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Review

Primary cilium and brain aging: role in neural stem cells, neurodegenerative diseases and glioblastoma

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ABSTRACT

Brain aging is characterized by a progressive loss of tissue integrity and function as a consequence of impaired homeostasis and regeneration capacities. The primary cilium is a highly conserved organelle that projects from the cell surface in a single copy in virtually all mammalian cell types including neural stem/progenitors cells and neurons. Increasing evidence in the last decade points out that primary cilium could be a relevant mediator of neural stem cell activity, neurogenesis, neuronal maturation and maintenance, and brain tumorigenesis. In this review, we summarize the current knowledge about primary cilia roles in these processes. There is currently sufficient background to propose that defective primary cilia contribute to age-related cognitive decline and brain tumor development due to their critical roles in cell cycle control and signaling transduction. This might have potential applications on therapy against age-associated brain diseases.

1. Introduction

1.1. Aging & central nervous system

Aging consists of a progressive loss of tissue integrity and function as a consequence of impaired homeostasis and regeneration capacities. This age-dependent decline produced by life-long accumulation of cellular damage leads to an impaired tissue function and reduced responsiveness to injury that ultimately increases the vulnerability to chronic diseases and death in aged individuals. Nine “hallmarks of aging” have been reported by López-Otín et al. (2013) in an effort to determine the molecular and cellular alterations underlying aging. Among them, stem cell exhaustion (reviewed in Oh et al., 2014) and cellular senescence (see Campisi, 2013; McHugh and Gil, 2018) are critical contributors due to their well-established roles in the decline of the regenerative and homeostatic potential of aged tissues. Thus, tissue-specific stem cells are responsible of replenishing tissues to maintain homeostasis, but the stem cell pools are progressively reduced with aging due to loss of self-renewal activity, an imbalance of stem cell quiescence and proliferation states, or cellular stress-induced senescence (Oh et al., 2014). On its part, cellular senescence consists of a stable cell cycle arrest accompanied by other phenotypic changes that limits the proliferation of damaged and aged cells (reviewed in Muñoz-Espín and Serrano, 2014). Senescent cells accumulate in aged individuals due to inefficient clearance and replacement mechanisms, which might lead to chronic inflammation and deleterious effects on tissue integrity and homeostasis that aggravate the aging phenotype. Remarkably, aging represents the major risk factor for highly prevalent human pathologies such as neurodegenerative disorders or cancer; in fact, aging and cancer are currently considered different manifestations of a common biological process, *i.e.*, the accumulation of cellular damage (Hanahan and Weinberg, 2011; López-Otín et al., 2013). They also share several hallmarks: thus, deregulation of stem cell activity and increased senescence are also involved in cancer formation and progression (Hanahan and Weinberg, 2011). Interestingly, the clonal dominance of mutational events in stem/progenitor cells increases exponentially with age, which would lead to the failure of tissue maintenance and cancer suppression mechanisms and thereby to the emergence of aging-associated diseases (Adams et al., 2015).

Aging has particularly devastating consequences on the central nervous system (CNS), where a functional decline of brain encompassing impaired neurogenesis is usually observed in aged people. There is compelling evidence that aging induces profound structural and functional changes in mammalian neural stem cells (NSCs) and their niche, thereby affecting neurogenesis and brain homeostasis (reviewed in detail by Fuentealba et al., 2012; Capilla-Gonzalez et al.,

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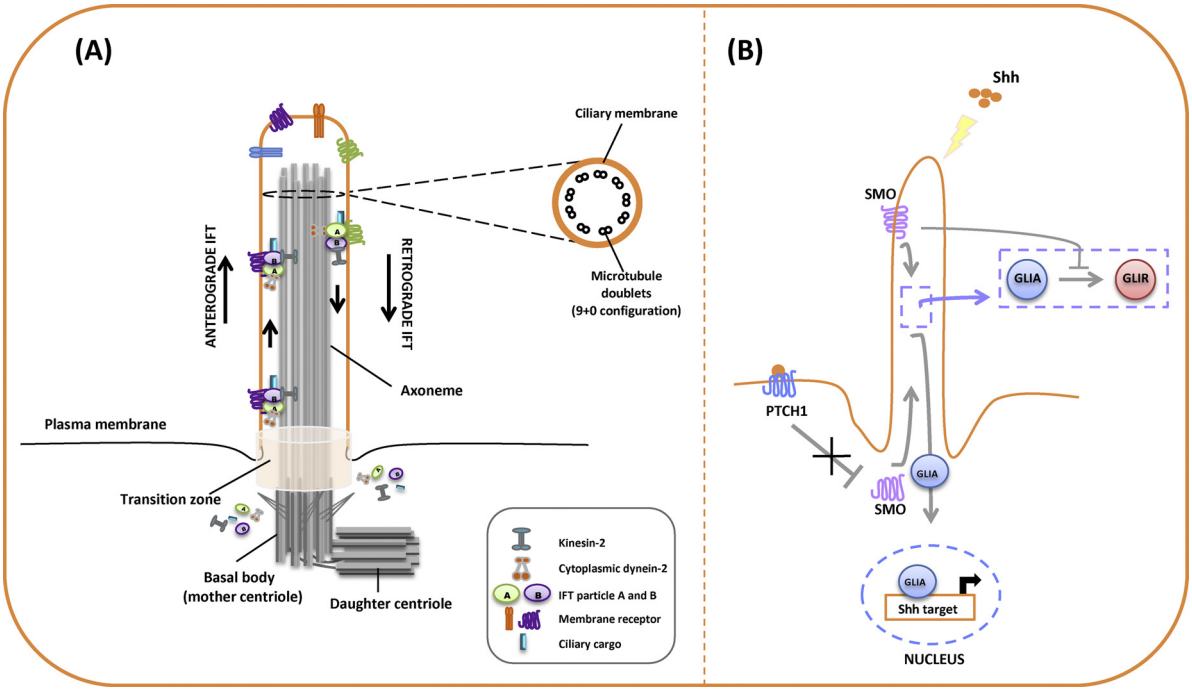

Fig. 1. The primary cilium: structure, intraciliary trafficking and signaling transduction.
(A) The primary cilium is a ubiquitous organelle that protrudes from the cell surface in a single copy. It consists of nine microtubule doublets (*axoneme*) that nucleate from the mother centriole (*basal body*), surrounded by a lipid membrane continuous with the plasma membrane that is enriched in signaling components such as membrane receptors. Cilia-targeted proteins are assembled into IFT particles that enter the cilium and move along the axoneme to the tip (*anterograde IFT*) and back (*retrograde IFT*) in a process mediated by the kinesin-2 and cytoplasmic dynein-2 motors. (B) Shh-induced signaling is the best-characterized cilia-regulated signaling pathway and indeed the transduction of this cascade depends completely on primary cilia. Briefly, when Shh is present, it binds PTCH1 and that leads to SMO translocation into the cilium, where it inhibits GLIR formation and activates the downstream signaling, and so GLIA move to the nucleus and activate the transcription of target genes.
IFT, intraflagellar transport; Shh, Sonic hedgehog; PTCH1, Patched 1; SMO, Smoothened, frizzled class receptor; GLIA, GLI transcriptional activator form; GLIR, GLI repressor form.

