Published in final edited form as:
Exp Neurol. 2014 October ; 0: 56–68. doi:10.1016/j.expneurol.2013.01.027.

Signals that regulate the oncogenic fate of neural stem cells and progenitors

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Abstract

Brain tumors have frequently been associated with a neural stem cell (NSC) origin and contain stem-like tumor cells, so-called brain tumor stem cells (BTSCs) that share many features with normal NSCs. A stem cell state of BTSCs confers resistance to radiotherapy and treatment with alkylating agents. It is also a hallmark of aggressive brain tumors and is maintained by transcriptional networks that are also active in embryonic stem cells. Advances in reprogramming of somatic cells into induced pluripotent stem (iPS) cells have further identified genes that drive stemness. In this review, we will highlight the possible drivers of stemness in medulloblastoma and glioma, the most frequent types of primary malignant brain cancer in children and adults, respectively. Signals that drive expansion of developmentally defined neural precursor cells are also active in corresponding brain tumors. Transcriptomal subgroups of human medulloblastoma and glioma match features of NSCs but also more restricted progenitors. Lessons from genetically-engineered mouse (GEM) models show that temporally and regionally defined NSCs can give rise to distinct subgroups of medulloblastoma and glioma. We will further discuss how acquisition of stem cell features may drive brain tumorigenesis from a non-NSC origin. Genetic alterations, signaling pathways, and therapy-induced changes in the tumor microenvironment can drive reprogramming networks and induce stemness in brain tumors. Finally, we propose a model where dysregulation of microRNAs (miRNAs) that normally provide barriers against reprogramming plays an integral role in promoting stemness in brain tumors.

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We apologize to authors whose work we did not cite, due to space restrictions in this review. Authors further declare no conflict of interest.

Keywords

brain tumor; progenitor; neural stem cell; glioma; medulloblastoma; reprogramming; miRNA

Introduction

Defined gradients of signaling factors coordinate self-renewal and differentiation in NSC populations during neural development. Genetic alterations or epigenetic regulation of genes that disturb this delicate balance in NSCs and restricted progenitors may lead to development of brain tumors.

The incidence of histologically and genetically distinct brain tumors peaks in defined time windows during childhood and in adults. In this review, we will focus on medulloblastoma and glioma, the most common primary malignant brain tumors in childhood and adults, respectively. Current therapies for medulloblastomas and gliomas include surgical resection, radiation and chemotherapy (Huse and Holland, 2010). Traditional histological classification defines three classes of human medulloblastoma that are associated with specific outcomes. Nodular/desmoplastic tumors (17%) with nodular accentuation of reticulin-free pale nodules/stromal reticulin have a more favorable outcome. Classic tumors (72%) have small and relatively uniform cells with nuclear molding, which tend to be associated with an intermediate outcome. Large cell/anaplastic tumors (LC/A) (11 %) with features of anaplasia; including large pleomorphic tumor cells with nuclear atypia, are often associated with poor prognosis (Ellison et al., 2011). Gliomas include ependymomas, astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas. The World Health Organization (WHO) classification divides glioma into four grades (I–IV) after malignancy. Grade I glioma, like pilocytic astrocytoma, is considered least malignant and is more prevalent in children or young adults. Within infiltrating gliomas the grading (II–IV) is based on histopathologic features of anaplasia including nuclear atypia, mitotic activity, microvascular proliferation and/or necrosis. The most malignant glioma, GBM (Table 1), can either present de-novo or arise from a lower-grade glioma (Louis et al., 2007). Advances in gene expression profiling have identified subgroups of human brain tumors that can be indistinguishable on histology but show distinct trancriptomal and/or genetic signatures (Figure 1). The transcriptomal signatures in tumors are associated with gene expression profiles reminiscent of NSCs or more differentiated progeny. Studies of GEM models support the notion that established brain tumors can be traced back to a defined precursor cell based on their gene expression profile (Chen et al., 2012; Gibson et al., 2010; Johnson et al., 2010; Schuller et al., 2008; Swartling et al., 2012).

Brain tumors that harbor stem cell-like tumor cells and display stemness signatures are found in highly malignant childhood and adult brain tumors of patients characterized by a poor prognosis (Ben-Porath et al., 2008; Clement et al., 2007; Hemmati et al., 2003; Laks et al., 2009; Singh et al., 2003). Subpopulations of these so-called BTSCs survive current therapies which is why considerable efforts aim to identify therapeutic approaches that also target these cells. Studies by Yamanaka et al. have elegantly demonstrated a small set of reprogramming genes that generate iPS cells from terminally differentiated somatic cells

(Takahashi and Yamanaka, 2006). Such reprogrammed iPS cells resemble embryonic stem cells and have implications for how we think about brain tumor heterogeneity. In fact iPS cells like embryonic stem cells are similar to cancer cells and form teratoma or sometimes even malignant teratocarcinoma (Okita et al., 2007; Shih et al., 2007) when injected in immunodeficient mice (Knoepfler, 2009).

In this review, we will discuss the signals and reprogramming networks that drive stemness in brain tumors. The clonal evolution model suggests that all tumor cells to some extent can sustain tumor growth. In contrast, the cancer stem cell model proposes that a stable hierarchy exists, where cancer stem cells undergo self-renewal and promote long-term tumor growth. We describe stemness as a fluid state in brain tumors that can be influenced by the tumor microenviroment or emerge from genetic alterations over time. Finally, we suggest that microRNAs (miRNAs), small non-coding RNAs that block translation or induce degradation of target mRNAs, function as switches that can modulate stemness in brain tumors.

Signals that drive cellular expansion in forebrain and hindbrain regions

Gradients of secreted molecules balance self-renewal and differentiation of embryonic NSCs and progenitors in a coordinated manner along rostrocaudal and dorsoventral axes during central nervous system (CNS) development. Radial glia and embryonic NSCs generate neurons, glial cells, and ependymal cells in temporal waves during neural development (Rakic, 1990). In the hindbrain, primary and secondary germinal zones give rise to defined neuronal populations in the cerebellum (Hatten and Heintz, 1995; Hoshino et al., 2005; Miale and Sidman, 1961). Postnatal NSC-derived neurogenesis was first restricted to the dentate gyrus of the subgranular zone and the subventricular zone (SVZ) lining the lateral ventricles (Curtis et al., 2007; Sanai et al., 2011). Recent studies suggest that NSCs may also be found lining the third and fourth ventricles (Weiss et al., 1996; Xu et al., 2005). Stemness has also been found in postnatal Bergmann glia in the cerebellum, another possible NSC population that can give rise to brain tumors (Koirala and Corfas, 2010; Sottile et al., 2006). While NSCs are rare, neuron-glial antigen 2 (NG2)-expressing oligodendrocyte progenitor cells (OPCs), also denoted polydendrocytes and synantocytes, constitute an abundant and widespread population of cycling cells in the adult rodent brain (Dawson et al., 2003; Nishiyama et al., 2009). In contrast to reduced numbers of NSCs, the population of OPCs may actually increase during life (Dawson et al., 2003; Shook et al., 2012). Coordinated activation of transcription factors drives networks that give regional patterning of NSCs and their progeny. This regional specification of NSCs and differentiated progeny continues into adulthood (Merkle et al., 2007; Robinson et al., 2012). Thus positional identity is an organizing principle underlying cellular subtype diversification in the brain and is controlled by a homeodomain transcriptional code (Hochstim et al., 2008). Below, we will review signals that expand neural precursors and brain tumors.

