The sensory cilia of *Caenorhabditis elegans**

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Abstract

The non-motile cilium, once believed to be a vestigial cellular structure, is now increasingly associated with the ability of a wide variety of cells and organisms to sense their chemical and physical environments. With its limited number of sensory cilia and diverse behavioral repertoire, *C. elegans* has emerged as a powerful experimental system for studying how cilia are formed, function, and ultimately modulate complex behaviors. Here, we discuss the biogenesis, distribution, structures, composition and general functions of *C. elegans* cilia. We also briefly highlight how *C. elegans* is being used to provide molecular insights into various human ciliopathies, including Polycystic Kidney Disease and Bardet-Biedl Syndrome.

1. General definition of cilia

Cilia are slender microtubule-based subcellular organelles that emanate from the cell surfaces of virtually all eukaryotic organisms. Two types of cilia exist: motile cilia (alternatively termed flagella), which are used for locomotion or for the generation of fluid flow, and non-motile (primary) cilia, which are implicated in sensing the chemical and/or physical extracellular environments. Eukaryotic cilia are evolutionarily distinct from the similarly-shaped microvilli or stereocilia that are built from an actin cytoskeleton, and from the bacterial flagellum that drives motility in some prokaryotes.

2. Historical perspective

In a letter to Max Perutz dated June 5, 1963, Sydney Brenner wrote that a key unresolved question in biology was how the nervous system developed, and proposed that another important area of research could be how multicellular organisms controlled flagellation and ciliation (http://elegans.swmed.edu/Sydney.html). Fittingly, many of the early studies on *C. elegans* were centered on its chemotactic behaviors, which we now understand depend on the functions of cilia present in sensory neurons, and some of the earliest mutants to be isolated were defective in their abilities to sense environmental conditions (Ward, 1973; Dusenbery, 1974; Dusenbery et al., 1975). Although at that time the link between chemosensation and cilia was not firmly established, electron microscopic reconstruction of the environmentally-exposed, cilia-based sensory system at the anterior end of the animal helped to make the link more evident (Ward et al., 1975; Ware et al., 1975).

3. *C. elegans* cilia: distribution and architecture

Unlike many organisms, including humans, the only ciliated cell type in *C. elegans* is the sensory neuron, and none of the cilia in the nematode are motile. Of the 302 neurons found in the adult hermaphrodite, a substantial number (60) possess cilia at the ends of their dendritic processes.

Cilia from all studied organisms are known to nucleate from a modified centriolar structure termed a ‘basal body’. Most often, the basal body is positioned in proximity to the cellular membrane from where the cilium emanates. *C. elegans* basal bodies have been described as more ‘degenerate’ and termed ‘transition zones’ by Perkins et al. (1986). Ultrastructurally, the *C. elegans* transition zone (also termed ‘proximal segment’) typically possesses a circular array of doublet microtubules (as opposed to the triplet microtubule arrangement most often associated with basal bodies in other organisms). In amphid and phasmid cilia, the transition zone is followed by a so-called ‘middle segment’ characterized by a canonical arrangement of 9 doublet microtubules, and this middle segment transforms into a ‘distal segment’ built of singlet microtubules (Figure 1); notably, in some ciliated neurons, these ultrastructural features may be somewhat divergent (Ward et al., 1975; Ware et al., 1975; Perkins et al., 1986). Additional singlet microtubules are often present in the central region of the *C. elegans* cilia (Figure 1), but these microtubules are likely distinct from the central pairs observed in motile cilia. On the whole, this organization of doublets transitioning to singlets at the distal end is very similar to that seen in the flagella of mating *Chlamydomonas* cells (Mesland et al., 1980) and may be a general property of sensory cilia, as it has also been observed in several vertebrate cell types (e.g., pancreatic, renal and olfactory cells; Reese 1965; Webber and Lee, 1975; Hidaka et al., 1995). The nature and positions of the *C. elegans* ciliated cell bodies and of representative dendritic ciliated endings are shown schematically in Figure 1.

