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MINI-REVIEWS

Neuron's little helper: The role of primary cilia in neurogenesis

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ABSTRACT

The generation of new neurons involves a great variety of cell-extrinsic and cell-intrinsic signals. The primary cilium, long regarded as an "evolutionary vestige," has emerged as an essential signaling hub in many cells, including neural progenitors and differentiating neurons. Most progenitors harbor an apically-localized primary cilium, which is assembled and disassembled following the cell cycle, while the presence, position and length of this organelle appears to be even more variable in differentiating neurons. One of the main extracellular cues acting through the cilium is Sonic Hedgehog, which modulates spatial patterning, the progression of the cell cycle and the timing of neurogenesis. Other extracellular signals appear to bind to cilia-localized receptors and affect processes such as dendritogenesis. All the observed dynamics, as well as the many signaling pathways depending on cilia, indicate this organelle as an important structure involved in neurogenesis.

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Hedgehog; neuroepithelium; neurogenesis; neuronal differentiation; neuronal migration; primary cilia

Introduction

In vertebrates, most neurons in the central nervous system (CNS) originate from the neuroepithelium, a tissue composed by highly proliferating cell progenitors forming the walls of the neural tube. Cell polarity is one of the main features of this tissue, holding a tight relationship with cell proliferation (as cells undergo interkinetic nuclear migration), and asymmetric cell divisions leading to neurogenesis, neuronal positioning and differentiation.[1,2] In some areas of the mammalian CNS such as the neocortex, two other types of progenitors are also originated from the neuroepithelium: radial glial cells ("apical progenitors;" which maintain an epithelial-like polarity) and basal progenitors (which are not polarized). Characteristically, neuroepithelial and radial glial cells have a very small apical membrane domain, which is limited by subapical adherens-type cell adhesions and harbors a tiny but powerful specialization: the primary cilium. Cilia are organelles related to flagella and essentially composed of a microtubule-based axoneme surrounded by plasma membrane and attached to a centriole-derived basal body. Two main varieties can be recognized: "motile cilia," present in a few cell types, and "primary cilia," present in most cell types (http://www.bowserlab.org/primarycilia/cilialist.html). Generally, these two types of cilia can be differentiated by the organization of their axonemes. Primary cilia usually lack the central microtubule pair found in motile cilia (a "9+0" configuration) and dynein arms: they are hence non-motile (Fig. 1). Cilia are typically interphase structures, being present in G1 (and G0) and disassembled during S or G2, as centrioles duplicate and form the centrosomes that drive the organization of the mitotic spindle during mitosis. Centriole duplication is semi-conservative, thus in each new centrosome one of the centrioles (called "mother") derives from the original pair, while the other (called "daughter") is generated de novo.[3,4] Cilia reassembly after mitosis depends on an intricate system of transport proteins composing the so-called "intraflagellar transport" (IFT) machinery. IFT is carried out by two complexes, IFT-A and IFT-B, which transport ciliary components out and into the cilium respectively. Therefore, anterograde (from basal body to ciliary tip) transport is mediated by IFT-B particles associated with the Kinesin II molecular motor, while retrograde (toward the basal body) movement involves IFT-A particles and cytoplasmic Dynein (Fig. 1).[5]

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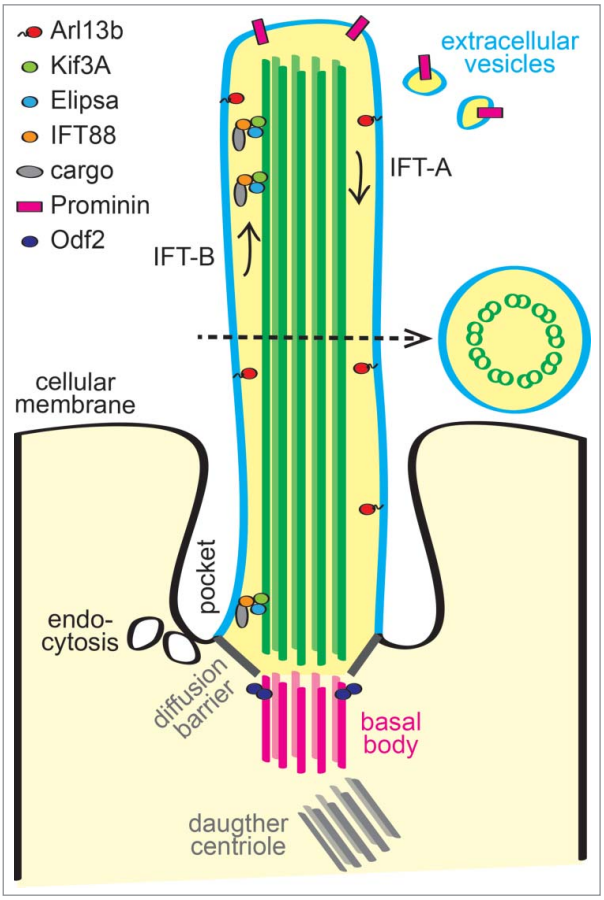

Figure 1. Schematic representation depicting the main features of primary cilia in neuroepithelial cells. The localization of most of the proteins mentioned throughout the review is shown. The core of a typical primary cilium is an axoneme with a 9+0 array of microtubule doublets, which is anchored at the basal body, the oldest centriole in the cell. A diffusion barrier at the base of primary cilia blocks simple diffusion of both cytosolic and membrane proteins. Thus, a specialized transport system is required for cilia formation and maintenance, as well as for intracellular transduction of several signaling pathways. Anterograde and retrograde transport is carried out through IFT-B and IFT-A complexes, respectively. In some cilia, a plasma membrane pocket or pit is present around the ciliary base. This ciliary pocket has been associated with active endo- and exocytosis. Primary cilia may also be sites of extracellular vesicles formation.