Interactions between growth factors and receptor tyrosine kinases lead to expansion of neural precursors during embryonic and adult phases. Fibroblast growth factor (FGF) signaling regulates patterning of both embryonic forebrain and hindbrain regions (Hebert and Fishell, 2008). In the telencephalic germinal zone, FGF2 promotes self-renewal of NSCs

in the anterior neural plate followed by emergence of epidermal growth factor (EGF)-responsive NSCs (Kilpatrick and Bartlett, 1995; Tropepe et al., 1999). Multipotent NSCs continue to respond to mitogenic EGF and FGF2 stimulation throughout adulthood (Gritti et al., 1999). The platelet-derived growth factor receptor α (PDGFRA) is expressed in the neural plate and allows NSCs to respond to platelet-derived growth factor-AA (PDGF-AA) (Forsberg-Nilsson et al., 1998). Later in development, PDGFA acts as a potent mitogen of OPCs expressing PDGFRA (Hall et al., 1996). It is controversial if postnatal SVZ NSCs express PDGFRA (Chojnacki et al., 2011; Jackson et al., 2006). Similar to embryonic development, SVZ NSC generate EGF-responsive NSCs and transitamplifying progenitors (TAPs) (Gonzalez-Perez et al., 2009). Infusion of FGF, PDGF-AA, or EGF into the ventricles and SVZ induce massive expansion of OLIG2+ cells (Gonzalez-Perez et al., 2009; Jackson et al., 2006; Kuhn et al., 1997), implicating a possible involvement of growth-factor signaling and NSCs in the development of gliomas.

A wealth of literature has demonstrated the roles of sonic hedgehog (SHH), wingless (WNT), and NOTCH signaling during expansive stages of brain development. A gradient of SHH is formed in a dorsal-ventral manner along the neural tube (Lee et al., 1997). SHH ligand binds to its receptors, patched homolog 1 (PTCH1) and smoothened homolog (SMO), and leads to the activation of GLI transcription factors that control normal brain growth and stem cell behavior during both embryonic and adult stages (Lai et al., 2003; Palma and Ruiz i Altaba, 2004). In the adult forebrain, SHH activation of SVZ NSCs produces specific neuronal progeny from dorsal and ventral regions (Ihrie et al., 2011). In the cerebellum, SHH is released by Purkinje neurons that act as a mitogen, stimulating granule neuron precursor (GNP) proliferation (Dahmane and Ruiz i Altaba, 1999; Wechsler-Reya and Scott, 1999). WNT proteins antagonize SHH and thereby regulate the dorso-ventral patterning of the neural tube (Alvarez-Medina et al., 2008). The WNT pathway maintains pluripotency in murine embryonic stem cells via paracrine and autocrine signaling (ten Berge et al., 2011) as well as controlling neuronal precursor cell fates (Chenn and Walsh, 2002). The WNT signals are divided into two different pathways: the canonical, or WNT/β-catenin, pathway is involved in cell-fate determination, whereas the non-canonical pathways are involved in the control of cell movement and tissue polarity (Katoh, 2007). Activation of β-catenin leads to amplification of the neural progenitor pool (Chenn and Walsh, 2002; Megason and McMahon, 2002). If stabilised β-catenin is overexpressed in transgenic mice, the brain is enlarged, and the neural precursor population is expanded (Chenn and Walsh, 2002). In adult forebrain, inhibition of WNT signaling abolished hippocampal neurogenesis (Lie et al., 2005). In the developing cerebellum, aberrant WNT signaling expands the stem cell pool and impairs differentiation (Pei et al., 2012a). The third pathway, NOTCH signaling, is known as a master regulator of NSCs and neural development (Louvi and Artavanis-Tsakonas, 2006; Yoon and Gaiano, 2005). NOTCH receptors are commonly activated by ligands expressed on neighboring cells. Activation of NOTCH receptors leads to cleavage of the NOTCH intracellular domain (NICD) by γ-secretase followed by induced expression of target genes such as (hairy and enhancer of split) Hes and Hes-related (HESR/HEY) family of basic helix-loop-helix (bHLH) transcription factors. NICD can also signal through a non-canonical pathway through protein-protein interactions and recombining binding protein suppressor of hairless (RBPJ)-independent gene activation (Sanalkumar et al., 2010).

NOTCH signaling has been suggested as an integral component that regulates maintenance of NSCs (Ables et al., 2011). The RNA-binding protein Musashi1 with expression restricted to NSCs and progenitor cells positively regulate NOTCH signaling through translational repression of numb mRNA (Imai et al., 2001; Kaneko et al., 2000). In the postnatal cerebellum, NOTCH2 expression prevents differentiation of GNPs and support continued proliferation (Fan et al., 2004; Solecki et al., 2001) while NOTCH1 is mainly expressed in postmitotic cells (Fan et al., 2004). In adult SVZ, activated, but not dormant, NSCs are regulated by NOTCH1 signaling (Basak et al., 2012; Chapouton et al., 2010; Mizutani et al., 2007).

Growth factors and SHH, NOTCH and WNT can all regulate MYC expression. There are three members of the MYC gene family (*MYC*, *MYCN* and *MYCL*). The role of MYC proteins, in particular MYCN, is essential for normal brain development (Knoepfler et al., 2002; Swartling, 2012). Using the Cre/Lox system, Knoepfler et al. (2002) demonstrated that loss of *Mycn* in Nestin+ embryonic neural precursors lead to a marked reduction in growth of the brain. The reduced size of the cerebellum was especially pronounced and is likely explained by the normally elevated MYCN expression in the rapidly proliferating cerebellar primordium. Strikingly, a further reduction of cerebellar granule neurons was found in *Myc* and *Mycn* double knockout mice (Wey et al., 2010). Together with myc-associated factor X (MAX), MYC can promote cell proliferation and maintain an undifferentiated state. However, this is normally disrupted by mitotic arrest deficient (MAD) which displaces MYC in the complex allowing formation of post-mitotic differentiated states. MYC belongs to a small family of reprogramming genes that cooperate to turn terminally differentiated cells into iPS cells (Takahashi and Yamanaka, 2006). In fact MYCN is able to replace MYC in inducing pluripotency (Park et al., 2008). In conclusion, multiple developmental pathways converge on transcriptional nodes that drive stemness and expansion of progeny.

Matching origin with transcriptomal profiles in childhood brain tumors

Genetic alterations in pathways that drive embryonic and perinatal expansion of neural precursors are found in human pediatric brain tumors, including medulloblastoma, pilocytic astrocytoma, and ependymoma. Design of GEM models based on these occurrences has advanced our current understanding of the developmental origins of brain tumors. The studies suggest that cooperation of genetic alterations and developmental programs determine the phenotype of the resulting brain tumor. In this section, we will review the cell of origin for human pediatric brain tumors based on data from current GEM models (Table 2). Furthermore, to understand the differential response of residual malignant ependymomas and medulloblastomas to therapy comparisons based on cross-species approaches of GEM models and profiling of human tumors have been highly informative.

