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Sensory roles of neuronal cilia: Cilia development, morphogenesis, and function in *C. elegans*

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1. ABSTRACT

In the free-living nematode *Caenorhabditis elegans*, cilia are found on the dendritic endings of sensory neurons. *C. elegans* cilia are classified as 'primary' or 'sensory' according to the '9+0' axonemal ultrastructure (nine doublet outer microtubules with no central microtubule pair) and lack of motility, characteristics of '9+2' cilia. The *C. elegans* ciliated nervous system allows the animal to perceive environmental stimuli and make appropriate developmental, physiological, and behavioral decisions. In vertebrates, the biological significance of primary cilia had been largely neglected. Recent findings have placed primary/sensory cilia in the center of cellular signaling and developmental processes. Studies using genetic model organisms such as *C. elegans* identified the link between ciliary dysfunction and human ciliopathies. Future studies in the worm will address important basic questions regarding ciliary development, morphogenesis, specialization, and signaling functions.

2. INTRODUCTION

In the nematode *C. elegans*, cilia are found on dendritic endings of sensory neurons. Ciliated sensory neurons located in the head and tail sense an extensive variety of extracellular and internal signals and mediate a wide spectrum of behaviors. In the wild, *C. elegans* lives at the water-soil interface, and must be able to navigate a complex environmental milieu. For example, animals must chemotax to attractive food sources while avoiding toxic substances. *C. elegans* cilia are sensory and nonmotile, with varieties in structure reflecting diversified sensory functions. Of the 302 neurons in the hermaphrodite, 60 have dendritic endings that terminate in cilia (1-5). The male possesses an additional 48 ciliated neurons (6). Interestingly, many of the genes required for the formation, maintenance, morphogenesis, or function of *C. elegans* cilia have human counterparts which, when mutated, cause diseases that present with

Table 1. *C. elegans* homologs of human ciliary disease genes are expressed in sensory neurons, localize to the cilium or transition zone, and have mutant phenotypes consistent with defects in ciliogenesis or sensory transduction

Expression/Function	**ADPKD**	**BBS**	**NPHP**
GFP expression pattern in ciliated nervous system:	Subset: Male only	All/most	All/most
Protein localization in cilium:	tz, cm	tz, ax	tz
Mutant defects:			
Osmotic Avoidance (Osm)	WT	√	√
Olfaction (Odr)	WT	√	√
Mating: Response (Rsp) Location of vulva (Lov)	√ √	WT WT	√ WT
GFP-tagged PKD-2 ciliary localization	√	WT	√
Lipid Storage	N.D.	√	N.D.

tz, transition zone; ax, ciliary axoneme; cm, ciliary membrane; N.D., not determined; WT, wild type; √, defective, ADPKD homologs are PKD1 = *lov-1*; PKD2 = *pkd-2*; MKS homologs are MKS1 = *mks-1* or *xbx-7* (Efimenko *et al.*, 2005); MKS3 = *mks-3* (cosmid number F35D2.4); BBS homologs are BBS1 = *bbs-1* (Y105E8A.5); BBS2 = *bbs-2* (F20D12.3); BBS3 = *bbs-3* (C38D4.8); BBS4 = *bbs-4 (*F58A4.14); BBS5 = *bbs-5* (R01H10.6); BBS7 = *bbs-7* (Y75B8A.12); BBS8 = *bbs-8 (*T25F10.5); BBS9 = *bbs-9* (C48B6.8); NPHP gene homologs are NPHP1 = *nphp-1*; NPHP2/inversin = Y32G9A.6, NPHP4 = *nphp-4*. The *C. elegans* genome does not possess homologs to all human ciliopathy genes. For example, there is no *C. elegans* counterpart of the human ARPKD gene product fibrocystin. For a comprehensive list of references, readers are directed to these reviews (7, 8).

cystic kidneys, including autosomal dominant polycystic kidney disease (ADPKD), Bardet-Biedl Syndrome (BBS), Meckel Gruber Syndrome (MKS), and Nephronophthisis (NPHP) (Table 1, (7, 8)).

Vertebrate primary cilia are best known for their sensory roles. In the visual system, the connecting cilium between the outer segment and the cell body in rod and cone cell is a modified primary cilium. Olfactory neurons possess primary cilia that are endowed with G protein coupled receptors (GPCRs) and signaling molecules. In the inner ear, the microtubule based kinocilium is connected to actin-based stereocilia via tip links. Primary cilia are also located on many non-dividing cells, and very recently have been shown to have important roles in physiology and development (9, 10). The wide range of primary cilia function is reflected by diversity in morphology and molecular components of each cilium type. While the same basic intraflagellar transport (IFT) machinery constructs all cilia, the mechanisms contributing to ciliary diversity are poorly understood.

3. ANATOMY OF THE *C.ELEGANS* CILIATED NERVOUS SYSTEM

The majority of the ciliated sensory neurons are concentrated in the head of the worm. From the nerve ring, dendrites lead to the nose, where cilia reside (Figure 1). Some cilia are exposed to the environment whereas the others are embedded in structural cells or the cuticle. Based on ultrastructural anatomy, the former are putative chemosensors while the latter likely function in a mechanosensory capacity.

C. elegans sensilla are comprised of glia-like structural cells (sheath and socket) and ciliated neurons. Both the sheath and socket cell encapsulate the dendrite (s) of ciliated neurons, but the socket cell lies more distally and often has an opening to the exterior (1, 11). The sheath and socket cells are responsible for dendrite extension to nose tip, dendritic pathfinding, tubulogenesis, and axon guidance (12-14).

The major sensory organs in the head are amphid sensilla which are comprised of a left and right pair of 12 neurons that can be divided into three different subtypes. The amphid channel neurons, of which there are eight, possess a simple 'rod like' ciliary structure and deliver chemosensory and mechanosensory functions (Figure 2a, details discussed below). The three pairs of amphid wing neurons (AWA, AWB, AWC) display an elaborate structure and are embedded in the sheath cell. The amphid wing neurons constitute the olfactory organ that sense many volatile odorants. One pair of amphid finger (AFD) neurons detects temperature and has a short cilium with many finger-like microvilli.

The cephalic (CEP) and outer labial quadrant (OLQ) sensilla exist in four sets in the head, constituting largely mechanosensory capacity. The paired outer labial lateral (OLL) sensilla possess a single cilium. Cilia of CEP, OLQ, and OLL reside beneath the cuticle (Figure 2b). At the apex of nose-tip, there are six inner labial sensilla each containing two inner labial neurons (IL1 and IL2). The IL1 cilia are embedded and involved in mechanosensation while IL2 cilia are exposed and proposed to be chemosensory (Figure 2c). Lastly, there are two other ciliated mechanosensory neurons BAG and FLP on the lateral tips of the head. In the tail, two phasmid neurons (PHA and PHB) on each side (left and right) have exposed cilia that are similar in structure to the single rod-like amphid channel cilia (Figure 2d). Most of amphid channel and phasmid neurons fill with fluorescent dye (Dye-filling, Figure 4a, detailed discussion later). When the worm encounters a chemical repellent such as SDS, phasmid and amphid neurons act antagonistically to regulate reversals required for escape behaviors (15). A subcuticular mechanosensary cilium is found on each of four lateral deirid ADE and PDE neurons (Figure 2e). In AQR and PQR neurons, a rudimentary cilium is exposed to the pseudocoelomic body fluid and involved in oxygen sensation and social feeding behavior (16).

