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Deregulated proliferation and differentiation in brain tumors

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Abstract

Neurogenesis, the generation of new neurons, is deregulated in neural stem cell (NSC)- and progenitor-derived murine models of malignant medulloblastoma and glioma, the most common brain tumors of children and adults, respectively. Molecular characterization of human malignant brain tumors, and in particular brain tumor stem cells (BTSCs), has identified neurodevelopmental transcription factors, microRNAs, and epigenetic factors known to inhibit neuronal and glial differentiation. We are starting to understand how these factors are regulated by the major oncogenic drivers in malignant brain tumors. In this review, we will focus on the molecular switches that block normal neuronal differentiation and induce brain tumor formation. Genetic or pharmacological manipulation of these switches in BTSCs has been shown to restore the ability of tumor cells to differentiate. We will discuss potential brain tumor therapies that will promote differentiation in order to reduce treatment-resistance, suppress tumor growth, and prevent recurrence in patients.

Keywords

Brain; Glioma; Medulloblastoma; Neurogenesis; Neural Stem Cell

INTRODUCTION

Pioneering work in the 1960s used radioactive thymidine incorporation to detect ongoing neurogenesis in the adult rodent brain (Altman, 1962). In the late 1990s, a cohort of patients receiving bromodeoxyuridine (BrdU) enabled Eriksson and colleagues to identify hippocampal neurogenesis in the adult human brain (Eriksson, et al., 1998). While a wealth of publications has described rodent neurogenesis, the extent of ongoing adult neurogenesis in humans is debated (Wang, et al., 2014, Yuan, et al., 2014). Neural stem cells (NSCs) and more differentiated precursor cells, capable of producing neurons and glial cells, have been

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found to give rise to brain tumors in mice. As initiating events during brain tumor formation, we and others have described reduced differentiation and aberrant proliferation of precursor cells. Recent studies have begun to delineate how such cancer-causing events induce a switch from asymmetric to symmetric cell division in transformed cells. We will focus this review on glioma and medulloblastoma (MB), the most common primary malignant brain tumors in adults and children, respectively. Gliomas are classified by grades I–IV (Louis, et al., 2007). Grade I pilocytic astrocytomas are more common in children while grade II–III oligodendrogliomas, astrocytomas, oligoastrocytomas, or ependymomas occur in both children and adults. Genome-wide characterization of both grade IV glioblastomas (GBMs) and grade II–III gliomas has identified molecularly and biologically distinct subgroups in children and adults (Cooper, et al., 2010, Phillips, et al., 2006, Sturm, et al., 2012, Verhaak, et al., 2010). Similarly, extensive profiling of MBs has established multiple subgroups of tumors (Taylor, et al., 2012). Although glioma and MB cells display distinct glial and neuronal phenotypes, both types of brain tumors have been described to originate from neural precursors capable of undergoing neurogenesis. We will first describe regions of forebrain and hindbrain neurogenesis and how the identities of these precursors match distinct subgroups of human gliomas and MBs. We will then summarize findings that characterize neuronal gene expression in these tumors and the ability of brain tumor stem cells (BTSCs) to produce neurons. We will then review factors that make BTSCs pluripotent capable of differentiating into not only neurons and glial phenotypes, but also cells from all three germ layers. Finally, we will suggest that a better understanding of the cell of origin and the initiating events during brain tumor formation can identify new therapeutic targets of the most treatment-resistant BTSCs, ultimately improving the outcome for glioma and MB patients. While the current standard of care includes surgery followed by radio- and chemotherapy, the prognosis for most patients is fatal. The overall survival of MB patients is about 70% but surviving children often succumb to severe “side-effects” due to treatment toxicities, especially from craniospinal radiotherapy (Gilbertson, 2004, Schmidt, et al., 2010). We propose that current advances in neurodevelopmental biology will inform the brain tumor field and may lead to novel therapies that target the root of cancer, rather than individual branches.

Association of forebrain neurogenesis and gliomagenesis

Neurogenesis, the generation of new neurons, is mainly confined to embryonic development of the central nervous system (CNS), but restricted regions continue to produce neurons after birth (Kriegstein and Alvarez-Buylla, 2009). Neuroepithelial stem cells in the ventricles of the forebrain and the spinal canal give rise to radial glial cells (Rowitch and Kriegstein, 2010). The latter in turn are successors that produce mature cells including neurons, oligodendrocytes, astrocytes and ependymal cells (Malatesta, et al., 2000). Radial glia cells express a cytoplasmic protein called brain lipid-binding protein (BLBP) (Feng, et al., 1994, Hartfuss, et al., 2001, Kurtz, et al., 1994). Cellular fate mapping using the *BLBP* promoter coupled to the Rosa26 reporter shows that most types of neurons in almost all brain regions (Anthony, et al., 2004) originate from BLBP-positive radial glia cells. In the mouse brain, neurogenesis continues throughout life and is restricted to two germinal regions; the subgranular zone (SGZ) of the hippocampus and the subventricular zone (SVZ) lining the lateral ventricles (Alvarez-Buylla and Lim, 2004, Seri, et al., 2001). In the adult

mouse SVZ, glial fibrillary acidic protein (GFAP) expressing neural stem cells (NSCs), also called type B1 cells, are thought to undergo asymmetric cell division to generate transit amplifying progenitors (TAPs, type C cells) that further differentiate into immature neuroblasts (type A cells). In mouse brain, type A cells use the rostral migratory stream (RMS) in their migration to the olfactory bulb where they differentiate into olfactory bulb neurons. More recent data demonstrate that cell-intrinsic differences of individual murine SVZ NSCs generate several distinct interneuron subtypes of the olfactory bulb (Merkle, et al., 2007, Merkle, et al., 2004). Although olfactory bulb neurogenesis is not detectable in adult humans, substantial hippocampal neurogenesis with comparable neuronal turnover rates is found in middle-aged humans and mice (Eriksson, et al., 1998, Spalding, et al., 2013). A novel carbon-14 dating approach recently suggested generation of striatal neurons in adult humans, possibly originating from the SVZ (Ernst, et al., 2014). However, another study showed that human and monkey striatal interneurons are derived from the medial ganglionic eminence (Wang C et al., J Neurosci, 2014). Is it possible that oncogenic transformation of forebrain NSCs, neural progenitors or even differentiated neurons can give rise to gliomas?

Similar to normal NSCs, recent findings suggest that treatment-resistant BTSCs in human GBMs possess extensive self-renewal ability, undergo asymmetric cell division, and can differentiate along the three main neural cell lineages, implicating a possible relationship (Hemmati, et al., 2003, Lathia, et al., 2011, Singh, et al., 2003).

Much effort has successfully generated genome-wide characterization of low- and high-grade gliomas into molecularly and biologically distinct subtypes in children and adults (Cooper, et al., 2010, Sturm, et al., 2012, Verhaak, et al., 2010). Recent studies suggest that GBM patients with tumors contacting the SVZ show worse prognosis and increased radiation doses of this region were associated with improved survival in GBM patients (Chen, et al., 2013, Jafri, et al., 2013). In contrast, we have previously shown that human oligodendrogliomas often lack association to the lateral ventricles where NSCs reside and can arise from oligodendrocyte progenitor cells (OPCs) in a murine glioma model (Persson, et al., 2010). Interestingly, oligodendrogliomas and a subset of GBMs display a proneural phenotype associated with improved survival and enriched for genes expressed in OPCs (SOX10, OLIG2, PDGFRA) (Cooper, et al., 2010, Verhaak, et al., 2010). In contrast, the classical and mesenchymal phenotypes of GBMs show worse prognosis and a higher degree of stemness-related genes (HES1, PDPN) (Phillips, et al., 2006, Verhaak, et al., 2010). Studies of several genetically-engineered murine models (GEMMs) found that glioma formation from NSCs leads to reduced neurogenesis, suggesting that initiation of glioma formation from NSCs is associated with a neurogenic-gliogenic shift (Chen, et al., 2012a, Li, et al., 2014a, Zhu, et al., 2005) (Figure 1).

Association of hindbrain neurogenesis and medulloblastoma formation

Neurogenesis is restricted to two germinal zones in the developing cerebellum (small brain) (Hatten and Heintz, 1995). The first is a structure called the rhombic lip (RL) where precursors expressing the mouse homolog of the *Drosophila* proneural gene *atonal (MATH1)* reside. They form granule cell neuron precursors (GNPs) that build up the

external germinal layer (EGL). GNPs later form glutamatergic granule neurons (Hevner, et al., 2006), the most abundant type of neuron in the brain (Grimmer and Weiss, 2006). Other cerebellar neurons can be formed from a second germinal region, the ventricular zone (VZ) closest to the 4th ventricle. The VZ is similar to the lateral VZ in the forebrain and is also composed of BLBP-positive radial glia cells.

Radial glia cells migrate into the cerebellum and give rise to Purkinje neurons, γ-Aminobutyric acid (GABA) expressing cells as well as interneurons including Basket and Stellate cells (Hoshino, et al., 2005). Release of sonic hedgehog (SHH) from Purkinje neurons stimulates proliferation of GNPs (Dahmane and Ruiz i Altaba, 1999, Wechsler-Reya and Scott, 1999). Bergmann glial cells are derived from radial glia and guide immature GNPs to migrate from EGL to form a new internal granular layer (IGL). Murine postnatal (P7) cerebellum contains multipotent NSCs that are positive for the stem cell marker Prominin (Lee, et al., 2005). The cerebellum starts to mature by 3 weeks of age in mice and at around 2 years of age in humans (Raaf and Kernohan, 1944). Postnatally, Bergmann glia continue to express members of the SRY (sex determining region Y)-box (SOX) family of transcription factors *SOX1* and *SOX2* together with the stem cell marker Nestin and proliferate upon damage to the cerebellum (Sottile, et al., 2006, Stamatakis, et al., 2004). In contrast to adult forebrain NSCs, there is no clear proof of adult cerebellar NSCs that are still mitotic and that can undergo neurogenesis. Neurogenesis in the brain stem is somewhat different from that in the forebrain and in the cerebellum. The ventricular zone of the medulla and pons generates various brainstem nuclei, including the spinal trigeminal nucleus and the nucleus of the solitary tract (Altman and Bayer, 1980) in which *Oligodendrocyte transcription factor 3* (*OLIG3*) and *Pancreas transcription factor 1 subunit alpha* (*PTF1A*) are essential in neuronal fate determination (Storm, et al., 2009). MATH1-positive cells from the lower rhombic lip structure migrate and give rise to mossy fiber neurons in the pontine gray nucleus (PGN) in the pons. In mammals, this process contributes to the greatest number of mossy fibers in the cerebellum where mossy fiber axons extend from PGN, cross the ventral brainstem midline, and enter the cerebellum (Cicirata, et al., 2005). Importantly, *Zinc finger of the cerebellum 1* (*ZIC1*) is involved in the regulation of the pontine neuron cell body position and axonal projections within the pons (Dipietrantonio and Dymecki, 2009).

Medulloblastoma is a grade IV malignant childhood disorder that is capable of disseminating from its primary site of origin. The cells of origin for MB are not clearly identified, and it is likely that more than one type of cell can generate any of the four different molecular subtypes of MB: Wingless (WNT), SHH, Group 3 or Group 4 (Northcott, et al., 2012a). The primary site of human MB is not always intra-cerebellar as suspected when considering MB to be a cerebellar disorder. In fact, only SHH MBs are found as “intra-cerebellar tumors” while WNT, Group 3 and Group 4 tumors are either extra-cerebellar only, or a mix of intra- and extra-cerebellar tumors (Wefers, et al., 2014). Neural stem cells, GNPs or other neural progenitor cells from the lower RL of the developing dorsal spinal cord all give rise to MB in GEMMs (Figure 2) as discussed below. Genetic alterations in MB are often subgroup-specific like mutations in *Catenin (cadherin-associated protein), beta 1* (*CTNNB1)* in the WNT subgroup, aberration in *Patched 1*

(*PTCH1*), *Smoothened* (*SMO*), *Suppressor of fused homolog* (*SUFU*) or *GLI family zinc finger 2* (*GLI2*) in the SHH subgroup, amplification of *v-myc avian myelocytomatosis viral oncogene homolog* (*MYC*) in group 3 and amplifications of Orthodenticle homeobox 2 (OTX2) in group 3 and 4 (Jones, et al., 2012, Northcott, et al., 2009b, Northcott, et al., 2012b, Parsons, et al., 2011, Pugh, et al., 2012, Robinson, et al., 2012). On the other hand, some alterations are found across subgroups such as amplifications of v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog *(MYCN)* (Taylor, et al., 2012a). As will be discussed below, all of these genes have been clearly implicated in various stages of brain and neuronal development, thus further linking MB formation to deregulated neurogenesis.