The observation that primary cilia are non-motile puzzled cell biologists for a long time, since no obvious function could be found. This scenario was turned upside down by the findings of the previous decade, showing that primary cilia are needed for the reception and transduction of a range of extracellular mechanical and chemical cues, as well as for paracrine signaling involving important developmental pathways such as those of Hedgehog (Hh), Wnt and PDGF.[6] In vertebrates, Hh signaling mainly acts through the primary cilium by modulating post-translational modifications of the transcription factors Gli2 and Gli3. In resting conditions, Gli2/3 factors are cleaved by the proteasome to a short repressor form. Hh inhibits proteasomal degradation, promotes ciliary translocation of Gli2/3, a process that is necessary to acquire full activity, and results in nuclear entry of these transcription factors.[7] In addition, more recent data has also underscored an important role for primary cilia as sites for signal production through the generation of extracellular vesicles.[8]

Although the presence of primary cilia in the neuroepithelium was originally described many decades ago, it was only in the last few years that it has come forth to the neuroscientific community. We will review here some of the recent work that aims at understanding cilia dynamics and functions during different processes related to neurogenesis and early neuronal differentiation in vertebrates.

Cilia and the cell proliferation/neurogenesis balance

The neuroepithelium is a highly proliferating tissue and thus cilia are expected to be very dynamic, constantly assembling and disassembling following the cell cycle (Fig. 2A). This concept led pioneering electron microscopists to perform the first detailed description of primary cilia apparent dynamics by analyzing the chick embryonic neural tube.[9] These early studies were extended recently using an *in vivo* approach in the same tissue, showing that centrosomes are located at the apical tip of neuroepithelial cells along most of the interphase.[10] In late G2, they translocate basally to meet the apically-moving nucleus, and duplicate to organize the formation of the mitotic spindle poles. This study also showed that the primary cilium, revealed by the presence of the ciliary GTPase Arl13b fused to GFP, disappears during G2, just before the basal migration of the centrosome. In addition to the axoneme, neuroepithelial cilia present another structural feature, the ciliary pocket (Fig. 1), which also apparently displays a dynamic behavior along the different stages of the cell cycle.[9,11] The ciliary pocket has been shown to be a site where endocytosis and exocytosis needed in signal transduction take place.[12] Furthermore, as described above, cilia are also known to play a secretory role, and in neuroepithelial cells they are putative sites of Prominin-enriched extracellular vesicles release (Fig. 1).[13] Thus, cilia in neuroepithelial

