To beat or not to beat: roles of cilia in development and disease

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Cilia and flagella appeared very early in evolution to provide unicellular organisms with motility in water. Adaptation to non-aquatic life in plants resulted in the almost complete elimination of these organelles, except for gametic transport in some phylogenetic groups. In contrast, cilia and flagella were retained and employed for a wide variety of functions requiring fluid movement in complex multicellular animals. The functions of cilia in diverse processes such as left–right axis pattern formation, cerebrospinal fluid flow, sensory reception, mucociliary clearance and renal physiology indicate that cilia have been adapted as versatile tools for many biological processes. In this review, we discuss recent discoveries that have extended knowledge of the roles of cilia in normal development, and the pathological consequences caused by their dysfunction in mammals. We also consider evolutionary relationships between cilia from lower and higher eukaryotes, outline the ciliary components required for assembly and motility, and review the terminology of axonemal heavy chain dynein genes.

ORIGIN AND EVOLUTION

Several hypotheses on the origin of cilia and flagella in eukaryotes have been proposed. The endosymbiont model postulates that these organelles may have derived from the symbiotic inclusion of spirochete bacteria (1), while the autogenous hypothesis favors the idea that cilia developed from further specialization of the cytoskeleton (2). In either case, the ancestral origin of the axoneme has been key for establishing main phylogenetic divergences. For instance, at the root of the eukaryote tree, the distinction between opisthokonts (animals, fungi, Chonozoa) and anterokonts (all other eukaryotes comprising plants and biciliates/bikonts) is based on whether the cilium is posterior or anterior (2,3). Cilia and flagella structure and function are very well conserved across evolution. The high degree of sequence conservation between flagellar proteins of unicellular organisms such as the biflagellate alga *Chlamydomonas reinhardtii* and mammalian ciliary proteins suggests that the functional role of the genes encoding cilia has been preserved throughout evolution. *Chlamydomonas* has been an advantageous system for studies of assembly and motility of cilia due to the ability to generate and detect mutants that cannot swim, and then to biochemically characterize their flagella. From these studies we can know that eukaryotic flagella are composed of more than 200 proteins (4,5). This large number of components is also present in mammalian cilia (6). Despite their overall structural similarities, the specialization of cilia for particular functions has resulted in significant variations of structure and regulation. To address these functional adaptations, a variety of model systems have been used. For instance, the gill cilia in mollusks have been studied for their capability to coordinate a precise filter feeding mechanism (7), the sperm flagellum in sea urchin employed for waveform motion analysis (8), the oviduct cilia in quail for analysis of ciliogenesis (9), and the cilia of the fish lateral line organ probed to understand sensory mechanics (10). In the last few years, the generation of gene-targeted mice with deficient axonemal components has been critical for the investigation of numerous ciliary functions necessary for mammalian physiology, and their relation to human pathology.

CILIA ULTRASTRUCTURE ASSEMBLY AND MOTILITY

Cilia and flagella consist of a highly ordered basic structure of nine peripheral microtubule doublets arranged around two central microtubules (9+2 axoneme; Fig. 1A). Each outer doublet is composed of an A and a B tubule (of 13 and 11 protofilaments each). A central pair of microtubules (C1 and C2), also structurally and biochemically asymmetric, is present in the center of the ring and extends the length of the axoneme

