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Convergence of Developmental Origins and Oncogenic Pathways in Malignant Brain Tumors

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Abstract

Brain tumors such as adult glioblastomas and pediatric high-grade gliomas or medulloblastomas are among the leading causes of cancer-related deaths, exhibiting poor prognoses with little improvement in outcomes in the past several decades. These tumors are heterogeneous and can be initiated from various neural cell types, contributing to therapy resistance. How such heterogeneity arises is linked to the tumor cell of origin and their genetic alterations. Brain tumorigenesis and progression recapitulate key features associated with normal neurogenesis; however, the underlying mechanisms are quite dysregulated as tumor cells grow and divide in an uncontrolled manner. Recent comprehensive genomic, transcriptomic, and epigenomic studies at single-cell resolution have shed new light onto diverse tumor-driving events, cellular heterogeneity, and cells of origin in different brain tumors. Primary and secondary glioblastomas develop through different genetic alterations and pathways, such as *EGFR* amplification and *IDH1/2* or *TP53* mutation, respectively. Mutations such as histone H3K27M impacting epigenetic modifications define a distinct group of pediatric high-grade gliomas such as diffuse intrinsic pontine glioma. The identification of distinct genetic, epigenomic profiles and cellular heterogeneity has led to new classifications of adult and pediatric brain tumor subtypes, affording insights into molecular and lineage-specific vulnerabilities for treatment stratification. This review discusses our current understanding of tumor cells of origin, heterogeneity, recurring genetic and epigenetic alterations, oncogenic drivers and signaling pathways for adult glioblastomas, pediatric high-grade gliomas, and medulloblastomas, the genetically heterogeneous groups of malignant brain tumors.

Graphical Abstract

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Declaration of Interests

The authors declare no competing interests.

Keywords

glioma; medulloblastoma; neural stem cells; glial progenitor cells; oligodendrocyte progenitors; oncogenic signaling network; Tumor suppressors; epigenetic regulation

INTRODUCTION

Brain tumors are primary tumors of the central nervous system. They include high-grade gliomas such as glioblastoma (GBM), low-grade gliomas, pediatric diffuse intrinsic pontine glioma (DIPG), as well as medulloblastoma in both children and adults (Liu et al., 2017; Sampetean and Saya, 2018). The prognosis for GBM remains poor with less than 5.5% of patients surviving past the 5-year mark (Brennan et al., 2013; Jansen et al., 2010; Ostrom et al., 2017). DIPG outcomes are even poorer, with an average overall survival of less than 1 year (Lapin et al., 2017). Treatment of high-grade gliomas poses many challenges due to the infiltrative and resistant nature of tumors to conventional radiotherapy and chemotherapies.

Gliomas are classified by the WHO according to the glial tissue lineage they most resemble: astrocytomas, oligodendrogliomas, mixed oligoastrocytomas, and other diffuse gliomas. Tumors are also graded from I to IV based on malignancy of the tumor with I being benign (Louis, 2007; Verhaak et al., 2010; Vitucci et al., 2011). Grade IV astrocytomas and oligoastrocytomas are classified as GBM (Louis, 2007; Vitucci et al., 2011). Gliomas are highly infiltrative; tumor cells often migrate along white matter tracts to infiltrate and invade regions outside the original location, making surgical removal difficult (Holland, 2001). These tumors display significant cellular and genetic heterogeneity (Filbin et al., 2018; Parsons, 2008; Patel et al., 2014; Tirosh et al., 2016), which may contribute to tumor recurrence and therapy resistance (Mackay et al., 2017; Morrissey et al., 2016). The impossibility of complete surgical resection along with resistance to both radiation therapy and chemotherapy make GBM and DIPG almost impossible to cure with current standard treatment methods (Lapin et al., 2017; Maher et al., 2001). Additionally, tumors that recur

after resection often progress to higher grades of glioma and become treatment resistance, which ultimately causes the mortality in patients (Ohgaki and Kleihues, 2009; van den Boom et al., 2003). Various efforts have been made recently to better understand brain tumors including investigations of cell of origin or tumor stem/initiating cells, transcriptome profiling, exome, genome, and epigenome sequencing, single-cell RNA sequencing, and use of genetically engineered mouse models. This review focuses on the convergence of developmental processes and brain tumorigenesis at molecular and cellular levels, highlighting potential vulnerabilities and targets for treating distinct subtypes of brain tumors.

