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# Cilia in vertebrate development and disease

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## Summary

Through the combined study of model organisms, cell biology, cell signaling and medical genetics we have significantly increased our understanding of the structure and functions of the vertebrate cilium. This ancient organelle has now emerged as a crucial component of certain signaling and sensory perception pathways in both developmental and homeostatic contexts. Here, we provide a snapshot of the structure, function and distribution of the vertebrate cilium and of the pathologies that are associated with its dysfunction.


**Key words: Cilia, IFT, Signaling**

## Introduction

Once considered to be vestigial organelles, cilia are microtubule-based structures found in unicellular flagellates and in multicellular organisms and have recently been discovered to have a profound influence on tissue development and homeostasis. Although the presence of cilia is restricted to specific cell types in invertebrates, their near ubiquitous localization on the apical surface of most vertebrate cell types suggests that this ancient organelle has evolved to facilitate a broad range of functions. Recent findings in humans and in model organisms have fuelled a renewed interest in the cilium as a sensory hub and as generator of fluid flow; both of these functions underpin fascinating developmental processes, such as the initiation of left-right (L-R) asymmetry (Hirokawa et al., 2006), as well as certain disease pathologies, such as the modulation of cancer progression and metastasis (Han et al., 2009; Wong et al., 2009). Consistent with the developmental roles of the cilium in vertebrates in fluid flow generation, mechanosensation, osmosensation, olfaction, photoreception, chemosensation and thermosensation (Berbari et al., 2009; Hirokawa et al., 2006), and based on the diverse range of cell types that can form a cilium, the clinical features of several human disorders have been attributed to dysfunctional cilia. In this poster article, we provide an overview of ciliary biology with an emphasis on signaling pathways and modes of ciliary dysfunction in which selected ciliary expression is associated with specific developmental events and disease states.

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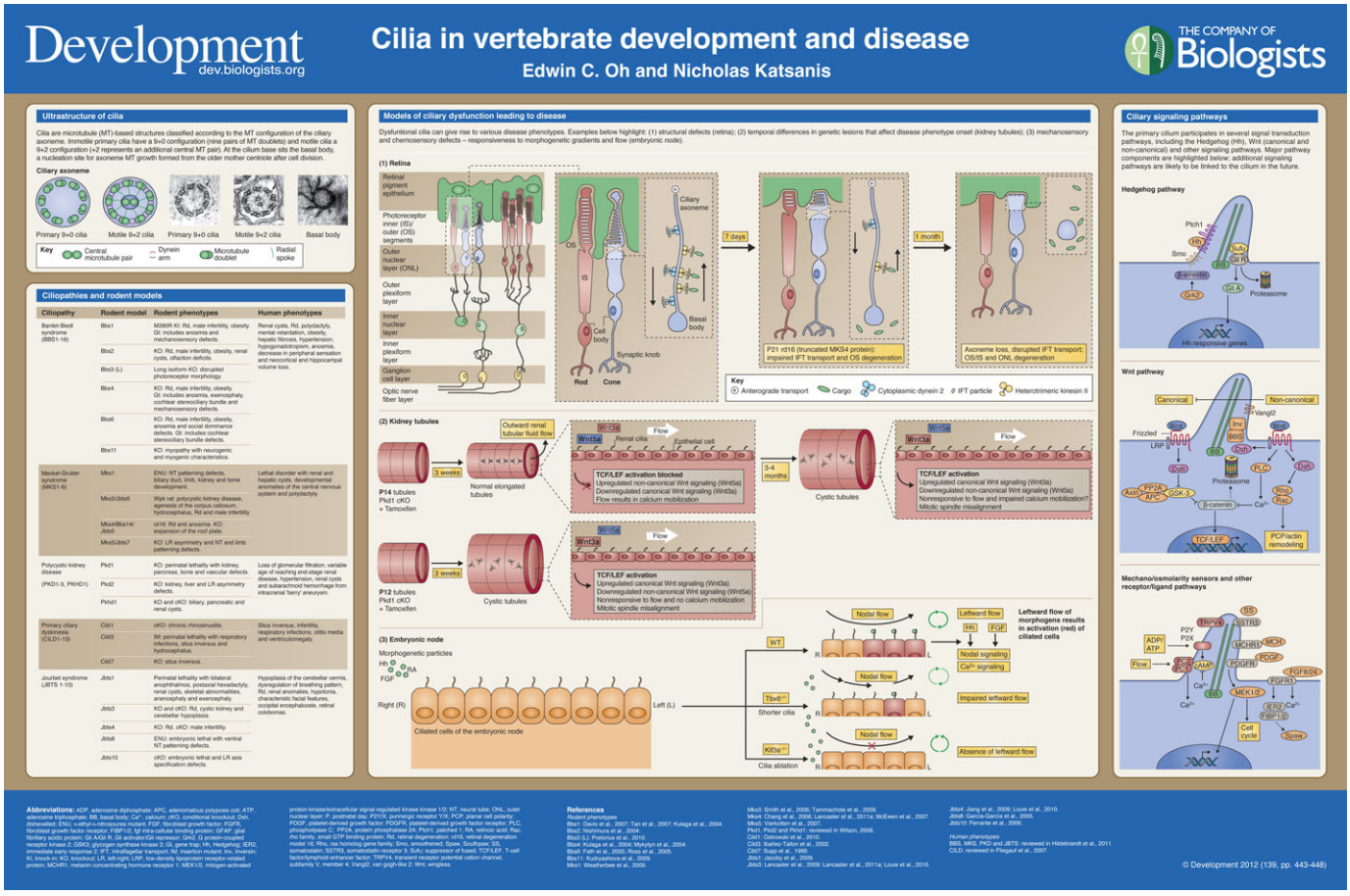