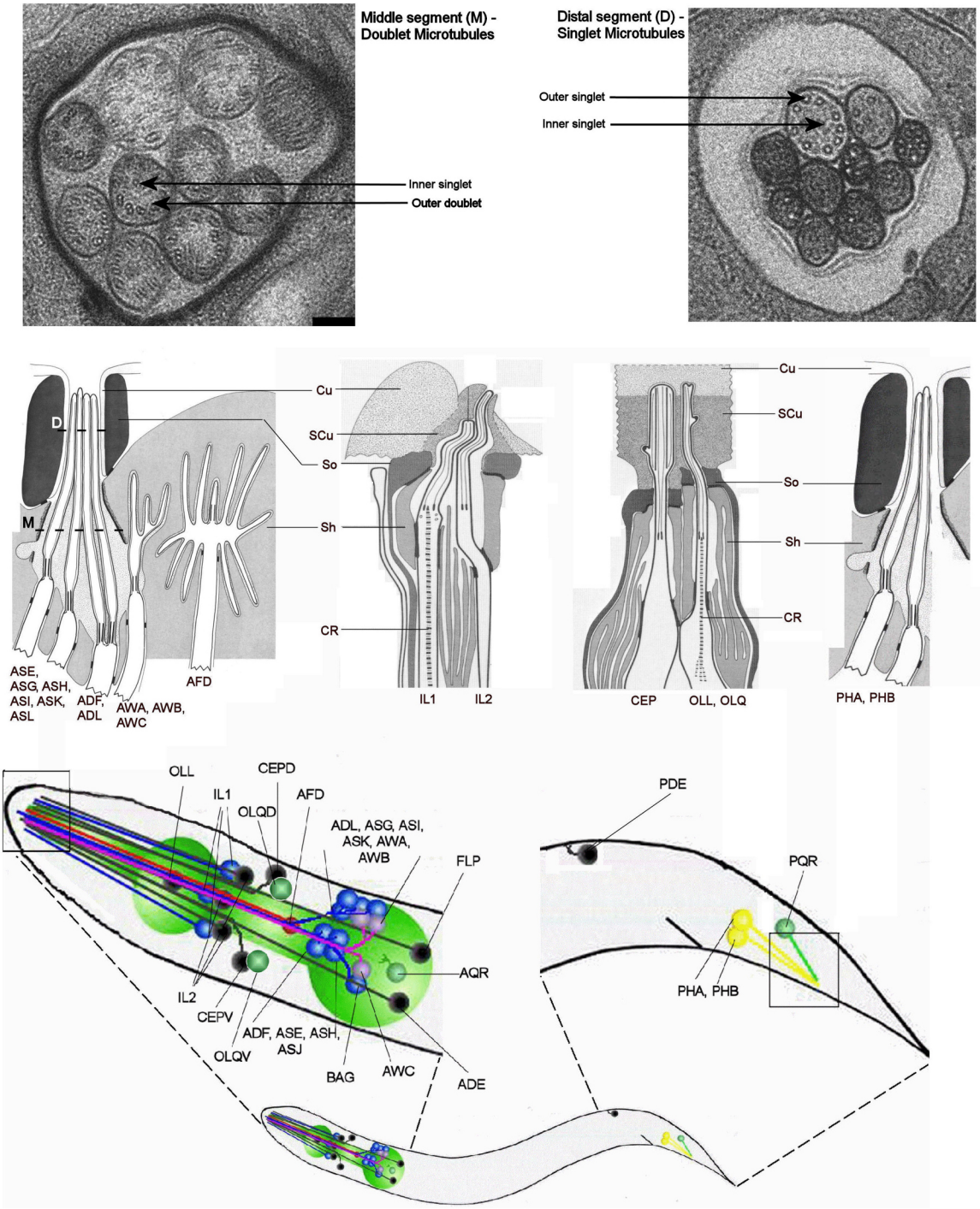

Figure 1. Ultrastructures of cilia and relative positions of all known ciliated neurons (cell bodies and associated dendrites) in the *C. elegans* hermaphrodite. The top two panels show electron micrograph cross-sections of amphid cilia in the middle segment (microtubule doublets; left panel) and distal segment (microtubule singlets; right panel; adapted from Evans et al., 2006). The worm figures illustrate the positions of the all ciliated cell bodies and their dendritic extensions. The four insets show, schematically, electron micrograph reconstructions of known ciliated endings (adapted from Perkins et al. (1986) for amphids and phasmids and Ward et al. (1975) for labial and cephalic neurons). Cu, cuticle; CR, ciliary rootlet; SCu, subcuticle; So, socket cell; Sh, sheath cell.

3.1. Amphids/Phasmids

The primary chemosensory organ of *C. elegans* is built from a collection of amphid neurons whose cell bodies are located in the anterior region of the pharyngeal bulb and possess axons that associate with the nerve ring. The

dendrites of these neurons extend to the anterior end of the animal and terminate with diverse ciliated structures (Figure 1). The proximal regions of amphid cilia are typically protected by a sheath cell and extend through a channel created by socket cells to become partially exposed to the external environment. The majority of amphid neurons possess cilia shaped as single rods (ASE, ASG, ASH, ASI, ASJ, ASK) or pairs of rods (ADF, ADL). Other amphids boast cilia that have membrane elaborations and possess unusual shapes; these are the wing neurons (AWA, AWB, AWC) and the amphid finger neuron (AFD), in which a small cilium is surrounded by approximately 50 villi. Both the wing and AFD neuron cilia terminate within a sheath cell, and thus are not exposed to the external environment. The lengths of amphid cilia range from ~7.5 µm (in the ASE, ASG, ASH, ASI, ASJ and ASK neurons) to ~1.5 µm for the AFD cilium (Ward et al., 1975; Ware et al., 1975; Perkins et al., 1986). Similar in structure to the single rod-like cilia found in amphids are the PHA and PHB phasmid cilia. These are located slightly posterior to the anus of the worm and are exposed to the external environment (Hall and Russell, 1991).

3.2. Inner/outer labial, cephalic neurons

The inner labial neuron types (IL1, IL2) are both arranged symmetrically in sets of 6 cells, ultimately terminating in the 6 “lips” that surround the mouth of the worm. Originating from a position anterior to the amphids, the dendrites of these neurons terminate in shorter cilia, and possess a seemingly more degenerate basal body. While the IL1 cilia consistently originate from basal bodies consisting of 7 doublet microtubules, those of IL2 neurons are more variable (ranging from 5–7 doublets). These neurons are further distinguished by the fact that, while the IL1 cilia ultimately terminate, or embed, in the subcuticle, the IL2 cilia are exposed to the external environment via openings in the cuticle (Ward et al., 1975; Ware et al., 1975).

The outer labial (2 lateral outer labial, or OLL neurons, and 4 quadrant outer labial, or OLQ neurons) and cephalic (CEP; 4 neurons) neurons similarly terminate, albeit in a more restricted fashion, in the cuticle near the sub-dorsal, sub-ventral, and lateral lips of *C. elegans*. The cilia found at the dendritic termini of CEP neurons possess a degenerate transition zone (6–8 doublet microtubules), while those found in the OLL/OLQ neurons have a canonical, 9 microtubule doublet arrangement. The cilia of CEP neurons are unusual in that, ~1µm from the basal body (within the subcuticle), the axonemal microtubules associate with additional microtubules, generating an electron-dense structure difficult to reconstruct via EM (Ward et al., 1975; Ware et al., 1975).

Interestingly, the IL1, OLL and OLQ neurons are unique in the fact that they have striated rootlet structures descending from their transition zones (WormAtlas; Ward et al., 1975; Ware et al., 1975). Ciliary rootlets are prominent fibrous polymers of the protein rootletin that emanate from the proximal end of the basal body (Yang et al., 2002). Rootlets have been implicated in the maintenance and longevity of vertebrate sensory cilia (Yang et al., 2005), as well as in providing scaffolding for kinesin-1-based intracellular transport (Yang and Li, 2005). It should be noted that very little is known about the rootlets of *C. elegans*; even a rootletin homolog has yet to be clearly identified.

3.3. Pseudocoelomic ciliated neurons

Two unusual ciliated cell types, AQR (located near the pharynx) and PQR (found posterior to the phasmids in the tail), are found, along with their cilia, to be directly exposed to the pseudocoelomic cavity of the worm. Extremely little is known about the ultrastructure of the cilia of these neurons, although they can be identified under a compound microscope using, for example, the GCY-36 protein fused to GFP (Cheung et al. 2004).

3.4. Ciliated deirid neurons

The 4 lateral, cervical deirid neurons are found in pairs, at the posterior end of the pharyngeal bulb (ADE) and slightly anterior to the anus (PDE). Like many of the other neurons discussed in this review, their ciliated dendritic endings are in a channel formed by a socket cell and an invaginated sheath cell. The cilia of both ADE and PDE terminate in the subcuticle, and thus are not exposed to the external environment. These ADE/PDE cilia are remarkably similar to those found in the 4 CEP neurons, and, interestingly, these 8 neurons constitute the complete dopaminergic neuron set for the hermaphrodite worm (Sulston and Brenner, 1975; Ward et al., 1975; Ware et al., 1975).

3.5. Additional ciliated neurons

BAG and FLP are two relatively uncharacterized ciliated neurons whose cilia both terminate in or near the lateral lips of the worm. Unlike many of the other neurons described in this review, their cilia are not surrounded by

support cells. Furthermore, their ultrastructures are quite complex, appearing via EM reconstruction as “bags” (BAG) or “flaps” (FLP) (Ward et al., 1975; Ware et al., 1975; Perkins et al., 1986).

3.6. Male-specific ciliated neurons

C. elegans males have 52 additional ciliated sensory neurons, the majority of which are found in the male tail rays/hooks, where the cilia perform sensory functions (Peden and Barr 2005). It should be noted, however, that only 48 of these 52 neurons are confirmed by EM to have cilia (Sulston et al., 1980). General descriptions of the structure and function of male-specific cilia are described in Table 1. While in many organisms spermatozoa possess motile cilia (flagella), those of *C. elegans* are aflagellar, relying on amoeboid locomotion to reach and fertilize oocytes (Nelson et al., 1982).

