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Chemosensory behaviors of parasites

Keely E. Chaisson and Elissa A. Hallem

Department of Microbiology, Immunology, and Molecular Genetics, University of California, Los Angeles Los Angeles, California 90095, USA

Abstract

Many multicellular parasites seek out hosts by following trails of host-emitted chemicals. Host seeking is characteristic of endoparasites such as parasitic worms as well as ectoparasites such as mosquitoes and ticks. Many of these parasites use carbon dioxide (CO₂), a respiration byproduct, in combination with host-specific chemicals for host location. Recent work has begun to elucidate the behavioral responses of parasites to CO₂ and other host chemicals, and to unravel the mechanisms of these responses. Here we discuss recent findings that have greatly advanced our understanding of the chemosensory behaviors of host-seeking parasites. We focus primarily on well-studied parasites such as nematodes and insects, while also noting broadly relevant findings in a few less well-studied parasites.

Keywords

parasitic helminths; nematode; entomopathogenic nematodes; EPN; olfaction; ectoparasite; mosquito; chemosensation; host seeking

Chemosensory behaviors of parasitic helminths

Parasitic helminths comprise a large group of worms from a number of different phyla, including roundworms in the phylum Nematoda and flatworms in the phylum Platyhelminthes. Some parasitize humans, while others parasitize non-human animals or plants. Human-parasitic species cause extensive morbidity, mortality, and economic loss worldwide, and are responsible for some of the most common neglected tropical diseases [1]. Parasitic helminths utilize a number of different strategies for host infection: (i) reliance on passive host ingestion, (ii) transmission by intermediate vectors such as mosquitoes and flies, and (iii) engagement in active host-seeking and host-invasion behaviors. The latter group consists of some of the most devastating human-parasitic worms, including the skin-penetrating intestinal nematodes *Strongyloides stercoralis*, *Ancylostoma duodenale* and *Necator americanus*, as well as blood flukes in the genus *Schistosoma*. For parasitic worms that actively seek out hosts, chemosensation is a critical sensory modality, allowing the parasites to recognize appropriate hosts by detecting host-emitted chemicals.

Parasitic nematodes

The most well-studied of the helminths are the nematodes, which comprise a large and highly diverse phylum that includes both free-living species such as the model nematode *Caenorhabditis elegans* and parasitic species. Human parasitic nematodes infect over a quarter of the world's population, and nematode parasites of livestock and plants cause economic and agricultural losses of billions of dollars each year [1,2]. The infective stages of many parasitic nematodes are developmentally-arrested larval stages that actively seek out hosts in which to complete their life cycles. The group of nematodes that host seek includes insect parasites, plant parasites, and skin-penetrating mammalian parasites.

The entomopathogenic nematodes (EPNs) comprise a guild of lethal parasites of insects that are of interest both as models for human parasitic nematodes and as biocontrol agents for a wide variety of insect pests and disease vectors. EPN infective juveniles (IJs) infect insect hosts either by entering through a natural body opening or by penetrating directly through the insect cuticle. EPNs rapidly kill their host, develop and reproduce inside the host cadaver until resources are depleted, and then exit as IJs to search for new hosts (Figure 1a–b). EPNs vary greatly in their host ranges; for example, *Steinernema carpocapsae* is a generalist that can infect over 250 different insect species under laboratory conditions, while *Steinernema scapterisci* is an orthopteran specialist whose only known natural host is the mole cricket [3]. EPN infective juveniles (IJs) are strongly attracted to live hosts, as well as carbon dioxide (CO₂) and a wide variety of other host-derived volatiles (Figure 1c) [4–6]. Attraction to live insect hosts is greatly diminished in the absence of CO₂, indicating that CO₂ is an essential host-seeking cue for these parasites [5, 6]. In addition to chemotaxing toward hosts, some EPNs in the genus *Steinernema* exhibit jumping, a highly specialized host-seeking behavior in which the IJ springs into the air and onto passing hosts [7]. *Steinernema* IJs jump in response to complex odor blends emitted by live hosts, as well as CO₂ and many individual host-derived odorants [5, 6].