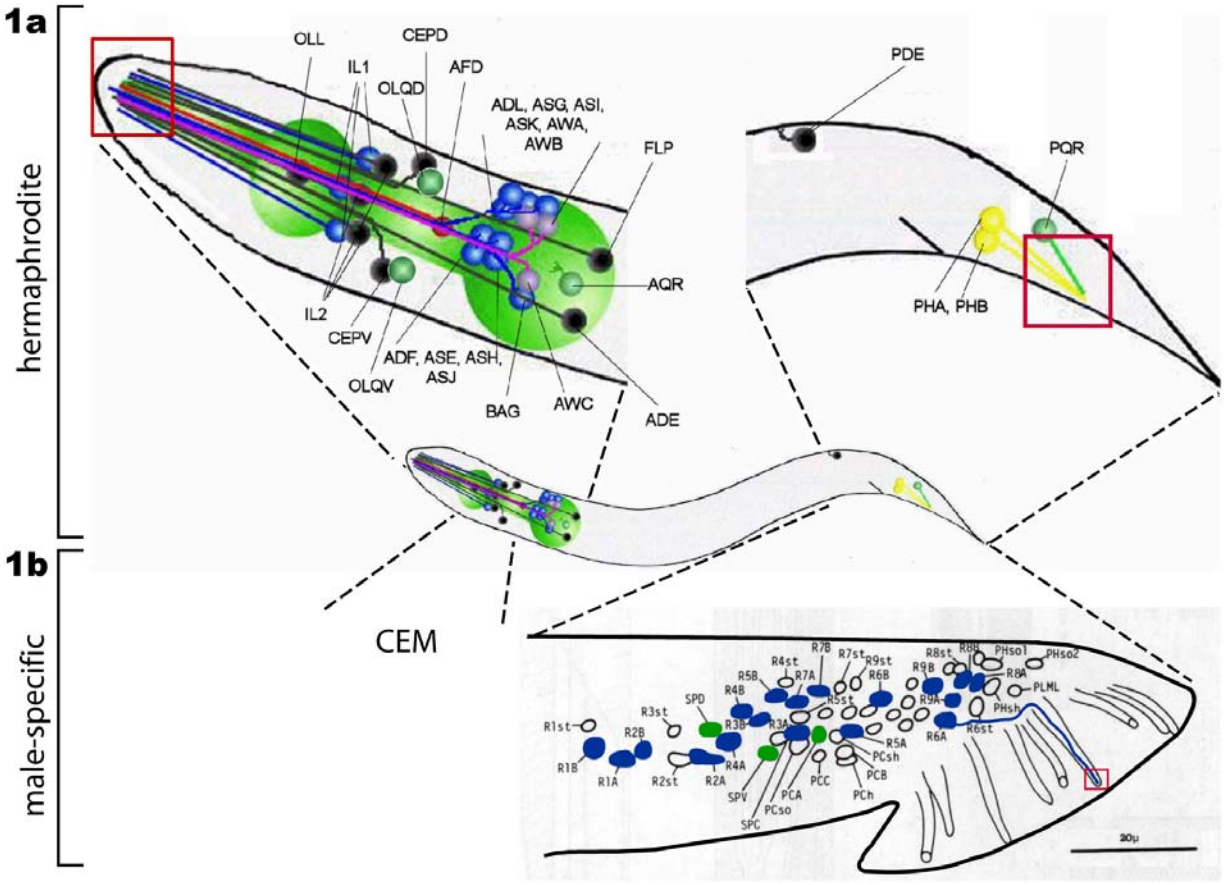

Figure 1. *C. elegans* ciliated sensory neurons. 1a. Ciliated sensory neurons are concentrated in the hermaphrodite head. This image is a lateral view from the left side. The core (non-sex specific) neuronal cell bodies are indicated with the names. The locations of ciliary endings are indicated as red box. ADL, ASG, ASI, ASK, ADF, ASE, ASH, and ASJ are amphid channel neurons. AWA, AWB, and AWC are amphid wing neurons. ADE, anterior deirid; AFD, amphid finger; CEPD, cephalic dorsal; CEPV, cephalic ventral; IL1 and IL2, inner labial 1 and 2; OLL, outer labial lateral; OLQD, outer labial quadrant dorsal; OLQV, OLQ ventral; PDE, posterior deirid; PHA/PHB, phasmid A/B. This cartoon is adapted from the Wormbook chapter (Inglis *et al.*: The sensory cilia of *C. elegans*, (2007)) with permission. 1b. The male possesses additional ciliated CEMs neurons in the head (not shown). The rest of male-specific ciliated sensory neurons are located in the tail: ray RnA/RnB (n=1-9, blue), spicule (SPV and SPD, green), p.c.s (PCA, green), and hook HOA/HOB (not shown). In this figure, the positions of left nuclei are shown. R6B dendritic process is drawn (blue line) from the cell body to the ray tip, where the cilium resides (red box). CEM, cephalic male; PCA/PCB/PCC, postcloacal; PCso; postcloacal socket; PCh, postcloacal hypodermal; PCsh; postcloacal sheath; PLML, posterior lateral microtubule left, RnA/RnB, ray neuron A/B (n=1-9); Rnst; ray structural; SPC/SPD/SPV; spicule neurons; The schematics of other dendrites are similar. Reproduced from (6) Copyright (1980), with permission from Elsevier.

The *C. elegans* males possess 87 additional male-specific neurons (17), of which 48 are ultrastructurally confirmed to be ciliated (Figure 1b). The four CEMs are the only male-specific neurons in the head, terminating in exposed cilia at the nose-tip. The CEMs neurons are responsible for chemo-attraction toward hermaphrodite- and female-driven cues (18, 19). With the exception of the CEM head neurons, these male-specific sensory neurons are located in the tail, which mediates male copulatory behaviors. In male tail, each of nine bilateral ray sensilla (numbered 1-9 from anterior to posterior) has a pair of cilia: RnA and RnB (n=number of the ray). The encapsulated A-type cilium lays side-by-side to the exposed (except for R6B) B-type cilium (Figure 2f). Ray neurons are required for a male to respond to contact with a potential mate and to turn at the end of the mate's body (20). A similar pairing of two cilia is observed in the hook sensillum, composed of HOA and HOB neurons. Similarly, HOB cilia are exposed whereas HOA are not (Figure 2g). Ablation of either hook neuron specifically abrogates location of vulva behavior during copulation, resulting in the location of vulva (Lov) defective phenotype.

The SPV and SPD spicule neurons are ciliated, exposed to the environment and proposed to sense sensory cues from the mate's uterus (Figure 2h, (20, 21)). The postcloacal sensilla (p.c.s.) are comprised of a left-right