Table 1. Description of individual ciliated neuron types and their reported functions

Ciliated neuron	Cilium structure	Exposed?	Embedded?	Dye fills?	General role	Reference(s)
ASE (L/R)	Single rod	Y			Chemoattraction	Ward et al. 1975; Ware et al. 1975; Perkins et al. 1986
ADF (L/R)	Pair of rods	Y		FITC, DiI	Dauer entry	Ward et al. 1975; Ware et al. 1975; Perkins et al. 1986
ASG (L/R)	Single rod	Y			Chemoattraction	Ward et al. 1975; Ware et al. 1975; Perkins et al. 1986
ASH (L/R)	Single rod	Y		FITC, DiI	Mechanosensory (Nose touch), chemorepulsion, osmo-avoidance	Ward et al. 1975; Ware et al. 1975; Perkins et al. 1986; Kaplan and Horvitz, 1993
ASI (L/R)	Single rod	Y		FITC, DiI	Chemoattraction	Ward et al. 1975; Ware et al. 1975; Perkins et al. 1986
ASJ (L/R)	Single rod	Y		FITC, DiI	Dauer exit/recovery	Ward et al. 1975; Ware et al. 1975; Perkins et al. 1986
ASK (L/R)	Single rod	Y		FITC, DiI	Chemoattraction	Ward et al. 1975; Ware et al. 1975; Perkins et al. 1986
ADL (L/R)	Pair of rods	Y		FITC, DiI	Chemorepulsion	Ward et al. 1975; Ware et al. 1975; Perkins et al. 1986
AWA (L/R)	Winged	N	Sheath cell		Chemoattraction	Ward et al. 1975; Ware et al. 1975; Perkins et al. 1986
AWB (L/R)	Winged	N	Sheath cell		Chemorepulsion	Ward et al. 1975; Ware et al. 1975; Perkins et al. 1986
AWC (L/R)	Winged	N	Sheath cell		Chemoattraction	Ward et al. 1975; Ware et al. 1975; Perkins et al. 1986
AFD (L/R)	Small, surrounded by dendritic villi	N	Sheath cell		Thermosensation	Ward et al. 1975; Ware et al. 1975; Perkins et al. 1986

Ciliated neuron	Cilium structure	Exposed?	Embedded?	Dye fills?	General role	Reference(s)
IL1 (DL/DR/ L/R/VL/V)		N	Subcuticle		Mechanosensation (Nose touch)	Ward et al. 1975; Ware et al. 1975; Perkins et al. 1986; Hart et al., 1995
IL2 (DL/DR/ L/R/VL/V)		Y		DiI, DiO	Unknown (presumably chemosensory)	Ward et al. 1975; Ware et al. 1975; Perkins et al. 1986
CEP (DL/DR/ VL/VR)		N	Cuticle	FITC (occasionally)	Mechanosensation (Basal slowing response)	Ward et al. 1975; Ware et al. 1975;
OLQ (DL/DR/ VL/VR)		N	Cuticle		Mechanosensation (Nose touch and basal slowing response)	Ward et al. 1975; Ware et al. 1975; Perkins et al. 1986; Kaplan and Horvitz, 1993;
OLL (L/R)		N	Cuticle		Mechanosensation (putative)	Ward et al. 1975; Ware et al. 1975; Perkins et al. 1986
BAG (L/R)		N	Behind cuticle		Unknown	Perkins et al. 1986
FLP (L/R)		N	Behind cuticle		Mechanosensation (Nose touch)	Perkins et al. 1986; Kaplan and Horvitz, 1993
ADE (L/R)	Single rod	N	Subcuticle	FITC (occasionally)	Mechanosensation (Basal slowing response)	Ward et al. 1975; Ware et al. 1975; Perkins et al. 1986; Sulston and Brenner, 1975
PDE (L/R)	Single rod	N	Subcuticle	FITC (occasionally)	Mechanosensation (Basal slowing response)	Ward et al. 1975; Ware et al. 1975; Perkins et al. 1986; Sulston and Brenner, 1975
PHA (L/R)	Single rod	Y		FITC, DiI	Chemorepulsion	Hall and Russell, 1991
PHB (L/R)	Single rod	Y		FITC, DiI	Chemorepulsion	Hall and Russell, 1991
AQR		Y (pseudocoelom)			Oxygen-sensation, social feeding	Cheung et al., 2005
PQR		Y (pseudocoelom)			Oxygen-sensation, social feeding	Hall and Russell, 1991; Cheung et al., 2005
Male-specific ciliated neurons						
CEM (DL/DR/ VL/VR)		Y			Male chemotaxis (putative)	Sulston et al. 1980
RnA (L/R) (n=1–9)		N	structural cell	rarely	Male mating behavior	Sulston et al. 1980
RnB (L/R)		Y (not R6B)		rarely	Male mating	Sulston et al. 1980

Ciliated neuron	Cilium structure	Exposed?	Embedded?	Dye fills?	General role	Reference(s)
(n=1–9)					behavior	
HOA		N	subcuticle		Sensing vulva in male-mating behavior	Sulston et al. 1980
HOB		Y			Sensing vulva in male-mating behavior	Sulston et al. 1980
PCA (L/R)		N			Sensing vulva, inducing spicule prodding behavior	Sulston et al. 1980
SPD (L/R)		Y			Sperm transfer	Sulston et al. 1980
SPV (L/R)		Y			Sperm transfer	Sulston et al. 1980

4. Cilium biogenesis and intraflagellar transport (IFT)

Ciliogenesis depends on the intraflagellar transport (IFT) of ciliary precursors from the transition zone, which sits at the junction between the dendrite of the sensory neuron and the cilium, to the growing ciliary structure (Figure 2). The many known components of the IFT machinery, some of which were first identified in *C. elegans* (Scholey et al. 2004 and see below) are listed in Table 2. Using time-lapse microscopy it has been shown that in *C. elegans*, two IFT motors of the kinesin-2 family, heterotrimeric kinesin-II and homodimeric OSM-3, move IFT-particles (consisting of two multi-protein subcomplexes, A and B; Cole et al., 1998) and presumably ciliary precursor proteins from the base of cilium to their sites of incorporation; this anterograde IFT-machinery, and probably also turnover products, are then transported back to the base of the cilium using the IFT-dynein motor (Movie 1; Figure 2; Orozco et al., 1999; Signor et al., 1999b; Snow et al., 2004). These two anterograde motors cooperate to build the middle and distal segments of cilia. In the middle segment, kinesin-II and OSM-3-kinesin function redundantly to move the same IFT-particles and to assemble the middle segment of the axoneme. In this segment, the slower-moving kinesin-II (0.5 μm s^{-1}) reduces the speed of the faster-moving OSM-3 (~1.3 μm s^{-1}) to give rise to the intermediate rate of motor-IFT-particle transport observed (~0.7 μm s^{-1}). Subsequently, at the middle-distal segment boundary, kinesin-II returns to the base of the cilium, liberating OSM-3, which now moves IFT-particles and bound cargo to the distal tip at its own faster velocity to extend the distal singlets of the axoneme (Snow et al., 2004; Figure 2). Thus, animals lacking functional kinesin-II (e.g., *kap-11* mutants) build a full-length cilium due to the redundant function of OSM-3, *osm-3* mutants specifically lack the distal segment, and *osm-3*; *kap-1* double mutants fail to make cilia because of the absence of functional Kinesin-II or OSM-3 (Snow et al., 2004). It should be noted that OSM-3 alone specifically extends distal singlets on some axonemes, but not others (Evans et al., 2006). An additional kinesin, KLP-6, has been implicated in male mating behavior and is required for proper localization of the human polycystin-2 homolog, PKD-2, to the cilium (Peden and Barr, 2005). This finding indicates that additional kinesin motors might be involved in ciliary transport, although intriguingly, IFT-like movement of the KLP-6 kinesin was not observed.

