Published in final edited form as:

Neuroscience. 2015 June 18; 296: 15–25. doi:10.1016/j.neuroscience.2014.06.054.

Sensory systems: their impact on *C. elegans* survival

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Summary

An animal's survival strongly depends on a nervous system that can rapidly process and integrate the changing quality of its environment and promote the most appropriate physiological responses. This is amply demonstrated in the nematode worm *Caenorhabditis elegans*, where its sensory system has been shown to impact multiple physiological traits that range from behavior and developmental plasticity to longevity. Because of the accessibility of its nervous system and the number of tools available to study and manipulate its neural circuitry, *C. elegans* has thus become an important model organism in dissecting the mechanisms through which the nervous system promotes survival. Here we review our current understanding of how the *C. elegans* sensory system affects diverse physiological traits, whose coordination would be essential for survival under fluctuating environments. The knowledge we derive from the *C. elegans* studies should provide testable hypotheses in discovering similar mechanisms in higher animals.

1. Introduction

The nervous system is an ensemble of different types of neurons that form a major anatomical structure. These neurons interact with each other via many neural circuits that regulate multiple physiological outputs. However, while neuronal activities within these circuits allow an animal to survive and thrive under different environments, the exact neuronal mechanisms involved remain unknown. In higher animals, the elucidation of these mechanisms continues to be difficult. For example, the human brain consists of 85 billion neurons (Azevedo et al., 2009), which makes the functional mapping of the human brain a daunting task. Therefore, Sydney Brenner's rationale in proposing a simpler model organism to study the myriad functions of the nervous system remains as true today as it was more than forty years ago (Brenner, 1973). Compared with humans, the *Caenorhabditis elegans* hermaphrodite only has 302 neurons (Figure 1), whose synaptic wiring diagram has been

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fully mapped with serial electron micrograph reconstruction (White et al., 1986). However, despite a small and compact nervous system (Figure 1), *C. elegans* is capable of generating complex physiological responses, *e.g.*, behaviors, developmental programs and different types of homeostatic responses [reviewed in (Alcedo and Zhang, 2013)]. Since this simple animal model also allows facile genetic and environmental manipulations [reviewed in (Alcedo and Zhang, 2013)], *C. elegans* easily lends itself to the functional dissection of the neural circuits that are necessary for an animal's survival.

2. The *C. elegans* sensory nervous system

C. elegans hermaphrodites have 302 neurons, and their relatively invariant structures and anatomical positions allow for the straightforward identification of each neuron (White et al., 1986), which can be easily manipulated or functionally imaged *in vivo* [reviewed in (Alcedo and Zhang, 2013)]. Many of these neurons extend processes into the nerve ring (Figure 1), which serves as the primitive brain of the animal (White et al., 1986). The nerve ring contains many synaptic connections and gap junctions between the different neurons (White et al., 1986). The *C. elegans* nervous system has around 6393 chemical synapses, 890 gap junctions, and 1410 neuromuscular junctions (White et al., 1986; Hall and Russell, 1991; Varshney et al., 2011), through which different signals can be exchanged between neurons and their targets. Like other animals, the worm signals through (i) small molecule neurotransmitters, such as acetylcholine, dopamine, serotonin and γ -aminobutyric acid, which can be released through synaptic vesicles (SVs), and (ii) peptide neurotransmitters, such as insulin-like peptides (ILPs), which are released from dense core vesicles (DCVs) (Bargmann, 1998; Edwards, 1998).

C. elegans has 60 ciliated sensory neurons: some function in chemosensation, like gustation or olfaction, while others function in thermosensation, mechanosensation or proprioception. Sensory cues are processed by the animal through different signaling pathways that involve G proteins and ion channels that are either gated by cyclic GMP (cGMP) or belong to the TRP versus the degenerin/epithelial Na⁺ channel (Deg/ENaC) family [(Chalfie and Wolinsky, 1990; Driscoll and Chalfie, 1991; O'Hagan et al., 2005; Inada et al., 2006; Li et al., 2006; Bounoutas and Chalfie, 2007); reviewed by (Bargmann, 2006)]. Several sensory receptors have already been identified, *e.g.*, the G protein-coupled receptors (GPCRs) that recognize odorants (Troemel et al., 1995; Sengupta et al., 1996), the TRP ion channel of the NOMPC family that plays a mechanosensory or proprioceptive role in the animal (Li et al., 2006) or the Deg/ENaC ion channel that is activated by a touch stimulus (Chalfie and Wolinsky, 1990; Driscoll and Chalfie, 1991; O'Hagan et al., 2005; Bounoutas and Chalfie, 2007).

