a growing concern with increasing therapeutic and agricultural administration [1]. Many parasitic nematodes have an environmental infective larval stage that engages in host seeking, a process whereby the infective larvae use sensory cues to search for hosts. Host seeking is a complex behavior that involves multiple sensory modalities, including olfaction, gustation, thermosensation, and humidity sensation. As the initial step of the parasite-host interaction, host seeking could be a powerful target for preventative intervention. However, host-seeking behavior remains poorly understood. Here we review what is currently known about the host-seeking behaviors of different parasitic nematodes, including insect-parasitic nematodes, mammalian-parasitic nematodes, and plant-parasitic nematodes. We also discuss the neural bases of these behaviors.

1. Host seeking by entomopathogenic nematodes

Entomopathogenic nematodes (EPNs) in the genera *Heterorhabditis* and *Steinernema* are parasites that infect and kill insects. EPNs are known as “beneficial nematodes” because they infect a wide variety of insect pests and disease vectors, and are used commercially throughout the world for biocontrol. EPNs are of interest not only as biocontrol agents, but also as models for understanding human-parasitic nematodes. EPNs are broadly distributed geographically, having been found on every continent except Antarctica [2]. Most EPNs, including many species commonly used for biocontrol such as *Steinernema carpocapsae* and *Heterorhabditis bacteriophora*, are generalists that are capable of infecting and killing many different insect species (Fig. 1A). However, some EPNs are specialists that primarily target a single type of insect [2]. For example, *Steinernema scapterisci* targets mole crickets [3] and *Steinernema diaprepesi* targets the larval stages of the root weevil *Diaprepes abbreviates*, a citrus pest [4].

1.1. Life cycle of EPNs

EPNs are infective during a particular life stage called the infective juvenile (IJ), alternatively described as the infective third-stage larva (L3i). IJs invade insect hosts by entering through an orifice such as the mouth or spiracles, or by penetrating through the cuticle [5]. The IJs contain a bacterial endosymbiont in their gut, and upon host entry they deposit their symbiotic bacteria into the insect. The worms and bacteria rapidly kill the insect, typically within 48 h of host entry. The worms grow and reproduce inside the insect cadaver, feeding off bacteria and cadaver tissue until food sources are depleted. New IJs then form and disperse into the environment to search for new hosts (Fig. 1B) [5].

1.2. Host-seeking strategies of EPNs

The host-seeking strategies of EPN species are typically described as varying along a continuum ranging from ambushing, in which the IJs remain relatively stationary and latch on to passing hosts, to cruising, in which the IJs disperse in search of hosts [6]. Ambushers often nictate, where the IJ stands on its tail and waves to facilitate attachment to passing hosts. Some ambushing *Steinernema* species also jump, where the IJ stands on its tail, curls, and propels itself into the air [6]. In general, ambushers are most effective at targeting motile hosts, while cruisers are most effective

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* Correspondence to: UCLA MIMG, 237 BSRB, 615 Charles E. Young Dr. E, Los Angeles, CA 90095, United States.

E-mail addresses: sgang@ucla.edu (S.S. Gang), ehallem@microbio.ucla.edu (E.A. Hallem).

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A Ecology of select nematode species

Nematode	Common Name	Infection route	Common host(s)
Caenorhabditis elegans	n/a	free-living	none
Steinernema carpocapsae	n/a	active invasion	insect
Heterorhabditis bacteriophora	n/a	active invasion	insect
Ancylostoma caninum	hookworm	skin-penetration	dog, fox, cat
Ancylostoma duodenale	hookworm	skin-penetration	human
Necator americanus	hookworm	skin-penetration	human
Nippostrongylus brasiliensis	hookworm	skin-penetration	rat
Strongyloides stercoralis	threadworm	skin-penetration	human, primate, dog
Strongyloides ratti	threadworm	skin-penetration	rat
Haemonchus contortus	barber's pole worm	passive ingestion	ruminants
Ascaris lumbricoides	giant roundworm	passive ingestion	human