Disruption of neurogenesis as an initiating event for brain tumor formation

A growth factor-mediated neurogenic-gliogenic switch in forebrain precursor cells—The mechanisms that control cell fate in neocortical NSCs are well understood. Less is known how discrete populations of postnatal NSCs maintain their neurogenic potential, but evidence indicates that both cell-extrinsic signals and cell-intrinsic epigenetic mechanisms are required (Fuentealba, et al., 2012, Ming and Song, 2011). The output of newborn neurons reflects the size of the NSC pool and regulation of cell fate determinants in type B1 NSCs and type C cells. A delicate balance and coordination between neurogenic and gliogenic factors determine the cell fate of NSC progeny and can be disrupted during pathological conditions. Multipotent cortical progenitors are maintained in a proliferative state by basic helix-loop-helix (bHLH) factors from the Inhibitor of differentiation (ID) and hairy and enhancer of split (HES) families (Ross, et al., 2003). The neocortex is derived from the telencephalon, where the proneural gene *Neurogenin 2* (*NEUROG2*) specifies a glutamatergic neuronal fate in dorsal progenitors (Fode, et al., 2000, Mattar, et al., 2008, Parras, et al., 2002, Schuurmans, et al., 2004), while the proneural gene *Achaete-scute family bHLH transcription factor 1* (*ASCL1*) specifies the identities of neocortical GABAergic neurons and embryonic OPCs that are derived from ventral progenitors (Britz, et al., 2006, Casarosa, et al., 1999, Castro, et al., 2011, Parras, et al., 2007). During development, the transition from proliferation to neurogenesis involves a coordinated increase in the activity of proneural bHLH factors (*ASCL1*, *NEUROG1*, and *NEUROG2*) and a decrease in the activity of HES and ID factors. Elegant work from Alvarez-Buylla's laboratory demonstrates that adult SVZ NSCs in distinct microdomains generate diverse types of olfactory bulb neurons (Merkle, et al., 2014, Merkle, et al., 2007). The transcription factor *Paired box 6* (*PAX6*) promotes the neurogenic potential of cortical radial glia during CNS development (Heins, et al., 2002). In the adult SVZ, expression of PAX6 in TAPs and SVZ neuroblasts is required for generating olfactory bulb neurons of the dopaminergic lineage (Kohwi, et al., 2005). In contrast, expression of OLIG2 specifies the SVZ TAP fate, opposes the neurogenic role of PAX6, and promotes oligodendrogenesis (Hack, et al., 2005, Marshall, et al., 2005). Conversely, PAX6 overexpression inhibits cell-intrinsic expression of OLIG2 (Jang and Goldman, 2011). OLIG2 is expressed by different precursors of glial cells, including OPCs, the most wide-spread population of cycling cells in the adult brain (Geha, et al., 2010, Zhou and Anderson, 2002). Infusion of epidermal growth factor (EGF) or platelet-derived growth factor AA (PDGF-AA) into the lateral ventricles and SVZ of adult mice induces massive expansion of OLIG2+ cells and depletion of neurogenesis

(Gonzalez-Perez, et al., 2009, Jackson, et al., 2006, Kuhn, et al., 1997). Establishment of murine embryonic ventricular zone and adult subventricular zone neurosphere cultures with EGF or fibroblast growth factor 2 (FGF-2) results in prominent down-regulation of transcription factors in telencephalic precursors and robust up-regulation of OLIG2 (Hack, et al., 2004). Several members of the SOX family of transcription factors play important roles in regulating neurogenesis (Wegner and Stolt, 2005). SOX9 is a glial fate marker responsible for generating astrocytes and oligodendrocytes in the developing brain and spinal cord (Stolt, et al., 2003). Transcriptionally, SOX9 regulates glial specification in collaboration with the *Nuclear factor I family member* (*NFIA*) by targeting the downstream effector *Mouse double minute 2 homolog* (*MDM2*) (Kang, et al., 2012). Therefore, high levels of SOX9 in glial precursor cells provide a barrier to neurogenesis. Detailed time-lapse studies monitoring OLIG2, ASCL1, and HES1 expression in NSCs derived from the ventral telencephalon show an oscillatory expression pattern, whereas the differentiated states correlated with sustained expression of single factors (Imayoshi, et al., 2013). In conclusion, this delicate balance of proneurogenic and progliogenic transcription factors is a prerequisite for normal neuronal and glial output in developing and adult germinal regions. Growth factor-mediated stimulation of neural precursor cells favors production of glial progeny, providing an explanation for how downstream signaling effectors can promote gliomagenesis.

Oncogenic RAS-MEK-ERK signaling as an initiating event during gliomagenesis—As a critical regulator of brain development, the RAS/extracellular-regulated kinase (ERK) signaling cascade influences neural cell fate determination by controlling the expression of transcription factors and bHLH factors (Li, et al., 2014b). Inactivation of *Neurofibromin 1* (*NF1*), a RAS GTPase-activating protein, promotes ERK-dependent expression of OLIG2 specifically in ASCL1+ TAPs, leading to increased gliogenesis at the expense of neurogenesis in neonatal and adult SVZ (Wang, et al., 2012b). *In utero* transduction found that increased activation of RAS/ERK signaling in neocortical progenitors promoted a *NEUROG2-ASCL1* genetic switch that promoted a glial cell fate (Wang, et al., 2012b). As a result, the authors found that activation of the ERK, but not other down-stream effectors of RAS, resulted in a massive expansion of OLIG2+ and SOX9+ progeny. Electroporation with the RAS^{V12} oncogene resulted in glioma formation. Interestingly, this study demonstrated that RAS/ERK signaling regulated *ASCL1* transcriptional activity by direct phosphorylation of multiple sites in dose-dependent manner. Moreover, they found that transactivation of the homebox genes *Distal-less 1/2* (*DLX1/2*) and *SOX9* reporters required phosphorylation of ASCL1. Their study elegantly demonstrates the importance of RAS/ERK activation for cell lineage determination in NSCs and progenitors. It also provides a basis for glioma initiation as a result of disrupted neurogenesis. In human gliomas, RAS activation is a common pro-proliferative event that is triggered by mutations of upstream receptor tyrosine kinases (RTKs), or downstream signaling components, such as *NF1* or the proto-oncogene *BRAF* (Jones, et al., 2008, Louis, et al., 2007, McLendon, et al., 2008). Reduced *NEUROG2* expression was necessary for self-renewal and tumorigenesis from BTSCs (Guichet, et al., 2013). Conversely, ASCL1 expression promoted self-renewal and tumorigenicity (Rheinbay, et al., 2013). We and others have employed GEMMs of glioma based on constitutive activation of the RAS-ERK

pathway in NSCs, OPCs, or astrocytes (Acquaviva, et al., 2011, Chen, et al., 2012a, Ding, et al., 2001, Persson, et al., 2010, Zhu, et al., 2005). Aberrant RAS/ERK signaling in NSCs and OPCs blocked differentiation and promoted gliomagenesis (Jackson, et al., 2006, Persson, et al., 2010). To identify a relationship between NSC origin and treatment-resistant BTSCs in developing gliomas, a recent study generated malignant GBMs from SVZ NSCs through conditional inactivation of the tumor suppressors *NF1*, *TP53*, and *Phosphatase and tensin homolog* (*PTEN)* under the *Nestin* promoter (Chen, et al., 2012a). They traced a restricted population of Nestin-expressing cells that propagated GBMs in mice and regrowth following treatment with the alkylating agent temozolomide. In conclusion, a developmental neurogenic-gliogenic switch in transcription factor and bHLH expression represents an initiating step for RAS/ERK-driven glioma formation derived from NSCs. In OPC-derived gliomas, RAS-ERK signaling blocks differentiation and promotes a switch from asymmetric to symmetric cell division (Jiang, et al., 2011, Persson, et al., 2010, Sugiarto, et al., 2011). Pharmacological inhibition of RAS-ERK signaling not only rescues cell fate specification in *NF1*-deficient neural progenitors (Wang, et al., 2012b), but may also block gliomagenesis and restore normal differentiation.

In GBMs, approximately 45% of adult human cases harbor amplifications or activating mutations in the *Epidermal growth factor receptor* (*EGFR*) (Frattini, et al., 2013, McLendon, et al., 2008). Increased EGFR signaling promotes self-renewal of NSCs and promotes a neuronal-glial switch (Ayuso-Sacido, et al., 2010, Gonzalez-Perez, et al., 2009, Sun, et al., 2005b). Sensitive fluorescence in situ hybridization (FISH) experiments found that approximately 29% and 21% of pediatric and adult high-grade gliomas, respectively, harbor *Platelet-derived growth factor A* (*PDGFRA*) amplifications (Phillips, et al., 2013). Stimulation of PDGFRA expressed on SVZ NSCs or OPCs promotes gliogenesis (Gonzalez-Perez, et al., 2009, Jackson, et al., 2006, Noble, et al., 1988, Phillips, et al., 2013, Richardson, et al., 1988, Woodruff, et al., 2004). Approximately 18% of adult GBMs show mutations or homozygous deletions of the *NF1* gene (Frattini, et al., 2013, McLendon, et al., 2008). As a negative regulator of RAS signaling, loss of *NF1* in NSCs increased gliogenesis at the expense of neurogenesis in the neonatal and adult SVZ (Wang Y et al., Cell, 2012). The tumor suppressor *RB1* also shows frequent deletions or inactivating mutations in GBM (Frattini, et al., 2013, McLendon, et al., 2008), while the normal functioning of *RB1* has clearly been linked to neurogenesis and there are indications that loss of its function might lead to increased neural progenitor proliferation and reduced neuronal differentiation (reviewed in (Sage, 2012)). In summary, recent advances have defined oncogenic RAS-MEK-ERK signaling as an initiating event during gliomagenesis, leading to changes in transcription factors controlling cell fate determination and promoting aberrant gliogenesis.