The pathogenesis of the childhood tumor medulloblastoma implies an early embryonic initiating aberration in a number of important developmental genes. Gene expression profiling of human medulloblastoma has recently divided medulloblastoma into four molecularly distinct subgroups: WNT, SHH, Group 3 and Group 4 (Cho et al., 2011; Kool et al., 2008; Northcott et al., 2011; Northcott et al., 2012a; Taylor et al., 2012a; Thompson et

al., 2006). Reliable signature pathway markers have been identified for both WNT and SHH medulloblastoma (Kool et al., 2008; Northcott et al., 2012b). The profile of Group 3 is of a photoreceptor/gamma-aminobutyric acid-ergic nature, showing moderate to high expression of retina-specific transcription factors, while Group 4 has neuronal/glutamatergic characteristics with overexpression of neuronal differentiation markers as well as glutamate receptor members (Kool et al., 2008).

Medulloblastoma of the SHH subgroup most likely develop from committed GNPs of the cerebellum (Yang et al., 2008) while the origin of the WNT subgroup has instead been located to progenitor cells in the embryonic dorsal brainstem/lower rhombic lip (Gibson et al., 2010) (Figure 2). MYC and MYCN amplifications are common (10–15%) in medulloblastoma (Pfister et al., 2009). In a cohort of 292 pediatric medulloblastoma patients, amplification of MYC and MYCN were significantly associated with a poor prognosis (Ryan et al., 2012). Interestingly, while MYC protein amplifications are common in Group 3 medulloblastoma, MYCN is often found amplified in either SHH or Group 4 medulloblastoma (Taylor et al., 2012a). To elucidate the origin of Group 3 medulloblastoma, Pei et al. soreted cerebellar cells based on expression of the stem cell marker with dominant negative *TP53* (Pei et al. 2012a). Similarly, Kawauchi et al. introduced MYC to *TP53* null GNPs sorted using neuronal lineage marker MATH1 (Kawauchi et al., 2012). Both murine models succeeded in recapitulating the LC/A phenotype of Group 3 medulloblastoma. The MYC-driven medulloblastoma demonstrated expression profiles overlapping with embryonic NSCs as well as iPS cells, suggesting a NSC origin or possibly de-differentiation as a result of MYC transformation (Eberhart, 2012). The definite origin of MYCN-amplified Group 4 is unclear, but MYCN-driven medulloblastoma models like the GTML model (Swartling et al., 2010) might aid in this purpose. Here GLT1-positive cerebellar cells drive an equal amount of either classic or LC/A medulloblastoma that are SHH-independent and orthodenticle homeobox 2 (OTX2)-positive (Swartling et al., 2010; Swartling et al., 2012). When GFAP-positive postnatal NSCs from the cerebellum were transduced with stabilized MYCN, Group 4 medulloblastoma formed after orthotopic transplantation. Similarly, MYCN drives SHH medulloblastoma from GFAP+ embryonic cerebellar NSCs suggesting the timing of transformation with MYCN determines medulloblastoma subtype (Swartling et al., 2012).

Pilocytic astrocytomas (PAs) can occur supra- and infratentorially and each is associated with a unique gene expression signature (Sharma et al., 2007). Activating BRAF alterations/gene fusions are common in PAs (Pfister et al., 2008) resulting in an activated mitogen-activated protein kinase (MAPK) pathway (Jones et al., 2008). Such PAs have been modeled in mice where a mutated active form (V600E) of *BRAF* is introduced into Nestin-expressing cells using the RCAS/tv-a system (Gronych et al., 2011). Children with the neurofibromatosis type 1 (*NF1*) tumor predisposition syndrome are prone to the development of *NF1*-associated optic or hypothalamic PAs (Listernick et al., 1995). The transcriptomal profile of *NF1*-associated tumors can be distinguished from other PAs (Sharma et al., 2007). Lee da et al., (Lee da et al., 2012) demonstrated that PAs arise from third ventricle NSCs, but not from lateral ventricle NSCs, after *NF1* loss in a GEM model.

Lee et al also found that activating *BRAF* mutation specifically increased proliferation of third ventricle NSCs (Lee da et al., 2012).

Infiltrating gliomas localized to the brainstem account for 10–15% of childhood brain tumors. Interestingly, tumors centered in the dorsal pons, midbrain, or medulla show a more favorable prognosis than those located in the ventral pons which are highly aggressive and termed diffuse intrinsic pontine gliomas (DIPGs). A wave of nestin expressing cells in the medulla and ventral pons peaks at 6 years of age in humans, a time that coincides with the incidence for DIPGs (Monje et al., 2011). Approximately half of the Nestin positive cells also express oligodendrocyte transcription factor 2 (OLIG2), a bHLH factor expressed in progenitor cells. Using GEM models, Monje et al. showed that SHH-responding OLIG2+ cells in the ventral pons expand at a time that corresponds to the peak of nestin-expressing cells in human pons and medulla. In human DIPG cultures, a subpopulation of NSC-like tumor cells displays a marker profile that corresponds to the suggested cell of origin. Improved GEM models of DIPG should help to discern if NSCs or OLIG2 expressing progenitors can give rise to this disease.

Recent studies suggest that mutations in the histone H3- alpha-thalassemia X-linked mental retardation protein (ATRX)- death domain associated protein (DAXX) chromatin remodeling pathway frequently occur in both pediatric and adult gliomas (Schwartzentruber et al., 2012; Sturm et al., 2012). Almost half of the studied pediatric GBMs displayed mutations in this chromatin remodeling pathway (Schwartzentruber et al., 2012). Histone H3 mutations was found in 78% of DIPGs and 22% of non-brainstem pediatric GBMs (Wu et al., 2012). Modeling of histone H3 mutations in murine GEM models will help to define the origin for these pediatric gliomas. Interestingly, *IDH1* and *H3F3A-ATRX-DAXX* mutations seem to be mutually exclusive in both pediatric and adult gliomas, which can be further divided into several subgroups using *IDH1* and *H3F3A* mutation status and global DNA methylation patterns (Schwartzentruber et al., 2012; Sturm et al., 2012). In medulloblastoma, distinct subclasses show amplification and inactivating mutations in regulators of histone H3 methylation (Northcott et al., 2009b; Robinson et al., 2012). Inactivating mutations of the histone-lysine N-methyltransferase genes *MLL2* and *MLL3* in 16% of medulloblastoma underscore the important role of histone methylation in human brain tumorigenesis (Parsons et al., 2011). Future studies will be required to dissect how alterations in the chromatin machinery contribute to malignant transformation.

Ependymomas are gliomas with evidence of ependymal differentiation, associated with the ventricular wall along the cerebrospinal axis (Louis et al., 2007). Both the layer of ependymal cells lining the ventricle wall and the intermixed SVZ NSCs are derived from radial glial cells (Merkle et al., 2004). Radial glia-like cancer stem cells were shown to propagate tumor growth of intracranial and spinal ependymomas (Taylor et al., 2005). Using a genomic cross-species approach, Johnson et al. matched the transcriptomal profile of human ependymoma samples with temporally and regionally defined NSCs (Johnson et al., 2010). Subsequent experiments demonstrated that radial glia isolated from the cerebrum of embryonic day 14.5 represents a likely source for supratentorial ependymomas.

Stemness reflects the origin or is acquired by the surrounding niche in adult gliomas

Molecular profiling of human high-grade astrocytoms lead to definition of proneural, proliferative, and mesenchymal astrocytomas that were associated with genetic alterations, pathway activation, and profiles analogous to NSCs and progenitors (Phillips et al., 2006). A more recent gene expression study classified GBMs into proneural, neural, classical, and mesenchymal subgroups that were highly associated with somatic mutations and copy number changes (Verhaak et al., 2010). Proneural gliomas express progenitor-associated genes whereas classical and mesenchymal tumors display stem cell signatures. GEM models have been an invaluable tool to study how genetic alterations drive gliomagenesis in a cell-context manner to shape the resulting gliomas.

