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Host-Microbe Interactions and the Behavior of *Caenorhabditis elegans*

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Abstract

Microbes are ubiquitous in the natural environment of *Caenorhabditis elegans*. Bacteria serve as a food source for *C. elegans* but may also cause infection in the nematode host. The sensory nervous system of *C. elegans* detects diverse microbial molecules, ranging from metabolites produced by broad classes of bacteria to molecules synthesized by specific strains of bacteria. Innate recognition through chemosensation of bacterial metabolites or mechanosensation of bacteria can induce immediate behavioral responses. The ingestion of nutritive or pathogenic bacteria can modulate internal states that underlie long-lasting behavioral changes. Ingestion of nutritive bacteria leads to learned attraction and exploitation of the bacterial food source. Infection, which is accompanied by activation of innate immunity, stress responses, and host damage, leads to the development of aversive behavior. The integration of a multitude of microbial sensory cues in the environment is shaped by experience and context. Genetic, chemical, and neuronal studies of *C. elegans* behavior in the presence of bacteria have defined neural circuits and neuromodulatory systems that shape innate and learned behavioral responses to microbial cues. These studies have revealed the profound influence that host-microbe interactions have in governing the behavior of this simple animal host.

Microbiology

Caenorhabditis elegans lives in a microbe-rich environment that defines the ecology and has shaped the evolution of the organism (Schulenburg and Félix, 2017). The basic dichotomy for *C. elegans* in its interactions with this microbial community is that bacteria are an essential source of nutrition but may also be pathogenic and cause infection and death. Ecological survey and sequence analysis of bacteria isolated from the natural environment from which *C. elegans* are isolated has revealed a community of *Proteobacteria*, *Bacteroidetes*, *Firmicutes*, and *Actinobacteria* (Samuel et al., 2016), with notable enrichment of alpha-*Proteobacteria* genera such as *Ochrobactrum* and *Pseudomonas* in close association with *C. elegans*, likely colonizing the intestine (Dirksen et al., 2016). These associated bacteria may benefit the *C. elegans* host as a food source and in other ways. At the same

time, the characterization of *C. elegans* strains in the wild has uncovered a broad range of pathogenic microorganisms, including bacteria, fungi, and viruses, which can cause sickness and death (Schulenburg and Félix, 2017).

The experimental study of *C. elegans* has typically involved laboratory cultivation on monoaxenic lawns of *Escherichia coli* OP50 seeded on agar plates supplemented with cholesterol (Brenner, 1974). Genetic and metabolomic characterization of alternative bacterial food sources for *C. elegans*, such as *Comamonas*, *Bacillus subtilis* and mutants of *E. coli*, has defined conserved requirements for micronutrients (Qi et al., 2017; Watson et al., 2014), novel mechanisms of host co-option of bacterial siderophores for iron acquisition (Qi and Han, 2018), and metabolic determinants of bacteria that can influence complex phenotypes such as lifespan (Han et al., 2017; Qi and Han, 2018; Saiki et al., 2008; Virk et al., 2012). Semi-defined axenic media has been developed for growth and cultivation of *C. elegans*, but live bacteria support optimal growth and development (Lenaerts et al., 2008).

Diverse bacteria are pathogenic to *C. elegans*. The human opportunistic pathogen *Pseudomonas aeruginosa*, which resides in soil and water, was shown to infect an evolutionarily diverse range of hosts, including *C. elegans* (Rahme et al., 1995; Tan et al., 1999). *Bacillus thuringiensis* produces a crystal pore-forming toxin that is highly toxic to *C. elegans* upon ingestion (Marroquin et al., 2000) and has attracted interest as a potential biocontrol method for nematodes that are pathogenic to animals and plants. The coryneform bacterium *Microbacterium nematophilum* causes a distinct mode of infection and host response through adherence to the rectal and post-anal cuticle, likely reflecting a natural infection of *C. elegans* (Hodgkin et al., 2000). A broad range of bacterial species, including environmental isolates and human pathogens, exhibit increased virulence towards *C. elegans*, compared with the survival of *C. elegans* on *E. coli* OP50 (Couillault and Ewbank, 2002). Experimental conditions and host status play an important role when considering the pathogenicity of a bacterial strain. As an illustration of this point, even *E. coli* OP50 can be considered as pathogenic in the presence of richer growth media or when colonizing aging or feeding-defective animals (Garigan et al., 2002; Garsin et al., 2001; Herndon et al., 2002; Kumar et al., 2019). Pathogenicity can also be altered by co-ingestion of non-pathogenic bacteria (Montalvo-Katz et al., 2013; Samuel et al., 2016). For example, factors secreted by *Enterococcus faecium* are protective against *Salmonella* pathogenesis (Rangan et al., 2016). The range of bacteria that can be pathogenic to *C. elegans* in the laboratory setting has been expanded by molecular engineering, for example by having *E. coli* strains carry plasmids expressing specific toxins of *B. thuringiensis* (Wei et al., 2003) or *P. aeruginosa* (McEwan et al., 2012), or even RNAi clones targeting essential *C. elegans* genes (Kamath et al., 2003).