Linking transcriptional regulators of hindbrain neurogenesis and medulloblastoma formation—Proneural genes are involved in early patterning and cell fate specification of the cerebellum. MATH1 is important for the generation of GNPs and for their expansion (Ben-Arie, et al., 1997). Similar to forebrain development, the *Neurogenic differentiation 1* (*NEUROD1*) gene is involved in cerebellar neuronal differentiation and acts as a master gene in granule cell differentiation (Miyata, et al., 1999). Progenitor cells in the ventricular zone (VZ) close to the fourth ventricle express fate

markers like PTF1A, NEUROG1 and NEUROG2. GABAergic interneuron precursors are produced from E13.5 to E16.5 from VZ progenitors (Maricich and Herrup, 1999). These interneuron precursors proliferate and express PAX2 until the first postnatal week when they migrate to the deep cerebellar nuclei (DCN). MASH1 suppresses gliogenesis and participates in the generation of GABAergic interneurons and (DCN) neurons. Members of the NOTCH and Bone morphogenic protein (BMP) families regulate cerebellar development in the VZ and in the roof plate, respectively. During embryogenesis BMPs stimulate production of glutamatergic neurons and expression of MATH1 (Alder, et al., 1999, Chizhikov, et al., 2006, Machold, et al., 2007). Depletion of NOTCH1 in the developing cerebellum leads to increased glutamatergic neurogenesis (Lutolf, et al., 2002, Machold, et al., 2007). Specifically, SHH signaling has been identified as a pathway stimulating the expansion and increased proliferation of glutamatergic cerebellar GNPs during their migration through the EGL in normal development of the cerebellum (Gilbertson and Ellison, 2008, Marshall, et al., 2014, Roussel and Hatten, 2011). Aberrant inactivation of SHH signaling antagonists, predominantly *PTCH1 and SUFU*, or activations of factors such as the *GLI2* gene that positively regulate SHH signaling including *SMO*, have all been found altered in the SHH MB subgroup. Inactivation of SHH antagonists or activation of SHH signaling inhibit cell cycle exit of cerebellar GNPs, reduce differentiation, and lead to abnormal cell growth (Gilbertson and Ellison, 2008, Marshall, et al., 2014, Roussel and Hatten, 2011), suggesting that GNPs may represent the cell of origin of the human SHH MB subgroup. In fact, while GNPs can directly generate SHH MB in mice, hindbrain NSCs adopt a GNP fate upon SHH pathway stimulation by activated SMO (Schuller, et al., 2008) or PTCH1 depletion (Yang, et al., 2008). Binding of SHH ligand to its receptors, PTCH1 and SMO homologue, leads to the activation of GLI transcription factors (Lai, et al., 2003, Palma and Ruiz i Altaba, 2004). Genome sequencing identified mutations in several key genes in the SHH-pathway including *PTCH1*, *SMO* and *SUFU* in as many as 87% of SHH MBs (Kool, et al., 2014). *PTCH1* mutations are found evenly distributed among infant, children and adult patients. On the other hand *SMO* mutations are only found in adult SHH MBs while *SUFU* mutations were exclusively found in infant SHH MBs. In mice, expression of an activated allele of *SMOM2* in multipotent GFAP+/OLIG2+ progenitors or unipotent GNPs both resulted in MB formation (Schuller, et al., 2008). Tumors formed were histologically similar and MATH1 positive despite being generated from different cell types. It is also possible that even late stage GNPs can dedifferentiate in order to give rise to these tumors. However, when instead depleting PTCH1 in various cell types to drive SHH MBs, tumors generated from NSCs develop more rapidly than tumors generated in GNPs (Yang, et al., 2008). Interestingly, two recent reports suggest that also cells from the cochlear nuclei in the spinal cord (Grammel, et al., 2012) or rare quiescent Nestin-positive cells in the EGL that are MATH1 negative (Zhao, et al., 2013) can give rise to SHH MBs. The latter study suggests that MATH1 is not required for generating GNPs or for generating all types of SHH MBs.

The cell of origin for MB subtypes still remains unclear, and it is likely that more than one type of cell can generate any of the four different molecular subtypes of MB: WNT, SHH, Group 3 or Group 4 (Northcott, et al., 2012a) (Table 1). Neural stem cells, GNPs, or other

neural progenitor cells from the lower RL of the developing dorsal spinal cord all give rise to MB in mouse models, as further discussed below (Figure 2).

Meanwhile, it has become increasingly clear that brain tumor development shares many characteristics with normal tissue and cell development (Swartling, et al., 2013b) where the cell types in normal brain and neuronal development undergo various changes in proliferation, differentiation and apoptotic capacities (Swartling, et al., 2013a). In MB, a hint at this coupling between normal brain and tumor development can be gathered from the age dependence of tumor subgroups. Additionally it has been proposed that the clustering of adult MBs, in contrast to the four subgroups in pediatric MBs, only contain three subgroups with Group 4 showing also a different appearance and outcome for pediatric and adult cases (Remke, et al., 2011) and similar observations have been made for WNT and SHH groups (Northcott, et al., 2011). Finally, a previous study from our own research group that used an orthotopic mouse model transplanted with NSCs previously transduced with a stabilized form of MYCN has also clearly showed that the cancer type and the subgroup affiliation of the induced tumors is influenced not only by the brain region but also the time point at which NSCs have been dissected and transduced (Swartling, et al., 2012). In summary, it is reasonable to conclude that the intrinsic programs of the respective tumor cells of origins are directly coupled or reflect certain brain or neuronal developmental programs. Tumorigenesis in this case is also restricted to certain developmental time windows, in which the given signaling pathways are susceptible to alterations or mutations of the respective cancer gene (Gilbertson and Ellison, 2008, Liu and Zong, 2012, Marshall, et al., 2014, Sanai, et al., 2005). However, Liu et al. found that genetic mutations resulted in brain tumor formation only as NSCs differentiated into more restricted precursor cells (Liu, et al., 2011). In addition, temozolomide treatment of human gliomas can induce a hypermutated phenotype in recurrent tumors (Johnson, et al., 2014). Moreover, radiotherapy promotes a proneural-mesenchymal transition of high-grade gliomas (Halliday, et al., 2014, Mao, et al., 2013). These studies suggest that, rather than trying to delineate the cell of origin based on the resulting tumor phenotype, it is more informative to perform careful analyses of GEMMs to delineate the cells that are most susceptible to defined genetic mutations.

Mutational analysis and transcriptomal profiling of human medulloblastoma subgroups imply distinct developmental origins—Development of GEMMs for MB have identified spatially and temporally defined neural precursors that generate tumors with gene expression signatures for different human MB subgroups. (Gilbertson and Ellison, 2008, Hatten and Roussel, 2011, Liu and Zong, 2012, Marino, 2005, Marshall, et al., 2014, Roussel and Hatten, 2011). Specifically, SHH signaling has been identified as a pathway stimulating the expansion and increased proliferation of cerebellar GNPs and granule cell progenitors (GCPs) during their migration through the EGL in normal development of the cerebellum (Gilbertson and Ellison, 2008, Marshall, et al., 2014, Roussel and Hatten, 2011). GNPs might be likely cell of origin candidates of human SHH tumors and while GCPs can directly generate SHH MB in mice, hindbrain NSCs turn on a GCP fate upon SHH pathway stimulation by activated SMO (Schuller, et al., 2008) or PTCH1 depletion (Yang, et al., 2008). The tumorigenic properties of MB cells might be brought about by the loss of other signals antagonizing SHH activity (Fan and Eberhart, 2008, Hatten and Roussel, 2011,

Roussel and Hatten, 2011). One example is the *Potassium channel tetramerisation domain containing 11* (*KCTD11, REN*) gene, often deleted in MB due to loss of chromosome 17p, expression of which is thought to antagonize SHH-induced proliferation and thus stimulating differentiation of GCPs (Argenti, et al., 2005, Di Marcotullio, et al., 2004). Another example is given by the BMP pathway, effectors of which are often found transcriptionally down-regulated in MB, and that has been found to facilitate GNP differentiation by antagonizing SHH-induced proliferation (Zhao, et al., 2008).

Similar to the SHH signaling pathway, WNT signaling has also been implicated in neural development and neural cell differentiation and proliferation (Ciani and Salinas, 2005, Lange, et al., 2006, Pei, et al., 2012a). Specifically, active WNT signaling is thought to interfere with the formation of a multi protein complex including Adenomatous polyposis coli (APC), AXIN2 and β-Catenin, thus abrogating β-Catenin phosphorylation and subsequent degradation and instead leading to an increased accumulation of β-Catenin proteins in the cell, which then causes downstream activation of other WNT targets and eventually down-regulates neuronal differentiation and up-regulates cell proliferation (Gilbertson and Ellison, 2008, Marino, 2005, Pei, et al., 2012a). In addition to activation of WNT signaling, deletion of exon 3 in the β-Catenin encoding gene *CTNNB1* is sufficient for β-Catenin accumulation in the cell due to evasion from the protein degradation machinery (Harada, et al., 1999, Zechner, et al., 2003). Since mutations activating WNT signaling (in particular deletions of exon 3 in the *CTNNB1* gene) are frequent in the WNT subgroup, it is reasonable to conclude that this is one factor determining the aberrant proliferation of this MB subgroup (Marshall, et al., 2014), although these alterations alone appear not sufficient for MB development (Pei, et al., 2012a). These WNT MBs have been suggested to derive from lower rhombic lip or embryonic dorsal brainstem progenitors (Gibson, et al., 2010).

Notch signaling plays a major role coordinating proliferation and differentiation in NSCs, GNPs and Bergmann glia in forebrain and hindbrain germinal regions (Helgesson, et al., 2007, Kool, et al., 2014, Machold, et al., 2007, Mathieu, et al., 2010, Rousseau-Merck, et al., 1985). Specifically, it has been shown that NOTCH1 is required for GNP differentiation (Kang, et al., 2012), while NOTCH2 stimulates GNP proliferation (Kool, et al., 2014). Since NOTCH1 expression levels are often found low and Notch2 expression is found upregulated in MB and other brain tumors (Fan, et al., 2004, Wefers, et al., 2014), deregulated Notch signaling might resemble another pathway that is contributing to tumorigenic proliferation in these cancers.

Hindbrain NSCs are suggested to represent the cell of origin for Group 3 and Group 4 MBs in GEMMs driven by MYC proteins (Kawauchi, et al., 2012, Pei, et al., 2012b, Swartling, et al., 2010, Swartling, et al., 2012). However, less is known about the intrinsic program of Group 3 and Group 4 MB, although there exist several hints at pathways or genes, which are ordinarly contributing to normal neural differentiation and proliferation but are deregulated in these tumors.

Aberrations in the MYC family genes, especially characterized by amplification of MYC and MYCN, are common in group 3 and 4 MB. It is well known that both MYC and MYCN transcription factors play roles in normal brain development, including cerebellar

development, as well as in determining the fate, proliferation and differentiation of neural progenitors (Knoepfler, et al., 2002, Wey and Knoepfler, 2010, Wey, et al., 2010, Zinin, et al., 2014). Additionally, MYC proteins have been widely implicated in various aspects of brain tumor biology (reviewed in (Swartling, 2012)). It has been shown that MYCN is a downstream target of SHH signaling and is often required for the induction of SHH induced proliferation discussed above (Hatton, et al., 2006, Kenney, et al., 2003, Oliver, et al., 2003), explaining why amplification or upregulated expression of MYCN is often seen in SHH-dependent MBs. However, amplification and aberrant expression of MYC as well as amplification of MYCN are also recognized as some of the most recurrent tumorigenic alterations in MB subgroup 3 and 4, respectively, and generally correlate with a poor clinical prognosis (Kool, et al., 2012, Korshunov, et al., 2012). Thus it is clear that SHH-independent aberrant expression of MYC and MYCN might be key factors determining the deregulated proliferation and differentiation properties of neural progenitors in these tumor subtypes, which is also underscored by the fact that current mouse models of these subgroups all depend on either MYC (Kawauchi, et al., 2012, Pei, et al., 2012b) or MYCN (Swartling, et al., 2010, Swartling, et al., 2012).

There is a possible role for members of the *OTX* gene family in MB tumorigenesis (de Haas, et al., 2006) and in driving and defining especially the group 3 and group 4 subclasses (Marshall, et al., 2014). Specific patterns of OTX1 and OTX2 have been found delineating borders and layers between and within hindbrain, midbrain and forebrain and regulated expression of these transcription factors has been assumed important for controlling neurogenesis, neural progenitor identity and fate as well as local brain regionalization (Pennartz, et al., 2004, Rajendran, et al., 2008, Su, et al., 2009, Sun, et al., 2005a, Zupanc, et al., 2005). Importantly, OTX2 has been shown to induce proliferation and impede differentiation of cancer cells in MB (Adamson, et al., 2010, Lachyankar, et al., 2000, Ross, et al., 2001), and since it is often found amplified in group 3 and group 4 MBs (Adamson, et al., 2010, Northcott, et al., 2012b), it might be argued to be a driver of those subgroups. Most recently, *growth factor independent 1* (*GFI1*) family proto-oncogenes were found as common drivers of Group 3 and Group 4 MB (Northcott, et al., 2014). Interestingly, in tumor cells *GFI1* genes are altered and directed proximal to active enhancer elements in the genome where they promote tumorigenesis. In conclusion, studies in mice have shown that genetic alterations and expression of transcription factors found in human MB subgroups lead to changes in developmental programs, known to play important roles for cell homeostasis and cell fate determination (Table 1).

