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The role of primary cilia in neuronal function

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Abstract

The “ciliopathies” are a newly defined group of disorders characterized by defects in the structure or function of the cellular primary cilium. Patients with these disorders display variably expressive fibrocystic renal disease, retinal blindness, polydactyly, obesity, and brain dysgenesis as well as neurocognitive impairments. Joubert syndrome is a ciliopathy defined by cerebellar vermis hypoplasia, oculomotor apraxia, intermittent hyperventilation, and mental retardation. Recent evidence suggests important roles for the primary cilium in mediating a host of extracellular signaling events such as morphogen, mitogen, homeostatic and polarity signals. Based upon the clinical features of ciliopathies and cilia mediated signaling pathways, the data support a role for the primary cilium in modulating neurogenesis, cell polarity, axonal guidance and possibly adult neuronal function.

Keywords

Ciliopathy; Joubert syndrome; Neuronal function; Primary cilia

Signaling function of cilia

Cilia are microtubule-based organelles that project from the surface of many cell types. These organelles can be divided into two types; motile cilia, which generate movement or flow, and nonmotile primary cilia, which move only passively. Both types contain nine parallel microtubules along their length, but only the motile cilia contain outer dynein arms, which are necessary for generating ciliary “strokes”. Nonmotile cilia play well-established roles in specialized sensory cells such as photoreceptors and cochlear hair cells, where they receive special sensory signals such as light and sound. The identification of non-motile cilia on the vast majority of non-mitotic cells throughout the body (Wheatley et al., 1996), initially suggested a non-functional vestigial role, since no known biological role could otherwise be ascribed. However, we now know that many receptors and ion channels are expressed on the membrane of primary cilia and they modulate various signaling pathways including sonic hedgehog (Shh), Wnt, and platelet-derived growth factor (PDGF α) that carry out diverse processes in tissue development and homeostasis. For example, binding of Shh ligand to Patched on the ciliary membrane regulates the concerted movement of Patched and Smoothened to activate downstream Shh signaling, which controls neural tube patterning and proliferation (Huangfu et al., 2003; Wechsler-Reya and Scott, 1999). The primary cilium is also involved in Wnt signaling through Wnt ligand, Frizzled receptor, and disheveled that regulates cell proliferation, fate determination, and migration (Simons et al., 2005; Wallingford and Habas, 2005). Additionally, it was shown that PDGF α signaling is coordinated by the

PDGFR α in primary cilia and it plays a key role in cell survival, growth, and migration (Schneider et al., 2005). The recognition that cilia modulate many important signaling pathways has captured the imagination of many studying disease mechanisms in neuroscience, cell biology, and signaling.

Key discoveries in the cilia field

It had long been established that cilia completely lack vesicles, and instead use a unique set of motor and motor-adaptor proteins, termed intraflagellar transport (IFT). Despite these findings, ciliary biology remained a sleepy field for many years. However, this landscape began to change when it was recognized that mutations in IFT genes (identified in lower organisms such as *Chlamydomonas*) lead to defects in development in mammals. Four recent discoveries have opened the field of ciliary biology in mammalian systems. (1) The discovery that IFT molecules are required for the signaling of some pathways, such as the Shh pathway (Haycraft et al., 2005; Huangfu et al., 2003). (2) The discovery that polycystic kidney disease can be caused by mutations in IFT molecules (Qin et al., 2001; Yoder et al., 1995). (3) The identification of a host of disorders that share partially overlapping phenotypic features, which have helped define the “ciliopathies” (Adams et al., 2007; Badano et al., 2006; Hildebrandt et al., 2009). (4) The application of bioinformatics and proteomics approaches to determine the protein constituents of the “ciliome” (Andersen et al., 2003; Avidor-Reiss et al., 2004; Blacque et al., 2005; Broadhead et al., 2006; Efimenko et al., 2005; Li et al., 2004; Stolc et al., 2005). These findings have provided the framework for more recent studies, which have further established additional IFT molecular components that function within primary cilia and that can modulate a host of other signaling pathways, including Shh, Wnt, platelet-derived growth factor, and others (Fig. 1) (Corbit et al., 2008; Ross et al., 2005; Schneider et al., 2005; Simons et al., 2005). The emerging theme is that primary cilia can act to modulate cellular responses to various environmental or signaling cues, by helping the cell recognize the context of the particular cue.