2015). Thus, it is accepted that neurogenesis decreases with age in the two main neurogenic niches in adults in mice: the ventricular-subventricular zone (V/SVZ) in the lateral ventricles and the subgranular zone (SGZ) in the hippocampal dentate gyrus (DG). This fact has also been described in humans (Sanai et al., 2011; Spalding et al., 2013), although there is still controversy over whether adult neurogenesis takes place and even persists throughout aging (Boldrini et al., 2018) or if, instead, it is already negligible in adult humans (Sorrells et al., 2018). The reduction of proliferative capacity of neurogenic regions is mainly due to a progressive depletion of the NSCs pool (*e.g.*, by increasing asymmetric and/or symmetric divisions that limit their capacity to self-renew and remain in the neurogenic niche) (Maslov et al., 2004; Encinas et al., 2011; Obernier et al., 2018) and/or increased transition into quiescent state of NSCs (Bouab et al., 2011). In addition to alterations in proliferation, several other structural and fate differentiation anomalies have been documented in relation to NSCs and their niche during aging (Bouab et al., 2011; Capilla-Gonzalez et al., 2014). Thus, an altered balance between neurogenesis and gliogenesis has been observed in the aged V/SVZ, leading to a reduction in neurons but sustained levels of astrocytes and oligodendrocytes. Moreover, astrocytic and ependymal cells acquire a reactive phenotype that results from accumulation of dense bodies and intermediate filaments in their cytoplasm, which may underlie the loss of stemness by astrocytes with aging. As a result, the V/SVZ undergoes substantial changes in its structural organization, *e.g.*, flattening ependymal cells and scattered distribution of their cilia, significant loss of NSCs, intermediate progenitor cells and migrating neuroblasts, and disruption of the rostral migratory stream to the olfactory bulb (Luo et al., 2006; Capilla-Gonzalez et al., 2014).

A complex and not yet well understood combination of cell-intrinsic factors (accumulation of DNA damage, deficient proteostasis, ultrastructural alterations) as well as extrinsic factors such as vasculature deterioration, changes in systemic factors and also in niche microenvironment are believed to underlie the loss of NSCs and neurogenic niches activity over time (see Conboy and Rando, 2012; DeCarolis et al., 2015). Particularly relevant are those changes in the secretory profile of NSCs and neighboring niche cells with aging, which are known to influence the niche microenvironment conditions necessary to maintain stemness and neurogenesis, and also to drive organism aging. Thus, an increased secretion of proinflammatory cytokines by microglia in the V/SVZ (Solano Fonseca et al., 2016) and reduced secretion of vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF2) by stem and progenitor cells are known to impair neurogenesis (Shetty et al., 2005; Bernal and Peterson, 2011). Changes in the choroid plexus secretome are known to influence NSCs behavior as well (Silva-Vargas et al., 2016). Moreover, secretion of exosomal microRNAs (miRNAs) by hypothalamic NSCs has been recently demonstrated to modulate aging speed (Zhang et al., 2017). Furthermore, epigenetic changes in NSCs and neurogenesis are widely considered as key players in the neural decline that characterizes aged individuals (reviewed by Delgado-Morales et al., 2017).

All these alterations in the activity of NSCs leading to impaired neurogenesis, among other factors, underlie the higher susceptibility to cognitive impairment and neurodegenerative disorders of aged individuals. In addition, increasing age represents an important risk factor for glioblastoma (GBM), the most frequent malignant primary brain tumor in adults (Chen et al., 2012), which has been experimentally documented that derives from neoplastic transformation of NSCs with low-level driver mutations in the V/SVZ (Alcantara Llaguno et al., 2009; Lee et al., 2018). Despite the outstanding advances in the last

decades, however, much is pending to learn about the cellular and molecular mechanisms that drive aging-associated changes in the CNS.

1.2. Overview of primary cilium

The primary cilium is a non-motile and highly conserved organelle that projects from the cell surface in a single copy in virtually all mammalian cell types (for comprehensive reviews, see Ishikawa and Marshall, 2011; Elliott and Brugmann, 2019). Notably, it is emerging in recent years as a relevant mediator of NSC activity, neurogenesis, neuronal maturation and maintenance, and also brain tumorigenesis.

Mature primary cilia consist of a *ciliary axoneme* (nine pairs of microtubules in *9 + 0* configuration) that extends from a modified mother centriole (*basal body*) and is surrounded by a bilayer lipid membrane continuous with the plasma membrane (Fig. 1A). Interestingly, a specialized region in the proximal axoneme called the *transition zone* maintains a specific ciliary composition, which is enriched in certain lipids and proteins such as membrane receptors and downstream signaling molecules (Garcia-Gonzalo and Reiter, 2017). Ciliary assembly and maintenance strongly rely on proper intraflagellar transport (IFT), a conserved bidirectional transport system that carries cilia-targeted cargoes along the axoneme to the ciliary tip (anterograde IFT) and back (retrograde IFT) by large protein complexes (*IFT particles*) in a process mediated by kinesin-2 and cytoplasmic dynein-2 motors (Lechtreck, 2015; Nachury, 2018). The primary cilium primarily acts as a central hub to receive and transduce extracellular signals in order to coordinate the cellular response to most of the signaling pathways. In fact, primary cilia are also known as *sensorial cilia* due to their function as signal receivers, representing the “sensorial antenna” of the cell. The primary cilium integrates all these molecular signals to elaborate biological responses to a broad range of developmental and physiological processes, playing key roles in cell cycle control and proliferation, tissue patterning, migration and polarity, and stem cell maintenance and differentiation (Elliott and Brugmann, 2019).

Clinically, defects in primary cilium structure and/or function lead to the development of *ciliopathies* (Mitchison and Valente, 2017; Reiter and Leroux, 2017), a growing group of inherited disorders that usually display neurological anomalies such as brain malformations, cognitive impairment or learning disabilities (Valente et al., 2014). Some relevant examples and their main clinical symptoms are listed below: **Joubert syndrome** (Mendelian Inheritance in Man [MIM]#213300; mid-hindbrain malformations with cerebellar vermis hypodysplasia, which constitutes a pathognomonic sign called “molar tooth sign” that is diagnosed by brain imaging, hypotonia, psychomotor delay, intellectual disability or nystagmus, among others), **Bardet-Biedl syndrome** (MIM#209900; retinal dystrophy, obesity, postaxial polydactyly, renal and urogenital anomalies together with intellectual and learning disabilities, psychomotor delay or hydrocephalus), **Meckel syndrome** (MIM#249000; cystic kidneys, postaxial polydactyly and occipital encephalocoele as well as corpus callosum hypoplasia or hydrocephalus), **orofaciodigital syndromes** (orofacial defects and preaxial/mesoaxial polydactyly with intellectual disability, cerebellar defects and corpus callosum agenesis). Furthermore, the close tie between primary cilia and cancer is becoming more and more evident (extensively reviewed by Basten and Giles (2013), Gradilone et al. (2017), Liu et al. (2018)), also for brain tumors. The role of primary cilia in cancer is highly context-dependent and can thereby act as tumor promoter or suppressor. Thus, since ciliogenesis is tightly coupled to cell cycle, the absence or decrease in primary cilia formation has been frequently reported in a number of malignant tumors such as cholangiocarcinoma, where primary cilia inhibit tumor development (Gradilone et al., 2017). However, the primary cilium can also play the opposite role and enhance cancer progression, as has been demonstrated for medulloblastoma (Han et al., 2009) and basal cell carcinoma (Wong et al., 2009), where certain subtypes require the presence of cilia to promote tumor growth.