Epigenetics, neurogenesis, and brain tumor formation

Epigenetics, heritable changes in gene activity that are not caused by changes in the DNA sequence, governs fine-tuning and precision of gene expression programs that define the molecular basis of differentiation and reprogramming in NSCs and more restricted progenitors. As NSCs differentiate, the genome becomes more transcriptionally restrained, due to chromatin condensation and maturation of heterochromatin. Epigenetic mechanisms include post-translational modifications of histones, incorporation of histone variants, changes in DNA methylation, chromatin remodeling, and implementation of RNAi pathways and non-protein coding RNAs. Recent molecular characterization of malignant

gliomas and MBs show that genetic alterations in cancer-causing genes produce broad epigenetic changes that play important roles in tumor initiation and progression.

Regulation of neurogenesis through post-translational modification of histones and DNA—Acetylation of the core histones H3, H4, H2A, and H2B is normally associated with a more relaxed chromatin conformation and thus activation of gene transcription. Opposite actions of histone acetyltransferases (HATs) and histone deacetylases (HDACs) on histone acetylation in NSCs regulate self-renewal and differentiation (Balasubramaniyan, et al., 2006). HDACs can form complexes with the DNA binding protein REST (RE1 silencing transcription factor; also called NRSF) and its co-repressor CoREST to repress expression of neuronal genes (Bruce, et al., 2004, Lunyak, et al., 2002). As NSCs differentiate into neurons, REST and its co-repressors dissociate from the REST binding site (RE1), triggering activation of neuronal genes (Ballas, et al., 2005).

In addition to post-translational modifications of histones, the methylation status of DNA plays critical roles in the regulation of gene expression during development (Bird, 2002). DNA methylation predominantly occurs at the cytosine residue of CpG dinucleotides to generate methylation of the 5′ site (5-mC) on the pyrimidine ring. DNA methyltransferases (DNMTs) and members of the methyl-CpG-binding domain (MBD) family are responsible for the generation and maintenance of methylation patterns in the DNA sequence (Nan, et al., 1998, Smith and Meissner, 2013). Although previously thought to be an irreversible process, recent studies suggest that reversible DNA methylation occurs (Popp, et al., 2010, Rai, et al., 2008).

In addition to 5-mC methylation of DNA, histone lysine methylation regulates transcription and modulates other chromatin-related processes such as replication (Zhang and Reinberg, 2001). The lysine (K) residues of histones H3 and H4 can be mono-, di-, and tri-methylated, whereas arginine (R) can be mono- or dimethylated. Specific histone methylation marks are associated with transcriptional activation and/or repression. In contrast to differentiated cells, members of the Ten-11 translocation family *TET1-3* have the capacity to oxidate 5-mC to 5-hydroxymethyl-cytosine (5-hmC), thought to be an intermediary toward 5-mC demethylation (Tahiliani, et al., 2009). Loss of or *TET2-3* leads to defective neuronal differentiation, suggesting that formation of 5-hmc and loss of H3K27me3 promotes brain development (Hahn, et al., 2013). In fact, increased 5-hmc levels during embryonic mouse brain development parallel neuronal differentiation where it preferentially associates with gene bodies of activated neuronal function-related genes (Hahn, et al., 2013). H3K4me3 and H3K27me3 mark genes that are actively transcribed or repressed, respectively. The gain of 5-hmC DNA methylation is often accompanied by the loss of H3K27me3 during neuronal differentiation (Hahn, et al., 2013). Histone methylation is also regulated by repressive Polycomb group (PcG) and activating Trithorax (TrxG) chromatin modifying complexes. The PcG gene *Polycomb repressive complex 2* (PRC2) acts to stabilize repressive chromatin structure through the function of chromatin modifiers, all of which are Histone methyltransferases (HMTs) responsible for depositing H3K27me2 and H3K27me3 marks on chromatin (Cao, et al., 2002). PRC2 contains *enhancer of zeste 2* (*EZH2*), a catalytically active core component that trimethylates H3K27 (Pereira, et al., 2010). A recent study found that expression of EZH2 in SVZ NSCs was required for NSC proliferation and neuronal

differentiation through direct repression of cyclin-dependent kinase inhibitor 2A (CDK2A; Ink4a) and OLIG2 transcription, respectively (Hwang WW et al., Elife, 2014). In contrast to PcG genes, the TRXG group of histone modifiers mediates post-translational modifications of active transcription such as H3K4me3. PcG-mediated gene silencing can be antagonized by mixed-lineage leukemia (MLL) HMTs that catalyze methylation of H3K4 or the Jumonji-family of proteins that removes methylation of H3K27me3. The TRXG member MLL1 is required for neurogenesis in the postnatal mouse brain (Lim, et al., 2009). MLL1-deficient SVZ NSCs progeny express the early proneural transcription factor ASCL1 and gliogenic OLIG2, but not DLX2, a key downstream regulator of neurogenesis. MLL1 deficiency leads to a switch from high levels of H3K4me3 to bivalent expression of H3K4me3 and H3K27me3 at the *DLX2* loci (Lim, et al., 2009).

Dynamic DNA methylation of bHLHs and members of the SOXC family have been implicated for both embryonic and adult neurogenesis ((see review (Covic, et al., 2010)). A closed conformation by H3K27me marks of *NEUROG1*, *NEUROG2*, and *NeuroD2* promoters and an open conformation (no H3K27me3) of SOX4 and SOX11 promoters suggest that SOXC family members in NSCs may control proneuronal gene expression (Mikkelsen, et al., 2007, Mohn, et al., 2008). Other PcG and TRXG chromatin remodeling genes that regulate NSC self-renewal and neuronal differentiation includes polycomb complex protein *BMI1* and the *Chromodomain-helicase-DNA-binding 7* (*CHD7*) protein (Fasano, et al., 2009, Feng, et al., 2013, Molofsky, et al., 2005, Molofsky, et al., 2003). In recent years, extensive literature has demonstrated the many roles that post-translational modifications of histones and DNA play in NSC biology.

miRNAs function as epigenetic modifiers and regulate neurogenesis—As 98% of the transcriptional output in mammalians consist of non-protein coding RNAs (ncRNAs), they regulate chromosome dynamics, chromatin modification, and epigenetic memory (Mattick, 2003). For example, small 21-nucleotide long microRNAs (miRNAs) regulate the stability and translation of target mRNAs. Knockouts of the miRNA processing enzymes Dicer and DGCR8 abolish the ability of embryonic stem cells to silence their self-renewal program and lead to severe defects in their ability to differentiate (Murchison, et al., 2005, Wang, et al., 2007). Down-regulation of REST removes the repression on miR9/9* and miR124 promoters, leading to a switch in the chromatin remodeling complex mSWI/SNF subunit composition and differentiation into neurons (Yoo, et al., 2009). Up-regulation of miR-184 and miR137 is mediated by the MBD proteins MBD1 and Methyl-CpG-binding protein 2 (MeCP2), respectively, and promotes neuronal differentiation during development (Liu, et al., 2010, Szulwach, et al., 2010). A regulatory circuit between let-7 miRNA and the RNA-binding protein Lin28 regulates neurogenesis in NSCs. As cells undergo neuronal differentiation, let-7 down-regulates expression of genes important for self-renewal including *ASCL1*, *NEUROG1*, *HMGA2*, *Lin28*, *MYC*, *MYCN*, *TLX* (Rehfeld, et al., 2014). Let-7-mediated down-regulation of TLX indirectly increases expression of cell cycle inhibitors and miR-9 (Zhao, et al., 2013). Let-7 also targets the oncofetal mRNA-binding protein Imp1, necessary for transition from proliferative fetal NSCs to more quiescent adult NSCs (Nishino, et al., 2013). In conclusion, we have described examples where both a

regulatory circuit of let-7 and lin28 miRNAs, or functions of miRNAs as epigenetic modifiers, can regulate neurogenesis and proliferation of neural precursors.

Distinct mutations are associated with subgroup-specific methylation signatures in human GBMs—Deregulation of chromatin structure by DNA methylation, acetylation and methylation of histones, and nucleosome repositioning, have all been linked to tumor suppressor gene silencing, cancer initiation and progression of brain tumors (Spyropoulou, et al., 2013). Genetic alterations that impact epigenetic regulation of genes may block differentiation and initiate brain tumor formation. Mutation of the *Isocitrate dehydrogenase* (*IDH1*) or *IDH2* genes in diffuse and high-grade gliomas lead to global hypermethylation of CpG islands (Noushmehr, et al., 2010, Parsons, et al., 2008). Diffuse gliomas and GBMs displaying *IDH1/2* mutations were classified into the proneural transcriptomal subgroup (Cooper, et al., 2010, Verhaak, et al., 2010, Yan, et al., 2009). Although the $IDH1^{R132H}$ mutation is present in astrocytic and oligodendrocytic tumors, the mutation is often co-expressed with *TP53* mutation in astrocytoma while it is associated with combined loss of chromosome 1p and 19q in oligodendroglioma. Despite a transcriptional signature similar to other proneural tumors, $IDH1^{R132H}$ mutant gliomas show accumulation of (2-HG) and a hypermethylated phenotype (Chaumeil, et al., 2013, Turcan, et al., 2012). Introduction of the $IDH1^{R132H}$ mutation increased expression of the NSC marker Nestin in immortalized human astrocytes and promoted a glial-neuronal switch in murine forebrain NSCs (Lu, et al., 2012, Turcan, et al., 2012) (Figure 1). The inability of $IDH1^{R132H}$-transduced NSCs to demethylate histones was proposed to block differentiation. Exome sequencing of high-grade pediatric gliomas, including supratentorial GBM and diffuse intrinsic pontine gliomas (DIPG) identified missense mutations Lys27Met (K27M) and Gly34Arg/Val (G34R/V) in genes encoding histone H3.3 (*H3F3A*) and H3.1 (*HIST3H1B*) (Schwartzentruber, et al., 2012, Wu, et al., 2012). Interestingly, Sturm and colleagues found *IDH* mutations occurred in a distinct group of patient samples from *H3F3A* mutants, and the K27 and G34 mutations were mutually exclusive and clustered into their own subgroup when examining gene expression and methylation profile of tumors harboring these mutations (Sturm, et al., 2012). Anatomically, the K27-mutant tumors arise in pontine and more rostral midline brain structures, whereas the G34-mutant tumors are usually hemispheric and found in the forebrain. K27 mutations occur in children while G34 mutations occur in adolescents and *IDH* mutations were found in young adults (Khuong-Quang, et al., 2012, Sturm, et al., 2012). G34 mutations correlated with hypermethylation and silencing of oligodendrocyte lineage genes such as *OLIG1* and *OLIG2*, while expressing the forebrain marker *FOXG1*. In contrast, K27 mutant tumors express *OLIG1* and *OLIG2*, but not *FOXG1* (Sturm, et al., 2012). Mutation of the chromatin remodeling gene *Alpha thalassemia/mental retardation syndrome X-linked* (*ATRX*) gene is more tightly associated with older patients and found in all tumors with G34 mutations in the Schwartzentruber et al study (Schwartzentruber, et al., 2012, Sturm, et al., 2012). Hypomethylation in G34 mutant tumors is especially prominent at chromosome ends, which may provide a link with alternative lengthening of telomeres (ALT), a phenomenon commonly observed with ATRX mutations (Sturm et al. 2012; Schwartzentruber et al. 2012). Overexpression of the G34 mutation induces expression of MYCN in normal human astrocytes and fetal glial cells (Khuong-Quang et al. 2012; Bjerke et al. 2013) (Figure 1). In summary, cohorts of human

GBMs show *IDH1/2* and *H3F3A* mutations that produce distinct methylation signatures, correlate with age of patients, and can be associated to certain brain regions. It is therefore plausible that these tumors derive from different populations of precursor cells.