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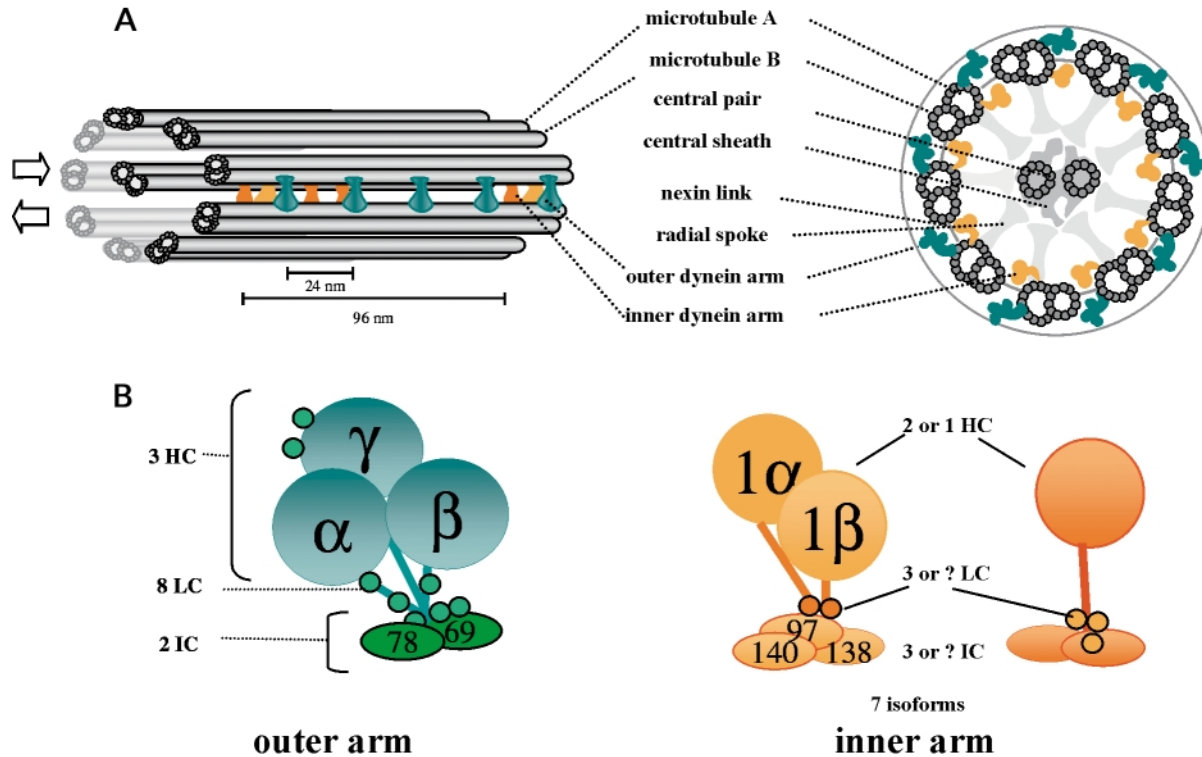
Figure 1. Axoneme structure and components. (**A**) Schematic diagram of the cilium axoneme in length and in cross section, indicating the different axonemal components. Nine microtubule doublets (microtubules A and B) surround two central microtubules (central pair), which are enclosed by the central sheath. The microtubules are interconnected by nexin links, radial spokes and dynein arms. Cilia beating originates from the sliding of microtubule doublets (double arrow on the left), which is generated by the ATPase activity of the dynein arms. The dynein arms are periodically distributed along the axoneme; outer dynein arms (green) with a 24 nm periodicity and inner dynein arms (light and dark orange) with a 96 nm periodicity. The dynein arms are multiprotein complexes that project from the A microtubule of every outer doublet; the outer arms (green) face towards the boundary of the axoneme, and the inner arms (orange) face the central sheath. (**B**) The outer arm of *Chlamydomonas* (in green) is composed of three globular HC dyneins (α, β and γ), two IC dyneins at the base of the complex (IC69 and IC78), and eight LC located at different positions (small circles); adapted from Takoda *et al*. (20). The inner arm (in orange) is more variable, there are at least eight HC organized into seven isoforms; one double-headed (light orange) and six single-headed (dark orange). The double-headed inner arm is composed of two HC (1α and 1β), three IC (IC97, IC138 and IC140) and three LC. The exact composition of the single-headed isoforms is not yet resolved.

(11–15). In some cases the axoneme lacks the central pair apparatus (9+0 axoneme). Based on whether the axoneme has a 9+0 or a 9+2 structure, cilia have been defined as primary cilia or motile cilia, respectively (16). Recent findings indicate that there are many exceptions to this definition and favor the distinction into four subtypes: motile 9+2 cilia (e.g. respiratory cilia), motile 9+0 cilia (e.g. nodal cilia), sensory 9+2 cilia (e.g. vestibular cilia), and sensory 9+0 cilia (e.g. renal monocilia and photoreceptor connective cilia; Fig. 3).

Within the microtubule core, a number of multiprotein complexes interconnect the different components. Among these are radial spokes, nexin links, central sheath and dynein arms (Fig. 1A). The dynein arms are attached to the peripheral microtubules with certain periodicity and generate motion by ATP-dependent reactions. The other components, mainly the central apparatus and radial spokes, provide the structural interface for transmitting regulatory signals to the arms (14,15,17). The dynein arms are large, multisubunit molecular motors formed by the combined assembly of polypeptides of different sizes: heavy (HC of 400–500 kDa), intermediate (IC of 45–110 kDa) and light chains (LC of 8–55 kDa; Fig. 1B). Within these multiprotein assemblies, the ATPase activity that resides in the HC molecules provides the energy to produce the