Innate recognition

The innate recognition of bacteria by *C. elegans* is evident from observations of behavioral phenotypes of *C. elegans* in the presence of bacteria and its metabolites. Behaviors such as feeding (Avery and Horvitz, 1990), defecation (Thomas, 1990), egg-laying (Trent et al., 1983), and locomotion (Sawin et al., 2000) are affected by the presence of bacteria. Insights into the molecular cues sensed by *C. elegans* have come from the characterization of chemotaxis behaviors of *C. elegans*, which demonstrate that *C. elegans* propagated in the

laboratory are attracted to a broad range of volatile organic molecules that are produced by bacterial metabolism and may serve as food cues (Bargmann and Horvitz, 1991; Bargmann et al., 1993; Ward, 1973). The genome of *C. elegans* encodes an expanded family of over 1000 chemoreceptor genes (Bargmann, 1998). Genetic analysis of chemotactic responses to diacetyl, which is produced by many bacteria, identified ODR-10 as a chemoreceptor for diacetyl (Sengupta et al., 1996). The chemical characterization of natural bacterial isolates that may serve as food for *C. elegans* in the wild has further revealed a number of volatile organic compounds that attract *C. elegans* (Worthy et al., 2018a). Bacterial food cues modulate dauer entry and exit (Golden and Riddle, 1984), and fatty acids derived from bacteria cause dauer larvae, which do not ingest bacteria, to exit dauer diapause (Kaul et al., 2014). In addition to chemosensation, *C. elegans* also detect the presence of bacteria through mechanosensation. Four classes of ciliated dopaminergic neurons are required for an innate slowing response that *C. elegans* display upon encountering a bacterial food source (Sawin et al., 2000). These neurons express mechanically-sensitive ion channels, display neuronal responses to mechanical forces, and also drive slowing in response to microbeads that are similar in size to bacteria (Kang et al., 2010; Sawin et al., 2000).