1.2.1. Ciliary signaling and its role in disease

Many of the core signaling pathways involved in development and homeostasis are known to signal through the primary cilium and/or are regulated by this organelle to some extent. In this sense, its regulatory role has been especially studied in the case of Sonic hedgehog (Shh) pathway but the primary cilium also regulates Wingless/int (Wnt), transforming growth factor beta (TGF-β), Notch and mechanistic target of rapamycin kinase (mTOR), as well as those signaling cascades triggered by ion channels, G-Protein coupled receptors (GPCRs), receptor tyrosine kinases (RTKs) or receptors for extracellular matrix proteins, among others (Christensen et al., 2017; Wheway et al., 2018). Considering that Shh is the best-characterized cilia-regulated signaling cascade, it is necessary to explain here the pivotal role that primary cilium plays in this pathway (extensively reviewed by Bangs and Anderson (2017)). In mammals, Shh-induced signaling is critically involved in organ development, homeostasis and regeneration, especially regarding neural specification and limb patterning. Remarkably, mammalian Shh signal transduction is entirely dependent on the primary cilium, which is enriched in the main mediators of the cascade, such as the membrane receptor Patched 1 (PTCH1), the transducer smoothened, frizzled class receptor (SMO) and GLI family zinc finger (GLI) transcription factors (Fig. 1B). The mechanism of transduction is well-established: briefly, in the absence of stimulus (no Shh ligand), PTCH1 and other negative regulators such as the G protein-coupled receptor 161 (GPR161) are localized in the ciliary membrane and the GLI3 repressor form (GLI3R) is produced, which moves to the nucleus and prevents expression of target genes. When Shh is present, it binds to PTCH1 leading to PTCH1 removal from the cilium and subsequent translocation of SMO into the cilium, where it inhibits GLI3R formation and activates downstream signaling. Thus, GLI2 dissociates from GLI/SUFU repressor complexes that accumulate at the ciliary tip and is then converted to the GLI2 transcriptional activator form (GLI2A), which activates the transcription of target genes in the nucleus.

Normal primary cilia formation is therefore essential to correctly transduce Shh signaling and indeed changes in cilia structure/function may alter Shh pathway activity and other cilia-regulated cascades leading to disease phenotypes. In the case of ciliopathies, the critical role of primary cilia in signaling pathways required for normal embryonic development of the CNS such as Shh and Wnt might underlie the neurological defects frequently manifested by patients. Furthermore, links between cilia and brain tumors are continuously increasing. The role of primary cilium has been particularly studied in the case of medulloblastoma, where cilia can promote or restrain Shh-driven medulloblatoma formation depending on the oncogenic driver event (Han et al., 2009). Moreover, ciliary regulation of Shh-medulloblastoma involves the phosphatidylinositol-3-kinase (PI3K) pathway to maintain primary cilia on tumor cells (Conduit et al., 2017). Remarkably, new lines of evidence point out that a moderate disruption of primary cilia by depletion of ADP ribosylation factor-like GTPase 13B (ARL13B) reduces oncogenic Shh signaling in medulloblastoma with no evident effects on most organ systems *in vivo*, which could represent a promising therapeutic strategy (Bay et al., 2018). On the other hand, the increasing importance of primary cilia in GBM has also recently been highlighted.

2. Primary cilium in adult neural stem cells and their niche: role in aging

2.1. Primary cilium in neurogenic niches during development and adult stage

Most mammalian cells have a primary cilium, as stated above, and neural progenitors, neurons or astrocytes are not an exception (Han and Alvarez-Buylla, 2010). The primary cilium is a key player in the regulation of brain patterning during development (Table 1). Thus, primary cilia are critical mediators of Shh signaling to drive proliferation

Table 1
Main findings that link primary cilia to neural stem cell activity.

YEAR	FINDING	REFERENCE(s)
2008	Primary cilia are critical mediators of Shh signaling to drive proliferation of neural progenitors from developing forebrain, cerebral	Spassky et al., Willaredt et al.
2009	cortex and cerebellum in embryonic stage	Gorivodsky et al.
2011		Besse et al.
2011	A shortened G_1 phase induces neural progenitors' expansion by increasing self-renewal and amplifying divisions of NSCs during corticogenesis, which involves a ciliary regulation	Li et al.
2008	Cilia-mediated Shh signaling regulates adult NSCs proliferation, maintenance and differentiation	Breunig et al., Han et al. Amador-Arjona et al.
2011		Tong et al.
2014		
2013	Asymmetric inheritance of the mother centriole with attached ciliary membrane is linked to stemness	Paridaen et al.
2014	Most of quiescent NSCs were described to be ciliated	Khatri et al.

Shh, Sonic hedgehog; NSCs, neural stem cells.

of neural progenitors from developing forebrain, cerebral cortex and cerebellum in embryonic stage (Spassky et al., 2008; Willaredt et al., 2008; Gorivodsky et al., 2009; Besse et al., 2011); interestingly, ciliary regulation of GLI3 repressor levels seems to be the central molecular event. Moreover, taking into account that cell cycle dynamics decisively mediates the proliferation and fate specification of neural progenitors during development (Dehay and Kennedy, 2007), it is important to highlight that primary cilium assembly/disassembly is tightly coupled to cell cycle and thereby it acts as a structural checkpoint to progress to S- and M-phase. In this sense, a shortened G_1 phase is known to induce neural progenitors' expansion by increasing self-renewal and amplifying divisions of NSCs during corticogenesis (Lange et al., 2009; Li et al., 2011), which involves a ciliary regulation (Li et al., 2011). In addition to the essential role of primary cilium in Shh signaling, the expansion of embryonic neural progenitors may be linked to an increased canonical Wnt signaling as a consequence of ciliary dysfunction (Willaredt et al., 2008).