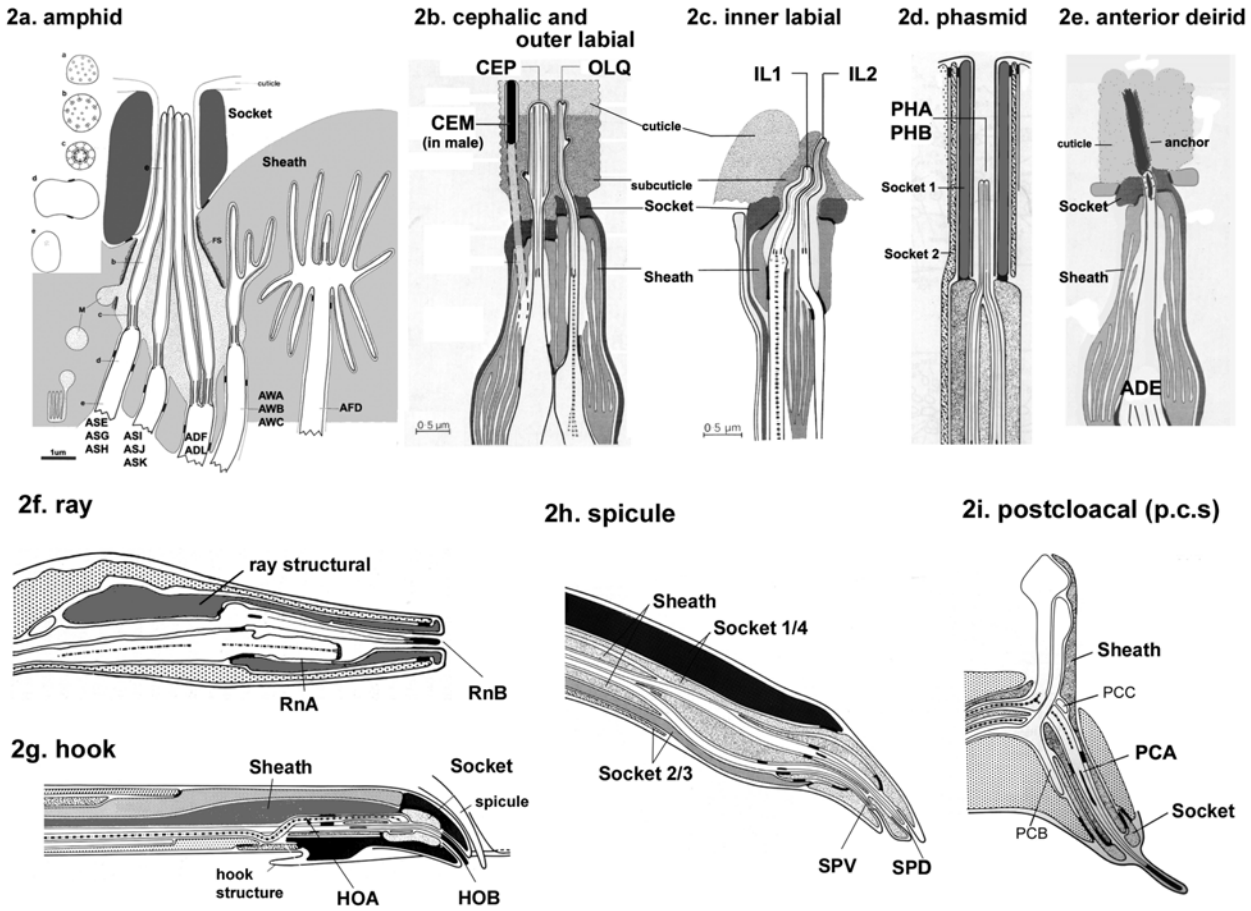

Figure 2. Ultrastructure of *C. elegans* cilia. 2a. Cilia in the amphid sensillum exhibit a variety of morphologies. The rod-like channel cilia are found in ASE, ASG, ASH, ASI, ASJ, ASK, ADF, and ADL neurons. ADF and ADL possess two cilia each, while the other cells possess a single cilium. These cilia are exposed to the environment through the cuticle. The amphid wing neurons (AWA, AWB, AWC) have complex ciliary structures. The AFD neuron possesses multiple villi. The sheath and socket cell encapsulate the amphid channel cilia, whereas the sheath cell encloses the amphid wing (AWA/AWB/AWC) and AFD cilia. Cross section views are shown on the left (a-e). This is modified from (4), Copyright (1986), with permission from Elsevier. . 2b. The cephalic and outer labial sensillum. In the male, the CEM neuron is also located in the cephalic sensillum. 2c. The inner labial sensillium contains IL1 and IL2 neurons. IL2 is embedded within subcuticular structure, while IL1 is exposed to the exterior. 2b and 2c were modified from (1) Copyright (1975, Ward *et a*l) with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. 2d. The phasmid sensillum in the tail. The PHA and PHB cilia extend in parallel to each other. Two phasmid socket cells (socket 1 and 2) surround the sensillum. 2e. The anterior deidrid ADE cilia. The image was provided by Sam Ward. 2f. Each ray sensillum contains a pair of cilia: RnA and RnB. RnA cilia are embedded whereas RnB (except R6B) cilia are exposed. The ray structural cell functions as both socket and sheath cell. 2g. The hook sensillum encloses HOA (embedded) and HOB (exposed). 2h. The spicule sensillum has SPV and SPD ciliated neurons, four syncytial socket cells, and two syncytial sheath cells. 2i. The postcloacal sensillum (p.c.s.) possesses one ciliated neuron (PCA), which ciliary tip ends within the cuticle. 2d and 2f-2i. Reproduced from (6) Copyright (1980), with permission from Elsevier.

arrangement of three neurons, of which one (PCA) pair is ciliated (Figure 2i). The p.c.s. acts in concert with the spicule neurons to regulate vulva prodding, spicule insertion, and sperm transfer into mate's uterus (20, 22).

Previous research on *C. elegans* anatomy, invariant cell lineage, and neuronal circuits has provided valuable tool sets for studying neuronal development and function. However, this 'simple' nervous system is capable of generating sophisticated behaviors. For example, the *C. elegans* nervous system exhibits plasticity as well as gender-specific differences between the hermaphrodite and male. The male wiring project (S.W. Emmons, M.Xu, and D.H.Hall, personal communication), which is actively in progress, will provide insights into how the core and male-specific neurons are specified and connected to govern diverse behaviors.

4. CILIA DEVELOPMENT – INTRAFLAGELLAR TRANSPORT

C. elegans cilia are built by an evolutionarily conserved mechanism called Intraflagellar transport (IFT) (Figure 3). The IFT machinery is driven by the anterograde

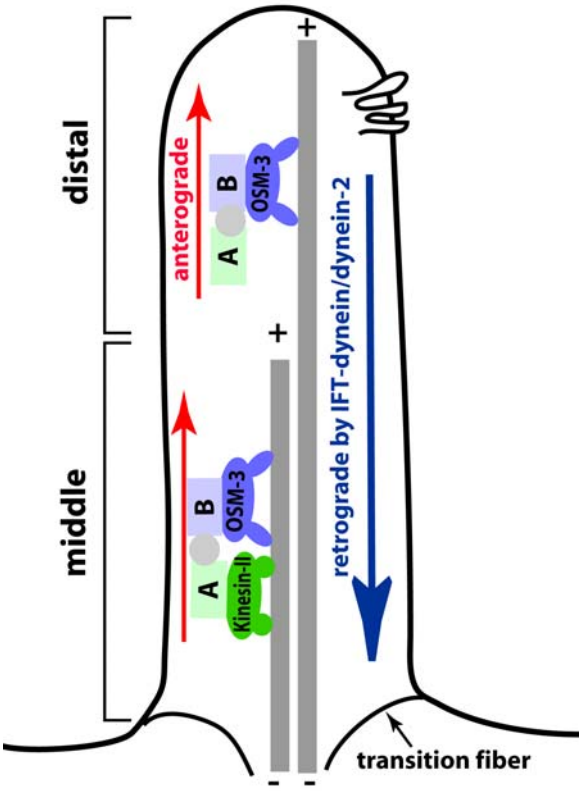

Figure 3. Intraflagellar transport (IFT) builds cilia. A simplified cartoon of IFT process in *C. elegans* amphid channel cilia. Two anterograde motors (OSM-3 and Kinesin-II) move IFT complexes on the microtubule doublets in the 4 um-long middle segment. In the 2 um-long distal segment, OSM-3 motor acts alone. The cytoplasmic dynein-2 (IFT-dynein) brings the IFT complex back to the base of the cilium. The six transmembrane protein in the ciliary membrane is a representative of sensory receptors in the cilium.

motor Kinesin-2 and the retrograde motor cytoplasmic dynein-2 (23). Associated with the IFT machinery are IFT subcomplex A, IFT-subcomplex B, IFT regulators, and cargos. First identified in the green algae *Chlamydomonas*, IFT process is essential for ciliogenesis in every organism examined to date. *C. elegans* has been particularly useful for studying IFT using *in vivo* time lapse video microscopy with green fluorescent protein (GFP)-tagged IFT components in combination with powerful genetic tools (24).

In *C. elegans,* the amphid channel cilia are divided into three ultrastructurally distinct segments: proximal, middle, and distal (Figure 3, (4)). The proximal segment, or "transition zone" is a modified basal body approximately 1 um in length and the place where IFT proteins accumulate for transport into the cilium proper (25). The 4 um-long middle segment of the cilium contains doublets of microtubules, whereas the 2 um long distal segment encloses singlets. In amphid channel neurons, two types of Kinesin-2 motors (homodimeric OSM-3 and heterotrimeric Kinesin-II) function redundantly to construct the middle segment of the cilium, while OSM-3 acts alone to build the distal segment. Recent studies using *C. elegans* genetics and comparative genomics have identified a myriad of components acting in the IFT process (26). For an extensive summary on IFT and cilia, readers are directed to recent reviews (24, 27).