CELLS OF ORIGIN AND GLIOMA STEM CELLS

A better understanding the cell of origin of brain tumors may allow diagnosis at a pre-malignant stage and identification of lineage-specific vulnerabilities for therapeutic targeting. Neural stem cells are candidates for targets of transformation because of their inherent self-renewing capacity and their longevity; however, recent studies demonstrated that, upon oncogenic alterations, progenitors or committed cells can serve as tumor-initiating cells by dedifferentiating and reacquiring stem-cell-like traits (Friedmann-Morvinski et al., 2012; Schwitalla et al., 2013). The cell of origin of gliomas, defined by Visvader as tumor-initiating cells that undergo genetic mutations leading to the initiation of cancer (Visvader, 2011) are controversial. Investigations into which cells can undergo mutagenesis to initiate cancer indicate that neural stem cells (NSCs), oligodendrocyte precursor cells (OPCs), and astrocytes all have the ability, upon pathological insult, to proliferate—a prerequisite for the accumulation of mutations that induce tumorigenesis (Figure 1A).

Neural stem/progenitor cells:

Neural stem/progenitor cells were an early contender for the cell of origin for gliomas; studies done using high-penetrance glioma mouse models showed that cells within the neural stem cell niche were more readily transformed than differentiated cell types outside of the niche (Alcantara Llaguno et al., 2009; Holland, 2000) (Figure 1A). Targeted deletion of tumor suppressor genes e.g. *Nf1*, *Trp53*, and *Pten*, in cells of the nestin- or GFAP-expressing neural progenitor cells led to fully penetrant GBM in mice, demonstrating the tumor-forming potential of NSCs in mice (Alcantara Llaguno et al., 2009; Zheng et al., 2008). The GFP reporter in the nestin-thymidine kinase-GFP transgenic mice was found to label quiescent neural stem cells in the adult subventricular zone as well as stem-like cells in tumor tissues of an animal model of glioma, suggesting the presence of stem-like cells in gliomas (Chen et al., 2012). Notably, ablation of the nestin-positive stem-like cells through activation of the thymidine kinase with ganciclovir attenuated tumor growth, although it failed to halt tumor progression (Chen et al., 2012), indicating that other nestin-negative progenitors may also contribute to the glioma growth. A recent study of a cohort of human GBMs using deep genomic sequencing indicated that normal subventricular zone tissue contained low-level GBM driver mutations, suggesting that NSCs migrate from the subventricular zone and lead to the development of high-grade malignant gliomas (Lee et al., 2018). Although these studies show that mutations in NSCs are sufficient for glioma

formation, they did not demonstrate that NSCs are necessary or exclusive players in gliomagenesis.

Astrocyte lineage cells:

Astrocytes are contenders as the cell of origin because proliferating astrocyte progenitors may exist in the postnatal brain (Ge et al., 2012), although whether differentiated astrocytes can undergo cell division in the postnatal brain still remains controversial. In addition, astrocyte precursor cells have yet been identified or defined (Figure 1A). Upon traumatic brain injury, we and others have shown that some astrocytes re-enter the cell cycle (Bardehle et al., 2013; Chen et al., 2008). Implantation of astrocytes that express oncogenes into mouse brains or ablation of tumor suppressor genes from mouse brains led to malignant gliomas, therefore these cells can form gliomas (Bachoo et al., 2002; Endersby et al., 2011; Ghazi et al., 2012; Liu et al., 2011; Munoz et al., 2013; Paugh et al., 2013; Radke et al., 2013). These experiments are not definitive, however, as the typical astrocyte marker GFAP is also expressed by NSCs (Fraser et al., 2004; Lee et al., 2000; Molofsky et al., 2012). Tamoxifen-induced human GFAP promoter driven-CreER (GFAP-CreER) deletion of tumor suppressors *Trp53*, *Pten*, and *Rb* in adult mice led to high-grade astrocytoma formation in or contiguous to the adult proliferative niches in SVZ (as expected from the ability of NSCs to form gliomas) as well as in non-proliferative zones (Chow et al., 2011). GFAP-expressing astrocytes could be the cells of origin in these zones. In addition, a recent study of astrocyte diversity in the adult brain suggests that a subpopulation of astrocytes is the malignant analog of glioma (Lin et al., 2017).