Loss of *TP53* alone is not sufficient to transform SVZ NSCs but will induce pleiotropic accumulation of cooperative oncogenic alterations that promote gliomagenesis (Gil-Perotin et al., 2006; Wang et al., 2009). Instead, combinations of *TP53*, phosphatase and tensin homolog *(PTEN)*, and *NF1* loss in NSCs generate gliomas whereas initial *Rb* loss leads to production of a primitive neuroectodermal neoplasm (PNET) phenotype (Alcantara Llaguno et al., 2009; Jacques et al., 2010; Zheng et al., 2008; Zhu et al., 2005). In patients, PNETs occur more frequently in hereditary retinoblastoma patients (Pacal and Bremner, 2006). Furthermore, patients diagnosed with supratentorial PNETs commonly show amplifications of cell cycle regulatory genes suggesting that the retinoblastoma-cyclin axis may be particularly important in this group of tumors. Introduction of activated MYCN into SVZ NSCs produce glioma-like tumors with PNET-like features (Swartling et al., 2012). Similarly, PNETs have been induced using amplification of *MYC* in combination with β-catenin or together with *TP53* loss (Momota et al., 2008). Interestingly, amplification of *MYC* is common in human CNS PNETs (Behdad and Perry, 2010). In conclusion, these studies suggest different combinations of transforming events in NSCs produce PNETs and gliomas, respectively.

A lentiviral approach using a combination of oncogenic K-RAS^{G12D} and AKT1 showed that SVZ NSCs are more easily transformed into glioma cells than differentiated astrocytes (Jacques et al., 2010; Marumoto et al., 2009) (Figure 2). Another study found that activated K-RAS^{G12D} and loss of *TP53* resulted in transformation of both SVZ NSCs and cortical astrocytes (Ghazi et al., 2012). Interestingly, cortical astrocytes gave rise to more aggressive GBM-like tumors displaying a mesenchymal phenotype. Surprisingly, NSC-derived tumors displayed progenitor-like markers while astrocyted-derived tumors displayed proteins commonly expressed in NSCs. In another model, combined overexpression of *BMI1 polycomb ring finger oncogene (BMI1)* and *Ink4/Arf* loss in primary astrocytes produced more malignant tumors compared to NSC counterparts. These studies suggest that *TP53* loss (in contrast to AKT1) dedifferentiate mature astrocytes and allow oncogenic K-RAS^{G12D} to generate gliomas displaying a high degree of stemness. In addition to NSCs and astrocytes, a recent study suggests that even neurons can give rise to malignant gliomas when transduced by oncogenic lentiviral vectors (including K RAS^{G12D}) (Friedmann-Morvinski et al., 2012).

As will be discussed below, it exemplifies how reprogramming of a non-stem cell origin can produce stem-like brain tumors.

As the largest population of cycling cells in the postnatal brain, OPCs represent a likely source of brain tumors. A transgenic mouse model, an RCAS/TVA model, and a mosaic analysis with double markers (MADM)-system based on different oncogenic drivers demonstrated that OPCs give rise to the proneural oligodendrogliomas (Lindberg et al., 2009; Liu et al., 2011; Persson et al., 2010). Proneural human GBMs commonly display *TP53* mutations, $IDH1^{R132H}$ mutations, *PDGFRA* amplifications, and *H3F3A* (Histone H3) mutations (Sturm et al., 2012; Verhaak et al., 2010). Interestingly, GBMs displaying *H3F3A* mutations were mutually exclusive with $IDH1^{R132H}$ mutations, showed distinct global methylation patterns, and were found in separate anatomic compartments (Sturm et al., 2012). In contrast, classical GBM are characterized by amplification of *EGFR* and *EGFRvIII* mutations, and many mesenchymal GBMs are associated with mutations and copy number loss of *NF1*. Profiling of grade II–III infiltrating gliomas demonstrated that most oligodendrogliomas and the majority of astrocytomas display a proneural signature (Cooper et al., 2010). Considering that the majority of infiltrating gliomas and commonly secondary GBMs display $IDH1^{R132H}$ mutations, the molecular evolution of human GBMs displaying wild-type or mutant $IDH1^{R132H}$ may result from largely nonoverlapping sets of molecular events in separate cell types of origin (Lai et al., 2011). Proneural grade II–IV gliomas that display a CpG island methylator phenotype are linked to $IDH1^{R132H}$ somatic mutations (Noushmehr et al., 2010; Turcan et al., 2012). As for the $IDH1^{R132H}$ mutant GBMs, methylation status can influence the tumor phenotype. Hypermethylation of the CpG island for the transcriptional coactivator with PDZ-binding motif (TAZ) ensure low levels in proneural GBMs (Bhat et al., 2011). Modulation of TAZ expression allowed GBM stem cells to toggle between a proneural and mesenchymal phenotype. Is it then possible that therapy-induced changes in the tumor microenviroment can promote epigenetic changes that influence the phenotype? Of interest, proneural GBMs tend to shift to a mesenchymal subclass upon recurrence (Phillips et al., 2006). Recurrent GBMs that received radiotherapy display approximately 10-fold increased levels of tumor-associated macrophages (TAMs) (Kioi et al., 2010). Radio-resistant GBM stem cells produce cytokines known to polarize TAMs to a tumor-promoting phenotype (Bao et al., 2006; Wu et al., 2010). Is it possible that TAM-produced cytokines can drive a mesenchymal phenotype considering that microglia/macrophage number and microglia/macrophage-related gene expression are highest in the mesenchymal GBM subtype (Engler et al., 2012). A mesenchymal GBM phenotype can also be promoted by hepatocyte growth factor (HGF)-dependent MET activity (De Bacco et al., 2012; Li et al., 2011). An elegant study by Lu et al. demonstrates that anti-angiogenic therapy lead to highly invasive tumors through increased phosphorylation of C-MET in a hypoxia-independent manner (Lu et al., 2012). Finally, necrosis in GBMs was found to promote a mesenchymal phenotype, including upregulation of signal transducer and activator of transcription 3 (STAT3) and CCAAT-enhancer-binding protein β (C/EBPβ), in a hypoxia-dependent manner (Cooper et al., 2012). Ectopic co-expression of these two factors reprograms NSCs towards a mesenchymal phenotype, while elimination leads to collapse of the mesenchymal signature in GBMs (Carro et al., 2010). These studies exemplify how a

brain tumor phenotype can be regulated by factors in the tumor microenvironment and not solely by genetic alterations.

Reprogramming networks drive stem cell-ness in brain tumors

Stemness reflects a state rather than a physical entity. The epigenetic and gene expression profiles of many cancers show significant overlap with embryonic stem cells, suggesting that similar transcriptional networks are active in both stem cells and cancer cells (Easwaran et al., 2012). MYC has been defined as one major player that account for the similar transcription programs in embryonic stem and cancer cells (Ben-Porath et al., 2008; Kim et al., 2010; Widschwendter et al., 2007). To reprogram differentiated somatic cells iPS cells, Yamanaka and colleagues identified combinations of a small set of genes (OCT4, SOX2, NANOG, C-MYC, KLF4, Lin28), previously known to maintain pluripotency and self-renewal in both human and murine embryonic stem cells (Takahashi and Yamanaka, 2006). These factors are highly expressed in stem cell-like cancer cells (e.g. cancer stem cells), suggesting that cancer stem cells derive from normal stem cells or alternatively more differentiated cells reprogrammed by genetic aberrations or environmental cues.