Subgroup-specific epigenetic regulators in human medulloblastoma—In recent years, several lines of evidence have emerged implicating epigenetic deregulation in the formation of MB (Batora, et al., 2014, Dubuc, et al., 2012, Hovestadt, et al., 2014, Jones, et al., 2013). The events in the underlying epigenome are exemplified mainly by aberrant patterns of DNA methylation, genomic alterations of the chromatin modeling and modifying machinery resulting also in deregulated patterns of histone modifications, as well as aberrant expression of numerous miRNAs. Initial studies on the role of these deregulations appear to converge on a common scheme by which these epigenetic aberrations might ablate tumor cell differentiation and enforce the maintenance of progenitor and proliferating cellular states (Batora, et al., 2014, Dubuc, et al., 2012, Jones, et al., 2013). A high degree of methylation in MB patients has been found to associate with a worsened clinical prognosis (Pfister, et al., 2007), while DNA methylation profiles in general have recently been shown to effectively reinforce the robustness of four distinct molecular subtypes of MB: Wingless (WNT), Sonic Hedgehog (SHH), Group 3 and Group 4 (Hovestadt, et al., 2013, Northcott, et al., 2012a, Schwalbe, et al., 2013). Targeted screens for aberrantly methylated gene loci revealed hypermethylation induced silencing of tumor suppressor genes such as the cell growth regulator *Hypermethylated in cancer 1* (*HIC1*) (Rood, et al., 2002), the cell cycle regulator *Cyclin-dependent kinase inhibitor 2A* (*CDKN2A)* (Fruhwald, et al., 2001) or the SHH signaling and WNT signaling antagonists PTCH1 (Diede, et al., 2010) and SFRP family members (Kongkham, et al., 2010). A recent study by Hovestadt et al. has further employed whole genome bisulfite sequencing coupled to RNA sequencing data to detect regions of DNA methylation and expression downstream of promoters in 34 human MBs (Hovestadt, et al., 2014). The study showed that overall DNA methylation and expression of genes displayed clear differences between MB subgroups, exemplified by a novel promoter of *Lin-28 Homolog B* (*LIN28B*), which was hypomethylated and thus leading to upregulated gene expression in almost all Group 3 and Group 4 MBs. *LIN28B* plays a role in downregulating the expression of tumor suppressors in the *LET-7* miRNA family and the study showed that increased expression of *LIN28B* correlated clearly with a worsened prognosis in these MB subgroups. Further efforts in detecting deregulated epigenetic mechanisms in MB formation have also revealed numerous miRNAs with up- and downregulated expression levels and potential implications in the onset of this disease (reviewed by (Batora, et al., 2014)). Downregulation of miRNAs in MB affects the tumor suppressor miR-218 (Venkataraman, et al., 2013), a cluster of miRNAs (miR-125b, miR-126, miR-324-5p and miR-326) that regulate proliferation by antagonizing SHH signaling (Ferretti, et al., 2008). Induced expression of miR-128a inhibits MB cell growth by downregulating the polycomb complex protein and oncogene BMI-1 (Venkataraman, et al., 2010). Furthermore, overexpression of miR-34a reduces MB cell proliferation and stimulates neural differentiation (de Antonellis, et al., 2011, Weeraratne, et al., 2011). MiR-17/92 is another important miRNA highly expressed in MB that operates downstream of the SHH pathway and has been suggested to act in concert with SHH signaling to promote MB cell proliferation (Northcott, et al., 2009a, Uziel, et al., 2009). Finally,

methylation of miR-9, the inhibitor of WNT signaling *Dickkopf 3* (*DKK3*), and *Kruppel-like factor 4* (*KLF4*) genes in human MB represents additional examples of epigenetic silencing (Fiaschetti G et al., Br J Cancer, 2014; Valdora F et al., Int J Mol Sci, 2013; Nakahara Y et al., Neoplasia, 2010).

The most intriguing implication of epigenetics in MB formation is via deregulated histone modifying and chromatin remodeling functions. Several large-scale genomic screens performed on MB patients, have consistently reported on alterations, predominantly somatic mutations but also copy number aberrations, in various HATs, HDACs, HMTs and Histone demethylases (HDMs) (Jones, et al., 2012, Northcott, et al., 2009b, Parsons, et al., 2008, Pugh, et al., 2012, Robinson, et al., 2012). A comprehensive list of the most prominent, recurrently mutated histone modifiers can be found in (Batora, et al., 2014, Jones, et al., 2013, Northcott, et al., 2012a). Specifically, the *Lysine (K)-specific demethylase 6A* (*KDM6A*) gene represents the most frequently mutated gene in MB subgroup 4 and these events comprise largely non-sense mutations, suggesting a loss of its H3K27me3/2 demethylating capacity (Northcott, et al., 2012a). Due to its ability to remove inactivating H3K27me3 marks, *KDM6A* has been implicated in facilitating cellular differentiation (Agger, et al., 2007) and promoting ES cell-derived neuronal differentiation (Shahhoseini, et al., 2013). In contrast, MLL2 and MLL3 are the most frequently mutated H3K4 methylases in MB, occurring with mutation rates of 5.8% (Northcott, et al., 2012a)/8% (Dubuc, et al., 2013) and 2.6% (Northcott, et al., 2012a), respectively. A majority of such mutations has been interpreted as loss-of-function events (Parsons, et al., 2011), suggesting an ablation of H3K4me3 operability, which is needed for induction of cell differentiation. Interestingly, mutations in MLL2 and KDM6A were found to be mutually exclusive, suggesting alternative but converging ways of maintaining a K27+ phenotype mainly in MB subgroups 3 and 4, a picture that is further supported when considering additional alterations affecting the H3K27/H3K4 machinery (Dubuc, et al., 2013). This scheme is also supportive of a previous finding by Robinson et al. (2012), documenting a mutual exclusivity between *EZH2* overexpression and the abrogated function of *KDM6A* or other epigenetic effectors such as *Zinc finger, MYM-type 3* (*ZMYM3*) in group 4 or *CHD7* in group 3 and 4 (Robinson, et al., 2012). Northcott et al. (2009) further showed a loss of the heterochromatic H3K9me2 mark in 41% of investigated MB patients (Northcott, et al., 2009b), suggesting a second avenue of epigenetic events with a converging phenotype in MB (Dubuc, et al., 2013). Finally, recurrent mutations also frequently effect chromatin remodelers (Batora, et al., 2014, Jones, et al., 2013, Northcott, et al., 2012a), the most prominent of which is the *SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4* (*SMARCA4*), which is enriched in WNT and group 3 tumors (Jones, et al., 2012, Pugh, et al., 2012, Robinson, et al., 2012). Interestingly, the chromatin remodeling complex SMARCA4, has previously been proposed to function as a neuronal-glial cell fate switch in NSCs (Matsumoto, et al., 2006). Further work is needed to better understand how genetic alterations in MBs influence epigenetics as a function of subgroup, with the goal of developing epigenetic-based therapies (for examples see later section of this review).

Neuronal differentiation of malignant brain tumors

Post-mitotic neurons display growth arrest and share few similarities with malignant brain tumors. Although a recent study found that lentiviral transformation of post-mitotic neurons can generate GBMs in mice (Friedmann-Morvinski, et al., 2012), glial precursor cells and GNPs, both able to differentiate into neuronal progeny, represent more likely origins for gliomas and MB. As described in a previous section, cancer-inducing genes can block neuronal differentiation and promote a glial phenotype as malignant gliomas develop. Still, human malignant glioma cells express proteins associated with an immature neuronal phenotype, including Class III beta-tubulin (TujI) and Doublecortin (DCX) (Yan, et al., 2011). In contrast, the majority of MB cells express proteins that are normally abundant in immature or mature neurons (Lastowska, et al., 2013, Maraziotis, et al., 1992). It raises the question of whether the extent of neuronal differentiation in gliomas and MBs is associated with a more differentiated phenotype and reduced tumorigenicity. As described earlier, proneural transcription factors promote neurogenesis during CNS development and in adult NSCs. However, the proneural genes *PAX6*, *NEUROG2*, and *ASCL1* can individually function as master regulators and induce functional neurons when introduced into cultured primary astroglial cells from the early postnatal cerebral cortex (Berninger, et al., 2007, Heins, et al., 2002). Expression of NEUROD1 in reactive astrocytes and NG2+ OPCs induced glutaminergic neurons, or a combination of glutaminergic and GABAergic neurons, respectively. Even mouse and human fibroblasts can be reprogrammed to transdifferentiate into neurons following expression of ASCL1 and two other neurogenic transcription factors (Torper, et al., 2013, Vierbuchen, et al., 2010). In human pediatric and adult brain tumors, subpopulations of stem-like BTSCs can differentiate into an immature neuronal phenotype (Hemmati, et al., 2003, Singh, et al., 2003).

To assess neuronal differentiation, most studies rely on expression of TujI, a marker of immature neurons (Katsetos, et al., 2001, Singh, et al., 2003). As a marker of migrating type A neuroblasts of the SVZ and SGZ, DCX is also expressed in invasive malignant gliomas (Daou, et al., 2005). Ectopic expression of DCX in human GBM cells effectively inhibited invasion, reduced self-renewal, inhibited tumorigenicity, and induced terminal differentiation into neuron-like cells (Santra, et al., 2011, Santra, et al., 2009). Introduction of NEUROG2 or NEUROD1 in GBM BTSCs resulted in massive cell death, proliferation arrest, and the few surviving cells differentiated into neuron-like cells (Guichet, et al., 2013). Overexpression of *PAX6* reduced tumorigenicity of human GBM cells and in a platelet-derived growth factor B (PDGFB)-driven murine glioma model (Appolloni, et al., 2012, Zhou, et al., 2005). SOX9 is a glial fate marker responsible for generating astrocytes and oligodendrocytes in the developing brain and spinal cord (Stolt, et al., 2003). Transcriptionally, SOX9 regulates glial specification in collaboration with the nuclear factor I family member, NFIA by targeting the downstream effector Mmd2 (Kang, et al., 2012). SOX9 is further under control of miR-124 which is essential for neurogenesis driven from adult stem cells residing in the lateral ventricles. SOX9 is required for NSC maintenance and multipotency. In NSCs, SOX9 is a direct target of miR-124a, the most highly expressed miRNA in the adult brain (Cheng, et al., 2009). The absent/low levels of miR-124a in NSCs increase as NSCs become activated and differentiate into neurons. Overexpression of miR-124a effectively increased neuronal differentiation in mouse SVZ (Akerblom, et al.,

2012, Silber, et al., 2008). We have previously shown that miR-124a, and to some extent miR-137 induction, increased neuronal differentiation in GBM tumorsphere cultures (Silber, et al., 2008). More surprisingly, miR-124a induction generated neuronal progeny from OPC-derived murine oligodendroglioma cells (Silber, et al., 2008). It is possible that activated RAS/MEK signaling in OPC-derived oligodendroglioma cells regulate other SOX genes (such as SOX10) that function as barriers to oligodendrocyte differentiation. However, SOX9 might be a target for miR-124a and enable aberrant neuronal differentiation in both normal OPCs and OPC-derived gliomas (Persson, et al., 2010). Hypermethylation of miR-124a was found in 82% of human GBMs and regulated by activity of REST (Tivnan, et al., 2014). Therefore, REST inhibitors or demethylating agents may represent effective therapies in GBM. In support of this notion, a recent report demonstrated that BTSCs in human GBMs are highly sensitive to *Lysine (K)-specific demethylase 1* (*LSD1*) suppression, leading to a collapse of the stem cell phenotype and reduced tumorigenicity (Suva, et al., 2014). Altogether, these studies suggest that neurogenic factors promote neuronal differentiation and reduce tumorigenicity in human malignant gliomas. It remains unclear if malignant brain tumor cells expressing neuronal markers show properties of normal neurons.