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## Ciliary biology

Tethered to most differentiated vertebrate cell types (Gerdes et al., 2009; Olsen, 2005), cilia are microtubule-based structures that can be classified as immotile 9+0 primary cilia or motile 9+2 cilia, depending on the presence of a central microtubule pair that is surrounded by nine pairs of microtubule doublets (Satir and Christensen, 2007). However, exceptions to these traditional classifications do occur; renal cilia have a motile 9+0 configuration (Kramer-Zucker et al., 2005), motile cilia of the mouse embryonic node have both 9+0 and 9+2 configurations (Caspary et al., 2007; Nonaka et al., 1998), and cilia in the frog appear to have an immotile 9+2 design (Reese, 1965). Although the number of motile cilia can range from 200 to 300 per cell type, a single immotile primary cilium is typically present on most cell types.

Pioneering studies in the green alga *Chlamydomonas reinhardtii* delineated a dynamic process of intraflagellar transport (IFT) that is responsible for the transport of cytoplasmic proteins along the ciliary axoneme. As schematized in the poster, the axoneme is a microtubule-based cytoskeleton that is enclosed by the ciliary membrane (Kozminski et al., 1993; Scholey, 2008). Anterograde transport (towards the plus end – the ciliary tip) is achieved by a heterotrimeric kinesin 2 motor (Scholey, 2008), whereas retrograde transport (towards the minus end – the ciliary base) is driven by cytoplasmic dynein 2 (Kardon and Vale, 2009; Scholey, 2008). Together with IFT particle A (retrograde) and B (anterograde) subcomplexes, these motors facilitate the transport of multi-subunit protein complexes along the axoneme. In vertebrates, the IFT A and B subcomplexes consist of at least six and 13 components, respectively (Cole and Snell, 2009; Scholey, 2008).

Through the use of genomic, transcriptomic and proteomic approaches, the molecular components of the cilia proteome have been studied (Andersen et al., 2003; Avidor-Reiss et al., 2004; Blacque et al., 2005; Broadhead et al., 2006; Efimenko et al., 2005; Keller et al., 2005; Li et al., 2004; Liu et al., 2007; Ostrowski et al., 2002; Pazour et al., 2005; Stolc et al., 2005) and ~2500 putative proteins identified (see www.ciliaproteome.org) (Gherman et al., 2006). These studies have led to the identification of candidate proteins that have been implicated, directly or indirectly, in transport mechanisms and structural components of the cilium, and in cilia-associated human disorders.

Recent interest in ciliary biology stems from studies in vertebrates that link this organelle to developmental processes, ranging in roles from the control of L-R extra-embryonic nodal fluid flow, which initiates L-R patterning, to the detection of fluid flow in the kidney, light perception by photoreceptors in the retina, and the mediation of morphogenetic signaling pathways (Badano et al., 2006). Within the last decade, defective cilia have been linked causally to at least 13 clinically discrete pathologies (Bardet-Biedl syndrome, Mekel-Gruber syndrome, Joubert syndrome, Senior-Loken syndrome, Alstrom syndrome, polycystic kidney disease, nephronophthisis, cholangiopathies, retinitis pigmentosa, primary ciliary dyskinesia, Hirschsprung disease, oral-facial-digital syndrome and cancer) (Badano et al., 2006; Brugmann et al., 2010; Han and Alvarez-Buylla, 2010; Masyuk et al., 2009) and are predicted to underscore >120 disorders of unknown etiology (Baker and Beales, 2009).