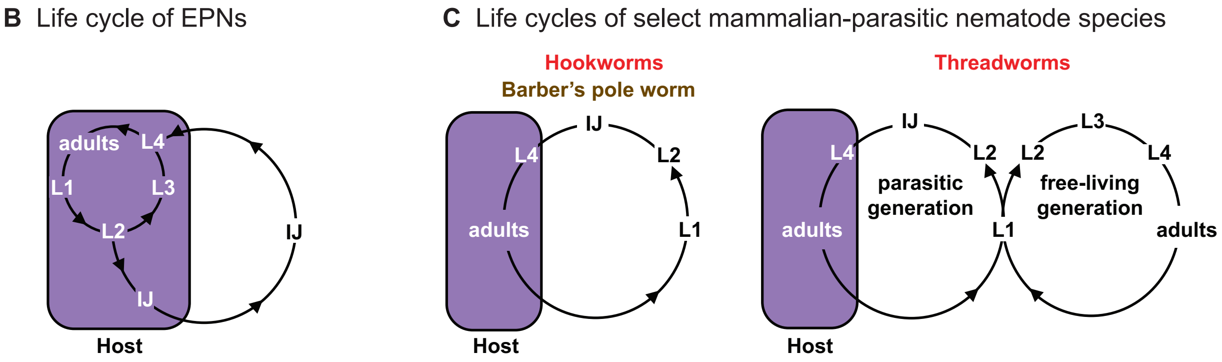

Fig. 1. Ecology and life cycles of parasitic nematodes. A. Ecology of select nematode species, with common hosts indicated [28,29,31,96–98]. Green = free-living, blue = entomopathogenic, red = skin-penetrating, brown = passively ingested. B. The life cycle of EPNs. EPN infective juveniles (IJs) infect by invasion through orifices or by penetration of the cuticle. The IJs and their associated bacteria rapidly kill the host. The nematodes develop and reproduce within the host cadaver for a number of generations, where they feed on bacteria in the insect body and the cadaver tissue. Once resources in the cadaver are exhausted, IJs emerge and search for a new host to infect [96]. C. Life cycles of mammalian-parasitic nematodes. Hookworms infect by skin penetration or orally. Inside the host, hookworms develop into adults that reproduce in the small intestine. Eggs are excreted with the host's feces and develop into IJs. IJs leave the feces in search of new hosts. Hookworms must infect a new host every generation [99]. Threadworms of the *Strongyloides* genus have a similar life cycle but can develop through a limited number of free-living generations outside the host. Some of the eggs excreted with the host's feces develop into IJs, while others develop into free-living adults that mate outside the host [28]. The life cycle outside the host of the barber's pole worm *Ha. contortus* is similar to that of hookworms, except that the IJs enter the host only by passive ingestion [97]. For B-C, L1-L4 are the first through fourth larval stages. For some parasitic nematode species IJs are alternatively described as infective third-stage larvae (L3i). Figures are adapted from Castelletto et al. (2014) [26].

at targeting non-motile hosts [7]. However, recent studies suggest that many species are capable of engaging in either ambushing or cruising depending on the environmental context. For example, although *Ste. carpocapsae* is generally considered a classical ambusher, it moves more in peat than sandy soil, suggesting that it can ambush or cruise depending on its environment [8]. The extent to which *Ste. carpocapsae* moves in the soil also depends on which insect hosts are present [7,9]. In addition, all EPN species examined so far exhibit robust chemotaxis in the presence of insect-derived odorants [10,11]. Thus, most EPNs appear to be capable of cruising toward host-emitted sensory cues under at least some conditions.

1.3. Responses of EPNs to olfactory cues

A number of studies have demonstrated that EPNs use olfactory cues to locate hosts to infect. IJs are attracted to the odor blends emitted by live insects and to a diverse array of insect-emitted odorants, including carbon dioxide (CO_2) (Fig. 2A–B) [10–15]. CO_2 is an essential host cue for EPNs: attraction to insect odor blends is greatly reduced or eliminated when CO_2 is removed (Fig. 2C) [11,12]. Jumping in *Steinernema* is stimulated by insect odor blends, CO_2, and host-specific odorants [10,11,16]. EPNs are also attracted to volatile components of insect feces [17]. A large-scale comparative analysis of olfactory behaviors across species revealed that different EPN species respond differently to odorants [10,11]; thus, EPNs appear to have specialized olfactory systems that contribute to host selection.

EPNs also respond to odorants emitted by insect-damaged plants [18]. For example, the odorant (E)-β-caryophyllene is released by maize roots in response to insect feeding and attracts the EPN *Heterorhabditis megidis* [19]. Similarly, *Ste. diaprepesi* is attracted to volatiles released by plant roots that have been damaged by its host *D. abbreviates* [4]. CO_2 acts synergistically with root volatiles to attract EPNs [18]. Thus, EPNs appear to use CO_2, insect odorants, and plant odorants to find insects to infect.

1.4. Responses of EPNs to other sensory cues

In addition to responding to olfactory cues, EPNs respond to a number of other sensory cues that may contribute to host seeking. For example, EPNs have been shown to aggregate at temperatures that approximate insect body temperature, which is slightly (<1 °C) above ambient temperature due to insect metabolic processes [20]. EPNs also respond to salt gradients. *Ste. carpocapsae* IJs can navigate in gradients of Na^+, Mg^{2+}, Ca^{2+}, $CO_3{}^{2-}$, and Cl^- and accumulate at different preferred concentrations for each ion [21]. EPNs also respond to electric fields, magnetic fields, vibration, and mechanical stimulation [22–26]. These other sensory responses are presumed to facilitate environmental navigation and/or host finding.