The defined wiring diagram of the worm nervous system has provided an anatomical basis for the functional dissection of the neural circuits that process olfactory, gustatory, thermosensory or mechanosensory cues (White et al., 1986; Mori and Ohshima, 1995; Hart et al., 1999; Tsalik and Hobert, 2003; Gray et al., 2005; Goodman, 2006; Inada et al., 2006; Chalasani et al., 2007; Biron et al., 2008; Kuhara et al., 2008; Suzuki et al., 2008; Iino and Yoshida, 2009; Macosko et al., 2009; Ha et al., 2010; Luo et al., 2014). These neural circuit studies have demonstrated that the sensorimotor circuits in the nematode are generally

shallow with a few interneuronal relays between the sensory neurons that detect environmental inputs and the motor programs that execute behavioral outcomes. However, the anatomical map of the worm nervous system also reveals ambiguity. For example, the postsynaptic partners of the different sensory neurons show a considerable amount of anatomical overlaps (White et al., 1986). Therefore, the functional mapping and analysis of the neural circuits that underlie sensory responses to various types of environmental cues are essential in understanding how this small nervous system coordinates physiological responses and optimizes survival under specific conditions.

3. The role of the sensory system in *C. elegans* physiology

The downstream outputs of the above sensory circuits modulate animal physiology. Unlike *Drosophila* and other higher animals, *C. elegans* has a shorter life cycle and lifespan (Brenner, 1974; Klass, 1977), which has made *C. elegans* a popular genetic model to study the physiology of development and aging. Under optimal environments, *C. elegans* develops through four larval stages, L1-L4, before becoming a reproductive adult (Figure 2). The *C. elegans* developmental life cycle and lifespan are modulated by different environmental cues, such as availability of bacterial food sources and temperature. For instance, low food availability can lead to developmental arrest (Figure 2) or altered longevity (Klass, 1977; Golden and Riddle, 1984). On the other hand, lower temperatures lengthen *C. elegans* developmental time and lifespan, while higher temperatures shorten both (Klass, 1977). These physiological phenotypes have been shown to be subject to the activity of specific sensory neurons, which would be expected since these neurons perceive the environmental cues that can affect an animal's development or lifespan (Bargmann and Horvitz, 1991; Schackwitz et al., 1996; Apfeld and Kenyon, 1999; Alcedo and Kenyon, 2004; Bishop and Guarente, 2007; Ouellet et al., 2008; Kim et al., 2009; Lee and Kenyon, 2009; Xiao et al., 2013; Maures et al., 2014). While the sensory effects on development and lifespan are not distinct to *C. elegans*, these initial findings, and future related studies in this animal, should provide a framework for understanding how sensory information processing could modulate survival in higher animals.

3.1. The sensory influence on *C. elegans* lifespan

The sensory influence on lifespan was initially identified in *C. elegans* (Apfeld and Kenyon, 1999). The longevity-influencing neurons can be gustatory, olfactory (Alcedo and Kenyon, 2004) or thermosensory (Lee and Kenyon, 2009) in their functions. This influence on lifespan involves not all, but only certain sensory neurons under a given environment (Alcedo and Kenyon, 2004). This suggests that neurons that detect a particular set of environmental cues would presumably only affect lifespan based on the presence of these cues (Maier et al., 2010). Accordingly, some sensory neurons shorten, whereas others lengthen, lifespan in a context-dependent manner [Figure 3; (Alcedo and Kenyon, 2004; Lee and Kenyon, 2009; Maier et al., 2010; Xiao et al., 2013; Maures et al., 2014)]. Indeed, some sensory mutants exhibit lifespan phenotypes only on certain types of bacterial food sources, which implies that sensory neurons can alter longevity through food-type recognition (Maier et al., 2010).

The food-type effects on lifespan involve mechanism(s) that are distinct from those that promote a long-life phenotype through restriction of food intake levels (Maier et al., 2010). Long-lived animals that are food-level restricted have slower developmental and reproductive rates (Klass, 1977). In contrast, the food-type (Maier et al., 2010) and sensory effects (Apfeld and Kenyon, 1999; Alcedo and Kenyon, 2004) on lifespan do not correlate with the food-type and sensory effects on feeding rates and developmental rates. In addition, whereas some sensory neurons affect lifespan independent of reproduction (Apfeld and Kenyon, 1999; Alcedo and Kenyon, 2004), certain food types lengthen lifespan and induce faster reproduction (Maier et al., 2010), the opposite of what is observed for long-lived food level-restricted animals (Klass, 1977).