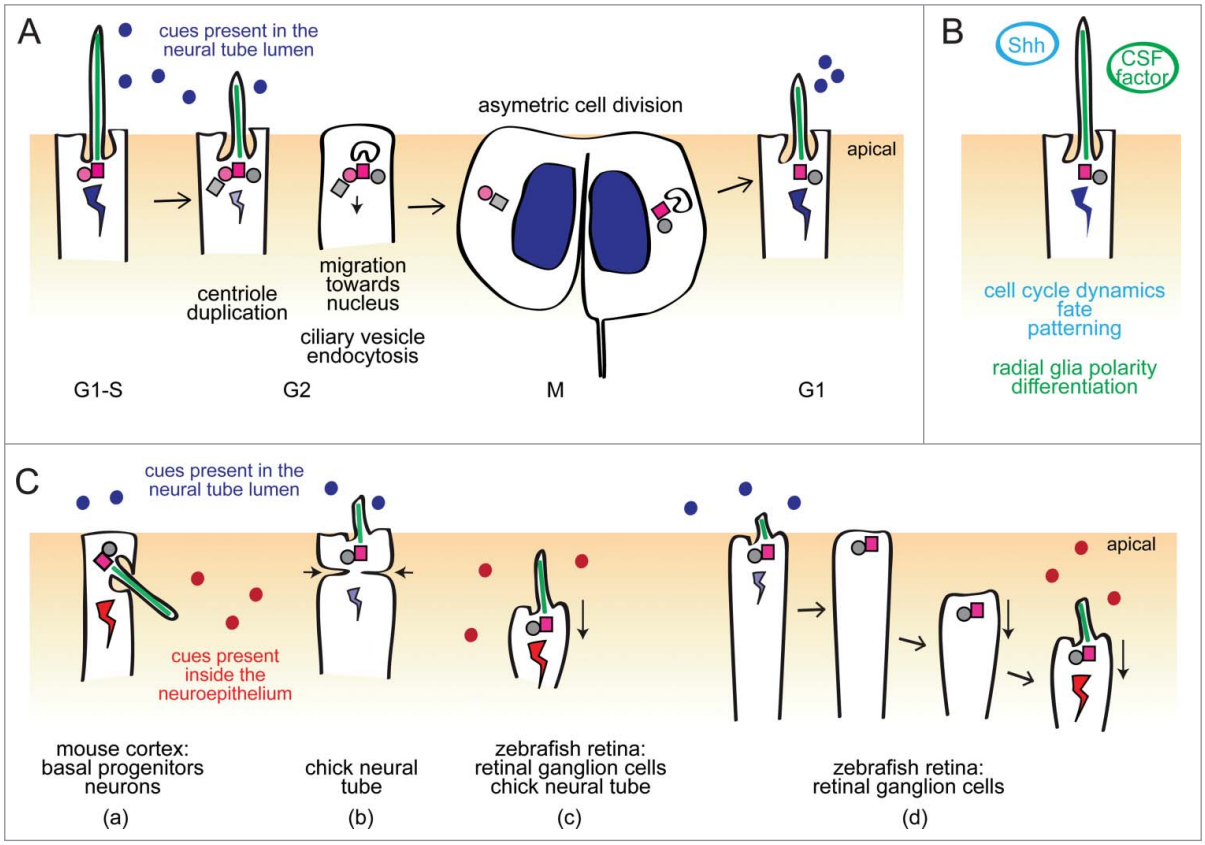

Figure 2. Primary cilia dynamics and functions during neuroepithelial cells proliferation and apical detachment. (A) During G2, centrioles are duplicated and primary cilia are reabsorbed to allow centrioles to migrate toward the nucleus and organize the mitotic spindle. In the neocortex, the ciliary membrane is endocytosed and remains associated to the eldest centriole (which was acting as a basal body). During the neurogenic period, the biased inheritance of this ciliary membrane is correlated with maintenance of the proliferative state.[18] While primary cilia are present (during interphase), they endow the cell with the capacity to sense cues present in the neural tube lumen. (B) Examples of signaling functions of primary cilia in early stages of neurogenesis. Primary cilia transduce signals (such as Shh) that are able to give identity to progenitor cells, thus affecting the patterning of the neural tube. Shh acting through primary cilia also regulates progenitor cell cycle dynamics. In radial glia progenitors, primary cilia is instructive in the maintenance of polarity as well as in sensing a cerebrospinal fluid (CSF) factor needed for neurogenesis. (C) Four different dynamic behaviors of cilia associated with cell detachment from the apical region of the neuroepithelium: (a) primary cilia re-localize to the basolateral surface in mouse cortex delaminating neurons or basal progenitors;[33] in chick neural tube, (b) primary cilia may be left behind due to apical abscission[35], or (c) remain at the apical tip of the cell during retraction;[10] (d) in retinal ganglion cells of the zebrafish retina, some cilia remain at the apical tip (like in c), but in most cases they are lost previous to retraction and then reformed at the tip of the retracting process.[11] In all these cases, primary cilia reduce (or even lose) their contact with signals present in the neural tube lumen and might begin to sense signals present inside the neuroepithelium.

cells might act as bidirectional signaling devices, both receiving and broadcasting still ill-characterized signals.

Functional studies aimed at understanding early cilia function in neural development found that Kif3a (a protein component of the ciliary kinesin) or Ift88 (part of the IFT-B transport complex) mouse mutants show severe disruption of cortical morphogenesis accompanied by the occurrence of rosette-like heterotopias, therefore suggesting an underlying cell polarity defect.[14–16] Likewise, targeted deletion of *Arl13b* at different developmental stages in mice forebrain, although apparently not affecting the early neuroepithelium, caused the reversion of apico-basal polarity of the radial glia scaffold, with the concomitant misplacement of radially-migrating neurons.[17] Importantly, the integrity of neuroepithelial polarity has been tightly correlated with asymmetry in neurogenic cell divisions, and primary cilia may also have a role in the regulation of this process.[1] Electron microscopy of the neurogenic mouse cortex revealed that cilia-derived membrane can be endocytosed prior to mitosis and inherited by one of the daughter cells along with the mother centriole, thus probably establishing intrinsic differences in the ability of each

daughter cell to ciliate.[18] Here, the maintenance of a proliferating progenitor state was associated with inheriting the older mother centriole (Fig. 2A). Similar results were obtained when analyzing a cilia-related target of Pax6, an essential transcription factor determining radial glial cell identity in the mammalian cortex. In these cells, Pax6 triggers the expression of the mother centriole-associated protein Odf2, which in turn is necessary for the formation of the distal appendages that link the mother centriole to the membrane. Interestingly, in Pax6-deficient radial glial cells, cilia reassembly is impaired and cells prematurely exit the cell cycle to generate post-mitotic differentiating neurons.[19] On the other hand, not only formation but also timely reabsorption of primary cilia is important when cells are about to exit the cell cycle. Inhibiting the reabsorption of the primary cilium prior to mitosis in both cultured pluripotent stem cells and cortical neural progenitors again resulted in the premature exit from the cell cycle and the onset of neuronal differentiation.[20,21] These observations are consistent with previous work showing a positive correlation between the length of G1 in mouse cortical progenitors, and their transition to a post-mitotic state to become neurons.[22] Finally, the naturally-occurring cilia length decrease that takes place along the process of neurogenesis may also act as a cell-autonomous mechanism for the control of neuronal specification.[11,13]

All this experimental evidence indicates that cilia have an important function in early stages of neurogenesis. How is this function achieved? One possibility could be that either the cilium itself or the basal body (in its double role in nucleating the axoneme and as a cytoplasmic microtubule organizing center) might be sources of cell-intrinsic signals acting on the cytoskeleton and thus affecting cell polarity and/or cell cycle progression. A second, and certainly more appealing possibility based on the growing amount of experimental data, is that extracellular signaling acting on cilia is in great part responsible for this function. Among the different signaling cascades, the Hh pathway, and in particular Sonic Hedgehog (Shh), likely plays a critical role (Fig. 2B). Interestingly, the first connection between this ubiquitous signaling pathway and cilia was provided by studies on the dorso-ventral patterning of the neural tube.[7] Since the early 1990s it has been known that a ventral-to-dorsal gradient of Shh arising from the floor plate is in part responsible for determining the neuronal-type fate of neuroepithelial progenitors located at different positions in the spinal cord of all analyzed vertebrates, mainly through the activation or repression of different transcription factors involved in neuronal specification.[23] A decade later, Huangfu and collaborators demonstrated for the first time that Shh signal transduction directly depended on cilia integrity, and that mutant mice defective in two IFT proteins (Ift88 and Ift172) presented an altered dorso-ventral distribution of transcription factors such as Pax6 and HB9 in the neural tube.[24]