Table 2. Components and available mutants of the intraflagellar transport machinery

Component	Gene model	Protein	Description/function	Mutants	Reference
Kinesin-II	F20C5.2	KLP-11	95KD Motor	*tm324*	Signor et al. 1999b
	Y50D7A.6	KLP-20	85KD Motor		
	F08F8.3	KAP-1	Accessory subunit	*ok676*	Signor et al. 1999b
OSM-3-kinesin	M02B7.3	OSM-3	Motor	*p802*	Shakir et al., 1993
IFT-dynein	F18C12.1	CHE-3	Motor	*e1124*	Wicks et al., 2000
	F02D8.3	XBX-1	Light intermediate chain	*ok279*	Schafer et al., 2003
	D1009.5	DYLT-2	Light chain	*tm2097*	Efimenko et al., 2005

Component	Gene model	Protein	Description/function	Mutants	Reference
IFT subcomplex A[1]	C27A7.4	CHE-11	IFT140	*e1810*	Qin et al., 2001
	Unknown		IFT139		
	F23B2.4	DAF-10	IFT122A	*e1387*	Bell et al., 2006
	Unknown		IFT122B		
	Unknown		IFT43		
IFT subcomplex B[1] (core)	Y41G9A.1	OSM-5	IFT88	*p813*	Haycraft et al., 2001
	F32A6.2		IFT81		
	C18H9.8		IFT(74/72)		
	R31.3	OSM-6	IFT52	*p811*	Collet et al., 1998
	Unknown		IFT46		
	Unknown		IFT27		
IFT subcomplex B[1] (periphery)	T27B1.1	OSM-1	IFT172	*p808*	Bell et al., 2006
	F38G1.1	CHE-2	IFT80	*e1033*	Fujiwara et al., 1999
	F59C6.7	CHE-13	IFT(57/55)	*e1805*	Haycraft et al., 2003
	Y110A7A.20		IFT20		
BBS proteins	Y105E8A.5	BBS-1	BBS-7 and BBS-8 act to stabilize IFT subcomplex A and B components and join/coordinate the two kinesin motors, OSM-3-kinesin and Kinesin-II	*ok1111*	Mak et al., 2006
	F20D12.3	BBS-2			Efimenko et al., 2005; Blacque et al., 2005
	C38D4.8	BBS-3			Fan et al., 2004
	F58A4.14	BBS-4			*Unpublished*
	R01H10.6	BBS-5			Blacque et al., 2005
	Y75B8A.12	BBS-7		*n1606*	Blacque et al., 2004
	T25F10.5	BBS-8		*nx77*	Blacque et al., 2004
	C48B6.8	BBS-9			Blacque et al., 2005
Motor activators	F54C1.5	DYF-1	Activates OSM-3-kinesin	*mn335*	Ou et al., 2005
	C27H5.7	DYF-13	Function unclear; required for building distal segment	*mn396*	Blacque et al., 2005
Various	ZK520.1/.3	DYF-2	IFT protein	*m160*	Efimenko et al., 2006
	C04C3.5	DYF-3	IFT protein; linked to PKD	*m185*	Murayama et al., 2005; Ou et al., 2005b
	C54G7.4	IFTA-1	IFT protein	*nx61*	Blacque et al., 2005
	T28F3.6	IFTA-2	IFT protein of the RAB family; not required for cilium formation	*tm1724*	Schafer et al., 2006

[1]IFT particle proteins isolated from *Chlamydomonas* (see Scholey et al., 2004)

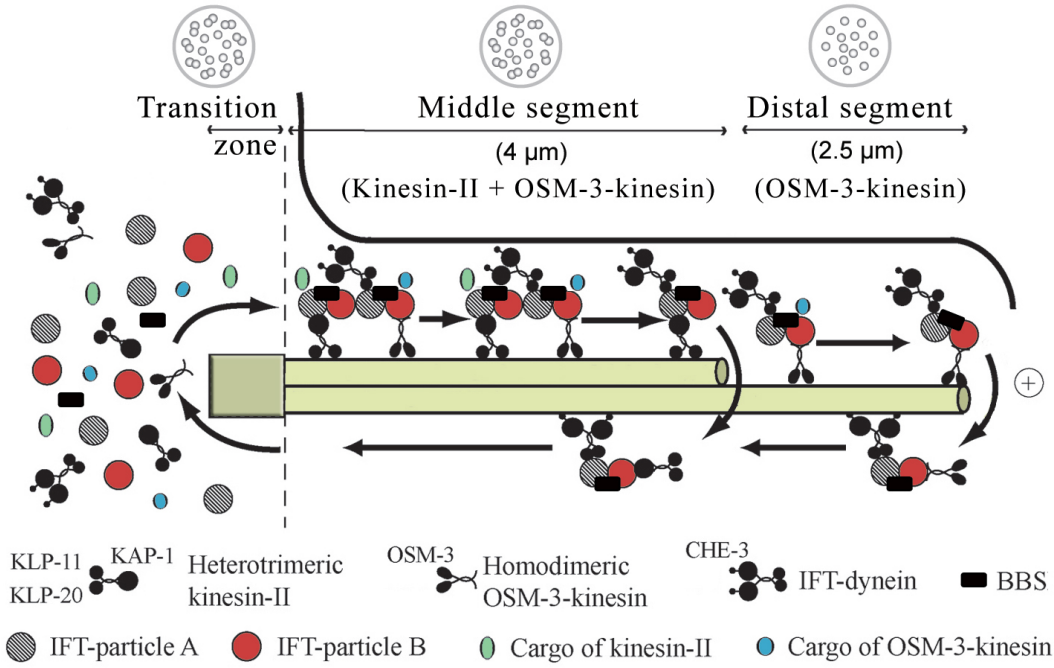

Figure 2. Intraflagellar transport in *C. elegans*. Intraflagellar transport in *C. elegans*. Components of the IFT machinery and ciliary cargo assemble at or near the transition zone (basal body). Two kinesins, heterotrimeric kinesin-II and homodimeric OSM-3-kinesin, separately bind IFT particle subcomplexes A and B, respectively, and transport these together with IFT-dynein and cargo along the middle segment in the anterograde (+) direction. In the distal segment, OSM-3-kinesin alone transports the IFT particles and dynein/cargo. BBS proteins act to stabilize the association between the motors and IFT particle subcomplexes A and B. Components of the IFT machinery and presumably other ciliary molecules are recycled back to the base of the cilium using the IFT-dynein molecular motor. The lengths of the transition zone (1 µm), middle segment (4 µm) and distal segment (2.5 µm) regions are shown (for amphid cilia) along with transverse view schematics of the microtubule arrangements (on top).