Considering that different types of sensory neurons perceive a wide range of environmental cues, it is to be expected that the sensory influence on lifespan will also involve many different mechanisms, besides food-type recognition. For example, the effect of food-level restriction on lifespan can also be mediated by sensory neurons that again affect lifespan depending on the environmental context (Bishop and Guarente, 2007). Under restricted food-level conditions, the gustatory ASI neurons promote longevity (Figure 3B); but under well-fed conditions, the same ASI neurons inhibit longevity [Figure 3A; (Alcedo and Kenyon, 2004; Bishop and Guarente, 2007)]. In addition to food-dependent cues, other cues, like temperature or sex pheromones, can promote context-dependent sensory effects on longevity. Two studies have found that the thermosensory neurons that lengthen lifespan at warmer temperatures (Lee and Kenyon, 2009) are not the same neurons that lengthen lifespan at colder temperatures [Figure 3D; (Xiao et al., 2013)]. Recently, a study has also demonstrated that the perception of *C. elegans* male pheromones shortens the lifespan of *C. elegans* hermaphrodites [Figure 3C; (Maures et al., 2014)]. A certain component of the sensory influence on lifespan has already been associated with reproductive physiology (Apfeld and Kenyon, 1999; Alcedo and Kenyon, 2004; Maier et al., 2010). Olfactory neurons can modulate a longevity-influencing signal from the somatic gonads of hermaphrodites (Alcedo and Kenyon, 2004). Interestingly, the male somatic gonad also affects hermaphrodite longevity: the transfer of seminal fluid from the male somatic gonad, more so than that of sperm, decreases hermaphrodite lifespan, whereas the act of copulation itself has no effect (Shi and Murphy, 2014). At present, it is unknown if this longevity influence on hermaphrodites from the male somatic gonad involves the activity of sensory neurons, although mating physiology is known to be regulated by the sensory system (Liu and Sternberg, 1995; Barrios et al., 2008; Gruninger et al., 2008). Nonetheless, the above studies should emphasize the variety of mechanisms that could underlie the sensory influence on lifespan, which may or may not include behavioral strategies, *e.g.*, in the case of food-level restriction or mating physiology, as part of the coordinated homeostatic responses that affect survival.

The context-dependence of the sensory influence on lifespan is further highlighted by the molecular mechanisms that underlie this phenomenon. For instance, this influence on lifespan is associated with food type-dependent signaling activities of specific neuropeptides (Maier et al., 2010), which suggests that other molecules will also alter lifespan only on certain food types. It is intriguing that not all sensory neurons modulate longevity through a

monocarboxylate transporter, MCT-1/2, which is expressed in the pharynx, a part of the animal's digestive system (Gaglia et al., 2012), and can presumably transport small metabolites derived from *C. elegans* food sources. Since this indicates that MCT-1/2 is not a general transporter of all metabolites, MCT-1/2 might also act with specific neuropeptides to process or modulate the food type-dependent sensory effects on lifespan. Another molecule that mediates the sensory influence on lifespan is *skn-1* (Bishop and Guarente, 2007), which encodes a NRF-like transcription factor expressed in the gustatory ASI neurons and the intestine (An and Blackwell, 2003). Similar to sensory neurons and neuropeptide signaling (Maier et al., 2010), *skn-1* appears to affect lifespan in a food type-dependent manner (Soukas et al., 2009). However, while *skn-1* can act specifically from the ASI neurons to mediate the lifespan effects of food-level restriction (Bishop and Guarente, 2007), it remains unclear how *skn-1* could mediate the food type-dependent sensory effects on lifespan.

Some of the longevity-influencing neurons, the gustatory ASI and the olfactory AWC neurons [Figure 3; (Alcedo and Kenyon, 2004; Bishop and Guarente, 2007)], also respond to thermal stimuli and form part of the thermosensory circuit in *C. elegans* (Biron et al., 2008; Kuhara et al., 2008; Beverly et al., 2011). While this reflects the polymodal nature of some of the *C. elegans* sensory neurons, it raises an intriguing possibility that cross-talk between different sensory modalities exists in affecting lifespan. Supporting this hypothesis, the longevity-promoting thermosensory AFD neurons [Figure 3; (Lee and Kenyon, 2009)] have been found to activate non-neuronal longevity-promoting heat shock responses that are modulated by chemosensory activities (Prahlad et al., 2008). Since this also suggests that different sensory activities are integrated by downstream target tissues, the sensory system likely optimizes survival through the coordination of different homeostatic responses to different types of environmental fluctuations. Because key homeostatic mechanisms entail the regulation of various types of hormone release, it is to be expected that the sensory influence on lifespan will also depend on hormone signaling. Indeed, the cold-sensing effects (Xiao et al., 2013) and a large part of the chemosensory effects on lifespan require insulin signaling (Apfeld and Kenyon, 1999; Alcedo and Kenyon, 2004; Maures et al., 2014), while the warm-sensing effects on lifespan require steroid hormone function (Lee and Kenyon, 2009).