Gradients of molecular oxygen and carbon dioxide are generated by bacterial metabolism, and *C. elegans* exhibits robust detection and behavioral responses to these gases (Bretscher et al., 2008, 2011; Chang et al., 2006; Cheung et al., 2005; Gray et al., 2004; Hallem and Sternberg, 2008), which can drive the behavior of *C. elegans* in a microbial environment. *C. elegans* detects molecular oxygen with cytosolic guanylyl cyclase receptors expressed in the AQR, PQR, URX, and BAG neurons (Cheung et al., 2005; Gray et al., 2004; Zimmer et al., 2009) and exhibits a peaked preference for oxygen levels around ~8% in the absence of bacterial food (Gray et al., 2004). Multiple sensory neurons including BAG and AFD are responsive to carbon dioxide levels (Bretscher et al., 2008, 2011; Hallem and Sternberg, 2008), which may also serve as a cue that modulates behavioral responses to bacterial density. Ambient laboratory oxygen levels (~21%) would be expected to drive *C. elegans* into a bacterial lawn, where oxygen levels can be substantially lower (Gray et al., 2004; Reddy et al., 2011). However, the wild-type laboratory strain, N2, exhibits aerotaxis behavior that is altered in the presence of bacteria, such that the peaked preference for ~8% O₂ levels is lost, with an increased attraction to higher levels of molecular oxygen. The altered aerotaxis behavior of N2 *C. elegans* in the presence of bacteria is caused by allele differences in the *npr-1* gene, encoding a neuropeptide receptor (de Bono and Bargmann, 1998; Chang et al., 2006; Cheung et al., 2005; Gray et al., 2004), and the *glb-5* gene, which encodes a neural globin (McGrath et al., 2009; Persson et al., 2009). The N2 strain carries a laboratory-acquired neomorphic 215V allele of *npr-1*, whereas natural isolates of *C. elegans* carry an ancestral 215F allele with reduced NPR-1 activity (de Bono and Bargmann, 1998; McGrath et al., 2009). Bacteria induce NPR-1-dependent differences in not only aerotaxis behavior, but a number of different behavioral phenotypes including differences in CO₂ avoidance (Bretscher et al., 2008; Hallem and Sternberg, 2008), aggregation in feeding behavior, and roaming versus dwelling locomotion on bacterial lawns (Cheung et al., 2005; Gray et al., 2004). Altered behavioral responses to gradients of molecular oxygen also underlie the NPR-1-dependent avoidance of *P. aeruginosa* lawns (Reddy et al., 2009). Of note, behaviors dependent on NPR-1 in the N2 strain can be attenuated in the presence of

immediate attractive or repulsive responses that are induced by activation of the ASH neurons (Tran et al., 2017).

The characterization of *C. elegans* sensory responses to microbe-derived molecules in its environment suggest these host animals recognize molecules produced by broad classes of bacteria as well as molecules that are highly specific to bacterial strains. Many molecules are attractive to *C. elegans*, as might be anticipated for cues of bacterial food, but the diverse repertoire of molecules that can elicit sensory responses also suggests the ability to recognize and respond to specific strains of bacteria, depending on the physiological context.

Bacterial food and internal state

The ingestion of nutritive bacteria can influence the subsequent behavior of *C. elegans*. Associative learning paradigms that involve pairing either the presence or absence of nutritive, non-pathogenic *E. coli* bacteria with environmental conditions such as temperature result in a learned preference for the conditions associated with the fed, not starved, state (Hedgcock and Russell, 1975; Mori and Ohshima, 1995; Torayama et al., 2007). In addition, *C. elegans* that are fed non-pathogenic bacteria with a wide range of nutritive qualities — “good food” versus “bad food” that differ in their ease of ingestion and metabolic factors — can also exhibit a learned change in preference that is calibrated for better versus poorer food (Shtonda and Avery, 2006). These learned changes in behavior can last from minutes to days, depending on the conditioning protocol, thus reflecting a stable change in preference.

The foraging behaviors of *C. elegans* are also strongly influenced by past and present bacterial feeding conditions. While feeding on *E. coli* OP50, *C. elegans* alternate between active “roaming” states and inactive “dwelling” states in which they either explore or exploit their food source, respectively (Fujiwara et al., 2002). The proportion of time that *C. elegans* spends in roaming versus dwelling states is controlled by satiety levels, chemosensory inputs, and internal sensing of bacterial food ingestion (Ben Arous et al., 2009; Fujiwara et al., 2002; Shtonda and Avery, 2006). Animals that have been deprived of bacterial food exhibit an “enhanced slowing response” upon encountering a bacterial lawn, suggesting an important role for satiety state in these modes of food exploration (Sawin et al., 2000). The acute ingestion of bacterial food also plays a central role in food exploration: animals that are exposed to a lawn bacteria rendered largely inedible as a result of pharmacological treatment, spend almost all of their time in the roaming state (Ben Arous et al., 2009).

Serotonin signaling has been shown to have a key role in mediating the effects of the ingestion of nutritive bacteria on behavior. Serotonin biosynthesis and the serotonergic NSM neurons were shown to be required for the enhanced slowing response (Sawin et al., 2000) and for maintenance of the dwelling state (Flavell et al., 2013). NSM neurons extend a sensory dendrite to the surface of the pharyngeal lumen and are acutely activated upon bacterial food ingestion (Rhoades et al., 2019). Feeding-dependent NSM activation requires the acid-sensing ion channels DEL-3 and DEL-7 that localize to the NSM sensory dendrite and appear to mediate detection of a heat-stable bacterial component, connecting microbial recognition in the *C. elegans* alimentary canal to the modification of feeding behaviors.