The two sequential anterograde IFT-pathways are coordinated by at least two types of regulator proteins. Two *C. elegans* homologs of human Bardet-Biedl Syndrome (BBS) proteins (BBS-7 and BBS-8) have been shown to stabilize the IFT-particle subcomplexes A and B which are bound to the Kinesin-II and OSM-3 IFT-motors, respectively (Blacque et al., 2004; Ou et al., 2005a; Snow et al., 2004). Abbrogation of BBS protein function results in slightly truncated cilia and chemosensory or lipid accumulation defects (Blacque et al., 2004; Mak et al., 2006). The implications for this observation are of interest given that BBS, which is characterized by a diverse array of ailments, including obesity, cystic kidneys, and retinal degeneration, is one of a growing number of known ciliopathies (Beales, 2005; Blacque and Leroux, 2006). At least eight genes encoding BBS proteins are present in *C. elegans* (Table 2). The second modulator of the sequential IFT pathway, a conserved ciliary protein also first characterized in *C. elegans*, DYF-1, specifically docks the OSM-3 kinesin onto IFT-particles and simultaneously activates its motor activity; a *dyf-1* mutant therefore specifically lacks the distal segment singlet microtubules (Ou et al., 2005a).

Movie 1. cilia of *C. elegans* as seen by time-lapse microscopy of GFP-labelled OSM-1.

The ability to analyze strains bearing GFP-tagged IFT proteins by time-lapse microscopy in *C. elegans* has provided researchers with a powerful means to dissect IFT function and study ciliary mutants (Orozco et al., 1999). Until now, this technique to study cilia function has distinguished *C. elegans* from the other prominent ciliary model

organism, *Chlamydomonas*. In addition to providing crucial information about BBS and various IFT-associated proteins such as DYF-1, such *in vivo* studies are complemented by the fact that in many *C. elegans* ciliary mutants, abnormal IFT causes defects in sensory cilia structures and sensory behavior. For example, *osm-3* and *che-3* mutants possess defects in the functions of the anterograde IFT-kinesin and retrograde IFT-dynein, respectively, and display structural defects in the sensory cilia and corresponding deficiencies in osmotic avoidance and chemotaxis (Signor et al., 1999a; Wicks et al., 2000). Notably, the first evidence that biochemically-fractionated IFT-particle subunits identified in *Chlamydomonas* are essential for ciliary assembly was based on the phenotypes of the corresponding *C. elegans* mutants, such as *osm-1*/IFT172, *osm-6*/IFT52, *osm-5*, *che-2*, *che-11* and *che-13* and *daf-10* (Brazelton et al., 2001; Cole et al., 1998; Qin et al. 2001; Scholey et al., 2004; Table 3). In addition, other components of the IFT machinery present in the *Chlamydomonas* flagellar proteome but not specifically identified in biochemical fractionations of IFT-particles (Pazour et al., 2005) have first been described in *C. elegans*, including DYF-2, a protein that may help bridge the IFT subcomplexes A and B (Efimenko et al., 2006), DYF-3, a protein associated with polycystic kidney disease that is likely part of IFT subcomplex B (Ou et al., 2005b), and IFTA-1 (IFT-Associated protein 1), a likely subcomplex A protein (Blacque et al., 2006). Each of these mutants are characterized phenotypically as having cilia structure and chemosensory defects.

Table 3. Cilia-related genes with corresponding genetic map positions and phenotypes

Name	Other name	Gene model	Genetic position (cM)	Ref. allele	*che*	*daf*	*dyf*	*osm*	Annotation	Reference
che-1	*tax-1*, *tax-5*	C55B7.12	I:1.20 +/– 0.015	*e1034*	+	/	/	+/–	C2H2-type transcription fact.	Uchida et al., 2003
che-2		F38G1.1	X:-19.76 +/– 0.06	*e1033*	+	+	+	+	IFT-particle B	Fujiwara et al., 1999
che-3	*osm-2*, *che-8*, *avr-1*, *caf-2*	F18C12.1	I:2.47 +/– 0.023	*e1124*	+	+	+	+	IFT-dynein heavy chain	Shakir et al., 1993
che-6			IV:0.00 +/– 0.000	*e1126*	+	/	/	/	Abnormal IL2 basal bodies	
che-10			II:–2.80 +/– 0.244	*e1809*	+	/	+	+		
che-11		C27A7.4	V:3.67 +/– 0.031	*e1810*	+	+	+	+	IFT-particle A	Qin et al., 2001
che-12			V:2.28 +/– 0.105	*e1812*	+	/	+/–	+	Sheath cell secretion	
che-13	*che-9*	F59C6.7	I:5.05 +/– 0.029	*e1805*	+	+	+	+	IFT-particle B	Haycraft et al., 2003
che-14	*ptd-1*	F56H1.1	I:0.45 +/– 0.015	*e1960*	+	/	+/-	/	Transmembrane receptor	Michaux et al., 2000
daf-6	*ptr-7*	F31F6.5	X:21.50	*e1377*	+	+	+	+	Sheath cell function	Perens and Shaham, 2005
daf-10	*osm-4*		IV:4.05 +/– 0.002	*e1387*	+	+	+	+	IFT-particle A	Bell et al., 2006
daf-19	*daf-24*	F33H1.1a	II:2.11 +/– 0.012	*m86*	+	+	+	+	RFX family transription fact.	Swoboda et al., 2000
dyf-1		F54C1.5a	I:-0.53 +/– 0.177	*mn335*	+	/	+	+	OSM-3-kinesin activator	Ou et al., 2005
dyf-2		ZK520.1/.3	III:21.40 +/– 0.10	*m160*	+	/	+	/	IFT protein	Efimenko et al., 2006
dyf-3		C04C3.5a	IV:-6.09 +/– 1.34	*mn331*	+	/	+	/	IFT protein associated with PKD	Murayama et al., 2005