In addition, Shh seems to have different functions in regulating the balance between the maintenance of cycling progenitors and the generation of post-mitotic neurons. In the retina, for example, the different neuronal types arise from multipotent progenitors, whose potentiality becomes progressively restricted along development. Shh has an important role in the control of progenitor proliferation and cell fate in this organ.[25,26] In the zebrafish, extra-retinal Shh initiates the generation of retinal ganglion cells, and these early differentiating neurons in turn secrete Shh, which helps the wave of neuronal differentiation to spread.[27] We have recently reported that early cilia impairment by knocking down IFT genes (*Ift88* and *Elipsa*) in the zebrafish retina, causes a significant reduction in progenitor cell proliferation affecting the generation of all differentiated cell types. However, a detailed *in vivo* analysis of differentiating cells in triple-labeled transgenic embryos and in cell transplantation experiments, demonstrated that retinal ganglion cells generation was preferentially reduced, with a concomitant proportional increase in cone photoreceptors.[11] In different areas of the brain, such as the cortex, hippocampus and cerebellum, it has been clearly demonstrated that primary cilia disruption severely affects cell cycle progression in neuronal progenitors, and that this effect is at least in great part due to impaired Shh signaling, mostly evidenced in Gli3 misprocessing.[28,29] Finally, and as discussed below, Hh is not the only signaling pathway acting through primary cilia. For example, as recently reported, signaling through an orphan cilia-localized G-Protein Coupled Receptor (GPCR) favor cell cycle exit and differentiation of radial glia progenitors, through binding to a cerebrospinal fluid factor up-regulated in the neurogenic phase (Fig. 2B).[30] Similarly, Hh signaling through cilia has been shown to be involved in the proliferation of neural progenitors and

neurogenesis in the two main neurogenic areas of the adult brain, the dentate gyrus of the hippocampus and the ventral ventricular-subventricular zone generating olfactory bulb neurons.[31,32] Hence, in different CNS areas and at different developmental stages, regulating the balance between primary cilia formation and disassembly can be used as a mechanism to control whether cells remain as progenitors or commit to become neurons, through the differential access or sensitivity to surrounding signaling molecules acting on cilia.

Cilia in delaminating and migrating progenitors and neurons

Neuroepithelial and radial glial cells are characterized by always remaining attached to the apical border. In some circumstances along the process of neurogenesis, however, cells must get rid of this apical attachment and move basally. This is clearly the case for most neurons, but also for cortical basal progenitors. A detailed analysis of cilia positioning in the ventricular side of the embryonic mouse brain unveiled an unexpected finding: the presence of basolateral (subapical) primary cilia that correlated with the apical detachment of basal progenitors in the telencephalon and of differentiating neurons in the hindbrain (Fig. 2C).[33] This correlation might not be, however, universal. In the zebrafish retina, where detaching retinal ganglion cells drag apical marker proteins at the tip or their apical processes, the same proportion of subapical cilia was observed before and after the initiation of neurogenesis.[11,34] Alternatively, an apical abscission mechanism has been described in chick neural tube.[35] The authors observed that detaching neurons actively left behind a small region of the apical process containing several apical complex proteins as well as the primary cilium (Fig. 2C). A previous report in the same tissue, however, demonstrated that apical cilia could remain continuously attached to the retracting apical process (Fig. 2C).[10] Of course, some experimental differences could explain at least in part this controversy, or, it could be that both apical abscission (leading to loss of apical components) and a more conservative detachment (keeping apical components) could coexist in different cells. Our observations in the zebrafish retina support this last idea: although we observed an apparent disassembly of cilia just before and for some time after apical detachment in most retinal ganglion cells, there were some cases in which the cilium remained intact during the process (Fig. 2C).[11] Probably the only tangible fact here at the moment is that, in many cases, differentiating neurons (or even progenitors) lose an apically-localized cilium around the time of detachment. If we consider, as discussed above, that cilia play an important role in maintaining the proliferative state of neural progenitors in different areas of the CNS, this event could facilitate cell cycle exit by rendering cells insensitive to mitogenic signals such as Shh. In addition, this loss of cilia could also play a role in neuronal type specification.

After being born, many neurons must migrate relatively long distances to their differentiation location, and primary cilia have been shown to be present also during this period. In the cerebral cortex, two main sorts of migration are evident: neurons born in the immediate ventricular or subventricular zone migrate radially (apico-basally) to become excitatory pyramidal neurons, and neurons born far away in ventrally-localized ganglionic eminences migrate tangentially (perpendicular to the apico-basal axis), to become inhibitory interneurons. Interestingly, cilia impairment by conditionally inactivating ciliary genes such as *Arl13b, Ift88* and *Kif3a* in mice, was shown not to have apparent effects on radial migration of pyramidal neurons, whereas it affected the ability of tangentially-migrating interneurons to reach the cortical plate.[36,37] Interestingly, Shh was shown to be necessary for microtubules and Golgi organization in these cells, although receptors for several other signals that could be involved in regulating neuronal migration were detected on their cilia.[37] Through detailed electron tomography studies on primary cultures, Baudoin and colleagues showed that the cilium is alternatively exposed or hidden during the two-stroke phases of migration of these neurons.[36] Indeed, there was a correlation with the position of the centrosome respect to the nucleus: in many migrating neurons with long nucleus-centriole distance, a small primary cilium was exposed to the surface, while centrioles positioned near the nucleus were associated to a large vesicle, sometimes with a short axoneme protruding into it (Fig. 3A). Cerebellar granule neurons migrating *in vitro* also displayed a dynamic centrosome and primary cilium that accompanied the two-stroke motility process of organelles during migration, and this dynamics was shown to depend on acto-myosin activity.[38]