Stemness in brain tumors is correlated with poor prognosis. The tumor suppressor genes *TP53* and *Ink4/Arf*, frequently deleted or mutated in gliomas, function as barriers for somatic cell reprogramming (Choi et al., 2011; Marion et al., 2009). In murine and human fibroblasts, *Arf* and *Ink4a*, respectively, play dominant roles as the main barriers to reprogramming by activation of TP53 and p21 / WAF1 (Li et al., 2009a). Such species-specific differences may be evident for other reprogramming factors. *PTEN* is a tumor suppressor that negative regulates phosphatidylinositide 3-kinase (PI3K)-Akt signaling in high-grade gliomas. *PTEN* knockdown induces the levels of reprogramming genes OCT4 and NANOG (Alva et al., 2011). Amplification of RTKs (*MET, EGFR, PDGFRA*) drive self-renewal, stemness, and tumor growth in human GBMs. For mesenchymal GBMs, c-MET activation was found to induce the expression of reprogramming genes and promote stemness in human GBMs (Li et al., 2011), an effect that could be reversed by NANOG blockade. Unfortunately, the authors did not investigate if c-MET-induced activation of MEK-ERK, PI3K-AKT, and STAT3 signaling pathways alone, or in combination, contributes to stemness and upregulation of reprogramming genes. STAT3 has been shown to mediate stemness and tumorigenicity down-stream of the nonreceptor tyrosine kinase BMX, PDGFRB, and the erythropoietin receptor (Guryanova et al., 2011; Kim et al., 2012). Less is known about the link between stemness and MEK-ERK/PI3K-AKT signaling. Blockade of EGFR reduced tumorigenesis and induced robust differentiation of human GBMs (Mazzoleni et al., 2010). On the other hand, *PDGFRA* amplification is characteristic in a subset of proneural GBMs that display an OPC rather than NSC signature. Intra-tumoral variation of *EGFR*, *MET*, and *PDGFRA* amplifications in GBM makes it more difficult to discern the contribution of individual RTKs to stemness (Little et al., 2012; Snuderl et al., 2011; Szerlip et al., 2012). These studies illustrate that genetic changes in glioma may contribute to stemness and reprogramming genes in stem cell-like tumor cells.

The SHH-Gli signaling pathway promotes an embryonic stem cell-like signature in both GBM and medulloblastoma (Wang et al., 2012; Zbinden et al., 2010). GLI1 was shown to

bind to the BMI1 promoter, a member of the Polycomb group (PcG) genes that partly regulate stemness by repressing the levels of Ink4a/Arf (Valk-Lingbeek et al., 2004). SHH-GLI signaling also regulates stemness in cerebellar NSCs through expression of NANOG in cerebellar NSCs (Po et al., 2010). A MYC network was suggested to account for similarities between embryonic stem and cancer cell transcription programs (Kim et al., 2010). Amplified *MYC* and *MYCN* in Group 3 and Group 4 medulloblastoma can directly contribute to stemness (Taylor et al., 2012a). *MYC* amplification can initiate medulloblastoma formation in combination with *TP53* loss and stabilizing mutations of MYC^{T58A} or aberrant expression of the repressor element-1 silencing transcription factor/neuron-restrictive silencer factor (REST/NRSF) (Pei et al., 2012b; Su et al., 2006). These studies suggest that induction of multiple reprogramming genes is necessary for medulloblastoma formation. In human GBMs, *MYC* was identified as a major down-stream target gene of the enhancer of zeste homologue 2 (EZH2), shown to be essential for stemness and tumorigenicity (Suva et al., 2009). Nucleostemin, a transcriptional target of MYC, is expressed in BTSCs and can substitute for MYC as a reprogramming factor in embryonic stem cells (Qu and Bishop, 2012). MYC can also be activated through WNT/β-catenin signaling (Hoffmeyer et al., 2012). Hoffmeyer et al., found that WNT/β-catenin signaling can also regulate telomerase activity in stem cells and cancer cells through the interaction with KLF4, a core component of the pluripotency transcriptional network. In the developing cerebellum, WNT signaling increased self-renewal and impaired differentiation through regulation of MYC, BMPs and the CDK inhibitor p21 (Pei et al., 2012a). In conclusion, many pathways converge on MYC that is contributing, but not sufficient, to drive stemness in brain tumors.

Stemness in brain tumor cells can also be induced by changes in the tumor microenviroment (Figure 2). A hypoxic environment was found to promote stem cell-ness in cultured human primary GBM cells (Li et al., 2009c). Hypoxia inducible factor 2 alpha (HIF2-alpha) was found to increase the levels of reprogramming genes (OCT4, NANOG, and C-MYC) and induced a stem cell phenotype in human GBM cells (Heddleston et al., 2009). In GBM patients, CD133+ cells were enriched in the inner core of the tumor mass compared to peripheral and neovascularised areas (Pistollato et al., 2010). Importantly, tumor cells expressing the stem cell marker CD133 also displayed higher levels of MGMT genes, implicating increased chemoresistance to the alkylating agent temozolomide. An acidic environment has been found in brain tumors (Vaupel et al., 1989). A recent study showed that HIF2α also mediates acidic stress-induced regulation of the reprogramming genes OCT4 and NANOG (Hjelmeland et al., 2011). In summary, genetic changes, activation of SHH and WNT signaling, or altered tumor microenviroment can all drive reprogramming networks and promote stemness in human brain tumors.

MiRNAs as regulators of stemness in brain tumors

Given that stemness correlates with aggressive behavior of brain tumors, it is important to identify signaling effectors that mediate stemness from intrinsic and microenviromental cues (Li et al., 2009c). Recent studies demonstrate an important role for miRNAs in regulating stem cell self-renewal and differentiation by repressing the translation of selected mRNAs in stem cells and differentiated daughter cells (Fineberg et al., 2009; Gangaraju and Lin, 2009).

REST/NRSF together with the corepressor for REST (coREST), have been shown to coordinate neural induction and neuronal differentiation programs during brain development (Abrajano et al., 2010; Ballas et al., 2005; Soldati et al., 2012). In brain tumors, overexpression of REST in medulloblastoma and glioblastoma promotes stemness and is associated with poor prognosis in patients (Conti et al., 2012; Fuller et al., 2005; Taylor et al., 2012b). REST can directly interact with cis elements upstream of the miR-21 gene, a repressor of NANOG, OCT4, and SOX2 (Singh et al., 2008). MiR-21 is highly expressed in human GBMs and recognized as an oncogene in glioblastoma (Chan et al., 2005) and cooperates with growth factors like PDGF to drive SOX2 expression in normal developing brain and in human glioblastoma (Polajeva et al., 2012). Enforced expression of the bHLH factor inhibitor of differentiation 4 (ID4) in *Ink4a/Arf* null NSCs drives gliomagenesis in a murine glioma model (Jeon et al., 2008). ID4 was found to repress miR-9 expression that results in reduced chemoresistance and stemness in human glioblastoma cells (Jeon et al., 2011). Jeon et al. found that reduced miR-9 levels promoted SOX2 expression in human glioblastoma cells. Interestingly, SOX2 expression increases transcription of nuclear receptor tailess (TLX, also known as NR2E1) in adult NSCs (Shimozaki et al., 2012). As a direct target of miR-9, enforced expression of TLX in SVZ NSCs resulted in glioma formation (Liu et al., 2010; Zhao et al., 2009). TLX is also a target of miR-137, a miRNA that is depleted in human glioblastoma, and when expressed, induced differentiation of GBM cells into a neuronal phenotype (Silber et al., 2008). In this publication, we found that introduction of miR-124a also promotes neuronal differentiation of human GBM cells. In the normal brain, the levels of miR-124a increase as adult SVZ NSCs differentiate into mature neurons (Cheng et al., 2009). Cheng et al. suggest that miR-124a directly targets SOX9, a gene that is required for maintenance of stemness and blocks neurogenesis in adult SVZ NSCs (Scott et al., 2010).