Although the IFT process builds every cilium, specialization is essential for both ciliary structure and function. Specialization of *C. elegans* sensory cilia occurs through a number of ways, including modulation of the IFT process (28-31), development of different ciliary structures (compare rod-like channel and finger-like wing cilia in Figure 1, (4)), and expression of a distinct set of sensory receptors and signaling molecules (32-35). *C. elegans* sensory cilia provide a unique and valuable tool to understand how ciliogenesis diverges from the core IFT process to produce functional diversity within the nervous system.

5. *C. ELEGANS* SENSORY ROLES OF CILIA

C. elegans continuously perceives its surroundings and adjusts its behaviors in order to survive its natural environment. In the laboratory, *C. elegans* exhibits a variety of sensory behaviors, including the drive for food, attraction/repulsion to chemicals, pursuit of mates, search for comfortable temperature, and entry or exit from the alternative dauer developmental stage. These sensory behaviors are mediated by cilia. Mutants with severe ciliary formation defects exhibit defects in most, if not all, sensory behaviors. One of the advantages of using *C. elegans* is genetic amenability that includes the hermaphroditic life cycle and ease in which to perform forward genetic screens (36-39). Genetics combined with the complete wiring diagram of the animal, electrophysiology, and *in vivo* optical imaging of calcium transients enables dissection of neural circuitries that control sensory behaviors (3, 40, 41). This approach yielded many genes acting in ciliary development and sensory neuron function. In this section, we will discuss how *C. elegans* interprets its surroundings into behaviors.

5. 1. Chemosensation

The simple soil living nematode *C. elegans* developed a fine taste of likes and dislikes among chemicals. Approximately 5% of the *C. elegans* genome is devoted to chemical recognition (42, 43). Some chemicals, whether soluble or volatile, are attractive while others are repulsive. When there is a gradient of an attractant on a plate, worms move towards the source (Figure 4b). Chemical cues also elicit escape behaviors, changes in locomotion, and trigger both developmental and physiological process.

Genetic screens identified different types of chemosensory mutants including *che* (chemotaxis towards Na^+ and Cl^- defective), *daf* (dauer formation defective), *osm* (osmotic avoidance defective), *odr* (odorant response defective), and *tax* (general chemotaxis defective). A subset of amphid and phasmid ciliated neurons fills with lipophilic fluorescent dyes such as FITC and DiI (Figure

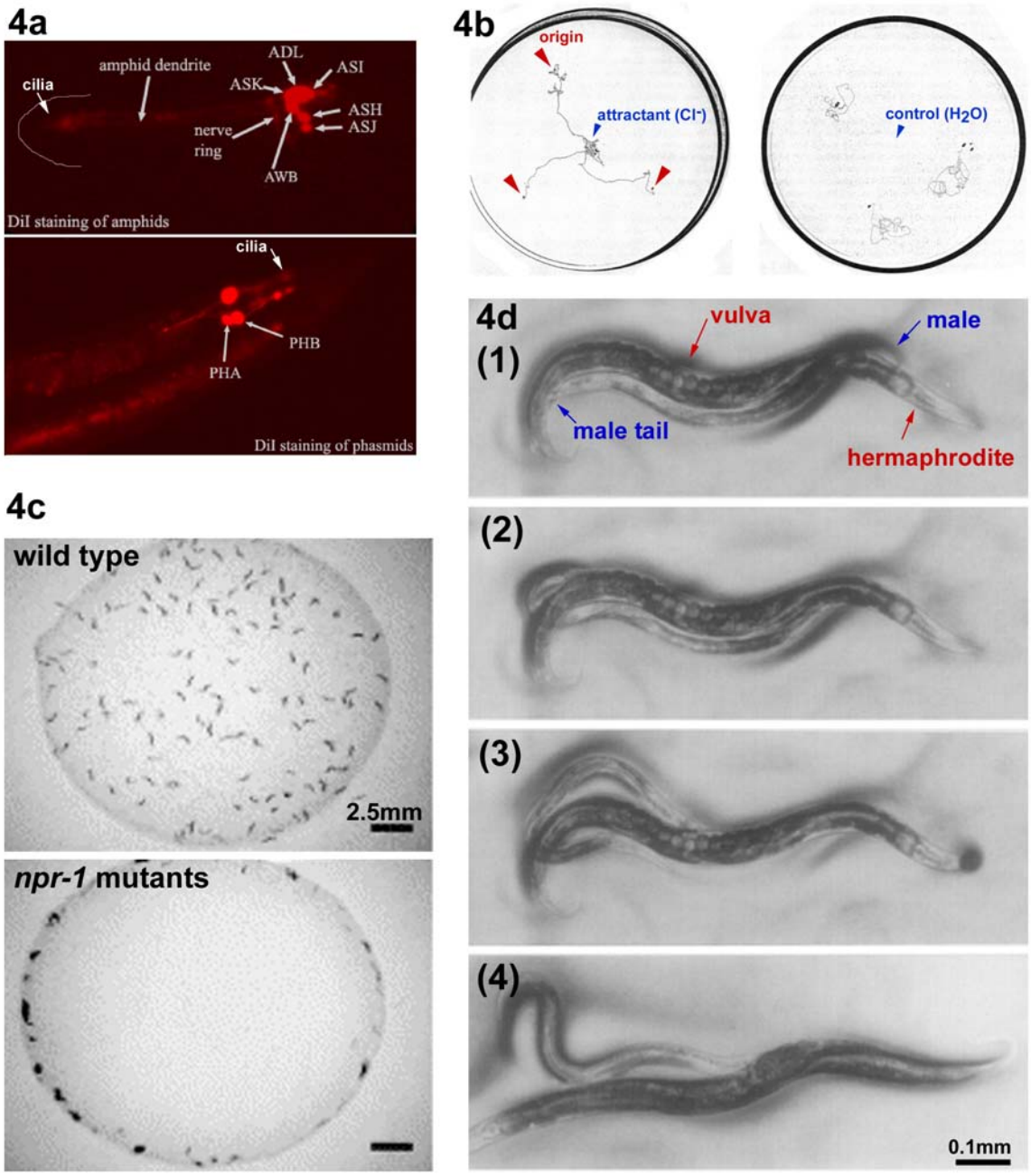

Figure 4. Assays for *C. elegans* ciliated neurons. 4a. Dye-filling assay. When worms are soaked in a lipophilic dye such as DiI, FITC, and DiO, certain ciliated sensory neurons fill with the dye. In this picture, DiI-filling in amphid and phasmid neurons are shown. This is adapted from Wormbook chapter (Shaham, Methods in Cell Biology (2005)) with permission. The original image is provided by Zeynep Altun, www.wormatlas.org. 4b. Chemotaxis. Worms are attracted to the Cl^- gradient towards the center of the plate. The worm tracks from the three origins indicated by the red arrowheads (left panel). When water is placed in the center as control, worms do not exhibit chemoattraction behavior (right panel). These images are modified from Ward *et al*, (1973). 4c. Social feeding. The laboratory standard strain N2 is a solitary feeder (top panel), whereas a natural isolate CB4856 and *npr-1* N2 mutants are social feeders (bottom panel). Social feeders also aggregate at the border of a bacterial lawn. These images are modified (61) Copyright (1998), with permission from Elsevier. 4d. Male Mating. (1) A male exhibits 'response' behavior by starting a backward movement with his ventral tail on the hermaphrodite body. (2) While continuing backing, he turns at the end of the body. In search of the vulva, his tail scans along the hermaphrodite. (3, 4) At the vulva, he stops backing and adjusts the precise location by fine back and forth movements to insert spicules (vulva location and spicule insertion). These images are reproduced from (20) Copyright (1995), with permission from Elsevier.