## Cilia-related disease

Most vertebrate cell types can develop a cilium during their life cycle, a fact highlighted by the finding that both human and mouse embryonic stem (ES) cells grow a primary cilium in culture (Corbit et al., 2008; Kiprilov et al., 2008). Although it is unclear why some cells do not ciliate in a differentiated state, this absence of cilia appears to be the exception to the rule. Mutations in certain ciliary genes, such as *KIF3A* and *KIF3B* (which encode kinesin family members 3A and 3B, two proteins that participate in IFT) affect early developmental processes, such as L-R patterning (Hirokawa et al., 2006). However, mutations in some genes, such as those encoding retinitis pigmentosa GTPase regulator (RPGR) and RPGR-interacting protein 1 (RPGRIP1), which cause retinitis pigmentosa (Ferreira, 2005), do not result in deleterious effects until later in development or postnatally. The variance in phenotypic severity can be attributed to the role of the affected protein; for example, whether core IFT transport components are mutated or whether mutations lie in protein cargo destined to the cilium. In this poster article, we present a snapshot illustrating the temporal and spatial variables that affect ciliary function and disease progression in the mouse retina, kidney and embryonic node. We highlight these specific tissue types to emphasize: (1) structural deficits: the loss of ciliary/centrosomal proteins leads to the degeneration of the ciliary axoneme and in turn photoreceptor death; (2) temporal regulation: the loss of a ciliary protein at postnatal day (P) 12 can result in cystic tubules within 3 weeks, whereas loss of the same protein at P14 can take up to 4 months to cause kidney failure; and (3) mechanosensory and chemosensory defects: the loss of ciliary proteins can alter responsiveness to morphogenetic gradients and flow and can lead to situs inversus.

## Cilia and developmental signaling

As a signaling conduit, the primary cilium participates in several signal transduction pathways, including the Hedgehog (Hh), Wnt (canonical and non-canonical), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) signaling pathways (Berbari et al., 2009; Gerdes et al., 2009; Gorbatyuk et al., 2007). We have highlighted the role of the major components of these pathways on the accompanying poster and provide a summary below, with the full expectation that additional signaling pathways will be linked, either directly or indirectly, to the cilium as we come to understand further the functions and protein content of this organelle.

### Hedgehog signaling

The Hh pathway regulates a broad range of key developmental activities. In mammals, the pathway is activated by the binding of the Hh ligands sonic hedgehog (Shh), Indian hedgehog (Ihh) and desert hedgehog (Dhh) to the transmembrane receptor patched (Ptch) and results in internalization of the receptor/ligand complex. Smoothened (Smo), which is normally repressed by Ptch, then facilitates the processing and potential nuclear-cytoplasmic distribution of Gli transcription factors through suppressor of fused (Sufu) (Chen et al., 2009; Humke et al., 2010; Lum and Beachy, 2004).

Recent data suggest that Hh signaling is regulated through the primary cilium. This connection was first established when a genetic screen to characterize mice with neural tube closure defects, a process that is mediated by Shh, identified mutants for components of anterograde and retrograde IFT: *Ift88*, *Ift172* and dynein cytoplasmic 2 heavy chain 1 (*Dync2h1*) (Huangfu et al., 2003). Disruption in *Kif3a* also led to similar patterning defects, supporting the notion that IFT proteins are necessary for Hh signaling. Dissection of the IFT-Hh signaling relationship further revealed that IFT proteins control the function of Gli transcription factors by regulating Gli repressor (GliR) and activator (GliA) forms. This observation is best illustrated in some IFT mutants that

show either a loss (loss of GliA resulting in defective neural patterning) or gain (loss of GliR resulting in defective limb development) of Hh signaling phenotypes (Liu et al., 2005; May et al., 2005).

Interestingly, Hh effectors localize to the cilium where they transduce the Hh signal. Ciliary targeting of Smo, for example, is augmented in response to Shh ligand in Madin-Darby canine kidney (MDCK) and mouse embryonic fibroblast (NIH-3T3) cell lines (Corbit et al., 2005). Importantly, a ciliary localization motif in Smo appears to control Smo translocation to the cilium (Corbit et al., 2005). Subsequent findings have demonstrated that Gli proteins and Sufu (a negative regulator of Gli) also localize to the primary cilium where, like other IFT proteins, they regulate physiological processes such as limb development and cell migration to the brain and craniofacial skeleton (Corbit et al., 2005; Han et al., 2008; Rohatgi et al., 2007; Spassky et al., 2008; Tobin et al., 2008; Willaredt et al., 2008).