It is important to note that the sensory influence on lifespan has also been found in at least one other animal. In *Drosophila*, odor-, pheromone- and certain taste-sensing neurons, as well as food odors and sex pheromones, have been shown to shorten, while other taste-sensing neurons have been found to extend, its lifespan (Libert et al., 2007; Poon et al., 2010; Gendron et al., 2014; Ostojic et al., 2014; Waterson et al., 2014). Accordingly, similar to *C. elegans*, the sensory effects on *Drosophila* lifespan involve more than one mechanism: e.g., the chemosensory effects on lifespan can also be dependent (Libert et al., 2007) or independent of food intake levels (Poon et al., 2010; Ostojic et al., 2014; Waterson et al., 2014). At the same time, just as the sensory effects on *C. elegans* lifespan are likely due to changes in homeostasis as a consequence of endocrine/hormone signaling, the sensory influence on *Drosophila* lifespan is correlated with altered lipid homeostasis or altered insulin signaling (Libert et al., 2007; Poon et al., 2010; Gendron et al., 2014; Ostojic et al., 2014; Waterson et al., 2014). Thus, the existence of this phenomenon in both animals

underscores the possibility that the sensory system will also affect lifespan in others. In mammals, both gustatory (Squire et al., 2003; Lundy Jr. and Norgren, 2004), olfactory and pheromonal (Boehm et al., 2005; Yoon et al., 2005) information can be relayed to the hypothalamus, which controls organismal homeostasis through the animals' endocrine system. The hypothalamic integration of external, as well as internal, sensory information may lead to homeostatic responses that will also modulate mammalian longevity. Interestingly, a study has recently demonstrated that pain perception via somatosensory neurons shortens mouse lifespan through the regulation of pancreatic insulin secretion (Riera et al., 2014), further supporting the idea that the sensory influence on lifespan is present across the animal kingdom.

3.2. The sensory influence on *C. elegans* developmental plasticity

There are a number of possible sensory-mediated homeostatic responses that can alter longevity. Here we focus on one of these responses, the dauer developmental program in *C. elegans* (Hall et al., 2010; Cornils et al., 2011). The dauer program is induced during the first larval stage (L1) by harsh environmental conditions, such as high population density and food scarcity [Figure 2; (Golden and Riddle, 1982, 1984)]. A dauer larva is developmentally arrested and is the alternative form of the third-stage larva [L3 (Figure 2); reviewed by (Riddle and Albert, 1997)]. The dauer's resistance to high stress equips it for long-term survival until adverse conditions improve, upon which dauers exit into the last larval stage prior to reproductive adulthood [Figure 2; (Golden and Riddle, 1984; Riddle and Albert, 1997)].

Throughout its life, each *C. elegans* secretes a glycosidic (Jeong et al., 2005; Butcher et al., 2007) dauer pheromone mixture (Golden and Riddle, 1982, 1984). Thus, a high dauer pheromone concentration in the environment signals high population density and presumably low food availability. In fact, a high ratio of dauer pheromone to food is sufficient to induce entry into dauer arrest, whereas an increase in food availability and a decrease in the pheromone mixture promote exit from the dauer state [Figure 4; (Golden and Riddle, 1982, 1984)]. These pheromone and food cues are sensed by different sets of chemosensory neurons that regulate the two developmental switches: dauer entry versus exit (Bargmann and Horvitz, 1991; Schackwitz et al., 1996; Ouellet et al., 2008; Kim et al., 2009; Kaul et al., 2014). In response to optimally low dauer pheromone to food ratios (Golden and Riddle, 1982, 1984; Ren et al., 1996; Schackwitz et al., 1996), the gustatory ASI, ADF and ASG neurons inhibit entry into the dauer state [Figure 4A; (Bargmann and Horvitz, 1991)]. However, high dauer pheromone levels are sensed by the gustatory neurons ASK (Kim et al., 2009), which together with the gustatory neurons ASJ promote dauer entry [Figure 4B; (Schackwitz et al., 1996)]. In contrast, dauer exit is inhibited by the chemosensory neurons IL2 (Ouellet et al., 2008), until the re-introduction of signals for increased food availability, like high concentrations of bacterial fatty acids, which are sensed by the gustatory ASJ neurons [Figure 4C; (Kaul et al., 2014)]. Accordingly, the ASJ neurons, which have context-dependent effects on the dauer program, promote dauer exit in response to improved environmental conditions (Bargmann and Horvitz, 1991), together with the olfactory AWC neurons [Figure 4C; (Ouellet et al., 2008)].