Characteristics of Joubert syndrome, ciliary dysfunctions and related signaling pathways

Joubert syndrome (JS) is a constituent of the newly emerging group of ciliopathy disorders that trace their pathophysiology back to defects either in the structure or function of primary cilia. JS is characterized by the triad of cerebellar vermis hypoplasia, oculomotor apraxia (jerky eye movements with inability to visually fixate) and intermittent hyperventilation (Joubert et al., 1968). The radiographic hallmark of JS is the presence of a unique feature on brain MRI known as the “molar tooth” sign, seen on axial image at the level of the midbrain–hindbrain junction, which has helped to narrow the phenotypic spectrum of the disorder, and led to the identification of genes mutated in these patients. Like the majority of ciliopathy diseases, the inheritance of JS is recessive, but there is tremendous phenotypic heterogeneity, even within single families, which is probably the result of multiple genetic or environmental modifier effects. The genes identified to date in JS appear to function at or near the primary cilium, either to regulate its structure or signaling events. For example, mutations in *CEP290*, a centrosomal protein, lead to JS with co-existent cystic kidneys and retinal degeneration (Valente et al., 2006). *CEP290* is implicated in the ciliary targeting of Rab8, a small GTPase to promote ciliogenesis through its interaction with the centriolar satellite component PCM-1 (Kim et al., 2008) and the function of *CEP290* is antagonized by the centrosomal protein CP110 (Tsang et al., 2008).

Mutations of the neuronal cilia localized *ARL13B*, a member of the Ras GTPase family, were also found in two families with the classical form of JS (Cantagrel et al., 2008). *ARL13B* mutant zebrafish displays curved tail and cystic kidney phenotypes (Cantagrel et al., 2008),

the hennin (*hnn*) mutant mice, a null allele of *ARL13B* exhibit defects in neural tube patterning, the structure of cilia and display aberrant Shh signaling (Caspary et al., 2007), suggesting the disruption of *ARL13B* causes JS phenotypes in human through abnormal ciliary structure and Shh signaling. Additionally, recently identified hypomorphic loss of function mutations in the cilium localized inositol polyphosphate-5-phosphatase E (*INPP5E*) were shown to lead to JS (Bielas et al., 2009). These mutations in *INPP5E* altered phosphatidylinositol (PtdIns) signaling and the stability of cilia in response to serum stimulation. Furthermore, blocking ciliary PDGFR α or PI3-kinase signaling restored ciliary stability, suggesting a link between PDGFR α and downstream signaling components with the primary cilium in JS (Bielas et al., 2009; Jacoby et al., 2009). Finally, Joubertin, the protein product of the *AHI1* gene that is mutated in JS (Dixon-Salazar et al., 2004), plays a key role as a positive modulator of the Wnt/ β -catenin signaling pathway in primary cilia and its disruption leads to cystic kidney, an additional feature in JS (Lancaster et al., 2009). Although the direct signaling pathways altered in JS are not well understood, these data suggest that like other ciliopathy diseases, the pathogenic mechanisms of JS will implicate defective transport or signaling of well-established pathways at or near the cilium (Fig. 2).

Phenotypic variability in Joubert syndrome and other ciliopathies

In addition to JS, other ciliopathies may include features of retinal blindness and sensorineural deafness. This likely represents a requirement for the unique structure or signaling capability of the cilium in multiple types of specialized sensory cells. Additional features of ciliopathies include progressive renal fibrocystic disease (nephronophthisis), obesity, polydactyly, short stature, and encephalocele. Clinical geneticists have attempted to categorize these features into specific syndromes, such as Usher, Senior-Loken, Meckel-Gruber, Bardet-Biedl, Dekaban-Arima, Oro-facial-digital, Jeune, Ellis-van Creveld among other syndromes (Tobin and Beales, 2009), but the recent observations that mutations in a single gene can lead to a broad array of phenotypes in these diseases has blurred these boundaries, and led to the emerging concept of a spectrum disease (Bergmann et al., 2008; Brancati et al., 2009; Frank et al., 2008; Leitch et al., 2008). Furthermore, there is increasing awareness that a single patient may carry deleterious or potentially deleterious genetic alterations in more than one “cilia” gene (Tory et al., 2007). The data suggests a network of ciliary proteins functioning to mediate partially overlapping and non-redundant functions.

Ciliary function in neurons

Many of these syndromes and conditions share some important neurological disturbances (Table 1), most consistently mental retardation (Gitten et al., 1998), which raises the question: What are the potential functions of primary cilia in neurons, beyond their unique roles in specialized sensory cells? In which developmental stages do neurons display primary cilia, and is there evidence that neuronal cilia perform important functions during development or in adulthood?