Nonetheless, ciliary involvement in adult neural progenitors has been scarcely explored despite the critical functions that primary cilia exert in signal transduction and cell cycle control (see Table 1 and Fig. 2). It seems quite clear, though, that primary cilium is required to proper expansion and maintenance of adult NSCs owing to its central role as the cellular signaling hub, especially for Shh pathway (reviewed by Álvarez-Buylla and Ihrie, 2014). Thus, cilia-mediated transduction of Shh signaling decisively regulates the proliferation, maintenance and differentiation of adult NSCs in both the V/SVZ (Tong et al., 2014) and SGZ (Breunig et al., 2008; Han et al., 2008; Amador-Arjona et al., 2011). In detail, blocking Shh signaling or ablating primary cilia in embryonic precursors to hippocampal adult NSCs impair the transition from these embryonic neural progenitors to radial astrocytes, thereby leading to a dramatic decrease in the number of quiescent adult neural progenitors *in vivo* (Breunig et al., 2008; Han et al., 2008). Instead, the post-natal ablation of cilia in adult NSCs specifically reduces the proliferation of transient progenitors and subsequent neurogenesis (Amador-Arjona et al., 2011). The primary cilium has, therefore, a pivotal role in the establishment and maintenance of both adult neurogenic niches, where an ongoing requirement of Shh signaling to modulate self-renewal and fate specification of neural progenitors is observed (Álvarez-Buylla and Ihrie, 2014). Of note, although Shh is the best-characterized cilia-regulated pathway, the regulation of most cellular signaling cascades by primary cilium might anticipate additional contributions to modulate how adult NSCs sense and respond to extracellular signals. Thus, primary cilia of NSCs in adult rat V/SVZ harbor platelet derived growth factor receptor alpha (PDGFRA) and epidermal growth factor receptor (EGFR) (Danilov et al., 2009), which suggest a ciliary regulation of RTK signaling in these neural progenitors. Furthermore, primary cilia extend toward the lateral ventricles filled with cerebrospinal fluid (CSF), which is enriched in additional signaling molecules that critically determine neural progenitor behavior such as bone morphogenetic proteins (BMPs), insulin like growth factors (IGFs) and Wnt ligands (see Taverna et al., 2014 and references therein), all of them well-known to be regulated by the primary cilium (Christensen et al., 2017; Wheway et al., 2018). Therefore, a ciliary regulation of several other signaling cascades to modulate adult NSC activity deserves further research.

It is also important to remark the influence of primary cilium on cell cycle control to modulate adult NSCs activity. In this sense, primary cilium is thought to play a key role in determining the stem cell division mode (symmetric or asymmetric) of neural progenitors and also the maintenance of stem cell character of daughter cells (Anderson and Stearns, 2009; Wang et al., 2009; Paridaen et al., 2013). In detail, an asymmetric inheritance of the mother centriole with attached ciliary membrane, which results in earlier ciliary re-assembly and subsequent Shh signaling activity, has been linked to the maintenance of stemness in the daughter cell that receives it using mouse embryonic neocortical stem cells (Paridaen et al., 2013). This difference in time to form primary cilia in daughter cells may affect their ability to sense and respond to extracellular signals in the CSF (Paridaen et al., 2013). This could influence fate specification and cell cycle progression also in adult NSCs, as well as decisively contribute to establish the quiescent or activated state of neural progenitors as has been proposed for adult NSCs (Khatri et al., 2014). Furthermore, it is also interesting to note that the Shh-responsive cell population in both adult neurogenic niches includes adult quiescent NSCs that can self-renew (Ahn and Joyner, 2005). This may reinforce the importance of primary cilium in this context taking into account that most quiescent NSCs were described to be ciliated (Khatri et al., 2014).

2.2. Primary cilium in neural stem cell aging

The progressive stem cell exhaustion in the adult neurogenic niches during aging is mediated by several mechanisms such as limited capacity to self-renew and increased senescence. In this sense, it is surprisingly that the potential involvement of primary cilium had hardly been addressed taking into account its critical role in cell cycle and signaling regulation. Few studies linking ciliary dysfunction to (neural) stem cell aging are available so far, although some direct and indirect evidence in this field is beginning to emerge (summarized in Table 2).

On the one hand, an age-related lengthening of the G_1 phase of cell cycle in activated NSCs that results in decreased proliferation and subsequent reduction in adult neural progeny has been recently reported in C57Bl/6 mice (Daynac et al., 2014; Daynac et al., 2016). On the other, the primary cilium controls G_1 length to regulate cell cycle progression and fate specification of neural progenitors during corticogenesis (Li et al., 2011). It is therefore tempting to speculate that age-dependent ciliary anomalies could underlie the unbalance between quiescent and activated NSCs that contributes to the stem cell pool decline characteristic of aged individuals. This point could be supported by recent findings that link abnormally long cilia with retarded ciliary disassembly and subsequent cell cycle re-entry delay of neural