Interestingly, some of the dauer program-regulating sensory neurons, ASI, ASG, ASJ, ASK and AWC (Bargmann and Horvitz, 1991; Schackwitz et al., 1996; Ouellet et al., 2008), have also been shown to affect lifespan [Figures 3 and 4; (Alcedo and Kenyon, 2004; Bishop and Guarente, 2007)]. The link between the dauer program and longevity is reflected by physiological differences between post-dauer and non-post-dauer animals (Kim and Paik, 2008; Hall et al., 2010; Cornils et al., 2011). For example, post-dauer adults live longer than non-post-dauers (Hall et al., 2010; Cornils et al., 2011). This difference in longevity could stem from the dauer-induced remodeling of both neuronal and non-neuronal tissues [(Albert and Riddle, 1983; Peckol et al., 2001; Cornils et al., 2011; Procko et al., 2011; Schroeder et al., 2013); reviewed by (Riddle and Albert, 1997)]. In dauers, the glial-like cells that are associated with some of the dauer- and longevity-influencing sensory neurons have altered morphology, which is also accompanied by the observed remodeling of the ciliated endings of ASI, ASG and AWC neurons (Albert and Riddle, 1983; Procko et al., 2011). These findings suggest that these neurons would have altered sensory functions in the arrested larvae, which is further supported by dauer-induced changes in ASI and AWC gene expression (Peckol et al., 2001; Cornils et al., 2011). Because some of the changes in neuronal and glial anatomy (Procko et al., 2011; Schroeder et al., 2013) and neuronal gene expression (Cornils et al., 2011) are irreversible upon dauer exit, the dauer-induced remodeling of these neurons and associated tissues could provide a mechanism for the increased longevity of post-dauers compared to non-post-dauer animals (Hall et al., 2010; Cornils et al., 2011).

Molecular mechanisms that have been implicated in the dauer program have also been found to affect *C. elegans* lifespan. For instance, induction of the unfolded protein response (UPR) in the endoplasmic reticulum (ER) of ASI neurons promotes dauer entry (Kulalart and Kim, 2013), whereas activation of UPR in the ER of all neurons (Taylor and Dillin, 2013) or in the mitochondria of downstream tissues (Durieux et al., 2011) promotes longevity. Since UPR results from perturbations in protein folding (Walter and Ron, 2011), it is possible that a suboptimal environment will deregulate protein homeostasis in specific neurons (Kulalart and Kim, 2013). This could then influence organismal homeostasis by modulating hormone release, e.g., from DCVs in different subcellular compartments of a neuron (Chung et al., 2013). One such peptide hormone affected could be the TGF- β -like DAF-7, which is expressed in ASI sensory neurons and has been shown to inhibit both dauer entry and longevity (Ren et al., 1996; Schackwitz et al., 1996; Shaw et al., 2007). Other peptide hormones, whose release could be regulated by UPR, belong to the insulin-like peptide (ILP) family, which also affects both dauer entry and exit, as well as lifespan (Pierce et al., 2001; Li et al., 2003; Cornils et al., 2011; Kulalart and Kim, 2013; Fernandes de Abreu et al., 2014). Hence, the activities of these peptide hormones could coordinate different physiological responses to maintain general homeostasis within the animal.

3.3. Behavioral responses for optimal survival

As alluded to in 3.1, certain behavioral responses are also likely associated with the sensory effects on *C. elegans* lifespan. For example, navigational behaviors towards optimal conditions versus avoidance of adverse conditions could minimize the stress an environment can impose on an animal. Indeed, *C. elegans* displays an amazing amount of flexibility in its

behavioral responses to the same sensory cues, *i.e.*, temperature, food availability, as well as food quality, that impact development, metabolism and lifespan. The mechanisms that underlie the sensory and circuit properties of such behaviors can be well characterized in *C. elegans*, since (i) its neuronal connectome has been completed with synaptic resolution (White et al., 1986) and (ii) its nervous system is accessible to optical measurements of its neuronal activities, as well as to spatial and temporal manipulation of neuronal function at the single cell level [reviewed by (Alcedo and Zhang, 2013)].

Given the profound impact of temperature on development and lifespan, it is not surprising that *C. elegans* displays robust behavioral responses to changing ambient temperatures. Compelling experiments have demonstrated that *C. elegans* migrates towards the temperature of its previous cultivation condition, T_s , and move isothermally at T_s [reviewed by (Garrity et al., 2010)]. The bidirectional movement up or down the temperature gradient to seek T_s is encoded by a sensorimotor circuit that detects temperature changes primarily through the AFD sensory neurons (Kimura et al., 2004; Clark et al., 2006; Kuhara et al., 2011; Luo et al., 2014). This thermotactic movement also requires the sensory neurons ASI and AWC (Biron et al., 2008; Kuhara et al., 2008; Beverly et al., 2011). All three neurons have differential responses to different temperature fluctuations, but act together to perceive ambient temperature, thereby coordinating a coherent behavioral response within a thermal gradient (Kimura et al., 2004; Clark et al., 2006; Biron et al., 2008; Beverly et al., 2011; Luo et al., 2014).