A comparison of the odor response profiles of *Heterorhabditis bacteriophora* and *Steinernema carpocapsae* IJs with *C. elegans* dauer larvae, which are analogous life stages, revealed that the parasitic species cluster together despite their phylogenetic distance (Figure 1d) [5]. This suggests an important role for chemosensation in the evolution of host range among EPNs. In future studies, it will be interesting to extend this type of comparison to include many more free-living and parasitic nematode species – including species with very different lifestyles, ecological niches, and host-seeking strategies – to better understand the relationship between ecology and chemosensory behavior. It will also be interesting to examine the relationship between chemosensory behavior and the evolution of proteins required for chemosensation, such as G protein-coupled receptors, G proteins, and guanylate cyclases.

In addition to responding to host-derived chemicals, EPNs respond to a number of other ecologically relevant chemical cues. For example, EPNs are attracted by odorants produced by insect-damaged plants as an indirect defense against predation [8–10]. However, some of the plant volatiles that attract EPNs also attract plant parasitic nematodes, suggesting an ecological cost to this plant defense mechanism [11]. EPNs also respond to ascarosides, a

large family of small-molecule pheromones that regulate reproductive diapause as well as mating, aggregation, and chemotaxis behaviors in nematodes [12–16].

Skin-penetrating mammalian-parasitic nematodes such as the human threadworm *Strongyloides stercoralis* and the human hookworms *Necator americanus* and *Ancylostoma caninum* also engage in host-seeking and host-invasion behaviors. These nematodes are passed out of an infected host as eggs or newly hatched larvae in infested feces, develop into infective larvae in the feces, and then migrate into the environment in search of new hosts [17]. Infection of new hosts occurs by skin penetration, primarily through the skin of the feet [17]. Many mammalian-parasitic nematodes have highly specific host ranges. For example, *Strongyloides fuelleborni kellyi* is an exclusive parasite of humans, and *Strongyloides ratti* is a natural parasite of rats but not of other rodents [17, 18]. Chemosensation is thought to be an important component of host specificity: *S. stercoralis* is attracted to mammalian skin extract [19], and the closely related rat parasite *S. ratti* is attracted to some components of mammalian sera [20]. For *S. stercoralis*, a major component of skin attraction is the odorant urocanic acid, which is found in the skin of many mammals and is a potent attractant even at low concentrations [19]. Both *S. stercoralis* and *S. ratti* also navigate through sodium chloride gradients [21, 22]. Like the *Strongyloides* species, the dog hookworm *Ancylostoma caninum* is attracted to hydrophilic extracts of dog skin [23]. CO₂ causes activation of *A. caninum* and *S. stercoralis*, and stimulates nictation (tail standing) behavior in *A. caninum* [23, 24]. In contrast to *A. caninum* and the *Strongyloides* species, chemoattraction to human skin has not been demonstrated for the human hookworms *Necator americanus* and *Ancylostoma duodenale* [25]. However, these species do display activation (increased locomotion) and penetration behaviors in response to chemosensory cues present in skin extract [26].

The fact that human hookworms have not been shown to display long-range host attraction is consistent with their foraging strategy: the infective larvae are thought to spend most of their time motionless, waiting for passing hosts [24, 26]. By contrast, *Strongyloides* species spend most of their foraging time actively searching for hosts [24]. This difference in foraging strategy is similar to the cruiser/ambusher distinction among EPNs: some EPNs are cruisers that actively chemotax through the soil searching for hosts, while others are ambushers that are thought to remain relatively stationary and primarily infect passing hosts [27]. However, ambushing EPNs are in fact capable of chemotaxing toward a wide variety of insect-derived odorants as well as live insects [5, 6], although they display less robust host attraction than cruising EPNs [6]. This suggests that ambushing EPNs exhibit long-range host seeking in response to appropriate chemosensory cues. The chemotaxis behavior of human hookworms has not been as thoroughly examined, so whether they are also capable of long-range host attraction is not yet clear.