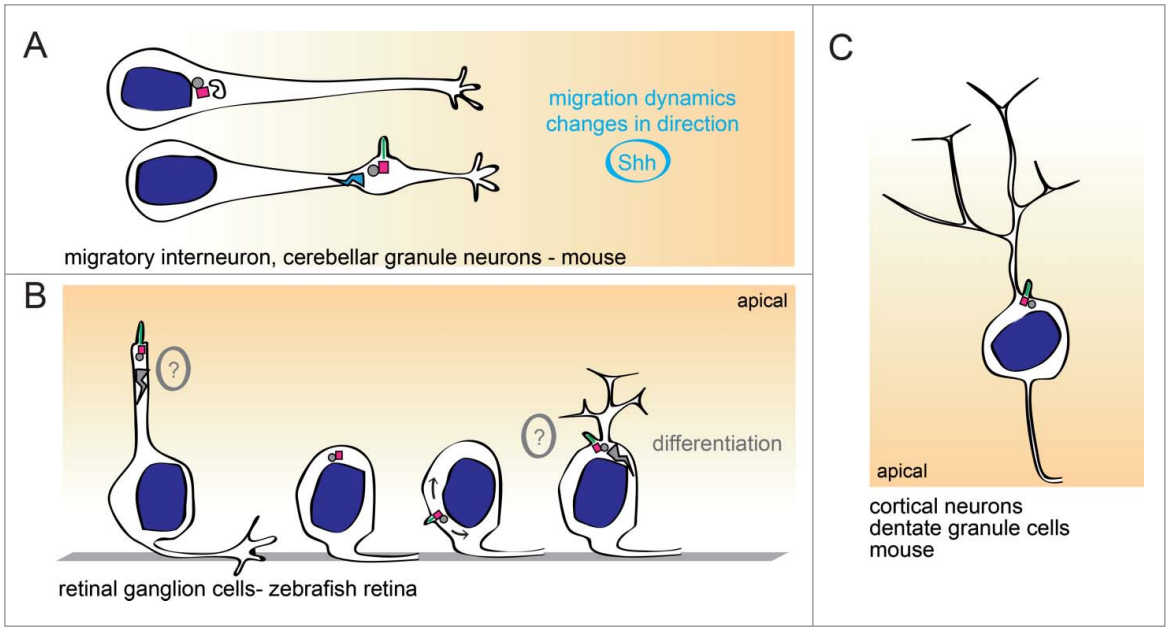

Figure 3. Primary cilia localization and functions during neuronal differentiation. (A) Migratory interneurons during tangential migration in the cortex display a primary cilium that cycles between a surface-exposed and an intracellular phase, a process that appears to be coordinated with the cell migration stages.[36] In these cells, primary cilia are important for migration dynamics and also for exiting the migratory stream into the cortical plate. Cerebellar granule neurons migrating *in vitro* also bear a primary cilium, which accompanies the two-stroke movement of the cell leading process.[38] (B) In zebrafish retinal ganglion cells, the primary cilium maintains an apical position during retraction of the apical process.[11] After this period, primary cilia may disappear for some time and/or change their position (arrows) around the cell surface. Interestingly, primary cilia are apically re-localized to the region where dendrites begin to outgrow. In these differentiating neurons, primary cilia may transduce still unknown signals affecting their differentiation. (C) In cortical neurons and hippocampus dentate granule cells of mice, primary cilia also localize to the base of dendrites, where they influence dendrite refinement.[44,45]

Cilia in neuronal differentiation

Neuronal differentiation is usually a relatively long process including a series of events that are more or less independently regulated by both cell-intrinsic and cell-extrinsic signals. Centrosomes have long been regarded as potential intrinsic signaling centers involved in neuronal orientation, axonogenesis and dendritogenesis.[39] As centrosomes may act as cilia basal bodies, and in many studies this was not taken into account, it could also be possible that extracellular signaling acting through cilia could be responsible for some of the observed or predicted modulatory functions. A presence of an apically localized centrosome and cilium has been described in differentiating retinal ganglion cells in mice and zebrafish, even from early stages of differentiation (Fig. 3B).[11,34,40] Remarkably, these structures are always located away from the site of axon outgrowth and close to the base of the forming dendrites. Prolonged erratic movements of the centrosome have been observed in these cells upon Laminin α1 knockdown, a treatment that also caused defects in neuronal polarization.[41] Interestingly, we recently observed the natural occurrence of similar erratic movements of the cilium, from some time after axon outgrowth to just before the onset of dendritogenesis, when cilia were directed to the base of the growing dendritic tree (Fig. 3B).[11] Most of the early maturing retinal ganglion cells, however, had no visible cilia (being most centrioles not docked to the plasma membrane), or just very short ones always apically localized (Fig. 3B).[11] Altogether, these results indicate that the centrosome/cilium might be important at early stages of neuronal differentiation, functionally linking neuroepithelial polarity to neuronal polarity, although the exact causal relationship and the molecular mechanisms are still missing.