Both diffusible and membrane-bound factors from hippocampal astrocytes can promote proliferation and neuronal fate commitment of hippocampal NSCs (Song, et al., 2002). In hippocampal co-culture experiments from mice lacking the intermediate filament proteins GFAP and Vimentin, reduced endocytosis of the NOTCH1 ligand Jagged1 and decreased Notch1 signaling in primary astrocytes resulted in increased neuronal differentiation of co-cultured neurospheres (Wilhelmsson, et al., 2012). High expression of GFAP and Vimentin in astrocytic gliomas may therefore inhibit neuronal differentiation. Several studies suggest incomplete neuronal differentiation in malignant gliomas and MBs (Varghese, et al., 2008). Differentiation protocols show that neuronal differentiation in GBM seems to be inhibited at the stage of the neuronal intermediate phenotype (Wolanczyk, et al., 2010). As a result of imperfect differentiation arrest differentiated human GBMs co-express neural and mesenchymal markers (Rieske, et al., 2009). However, differentiation of GBM BTSCs into a neuronal phenotype showed that differentiated cells displayed high electrical membrane resistance and the ability to generate action potentials, consistent with more mature neurons (Varghese, et al., 2008). Furthermore, neuronal differentiation was only observed following short-term passaging of human GBMs xenografts (Higgins, et al., 2013). In a later section, we will discuss the therapeutic potential of differentiating brain tumors into neurons and other differentiated phenotypes. Current studies suggest that neuronal differentiation in human brain tumors only reaches an intermediate stage, potentially avoiding aberrant integration with surrounding normal brain and seizures.

Pluripotent brain tumors - beyond neural differentiation

Initial studies of human primary GBM cells demonstrated these cells to be multipotent; capable of differentiating along neuronal and glial cell lineages. Recent studies have shown that subpopulations of stem-like human GBM cells can differentiate into endothelial cells, pericytes, and into multiple mesenchymal lineages (Cheng, et al., 2013, Ricci-Vitiani, et al., 2010, Ricci-Vitiani, et al., 2008, Tso, et al., 2006, Wang, et al., 2010). How can GBMs

originating from a neuroectodermal cell differentiate along mesenchymal cell lineages? Introduction of the two transcription factors *CCAAT/enhancer-binding protein β* (*C/EBPβ*) and *Signal transducer and activator of transcription 3* (*STAT3*) reprogramed fetal human NSCs towards a mesenchymal phenotype and blocked differentiation along neural cell lineages (Carro, et al., 2010). Recent studies found that radiation induces a proneural-mesenchymal shift in a murine proneural glioma model and human GBMs (Halliday, et al., 2014, Mao, et al., 2013). Interestingly, the authors found that transcriptional targets downstream of C/EBPβ and STAT3 signaling were induced in the murine gliomas following radiation (Halliday, et al., 2014). In human GBMs, depletion of C/EBPβ and STAT3 collapsed the mesenchymal signature and reduced aggressiveness (Carro, et al., 2010). These data suggest that transformation of multipotent NSCs or more differentiated progeny can give rise to GBM cells that are pluripotent. Such plasticity of brain tumor cells should provide a survival benefit to changes in the tumor microenvironment following therapy.

Pluripotency of somatic cells was elegantly demonstrated by Yamanaka and colleagues in a landmark study showing that four factors (*OCT4*, *SOX2*, *MYC* and *KLF4*) can convert human skin fibroblasts into induced pluripotent stem (iPS) cells (Takahashi and Yamanaka, 2006). More recent studies found that other factors (like LIN28 and NANOG) can also promote generation of iPS cells (Park, et al., 2008). Conversion of adult multipotent NSCs into iPS cells required even fewer factors (excluding MYC and SOX2) (Kim, et al., 2008). High levels of these reprogramming factors are expressed in aggressive human cancers, including malignant gliomas (Ben-Porath, et al., 2008). Low- and high-grade human gliomas express *NANOG*, *KLF4*, *SOX2*, and *MYC*, where *NANOG* expression was found as a predictor of survival (Elsir, et al., 2014). In this section, we will review the effects of these reprogramming factors on pluripotency and tumorigenicity in malignant brain tumors. The three transcriptional factors *NANOG*, *OCT4* and *SOX2* are thought to play central roles in cancer stem cells and embryonic stem (ES) cells (Kashyap, et al., 2009). The theory was supported in glioma by a study of Guo *et al.* (Guo, et al., 2011), in which they demonstrate expression of *NANOG*, *OCT4* and *SOX2* in the majority of GBM BTSCs. Interestingly, expression of those transcription factors was not only associated with Nestin-positive NSCs, but they were also dependent of the grade in gliomas, suggesting their involvement in glioma progression (Guo, et al., 2011, Yang, et al., 2013) and increased malignancy (Holmberg, et al., 2011). Over-expression of *NANOG*, *OCT4* and *SOX2* in cultured human glioma samples further demonstrates their importance in stemness maintenance (Clement, et al., 2007). Similar to GBMs, expression of the cell-surface antigen CD133 (AC133) has been suggested to label a subpopulation of BTSCs in human MB (Hemmati, et al., 2003, Singh, et al., 2003). However, CD15 rather than CD133 seems to be a tumor propagating marker for SHH-driven MB (Read, et al., 2009, Ward, et al., 2009). Most studies have investigated BTSCs in GBMs while reprogramming ability and multi-lineage potential is less known for MB BTSCs.

NANOG is a transcription factor involved in maintaining self-renewal capacity of ES cells (Cavaleri and Schöler, 2003). NANOG is often found to be enriched in subset of glioma cells positive for certain stemness markers (Clement, et al., 2007, Niu, et al., 2011, Zbinden, et al., 2010). GLI1 is an important effector of the SHH signaling pathway and is up-

regulated together with NANOG in human glioma (Clement, et al., 2007, Zbinden, et al., 2010). Indeed, NANOG is activated through the SHH mediator GLI1 in both NSCs and mouse and human MB stem cells (Po, et al., 2010), suggesting NANOG involvement in SHH-driven stemness of brain tumors. The tumor suppressor *TP53* is often mutated in human glioma patients (England, et al., 2013) and seems to be an important negative regulator of GLI1/NANOG signaling (Zbinden, et al., 2010). Another study found that self-renewal in NSCs is promoted by NANOG (Garg, et al., 2013). NANOG was found to increases the transcription of the microRNA cluster 17–92, resulting in inhibition of *Trp53inp1*, a down-stream component of the *TP53* pathway, promoting self-renewal. Up-stream SHH-GLI1 signaling was suggested to regulate NSC self-renewal either through direct inhibition of the *TP53* pathway or indirect regulation of transcriptional activation of NANOG.

OCT4 is expressed in many human gliomas (Du, et al., 2009). In this study, authors showed that OCT4 expression in C6 rat glioma cells increase the self-renewal capacity and promotes an undifferentiated phenotype. In addition, RNA interference of *OCT4* reduced tumor-forming capacity and increased sensitivity to temozolomide treatment in cultured glioma cells (Ikushima, et al., 2011).

SOX2 levels are reduced as NSCs and progenitors differentiate along neural cell lineages (Uwanogho, et al., 1995). High-grade gliomas express high levels of SOX2, varying between 50–100% nuclear staining (Annovazzi, et al., 2011). Human MBs also express SOX2, especially desmoplastic and nodular tumors that fall into the SHH subgroup (Ahlfeld, et al., 2013). Interestingly, SOX2 positive MB cells are the likely BTSCs for the SHH subtype (Vanner, et al., 2014). These tumor cells are slowly dividing and produce rapidly cycling doublecortin-positive neuronal cells that will comprise tumor bulk. SOX2 positive tumor cells further show resistance to chemotherapy, suggesting that this population is responsible for recurrences. SOX2 is an important factor responsible for brain tumor progression as depletion of SOX2 by ectopic expression of SOX21 diminishes capability of GBM cells to form *in vitro* spheres and additionally induces aberrant differentiation and apoptosis (Caglayan, et al., 2013, Ferletta, et al., 2011). However, elevated SOX2 levels reduced proliferation and CD133 expression in GBM and MB cell lines, suggesting that the threshold level of SOX2 expression regulate stemness and cell fate in brain tumor cells (Cox, et al., 2012).

MYC markedly promotes generation of iPS cells, but also increases tumor formation. Accordingly, the expression levels in reprogrammed cells and MYC-transformed cells are quite similar when comparing differentially expressed (Riggs, et al., 2013). However, different functional moieties on the MYC proteins are involved in the transformation and promotion of directed reprogramming (Nakagawa, et al., 2010).

Malignant primary brain tumor cells often express pluripotency genes and stemness, suggesting that the high degree of tumor plasticity is driven by oncogenic drivers. However, recent studies show that also the tumor microenvironment and therapy can have profound effects on brain tumor plasticity and promote a mesenchymal tumor phenotype. For example, GBMs displaying a high degree of necrosis or angiogenesis express higher levels

of the master transcriptional regulators CEPB and STAT3 that drive a mesenchymal phenotype (Cooper, et al., 2012). Other studies found that hypoxia and tumor-associated macrophages promote stemness in human GBMs (Heddleston, et al., 2009, Seidel, et al., 2010, Wang, et al., 2012a, Yi, et al., 2011). In addition, temozolomide treatment induced expression of OCT4 and SOX2 in cultured human GBM cell lines and primary GBM cells (Auffinger, et al., 2014). The acquired stem cell phenotype showed increased self-renewal capacity and increased tumorigenicity following xenografting into recipient mice. In summary, reprogramming factors are found at high levels in brain tumors (Ben-Porath, et al., 2008, Clement, et al., 2007). The mechanisms involved in stemness and dedifferentiation are extensively studied and there is an increasing amount of reports on how transformation and reprogramming are driven by common transcriptional networks (reviewed in (Semi, et al., 2013, Swartling, et al., 2013a)). A core set of four neurodevelopmental transcription factors (*SOX2*, *OLIG2*, *Sal-like protein 2* (*SALL2*), and *POU domain, class 3, transcription factor 2* (*POU3F2*)) was recently shown to be essential for GBM propagation and maintenance of BTSCs (Suva, et al., 2014). Expression of these factors in differentiated GBM cells "induced" a BTSC phenotype by reprogramming the epigenetic cell state, providing an epigenetic basis for a developmental hierarchy in GBMs that underscores the cellular plasticity.

Potential therapeutic avenues to induce neuronal differentiation in brain tumors

The presence of specific BTSCs is associated with unfavorable outcome in many brain cancer types (Piccirillo and Vescovi, 2007, Visvader, 2011). Current cancer therapies effectively target the tumor bulk of brain tumor cells but leave behind BTSCs that underlie regrowth and recurrence (Chen, et al., 2012a). Development of differentiation regimens of cancers (Table 2), rather than cytotoxic therapies, may be an effective way to reduce treatment-resistance and prevent regrowth of brain tumors.

Retinoic acid—Retinoic acids have for many years been known for their anti-tumor effect, predominantly causing growth arrest and differentiation of target cells (Connolly, et al., 2013). All-*trans* retinoic acid (ATRA) induces arrest in G1 phase and promotes apoptosis in human squamous cell carcinoma (Zhang, et al., 2014). The authors found that RAS-ERK signaling pathway is a direct target of ATRA that acts by decreasing levels of activated ERK and c-Jun NH2-terminal kinase 1/2 (JNK1/2). Effects of ATRA have been well characterized in acute pro-myelocytic leukemia, with important roles in targeting transcription, proteolysis and differentiation (Dos Santos, et al., 2013). The differentiation potential observed in case of ATRA is rather promising not only in case of leukemia, but also in other cancer types such as glioma (Table 2). A recent study showed proof of concept results where ATRA treatment reduced proliferation and induced apoptosis in U87 GBM cells (Shi, et al., 2013). Differentiation potential and anti-tumor effect of ATRA have also been evaluated in preclinical MB models, where growth arrest and extensive apoptosis have been observed both *in vitro* on human MB cell lines and mouse xenografts (Patties, et al., 2013, Spiller, et al., 2008). Potential of ATRA to differentiate BTSCs has been evaluated in several clinical trials alone (Phuphanich, et al., 1997) or in combination with temozolomide (Grauer, et al., 2011, Jaeckle, et al., 2003), celecoxib (Levin, et al., 2006) or cytosine arabinosine (Defer, et al., 1997) (Table 2). Therapeutic effect was either lost after six

months of treatment (Defer, et al., 1997) or there was no difference in progression-free survival (PFS) (Grauer, et al., 2011). Modest effects of ATRA on PFS were only observed in a small subset of patients at low-dose ATRA treatment (Jaeckle, et al., 2003, Levin, et al., 2006, Phuphanich, et al., 1997). As the authors proposed, better understanding of ATRA response mechanism is crucial for therapy success, as well as increase of dosage, which could be beneficial to proven modest responders to low-dose ATRA treatment. Although ATRA has been proven for its differentiation potential in brain tumor cells, the current clinical evaluation does not provide conclusive results, asking for other treatment modalities aiming to differentiate BTSCs, some of which we will further describe below.