Plant-parasitic nematodes use CO₂ in combination with soluble and volatile host-specific chemicals to locate the roots of host plants [4, 11, 28]. In the case of the root-knot nematodes *Meloidogyne incognita* and *Meloidogyne graminicola*, infective larvae are attracted to host plants but show little or no attraction to non-host plants [28]. Moreover, when given a choice between a short route and a long route to reach a host plant, nematodes preferentially choose the short route; however, nematodes often travel the long route to reach

a non-host plant. Thus, plant-parasitic nematodes respond differently to chemical blends produced by hosts versus non-hosts [28].

A number of other nematode parasites also display chemosensory behaviors. One example is the gastropod parasitic nematode *Phasmarhabditis hermaphrodita*. *P. hermaphrodita* shows attraction to mucosal extracts from slugs, indicating that it uses chemosensory cues to locate slug hosts [29–31]. However, attraction of *P. hermaphrodita* to potential hosts does not correlate with reproductive success inside the host, suggesting that other factors play an important role in host selection [30]. By contrast, the response of *Steinernema carpocapsae* to host volatiles following exposure to host cuticle is positively correlated with both host mortality and parasite reproduction inside the host, suggesting that at least some EPNs use chemosensory cues for host selection [32]. Thus, although *P. hermaphrodita* and *S. carpocapsae* have apparently similar life styles – both are lethal parasites of small invertebrates that engage in host seeking – the two species appear to rely on different mechanisms for appropriate host selection.

Insight into the cellular and molecular mechanisms underlying chemosensation in parasitic nematodes has come largely from studies of the free-living model nematode *C. elegans*. Despite profound differences in body size and lifestyle among nematodes, sensory neural anatomy and function are highly conserved across species [33]. Thus, many of the neural circuits and signaling pathways that operate in *C. elegans* are likely to operate similarly in parasitic nematodes. *C. elegans* shows directional chemotaxis in response to volatile chemicals such as alcohols, esters, and aldehydes; soluble chemicals such as salts and pheromones; and gases such as oxygen (O₂) and CO₂ [34]. Olfactory and gustatory responses are mediated primarily by neurons located in the main chemosensory organs of *C. elegans*, the paired amphid sensilla [34], while responses to O₂ and CO₂ are mediated by a distributed network of head and tail neurons [35–39]. Chemoreceptor genes in *C. elegans* are encoded by large families of G protein coupled receptors (GPCRs) and guanylate cyclases (GCs) [34]. Specific receptors have been identified for a few chemicals, including O₂ [35, 40], ascarosides [41,42], and the odorant 2,3-butanedione [43]. The CO₂ receptor has not yet been identified, although the receptor guanylate cyclase GCY-9 is required for CO₂ response and may be a receptor for CO₂ or a CO₂ metabolite [39, 44].

In parasitic nematodes, chemosensory neuron function has been investigated in only a few cases. As in *C. elegans*, the amphidial ASE and ASH sensory neurons of *S. stercoralis* mediate chemoattraction and chemorepulsion to soluble chemicals, respectively [21, 45]. In addition, the BAG sensory neurons mediate CO₂ repulsion by *C. elegans* adults and CO₂ attraction by *C. elegans* dauers and EPN IJs, demonstrating that the neural basis of CO₂ response is at least partly conserved across species regardless of whether CO₂ is a repulsive or attractive cue [5, 37]. The molecular basis of chemoreception in parasitic nematodes has not yet been investigated. However, recent breakthroughs in the development of techniques for stable genetic transformation of *S. stercoralis* and *S. ratti* [46, 47] should enable new avenues of research into the molecular mechanisms that underlie chemosensation in these parasites.

