Bardet-Biedl Syndrome and the Neuronal Primary Cilium

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One structure often overlooked in considerations of the cell biology of the brain is the primary cilium, but the importance of cilia in neuronal development and function is becoming apparent (Han & Alvarez-Buylla, 2010). In part, this awareness stems from recognition that specific defects in ciliary structure or function can have profound effects on the nervous system as well as other tissues (Cardenas-Rodriguez & Badano, 2009). Most biologists are familiar with the motile cilia, such as those on ependymal cells that line the ventricular surface (Del Bigio, 2010), but most mammalian cells also have a single primary cilium that is nonmotile. This hair-like extension is typically 200–200 nm in diameter and may be as much as 10μm in length (Han & Alvarez-Buylla, 2010), but is rarely seen in standard histological preparations (Peters et al., 1991). The primary cilium extends from a modified centriole in neurons and neuronal progenitors as well as glia, though the prevalence of these structures in the central nervous system has only come to be appreciated in the last few decades (Louvi & Grove, 2011).

Primary cilia have multiple functions in the central nervous system (Praetorius & Spring, 2005). For example, the photoreceptors of the retina are all modified primary cilia (see Ch. 51). Indeed, primary cilia in the nervous system are best described as sensory organelles that play a key role in mechanosenory and chemosensory functions. The location of specific receptors for signals critical in neurodevelopment on primary cilia is particularly striking (see Ch. 28). Three distinct pathways critical for normal development of the nervous system have been shown to require a primary cilium: Sonic Hedgehog (Shh), platelet-derived growth factor (PDGF) and Wnt signaling (Louvi & Grove, 2011). In mammalian cells, critical components of the Shh pathway are located in the primary cilium and shuttle between cytoplasm and cilium. Shh is critical for

ventralization of the neural tube, formation of spinal motor neurons and differentiation of oligodendrocytes, as well as for playing a wide range of other roles in neural development by regulating transcription of specific genes. Similarly, PDGF receptors are localized to the primary cilium and signal through cytoplasmic kinases like Akt and MAP kinases (see Ch. 25). PDGF signaling may be important for cell polarity and regulation of cell migration. Finally, the primary cilia appear to suppress the canonical Wnt pathway mediated by β-catenin and GSK3β. They may activate a noncanonical pathway that orients sheets of neuroepithelial cells and they may influence neuronal migration.

Given these diverse functions, it is not surprising that ciliopathies are pleiotropic and typically affect a wide range of cell types and tissues. Many of the phenotypes reflect alterations in brain structure or function. One example of human disease associated with defects in primary cilia is Bardet-Biedl Syndrome (BBS), a genetically heterogeneous autosomal recessive disease that results from mutations in 1 of 12 genes (Sheffield, 2010). The syndrome was first recognized as a discrete pathology in 1920, but the role of cilia in this disease was not recognized for more than 60 years. These gene products form a complex associated with the *basal body* (kinetosome, organelle formed from a centriole and a short cylindrical array of microtubules found at the base of the cilium). BBS gene complexes are required for the generation and maintenance of cilia, both primary and motile. BBS patients exhibit a constellation of symptoms that include both neuronal and nonneuronal pathology. Pathologies involving the nervous system include degeneration of photoreptors, anosmia, mental retardation or developmental delay, posterior encephalocoele (a neural tube defect caused by the tube's failure to completely close), and obesity. Nonneuronal effects may include hypogonadism, kidney defects, polydactyly, diabetes, and *situs inversus* (randomization of normal organ locations, i.e., heart on right side

instead of left side of chest). Although some of these pathologies, such as *situs inversus* and hypogonadism, are likely due to loss of motile cilia, others are clearly due to a loss of nonmotile, primary cilia. For example, failure to maintain sensory primary cilia is associated with retinal degeneration and renal failure. In turn, loss of signaling through primary cilia is likely to contribute to mental retardation, obesity, and anosmia, among other issues. Until the role of the primary cilium was recognized, the pleiotropic nature of BBS had baffled physicians looking for a common thread through all of these pathologies. Thus, a better understanding of the cell biology of the nervous system has illuminated a baffling and complex set of genetic disorders.

References

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