Name	Other name	Gene model	Genetic position (cM)	Ref. allele	*che*	*daf*	*dyf*	*osm*	Annotation	Reference
dyf-4			V:4.31 +/– 0.29	*m158*	+	/	+	/		
dyf-5			I:3.62 +/– 0.036	*mn400*	+	/	+	/		
dyf-6			X:2.19 +/– 0.050	*m175*	+	/	+	/	IFT protein	Bell et al., 2006
dyf-7			X:2.18 +/– 0.046	*m537*	+	/	+	/		
dyf-8		C43C3.3	X:1.44 +/– 0.005	*m539*	+	+	+	+	Transmembrane receptor (endoglin family)	Wicks and Plasterk, pers. comm.
dyf-9			V:24.22 +/– 0.35	*n1513*	+	+	+	/		
dyf-10			I:1.53 +/– 0.040	*e1383*	+	/	+	/		
dyf-11			X:-18.26 +/– 0.25	*ad1303*	+	/	+	/		
dyf-12			X:2.18 +/– 0.074	*nr2344*	+	+	+	/		
dyf-13		C27H5.7a	II:0.25 +/– 0.017	*mn396*	+	+	+	/	Distal segment assembly	Blacque et al., 2005
osm-1		T27B1.1	X:24.06 +/– 0.029	*p808*	+	+	+	+	IFT-particle B	Bell et al., 2006
osm-3	*caf-1*, *klp-2*	M02B7.3a	IV:-2.27 +/– 0.087	*p802*	+	+	+	+	IFT-kinesin	Shakir et al., 1993
osm-5		Y41G9A.1	X:-12.68 +/– 0.02	*p813*	+	+	+	+	IFT-particle B	Haycraft et al., 2001
osm-6		R31.3	V:3.52+/– 0.025	*p811*	+	+	+	+	IFT-particle B	Collet et al., 1998
osm-12	*bbs-7*	Y75B8A.12	III:16.09+/–0.297	*n1606*	+	/	+	+	Distal segment assembly, IFT particle stability	Blacque et al., 2004
bbs-1		Y105E8A.5	I:24.52 +/– 0.030	*ok1111*	+	/	+	+	Distal segment assembly, IFT particle stability	May et al., 2006
bbs-8		T25F10.5	V:0.13 +/– 0.001	*nx77*	+	/	+	+	Distal segment assembly, IFT particle stability	Blacque et al., 2004

Whereas our understanding of the IFT transport process has matured significantly in the last few years, very little is known about the nature of the proteins that require IFT-mediated transport to reach their ciliary destination. Indeed, only radial spoke proteins had been found to be *bona fide* IFT cargo proteins in *Chlamydomonas* (Qin et al., 2004); now, several have surfaced in *C. elegans*. One class of IFT-cargo are the cilia-localized TRP-type channels OSM-9 and OCR-2, which are implicated in various chemosensory responses (Tobin et al., 2002). Both have been shown to undergo IFT (Qin et al., 2005), marking the first account of a non-axonemal component being visualized to move along a cilium. Interestingly, OSM-9 and OCR-2 depend on each other for their ciliary localization, and ectopic expression of OCR-2 in AWC neurons is sufficient to drive OSM-9 to the cilia in this neuron (Tobin et al., 2002). Another apparent IFT cargo is TUB-1, the *C. elegans* homolog of the mammalian protein *Tubby*, which is associated with an obese phenotype (Kleyn et al., 1996; Noben-Trauth et al., 1996). TUB-1 motility has been visualised in both dendrites and cilia, and its function is required for normal lipid homeostasis, life span, and chemotaxis (Mukhopadhyay et al., 2005). Lastly, IFTA-2, a RAB-like protein expressed exclusively in ciliated cells has been shown to undergo IFT, but interestingly, is not required for building an intact cilium. Instead, IFTA-2 may represent a signalling molecule that is required for cilia functions; consistent with this notion, the *ifta-2* mutant has an extended lifespan and dauer formation defects that have previously been ascribed to cilia dysfunction (Schafer et al. 2006).

5. Transcriptional regulation of cilium morphogenesis

A defining moment in *C. elegans* cilia research was the publication by Swoboda et al. (2000) which demonstrated that many, if not all genes involved in ciliogenesis are under the transcriptional control of the single RFX-type transcription factor found in the nematode, DAF-19. The promoter element recognized by DAF-19, termed "X box," is normally 14 nucleotides in length and is typically positioned ~100 nucleotides upstream from the start codon of the ciliary gene (Swoboda et al., 2000; Haycraft et al., 2001; Ansley et al., 2003; Haycraft et al., 2003; Blacque et al., 2005; Efimenko et al., 2005). When present at this canonical position, an X box drives the specific expression of a gene in most or all 60 ciliated cells. Interestingly, an X box is found upstream of the *daf-19* gene itself, indicating that its activity is self-regulated (Swoboda et al., 2000). Consistent with the role of DAF-19 as a master regulator of ciliogenesis, *daf-19* mutants lack all signs of cilia (Perkins et al., 1986; Swoboda et al., 2000). As expected, genes encoding IFT and BBS proteins also possess X boxes. However, unlike *daf-19* mutants, disruption of these genes leads to abnormal (truncated) ciliary structures (Perkins et al., 1986; Starich et al., 1995; Blacque et al., 2004; Ou et al., 2005a). For ciliary genes expressed in a subset of ciliated sensory neurons (such as some receptors and possibly other cargo proteins), X boxes are normally absent but other cell type-specific regulatory elements likely exist.

It is notable that following the discovery by Swoboda et al. (2000) of the critical importance of DAF-19 in regulating cilium formation, RFX transcription factors have been implicated in ciliogenesis in other organisms. In mice, RFX3 is required for the development of embryonic nodal cilia (Bonnafe et al., 2004). Similarly, an RFX protein in *Drosophila* has been connected to the development of ciliated structures in sensory neurons (Dubruille et al., 2002).

6. The *C. elegans* ciliome

Recent studies in several organisms have contributed to an effort to amalgamate a complete list of ciliary proteins, or 'ciliome.' Comparative genomic studies were performed in *Chlamydomonas* (Li et al., 2004) and *Drosophila* (Avidor-Reiss et al., 2004), taking advantage of the fact that subtracting the genomes of ciliated organisms (including *C. elegans*) from those lacking cilia (e.g., *Arabidopsis thaliana*) provides considerable enrichment for ciliary genes. Other more direct approaches aimed at identifying ciliary proteins, in the form of proteomic analyses, were performed using *Chlamydomonas* (Pazour et al., 2005), human airway cells (Ostrowski et al., 2002), *Tetrahymena* (Smith et al., 2005) and *Trypanosoma brucei* (Broadhead et al., 2006). Of note, all of the above studies were accomplished using experimental systems or cells that possess motile cilia (with the exception of *Drosophila*, which also has non-motile cilia). Helping to address this shortfall, *C. elegans* has been used to assemble a sensory cilium-specific proteome, using both bioinformatic and genomic approaches. Two recent genome-wide studies in *C. elegans* were used to identify several hundred putative X box sequences in gene promoters (Blacque et al., 2005; Efimenko et al., 2005), and other studies (Avidor-Reiss et al. 2004; Li et al., 2004) scanned putative ciliary genes for X boxes in *C. elegans* and *Drosophila*. Blacque et al. (2005) also combined data from the X box search with comparative analyses of SAGE (transcriptome) libraries (ciliated neuron, pan-neuronal, gut and muscle) to enrich for genes preferentially expressed in ciliated neurons. Similarly, Kunimoto et al. (2005) developed a list of ciliated sensory neuron-expressed genes by performing a targeted pulldown of mRNA polyA tails. The ability to isolate individual cell types from *C. elegans* is also proving to be a powerful means to uncover the specific transcriptomes and functions of ciliated cells. Recently, Colosimo et al. (2004) isolated AWB olfactory and AFD thermosensory neurons, and used microarrays to obtain their expression profiles.