While serotonin appears to promote states of slow locomotion, the neuropeptide pigment dispersing factor (PDF) is required for sustained roaming states (Flavell et al., 2013) and for mate search behaviors (Barrios et al., 2012), in which male *C. elegans* leave a bacterial food source to search for a mating partner (Lipton et al., 2004). PDF signaling appears to be antagonized by serotonin release (Flavell et al., 2013) and, in males, it promotes expression of *daf-7* in ASJ neurons (Hilbert and Kim, 2018), which promotes mate searching behavior (Hilbert and Kim, 2017). *daf-7* expression in ASJ is also positively regulated by satiety, thus allowing it to serve as a signal that integrates multiple internal cues to promote exploration. Increased motion through bacterial lawns during roaming states also activates dopamine signaling via the dopaminergic PDE neurons that appear to integrate the presence of food with the animal's own motion (Cermak et al., 2020). Activation of dopaminergic neurons during roaming elevates egg-laying rates, allowing animals disperse their eggs across bacterial food sources.

Slower metabolic changes arising from bacterial food ingestion also influence foraging. Rictor/TORC2 signaling in intestinal cells promotes *daf-7* expression in ASI neurons and elevates roaming behavior in a PDF-dependent manner (O'Donnell et al., 2018). The ETS-5 transcription factor functions in ASG and BAG sensory neurons to limit intestinal fat storage and promote PDF-dependent roaming (Juozaityte et al., 2017). Interestingly, the effects of *ets-5* on roaming can be reversed by altering intestinal fat storage. In addition to ASG and BAG, the URX and ASI sensory neurons also impact fat storage (Palamiuc et al., 2017; Witham et al., 2016). URX has also been shown to detect the mobilization of peripheral fat stores, suggesting bi-directional communication (Witham et al., 2016). Genetic analysis of the sterol response element binding protein pathway for fat metabolism has also suggested a critical role for fat metabolism in the regulation of food-induced quiescence behaviors in *C. elegans* (Hyun et al., 2016). Reduced food intake can also alter the production of other metabolites that act on the nervous system. For example, 2 h of fasting reduces levels of kynurenic acid, which alters NMDA signaling and downstream serotonin signaling to impact feeding (Lemieux et al., 2015). Our current understanding of how specific species of bacteria might alter metabolic state to impact behavior remains more limited. However, a recent study showed that *Providencia* bacteria in the *C. elegans* gut produce the neurotransmitter tyramine, which is converted to octopamine by the *C. elegans* host to alter aversive sensory responses (O'Donnell et al., 2020), which were previously shown to be regulated by feeding state (Chao et al., 2004). A large number of neuroactive metabolites are produced by non-pathogenic bacteria, suggesting that other bacterial species-specific signals produced in the gut may similarly influence behavior.

The chemosensory and mechanosensory detection of bacteria can also influence *C. elegans* foraging states. When animals are removed from an *E. coli* food source, they exhibit a "local search" state where they display a high frequency of high-angle turns for ~15 minutes, before switching to a "global search" state where they dramatically reduce turning (Gray et al., 2005; Hills et al., 2004; Wakabayashi et al., 2004). The frequency of turning during the local search state depends on the density of the *E. coli* food lawn from which animals were removed (López-Cruz et al., 2019). In this case, chemosensory and mechanosensory neurons are required for bacterial food detection, as depletion of glutamate from both populations of sensory neurons abolishes local search (López-Cruz et al., 2019). Together, these studies of

internal states reveal that the *C. elegans* nervous system surveys the past and present levels of non-pathogenic bacteria through multiple sensory modalities in order to change behavior over long time scales.