sliding movement between microtubules, which results in the beating of the cilium. The capability of dynein arms to function as microtubule-based molecular motors requires the integrity of many dynein components. Numerous dysmotile strains of *Chlamydomonas* have been reported. By analyses of these mutant strains, a remarkable number of genes encoding axonemal dyneins have been identified. These studies, summarized in several recent reviews (11–15), indicate that 30–40 axonemal dyneins (~14 HC, ~7 IC and ~15 LC) combine to form different dynein arms. The outer arm (Fig. 1B left) is invariably formed of 3 HC (α, β and γ), two IC (IC69 and IC78) and 8 LC. The inner arm composition is more diverse (Fig. 1B right). So far, seven inner arm isoforms have been partially resolved biochemically; one two-headed isoform and six single-headed. Three other inner arm HCs yet unresolved are suspected to form more isoforms (15,17). Every isoform includes different IC and LC. For instance, the two-headed isoform I1, also called isoform f, is composed of two HCs (1α and 1β), three ICs (IC97, IC138 and IC140) and three LCs. Less is known about the organization of the single-headed isoforms. It appears that all six forms associate with actin, three assemble with p28, and the other three with the calcium-binding centrin (14,15).

Most of the homologous genes encoding axonemal polypeptides in mammals have been identified. At present some of them have been renamed several times and a consensus nomenclature is emerging (Table 1). The high degree of sequence conservation and similar ultrastructural defects observed in *Chlamydomonas* flagellar mutants and defective cilia from patients have facilitated the determination of the corresponding homologs in some cases. For instance, DNAH5 and DNAI1 seem to be the homologs of *Chlamydomonas* outer arm HCγ and IC78, respectively (18,19). Linkage studies of these axonemal deficiencies and ciliary dysfunction will be discussed later in this review. Additional and more comprehensive comparative analyses need to be done to determine the homologs of additional dyneins, some of which have several splicing variants.

The extraordinary complexity of dynein arm function seems to be further complicated with the existence of docking complexes and signalling enzymes. The docking complex that attaches the outer arm (ODA-DC) is composed of three polypeptides (20), whereas the one for the inner arm has not yet been solved but it is suspected to interact via IC140 (21). Important evidence for the regulatory role of the central pair apparatus and the radial spokes in dynein arm activity has come with the discovery of a number of kinases and phospahatases anchored to them (14,15,17). Among these are casein kinase 1 (CK1) and phosphatases PP2A and PP1c in C1 microtubules, kinase A anchor proteins (AKAPs) AKAP-240 in C2 microtubules and AKAP-97 (also known as RSP3) in radial spokes, and the calmodulin binding kinase RSP2 in radial spokes. The elucidation of the signalling cascades that control flagellar function will extend our understanding of the axoneme function.

LEFT–RIGHT PATTERNING ASYMMETRY

The recent discovery that cilia are able to generate the current flow necessary to initiate the signaling cascade for left–right patterning in embryos has made an important impact on developmental biology (22,23). Many recent reviews have covered this topic (24–31). The ventral surface of the embryonal node in mammals, or of the equivalent structures in other vertebrates (32), is covered with monocilia that rotate in a clockwise direction generating a leftward flow or 'nodal flow' (Fig. 2). When nodal cilia are immotile or absent, nodal flow does not occur. This leads to randomization of body situs (Fig. 2B) (22,33,34). Two hypotheses have been proposed to explain the determination of left–right body asymmetry by nodal flow. One hypothesis postulates that one or more unknown extracellular morphogens (i.e. retinoic acid) might be transported to the left side of the embryo and asymmetrically trigger/s the laterality signaling cascade (35). A second hypothesis proposes that, within the node, motile cilia located at the center generate the nodal flow, and that sensory cilia situated at the periphery of the node might detect this flow and initiate the signaling cascade. In support of this second hypothesis, loss of function of polycystin-2, which is a cation channel, results in mice with randomization of left–right body asymmetry (36,37). In addition, artificial nodal flow experiments with mouse embryos have provided direct evidence for the role of

mechanical fluid flow in left–right determination in the absence of a morphogen (38). Studies are currently in progress to clarify this question. The embryonal monocilium has the 9+0 structure and for long time was considered immotile and lacking dynein arms (30,31). The finding that mutations in several dyneins (22,39,40) lead to randomization of left–right asymmetry has proven the opposite. Likewise, monocilia (with lrd dynein) have been detected in the nodal equivalent structures in chicken (Hensen's node), frog (dorsal blastopore) and zebrafish (dorsal forerunner cells; Fig. 2C) (32), establishing that the nodal flow mechanism is conserved in all vertebrates. Nevertheless, recent evidence suggesting that left–right patterning occurs prior to node formation in lower vertebrates (28,41) may indicate the existence of more than one mutually reinforcing or distinct mechanisms across vertebrate groups.