For induction of iPS cells, cooperative actions of miR-34a and the cyclin-dependent kinase inhibitor p21 were found to regulate somatic reprogramming downstream of TP53 (Choi et al., 2011). MiR-34a cooperated with miR-34b and c to repress Nanog, SOX2, and MYCN. In human ES cells, low expression of deacetylated and inactive TP53 activates miR-34a and miR-145, which in turn repress reprogramming factors (Jain et al., 2012). In murine E14 NSCs, miR-34a expression induces neuronal differentiation and neurite elongation (Aranha et al., 2011). In another study, miR-34a levels were further down-regulated in *TP53* mutant GBMs, and when introduced, down-regulated NOTCH1/2 signaling and MET activity, leading to suppressed stemness in human GBM (Guessous et al., 2010). In addition to GBMs, miR-34a down-regulated MET activities in human medulloblastoma cells (Li et al., 2009b). MicroRNA-34a induces apoptosis, G2 arrest, and senescence in medulloblastoma and renders these cells more sensitive to chemotherapeutic agents in part via the oncogenic MAGE-A gene family and TP53 (Weeraratne et al., 2011). In a GEM model (*Ptch1+/−:TP53−/−*) of medulloblastoma, transduction of miR-34a into tumor spheres reduced expression of the NOTCH ligand Delta-like 1 (Dll1) and other targets, leading to a reduced stem cell-like phenotype and induction of neuronal differentiation (de Antonellis et al., 2011). MicroRNA-199b-5p also impairs NOTCH pathway through negative regulation of HES1 in medulloblastoma initiating cells (Garzia et al., 2009). MiR-199b-5p over-

expression blocks expression of several stem-cell genes and decreases the population of CD133-positive medulloblastoma cells.

Through different mechanisms, all four transcriptional subgroups of medulloblastoma display aberrant expression of the miR-17/92 cluster (Fernandez et al., 2009). Aberrant expression of miR-17-92 in primary cerebellar granule precursors is not sufficient to induce medulloblastoma formation, but rather cooperate with SHH signaling to drive their expansion (Northcott et al., 2009a; Uziel et al., 2009). Other miRs important for the SHH pathway are miR-125b and miR-326 that suppresses SMO and miR-324-5p, which targets the downstream transcription factor GLI1 (Ferretti et al., 2008). Finally, miRNAs can also be regulated indirectly by drug treatment. For example, a lovastatin-regulated miRNA, miR-33, represses human MYC expression in miR-33 positive medulloblastoma cells (Takwi et al., 2012).

So-called “onco-miRs” have been found to regulate expression of tumor suppressor genes and oncogenes in cancers (for a review of “onco-miRs” and glioma see (Gonzalez-Gomez et al., 2011)). Future studies are needed that reveal how genetic alterations in turn regulate miRNAs that modulate self-renewal and differentiation in brain tumors. In conclusion, changes in the tumor microenvironment and genetic alterations regulate miRNA levels in a cell-context dependent manner that promotes expression of reprogramming genes and stemness in malignant brain tumors (Figure 3).

Conclusions

To effectively understand the susceptibility of neural precursor populations to generate brain tumors, important driver mutations needs to be defined and passenger mutations needs to be sorted out. Large scale whole genome sequencing and gene expression analyses of glioma samples have offered better genetic details; including frequencies of amplifications of known cancer genes like the *EGFR, PDGFRA* or *PIK3CA/PIK3R1* but also identified novel cancer gene alterations in the *IDH1/2*, in CIC (homolog of the Drosophila gene *capicua*) as well as mutations in the far-upstream element (FUSE) binding protein, *FUBP1* (Bettegowda et al., 2011; Parsons et al., 2008; Verhaak et al., 2010). Similar recent large-scale efforts in medulloblastoma found for instance inactivating mutations of the histone-lysine N-methyltransferase genes *MLL2* or *MLL3*, regulators of H3K27 and H3K4 trimethylation like *KDM6A* and *ZMYM3* and mutations in the RNA helicase gene *DDX3X* (Jones et al., 2012; Parsons et al., 2011; Pugh et al., 2012; Robinson et al., 2012). Such novel candidate genes should be carefully studied in sophisticated GEM models to understand if they are drivers or passengers in brain tumors.

Even though GEM models have been extremely valuable to understand the etiology of brain tumors, cell transformation differences between humans and rodents suggest that more studies should probe the ability to transform isolated human brain precursor cells (Rangarajan et al., 2004; Rangarajan and Weinberg, 2003). Studies by Kriegstein *et al.* highlight differences between mouse and human cortical development, including species-specific precursor populations that can serve as the cell of origin for human brain tumors (Hansen et al., 2010; Lamonica et al., 2012). Comparisons of the transcriptional profiles of

murine and human OPCs reveal significant differences between fetal and human counterparts, as well as between rodent and human OPCs (Sim et al., 2009). These cellular differences and the disparity in developmental timing between human and mouse brains needs to be clarified in order to fully understand brain tumor development mechanisms.

In this review, we have discussed the signals and reprogramming networks that drive stemness in brain tumors. We argue that BTSCs and stemness in brain tumors can reflect a NSC origin but also be induced in restricted progenitors and differentiated glial cells. The traditional clonal evolution model suggests that all tumor cells are equivalent and can sustain tumor growth. In contrast, the cancer stem cell model proposes that a stable hierarchy exists, where only cancer stem cells undergo self-renewal and promote long-term tumor growth. We envision stemness as a fluid state in brain tumors that can be influenced by the tumor microenviroment, and emerge from genetic alterations over time. Is stemness then a driver or a passenger state in brain tumorigenesis and progression? If brain tumor stemness is a driver and needs to be controlled we suggest that modulation of miRNAs and blockade of HIF induction could function as excellent switches to reverse stemness and obstruct brain tumor progression.

Acknowledgments

Supported by research grants to AIP from the TDC Foundation, the American Cancer Society, and NIH/U54CA163155-01, to FJS from the Swedish Childhood Cancer Foundation, the Swedish Cancer Society, the Swedish Research Council, the Swedish Society of Medicine, Hjärnfonden, Åke Wibergs stiftelse, Lions Cancerforskningsfond, Stiftelsen Lars Hiertas Minne and the Association for International Cancer Research, and to JJP from the NIH (K08NS063456 and 1R01 NS081117-01).