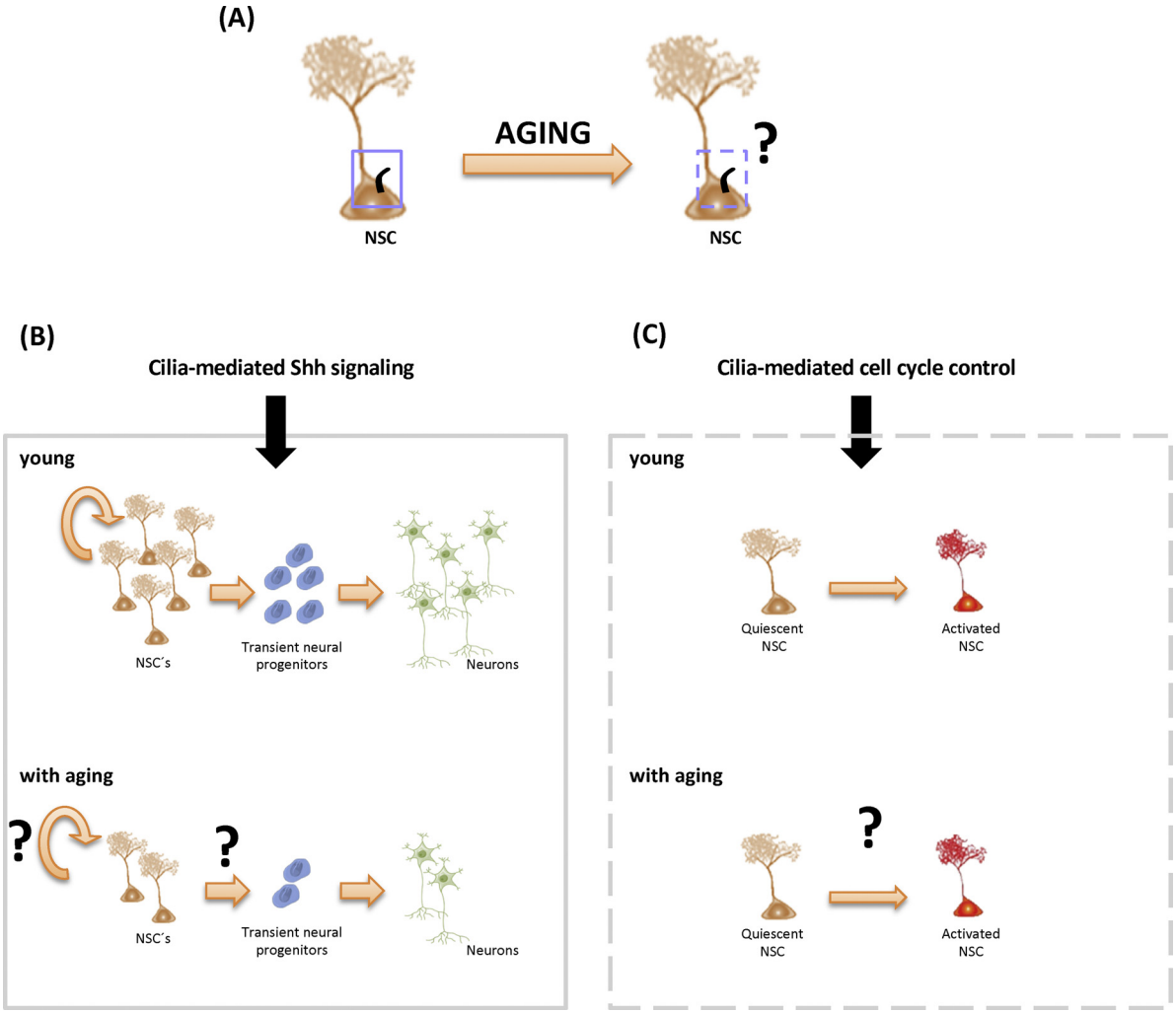

Fig. 2. Roles of primary cilium in neural stem cells in adult stage and aging.
(A) Adult NSCs assemble a primary cilium with important roles in their expansion and maintenance. However, the impact of primary cilia in NSC during aging is unknown despite its critical role in cell cycle and signaling regulation. (B) In this sense, cilia-mediated transduction of Shh signaling is crucial for self-renewal, maintenance and differentiation of NSCs during adult stage. However, if primary cilia are involved in the progressive decline in aged NSC and transient progenitor's number and subsequent differentiation has not yet been determined. (C) The primary cilium through cell-cycle control has also been involved in maintaining the balance between quiescent and activated adult NSCs. Again, a potential role of primary cilium in the deregulation of NSC states during aging has not been investigated for now.
NSC, neural stem cell; Shh, Sonic hedgehog.

progenitors derived from Seckel patient-induced pluripotent stem (iPS) cells (Gabriel et al., 2016). This led to a premature differentiation and decline of the neural progenitor pool that could explain the phenotype associated with Seckel syndrome (Gabriel et al., 2016), which is a rare inherited syndrome characterized by prenatal and postnatal growth delay with microcephaly. Moreover, TGF-β signaling promotes NSCs quiescence in the adult neurogenic niches (Kandasamy et al., 2014) and is also responsible of the G_1 lengthening in activated NSCs abovementioned (Daynac et al., 2014). This could also suggest a ciliary regulation of the NSCs quiescence/activation balance considering the known regulatory role of primary cilium in the TGF-β pathway (Christensen et al., 2017).

Cellular senescence could be another cause that explains the age-related exhaustion of NSCs. Although the existence and impact of senescence in brain aging is far to be understood (see Carrasco-Garcia et al., 2017), some evidence points out that NSCs senescence could

Table 2
Main findings that link primary cilia to cell aging.

YEAR	FINDING	REFERENCE(s)
2010	Primary-cilium dependent Hh signaling suppresses $p16^{INK4a}$ expression and subsequent senescence in primary human mammary epithelial cells	Bishop et al.
2014	Senescent human fibroblasts display increased frequency and length of primary cilia	Breslin et al.
2016	Neural progenitors derived from Seckel patient iPS have abnormally long primary cilia and show a delayed cell cycle re-entry that leads to NSC pool decline	Gabriel et al.
2017	Primary cilia are lost in senescent human fibroblasts due to a plasma membrane hypopolarization that is accompanied by high basal autophagy levels and activation of mTORC1	Carroll et al.

Hh, hedgehog; iPS, induced pluripotent stem cells; NSC, neural stem cell; mTORC1, mechanistic target of rapamycin complex 1.

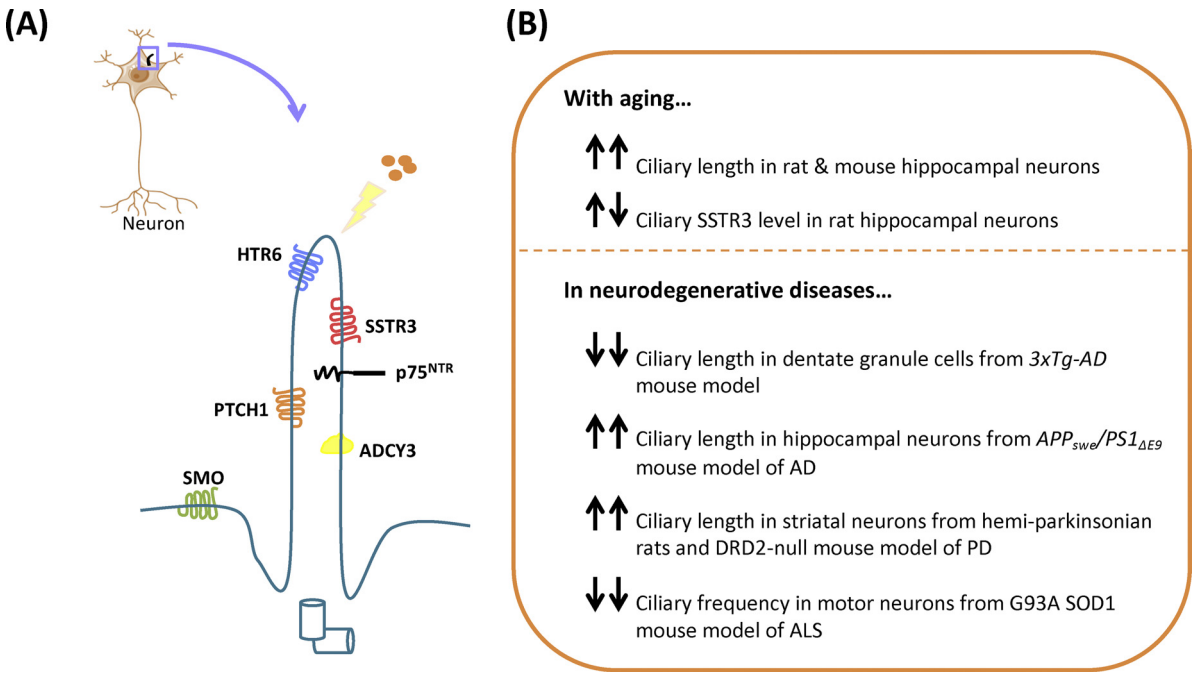

Fig. 3. Primary cilium in neurodegenerative diseases.
(A) Mature neurons harbor a primary cilium enriched in a wide range of membrane receptors and other signaling downstream molecules that activate signaling cascades important for neural function and cognitive activity. (B) During aging, an increase in hippocampal neuron´s primary cilium length and also changes in ciliary expression of signaling molecules such as SSTR3 have been reported from rodent models. Moreover, evidences of ciliary alterations from neurodegenerative mice models of AD, PD and ALS are emerging and point out that primary cilia play a neuromodulatory role with impact on degenerative brain diseases.
HTR6, 5-hydroxytryptamine receptor 6; SSTR3, somatostatin receptor 3; $p75^{NTR}$, p75 neurotrophin receptor; PTCH1, Patched 1; ADCY3, adenylate cyclase 3; SMO, Smoothened, frizzled class receptor; AD, Alzheimer´s disease; PD, Parkinson´s disease; ALS, amyotrophic lateral sclerosis.