Infection and internal state

Infection following the ingestion of *P. aeruginosa* PA14, which is not only a good food source for *C. elegans*, but also highly pathogenic (Tan et al., 1999), causes an aversive learned response that is distinct from the effect of feeding on nutritive non-pathogenic bacteria. The initial innate preference of *C. elegans* for *P. aeruginosa* PA14 over *E. coli* OP50 was found to be reversed after feeding on *P. aeruginosa* PA14, with a subsequent preference for *E. coli* OP50 and aversion to *P. aeruginosa* PA14 (Ha et al., 2010; Zhang et al., 2005).

P. aeruginosa can kill *C. elegans* through multiple modes of toxicity that depend on bacterial strain and experimental conditions, including rapid toxicity from the secretion of diffusible toxins over the course of minutes (Darby et al., 1999; Kirienko et al., 2013; Mahajan-Miklos et al., 1999), or the development of an intestinal infection associated with intraluminal, extracellular bacterial proliferation and distention of the intestinal lumen with effacement of epithelial cells (Irazaqui et al., 2010; Tan et al., 1999) over the course of several hours (Tan et al., 1999). Infection of *C. elegans* by *P. aeruginosa* induces the activation of host innate immunity (Kim and Ewbank, 2018). The host response integrates innate immunity with cellular stress response pathways, such as the endoplasmic reticulum Unfolded Protein Response (Richardson et al., 2010) and mitochondrial stress pathways (Pellegrino et al., 2014), as well as responses to exogenous, toxin-mediated effects on mRNA translation (Dunbar et al., 2012; McEwan et al., 2012). The widespread induction of stress-activated signaling pathways, immune and stress-responsive genes, and morphological changes to the host reflect the disruption of normal physiology and homeostasis caused by infection with pathogenic bacteria. The broad activation of cellular stress responses with infection has itself been proposed to be a mechanism by which immune defense is activated (Liu et al., 2014; Pukkila-Worley, 2016; Reddy et al., 2016). Whereas specific microbial cues for the activation of innate immunity in *C. elegans* remain elusive, evidence points to a key role for host damage resulting from infection in activating innate immunity. The PMK-1 p38 mitogen-activated protein kinase pathway is activated by both bacterial infection (Fletcher et al., 2019; Kim et al., 2002; Troemel et al., 2006) and pore-forming toxin activity (Huffman et al., 2004). In the epidermal response to fungal infection, host damage may be signaled by the endogenously produced metabolite 4-hydroxyphenyllactic acid, which acts through GPCR signaling to activate PMK-1 and antifungal immunity (Zugasti et al., 2014).

The evolutionarily ancient role for host damage in the activation of innate immunity parallels its apparent role in the development of aversive behavior. Consistent with the kinetics of infection and modified choice behaviors, *C. elegans* exhibits avoidance of a lawn of pathogenic bacteria following bacterial infection (Melo and Ruvkun, 2012; Pradel et al., 2007; Pujol et al., 2001; Reddy et al., 2009; Schulenburg and Müller, 2004). Whereas morphological changes such as intestinal distention accompany the development of pathogen infection (Tan et al., 1999), such changes are only correlative, and host damage in

the absence of such changes has been shown to be sufficient for *C. elegans* lawn avoidance behavior. *C. elegans* avoids bacteria such as *Bacillus thuringiensis* (Schulenburg and Müller, 2004), which produces a pore-forming toxin that rapidly kills *C. elegans* over a time scale of minutes without associated intestinal proliferation of bacteria (Marroquin et al., 2000). The development of a lawn avoidance response is also observed in the presence of *Microbacterium nematophilum*, which causes a distinct mode of infection resulting in the induction of a rectal swelling response and sickness (McMullan et al., 2012; Yook and Hodgkin, 2007). Moreover, *E. coli* strain HT115, which is used for feeding RNAi-based experiments and is a nutritious food source of *C. elegans* can be engineered to be toxic to *C. elegans* through the expression of dsRNA targeting genes that are essential for viability of *C. elegans* (Kamath et al., 2003). Aversion to the *E. coli* HT115 lawn develops over the time course that RNAi exerts toxic effects on the host, and even the addition of abiotic toxins to the lawn can also induce *C. elegans* to leave a bacterial lawn (Melo and Ruvkun, 2012). Notably, the subsequent lawn aversive behavior is not specific for *E. coli* HT115 only but also observed in response to other *E. coli* and even other bacterial species.