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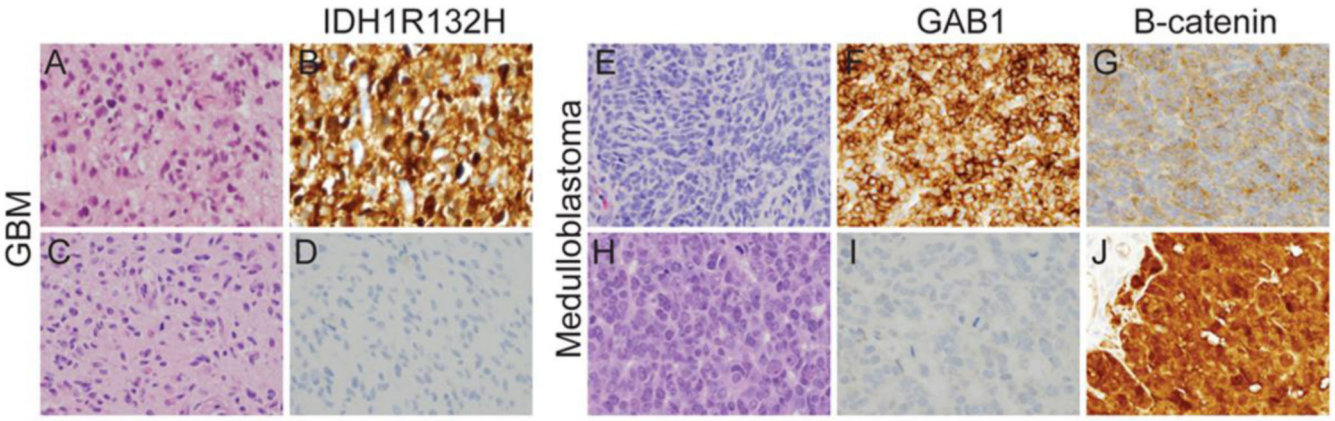

Figure 1. Molecular heterogeneity in GBM and medulloblastoma

Representative H&E stained sections of GBM from two different patients demonstrate similar histologic features **(A,C)** despite distinct molecular profiles. Tumor in **(A)** is $IDH1^{R132H}$ mutant **(B)** while tumor in **(C)** is negative for the mutation **(D)** based on immunoreactivity with an antibody directed against the R132H epitope (H09). In addition, tumor in **(A)** is negative and tumor in **(B)** is positive for amplification of EGFR by FISH (data not shown). H&E stained sections of medulloblastoma can also appear similar on H&E **(E,H)** despite prominent molecular differences. Tumor in **(E)** has upregulation of GAB1 **(F)** suggesting activity of the SHH signaling pathway and the tumor in **(H)** exhibits prominent nuclear immunoreactivity for B-catenin **(J)** suggesting activation of the WNT signaling pathway. Magnification 400×.

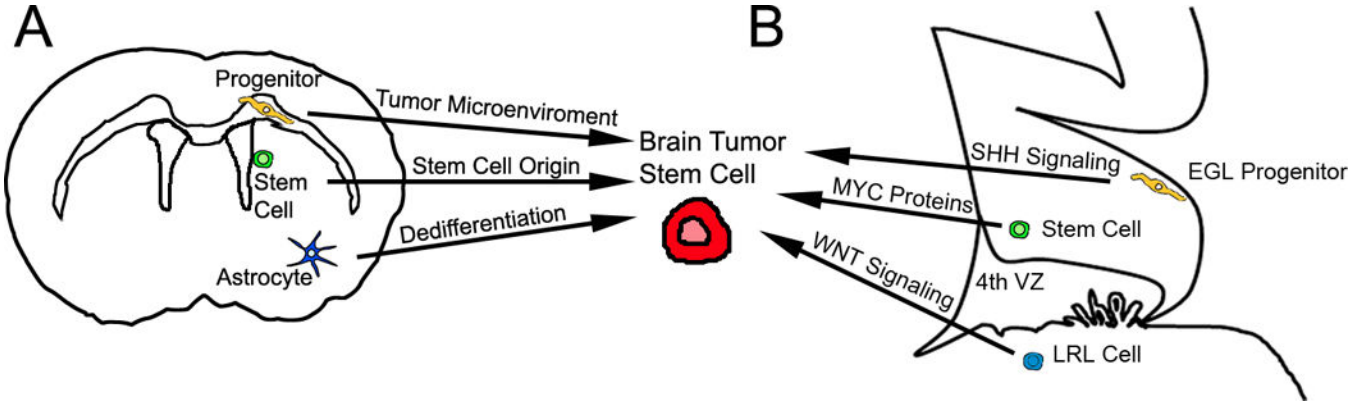

Figure 2. Different origins for stemness in brain tumors

(A) Gliomas originating from a non-stem cell (progenitor or more differentiated cell) may acquire stemness from exposure to the surrounding microenviroment during tumor progression or after relapse. Secondly, stemness in gliomas can also be derived from a NSC origin. Finally, stemness in gliomas can result from genetic alterations that can reprogram more differentiated neural cells into stem-like tumor cells. **(B)** Recent studies suggest that SHH signaling in an EGL precursor, amplification or overexpression of MYC proteins (like MYC and MYCN) from cerebellar stem cells, or aberrant WNT signaling in precursors located in the LRL, are possible origins for stem cell-like medulloblastoma cells. The schematic figure depicts views of cerebrum and cerebellum of an adult and embryonic (E16) mouse brain, respectively. EGL: external granule layer. LRL: lower rhombic lip.