Nerve growth factor—Nerve growth factor (NGF) treatment induces differentiation of cancer stem cells of multiple cancers. One study shows remarkable effects of NGF on reducing the number of stem cells present in androgen-independent prostate cancer, where authors showed decreased proliferative capacity both *in vitro* and *in vivo* (Chen, et al., 2012b). Neuroblastoma, a childhood nerve-sheet tumor originating from the peripheral nervous system, is highly responsive to NGF signaling (Verdi and Anderson, 1994), showing significant neuronal differentiation (Matsumoto, et al., 1995, Nakagawara, et al., 1993) and apoptosis (Lavoie, et al., 2005). Similarly, rat C6 glioma cells respond to NGF treatment both *in vitro* and *in vivo* by reducing proliferative potential and inducing neuronal differentiation (Kimura, et al., 2002). NGF signaling is crucial in differentiation of cancer stem cells, predominantly through Tropomyosin receptor kinase A (TRKA) and TRKB receptor activation. High expression of these TRK receptors is found in low-grade gliomas, while highly aggressive and malignant gliomas have almost completely suppressed TRK expression (Wadhwa, et al., 2003), demonstrating the importance of the NGF pathway in glioma progression and clinical outcome. Success of NGF treatment is hence dependent on TRK receptor expression. In attempt to differentiate MB cell lines DAOY, Muragaki *et al.* overexpressed TRK receptors and subsequently evaluated effects of NGF on cell survival (Muragaki, et al., 1997). As expected, authors indicated reduced metabolism and increased apoptosis in cells with upregulated TRK, thus bringing up another potential therapeutic approach in fighting MB. A small GTPase Rab7 seems to suppress TRK levels in gliomas (Saxena, et al., 2005) and it was recently identified as a target for farnesyl-transferase inhibitors (Lackner, et al., 2005), suggesting such drugs could work in differentiating brain tumors cells. Farnesyl-transferase inhibitor Manumycin A was also shown to be effective against MB cell lines in preclinical trials by inducing G1 arrest and apoptosis (Wang and Macaulay, 1999). Another farnesyl-transferase inhibitor Tipifarnib was recently evaluated in a clinical setting, where GBM and MB patients were evaluated for response (Fouladi, et al., 2007). Although none of the MB patients showed response, 10% of evaluated GBM patients showed either partial response or stable disease within four-year trial.

BMP—Bone morphogenetic proteins (BMPs) form a group of proteins with multiple functions in the adult brain stem cell niche, favoring the astroglial fate of cells. In attempt to differentiate cells, Piccirillo *et al.* (Piccirillo, et al., 2006) showed arrest in proliferation of GBM cells after BMP4 exposure. They observed accumulation of cells in G0/G1 phase and reduction in the number of cells with active DNA synthesis. The effect was not only observed *in vitro*, but also *in vivo*, where tumor-bearing animals survived significantly

longer when treated with BMP4-releasing carrier beads. In a recent study, overexpression of BMP4 showed a robust antitumor effect on GBM cells (Duggal, et al., 2013). BMP2 and BMP4 also inhibit MB proliferation by inducing neuronal differentiation. This inhibition is caused by a rapid proteasome-mediated degradation of MATH1 (Zhao, et al., 2008). Despite the increasing number of preclinical studies evaluating therapeutic effects on BTSCs, BMP targeted therapies have still not entered clinical trials. BMPs are currently approved modes of treatment for several bone-related malformations and injuries including open fractures of long bones (Gautschi, et al., 2007), proving the safety of those agents for patients.

AMPK and mTOR—In an attempt to differentiate malignant astrocytoma cells and overcome reprogramming induced by *TP53* and *Ink4a* mutations, Zhang *et al*. successfully delayed G1 phase and M phase entry by activating AMP-activated protein kinase (AMPK) by Isoxazole treatment (Zhang, et al., 2011). Moreover, cells treated with Isoxazole show re-expression of neuronal markers, *e.g.* TuJ1. It is suggested that BTSCs reprogram their metabolism for optimal growth and proliferation, where AMP-activated protein kinase (AMPK) has an important role. AMPK is activated in both human and mouse gliomas and its activity can be suppressed by using AMPK-agonists AICAR and metformin (Liu, et al., 2014). Both drugs are nowadays evaluated in more than 50 different clinical trials and have recently been identified as potential therapeutics against gliomas (Liu, et al., 2014). Both drugs were able to induce G2M arrest previously correlated with cell differentiation (Xiang, et al., 2008). Several mTOR inhibitors including sirolimus (rapamycin), everolimus (RAD-001) and temsirolimus (CCI-779) are currently evaluated in approximately 40 clinical trials involving patients with diagnosed gliomas and GBMs (https://clinicaltrials.gov). Recently completed phase II clinical trial involving temsirolimus treatment in combination with temozolomide and bevacizumab however did not show any partial response in all 13 GBM patients, providing only two patients with stable disease (Lassen, et al., 2013). Similarly, none of the 18 recurrent GBM patients involved in phase II study of sorafenib in combination with temsirolimus remained progression free at six months, with only two partial responses reported (Lee, et al., 2012). Everolimus on the other hand seems to be promising in GBM patients in combination with bevacizumab, temozolomide and radiation (Hainsworth, et al., 2012). More than half of the patients enrolled in this trial (61%) had objective response with a median progression-free survival 11.3 months and overall survival of 13.9 months. Combined, AMPK and mTOR inhibitors show promise in GBM. Despite strong therapeutic effect in preclinical studies, failing to provide benefits in clinical settings require more advanced inhibitors that specifically target the mTOR pathway.

HDAC inhibition—Use of HDAC inhibitors has emerged as a potential strategy to reverse aberrant chromatin changes and induce cell differentiation in cancer. The HDAC inhibitor valproic acid is FDA-approved for use in several neurological disorders. Several classes of HDAC inhibitors reduce GBM cell proliferation *in vitro* and tumor growth in GBM xenograft models (Asklund, et al., 2012, Benitez, et al., 2008, Yin, et al., 2007). In GBM patients, valproic acid treatment during radiotherapy improved overall survival (Barker, et al., 2013). Furthermore, dual inhibition of LSD1 and HDAC cooperated to induce cell death in GBM cell lines (Singh, et al., 2011). In MB, HDAC inhibition reversed GNP proliferation in a SHH-driven GEMM of MB (Lee, et al., 2013). In human MB cell lines, the incubation

with the HDAC inhibitor sodium butyrate promoted cell death and induced neuronal differentiation (Nor, et al., 2013). Clinical trials suggest that the HDAC inhibitors vorinostat and valproic acid are well-tolerated in GBM patients (Galanis, et al., 2009, Weller, et al., 2011). Valproic acid treatment is well-tolerated in GBM patients (Weller, et al., 2011). These studies validate HDAC inhibition as a potential target in human GBM and MB patients.

DNMT, EZH2, and IDH1^{R132H} inhibition—Widespread resetting of DNA methylation pattern in GBM BTSCs inhibited malignant properties (Stricker, et al., 2013). Inhibition of the PRC2 complexing protein EZH2 in human GBMs reduced tumor growth by both H3K27me3-dependent and STAT3-dependent pathways (Kim, et al., 2013). In another study, pharmacological inhibition of EZH2 impaired invasion into surrounding brain tissue of xenografted GBMs (Natsume, et al., 2013). Furthermore, the DNMT1 inhibitor Decitabine successfully inhibited differentiation and suppressed tumor growth of *IDH1*^{R132H} mutant human glioma cells (Turcan, et al., 2013). A more personalized approach include the successful use of a small molecule *IDH1*^{R132H} inhibitor AGI-5198 that increased glial differentiation in murine NSC cultures and delayed growth of human *IDH1*^{R132H} mutant glioma xenografts (Rohle, et al., 2013).

MYC/MYCN—G34R or G34V *H3F3A* mutations are also found in children and young adults, but these do not result in inhibition of PRC2. Instead, G34R/V mutations result in altered binding of proteins that recognize trimethylated H3K36 (H3K36me3) (Bjerke, et al., 2013). This results in a gene expression signature that is more commonly seen in the developing forebrain and that is associated with increased *MYCN* transcription. This is in line with data that we demonstrated and which showed that constitutively activated T58A MYCN can drive gliomagenesis in forebrain murine NSCs (Swartling, et al., 2012). Glial differentiation by the transcriptional co-activator p300 was blocked by overexpression of MYC that instead promoted a stem cell-phenotype (Panicker, et al., 2010). Interestingly, MYC was found to be a direct target of EZH2 and essential for maintenance of the stem cell-phenotype (Suva, et al., 2009). These studies show that *H3F3A* mutations in GBMs converge on MYC and MYCN. As a major engine and driver of an undifferentiated state in GBMs, future therapies targeting MYC are expected to induce differentiation and apoptosis. However, aberrant recruitment of the PRC2 complex to K27M mutant H3.3 and enzymatic inhibition of EZH2 was found to produce a global reduction of the repressive histone mark H3K27me3 (Bender, et al., 2013), suggesting that EZH2 inhibition might accelerate tumor growth in K27M mutant tumors (Lewis, et al., 2013). Alternative pathways to inhibit MYC-driven MBs include cell cycle arrest following epigenetic regulation using BET bromodomain inhibition or Aurora kinase A inhibition (Bandopadhayay, et al., 2014, Bjerke, et al., 2013).

Use of location and time to delineate a relationship between cell of origin and brain tumor type

Refined transcriptomal profiling of gliomas and MB have enabled researchers to associate tumor subgroups with genetic alterations and methylation signatures. Interestingly, several studies show that subgroups of primary malignant brain tumors associate with the patient

age and the location in the brain, implicating that temporally and regionally restricted populations of neural precursors give rise to distinct subsets of tumors. As the tumor phenotype change and accumulate new driver mutations, it becomes even more difficult following therapy to delineate a relationship between the origin and tumor phenotype. Therefore this discussion will only focus on primary non-recurrent brain tumors.

The methylation profiles of pediatric and adult GBMs were found to correlate with mutational status and cytogenetic aberrations (Sturm D et al. Cancer Cell, 2012). Young children are diagnosed with GBMs that often display *H3F3A* K27M mutations and a hypomethylated phenotype. In contrast, GBMs in older children are associated with *H3F3A* G34R/V mutations that display a hypermethylated phenotype. While most *H3F3A*^{K27M} tumors are found in brainstem regions, *H3F3A*$^{G34R/V}$ tumors are instead observed in cortical forebrain lobes. Interestingly, *H3F3A*$^{G34R/V}$ tumors express low levels of OLIG2, expressed at high levels in other GBM subgroups, but are still aggressive tumors. In young adults, *IDH1*^{R132H} mutated GBMs are highly hypermethylated and associated with a better prognosis. Despite the different methylation signatures, *H3F3A* and *IDH1*^{R132H} mutated tumors are highly associated with *TP53* mutations. It has been suggested that a population of SHH-responsive glial progenitors expressing OLIG2 and Nestin peaks in the ventral pons when most *H3F3A*^{K27M} GBMs and diffuse intrinsic pontine gliomas (DIPGs) are diagnosed in patients (Monje M et al. PNAS, 2011). It is possible that cooperation of *TP53* and *H3F3A*$^{G34R/V}$ mutations in SVZ NSCs of young children produce GBMs during late childhood (Figure 1). Development of *IDH1*^{R132H} mutation in young adults is consistent with transformation of white matter OPCs as the major population of cycling cells. In childhood GBMs displaying PDGFRA amplifications, SVZ NSCs and OPCs are two populations susceptible to transformation. In adults, PDGFRA amplified tumors are more likely to originate from OPCs, known to be highly dependent of PDGF signaling. During late adulthood, it remains unclear if remnants of transformed NSCs, OPCs, or dedifferentiated astrocytes produce tumors displaying a mesenchymal gene expression signature or GBMs displaying EGFR amplifications. Interestingly, studies of a GEMM of pediatric low-grade glioma found that tumors arise from NSC lining the third ventricle, and not from SVZ NSCs lining the lateral ventricles (Lee DY et al. Cancer Cell, 2012).