### Wnt signaling

Similar to the Hh pathway, several Wnt and planar cell polarity (PCP) components (e.g. adenomatous polyposis coli, Apc; van gogh-like 2, Vangl2; and β-catenin) have been localized to the cilium (Corbit et al., 2008; Ross et al., 2005). Loss of ciliary and basal body proteins results in dysregulation of β-catenin signaling (Corbit et al., 2008; Gerdes et al., 2007; Lancaster et al., 2011a; Lancaster et al., 2011b), with concomitant defects in non-canonical signaling (impaired convergent extension movements, neural tube closure failure and disorganization of stereocilia in the mouse inner ear), highlighting an emerging role for the basal body and primary cilium in Wnt/PCP signaling (Ferrante et al., 2009; Gerdes et al., 2007; Hunkapiller et al., 2010; Lancaster et al., 2009; McDermott et al., 2010; Simons et al., 2005).

The physiological relevance of dysregulated Wnt/PCP signaling is evident in the development and function of several vertebrate organs, such as kidney, cochlea and neural tube. By patterning the planar surface of an epithelium or tissue, PCP proteins, such as disheveled 1 (Dvl1), Dvl2 and Dvl3, can regulate the apical movement of basal bodies from deep within the cytoplasm to the cell surface and, thus, cilia formation and positioning in the *Xenopus* mucociliary epithelia (Park et al., 2008). In the mouse node, the rotational axis of the primary cilium is tilted towards the posterior side (where velocity of fluid flow is highest), presumably because the basal body is preferentially located at the posterior side of node cells (Nonaka et al., 2005; Okada et al., 2005). Recent evidence suggests that the posterior displacement of centrioles and of cilia in nodal cells is regulated by the asymmetric localization of PCP components and the interaction of PCP signals and fluid flow (Borovina et al., 2010; Guirao et al., 2010; Hashimoto et al., 2010).

Although evidence for the relationship between Wnt signaling and the basal body and cilium has been robust, two recent reports have described normal Wnt signaling in mice with single-gene mutations in the cilia-associated genes *Ift88*, *Ift172*, *Kif3a* and *Dync2h1* (Ocbina et al., 2009), and in zebrafish without cilia (for example, the maternal-zygotic *ift88* mutant) (Huang and Schier, 2009; Ocbina et al., 2009). These data suggest that the previously published Wnt defects are cilia-independent and represent a secondary, unrelated function of some basal body/axonemal proteins. Alternatively, or additionally, the specific genetic lesion (Lancaster et al., 2011b) and background of the animals used in these studies might explain why the same assays yielded different data in different animal colonies. Variable penetrance and expressivity is a common feature of disease phenotypes across phyla (most notably in humans) (Nadeau, 2001; Weatherall, 2001); as such, alleles that exacerbate, or, more excitingly, protect against defective signaling downstream of ciliary dysfunction might be of significant medical utility.

### Other signaling pathways

Additional receptor-ligand components have been localized to the cilium. Although their precise roles in this organelle remain to be elucidated, the examples discussed below reflect our growing appreciation of the complexity of ciliary signaling.

Somatostatin receptor 3 (Sstr3), melanin-concentrating hormone receptor 1 (Mchr1) and serotonin subtype 6 receptor (5-$HT_6$) are G-protein coupled receptors (GPCRs) that localize to the cilium in neurons (Berbari et al., 2008; Brailov et al., 2000; Handel et al., 1999). Interestingly, Bardet-Biedl syndrome (BBS) proteins are required for ciliary function in diverse cell types, and loss of Bbs4 and Bbs2 results in mislocalization of the Sstr3 and Mchr1 receptors and attenuation of GPCR signaling. Given the role of Mchr1 in the regulation of feeding behavior, the depletion GPCRs from the ciliary axoneme has been linked to the hyperphagia feeding phenotypes observed in Bbs mutant mice (Berbari et al., 2008).

Platelet-derived growth factor receptor alpha (Pdgfrα) signaling through the cilium leads to the activation of two pathways: the Akt and the MEK1/2-ERK1/2 (mitogen-activated protein kinase kinase-extracellular signal regulated kinase) pathways (Schneider et al., 2005). Similar to Hh signaling, the localization of Pdgfr to cilia is necessary for PDGF-A activation in cultured embryonic fibroblasts derived from *orpk* mice (Oak ridge polycystic kidney – a mouse mutant with a hypomorphic *Ift88* allele) (Schneider et al., 2005; Yoder et al., 1997). Although these data suggest that Pdgfrα has a mitogenic signaling role during development, the relevance of this pathway in vivo is currently unclear.