4a). Using this assay, *Dyf* (dye-filling defective) mutants were isolated (4, 26, 44). Although the exact mechanism of dye-filling is unknown, it is generally assumed that the exposed cilium takes up the dye from the outside and stains the entire neuron. Most of *Dyf* mutants exhibit defects both in general ciliogenesis and chemotaxis. However, it is worth noting that worms expressing a constitutively active form of GPA-3 (a G alpha subunit) are *Dyf* without apparent ciliogenesis defects (45). In contrast, Kinesin-II *kap-1* and *klp-11* mutants are non-*Dyf* but have defects in IFT and ciliary morphogenesis (28-30, 46). Using relatively simple assays (such as dye-filling, chemotaxis, and osmotic avoidance), *C. elegans* geneticists have identified a wealth of mutants with defects in ciliary structure and function ((4, 26, 44), J. Hu and M.M.Barr personal communication). From these screens, there remain many uncloned loci, hinting that far more molecular mechanisms in ciliated sensory neurons remain to be discovered.

Cloning of *che, daf, osm, odr*, and *tax* mutations have revealed two major categories of genes. First, genes required for general ciliogenesis such as the IFT machinery were identified. In this category, most, if not all, ciliogenesis is abrogated, resulting in stunted/malformed cilia that are functionally compromised. The second class includes genes encoding cell-type specific membrane receptors and downstream signaling molecules. Mutations in this class do not preclude general ciliogenesis, but cause specific cilium structural and/or sensory defects. For example, mutant phenotypes in *Odr* and some *Daf* mutants are restricted to a subset of chemosensory defects. This category will be discussed in a later section.

Extensive studies on molecular mechanisms of IFT regulation revealed functional modules acting in *C. elegans* amphid channel cilia (26). In addition to the core IFT-A and IFT-B that were originally isolated via biochemical approaches in *Chlamydomonas* (47-50), BBS (Bardet-Biedl syndrome) proteins (51), anterograde motor Kinesin-II and OSM-3 (52), the retrograde motor dynein-II complex, and linkers between modules were identified (46, 53-55). Furthermore, previously known chemotaxis mutants fall into one of the functional modules by genetic and phenotypic analysis of IFT in amphid cilia (26). In contrast, cell-type specific regulation of IFT is not well understood. It will be interesting to determine how cilia in sensory neurons in *C. elegans* are specialized for their function in terms of IFT regulation as well as receptor-signaling pathway aspects.

5. 2. Mechanosensation

C. elegans responds to various types of mechanical stimuli, including nose touch, viscosity of the bacterial food lawn, and mating cues. Among these, light nose touch avoidance behavior requires ciliated neurons evoking backward movement upon encountering an obstacle (an eyelash in assays) at the nose tip.

Nose touch response is mediated by three sets of ciliated head neurons in the head: two ASHs, four OLQs, and two FLPs. Although these neurons act in parallel in nose touch response, each neuron mediates a fraction of the behavior: ASH 45%, FLP 29%, and OLQ 5% (56). The ASH, an amphid channel neuron, is a master nociceptive neuron in *C. elegans*. As a polymodal neuron, ASH has an exposed cilium and senses various repulsive signals, such as nose touch (56), high osmolarity (57), and noxious chemicals (32, 58). All of these stimuli evoke the same simple behavior: a rapid backward movement to reverse directions. Unlike ASH cilia, OLQ and FLP cilia are encased in the cuticle.

A worm slows down when entering a bacterial lawn. The basal slowing response requires four CEPs, two ADEs, and two PDE neurons (59). In these neurons, cilia are embedded in the cuticle: CEP cilia at the nose tip, ADE and PDE cilia in the anterior and posterior deirid sensilla along the body. Well-fed worms entering a bacterial lawn sense the changes in viscosity by these subcuticular cilia, resulting in the reduction of locomotory rate. This basal slowing response is dependent on dopamine. Consistent with this observation, CEP, ADE, and PDE are the only dopaminergic neurons in the hermaphroditic nervous system. *C. elegans* also exhibits a characteristic head movement, called foraging behavior. When encountered by an object during foraging, worms show a rapid head withdrawal reflex, which is mediated by four OLQ and six IL1 head neurons. Additionally, OLQ and IL1 neurons regulate the rate of spontaneous foraging (60).

5. 3. Social Behavior

C. elegans social feeding behavior refers to aggregation on a bacterial lawn (Figure 4c). A natural isolate *C. elegans* strain CB4856 and neuropeptide receptor *npr-1* mutant of the laboratory standard N2 strain exhibit social feeding behavior. The social feeders also accumulate at the edge of the bacterial lawn, which is referred as bordering (61). The social behavior is mediated by integration of information from nociceptive head neurons, oxygen levels, and food (16, 61-63). In ASH and ADL ciliated neurons, TRPV channels OSM-9 and OCR-2 sense the signals to promote social feeding and bordering. This activity, interestingly, is suppressed by other ciliated neurons, suggesting involvement of multiple sensory inputs (63).

Oxygen sensation by AQR, PQR (ciliated), and URX (non-ciliated) neurons is also required for social feeding and bordering (16, 62, 63). Supposedly, environmental oxygen levels are reflected in the pseudocoelomic body fluid, to which the AQR and PQR cilia are exposed. In these neurons, the soluble guanylate cyclase GCY-35 functions as an oxygen sensor by directly binding to molecular oxygen. The downstream cyclic GMP channels TAX-2/TAX-4 promote the AQR/PQR/URX neuronal activity, which is suppressed by NPR-1 (64).

5. 4. Complex behaviors: male copulation

The *C. elegans* mating behavior is largely one-sided; males are obsessed with pursuing self-fertile and disinterested hermaphrodites. However, the adult hermaphrodite does provide chemical and mechanical cues

to the male. Accordingly, the male-specific nervous system is dedicated to male sexual behaviors (6, 20, 65). Male mating is the most complex *C. elegans* behavior. A typical male mating ritual can be divided into sub-steps, including [1] attraction to long- and short-range hermaphrodite chemical cues, [2] response to contact with the hermaphrodite, [3] backing and turning along the mate's body, [4] location of vulva, [5] copulatory spicule insertion into the vulva, and [6] sperm transfer to the uterus (Figure 4d). During this copulatory process, the male utilizes male-specific ciliated neurons (Figure 1b) to perceive both chemical and mechanical signals from the hermaphrodite.

5.4.1. Sexual attraction

The adult hermaphrodite provides chemical cues to attract the males. In a 'holding assay' with hermaphrodite-conditioned agar plates, only adult males exhibit frequent backward movement and linger in the conditioned part of the plate (66). Intact cilia are required for detection of this hermaphrodite cue. In another assay that measures sex drive, adult males leave a food source in search of a mate at a higher frequency than hermaphrodites or larval males, which prefer to stay in bacterial lawns (67). This male 'leaving behavior' is suppressed by a hermaphrodite on the food source, suggesting that short range chemical and mechanical cues are provided by hermaphrodites.

The male may detect long-range chemical cues from potential mates using four CEM male-specific head neurons. A potent female-derived pheromone from female-male species of *Caenorhabditis* (*C. remanei* and *C. sp*.) is reported to attract *C. elegans* males (18). Killing the CEM neurons significantly diminishes male chemotaxis toward the female-derived pheromone, indicating that the CEMs are required for detecting chemical cues. The male specific ciliary receptors PKD-2 and LOV-1 are required for chemotaxis to the female pheromone (18). These data suggest that PKD-2 and LOV-1 receptors in CEM neuronal cilia act as chemosensors of the female-derived pheromone, indicating a multiplicity of pheromone receptors acting in the male nervous system. This is in contrast to the 'holding assay' where *pkd-2* and *lov-1* are not required (65). It will be interesting to define the differences in content and potency in hermaphrodite and female-derived chemical cues.