Cilia may however be again important at later stages of neuronal maturation, as has been evidenced in different cell types of the mouse brain. In the mouse cortex, primary cilia re-form at late fetal stages, after both excitatory and inhibitory neurons have reached their final destination, and continually

grow postnatally for about 3 months to reach a maximum average length of 4–5 μm.[42] What could be the function of primary cilia here? One possibility is that this cilia growth is just a preparation for their signaling roles in adult neurons. As an example, in the cilia of postnatal rat hippocampal neurons there is a progressive accumulation of the Somatostatin Receptor 3 (SSTR3), which is involved in the detection of extracellular neurotransmitters.[43] Alternatively these cilia could have a function in late processes of neuronal maturation, such as dendrite extension, branching or refinement, an idea that would be consistent with a preferential cilia localization near the base of the dendritic tree in different neuronal cell types (Fig. 3C). Guadiana and collaborators demonstrated that the overexpression of two ciliary GPCRs (5HT6 and SSTR3) caused an aberrant growth, and even branching, of cilia in mouse neocortical pyramidal neurons.[44] Both this treatment and the expression of a dominant-negative (DN) form of Kif3A, caused a significant reduction in dendrite extension and branching, indicating that a fine balance in cilia structure/function must be maintained for dendritic trees to properly differentiate. A similar effect was observed upon cilia impairment with DN-Kif3A on postnatally-born hippocampal granule cells, where canonical Wnt upregulation led to defects in dendritic refinement and glutamatergic synaptogenesis.[45]

Conclusions and perspectives

Although clearly still very incomplete, information gathered until now on the behavior and possible roles of the primary cilium along the process of neurogenesis and neuronal differentiation points to a great versatility of this organelle, which might be used for different functions at different moments, and in different cell types. In general, however, the "cell antenna" role of cilia emerges as the most prominent mechanism for modulating these processes. The variable presence, position and length of cilia in neuronal progenitors and differentiating neurons described above, may underlie the diversity of neuronal types found in the brains of vertebrates, and might as well provide for an extremely sensitive mechanism for evolutionary change. In the species considered to have reached the maximum complexity and the highest performance regarding brain evolution, *Homo sapiens*, the essentiality of this organelle for proper brain development becomes evident in some human conditions resulting from cilia dysfunction: the ciliopathies. Characteristic clinical features in some of these conditions include CNS structural defects and intellectual disability.[46] A recent study in which 30 of the genes known to cause neural development-associated ciliopathies were knocked down by shRNA in mice, reveals that actually many of them are necessary for most of the neurogenic processes described above.[47] One open question is if these genes (as many others) actually cause neurodevelopmental defects through the cilium or through extraciliary functions they may have, a possibility that will undoubtedly increase the level of complexity associated to the role of the cilium and ciliary proteins in these processes. In summary, a complete and in-depth study of the dynamics of these organelles, the identification of the relevant signaling cascades operating through them, and a systems biology approach to understand the crosstalk between signaling pathways will be required to completely understand the role of cilia in neurogenesis and neuronal differentiation.

Abbreviations

CNS	central nervous system
GPCR	G-Protein Coupled Receptor
Hh	Hedgehog
IFT	intraflagellar transport
Shh	Sonic Hedgehog

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References

[1] Taverna E, Götz M, Huttner WB. The cell biology of neurogenesis: toward an understanding of the development and evolution of the neocortex. Annu Rev Cell Dev Biol 2014; 30:465-502; PMID:25000993; http://dx.doi.org/10.1146/annurev-cellbio-101011-155801

[2] Zolessi FR. Vertebrate neurogenesis: cell polarity. Zolessi FR. Vertebrate neurogenesis: cell polarity. In: ELS. Chichester (UK): John Wiley & Sons, Ltd.; 2016. p. 1-14.

[3] Avasthi P, Marshall WF. Stages of ciliogenesis and regulation of ciliary length. Differentiation 2012; 83: S30-42; PMID:22178116; http://dx.doi.org/10.1016/j.diff.2011.11.015

[4] Irigoin F, Badano JL. Keeping the balance between proliferation and differentiation: The primary cilium. Curr Genomics 2011; 12:285-97; PMID:22131874; http://dx.doi.org/10.2174/138920211795860134

[5] Pedersen LB, Rosenbaum JL. Intraflagellar transport (IFT) role in ciliary assembly, resorption and signalling. Curr Top Dev Biol 2008; 85:23-61; PMID:19147001; http://dx.doi.org/10.1016/S0070-2153(08)00802-8

[6] Cardenas-Rodriguez M, Badano JL. Ciliary biology: Understanding the cellular and genetic basis of human ciliopathies. Am J Med Genet C Semin Med Genet 2009; 151C:263-80; PMID:19876935; http://dx.doi.org/10.1002/ajmg.c.30227

[7] Sasai N, Briscoe J. Primary cilia and graded Sonic Hedgehog signaling. Wiley Interdiscip Rev Dev Biol 2012; 1:753-72; PMID:23799571; http://dx.doi.org/10.1002/wdev.43

[8] Wood CR, Rosenbaum JL. Ciliary ectosomes: transmissions from the cell's antenna. Trends Cell Biol 2015; 25:276-85; PMID:25618328; http://dx.doi.org/10.1016/j.tcb.2014.12.008

[9] Sotelo JR, Trujillo-Cenóz O. Electron microscope study on the development of ciliary components of the neural epithelium of the chick embryo. Cell Tissue Res 1958; 49:1-12

[10] Spear PC, Erickson CA. Apical movement during interkinetic nuclear migration is a two-step process. Dev Biol 2012; 370:33-41; PMID:22884563; http://dx.doi.org/10.1016/j.ydbio.2012.06.031

[11] Lepanto P, Davison C, Casanova G, Badano JL, Zolessi FR. Characterization of primary cilia during the differentiation of retinal ganglion cells in the zebrafish. Neural Develop 2016; 11:10; http://dx.doi.org/10.1186/s13064-016-0064-z