Food-dependent cues that play essential roles in development and lifespan also modulate robust behavioral responses. In particular, food availability and food quality can alter olfaction-dependent behaviors (Nuttley et al., 2002; Chao et al., 2004; Remy and Hobert, 2005; Zhang et al., 2005; Shtonda and Avery, 2006; Torayama et al., 2007; Tsui and van der Kooy, 2008; Stetak et al., 2009; Ha et al., 2010; Kauffman et al., 2010; Amano and Maruyama, 2011). For example, the presence versus absence of food decreases or increases, respectively, the latency of the animal's response to a repulsive odor, octanol, in which food levels modulate the properties of an olfactory sensorimotor circuit (Chao et al., 2004). In addition, the pairing of attractive odors, such as those sensed by AWC olfactory neurons, with food, either during the larval L1 (Remy and Hobert, 2005) or adult stage (Torayama et al., 2007; Kauffman et al., 2010), enhances the attractive response in adults.

Because *C. elegans* feeds on bacteria in its natural habitat, pathogenic bacteria also represent a commonplace ecological factor that can affect this animal's survival. Pathogenic bacteria have been shown to shorten worm lifespan through infection or secreted toxins [reviewed by (Zhang and Zhang, 2009)]. Recent studies have indicated that *C. elegans* engages innate immune and neuronal systems to generate coordinated physiological responses upon exposure to pathogenic bacteria (Zhang et al., 2005; Styer et al., 2008; Reddy et al., 2009; Ha et al., 2010; Melo and Ruvkun, 2012). Bacterial pathogens, such as the gram-negative *Pseudomonas aeruginosa* PA14, evoke *C. elegans* transcription of genes that are associated with innate immunity and core cellular activities, such as protein synthesis and mitochondrial function (Melo and Ruvkun, 2012). The likely disruption of essential cellular activities that results from pathogen exposure is presumably sensed by the nervous system, which would lead to a coordination of immune and behavioral responses (Zhang et al., 2005;

Ha et al., 2010; Melo and Ruvkun, 2012). At the behavioral level, *C. elegans* stays on lawns of benign bacteria, but will avoid lawns of pathogenic bacteria (Zhang et al., 2005; Pradel et al., 2007; Reddy et al., 2009). Prolonged exposure to pathogens also induces a learned aversive response to the odor of the pathogenic bacteria [(Zhang et al., 2005; Ha et al., 2010); reviewed by (Schulenburg and Ewbank, 2007)]. Functional mapping of this learned response has identified a sensorimotor neural network that underlies the pathogen-induced olfactory learning, which acts downstream of the olfactory sensory neurons, AWC and AWB (Ha et al., 2010). Accordingly, intracellular calcium imaging has shown that the aversive experience generates behavioral changes by modulating the signaling pathways downstream of the olfactory response (Ha et al., 2010).

How can these diverse physiological traits be orchestrated to promote pathogen resistance within the animal? A mechanism that plays an essential role in mediating learned aversion to the smell of pathogenic bacteria is serotonin signaling (Zhang et al., 2005; Ha et al., 2010). Serotonin is also required in the aversion generated by disruption of the worm's core cellular machinery after ingestion of pathogenic bacteria (Melo and Ruvkun, 2012). Thus, the serotonin signal can link both behavioral and cellular responses to the pathogen invasion. Another signal that can coordinate behavior with resistance to pathogen infection is NPR-1, the *C. elegans* homolog of the mammalian neuropeptide Y receptor (de Bono and Bargmann, 1998). *npr-1* is expressed in multiple neurons and a decrease in NPR-1 activity triggers animal aggregation behavior at the border of bacterial lawns (de Bono and Bargmann, 1998; Macosko et al., 2009). These NPR-1-mediated aggregation and bordering behaviors have been reported to impact susceptibility to pathogen infection (Styer et al., 2008; Reddy et al., 2009).