Cerebellar development

When we consider the striking cerebellar hypoplasia in JS and other ciliopathies, the central role of Shh in proliferation of cerebellar granule neurons (Wechsler-Reya and Scott, 1999), and the critical role for the cilia in transducing Shh signals (Corbit et al., 2005; Liu et al., 2005; Rohatgi et al., 2007), one might speculate that defects in responsiveness to Shh might underlie the cerebellar defect in ciliopathy conditions. Using conditional alleles for murine *Ifi88* (orthologue of the *Chlamydomonas Ifi88* gene, which is necessary for IFT) and *Kif3a* (necessary for plus-end directed IFT movement), recent work has demonstrated defective expansion of the Shh-dependent cerebellar granule neuron progenitor pools in cilia deficient mutants (Chizhikov et al., 2007; Spassky et al., 2008). While the cerebellar dysgenesis in

ciliopathy disorders likely accounts for the ataxic phenotypes, the degree to which these relates to the neurocognitive disease in these patients is not understood.

Hippocampal neurogenesis

Since both Shh and Wnt signaling play key roles in regulating progenitor cell maintenance in telencephalic stem cell niches (Pozniak and Pleasure, 2006), one might similarly speculate that mutations in ciliary proteins may lead to defective formation of adult neuronal stem cell regions such as the hippocampus. When directly examined in the *Kif3a* conditional mutant crossed with *Gfap::Cre*, as well as mutants of *Ift88* and *Ftm*, all showed defective adult hippocampal neurogenesis and altered Shh signaling. However, the defect was not rescued by constitutive activation of the Shh pathway, suggesting that pathways other than Shh may be influenced by these genetic mutations (Han et al., 2008). A mutation in a new gene known as *Stumpy* also leads to ciliary biogenesis defects, reduction in hippocampal neural precursors and abrogated Shh activity (Breunig et al., 2008). In addition, blocking adult hippocampal neurogenesis can lead to deficits in learning and memory cognitive functions (Shors et al., 2001). Therefore, although no direct behavioral defects were evaluated in these mice, the possibility remains that at least some of the cognitive defects associated with ciliary defects are mediated by the essential role of cilia in neurogenesis within the hippocampus.

Polymicrogyria and other structural brain defects

There are many reports of defective neocortical development associated with ciliopathy diseases, most notably in the case of JS and related disorders, where generalized polymicrogyria and other structural brain lesions have been noted (Dixon-Salazar et al., 2004; Giordano et al., 2009; Gleeson et al., 2004). Similarly, patients with Meckel-Gruber or Bardet-Biedl syndrome can display occipital encephalocele, microcephaly, holoprosencephaly, and other structural brain defects (Ahdab-Barmada and Claassen, 1990; Rooryck et al., 2007). Thus, ciliary function is likely required for some aspects of neuronal development within the cerebral cortex, although mechanisms remain to be determined.

Axonal guidance

Early studies have shown that there are obvious defects in decussation of some of the major afferent and efferent axonal tracts within the brain of patients with JS (Friede and Boltshauser, 1978; ten Donkelaar et al., 2000; Yachnis and Rorke, 1999). These include most notably the finding that at least some patients with JS are completely missing the pyramidal decussation, which is the major site of crossing of the corticospinal tract (CST). Diffusion tensor imaging, an MRI-based method to label the orientation of tracts, identified failed CST decussation as well as failed decussation of the superior cerebellar peduncle (SCP) tract (the outflow tract of the cerebellum) in 6 of 6 JS subjects (Poretti et al., 2007). Absent SCP decussation was identified in an additional 6 JS patients, and not in 16 aged-matched controls (Spampinato et al., 2008). Further work demonstrated bilateral functional MRI (fMRI)-based activation of sensorimotor and cerebellar cortical activation upon volitional finger tapping, suggesting defective functional brain organization resulting from these defects (Parisi et al., 2004). The preponderance of evidence suggests that at least in some patients with ciliopathies, there is defective axonal tract decussation, which may underlie some of the observed cognitive and motor defects. Despite these interesting findings, many questions remain. First, since many genes for JS are known, are there genotype–phenotype correlations that would predict which patients display altered axonal guidance? Second, how could the cellular defects resulting from these mutations, which predominantly affect the function of the primary cilia (located adjacent to the cell body), lead to defects in guidance of the axon (usually located quite distal from the cell body)? Third, how do these axonal defects contribute to the cognitive or motor defects in the ciliopathies?

Potential functions of primary cilia in cognition

A surprising finding in the field of neurobiology was that most or all neurons display a primary cilium. Early electron microscopy studies demonstrated evidence of primary cilia in developing and adult neural tissue (Del Cerro and Snider, 1969; Mandl and Megele, 1989), as well as more recent studies using a host of cilia-specific antibodies (Bishop et al., 2007; Handel et al., 1999). In *C. elegans* olfactory epithelium, sensory signaling is required to maintain the architecture of the specialized neuronal cilia (Moussaif and Sze, 2009; Mukhopadhyay et al., 2008), suggesting that extracellular signals may regulate the size and shape of neuronal cilia.