The first link between cilia and left–right determination was suspected by Kartagener who observed that patients with the heart and abdominal viscera positioned in reversed mirror-image (also called *situs inversus*) also had respiratory problems, and named that condition Kartagener's syndrome (KS) (42). This condition is also called primary ciliary dyskinesia (PCD) and it is discussed in the following section. Since then, numerous KS case reports have been published. In families with KS all affected individuals have respiratory distress, but only half of the affected siblings have *situs inversus*, due to randomization of the left–right body asymmetry.

Several mouse mutants with *situs inversus* and impaired nodal flow have been described. Identification of the mutations responsible for these phenotypes has implicated genes encoding ciliary components required for cilia motility (dyneins) or for ciliogenesis (kinesins and others). For instance, mice that are deficient in axonemal dyneins, Mdnah5 (39) and lrd (22,34), have randomized situs. Other mutant mice, such as kinesin Kif3A- and Kif3B- and Polaris- (Tgt737) deficient mice, lack nodal monocilia and thus show also *situs inversus* (23,43,44). More ambiguous cases are Hfh4-deficient mice which lack epithelial cell cilia, but do have monocilia and randomization of situs (45,46), and *inv* mice with a mutation in the *inversin* gene that causes slower nodal flow resulting in inversion instead of randomization (33,47). The earliest event in the laterality cascade described so far is the ion flux created by an H^+/K^+-ATPase transporter which is asymmetrically expressed at the four-cell stage in lower vertebrates (41). Experiments addressing whether this or other transporters and channels exist in mammals will establish whether this is a general mechanism. Beyond the symmetry breaking point, complex interactions involving several signaling pathways and homeobox transcription factors mediate asymmetric cascades of gene expression. Mutant mice for genes involved in left–right patterning such as *nodal*, *lefty*, *pitx2*, *sonic hedgehog*, and others show more complex and severe left–right patterning defects and have been the subject of numerous reviews (27–31).

CILIARY DYSFUNCTION IN DISEASE

Cilia are present in almost all organs of the human body (16). There is increasing evidence that dysfunction of this large organelle is involved in many different human disorders. Sites

Table 1. Axonemal heavy chain dyneins

Human			Mouse			Linkage to PCD	References
NCBI/HUGO	Other name	Chromosome locus	NCBI	Other name	Chromosome locus		
DNAH1	hdhc7	3p21	Dnahc1	Mdhc7	14cM8.3	—	92–96
DNAH2	Dnahc2	17p13	Dnahc2	—	11cM40.0	—	92,94
DNAH3	hdhc8	16p12	—	Mdhc8	7	—	93–95
DNAH5	Dnahc5	5p15.2	Dnahc5	Mdnah5	15cM8.2	Linked to PCD	18,39,40,92
DNAH6	Dnahc6	2p11-12	Dnahc6	Mdhc6	6cM31.0	—	92,95
DNAH7	hdhc2	2q33.1	—	Mdhc2	1C1.1	—	93,95,97
DNAH8	hdhc9	6p21	Dnahc8	Mdhc9	17cM16.4	—	93,95
DNAH9	DNAH17L	17p12	—	Mdhc1	11 B3	—	59,92,93,95
DNAH10	—	13q14	Dnahc10	Mdhc4	14	—	93,95
DNAH11	hdhc4	7p21	Dnahc11	lrd	12cM60.0	Linked to PCD	22,34,57,93–95
DNAH12	Dnahc3	3p21.1	Dnahc3	Mdhc3	14cM6.0	—	92–94,98
DNAH13	DNCH1	14q32	Dnahc13	Dnchc1	12cM55.0	—	94
DNAH14	HL18	1p36	—	—	4	—	92
DNAH17	DNEL2	17q25	—	—	11	—	99

Sequence alignments, human–mouse homologies and comparison of approved gene symbols (HUGO/NCBI nomenclature) with previous alternative names were done using a number of URLs (www.gene.ucl.ac.uk/nomenclature/genefamily/dynein.html; www.ncbi.nlm.nih.gov/LocusLink/; www.ncbi.nlm.nih.gov/ Homology/; www.ncbi.nlm.nih.gov/Homology/; www.ncbi.nlm.nih.gov/blast/; www.ncbi.nlm.nih.gov/UniGene; and www.ncbi.nlm.nih.gov:80/entrez/;query. fcgi?CMD=&DB=omim); specific references for individual axonemal dyneins are indicated in the table.

of action of cilia that have been implicated in human disease are illustrated in Figure 3. Many other organs also have cilia and their functional relevance remains to be elucidated. For a detailed review of cell types where cilia have been detected refer to http://members.global2000.net/bowser/cilialist.html. Studies of PCD have aided our understanding concerning ciliary dysfunction in human disease.