While the cellular mechanisms by which the above signaling pathways coordinate *C. elegans* behavior with pathogen resistance remain to be explored, the immune responses of other animals have also been associated with certain behavioral responses, such as decreased appetite [reviewed by (Hart, 1988; Exton, 1997); (Adamo, 2005; Ayres and Schneider, 2009)]. For example, the moth *Manduca sexta* (Adamo, 2005), the fruit fly *Drosophila* (Ayres and Schneider, 2009) and mammals [reviewed by (Hart, 1988; Exton, 1997)] can exhibit reduced feeding upon infection. Interestingly, loss of the sensory receptor *Gr28b* in *Drosophila* not only causes a food-restricted phenotype but also leads to a surprising variability in the animal's innate immune responses: increased tolerance of *Salmonella typhimurium* versus decreased resistance to *Listeria monocytogenes* (Ayres and Schneider, 2009). This variability in the immune responses of *Gr28b* mutants could arise from the loss of coordinated transcription of different antimicrobial genes (Ayres and Schneider, 2009), which again supports the idea that the sensory system coordinates several physiological outputs to optimize survival, whether it is in *C. elegans* or other animals.

4. A mechanism for optimal survival: the ILP-to-ILP network

How does an animal orchestrate a wide range of diverse physiological outputs, such as development, metabolism, lifespan, as well as behavior, in response to complex environmental cues? Several recent studies have provided insights into a possible mechanism, *i.e.*, the combined functions of a *C. elegans* ILP family, which could coordinate

multiple physiological traits that are important for survival (Cornils et al., 2011; Chen et al., 2013; Fernandes de Abreu et al., 2014).

The *C. elegans* genome encodes 40 putative ILP genes, some of which are expressed in different subsets of sensory neurons and/or interneurons (Pierce et al., 2001; Li et al., 2003; Husson et al., 2007; Cornils et al., 2011; Chen et al., 2013; Ritter et al., 2013). The ILPs are hypothesized to serve as ligands for the DAF-2 insulin-like receptor and modulate the downstream signaling cascade (Riddle et al., 1981; Vowels and Thomas, 1992; Kenyon et al., 1993; Lin et al., 1997; Ogg et al., 1997; Pierce et al., 2001; Li et al., 2003), thereby regulating physiology. Recently, the identities of the particular ILPs that regulate the dauer program, longevity (Pierce et al., 2001; Li et al., 2003; Murphy et al., 2007; Cornils et al., 2011; Fernandes de Abreu et al., 2014; Maures et al., 2014) and certain behavioral responses (Kodama et al., 2006; Tomioka et al., 2006; Chen et al., 2013) have been identified.

Notably, these ILPs act as a combinatorial code to determine distinct phenotypes, such as dauer entry, dauer exit, longevity and learning behavior (Cornils et al., 2011; Chen et al., 2013; Fernandes de Abreu et al., 2014). Thus, specific combinations of ILPs presumably process a variety of environmental inputs to promote different outputs, an idea that is also supported by the observation that specific ILPs exhibit different transcriptional responses to these inputs (Li et al., 2003; Cornils et al., 2011; Chen et al., 2013; Ritter et al., 2013).

The question then is how these multiple ILPs could modulate DAF-2 receptor signaling in response to the environment. First, it is possible that these ILPs bind as monomers, homodimers or heteromers to the DAF-2 receptor with different binding affinities (Adams et al., 2000; Lawrence et al., 2007; Alvino et al., 2011), which could then lead to different levels of cellular DAF-2 signaling and transcriptional readouts, and consequently distinct physiological outputs. Since these ILPs differ in expression patterns (Pierce et al., 2001; Li et al., 2003; Cornils et al., 2011; Chen et al., 2013; Ritter et al., 2013), the nature of the potential ILP-ILP complexes could depend on the range and stability of the ILPs in question. Some ILPs may act as long-range signals, like hormones, or they may act within circuits as short-range signals. Thus, some ILPs could induce widespread and/or local activation of the DAF-2 receptor. Second, the possibility that some of the ILPs do not bind DAF-2 has not been ruled out: these ILPs may sequester other ILPs from DAF-2 or they may bind other receptors whose activities could then modulate DAF-2 signaling, depending on the environmental context.

While the nature of the ILP-receptor interactions remains to be resolved, the *C. elegans* ILP family has been shown to be organized into an ILP-to-ILP transcriptional regulatory network, which suggests a mechanism through which phenotypic specificity and combinatorial coding can be implemented (Chen et al., 2013; Fernandes de Abreu et al., 2014). Such network organization could coordinate different subsets of ILP activities in various processes, where certain ILPs serve as important information relays within this network. One such ILP is INS-6, which acts from different neurons to relay different sensory inputs that would specifically regulate developmental plasticity versus behavioral plasticity, or longevity (Cornils et al., 2011; Chen et al., 2013; Fernandes de Abreu et al., 2014). Under optimal environmental conditions, *ins-6* acts from the ASI sensory neurons to inhibit dauer entry or facilitate a learned aversion of bad food sources (Cornils et al., 2011;

Chen et al., 2013). However, dauer-inducing conditions down-regulate *ins-6* expression in ASI (Cornils et al., 2011; Chen et al., 2013), raising the possibility that these conditions impact both development and behavior via regulation of *ins-6*. Thus, these findings suggest how integration of sensory information through the ILP network can coordinate distinct physiological processes under diverse environments to enhance survival.