Taken together, these complementary studies have resulted in the compilation of comprehensive lists of known and candidate ciliary proteins, as outlined in several review articles (Inglis et al., 2006; Gherman et al., 2006; Fliegauf and Omran, 2006). In addition, two websites provide useful resources for ciliary researchers, including the ability to search the different ciliary datasets (http://www.ciliome.com and http://www.ciliaproteome.org). Following the identification of putative ciliary genes, it is straightforward to test in *C. elegans* whether these genes are likely to be required for cilia function. Specifically, these genes, as tested by expression using a promoter fused to GFP, should be at least expressed in some, or all ciliated sensory neurons. For example, many novel putative ciliary genes were found to be expressed specifically in ciliated neurons in Blacque et al. (2005) and Efimenko et al. (2005). Further analysis of putative ciliary genes may also include making translational fusions to GFP to determine if the protein is associated with ciliary structures, including transition zones and the ciliary axoneme (e.g., see Blacque et al., 2005). Lastly, testing of the mutant for ciliary phenotypes such as Che, Osm, Dyf and Daf, or changes in lifespan, as described below, can provide strong evidence that a particular gene plays an important role in the differentiation of ciliated cell(s), in the formation of cilia, and/or in the physiological function(s) of cilia.

7. Understanding *C. elegans* ciliary functions through ciliary mutant analysis

The availability of large numbers of existing ciliary mutants is in large part the result of the vision of molecular biologist Sydney Brenner, who foresaw the value of this organism for studying the genetics of development and nervous system function. To this end, he and many of his scientific progeny sought nervous system mutants that displayed behavioral and structural defects, a number of which affect cilia and/or ciliated cell function or differentiation. Table 3 shows a selection of genes known to affect cilia formation and function, along with map positions and phenotypes.

7.1. Dye filling (Dyf) phenotype

The simplest method presently used to assay the structural integrity of sensory cilia is to test the ability of worms to take up a fluorescent dye. One type of dye (DiI) preferentially fills amphid head neuronsand phasmid tail neurons, presumably via their exposed ciliated endings, although the exact mechanism of dye uptake is unclear (Perkins et al., 1986; Starich et al., 1995). The dye enters 6 amphid (ASI, ADL, ASK, AWB, ASH and ASJ) and the two phasmid (PHA and PHB) neurons (Herman, 1984). Similar staining patterns are seen with DiO or FITC (Hedgecock et al., 1985). Among others, mutants with abrogated BBS or IFT proteins exhibit an abnormal dye filling (Dyf) phenotype (Table 3). Although this phenotype has been tightly associated with abnormal cilia, alterations to the ciliated neuron sheath and socket cells may also confer a Dyf phenotype if the cilia in question lose access to the environment-as seen for example in *daf-6* mutants (Perens and Shaham, 2005). It should be noted, however, that the lack of a Dyf mutant phenotype does not always imply proper cilium structure or function, e.g., the non-Dyf mutant *ifta-2* exhibits at least two ciliary mutant phenotypes, increased longevity and defective dauer formation (Schafer et al. 2006).

7.2. Chemosensory (Che) and osmosensory (Osm) phenotypes

In addition to the dye-filling experiments, a number of behavioral assays have been employed to identify mutant worms with defective cilia. The osmotic avoidance abnormal (Osm) phenotype is often associated with cilia defects in *C. elegans* (Perkins et al., 1986; Table 3). Unlike wild-type worms, *osm* mutants fail to avoid regions with high osmotic strength, such as 4M NaCl or 8M glycerol (Culotti and Russell, 1978). Similarly, chemotaxis to both volatile and non-volatile compounds is dependent on the cilia present at the tips of a number of sensory neurons; defects in this sensory process represents an abnormal che motaxis (Che) phenotype (Ward, 1973; Bargmann et al., 1993). Numerous *osm* and *che* mutants have been identified (Culotti and Russell, 1978; Ward, 1973). Interestingly, virtually all such mutants that possess abrogated cilia structures display most, if not all, of the aforementioned mutant phenotypes, indicating a vital role for cilia in the regulation of responses to external stimuli (Lewis and Hodgkin, 1977), and many of the *osm* and *che* mutants isolated have been found to encode proteins essential for cilia structure/function (Tables 2 and 3; Perkins et al., 1986). A thorough treatment of chemosensation is presented in the Wormbook chapter by Cornelia Bargmann (see Chemosensation in *C. elegans*).

7.3. Mechanosensory (Mec) phenotypes

Despite the observation that some touch-response cells are non-ciliated (Chalfie and Sulston, 1981), two mechanosensory mutants, *mec-1* and *mec-8*, also display a Dyf phenotype (Perkins et al., 1986). Indeed, the ASH, ADE, PDE, CEP, FLP, IL1, OLQ, and OLL ciliated neurons have been connected to mechanosensation (Table 1; Sawin et al., 2000; Hart et al. 1995; Kaplan and Horvitz, 1993), suggesting that cilia may possess a mechanosensory role, similar to that of the kidney tubule cilia that sense fluid flow in mammals (Nauli and Zhou, 2004). Furthermore, the ciliary mutants *che-2*, *che-3*, *che-13*, *osm*-6, *che-12* and *osm-3* all show significantly reduced abilities to respond to a touch on the nose of the animal (Kaplan and Horvitz, 1993). For a complete review of mechanosensation in *C. elegans*, see Mechanosensation. Interestingly, the amphid ASH neuron has been connected to both noxious chemical avoidance (Bargmann et al., 1990) and nose-touch response, raising intriguing parallels between this neuron and the nociceptive neurons of vertebrate cells (Kaplan and Horvitz, 1993).

7.4. Male mating phenotypes

Another interesting role played by cilia in *C. elegans* involves male mating behavior. Male worms with defective cilia function are unable to sense the chemical cue(s) underlying mate-finding (Lipton et al., 2004). In addition to being defective in locating hermaphrodites, males with abrogated cilium function also show compromised abilities to locate the vulva and ejaculate (Barr and Sternberg, 1999; Qin et al., 2001). For a detailed description of male mating behavior, see Male mating behavior.