contribute to the brain functional decline in aged individuals. Thus, an age-dependent increase of $p16^{INK4a}$ levels, one of the master activators of cellular senescence, has been detected in neural progenitors from V/SVZ of aging wild-type mice (Molofsky et al., 2006), which contributes to reduce the NSCs pool during aging. Consequently, *$p16^{INK4a}$*-deficient mice displayed a smaller decline in NSCs function (Molofsky et al., 2006). Given that the transition to an irreversible senescence state from a previous reversible quiescence by derepression of $p16^{INK4a}$ has been reported in geriatric muscle stem cells (Sousa-Victor et al., 2014), the strong link between primary cilium dynamics and quiescence might anticipate an important role in cellular senescence. However, very few studies have attempted to explore this issue. Bishop et al. (2010) provided the first evidence demonstrating that primary cilium-dependent Shh signaling partially suppresses the expression of $p16^{INK4a}$ and concomitant senescence in primary human mammary epithelial cells (HMECs). Moreover, depletion of $p16^{INK4a}$ (or increased Shh signaling) was demonstrated to promote the formation of primary cilia, and in fact, HMECs containing primary cilia displayed the lowest levels of $p16^{INK4a}$ (Bishop et al., 2010). Conversely, Breslin et al. (2014) reported that senescent human fibroblasts display increased frequency and length of primary cilia together with lower expression of key Shh signaling components; in turn, Shh signaling inhibits ciliogenesis and replicative senescence. Remarkably, this work suggests that extending ciliary length could be a novel mechanism to induce senescence, with potential impact in cancer and aging (Breslin et al., 2014). These results, although opposite, point out an important role of primary cilia to establish senescence; additional evidence comes from studies in the kinesin family member 3a (*Kif3a*) knockout mouse model of cystic kidney disease, where silencing the ciliary gene *Glis2/Nphp7*, a repressor of Shh pathway, induces cellular senescence in kidney epithelial cells (Lu et al., 2016). Interestingly, Kif3a is a component of the kinesin-2 motor, a protein complex involved in anterograde IFT transport, which is essential to ciliogenesis and has key roles in other CNS tumors such as medulloblastoma (Han et al., 2009; Barakat et al., 2013).

Finally, it is interesting to mention that senescent human fibroblasts were described to exhibit lack of primary cilium elongation due to a plasma membrane hypopolarization (Carroll et al., 2017). This resulted in high basal autophagy levels and constitutive activation of the mechanistic target of rapamycin complex 1 (mTORC1), which became insensitive to growth factor signals (Carroll et al., 2017). Remarkably, these findings link cellular senescence, autophagy and nutrient sensing, which constitute all of them biological processes deregulated during aging, with alterations in primary cilium. In this sense, aging-related exhaustion of NSCs could be also mediated by defects in proteostasis. Protein homeostasis is essential to stem cell maintenance and it has been recently shown to depend on proper ciliary function as primary cilia have been involved in the two main proteolytic systems: autophagy-lysosomal and ubiquitin-proteasome systems (Pampliega et al., 2013; Liu et al., 2014; reviewed in Cao and Zhong, 2016; Gerhardt et al., 2016). Thus, quiescent NSCs from aged mice display lysosomal defects, larger accumulation of insoluble protein aggregates and reduced ability to activate (Leeman et al., 2018). Moreover, the proteasomal activity of neural progenitors also declines with age, which impairs self-renewing, proliferation and neuronal differentiation abilities (Zhao et al., 2016). Primary cilia might therefore act as a central hub to regulate some of the aging-related hallmarks, such as stem cell exhaustion, cellular senescence or deficient proteostasis, although further research is required to explore these links.

3. Primary cilium in neurodegenerative diseases associated with aging

Neurodegenerative disorders related to aging, such as Alzheimer´s disease (AD) and Parkinson´s disease (PD) as the most prevalent examples, represent an increasing worldwide health challenge. There is thereby an urgent need to identify and validate potential biomarkers

and therapeutic targets trying to improve the diagnosis and treatment of these patients. In this sense, the role of primary cilia in NSCs maintenance, neurogenesis and neural aging abovementioned, as well as their impact on neuronal connectivity, synaptic integration and intellectual function that will be explained below, make primary cilium a potential key player in the fight against these devastating diseases (summarized in Fig. 3).

Recent findings point out that neuronal primary cilia are required to the synaptic integration of newborn neurons in the hippocampal DG. Thus, defective cilia through increased canonical Wnt signaling lead to a shortening of dendrites in these neurons that fail to integrate into the adult brain (Kumamoto et al., 2012). Similar results were obtained in neocortical pyramidal neurons, which also displayed defects in dendrite growth and arborization (Guadiana et al., 2013). Moreover, disrupted GPCR-mediated signaling in neuronal primary cilia has been reported to impair striatal interneuron´s connectivity and inhibitory circuit formation, leading to an excitatory/inhibitory imbalance (Guo et al., 2017). In addition, functional studies in mice support that disruption of cortical and hippocampal primary cilia modulates cognitive function since it promotes alterations in behavior, learning, memory and novel object recognition (Einstein et al., 2010; Berbari et al., 2014; Rhee et al., 2016). Of note, much of the currently available evidence about ciliary involvement in neuronal function comes from studies that target signaling molecules that are specifically enriched in the neuronal ciliary membrane such as adenylate cyclase 3 (ADCY3) and somatostatin receptor 3 (SSTR3), whose levels are known to vary with age (Stanić et al., 2009); this may support the neuromodulatory role of primary cilia also during aging. It is also interesting to mention that neurons in aged rat hippocampus and neocortex continue to assemble primary cilia without documented changes in ADCY3 and SSTR3 expression, but an age-related increase of ciliary length in certain regions of the hippocampus (not for the DG) has been described (Guadiana et al., 2016). This is consistent with previous data reported in aged mouse hippocampus (Chakravarthy et al., 2012).

Focusing now on specific roles of the primary cilium in neurodegenerative diseases, several studies have reported intriguing findings in the last few years that link ciliary alterations with cognitive decline and disease progression, mainly from AD models (Table 3). Thus, primary cilia from dentate granule cells, which are selectively enriched in the p75 neurotrophin receptor ($p75^{NTR}$) that is known to bind amyloid beta (Aβ) peptides (Chakravarthy et al., 2010), are significantly shortened in 6–24 months-old triple transgenic AD mouse model (*3xTg-AD*) (Chakravarthy et al., 2012). In detail, while ciliary localization of receptors such as SSTR3 and $p75^{NTR}$ is maintained in the transgenic mouse, primary cilia length was reduced by half compared with wild-type individuals, which was suggested to influence the impairment in adult neurogenesis and memory function characteristic of this AD-model mouse (Chakravarthy et al., 2012). Remarkably, the above results were confirmed in the *3xTg-AD* model but not in other models that accumulate only either Aβ or tau protein, where ciliary length remain unchanged (Chakravarthy et al., 2012). Furthermore, it is well-established that somatostatin levels decrease in AD resulting in recognition memory deficits (Burgos-Ramos et al., 2008). This fact, together with SSTR3 is expressed exclusively on neuronal cilia in brain and also that neuronal cilia-mediated somatostatin signaling is essential for object recognition memory (Einstein et al., 2010), make primary cilium a potential target for AD and/or other types of dementia. Experiments focused on other neuronal cilia-located receptors such as 5-hydroxytryptamine receptor 6 (HTR6), which is considered a promising drug candidate for AD treatment (Ramírez, 2013), showed that HTR6 is upregulated in the hippocampus and also that hippocampal neurons from $APP_{swe}/PS1_{\Delta E9}$ AD mouse model have longer primary cilia than corresponding wild-type mice (Hu et al., 2017). Notably, the authors suggest that HTR6 influences cognition by regulating primary cilium function, and indeed, $APP_{swe}/PS1_{\Delta E9}$ mice treated with the HTR6 antagonist SB271046 recovered a normal cognitive function possibly through restoration of ciliary length (Hu et al., 2017). In addition, Morelli et al. (2017) have suggested that primary cilia may be involved in the maturation of human cholinergic neurons from the basal forebrain, whose degeneration is associated with the cognitive impairment observed in AD patients.