5. Perspectives

It is a given that our complex environments have a strong impact on our physiology. However, due to the complex nature and lack of a complete map of the mammalian brain, the neuronal and molecular mechanisms that underlie these environmental influences on physiology would be much harder to address in mammals. In this review, we have highlighted the advantages of *C. elegans* as a model organism in which to dissect how sensory processing optimizes survival. Indeed, the discovery of an ILP network (Fernandes de Abreu et al., 2014) that could implement combinatorial coding of diverse environmental inputs into specific phenotypic outputs offers an intriguing mechanism through which sensory integration orchestrates an animal's physiology. Other animals, including mammals and humans, also have large ILP families (Brogiolo et al., 2001; Ikeya et al., 2002; Rulifson et al., 2002; Sherwood, 2004; Colombani et al., 2012; Garelli et al., 2012) that are expressed in neuroendocrine tissues that could process sensory inputs. For instance, *Drosophila* has eight ILPs (Brogiolo et al., 2001; Ikeya et al., 2002; Rulifson et al., 2002; Colombani et al., 2012; Garelli et al., 2012), whereas humans have ten, which include the relaxin peptides (Sherwood, 2004). Moreover, the roles of ILP signaling in physiology are conserved across species (Kenyon et al., 1993; Man et al., 2000; Clancy et al., 2001; Tatar et al., 2001; Blüher et al., 2003; Holzenberger et al., 2003; Kodama et al., 2006; Tomioka et al., 2006; Taguchi et al., 2007; Kauffman et al., 2010; Chen et al., 2013). Thus, it would be exciting to determine in the future: (1) whether the ILP families in these other animals also act as a combinatorial code in processing sensory information into specific phenotypic traits; and (2) whether these animals' ILP families are also organized into networks that allow coordination of different physiological readouts for increased survival.

Acknowledgements

We apologize to the authors whose work we were unable to cite due to space constraints. This work was supported by Wayne State University to J. A. and The Esther A. and Joseph Klingenstein Fund, March of Dimes Foundation, The Alfred P. Sloan Foundation, The John Merck Fund and NIH (R01 DC009852) to Y. Z.

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Highlights

- Importance of *C. elegans* in dissecting the sensory circuits for optimal survival
- The sensory system coordinates multiple physiological traits to promote survival
- The sensory influence on lifespan
- The impact of developmental plasticity and behavior on lifespan
- An insulin-like peptide network that orchestrates physiology for survival

Figure 1.

A schematic diagram of the *C. elegans* anatomy. The nervous system of the animal is shown, which consists of the head ganglia, the nerve ring, the dorsal and ventral nerve cords, a few lateral neurons and the tail ganglia. Many of the animals' sensory neurons are found in the head and tail ganglia. A few of the sensory neurons are also found throughout the length of the animal. This diagram is drawn according to www.wormatlas.org.

Figure 2.

The *C. elegans* hermaphrodite life cycle. *C. elegans* development progresses through four larval stages (L1-L4) prior to reproductive adulthood under favorable conditions, *i.e.*, abundant availability of bacterial food sources, low population density and ideal temperatures. When presented with harsh conditions, *C. elegans* L1 larvae undergo an alternate developmental program, known as dauer. When conditions improve, dauer larvae, which are developmentally arrested, can exit into L4 to become a reproductive adult.

Figure 3.

Context-dependent sensory effects on *C. elegans* lifespan. (A) Chemosensory neurons detect food type-derived cues that inhibit or promote longevity. (B) A decrease in food intake levels, also commonly known as dietary restriction, increases the lifespan of *C. elegans* through the chemosensory neuron ASI, which involves *skn-1* signaling. (C) Male *C. elegans* secrete pheromone(s) that shorten the lifespan of hermaphrodites. (D) *C. elegans* thrive under temperatures ranging from 15 to 25°C, which requires the activities of thermosensory neurons. See text for references.

Figure 4.

Sensory influences on developmental plasticity in *C. elegans*. Throughout their lives, *C. elegans* secrete a pheromone mixture, known as dauer pheromone, whose environmental concentration reflects population density. (A) A combination of low dauer pheromone and abundant food is detected by specific chemosensory neurons that ensure reproductive growth, *i.e.*, *C. elegans* develops from L1-L4 to become a reproductive adult. (B) In contrast, a combination of high pheromone and low food is detected by other chemosensory neurons that promote dauer developmental arrest. (C) Once in the dauer stage, environmental conditions are sensed by other neurons that either inhibit or promote exit from arrest. See text for references.