[12] Pedersen LB, Mogensen JB, Christensen ST. Endocytic control of cellular signaling at the primary cilium. Trends Biochem Sci 2016; 41:784-97; PMID:27364476; http://dx.doi.org/10.1016/j.tibs.2016.06.002

[13] Dubreuil V, Marzesco A-M, Corbeil D, Huttner WB, Wilsch-Brauninger M. Midbody and primary cilium of neural progenitors release extracellular membrane particles enriched in the stem cell marker prominin-1. J Cell Biol 2007; 176:48-95; http://dx.doi.org/10.1083/jcb.200608137

[14] Gazea M, Tasouri E, Tolve M, Bosch V, Kabanova A, Gojak C, Kurtulmus B, Novikov O, Spatz J, Pereira G, et al. Primary cilia are critical for Sonic hedgehog-mediated dopaminergic neurogenesis in the embryonic midbrain. Dev Biol 2016; 409:55-71; PMID:26542012; http://dx.doi.org/10.1016/j.ydbio.2015.10.033

[15] Willaredt MA, Hasenpusch-Theil K, Gardner HAR, Kitanovic I, Hirschfeld-Warneken VC, Gojak CP, Gorgas K, Bradford CL, Spatz J, Wölfl S, et al. A Crucial Role for Primary Cilia in Cortical Morphogenesis. J Neurosci 2008; 28:12887-900; PMID:19036983; http://dx.doi.org/10.1523/JNEUROSCI.2084-08.2008

[16] Wilson SL, Wilson JP, Wang C, Wang B, McConnell SK. Primary cilia and Gli3 activity regulate cerebral cortical size. Dev Neurobiol 2012; 72:1196-212; PMID:21976438; http://dx.doi.org/10.1002/dneu.20985

[17] Higginbotham H, Guo J, Yokota Y, Umberger NL, Su C-Y, Li J, Verma N, Hirt J, Ghukasyan V, Caspary T, et al. Arl13b-regulated cilia activities are essential for polarized radial glial scaffold formation. Nat Neurosci 2013; 16:1000-7; PMID:23817546; http://dx.doi.org/10.1038/nn.3451

[18] Paridaen JTML, Wilsch-Bräuninger M, Huttner WB. Asymmetric inheritance of centrosome-associated primary cilium membrane directs ciliogenesis after cell division. Cell 2013; 155:333-44; PMID:24120134; http://dx.doi.org/10.1016/j.cell.2013.08.060

[19] Tylkowski MA, Yang K, Hoyer-Fender S, Stoykova A. Pax6 controls centriole maturation in cortical progenitors through Odf2. Cell Mol Life Sci CMLS 2015; 72:1795-809; PMID:25352170; http://dx.doi.org/10.1007/s00018-014-1766-1

[20] Li A, Saito M, Chuang J-Z, Tseng Y-Y, Dedesma C, Tomizawa K, Kaitsuka T, Sung C-H. Ciliary transition zone activation of phosphorylated Tctex-1 controls ciliary resorption, S-phase entry and fate of neural progenitors. Nat Cell Biol 2011; 13:402-11; PMID:21394082; http://dx.doi.org/10.1038/ncb2218

[21] Gabriel E, Wason A, Ramani A, Gooi LM, Keller P, Pozniakovsky A, Poser I, Noack F, Telugu NS, Calegari F, et al. CPAP promotes timely cilium disassembly to maintain neural progenitor pool. EMBO J 2016; 35:803-19; PMID:26929011; http://dx.doi.org/10.15252/embj.201593679

[22] Lange C, Huttner WB, Calegari F. Cdk4/cyclinD1 overexpression in neural stem cells shortens G1, delays neurogenesis, and promotes the generation and expansion of basal progenitors. Cell Stem Cell 2009; 5:320-31; PMID:19733543; http://dx.doi.org/10.1016/j.stem.2009.05.026

[23] Matise MP. Molecular genetic control of cell patterning and fate determination in the developing ventral spinal cord. Wiley Interdiscip Rev Dev Biol 2013; 2:419-25; PMID:23799585; http://dx.doi.org/10.1002/wdev.83

[24] Huangfu D, Liu A, Rakeman AS, Murcia NS, Niswander L, Anderson KV. Hedgehog signalling in the mouse requires intraflagellar transport proteins. Nature 2003; 426:83-7; PMID:14603322; http://dx.doi.org/10.1038/nature02061

[25] Stenkamp DL. Development of the vertebrate eye and retina. Prog Mol Biol Transl Sci 2015; 134:397-414; PMID:26310167; http://dx.doi.org/10.1016/bs.pmbts.2015.06.006

[26] Cwinn MA, Mazerolle C, McNeill B, Ringuette R, Thurig S, Hui C, Wallace VA. Suppressor of fused is required to maintain the multipotency of neural progenitor cells in the retina. J Neurosci 2011; 31:5169-80; PMID:21451052; http://dx.doi.org/10.1523/JNEUROSCI.5495-10.2011

[27] Stenkamp DL, Frey RA. Extraretinal and retinal hedgehog signaling sequentially regulate retinal differentiation in zebrafish. Dev Biol 2003; 258:349-63; PMID:12798293; http://dx.doi.org/10.1016/S0012-1606(03)00121-0

[28] Sarkisian MR, Guadiana SM. Influences of primary cilia on cortical morphogenesis and neuronal subtype maturation. The Neuroscientist 2015; 21:136-151; PMID:24740576; http://dx.doi.org/10.1177/1073858414531074

[29] Willaredt MA, Tasouri E, Tucker KL. Primary cilia and forebrain development. Mech Dev 2013; 130:373-80; PMID:23085524; http://dx.doi.org/10.1016/j.mod.2012.10.003