7.5. Dauer and lifespan phenotypes

Worms completely lacking sensory cilia appear to constitutively enter the alternate life stage known as dauer (i.e., Daf-constitutive or Daf-c), offering an intriguing connection between cilia, lifespan and stress resistance. The basis for this connection is the observation that abrogation of DAF-19 function, which leads to a complete loss of cilia, results in significantly longer-lived worms (in the dauer stage). It should be noted, however, that since DAF-19 is a transcription factor, the Daf-c phenotype observed might be due to effects on downstream targets unrelated to ciliogenesis, although, only cilia-associated proteins have been shown to be regulated by DAF-19. Perhaps more convincingly, initial analysis of Daf mutants indicated that dauer-forming or exit responses were mediated by environmental stimuli (Riddle et al., 1981). Interestingly, cilium structure mutants such as *daf-6* and *daf-10* frequently show an inability to enter dauer (Daf-defective or Daf-d; Perens and Shaham, 2005; Bell et al., 2006). Furthermore, there are other potentially fascinating connections between cilia and longevity in *C. elegans* that do not appear to specifically involve the dauer pathway. Laser ablation of certain ciliated neurons results in increased lifespan, and a number of ciliary mutants live longer, perhaps due to their altered sensory perception (Apfeld and Kenyon, 1999). Further connections between sensory cilia and longevity have been discovered through analysis of oxidative stress mutants, which showed that mutants resistant to methyl viologen (also known as paraquat) were frequently found to be defective in cilia. MEV-4 (methyl viologen resistant 4), for example, was found to be CHE-11, an integral component of IFT subcomplex A (Fujii et al., 2004).

7.6. Thermosensory phenotypes

Although a direct connection between cilia and thermosensation of physiological temperatures has yet to be established (Perkins et al., 1986), the sole thermosensory neuron in *C. elegans*, AFD, is indeed ciliated, raising the possibility that cilia, perhaps in addition to its microvilli (Ward et al., 1975; Ware et al., 1975; Perkins et al., 1986), may be required for proper function of this neuron. One study has revealed that several ciliary mutants display abnormal responses to noxious temperatures, although the sensory neurons implicated in the response remain unidentified (Wittenburg and Baumeister, 1999).

7.7. Lipid accumulation phenotypes

Recently, connections have been made in *C. elegans* between sensory cilia and lipid accumulation. The *C. elegans* mutant *tub-1*, in which the worm homolog of the mouse protein *Tubby* is disrupted, was discovered by Ashrafi et al. (2003) to have a two-fold increase in fat content via Nile Red analysis (which assesses lipid content) compared to wild-type. TUB-1 has subsequently been shown to localize to the axons, dendrites, and cilia of the amphid, phasmid, AQR and PQR neurons (Mak et al. 2006). Chemotaxis in *tub-1* mutants is impaired, although *tub-1* mutants show no abrogation of ciliary structure based on a normal DiI-filling phenotype (Mak et al., 2006; Mukhopadhyay et al., 2005). A screen for mutants which enhanced the Nile Red accumulation phenotype of *tub-1* identified that a mutation in a 3-ketoacyl-coA thiolase, known as *kat-1*. Interestingly, a screen for mutants that enhanced the *kat-1* mutant Nile Red-accumulation phenotype resulted in the identification of *bbs-1*, a conserved gene implicated in the obesity-associated Bardet-Biedl Syndrome (Mak et al. 2006). Although TUB-1 has been strongly connected to intestinal/muscle KAT-1, additional research has indicated that the protein is positioned between DAF-2 and DAF-16 in the dauer signaling pathway (Mukhopadhyay et al., 2005).

8. *C. elegans* as a model system to study ciliopathies

Defects in the highly conserved components of cilia and the IFT machinery are now understood to contribute to several human ciliary disorders. These include Primary Ciliary Dyskinesia (PCD) which arises from defects in motile cilia, as well as several related to sensory cilia dysfunction, such as polycystic kidney disease (PKD), Bardet-Biedl syndrome (BBS), Meckel syndrome (MKS) and nephronophthisis. *C. elegans* has emerged as an important model system for studying the molecular bases of some of these sensory-related ciliopathies, as illustrated below.

Although *C. elegans* does not develop a kidney, several disease genes associated with defects in renal cilia function have homologs in *C. elegans*. Mutations in worm homologs of the autosomal dominant polycystic kidney-disease loci PKD1 and PKD2, *lov-1* and *pkd-2*, were shown to produce defects in male mating behavior and provided the first link between ciliary dysfunction and PKD (Barr and Sternberg, 1999). This breakthrough finding has been confirmed in a number of model systems, including zebrafish, where most mutant animals displaying cystic kidneys possess disruptions in genes associated with cilia function (Sun et al., 2004). Additionally, it has been shown that *C. elegans* LOV-1 is required for the proper targeting of PKD-2 to the cilium of in the male-specific

neurons CEM, as well as 8 pairs of ray neurons (Bae et al., 2006). A further finding is that in a *daf-10* mutant background (which disrupts IFT subcomplex A), the ciliary localization of PKD-2 is significantly altered, resulting in accumulations in the transition zone as well as the dendrite (Bae et al., 2006).

Worm homologs of the proteins NPHP-1 and NPHP-4, which are implicated in the kidney disorder nephronophthisis, localize specifically to the transition zones of sensory cilia, where they appear to be involved in IFT-independent sensory signal transduction (Jauregui and Barr, 2005; Winkelbauer et al., 2005; Wolf et al., 2005).

Studies in *C. elegans* also provided the first evidence that BBS proteins-which are implicated in a wide array of ailments, including obesity, retinal degeneration and cystic kidney disease-are essential ciliary proteins that contribute to intraflagellar transport by stabilizing the association between kinesin motors and intraflagellar subcomplex assemblies (Ansley et al., 2003, Blacque et al., 2004; Ou et al., 2005a). Remarkably, all but 3 of the 11 known human *BBS* genes possess *C. elegans* orthologues, making the nematode an excellent model system to study this multigenic and pleiotropic disorder.

Finally, two genes (*MKS1* and *MKS3*) associated with Meckel-Gruber syndrome (MKS) (Kyttala et al., 2006; Smith et al., 2006), the most common form of syndromic neural tube defects, were recently cloned, and both of their *C. elegans* homologs (*xbx*-7/R148.1 and F35D2.4, respectively) were found to be specifically expressed in ciliated sensory neurons (Efimenko et al., 2005; Blacque et al., 2005). This observation strongly suggests that MKS is a ciliopathy. It will therefore be of interest to analyze the subcellular localization and functions of the *C. elegans* MKS proteins in order to provide important clues as to the cause of the disorder.

9. Concluding remarks

Given the diverse array of *in vivo* tools available for studying intraflagellar transport, ciliary integrity, and cilia mutants, *C. elegans* sits in a unique position to facilitate our understanding of cilium biogenesis and fundamental cilia functions as they relate to a complex multicellular organism. For instance, although much insight has been gained to date on the molecular makeup of the intraflagellar transport machinery, additional proteins that participate in and regulate the IFT process will likely be found, and the functions of some of the known players will likely be clarified using *C. elegans* as a model system. There are a large number of different modalities under the control of cilia function, but others are bound to be discovered, and importantly, parallels with mammalian systems-insofar as lipid homeostasis and longevity is concerned, for example-will ultimately become apparent. The nematode is also well poised to help shed additional light on the molecular etiology of various ciliopathies. For example, identification of additional Dyf mutants and characterization of their phenotypes may help uncover new genes related to Bardet-Biedl syndrome or other ciliopathies. In brief, *C. elegans* researchers should be able to make excellent progress in the study of this fascinating cellular organelle that is drawing an increasing amount of attention due to its breadth of physiological functions and association with a wide range of ailments.

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