For MB, SHH tumors are unique since they occur in infants but not in older children (Taylor MD et al., Acta Neuropathol, 2012). Similar to WNT tumors, they can also occur in adults. Since several populations of cerebellar and brain stem precursors expand around birth and during early childhood, it has been difficult to assign a unique cell of origin for each MB subgroup. However, development of novel GEMMs for MB has identified specific cell populations that can generate tumors matching gene expression profiles of human MB subgroups (Poschl J et al. Acta Neuropathol, 2014). To identify the cell of origin, most studies have relied on GEMMs that rely on oncogenic expression under a specific gene promoter. A better spatial and temporal resolution can be attained by using a cross-species analysis approach where murine tumors, generated from temporally defined precursors, are compared to cohorts of human tumors. This approach was elegantly employed to define the cell of origin for different ependymoma subtypes (Johnson RA et al. Nature, 2010). However, this approach is more difficult to use for gliomas and MBs where multiple

candidates of precursor populations can produce tumors. Given that there are major differences in the development of neocortex and postnatal neurogenesis between mouse and humans, future work should validate that tumor-susceptible precursor populations expand during corresponding time windows also in humans.

CONCLUSION

Advances in NSC biology have identified genes and pathways that regulate neurogenesis in animals and humans. In parallel, genome-wide characterization of human gliomas and MBs has identified genetically and epigenetically distinct subgroups. Of interest, genetic alterations in pathways regulating normal neurogenesis are often perturbed in human brain tumors, and when reversed, often promote neuronal differentiation. Newly developed GEMM of gliomas and MBs have demonstrated that subgroup-specific genomic alterations in precursor cells often disrupt normal differentiation and promote tumorigenesis in a cell context-dependent manner. Studies of GEMMs and human brain tumors serve complimentary roles and are both important to identify driver mutations that maintain tumor growth and as pre-clinical tools for targeted therapy. Direct pharmacological targeting of driver mutations or down-stream effectors, manipulation of the tumor microenvironment, or cell-based therapies all represent novel approaches to reduce levels of reprogramming genes, induce differentiation, and reduce treatment-resistance in brain tumors.

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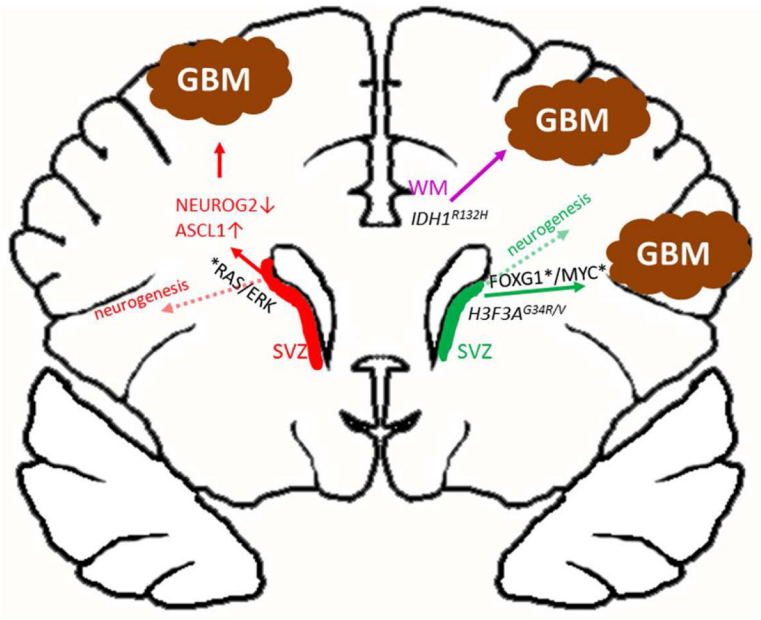

Figure 1. Deregulation of neuronal and glial differentiation as a priming step in GBM formation

Schematics of frontal lobes and lateral ventricles in the anterior regions of the adult cerebrum. Genetic alterations in SVZ neural precursors in the RAS/ERK pathway induce a NEUROG2-ASCL1 switch that induces gliomagenesis (Li, et al., 2014). The inability of *IDH1*^{R132H} mutation to transform nestin-expressing NSCs, the high frequency of *IDH1*^{R132H} mutation in oligodendroglioma (shown to originate from white matter OPCs), and the association of these tumors to the frontal cortex suggest that expression of *IDH1*^{R132H} mutation in white matter (WM) progenitors inhibits differentiation and drive formation of proneural gliomas (Phillips, et al., 2006, Sturm, et al., 2012). Similarly, childhood GBMs displaying G34R/V mutation in the *H3F3A gene* express high levels of *FOXG1* and *MYC*, but low/no levels of the OPC-related gene OLIG2, implicating a NSC origin. Misexpression (activation/upregulation (*) or (loss) of important cancer genes is shown in black.

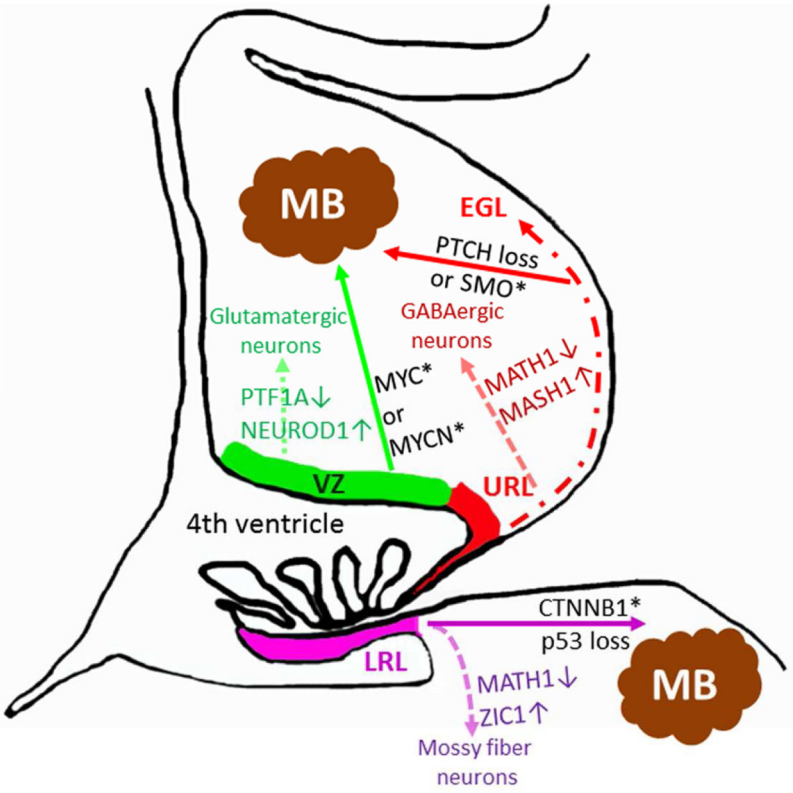

Figure 2. Transformation of neuronal precursors disrupts neurogenesis and drives MB formation

Schematic figure of the cerebellum and the dorsal brain stem during embryonic development. Various developmental pathways (dotted arrows) drives glutamatergic or GABAergic neurogenesis from stem cells in the ventricular zone (VZ) (green) or from granule neuron precursors in the upper rhombic lip (URL)/external granular layer (EGL) (red), respectively (for further details see (Swartling, et al., 2013)). Similarly, mossy fiber neurons are derived from the lower rhombic lip (LRL) (purple) of the brain stem (Cicirata, et al., 2005). Misexpression (activation/upregulation (*) or (loss) of important cancer genes including *CTNNB1* (Gibson, et al., 2010), *SMO/Ptch* (Schuller, et al., 2008, Yang, et al., 2008), *MYC/MYCN* (Kawauchi, et al., 2012, Pei, et al., 2012, Swartling, et al., 2010, Swartling, et al., 2012) are shown in black. As described in this review such cancer genes are involved in driving medulloblastoma (MB) in a cell context-dependent fashion from cells within VZ, URL/EGL or LRL.

Table 1

Cell of origin for murine tumors matching human MB subgroups

MB subgroup	Driver genes*	Pathways	Originating cell**
WNT	*CTNNB1*, *TP53* loss	WNT	LRL progenitor of developing brain stem
SHH	*SHH*, *SMO*, *SUFU*, *MYCN*, *GLI2*, *hTERT* promoter mutations, *TP53* loss, *PTCH* loss,	SHH	URL progenitor/EGL cell, Nes+ EGL cerebellar cell or choclear brain stem cell
Group 3	*MYC*, *GFI1/GFI1B*, *OTX2*, *LIN28B*	Various	Cerebellar NSCs
Group 4	*MYCN*, *GFI1/GFI1B*, *KDM6A*, *CDK6*, *SNCAIP*, *LIN28B*	Various	Unknown/cerebellar NSCs

* a vast selection of the most important cancer driver genes for these brain tumors

** potential cellular origin as supported from literature and various brain tumor models

Table 2

Potential differentiation therapies for brain tumors

Compound	Cancer type	Phase	Targeted pathway
Retinoic acid	Acute promyelocytic leukemia Glioma Medulloblastoma	Clinical practice (Dos Santos, et al., 2013) Preclinical trials (Patties, et al., 2013, Shi, et al., 2013, Spiller, et al., 2008) Clinical trials (Defer, et al., 1997, Grauer, et al., 2011, Jaeckle, et al., 2003, Levin, et al., 2006, Phuphanich, et al., 1997)	MAPK/ERK, JNK
NGF	Prostate cancer Neuroblastoma Medulloblastoma Glioma	Preclinical trials (Chen, et al., 2012b, Kimura, et al., 2002, Lavoie, et al., 2005, Muragaki, et al., 1997, Zhu, et al., 2013)	NGF/Trk
Farnesyl-transferase inhibitors	Glioma Medulloblastoma	Preclinical trials (Lackner, et al., 2005, Wang and Macaulay, 1999) Clinical trials (Fouladi, et al., 2007)	NGF/Rab7
BMP4/Vaccinia virus expressing BMP4	Medulloblastoma Glioblastoma multiforme	Preclinical trials (Zhao, et al., 2008), (Duggal, et al., 2013, Piccirillo, et al., 2006)	BMP pathway
Isoxazole	Glioblastoma multiforme (astrocytoma)	Preclinical trials (Zhang, et al., 2011)	G1 blockade
AICAR	Glioma Other cancers	Clinical and preclinical trials (Liu, et al., 2014)	mTOR pathway
Metformin	Glioma Other cancers	Clinical and preclinical trials (Liu, et al., 2014)	mTOR pathway
HDAC inhibitors	Glioma Medulloblastoma	Clinical and preclinical trials (Galanis, et al., 2009, Lee, et al., 2013, Nor, et al., 2013, Weller, et al., 2011)	HDAC inhibition
Decitabine	Glioma	Preclinical and clinical trials (Turcan, et al., 2013)	DNMT
IDH1^{R132H}	Glioma	Preclinical trials (Rohle, et al., 2013)	*IDH1^{R132H}*