5.4.2. Response

When a male comes in contact with a potential mate, he ceases forward locomotion, places the ventral side of his tail onto the mate's body, and starts backing. This process is called 'response' and is dependent on bilateral ray neurons (1 to 9) in the tail. Each ray process consists of a glia-like structural cell and two ciliated neurons, RnA and RnB (n=1-9) (Figure 2f). These three cells are encapsulated in the cylindrical cuticle (6). Dorsally open rays (numbered 1, 5, and 7) are responsible for response to dorsal contact with a potential mate. Ventrally open rays (numbered 2, 4, and 8) mediate response to ventral contact (20). The requirement of mechanosensation for response behavior seems obvious; however, response may also require short-range chemical cues from hermaphrodites (J. Wang and M.M.B., personal communication).

Mutants with general ciliogenesis defects (*osm-1, osm-5, osm-6*, and *che-3*) exhibit response, location of vulva, and premature sperm transfer defects (34, 49). Specific sensory defects without abnormal ciliogenesis were found in *pkd-2*, *lov-1*, and *klp-6* mutants (34, 68, 69). PKD-2 and LOV-1 are the *C. elegans* homologues of human *PKD2* and *PKD1,* encoding polycystin-2 and polycystin-1 respectively (Table 1). Polycystin-1/LOV-1 and -2/PKD-2 are members of the TRPP (transient receptor potential-polycystin) channel family (70). The polycystins may form a mechanosensitive channel complex on ciliary membrane in human renal epithelial cells and *C. elegans* sensory neurons. *klp-6* encodes a Kinesin-3 and regulates GFP-tagged PKD-2 localization. As expected by specific behavioral defects in *pkd-2, lov-1* and *klp-6* mutants, the genes are expressed in a subset of male-specific neurons: CEMs, RnBs (1-5, 7-9), and HOB. Additionally, *klp-6* is expressed in the core IL2 neurons, which have no known function in the *C. elegans* nervous system.

The *C. elegans* homologs of the Bardet-Biedl Syndrome and Nephronophthisis ciliopathy genes are expressed in male ciliated neurons (71, 72). However, *bbs-7, osm-12*, *nphp-1*, and *nphp-4* single mutant males exhibit wild-type response and vulva location behavior (Table 1, 34, 72). *nphp-1; nphp-4* double mutant males have a slight response defect (72). Unlike the IFT polypeptide and motor mutations, the *bbs* and *nphp* mutations do not disrupt PKD-2::GFP ciliary localization (28, 31), perhaps explaining why these mutant males mate normally.

5.4.3. Location of vulva

While backing, the male tail scans along the hermaphrodite to search for the vulva. The hook sensillum, which encloses the hook B (HOB) and hook A (HOA) neuron (Figure 2g), is required for the initial stopping in the approximate region of the vulva (20). Further adjustments by small back and forth movements allow precise location of the vulva. This latter step is mediated by p.c.s. and spicules neurons (20). Cilia are found in the majority of sensory neurons involved during vulva location. The HOB, SPV, and SPD cilia open to the exterior, whereas the HOA and PCA cilia are encapsulated in the cuticle (6). Based on the ciliary ultrastructure of the male-specific neurons, both mechanosensation and chemosensation regulate vulva location.

5.4.4. Spicule insertion and Sperm transfer

The spicules are inserted into the vulva, into the uterus, followed by sperm transfer. Like other male copulatory behavioral steps, spicule insertion involves ciliated neurons. The hook and p.c.s. neurons coordinate the initial prodding of spicules (22). The p.c.s. and spicule neurons regulate spicule penetration and the SPV ciliated neurons inhibit premature sperm transfer (20). A seven transmembrane receptor *sra-1* (serpentine receptor a) is expressed in ciliated spicule neurons, suggesting sensory role in spicule insertion or sperm transfer (32). Sperm transfer defects were observed in *osm-5* general ciliogenesis mutants, indicating sensory inputs from cilia regulate ejaculation (49).

Table 2. Sensory function of ciliated neurons in *C. elegans*

Nervous system	Sensillum	Neuron	Function	Dye-filling
Core	Amphid	ASE	Water-soluble chemotaxis, avoidance	-
		ASG	Dauer formation, lifespan, chemotaxis	-
		ASH	Nociception (osmotic avoidance, nose touch, chemorepulsion), social feeding	FITC, DiI
		ASI	Dauer formation, chemotaxis, navigation	FITC, DiI
		ASJ	Dauer recovery, chemotaxis, lifespan	FITC, DiI
		ASK	Avoidance, chemotaxis, lifespan, navigation	FITC, DiI
		ADF	Dauer formation, chemotaxis	FITC
		ADL	Avoidance, social feeding	FITC, DiI
		AWA	Volatile chemotaxis, lifespan	-
		AWB	Volatile avoidance	DiI
		AWC	Volatile chemotaxis, lifespan, navigation	-
		AFD	Thermosenation	-
	Cephalic	CEP	Mechanosensation (basal slowing response)	FITC[1]
	Outer labial	OLQ	Mechanosensation (basal slowing response and nose touch)	-
		OLL	Unknown (presumably mechanosensory)	-
	Inner labial	IL1	Mechanosensation (nose touch)	-
		IL2	Unknown (putative chemosensory)	DiI, DiO
	Phasmid	PHA, PHB	chemorepulsion	FITC, DiI
	Deirid	ADE, PDE	Mechanosensation (basal slowing response)	FITC[1]
		AQR, PQR	Oxygen sensation, social feeding	-
		BAG	Unknown	-
		FLP	Mechanosensation (nose touch)	-
Male-specific	Cephalic	CEM	Sexual attraction to pheromone	-
	Ray	RnA, RnB	Response and turning during mating	-
	Hook	HOA, HOB	Vulva location, spicule prodding	-
	Spicule	SPV SPD	Inhibition of ejaculation Sperm transfer	- -
	Postcloacal	PCA	Spicule prodding and insertion, sperm transfer	-

Column 1 refers to the "core" nervous system that is present in males and hermaphrodites or the "male-specific" nervous system that is exclusive to the male. FITC: fluorescein isothiocyanate; DiI: 1,1'-Dioctadecyl 3,3,3',3'-Tetramethylindocarbocyanine Perchlorate; [1]: occasionally dye fills with FITC. Detailed reference lists are included in Table 1.

5.5. Thermosensation

The *C. elegans* thermotaxis behavior is extremely sensitive, experience dependent, and mediated by ciliated neurons. Worms crawl to their cultured temperature in a spatial temperature gradient within a mere 0.1 Celsius degree (38). In addition, animals show short-term and long-term adaptation to the surrounding temperature. Two AFD amphid finger neurons in the head govern the sensory and adaptive aspects of thermotactic behaviors (73). The elaborate finger-like villi on the AFD ciliated neuron are embedded in amphid sheath cells. When severed at the middle of the AFD dendrite, only the distal part containing the sensory cilium and finger villi retained calcium response to temperature stimuli, suggesting that AFD sensory cilia confer thermal detection and adaptation (74).

ttx (thermotaxis defective) mutants were isolated from a genetic screen looking for athermotactic mutants (38). *ttx-1,* a homolog of otd/Otx, specifies AFD neuronal fate and function (75). *ttx-4* encodes a protein kinase C (nPKC-epsilon/eta) and negatively regulates thermosensation function of AFD neurons. *ttx-4* also act in signaling pathways in nociceptive ASH neurons and olfactory AWA and AWC neurons (76). This data suggests that a signaling molecule such as PKC may have a distinct function in different sets of neurons to regulate diverse sensory behaviors.

5.6. Adaptation

C. elegans exhibits a reduced chemotatic behavior after a prolonged exposure to a chemical. This adaptation occurs in AWC, ASE, and ASH sensory neurons (77-82). The AWC adaptation requires components in G-protein coupled receptor (GPCR) pathways, including beta-arrestin ARR-1, which is responsible for internalization of activated GPCR (83) and G alpha protein GOA-1 (82). The TRPV gene *osm-9* and an uncloned gene *adp-1* act both in AWC and ASE adaptation, suggesting these two neurons share a common genetic pathway for odorant and salt adaptation (78, 80, 84). The G gamma protein GPA-1 is involved in ASE and ASH adaptation (81, 85).