[30] Takeo Y, Kurabayashi N, Nguyen MD, Sanada K. The G protein-coupled receptor GPR157 regulates neuronal differentiation of radial glial progenitors through the Gq-Ins(1,4,5)*P*3 pathway. Sci Rep 2016; 6:25180-92; PMID:27142930; http://dx.doi.org/10.1038/srep25180

[31] Amador-Arjona A, Elliott J, Miller A, Ginbey A, Pazour GJ, Enikolopov G, Roberts AJ, Terskikh AV. Primary cilia regulate proliferation of amplifying progenitors in adult hippocampus: implications for learning and memory. J Neurosci 2011; 31:9933-44; PMID:21734285; http://dx.doi.org/10.1523/JNEUROSCI.1062-11.2011

[32] Tong CK, Han Y-G, Shah JK, Obernier K, Guinto CD, Alvarez-Buylla A. Primary cilia are required in a unique subpopulation of neural progenitors. Proc Natl Acad Sci 2014; 111:12438-43; PMID:25114218; http://dx.doi.org/10.1073/pnas.1321425111

[33] Wilsch-Brauninger M, Peters J, Paridaen JTML, Huttner WB. Basolateral rather than apical primary cilia on neuroepithelial cells committed to delamination. Development 2012; 139:95-105; PMID:22096071; http://dx.doi.org/10.1242/dev.069294

[34] Zolessi FR, Poggi L, Wilkinson CJ, Chien CB, Harris WA. Polarization and orientation of retinal ganglion cells in vivo. Neural Develop 2006; 1:2; http://dx.doi.org/10.1186/1749-8104-1-2

[35] Das RM, Storey KG. Apical abscission alters cell polarity and dismantles the primary cilium during neurogenesis. Science 2014; 343:200-4; PMID:24408437; http://dx.doi.org/10.1126/science.1247521

[36] Baudoin JP, Viou L, Launay PS, Luccardini C, Espeso Gil S, Kiyasova V, Irinopoulou T, Alvarez C, Rio JP, Boudier T, et al. Tangentially migrating neurons assemble a primary cilium that promotes their reorientation to the cortical plate. Neuron 2012; 76:1108-22; PMID:23259947; http://dx.doi.org/10.1016/j.neuron.2012.10.027

[37] Higginbotham H, Eom TY, Mariani LE, Bachleda A, Hirt J, Gukassyan V, Cusack CL, Lai C, Caspary T, Anton ES. Arl13b in primary cilia regulates the migration and placement of interneurons in the developing cerebral cortex. Dev Cell 2012; 23:925-38; PMID:23153492; http://dx.doi.org/10.1016/j.devcel.2012.09.019

[38] Trivedi N, Ramahi JS, Karakaya M, Howell D, Kerekes RA, Solecki DJ. Leading-process actomyosin coordinates organelle positioning and adhesion receptor dynamics in radially migrating cerebellar granule neurons. Neural Develop 2014; 9:26; http://dx.doi.org/10.1186/1749-8104-9-26

[39] Sakakibara A, Ando R, Sapir T, Tanaka T. Microtubule dynamics in neuronal morphogenesis. Open Biol 2013; 3:130061; PMID:23864552; http://dx.doi.org/10.1098/rsob.130061

[40] Hinds JW, Hinds PL. Early ganglion cell differentiation in the mouse retina: An electron microscopic analysis utilizing serial sections. Dev Biol 1974; 37:381-416; PMID:4826283; http://dx.doi.org/10.1016/0012-1606(74)90156-0

[41] Randlett O, Poggi L, Zolessi FR, Harris WA. The oriented emergence of axons from retinal ganglion cells is directed by laminin contact in vivo. Neuron 2011; 70:266-80; PMID:21521613; http://dx.doi.org/10.1016/j.neuron.2011.03.013

[42] Arellano JI, Guadiana SM, Breunig JJ, Rakic P, Sarkisian MR. Development and distribution of neuronal cilia in mouse neocortex. J Comp Neurol 2012; 520:848-73; PMID:22020803; http://dx.doi.org/10.1002/cne.22793

[43] Stanić D, Malmgren H, He H, Scott L, Aperia A, Hökfelt T. Developmental changes in frequency of the ciliary somatostatin receptor 3 protein. Brain Res 2009; 1249:101-12; PMID:18992731; http://dx.doi.org/10.1016/j.brainres.2008.10.024

[44] Guadiana SM, Semple-Rowland S, Daroszewski D, Madorsky I, Breunig JJ, Mykytyn K, Sarkisian MR. Arborization of dendrites by developing neocortical neurons is dependent on primary cilia and Type 3 adenylyl cyclase. J Neurosci 2013; 33:2626-38; PMID:23392690; http://dx.doi.org/10.1523/JNEUROSCI.2906-12.2013

[45] Kumamoto N, Gu Y, Wang J, Janoschka S, Takemaru K-I, Levine J, Ge S. A role for primary cilia in glutamatergic synaptic integration of adult-born neurons. Nat Neurosci 2012; 15:399-405; PMID:22306608; http://dx.doi.org/10.1038/nn.3042

[46] Valente EM, Rosti RO, Gibbs E, Gleeson JG. Primary cilia in neurodevelopmental disorders. Nat Rev Neurol 2013; 10:27-36; PMID:24296655; http://dx.doi.org/10.1038/nrneurol.2013.247

[47] Guo J, Higginbotham H, Li J, Nichols J, Hirt J, Ghukasyan V, Anton ES. Developmental disruptions underlying brain abnormalities in ciliopathies. Nat Commun 2015; 6:7857-68; PMID:26206566; http://dx.doi.org/10.1038/ncomms8857