In addition to this generalized aversive response, exposure to pathogenic *P. aeruginosa* PA14 also causes a learned change in bacterial preference, where the preference for *P. aeruginosa* PA14 over *E. coli* OP50 is reversed. This change can be elicited by at least 4 h of *P. aeruginosa* PA14 exposure in adulthood or 12 h of exposure during the L1 larval stage (Jin et al., 2016; Zhang et al., 2005). In addition, 24 h of PA14 exposure beginning at the L4 larval stage can also reduce PA14 preference in progeny for up to four generations later (Moore et al., 2019). The molecular and circuit mechanisms by which exposure to *P. aeruginosa* elicits a change in *C. elegans* preference have been carefully examined. Infection with *P. aeruginosa* induces the increased transcription of *tph-1* from the ADF neurons, and *tph-1* mutants are defective for learned aversive choice behavior following *P. aeruginosa* PA14 infection (Zhang et al., 2005). *tph-1* mutants exhibit increased susceptibility to killing by *P. aeruginosa* compared to wild-type, a difference that is abrogated when animals are constrained such that they cannot avoid the *P. aeruginosa* lawn (Shivers et al., 2009).

Circuit-level studies have localized the site of learning within sensorimotor circuits that underlies the learned change in bacterial preference. AWB and AWC olfactory neurons detect *P. aeruginosa* PA14 and *E. coli* OP50 odors, but their sensory responses to these cues are not altered after *P. aeruginosa* PA14 exposure (Ha et al., 2010). In addition, a subset of neurons in the downstream circuitry, such as AIY, AIZ, and AIB neurons, are required for navigation towards food sources in naïve animals, but not required for learned changes. In contrast, RIA and SMD neurons are not required for naïve food choice, but are required for the learned change in food preference after *P. aeruginosa* PA14 exposure (Jin et al., 2016; Zhang et al., 2005). These results suggest that RIA and SMD neurons are likely modulated during *P. aeruginosa* PA14 exposure. This modulation appears to require serotonergic signaling from ADF (Ha et al., 2010) and *ins-6* and *ins-7* insulin-like peptides whose expression also changes after learning (Chen et al., 2013). Thus, *P. aeruginosa* PA14 elicits changes in neuroendocrine signaling that impact specific nodes in the sensorimotor circuit to alter food preference. Interestingly, neuroendocrine signals from the gut are also critical for food aversion, as the dynamic expression of an intestinal insulin, *ins-11*, modulates aversive responses to *P. aeruginosa* (Lee and Mylonakis, 2017). In addition, changes in

neuroendocrine signaling that modulate learning may be accompanied by changes in neuroendocrine signaling that alter innate behaviors, as is observed in the modulation of *P. aeruginosa* PA14 avoidance behavior by dynamic *daf-7* expression (Meisel et al., 2014).

The observations that *C. elegans* exhibits a preference for one bacterial species over another, and that this preference can be changed based on experience, suggest that *C. elegans* can discriminate among bacterial species, which may be enabled in part by the diversity of microbial ligands that it can recognize. At the same time, the observations that *C. elegans* will leave a lawn of bacteria following infection and damage, and that the subsequent aversive response may not be specific for the bacteria causing the damage, suggest that a behavioral state characterized by a more general aversion to bacteria may also develop. This distinction underscores differences in assays for aversive behavior following infection. Lawn-leaving behavior may be influenced by changes in internal states that confer both specific and non-specific responses to bacteria. It is also possible that non-specific lawn aversion determinants, such as differential oxygen or carbon dioxide levels, may act differentially on the attraction or repulsion of *C. elegans* to particular bacteria to also influence the choice of *C. elegans* between two different bacterial strains.