Respiratory cilia and cilia/flagella of the reproductive system

PCD, also known as immotile cilia syndrome (ICS; OMIM 242650) and KS (OMIM 244400), is characterized by recurrent infections of the upper and lower respiratory tract (48). Motile cilia covering epithelial cells lining the upper and lower airways are responsible for the clearance of the airway (Fig. 3). In PCD airway cilia are immotile, dysmotile or absent, which results in a reduced mucociliary clearance of the airways. Symptoms such as respiratory distress (49), chronic rhinosinusitis and otitis media, persistent cough, and asthma are characteristic of PCD. Often, recurrent infections progress and cause a destructive dilation of the bronchial airway called bronchiectasis (42). Male infertility due to sperm immotility is frequent in PCD (50,51). Female subfertility is less common and is caused by dysfunction of motile cilia from the fallopian tubes and the uterine lining, which are responsible for the oocyte transport (50,52). Sperm tails, cilia of the testis efferent ducts and cilia of the female reproductive system share with respiratory cilia the 9+2 ultrastructure (Fig. 3). In most PCD patients ultrastructural defects of cilia can be detected by electron microscopy (53). The most common structural defects consist of total or partial absence of dynein arms (~80%), absence or dislocation of central tubules (~10%), defects of radial spokes (~6%) and peripheral microtubular abnormalities (3%). Less frequent abnormalities include ciliary aplasia, basal apparatus alterations, axoneme-less cilia, hockey-stick cilia and long cilia. Many of the above-mentioned ultrastructural defects might also

be caused by secondary alterations such as inflammation due to viral infection. Interestingly, in ~3% of patients with PCD no ultrastructural defects can be detected. Diagnosis of PCD can be established by electron microscopy if the specific ultrastructural defects of cilia or sperm tails are detected in an individual with a clinical picture compatible with PCD. Alternatively, diagnosis requires the demonstration of immotility or severe dysmotility of cilia or spermatozoa by direct light microscopy in the absence of secondary alterations (52).

PCD represents a heterogeneous group of genetic disorders affecting 1/20 000 individuals at birth (52). Inheritance in most cases is autosomal recessive (54). Considering the heterogeneity of ultrastructural defects causing PCD it was expected that genome-wide linkage studies would reveal extensive locus heterogeneity (55). Mutations in *DNAI1* and *DNAH5* genes encoding outer arm dyneins have been demonstrated in patients with PCD and randomization of left–right asymmetry has been linked to their respective chromosome loci (Table 1) (19,40,56). Recently, a loss-of-function mutation in *DNAH11* was identified in an individual with situs inversus (57). Other genes encoding axonemal dyneins appear as ideal candidates for human PCD (Table 1). However, candidate gene analyses in *TCTEX2, DNAI2* and *DNAH9* encoding different dynein chains were unsuccessful (58–60).

Rare disease manifestations of PCD

In a minority of PCD patients the disease is associated with other organ manifestations (61). In this review we will concentrate on PCD-associated diseases where data are available to support a role of ciliary dysfunction in the pathogenesis. These include hydrocephalus internus, eye anomalies such as retinitis pigmentosa and corneal anomalies, and cystic kidney disorder.