6. NEUROENDOCRINE SIGNALING

In yet another example of evolutionary conservation of function, ciliated neuron function and obesity are linked in *C. elegans*, mice, and humans (86, 87). In both worms and mammals, mutations in the *tubby* gene result in increased fat storage. The *C. elegans tub-1* homolog is expressed in the ciliated nervous system, and a TUB-1::GFP fusion protein moves along dendrites and cilia. *tub-1* and *bbs-1*, the *C. elegans* ortholog of Bardet-Biedl Syndrome gene 1, act in the same genetic pathway to control lipid homeostasis (87). *bbs-1* acts in nine classes of ciliated neurons (ASG, ASI, ASJ, ASK, AWB, AWC, AQR, PQR, URX) to send neuroendocrine signals, which in turn regulate intestinal fat storage. In addition to a role in regulating body fat content, *tub-1* also regulates lifespan via a distinct mechanism (86). *C. elegans* cilium structure mutants are long-lived and shorter compared to wild-type animals (88, 89), however what ciliated neurons mediate lifespan and body size are not known.

Table 3. Both general and cell-type specific factors regulate ciliary localization of sensory receptors

Ciliary Receptors	Cell-type specific	General
GPCR ODR-10 & STR-2	A novel transmembrane protein/ODR-4 Uncloned gene *odr-8*	AP-1/UNC-101
TRPV OSM-9	TRPV partner OCR-2 (in ASH and AWA)	AP-1/UNC-101 IFT components[1]
TRPP PKD-2	TRPP partner LOV-1, Kinesin-3 KLP-6, Casein kinase-2[2] and calcineurin TAX-6[2], Endosomal proteins STAM-1[2] and Hrs[2]	

[1] IFT involvement may be indirect and the requirement in GPCR localization is not determined; [2]The requirement of these factors in downregulating other ciliary receptors is not determined. For reference, please see the text.

7. MECHANISMS FOR CILIARY RECEPTOR LOCALIZATION

Each *C. elegans* ciliated neuron gains its functional specialty by expressing a combination of multiple sensory receptors and signaling molecules. Receptors in ciliated neurons include seven transmembrane receptors (ODR-10, STR-2, SRD-1, SRG-2), TRP channels (OSM-9, OCR-2, PKD-2, LOV-1), and cyclic nucleotide-gated channels (TAX-2), which function to initiate sensory transduction. How receptor proteins are targeted to, distributed in, and removed from the cilium is an interesting and relatively open question. Work in *C. elegans* has revealed mechanisms for ciliary localization involves both general and cell-type specific factors.

General mechanisms for ciliary localization of receptors include a vesicular transport system mediated by clathrin coated vesicle adaptor protein-1 (AP-1) (Table 3). In *unc-101* (*C. elegans* AP-1 mu1 subunit) mutants, GFP-tagged ODR-10, STR-1, STR-2, OSM-9, and PKD-2 are similarly mislocalized to the entire neurons, as opposed to the normal restricted pattern in the cilium and cell body of vastly different sets of ciliated sensory neurons (28, 90). In *C. elegans* neurons, the AP-1 complex appears to be required for packaging ciliary receptors into dendritic vesicles (90) as in polarized cells where AP-1 complex involves in protein sorting at the trans-Golgi network (91, 92). The link between vesicular trafficking and ciliary targeting has recently been shown in mammalian systems. The phosphatidylinositol-4-phosphate adaptor protein-2 (FAPP2) is required for formation of a barrier between the ciliary membrane and the apical plasma membrane in the Madin-Darby canine kidney (MDCK) cells. In the absence of FAPP2, vesicles accumulated at the base of cilia and the ciliogenesis was abrogated (93, 94). It will be interesting to determine whether this pathway operates as part of the general ciliary trafficking system in *C. elegans* sensory neurons.

In addition to the general vesicular transport system, cell-type specific factors play essential roles in ciliary localization of receptors (Table 3). In amphid wing neurons, a novel membrane protein ODR-4 and an uncloned gene *odr-8* are required for ciliary localization of two seven transmembrane odorant receptors ODR-10 and STR-2. In *odr-4* and *odr-8* mutants, GFP-tagged ODR-10 and STR-2 are retained in the cell bodies of AWA and AWC neurons, respectively, and do not localize to cilia as in wild-type animals (95). *odr-4* and *odr-8* act as specific factors for ODR-10 and STR-2 localization; other ciliary receptors such as OSM-9, TAX-2, SRD-1, and SRG-2 localize normally in *odr-4* and *odr-8* mutant backgrounds (95). When ectopically expressed in other neurons, GFP-tagged ODR-10 is only partially dependent on *odr-4* and *odr-8* for ciliary localization.

The requirement of cell-type specific factors extends to transient receptor potential (TRP) channel localization in *C. elegans*. In addition to forming functional complexes, TRP channel subunits influence subcellular localization of the partners. Two TRPV (TRP-vanilloid) channels OSM-9 and OCR-2 depend on each other for their ciliary targeting in the AWA and ASH neurons where these TRPVs function in nociception (35). Similarly, two TRPP (TRP-polycystin) proteins PKD-2 and LOV-1 facilitate each other's ciliary targeting in male specific neurons required for male mating behaviors (28). The *pkd-2* expressing neurons contain unidentified cell-type specific localizing factors for GFP-tagged PKD-2: when ectopically expressed in other neurons, unlike ODR-10 in the AWB neuron that normally do not express *odr-10*, PKD-2 is retained in the cell bodies (28). These data suggest that cell-type specific localizing factors differ in their requirement stringency, depending on ciliary receptors and neuronal cell types.

Once targeted to the ciliary region of the neuron, receptors encounter multifaceted mechanisms that regulate trafficking into, within, and out of the cilium (Figure 5). Within the cilium, the IFT process transports a GFP-tagged OSM-9 but not PKD-2, suggesting PKD-2 may be distributed in the cilium by an alternative pathway (69, 96). However, a small proportion of *Chlamydomonas* PKD-2 does move in flagella in an IFT-dependent manner (97), indicating that the majority of PKD-2 is tethered or indeed localized in an IFT-independent manner (69). Increased levels of GFP-tagged PKD-2 were observed in a number of mutant backgrounds, implicating that multiple molecular pathways are involved in downregulation of PKD-2 from the cilium (Figure 5b). These pathways include the Kinesin-3 KLP-6, IFT components, endosomal proteins STAM-1 (signal transduction adaptor molecule) and Hrs (hepatocyte growth factor regulated tyrosine kinase substrate) (28, 49, 69, 98). Posttranslational modifications also affect PKD-2 ciliary levels. STAM-1 and Hrs sort ubiquitinated PKD-2 to a lysosomal degradation pathway (98). CK2 (casein kinase 2) and TAX- 6 (the calcineurin) act antagonistically in cilia to regulate ciliary localization of PKD-2 by affecting phosphorylation status of PKD-2 (99). It is largely unknown if removal of sensory receptors from cilia via ubiquitination and/or phosphorylation is a general mechanism acting in *C. elegans* sensory neurons or conserved in other ciliated organisms.