Summary

The behavioral responses of *C. elegans* animals to microbial cues in their environment rely on the innate recognition of a vast and diverse set of bacterial sensory cues. Behavioral responses to these molecular and mechanosensory cues are influenced by experience and context, endowing *C. elegans* with a great deal of flexibility in how it responds and adapts to its microbial environment. Changes in satiety, tissue damage resulting from pathogenic infection, and recognition of specific bacterial metabolites can alter how the neural circuits in this animal process subsequent microbial cues. Nutritive bacteria can elicit a range of adaptive behavioral changes include learned attraction and stable switches to exploitative foraging behaviors. Pathogenic bacteria can elicit generalized responses, like bacterial aversion, as well as highly specific changes, like learned avoidance of harmful food sources. Thus, evolutionary ancient mechanisms to sense bacteria, as well as host damage arising from pathogenic bacteria, triggers not only cell-autonomous innate immune responses, but also organism-wide behavioral responses that are controlled by a nervous system that can flexibly respond to microbial sensory cues. These studies of host-microbe interactions in *C. elegans* may ultimately inform our understanding of how microbes impact nervous system function in more complex animals (Li and Liberles, 2015; Yang and Chiu, 2017).

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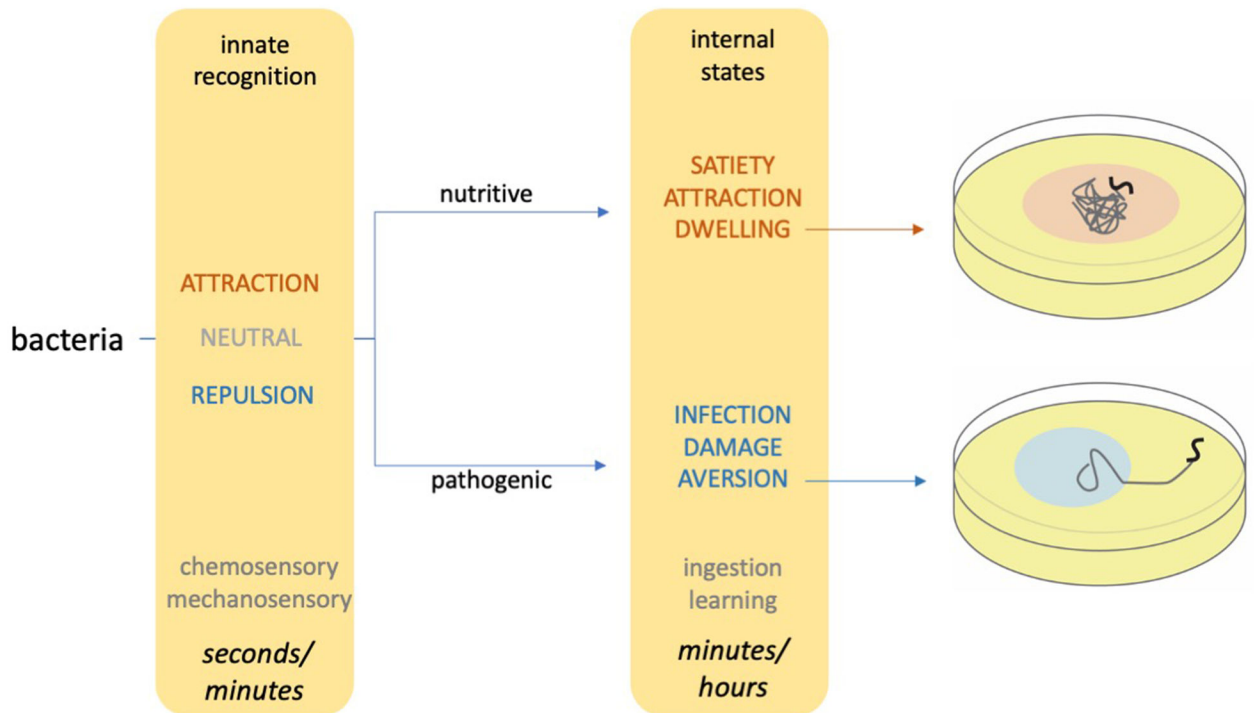


Figure 1. *C. elegans* behavioral responses to bacteria unfold over multiple time scales.

C. elegans consume diverse bacteria that differ in their nutritive qualities and their pathogenicity. Innate recognition of bacteria allows animals to generate rapid behavioral responses to bacterial odors and textures (left). After bacteria are ingested, animals undergo internal state changes that underlie long-lasting behavioral changes (middle). These long-lasting changes include alterations in their foraging strategies (right) and learned changes in bacterial preference.