Parasitic trematodes

Trematodes comprise a class of parasitic flatworms in the phylum Platyhelminthes. Trematodes in the genus *Schistosoma* are skin-penetrating parasites of mammals, commonly known as blood flukes [48]. Over 200 million people are estimated to be infected with human parasitic schistosomes, which cause the disease schistosomiasis [1]. Schistosomes have complex life cycles involving two host species, one of which is a mollusk and the other a vertebrate (Figure 2) [49]. During one phase of the life cycle, infective larvae called miracidia infect a molluscan host; during a different phase of the life cycle, infective larvae called cercariae infect a vertebrate host [49]. In contrast to human parasitic nematodes, which typically have very specific host ranges, some human parasitic schistosomes have broad host ranges. For example, *Schistosoma mansoni* infects humans, non-human primates, and rodents, and *S. japonicum* infects humans, cattle, dogs, pigs, rodents, and a number of other mammals [48].

Both molluscan-parasitic miracidia and vertebrate-parasitic cercariae demonstrate hostseeking behaviors in response to chemosensory cues (Figure 2). Within 1–3 hours of hatching, miracidia of many species exhibit long-range dispersal behaviors in which the larvae use phototactic and geotactic cues to migrate to snail habitats; during this time, miracidia appear to be insensitive to host chemosensory cues [49]. After 1–3 hours, miracidia exhibit short-range host-seeking behaviors and are capable of responding to snail-secreted chemicals [49]. Response to snail-derived odor clouds increases miracidial transmission success, confirming an important role for chemosensation in the host infection process [50]. The snail-derived cues that attract miracidia are not fully understood but are thought to include amino acids, fatty acids, ammonia, and a number of different glycoproteins [49].

Cercariae also rely on chemosensory cues for host finding and host invasion. For example, many schistosome cercariae are attracted to skin-derived chemicals such as fatty acids and amino acids; many of the same cues stimulate skin attachment and penetration behaviors [51, 52]. *S. mansoni* cercariae respond to ceramides, a class of lipids found on the outermost layer of human skin, with prolonged skin attachment [53]. Following infection, *S. mansoni* cercariae use chemosensory cues to migrate within host tissue [54]. In addition to schistosomes, other trematodes also engage in host-seeking behaviors, although the responses of these species to host chemosensory cues are less well understood [52].

Chemosensory behaviors of ectoparasites

Many ectoparasites rely on chemosensory cues to locate hosts and mates, select oviposition sites, and find food sources [55]. This includes ectoparasitic insects such as mosquitoes, bed bugs, kissing bugs, and tsetse flies, as well as non-insect invertebrates such as ticks. Ectoparasites that target humans transmit diseases such as malaria, dengue virus, West Nile virus, yellow fever, filariasis, trypanosomiasis, and leishmaniasis [55]. A better understanding of the chemosensory cues that attract and repel these parasites is therefore of great interest for the development of specific and effective traps and repellents.

Mosquitoes

Many mosquitoes track hosts over long distances – in some cases, as far as 70 meters – using host-emitted chemosensory cues [55, 56]. The anthropophilic species *Anopheles gambiae*, which transmits malaria, and *Aedes aegypti*, which transmits dengue and yellow fever, target human hosts using CO₂ in combination with human skin and sweat odorants such as ammonia, lactic acid, and other carboxylic acids [55, 56]. The behavioral responses to human skin and sweat odorants are highly concentration- and mixture- dependent: some odorants are attractive only in combination with other odorants and at specific concentrations [57]. Odorants emitted by skin microbiota also attract *An. gambiae* [58] and enhance the effectiveness of traps containing human-derived odorants in some cases [59, 60]. In contrast to *An. gambiae* and *Ae. aegypti*, which specifically target humans, other species have much broader host ranges. For example, *Culex quinquefasciatus* blood-feeds from a broad range of mammalian and avian hosts and locates hosts using CO₂ in combination with host odorants such as nonanal, which is secreted by both birds and mammals [61]. CO₂ is critical for the long-range host-seeking behaviors of at least some mosquito species. For example, a brief encounter with CO₂ but not skin odors induces a rapid upwind flight surge in *Ae. aegypti* [62], and exposure of *Ae. aegypti* and *Cx. quinquefasciatus* to odorants that block CO₂-sensing neurons impairs their ability to locate hosts [63].