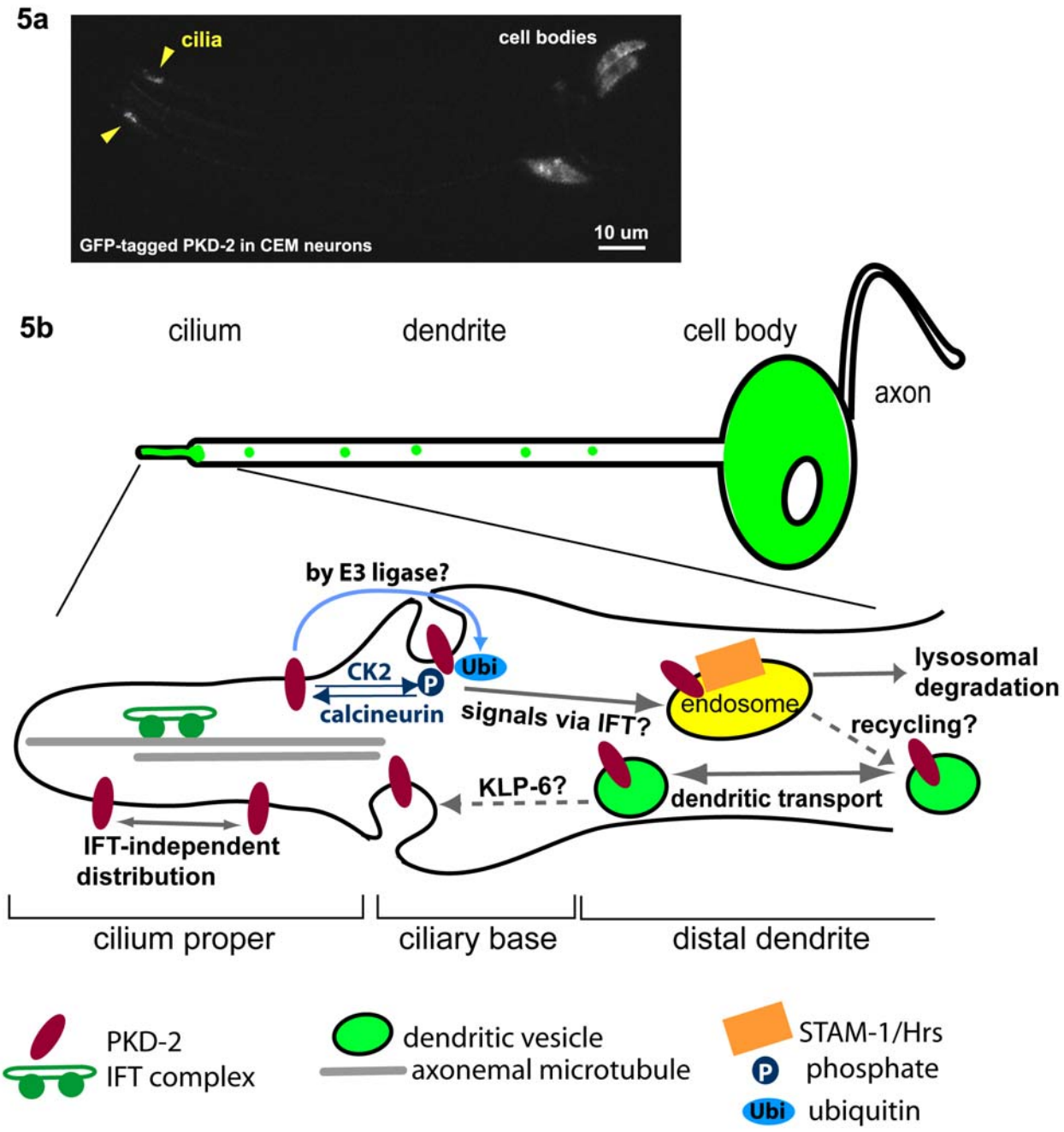

Figure 5. Trafficking of ciliary receptors. a. A GFP-tagged PKD-2 localizes to ciliary endings and cell bodies of the male-specific CEM head neurons. Dendritic vesicles are not evident in this image due to the low exposure setting. b. A working model for PKD-2 trafficking at the ciliary region. PKD-2 containing vesicles are transported through the dendrite. At the ciliary base, PKD-2 is loaded onto the ciliary membrane followed by distribution by an IFT-independent manner. Phosphorylated and/or ubiquitinated PKD-2 proteins are readily removed from the cilium via endosomal STAM-1/Hrs complexes for lysosomal degradation. IFT-dependent signals and a Kinesin-3 KLP-6 may regulate PKD-2 levels in cilia, although the site of action is yet to be determined.

8. THE DAF-19 RFX TRANSCRIPTION FACTOR - THE MASTER REGULATOR OF CILIOGENESIS

daf-19 encodes a regulatory factor X (RFX)-type transcription factor that is expressed in all ciliated neurons (100). *daf-19* mutants lack all cilia and are severely sensory defective (4). DAF-19 directly regulates ciliary gene expression via an X-box (XBX) promoter motif. A genome-wide search revealed 750 *xbx* gene candidates (101). Serial analysis of gene expression (SAGE), mRNA-

tagging, and microarray methodologies identified numerous candidate ciliary genes (55, 102). Comparative genomics of the conserved X-box sequence of three different *Caenorhabditis* species (*C. elegans*, *C. briggsae*, and *C. remanei*) identified 93 genes (103). DAF-19 targets include genes required for ciliary formation and morphogenesis, IFT, and sensory signaling, and orthologs of human ciliary disease genes, including the BBS, MKS (Meckel-Gruber Syndrome), and NPHP (Nephronophthisis) genes (55, 71, 101, 102, 104). *daf-19* also indirectly regulates the transcription of the *C. elegans* ADPKD gene *pkd-2* (105). RFX transcription factors also regulate ciliogenesis in *Drosophila*, zebrafish, and mice (106-109).

9. *C. ELEGANS* MODELS FOR HUMAN DISEASES OF CILIA

Cystic kidneys are one of the most common inherited human pathologies, and shared among several genetic disorders including autosomal dominant and autosomal recessive polycystic kidney disease (ADPKD and ARPKD), BBS, MKS, and NPHP (110, 111). The ciliary hypothesis of cystic kidney disease posits that gene products that are implicated in cystic kidney disease localize to the cilium or basal body (112). Studies in *C. elegans* were the first to link ADPKD to cilia (34), followed by a series of papers demonstrating that primary cilium localization and function of the ADPKD gene products are evolutionarily conserved (113-115). Since these initial findings, the cilium has piqued the interest of both basic biologists and clinicians.

C. elegans is the ultimate model system to study the formation, morphogenesis, and sensory functions of primary cilia at the genetic, molecular, cellular, and biological networks levels. The *C. elegans* genome contains many of the human ciliopathy disease genes (Table 1, (7, 8). The *C. elegans* ADPKD genes *lov-1* and *pkd-2* are required for the sensory functions of a subset of male-specific ciliated neurons (34, 68). The BBS genes *bbs-7* and *bbs-8* appear regulate IFT and ciliogenesis in amphid channel and phasmid cilia (51, 116). The MKS genes *mks-1/xbx-7* and *mks-3* possess an X-box in their promoters (55, 101), suggesting a broad role in the ciliated nervous system although physiological functions of the worm MKS homologs have not been reported. Likewise, the NPHP homologs *nphp-1*, *nphp-2*, and *nphp-4* are expressed in the ciliated nervous system of the male and hermaphrodite (55, 72, 104, 117). *nphp-1* and *nphp-4* appear to play cell type specific roles in cilia formation, ciliary length control, and sensory signal transduction (31, 72, 104). The human ciliary proteome is comprised of a daunting 1,000 candidates, some of which represent human disease genes (118). By studying orthologous ciliary genes in multicellular animals such as *C. elegans*, ascertaining function and defining molecular networks is experimentally tractable.

10. CONCLUDING REMARKS

Only recently has research on sensory and signaling function of primary cilia been pursued throughout the evolutionary ladder. However, many significant and intriguing questions remain unanswered. In mammals, how are cilia in different organs specified in terms of structure and function? How does the IFT process coordinate its general and cell-type specific functions? How does the ciliary membrane differ from the plasma membrane? What mechanisms regulate the ciliary localization of sensory receptors? How do sensory receptors gain entry/exit to/from cilia? Studies from the nematode *C. elegans* will continue to be a valuable source to understand basic cell biology of ciliogenesis as well as to identify new genes responsible for causing ciliopathies.

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