On the other hand, several other neurodegenerative disorders such as PD and amyotrophic lateral sclerosis (ALS) might be also linked to defective primary cilia. Thus, cilia-mediated Shh signaling was recently shown to promote the development of midbrain dopaminergic neurons, whose deterioration is thought to underlie PD (Gazea et al., 2016). In particular, ciliary disruption by conditional inactivation of *Ift88* in mouse embryos´ midbrain led to ciliary loss and subsequent downregulation of Shh signaling, what finally triggered a reduction in midbrain dopaminergic progenitors and mature neurons (Gazea et al., 2016). In addition, loss of dopaminergic inputs on striatal neurons, which receive most of dopaminergic projections from the midbrain, induces the elongation of neuronal primary cilia in both hemi-parkinsonian rats and dopamine receptor D2 (DRD2)-null mice (Miyoshi et al., 2014). Primary cilia have also related to ALS pathogenesis, since a significant reduction in motor neurons harboring a primary cilium (using ADCY3 as ciliary marker) was reported in G93A SOD1 mice, the most studied model of ALS (Ma et al., 2011). Connected with this, a recent study by Kopinke et al. (2017) showed that intramuscular adipogenesis typically displayed by aged people and patients with muscular dystrophies, which is modulated by ciliary Shh signaling, can be reduced through removing primary cilia from muscle-resident fibro/adipogenic progenitors.

4. Primary cilium in glioblastoma and glioma stem cells

Glioblastoma (GBM) represents the most common and aggressive primary brain tumor in adults. Remarkably, NSCs in the V/SVZ were confirmed as the cells of origin leading to GBM formation (Alcantara Llaguno et al., 2009; Lee et al., 2018). Taking into account that (i) aging is a major risk factor for cancer development, including GBM (Chen et al., 2012), (ii) there is a decline of adult NSCs functional capacity and genetic integrity with age, and (iii) the primary cilium has been linked to NSCs expansion, differentiation and aging, it is interesting to summarize here the current knowledge about which are the ciliary roles in GBM (see also Table 4 and Fig. 4).

The critical roles of primary cilium in both cellular signaling and cell cycle progression make it an important regulator of tumorigenesis and cancer progression for many different tumors (see Basten and Giles, 2013; Gradilone et al., 2017; Liu et al., 2018). Growing evidence points

Table 3
Main findings that link primary cilia to neurodegenerative diseases.

YEAR	FINDING	REFERENCE(s)
2011	A significant reduction in motor neurons harboring a primary cilium was reported in G93A SOD1 mouse model of ALS	Ma et al.
2012	Primary cilia from dentate granule cells are shortened in 6-24 months-old *3xTg-AD* mouse model	Chakravarthy et al.
2016	Ciliary loss in mouse embryos´ midbrain leads to downregulation of Shh signaling and subsequent reduction in midbrain dopaminergic progenitors and mature neurons	Gazea et al.
2017	Hippocampal neurons from $APP_{swe}/PS1_{\Delta E9}$ AD mouse model have longer primary cilia	Hu et al.

ALS, amyotrophic lateral sclerosis; Shh, Sonic hedgehog; AD, Alzheimer´s disease.

Table 4
Main findings that link primary cilia to glioblastoma.

YEAR	FINDING	REFERENCE(s)
2009	GBM cells are generally unable to assemble mature primary cilia in human conventional cell lines, patient-derived cell cultures and human biopsies	Moser et al.
2014		Moser et al.
2014	Ciliated subpopulations of GBM cells are found in GBM tumors, which co-stain with Ki-67 and ZEB1	Sarkisian et al.
2016a	Ciliary loss in primary cell lines is associated with increased sensitivity to TMZ, the first-line drug for this tumor	Hoang-Minh et al.
2016b	Primary cilia are able to modulate GBM growth through Shh and LPA signaling, both *in vitro* and *in vivo*	Hoang-Minh et al.
2018		Loskutov et al.

GBM, glioblastoma; ZEB1, zinc finger E-box binding homeobox; TMZ, temozolomide; Shh, Sonic hedgehog; LPA, lysophosphatidic acid.

out that this is also the case of GBM (reviewed by Álvarez-Satta and Matheu, 2018). Thus, GBM cells have been described as mostly unable to assemble mature primary cilia in human conventional cell lines, patient-derived cell cultures and human biopsies (Moser et al., 2009; Moser et al., 2014; Sarkisian et al., 2014). In support of this, the downregulation of ciliary gene expression patterns in GBM patients from The Cancer Genome Atlas Network (TCGA) cohort was reported (Shpak et al., 2014). By contrast, small subpopulations of cells with apparently functional primary cilia (8–25% of total cells analyzed) have also been detected in human primary cultures and biopsies (Sarkisian et al., 2014). With regard to the roles exerted by primary cilia in GBM, functional studies targeting different ciliary genes to inhibit ciliogenesis in cells lines and patient-derived cultures showed uneven results, suggesting that primary cilia are likely to play a dual role in GBM cell proliferation. On the one hand, reduced ciliogenesis has been linked to an unrestrained growth of cells (Yang et al., 2013; Loskutov et al., 2018) but also to a decreased proliferation (Hoang-Minh et al., 2016a). In addition, the ciliated cell population identified in tumor samples co-stain with the proliferation marker Ki-67, which suggests that primary cilia may contribute to GBM growth (Sarkisian et al., 2014). Remarkably, cilia-mediated Shh and LPA (lysophosphatidic acid) signaling was shown to modulate GBM proliferation both *in vitro* and *in vivo* (Hoang-Minh et al., 2016b; Loskutov et al., 2018), highlighting the key role of the primary cilium as signaling hub also in GBM. In this sense, aberrant PI3K signaling, one of the three core pathways frequently altered in GBM (TCGA, 2008), has been related to primary cilia loss in U-251 MG cells, which would lead to uncontrolled proliferation (Yang et al., 2013). Apart from their potential roles in GBM formation, primary cilia may also impact key features such as chemoresistance, tumor invasion and patient survival. Thus, GBM ciliated cells from biopsies and patient-derived cultures express the zinc finger E-box binding homeobox 1 (ZEB1) transcription factor (Sarkisian et al., 2014), which is a master mediator of the epithelial-mesenchymal transition (EMT) and therefore has a major influence on tumor invasion and chemoresistance (Siebzehnrubl et al., 2013). Moreover, ciliary loss in primary cell lines was associated with increased sensitivity to temozolomide (TMZ) (Hoang-Minh et al., 2016a), the first-line drug in the treatment of this tumor.