Ependymal cilia

Several reports indicate an association of PCD and *hydrocephalus internus*, or transient dilatation of inner brain
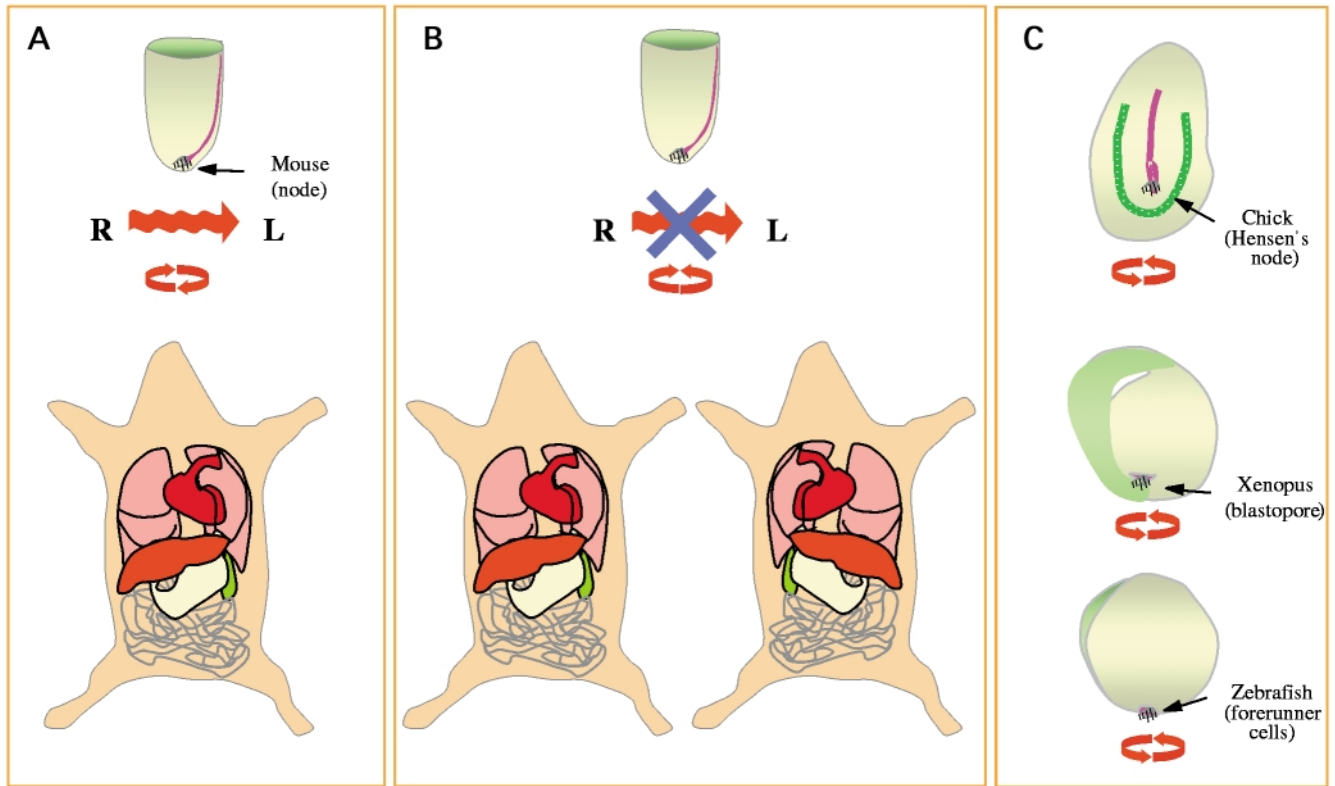
Figure 2. Determination of left–right asymmetry; nodal flow model. (**A**) Illustration of a mouse embryo (~E7.5–E8.5), indicating the embryonal node where monocilia are located. The vortical motion of nodal monocilia generates a leftward flow of the fluid surrounding the embryo in the node region. This movement, known as 'nodal flow' and indicated with red arrows, is an initiating event for the determination of the left–right patterning. (**B**) When nodal flow is impaired, randomization of body situs occurs. This randomization is illustrated with the schematic drawing of mice showing visceral organs and heart. Since left–right patterning is determined randomly in nodal flow mutants, some mutant mice will be *situs solitus* (normal disposition of organs) and some will present *situs inversus* (mirror-image reversal of organ asymmetry). In some cases partial *situs inversus* can also occur. (**C**) Left–right signaling regions in chick, *Xenopus* and zebrafish embryos are indicated with arrows. Monocilia containing lrd dynein have been detected in the chick Hensen's node, in the ventral cells of the blastopore in frog, and in the dorsal forerunner cells in fish, indicating that the nodal flow mechanism is conserved in vertebrates. Illustrations in (C) are adapted from Essner *et al*. (32).

ventricles, which exists in a minority of PCD patients (62–67). In families with occurrence of hydrocephalus and PCD, hydrocephalus is not present in every affected PCD individual (unpublished data). Thus, the genetic defect leading to the respiratory phenotype of PCD does not always results in development of hydrocephalus. There are several animal models of PCD that also develop hydrocephalus, supporting the idea that ciliary function is important for prevention of hydrocephalus (39,68–71). The ependymal cells lining the ventricles of the brain carry motile cilia with a 9+2 ultrastructure, as do cilia of the respiratory and reproductive tract (Fig. 3). Ependymal cilia have been studied in rats extensively, where they beat at a frequency of ~40 Hz, approximately twice the frequency of respiratory cilia. In addition, ependymal cilia are significantly longer (8 μm) when compared with respiratory cilia (5 μm) (72). The functional relevance of ependymal cilia beating is still not completely understood. The development of hydrocephalus in mice with targeted mutation of cilia-related genes such as *Mdnah5, hfh4* and *Tg737* strongly suggests that ependymal cilia play an important role in transport of cerebro-spinal fluid (39,44,45,73). However, it is unlikely that ciliary beating is responsible for bulk transport of cerebro-spinal fluid, which is produced in the choroid plexus, since bulk transport is mostly achieved by the changing blood pressures of the brain

vessels during systole and diastole (74). Ependymal ciliary function might be particularly important for the circulation of cerebro-spinal fluid at the narrowest portions such as the aqueduct of Sylvius and foramina.