What function could these organelles serve in neurons? Future studies aimed at removing cilia or disturbing ciliary function in subregions of adult brain will be required to address this question. For instance, Bardet-Biedl syndrome (BBS) and Alström (AS) patients frequently display hyperphagia-induced obesity, but the origins have remained elusive. Recent studies have pointed to a role for these proteins in mediating leptin signals, possibly by mediating ciliary function. Disruption of *Ift88* or *Kif3a* in brain has been shown to result in obesity, an effect that was narrowed to the pro-opiomelanocortin (POMC)-expressing cells in the hypothalamus (Davenport et al., 2007). Disruption of *Bbs2*, *Bbs4* or *Bbs6* genes in mice also results in obesity, which was traced to a defect in leptin receptor trafficking (Seo et al., 2009). It remains to be determined whether leptin receptors are clustered in or near the cilium and to what extent leptin signaling is modulated by the cilium.

This work also raises the question of which other receptors might localize to primary cilia, and thus might be under regulatory control. For example, BBS2 and BBS4 are required for localization of some G protein-coupled receptors such as somatostatin receptor type 3 (SSRT3) and melanin-concentrating hormone receptor 1 (MCHR1) to primary cilia in neurons, which suggests that these signaling pathways may be modified by cilia function (Berbari et al., 2008b). Moreover, ciliary localization sequences have recently been identified within the third intracellular loop of several G-protein coupled receptors including serotonin receptor 6 (HTR6) and melanin-concentrating hormone receptor 1 (MCHR1) (Berbari et al., 2008a). This and other findings suggest that the number of signaling pathways that are potentially influenced by the cilium has the potential to grow as we gain a deeper appreciation of this key signaling organelle in neuronal function.

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Fig. 1.

Schematic diagram of primary cilium. Primary cilia lack the central microtubule pair and their cross-section show '9+0' arrangement (inset). Cilia structure and function are maintained by intraflagellar transport (IFT) within primary cilia. The protein cargo is produced in the Golgi apparatus, moves towards the cilium, and binds to the IFT complex. IFT complex/cargo assembly can be transported along microtubules. The anterograde movement (toward the tip of the cilium) of IFT complex/cargo assembly relies on kinesin 2, while dynein 2 transports in the retrograde direction (toward the basal body of the cilium). Functionally, primary cilia are involved in various signaling pathways including Sonic hedgehog (Shh), Wnt, platelet-derived growth factor (PDGF), and G-protein coupled receptor (GPCR). These signaling pathways

play important roles in regulating various neuronal functions including cerebellar development, hippocampal neurogenesis, and obesity. Abbreviations: PTCH, Patched 1; PDGFR, Platelet-derived growth factor receptor.

Fig. 2.

JS genes implicated in the Shh, Wnt, and PDGF α signaling pathway. ARL13B and INPP5E localize to the cilium, whereas AHI1 and CEP290 localize to the basal body. CEP290, a centrosomal protein, is involved in Rab8 contained vesicle transport and ciliogenesis through its interaction with PCM-1. The disruption of ARL13B causes defects in ciliary structure and Shh signaling. ARL13B is required for body axis formation, renal function, and neural tube patterning. INPP5E plays an essential role in stabilizing cilia in response to serum stimulation, possibly by controlling PDGF α signaling. AHI1 interacts with and facilitates β -catenin (β -Cat) accumulation in the nucleus to positively modulate Wnt signaling. Wnt/ β -catenin signaling via AHI1 is essential for maintaining renal homeostasis.

Table 1

Clinical features of the ciliopathies.

Ciliopathies	Neurological deficits	Other deficits
Joubert syndrome (JBTS)	cognitive impairment cerebellar malformation oculomotor apraxia encephalocele polymicrogyria	cystic kidney polydactyly retinal degeneration
Bardet-Biedl syndrome (BBS)	cognitive impairment obesity	retinal degeneration cystic kidneys polydactyly
Meckel syndrome (MKS)	cognitive impairment encephalocele hydrocephalous	cystic kidney polydactyly
Ellis Van Creveld syndrome (EVC)	cognitive impairment	short stature polydactyly cardiac defects
Oro-facial-digital syndrome type 1 (OFD1)	cognitive impairment cerebellar malformation	malformation of the face and oral cavity
Jeune syndrome (JATD)	cognitive impairment	skeletal dysplasia cystic kidneys