After a blood meal, female ectoparasitic mosquitoes seek out suitable aquatic environments in which to lay eggs. The host-seeking behavior of female mosquitoes is inhibited following a blood meal and a distinct but overlapping set of olfactory cues is used to locate oviposition sites [64–66]. In *An. gambiae* females, responses to indole and phenolic compounds are increased and responses to ammonia are decreased following a blood meal [66, 67]. Gravid *Culex* mosquitoes are attracted to the oviposition site odorants trimethylamine, nonanal, and 3-methylindole, and a synthetic blend of trimethylamine and nonanal was an effective trap for gravid females in field studies [65]. The changes in olfactory behavior that occur after blood feeding are at least partly a result of changes in the peripheral olfactory organs: the odor sensitivities of some olfactory neurons and the expression levels of some odorant receptors are altered following a blood meal [64, 66–68].

The primary olfactory organs of mosquitoes are the antennae and maxillary palps [55]. The surfaces of these organs are covered with sensory hairs called sensilla, which house the dendrites of the olfactory receptor neurons (ORNs); each sensillum contains the dendrites of one or a small number of ORNs. Electrophysiological recordings from mosquito ORNs have demonstrated that individual ORNs are tuned to overlapping subsets of odorants, and respond strongly to many odorants that are known host-seeking and oviposition cues [55]. Odorant detection in mosquitoes and other insects is mediated by members of the odorant receptor (OR), ionotropic glutamate receptor (IR), and gustatory receptor (GR) families [55, 69, 70]. Insect odorant receptors have been most thoroughly characterized in the model organism, *Drosophila melanogaster*. In *D. melanogaster*, each receptor is expressed in a small subset of ORNs, with a few exceptions [55, 71]. Members of both the OR and IR families function as odorant-gated heteromeric cation channels; in most cases, the channel consists of one ligand-specific receptor and one more broadly expressed co-receptor [71–

75]. Many of the ORs are broadly tuned to acetate esters, alcohols, and ketones [76]. By contrast, IRs are more narrowly tuned to carboxylic acids and amines [71, 75].

Large-scale functional analyses of the *An. gambiae* OR family using both *in vivo* and heterologous expression systems revealed that many AgORs are strongly tuned to host and oviposition attractants such as 4-methylphenol, indole, and 1-octen-3-ol [77–79] (Figure 3a). To functionally compare the odorant receptor repertoires of *An. gambiae* and *D. melanogaster*, multidimensional odor spaces were constructed for each species in which each axis of the space corresponds to the responses conferred by a single OR in spikes/sec. A comparison of *An. gambiae* and *D. melanogaster* odor space revealed that esters are more widely distributed in *D. melanogaster* odor space and aromatics are more widely distributed in *An. gambiae* odor space (Figure 3b). Thus, the electrophysiological responses evoked by different esters differ more for *D. melanogaster* than *An. gambiae*, while the opposite is true for aromatics. These results suggest that mosquitoes may be better than fruit flies at discriminating among aromatics, some of which are emitted by human hosts, while fruit flies may be better at discriminating among esters, some of which are emitted by fruits [77].

A number of ORs from other mosquito species that respond to host and oviposition attractants have also been characterized [55, 80, 81]. The mosquito IRs are less well characterized, although the *An. gambiae* IR AgIR76b was found to mediate behavioral responses to butylamine in mosquito larvae [82]. Given that many of the *D. melanogaster* IRs are tuned to odorants known to be important for mosquito host seeking such as carboxylic acids and amines [71, 75], a functional analysis of the mosquito IR repertoire will be of great interest.