Cilia of the eye

Corneal anomalies in PCD patients have been reported (75). In particular, keratoconus is common in patients with PCD. Interestingly, the endothelium covering the back of the cornea carries monocilia. These monocilia may have a sensory function necessary to maintain corneal integrity. Other patients suffer from PCD and associated retinitis pigmentosa or deterioration of the photoreceptor cells of the retina (75–78). Vertebrate photoreceptor cells are polarized sensory neurons consisting of a photosensitive outer segment and an inner segment bridged by a connecting cilium (79). The connecting cilium is a nonmotile primary cilium (9+0 structure; Fig. 3). The movement of large protein complexes along flagellar or ciliary microtubules termed intraflagellar transport (IFT) is essential for assembly and maintenance of cilia and has been proposed as the transport mechanism in the connecting cilium (80). In support of this, the IFT particle, IFT88 (also known as Polaris or Tg 737) has been localized to the photoreceptor
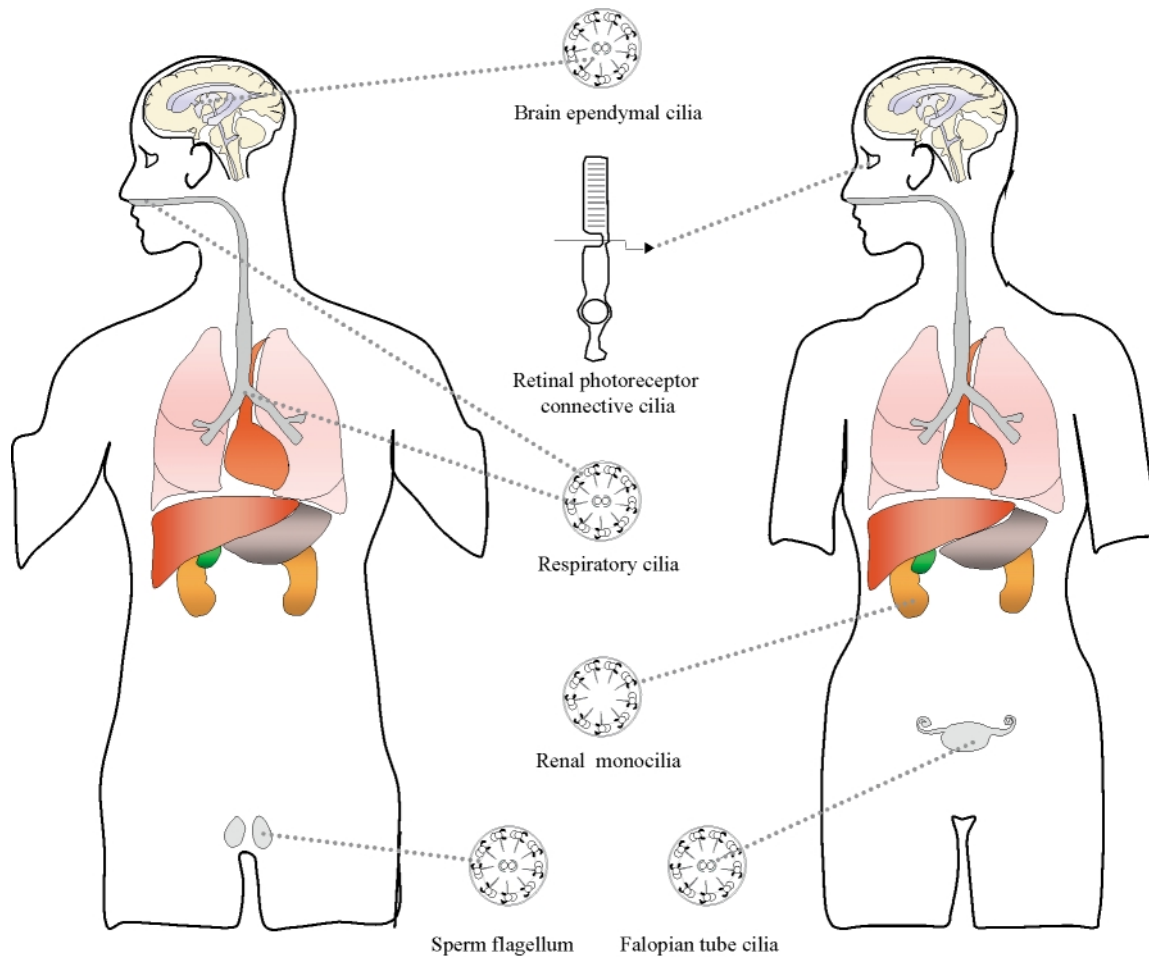
Figure 3. Cilia malfunction in diverse human disorders. Representation of a male and a female individual, showing the sites of action of cilia that have been implicated in human disease. Also indicated are the different axonemal structures of each particular cilia type. In the brain, the ependymal cells lining the ventricles carry motile cilia with a 9+2 ultrastructure. In the retina, the light sensitive photoreceptor cells consist of an outer and an inner segment which are linked by a connective cilium which might have a 9+0 ultrastructure. The back-side of the cornea carries monocilia as well. In the upper and lower respiratory tract, epithelial cells are covered with motile cilia of 9+2 ultrastructure. In kidney, monocilia of presumably a 9+0 structure are present in glomerulus and tubular cells. The axoneme structure of renal monocilia and photoreceptor connective cilia is supposed to be 9+0 but no electron microscopy has verified yet whether these cilia have the microtubule central pair and/or dynein arms. The sperm flagellum and cilia of the testis efferent ducts have a 9+2 structure. Similarly, motile cilia of a 9+2 structure line the uterus and fallopian tubes.