Nothing is known over whether primary cilia might have a role in the malignant transformation of NSCs that drive GBM formation. Nor

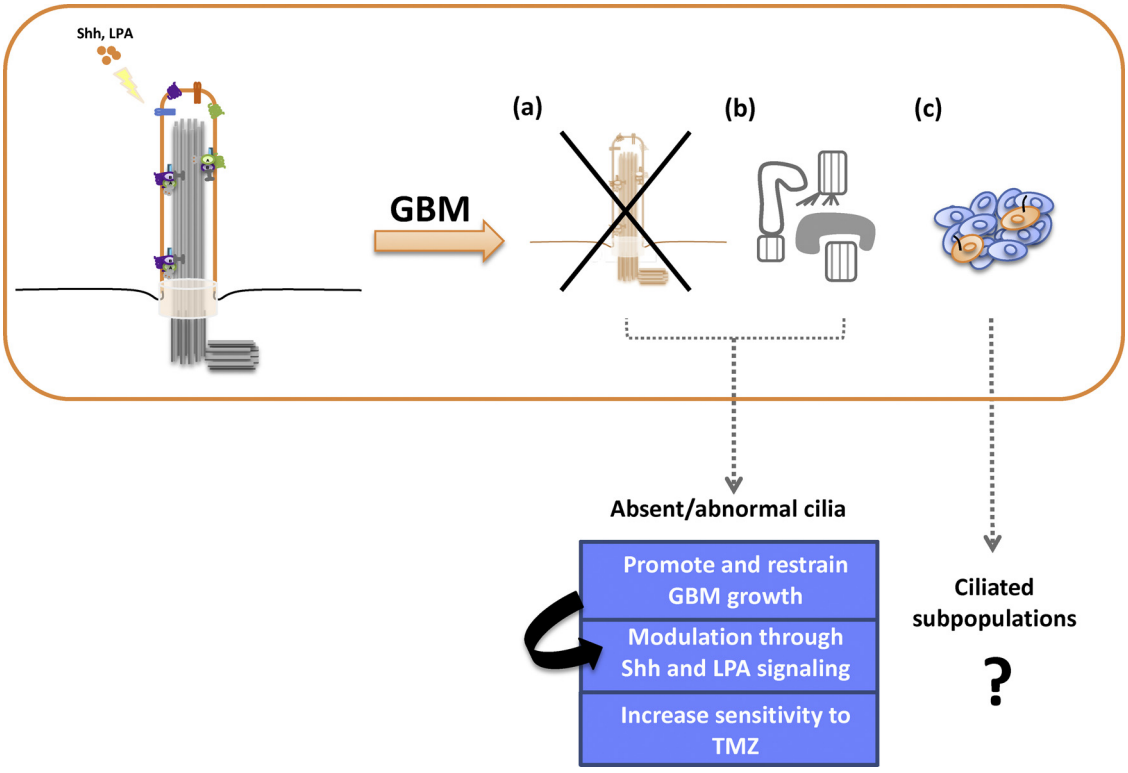

Fig. 4. Impact of primary cilium on glioblastoma tumors.
Primary cilia formation is disrupted in GBM, where cells are generally unable to assemble mature cilia (a) and aberrant forms in different intermediate states are found (b). The primary cilium plays a dual role in GBM progression: ciliary loss can promote and restrain GBM growth by modulating Shh and LPA signaling, in addition to increase sensitivity to TMZ. Moreover, small subpopulations of GBM cells remain ciliated **(c)** but their function is currently unknown.
GBM, glioblastoma; Shh, Sonic hedgehog; LPA, lysophosphatidic acid; TMZ, temozolomide.

do we know if this organelle is able to influence the expansion and/or maintenance of glioma stem cells (GSCs), which represent a small population of GBM cells that decisively contributes to tumor initiation, recurrence and therapy resistance (Galli et al., 2004; Singh et al., 2004; reviewed in Carrasco-Garcia et al., 2013; Lathia et al., 2015). To this regard, $CD15^+$ medulloblastoma cells, which display cancer stem cell properties and are believed to propagate medulloblastomas, do not form primary cilia (Gate et al., 2015). However, recent findings might anticipate a potential involvement of primary cilium in acquiring stem cell properties by tumor-initiating cells. In their study, Guen et al. (2017) demonstrated that EMT programs, which are essential to promote and maintain stemness in mammary stem cells and mammary tumor-initiating cells, induce primary cilia assembly and thus Shh signaling. Consequently, stem cell properties and tumorigenic capacity of these cells are abrogated when ciliogenesis is inhibited (Guen et al., 2017). It is interesting to note that key EMT-associated factors such as ZEB1 have been involved in GBM initiation, invasion and chemoresistance (Siebzehnrubl et al., 2013); therefore, it is tempting to speculate that primary cilia play any role in these processes.

5. Conclusion

The primary cilium has emerged over the last decade as a key regulator of cell maintenance and tissue homeostasis through the control of central events such as cell cycle progression and signaling transduction, which are progressively disrupted in aged individuals. This might anticipate that primary cilia have a great impact on aging and age-related diseases such as cancer and neurodegenerative disorders, a field scarcely explored so far. Aging often leads to a progressive cognitive decline that is a well-established consequence of NSCs activity loss and subsequent impaired neurogenesis; in addition, age represents a major risk factor for GBM, the most common primary brain tumor in adults. Increasing evidence links ciliary anomalies to NSCs pool depletion, decreased neurogenesis and NSCs quiescent/active unbalance during aging, as wells as deficient proteostasis and cellular senescence. Furthermore, alterations in ciliary length are commonly reported from AD models, involving cilia in neurodegeneration. Primary cilia also have important roles in GBM development and progression.

The key role of primary cilium in maintaining adult NSCs pool and neural activity as well as in tumorigenesis and cancer progression, make it a promising candidate in the fight against age-related brain pathologies. Primary cilia might therefore act as a central hub to modulate some of the aging-related hallmarks such as stem cell exhaustion, cellular senescence or deficient proteostasis, all of them issues that remain understudied. Apart from focusing on the specific roles of primary cilia in the CNS aging, it would be interesting to address the functional comparison between the absence of primary cilia *versus* the presence of abnormal cilia with regard to cilia-mediated signaling outcomes. This has important implications for medulloblastoma (Han et al., 2009; Bay et al., 2018) but it is currently unknown the impact on GBM and/or neurodegenerative disorders. In addition, the role of primary cilium in other CNS cellular components such as astrocytes and its contribution to age-related cognitive decline deserve more research as it is virtually non-existent.

Further research is therefore required to go deeper in the potential involvement of primary cilia in neural aging and their impact on age-related diseases, and indeed emerging data justify more research efforts in this field. We expect major progress in the coming years that might allow designing cilia-targeted therapies to offer new strategies against age-related pathologies.

Declaration of conflict of interest

None.

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