CO₂ reception in many insects is mediated by conserved members of the GR family: Gr21a and Gr63a function as CO₂ receptors in *D. melanogaster*, and three orthologs of these receptors function as CO₂ receptors in mosquitoes and a number of other insects [83–86]. In *D. melanogaster*, the CO₂ receptors are expressed in a specific class of antennal neurons; in mosquitoes, the CO₂ receptors are expressed in maxillary palp neurons. The recent finding that certain odorants can interfere with CO₂ receptor activation and disorient mosquitoes [63, 87] suggests that CO₂ receptors may be powerful targets for mosquito control strategies. Accessory olfactory proteins such as odorant binding proteins (OBPs) also contribute to olfactory responses [55] and are likely to be useful targets for insect control. Interestingly, dengue virus was recently shown to increase the expression of some OBPs as well as a number of other olfactory proteins, raising the possibility that the virus might enhance mosquito blood-feeding or hostseeking behaviors [88].

Other ectoparasites

Other ectoparasitic insects and non-insect invertebrates locate hosts using many of the same volatile cues as mosquitoes. For example, human-parasitic ticks, bed bugs, kissing bugs, and tsetse flies are attracted to host odorants such as CO₂, 1-octen-3-ol, indole, lactic acid, and 4-methylphenol [89–98]. For some ectoparasites, such as the fish louse *Argulus coregoni*, the role of olfaction in host-seeking behavior is developmental stage specific: young *A. coregoni* rely primarily on visual cues for host location, while adult *A. coregoni* rely on a

combination of visual and olfactory cues [99]. Other species, such as the hedgehog parasitic tick *Ixodes hexagonus*, rely on subtle differences in host odor profiles for host selection. *I. hexagonus* is more attracted to the odor of sick hedgehogs than healthy hedgehogs and is more likely to parasitize sick hedgehogs [100]. The molecular basis of olfaction in many of these ectoparasites remains largely unexplored and will be an interesting avenue for future research.

Concluding remarks and future directions

A consistent theme across species that engage in host seeking is the reliance on a combination of general and specific host sensory cues. General cues typically include CO₂ as well as nonchemosensory stimuli such as heat, while specific host cues are often a unique blend of host-derived odorants. The requirement for general versus specific cues varies greatly for different parasites, different parasite-host combinations, and different host-seeking behaviors. For example, the universal cue CO₂ is sufficient to elicit hostseeking behaviors from EPNs [5, 6]. However, removing CO₂ from the host odor blend abolishes attraction to some hosts but not others, indicating that the requirement for general versus specific host cues is host-dependent [5, 6]. Parasites also differ in whether they rely on CO₂ for long-range versus short-range host-seeking behaviors. For example, in the case of *Cx. quinquefasciatus*, CO₂ is more important for long-range host-seeking behavior, while host-specific odorants are more important for short-range landing behavior [101]. Similarly, *Steinernema carpocapsae* requires CO₂ for long-range chemotaxis but not short-range jumping to waxworm odor [5]. By contrast, CO₂ is a short-range activation cue for human hookworms in combination with warmth and/or moisture [25]. Thus, although general host cues such as CO₂ are used by many parasites, the ways in which they are used for host seeking are often species-specific.