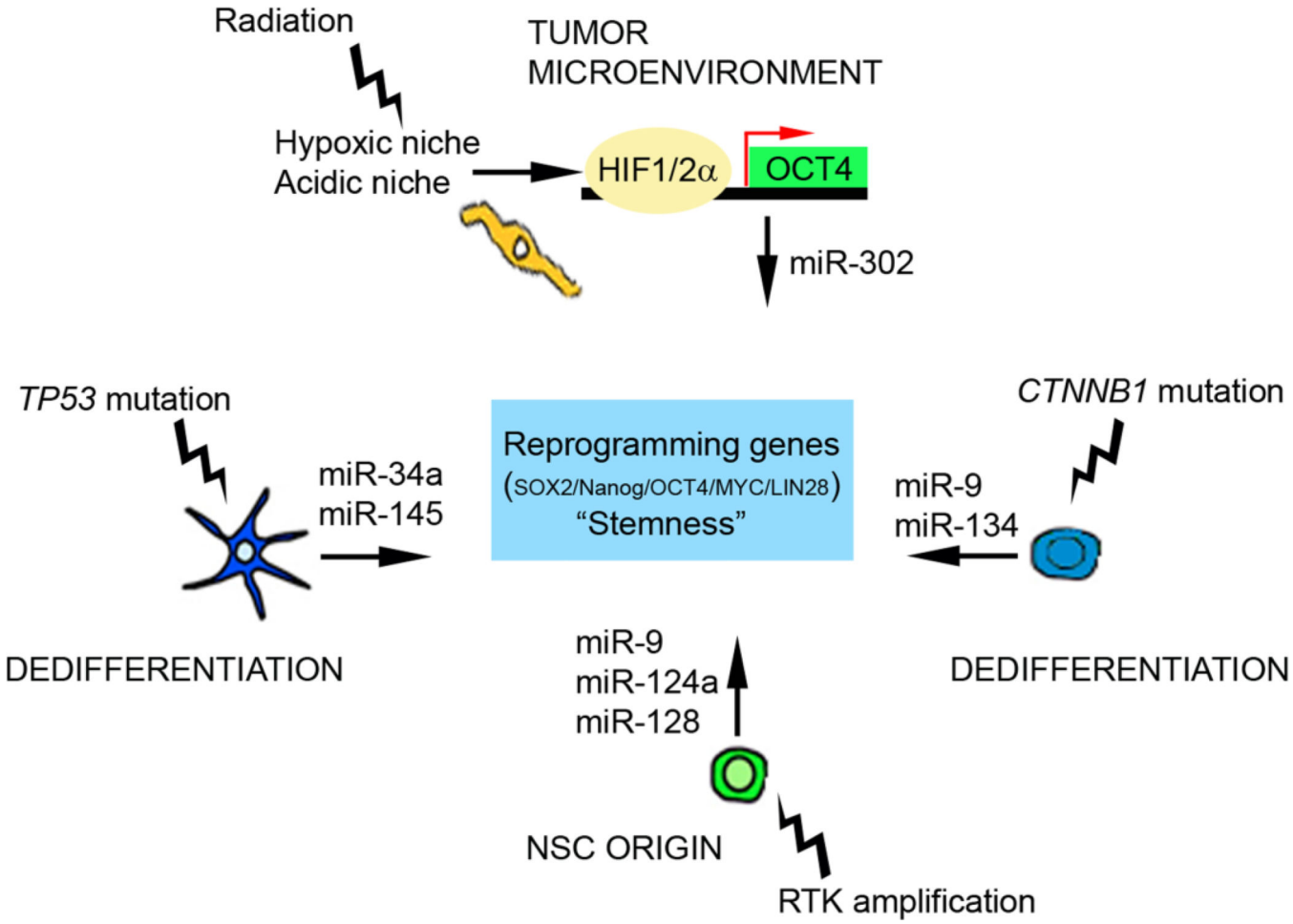

Figure 3. MiRNAs as mediators of reprogramming and stemness in brain tumors

P53 mutations in brain tumors can drive stemness in tumor cells by down-regulating miR-34a and miR-145. Tumor microenviroment can drive stemness in heavily treated brain tumors displaying an hypoxic niche, by induction of reprogramming genes such as OCT4 reduced levels of miR-302. We propose that activating genetic alterations in the RAS pathway of NSCs produce reduced levels of miRNAs that promote self-renewal and stemness. To exemplify how a dedifferentiated cell might promote a stem cell-like tumor phenotype, *CTNNB1* mutations (β-catenin) reduce levels of miR-9 and miR-134.

Table 1

Abbreviations.

ABBREVIATION	WORD
ATRX	**alpha thalassemia/mental retardation syndrome X-linked**
bHLH	Basic helix-loop-helix
BMI1	BMI1 polycomb ring finger oncogene
BTSC	Brain tumor stem cell
C/EBPβ	CCAAT-enhancer-binding protein β
CIC	Homolog of the Drosophila gene *capicua*
CNS	Central nervous system
CTNNB1	β-catenin
DAXX	Death domain associated protein
DIPG	Diffuse intrinsic pontine glioma
EGF	Epidermal growth factor
EZH2	Enhancer of zeste homologue 2
FGF	Fibroblast growth factor
GBM	Glioblastoma
GEM	Genetically-engineered mouse
GNP	Granule neuron precursor
HES	Hairy and enhancer of split
HGF	Hepatocyte growth factor
HIF2α	Hypoxia inducible factor 2α
ID4	Inhibitor of differentiation 4
IDH1/2	Isocitrate dehydrogenase 1/2
iPS	Induced pluripotent stem
MAD	Mitotic arrest deficient
MADM	Mosaic analysis with double marker
MAPK	Mitogen-activated protein kinase
MAX	Myc-associated factor X
MGMT	Methylated-DNA-protein-cysteine methyltransferase
MLL	**Myeloid/lymphoid or mixed-lineage leukemia**
NF1	Neurofibromatosis type 1
NG2	Neuron-glial antigen 2
NSC	Neural stem cell
OLIG	Oligodendrocyte transcription factor
OPC	Oligodendrocyte progenitor cell
OTX2	Orthodenticle homeobox 2
PA	Pilocytic astrocytoma
PDGFRA	Platelet-derived growth factor α
PI3K	Phosphatidylinositide 3-kinase

ABBREVIATION	WORD
PTCH1	Patched homolog 1 or rather: **Patched 1**
PTEN	Phosphatase and tensin homolog
REST/NRSF	Repressor element-1 silencing transcription factor/neuron-restrictive silencer factor
SHH	Sonic Hedgehog
SMO	Smoothened homolog or rather: **Smoothened, frizzled family receptor**
SOX	SRY-related HMG box
STAT3	Signal transducer and activator of transcription 3
SVZ	Subventricular zone
TAM	Tumor-associated macrophage
TAPs	Transit-amplifying progenitors
TAZ	Transcriptional coactivator with PDZ-binding motif
TLX	Transcription of nuclear receptor tailess
WNT	Wingless or rather: **Wingless-type MMTV integration site**

Table 2

Examples of selected Murine brain tumor models with defined cells of tumor origin.

Brain Tumor Type	GEM Model	Cell of Origin	Reference
Astrocytoma/GBM	*K-RASG12D:AKT1*	Astrocyte/Neuron/NSC	(Friedmann-Morvinski, et al., 2012)
Astrocytoma/GBM	Nestin-ΔTK	Stem Cell	(Chen, et al., 2012)
Astrocytoma/GBM	*Ink4a/Arf−/−*, EGFR+	Astrocyte	(Bachoo, et al., 2002)
Astrocytoma/GBM	*Nf1; Trp53*+/−	Astrocyte (GFAP+)	(Reilly, et al., 2000, Zhu, et al., 2005)
Oligodendroglioma	S100b-*verbB*	OPC	Weiss et al. (2003), Persson et al. (2010)
Oligodendroglioma	RCAS-*PDGFB*/CNP-TVA	OPC	(Lindberg, et al., 2009)
Oligodendroglioma	MADM-*Nf1;Trp53 mut*	OPC	(Liu, et al., 2011)
PNET	*Rb;Trp53*$^{\text{LoxP/LoxP}}$	Stem Cell (GFAP+)	(Jacques, et al., 2010)
Ependymoma	*Ink4a/Arf−/−*, *EphB2*+	Radial Glia (BLBP+)	(Johnson, et al., 2010)
DIPG	Olig2-*SmoM2*	Brain Stem Progenitor	(Monje, et al., 2011)
Medulloblastoma (WNT)	*Ctnnb1*$^{lox(ex3)}$, *Trp53*$^{flx/flx}$	Brain Stem Precursor (BLBP+)	(Gibson, et al., 2010)
Medulloblastoma (SHH)	*Ptch* loss	EGL Progenitor / Cerebellar Stem Cell	(Goodrich, et al., 1997, Yang, et al., 2008)
Medulloblastoma (SHH)	ND2-*SmoA* or *SmoM2*	EGL Progenitor / Rhombic Lip Progenitor	(Hallahan, et al., 2004, Mao, et al., 2006, Schuller, et al., 2008)
Medulloblastoma (SHH)	Retroviral *Shh in utero* or RCAS-*Shh*/Nestin-TVA	Embryonic Cerebellar Cell or Nestin+ Cerebellar Cell	(Rao, et al., 2003, Weiner, et al., 2002)
Medulloblastoma (mostly non-SHH)	Glt1-*MYCN*	Non-EGL Cell (GLT1+)	(Swartling, et al., 2010)
Medulloblastoma (Group 3 or 4)	*Myc*^{T58A}/*Trp53*+/− or *Mycn*^{T58A}	Cerebellar Stem Cell	Kawauchi et al. (2012), Pei et al. (2012b), Swartling et al. (2012)