connecting cilia and mice with a mutation in the encoding gene have abnormal photoreceptor outer segment and retinal degeneration (see also renal cilia) (81). Therefore, human orthologs of *Chlamydomonas* IFT genes should be considered as candidates for retinal degeneration.

Renal cilia

Kartagener and Horlacher described in 1935 the occurrence of cystic kidney disease in association with PCD (82). Other reports describing the concomitant occurrence of bronchiectasis and cystic kidney disease, or of *situs inversus* and cystic dysplasia of kidneys and pancreas, support a role of renal ciliary dysfunction in human cystic kidney disorders (83–85). In the kidney, glomerulus cells and tubular cells carry monocilia with a 9+0 ultrastructure resembling nodal cilia (Fig. 3).

Polycystin-1 and polycystin-2 responsible for human autosomal dominant polycystic kidney disease type 1 and 2

(ADPKD1, ADPKD2) appear to be involved in renal ciliary function. Localization of murine polycystin-1 and polycystin-2 to renal cilia has been shown, and elevated ciliary levels of polycystin-2 in $Tg737^{orpk}$ mice with polycystic kidney disease have been demonstrated (86,87). The $Tg737$ gene was originally identified based on its association with the mouse *Oak Ridge Polycystic Kidney* (*orpk*) insertional mutation ($Tg737^{orpk}$) (88). Additional studies demonstrated that $Tg737$ encodes the protein Polaris which is present in cilia in many organs (73,89). Accordingly, a targeted mutation in $Tg737$ caused a wide spectrum of phenotypes comprising polycystic kidney disease, liver and pancreatic defects, hydrocephalus, and randomization of left–right asymmetry (73,89). Insights into the potential function of Polaris have been inferred from studies in *Chlamydomonas*, which demonstrated that IFT88, the ortholog of Polaris, is required for axonemal assembly (90). IFT88 mutant alga either lack flagella or show abnormal growth of their flagella. In analogy murine renal tubular cells

carrying *Tg737* mutations have shortened renal monocilia (90). Interestingly, polycystin-2 deficient mice also show, besides renal involvement, randomization of left–right body asymmetry supporting the role of polycystin-2 for ciliary function. Recently, the underlying genetic defect of the congenital polycystic kidney (cpk) mouse model was identified in the *cystin* gene, which is also expressed in renal monocilia (91). The cpk phenotype mimics human autosomal-recessive polycystic kidney disease, including the observed concomitant biliary liver cirrhosis. The function of renal cilia is still speculative, but it is thought that cilia might have a sensory function or have a specific role during embryogenesis. However, evidence is very strong that renal ciliary dysfunction contributes to cystic kidney disease.

CONCLUSIONS AND PERSPECTIVES

The unexpected roles of cilia in left–right patterning or in renal function are suggestive that other unique ciliary functions will soon be discovered. The further elucidation of the diverse functional roles of cilia will help our understanding of many different disorders. Hopefully this knowledge might also result in novel therapeutic options. Numerous additional genes encoding ciliary components are currently being identified. Their mode of assembly and function remains to be determined. Furthermore, the isolation of novel specific signaling molecules and mechanisms controlling the motility of the cilium is adding more complexity to ciliary function *in vivo*. Altogether these novel genes, functions and regulatory mechanisms will bring an answer not only to the question to beat or not to beat, but how, where and how much to beat.

ACKNOWLEDGEMENTS

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