An important direction for future research will be to further investigate the extent to which chemosensory behavior contributes to host selection and the evolution of host specificity. Appropriate host selection is critical for endoparasites: many species have narrow host ranges, and infection of a non-host or dead-end host is often fatal. For a few parasites, attraction to host-derived chemicals has been shown to correlate with host suitability. For example, *Steinernema carpocapsae* is more attracted to hosts that support higher levels of mortality and parasite reproduction [32]. In the case of the human parasitic trematode *Schistosoma haematobium*, the miracidia are more attracted to hosts than sympatric nonhosts but are unable to discriminate hosts from allopatric non-hosts, suggesting that their chemosensory preferences have evolved to facilitate host selection [102]. However, for both species, long-range chemosensory behavior is not sufficient to ensure appropriate host selection: *Steinernema carpocapsae* is also attracted to non-host isopods [6], and the preference of *Schistosoma haematobium* miracidia for hosts over sympatric nonhosts is not absolute [102]. This suggests either that these parasites sometimes attempt to infect poor hosts, that host selection is further refined by host recognition and penetration behaviors, or both. Further work will be necessary to distinguish between these possibilities, and to investigate the relationship between host attraction and host suitability in other parasites.

Recent progress in understanding the behavioral responses to host odor cues and the mechanisms that underlie these responses has already led to the design of more specific and effective parasite control strategies. In the case of *An. gambiae*, the discovery that human skin microbiota play an important role in host seeking [58] led to the finding that the addition of some skin microbiota-derived odorants enhance the effectiveness of existing traps [59, 103], and the large-scale decoding of the AgOR repertoire [77] led to the finding that some of the odorants that strongly activate AgORs can increase trap effectiveness [104]. In addition, a better understanding of insect odorant receptor function led to the finding that the broad-spectrum insect repellent DEET directly modulates the odorant receptor complex [105], paving the way for future studies aimed at designing alternative insect repellents. The odor-driven behaviors of human endoparasites are much less well understood, but the possibility of developing chemically-baited traps or repellents for these parasites based on knowledge of the function and organization of their chemosensory systems is an exciting avenue for future research. Finally, a comparison of odorants that are attractants for different parasites reveals that many of the chemosensory cues that elicit host-seeking behaviors are conserved across phyla (Figure 4), raising the possibility that traps could be designed that target multiple phylogenetically diverse species of parasites. Multicellular parasites are a major cause of disease worldwide, and a better understanding of how they respond to host chemical cues at the molecular and cellular level should greatly facilitate the development of more effective control strategies.

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Figure 1. Chemosensory responses of entomopathogenic nematodes (EPNs)

(a) Life cycle of EPNs. EPN IJs infect insect larvae either by entering through a natural body opening or by penetrating through the insect cuticle. IJs are associated with symbiotic bacteria, which they deposit into the host. The bacteria play an important role in overcoming the insect immune system. The nematodes develop and reproduce in the host cadaver for a few generations, feeding off the bacteria and digested insect tissue. New IJs then form and exit the cadaver to search for new hosts [106]. (b) IJs exiting a *Galleria mellonella* cadaver. Arrowhead indicates a clump of IJs; arrow indicates a single IJ. (c) The behavioral responses of *H. bacteriophora* IJs, *S. carpocapsae* IJs, and *C. elegans* dauers to the indicated odorants in a chemotaxis assay. The chemotaxis index ranges from 1 (perfect attraction) to -1 (perfect repulsion). Responses are color-coded according to the color scale on the lower right. (d) The odor response profiles of the EPNs are more similar to each other than to that of *C. elegans* despite their phylogenetic distance. Left, behavioral dendrogram of olfactory responses across species. Behavioral distance is based on the Euclidean distances between

species based on their odor response profiles. Right, phylogenetic neighbor-joining tree. Branch lengths in the phylogenetic tree are proportional to genetic distances between taxa. Reprinted from [5] with permission. Abbreviations: EPNs, entomopathogenic nematodes; IJs, infective juveniles.

Figure 2. Representative schistosome life cycle

Eggs are passed in the urine or feces of the vertebrate host [49]. In the environment, the eggs hatch and release miracidia. Miracidia seek out snail hosts using temperature, gravity, light, and chemosensory cues; they then penetrate the snail. After multiple rounds of asexual reproduction in the snail, cercariae emerge from the snail and disperse. Cercariae orient themselves in the water column using temperature, gravity, and light [49]. When vertebrate hosts enter the water near cercariae, host skin compounds such as fatty acids and amino acids as well as warmth attract cercariae to the host and stimulate sustained attachment to and penetration of the host's skin [49, 51, 53]. Within the host, cercariae use chemical gradients to guide migration to the intestines or bladder, pair, reproduce sexually, and lay eggs [54]. Some of the host-derived chemical cues for miracidia and cercariae are shown in red [49, 51–53].