The established role of FGF signaling in L-R patterning, through the release of nodal vesicular parcels (NVPs) of Shh and retinoic acid (Tanaka et al., 2005), has also spearheaded new studies into understanding the relationship between morphogenetic fields and ciliary biology. Importantly, transient inhibition of FGF signaling revealed defects in the release of NVPs and calcium signaling but not nodal flow, suggesting that FGF and NVP signaling had no effect on ciliogenesis (Tanaka et al., 2005). However, FGF signaling has recently been implicated in IFT transport and ciliary length (Hong and Dawid, 2009; Neugebauer et al., 2009; Yamauchi et al., 2009). Knockdown studies of both Fgfr1 and FGF ligands cause laterality defects and shortened cilia in the L-R organizer of both zebrafish (Kupffer's vesicle) and *Xenopus* embryos (gastrocoel roof plate) (Hong and Dawid, 2009; Neugebauer et al., 2009; Yamauchi et al., 2009), suggesting that FGF defects might arise from impaired ciliary function.

## Mechanosensation and osmosensation

The discovery that the cation channel proteins polycystin-1 (PC1; Pkd1 – Mouse Genome Informatics) and polycystin-2 (PC2; Pkd2 – Mouse Genome Informatics) localize to primary cilia in MDCK cells provided the first evidence that cilia function in mammalian mechanosensation (Praetorius and Spring, 2001; Praetorius and Spring, 2003). In the mouse embryonic node, ciliary localization of PC1 and PC2 is crucial for a fluid-induced $Ca^{2+}$ and cyclic adenosine monophosphate (cAMP) response, influencing cellular responses during development. Given the essential roles of PC1 and PC2, mutant mouse models reveal disease phenotypes that are

typically associated with ciliary dysfunction, such as laterality defects and polycystic kidney disease (McGrath and Brueckner, 2003; Nauli et al., 2003). As PC2 also localizes to motile cilia, it is likely that PC2 regulates both the motility of cilia and $Ca^{2+}$ levels at the node (McGrath et al., 2003; Sleigh and Barlow, 1982). The expression of the purinergic receptors P2X and P2Y, which belong to a family of cation channels that bind to extracellular nucleotides, along the ciliary axoneme also mediates changes in intracellular cAMP levels (Masyuk et al., 2008). Interestingly, components of the A-kinase anchoring protein (Akap) signaling complex have been discovered on cilia present on cholangiocytes (bile duct epithelial cells), further supporting the role of the cilium in detecting changes in bile flow, and demonstrating how changes in fluid flow can influence organogenesis (Masyuk et al., 2008).

Osmosensation in cilia is partly facilitated by the expression of transient receptor potential vanilloid 4 channel (Trpv4), a homolog of *Caenorhabditis elegans* osmotic avoidance abnormal family member 9 (OSM-9). Activation of Trpv4 results in an increase in intracellular $Ca^{2+}$ concentrations and might influence ciliary beat frequency and ductal bile formation (Gradilone et al., 2007; Lorenzo et al., 2008).

## Perspectives

Our understanding of the role of the cilium in developmental genetics and in human disease has advanced significantly in recent years. Over the next ten years, we are likely to witness more disease states associated with dysfunctional cilia (Baker and Beales, 2009; Gilissen et al., 2010; Walczak-Sztulpa et al., 2010), providing additional avenues by which to link developmental processes to disease pathology. Given the diversity of cilia and the unique composition of protein complexes at the transition zone in different tissue types (Garcia-Gonzalo et al., 2011), the spatiotemporal and genetic context-dependent functions of cilia will need to be examined. This is particularly pertinent in light of recent findings, which show Smo-dependent and -independent (potentially cilia-dependent and -independent) regulation of tumorigenesis (Han et al., 2009; Wong et al., 2009) and the discrepancy of Wnt phenotypes in some IFT mutant models (Huang and Schier, 2009; Ocbina et al., 2009). Finally, given the localization of IFT proteins in other non-ciliary compartments, such as the Golgi complex (Follit et al., 2006), and in non-ciliated cell types, such as lymphocytes (Finetti et al., 2009), we must be careful not to link all IFT mutant phenotypes to ciliary dysfunction, as it is likely that a subset of ciliary proteins will have distinct subcellular roles in cycling and non-cycling cells (Delaval et al., 2011).

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#### Competing interests statement

The authors declare no competing financial interests.

#### Development at a Glance

A high-resolution version of the poster is available for downloading in the online version of this article at http://dev.biologists.org/content/139/3/443.full

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