A Odor response profiles of the AgOR repertoire

B A comparison of *An. gambiae* and *D. melanogaster* odor space

Figure 3. Odor coding by the *An. gambiae* AgOR repertoire

(a) Responses of AgORs to 110 odorants using the *D. melanogaster* ‘empty neuron’ system [76] for receptor decoding. The ‘empty neuron’ consists of an antennal olfactory neuron that lacks its endogenous odorant receptors. Odorant receptors of interest can be ectopically expressed in the ‘empty neuron’, and their odor responses can then be determined by single-unit electrophysiology [76]. AgOR response intensities are color-coded according to the scale on the right. (b) A comparison of *An. gambiae* and *D. melanogaster* odor space. For each species, the odor space is an n -dimensional space in which each axis represents the

responses of one receptor in spikes/s, and n represents the total number of receptors tested. Each tested odorant was mapped to a particular position in this space based on the electrophysiological responses it elicited from each receptor in the 'empty neuron' system. To generate the graphs, principal component analysis was used to represent the n -dimensional odor spaces in three dimensions; the axes of the graphs correspond to the first three principle components. Left, *An. gambiae* odor space. Right, *D. melanogaster* odor space. Aromatics are more widely distributed in *An. gambiae* odor space, and esters are more widely distributed in *D. melanogaster* odor space. This suggests that mosquitoes may be better than fruit flies at discriminating among aromatics, some of which are emitted by human hosts, while fruit flies may be better at discriminating among esters, some of which are emitted by fruits. Reprinted from [77] with permission.

Odorant	Chemical Structure	Parasite	Source	References
acetone		kissing bugs tsetse flies ticks	human skin mammalian breath	[6, 57, 89, 92, 94, 97]
ammonia		mosquitoes kissing bugs schistosomes	human skin human sweat	[49, 55, 56, 57, 93]
carbon dioxide	$O=C=O$	mosquitoes kissing bugs tsetse flies bed bugs ticks EPNs human hookworms human threadworms	mammalian breath aerobic respiration	[4, 5, 6, 23, 24, 26, 55, 56, 62, 89, 93, 97, 101]
carboxylic acids		mosquitoes kissing bugs tsetse flies bed bugs ticks EPNs human hookworms human threadworms schistosomes	mammalian skin mammalian sweat rumen fluid	[4, 5, 19, 26, 49, 51, 52, 56, 57, 92, 93, 94, 95, 98]
indole		mosquitoes tsetse flies ticks	human sweat rumen fluid mosquito oviposition sites	[61, 92, 100]
lactic acid		mosquitoes kissing bugs bed bugs	human skin human sweat	[55, 56, 57, 93, 94, 95]
3-methylindole (skatole)		mosquitoes tsetse flies	human sweat animal feces rumen fluid mosquito oviposition sites	[61, 65, 92]
4-methylphenol		mosquitoes tsetse flies	human sweat rumen fluid mosquito oviposition sites	[6, 55, 97]
nonanal		mosquitoes kissing bugs EPNs	human skin human sweat birds mosquito oviposition sites	[5, 61, 65, 93]
1-octen-3-ol		mosquitoes kissing bugs tsetse flies ticks	human skin human sweat human breath rumen fluid	[93, 94, 97, 98]

Figure 4. Some of the common olfactory cues used by multicellular parasites for host finding
Only odorants used by more than one family are shown. Many of the odorants listed are common in nature, so sources listed are representative but not exhaustive. Any chemical compound (R) containing a carboxyl group, as shown, is considered a carboxylic acid.