Oligodendrocyte precursor cells:

OPCs are the most abundant cycling cell population of the adult central nervous system (Dawson et al., 2003; Imamoto et al., 1978) and represent the main pool of proliferative progenitor cells (~ 70%) in the normal adult rodent brain (Dawson et al., 2003; Dimou et al., 2008). Almost all mitotic cells co-express the OPC markers OLIG2 or NG2 in the human hippocampus (Geha et al., 2010). Their prevalence and mitotic characteristics throughout brain development make them possible cells of origin in brain tumorigenesis (Figure 1A). OPCs can be transformed and form malignant gliomas through overexpression of PDGF, the mitogen for OPCs (Dai, 2001; Lindberg et al., 2009; Uhrbom et al., 1998). Inactivation of p53 and Nf1 specifically in adult OPCs directed by NG2-CreER gives rise to malignant gliomas. (Galvao et al., 2014). Similarly, deletion of *Nf1*, *Trp53*, and *Pten* in the NG2-expressing OPCs in adult mice leads to GMB formation, although the tumors are more restricted to the ventral brain regions (Alcantara Llaguno et al., 2015).

In human brain tumors, OLIG2 is present, to various extents, in all grades of pediatric and adult diffuse gliomas including astrocytomas, oligodendrogliomas, and GBMs (Ligon et al., 2004; Lu et al., 2001; Otero et al., 2011). OLIG2, an essential transcription factor for OPC specification during central nervous system development, is expressed in OPCs and their primitive progenitors and controls the OPC-astrocyte fate switch in the developing brain (Lu et al., 2002; Takebayashi et al., 2002; Zhang et al., 2016b; Zhou and Anderson, 2002; Zhu et al., 2012). Notably, we and others showed that a large population of OLIG2⁺ cells in human gliomas, particularly proneural GBMs, expresses the proliferative marker Ki67 and the stem-

cell marker CD133, suggesting that proliferative OLIG2⁺ cells are tumor-propagating cells (Ligon et al., 2007; Lu et al., 2016; Singh et al., 2016).

Strikingly, mosaic analysis with double markers (MADM) at a single-cell level revealed a critical role of OPCs in proliferation and expansion of glioma cells (Zong et al., 2005). Introduction of glioma-initiating mutations in *Trp53/Nf1* in NSCs results in an expansion of OPC-like cells rather than proliferation of NSCs themselves prior to malignancy (Liu et al., 2011), suggesting that OPCs are a cell of origin, or transit-amplifying cells, for this model of glioma even when the initial mutations are in NSCs. In addition, in the OPC-expressing NG2-Cre-driven MADM, *Trp53/Nf1* deletion initiated in OPCs results reactivation and subsequent expansion of mutant OPCs prior to their malignant transformation (Liu et al., 2011), suggesting that OPCs themselves can be directly transformed into malignant tumor cells likely through step-wise genetic and epigenetic reprogramming.

Recent single-cell transcriptomics analyses of different human gliomas with distinct driver mutations, including oligodendrogliomas, astrocytomas, GBMs, and DIPGs, revealed a prominent primitive OPC-like progenitor population that has a stemness-associated signature (Filbin et al., 2018; Patel et al., 2014; Tirosh et al., 2016; Venteicher et al., 2017). These observations indicate that human gliomas that arise from distinct genetic mutations may originate from the primitive OPC-like progenitors (pri-OPCs), the early progenitor cells preceding OPC commitment (Weng et al., 2019). The highly proliferative pri-OPCs may function as transit-amplifying cells during the onset of tumorigenesis and recurrence. The analyses of different tumorigenic phases at the single-cell level in a murine glioma model indicate that reprogramming of the OPC intermediates into a stem-like state, rather than direct stem-cell proliferation, resulted in their malignant transformation (Weng et al., 2019).

Once tumor development is initiated, how do tumor cells sustain or self-renew? The cancer stem cell theory posits that a small population of cells expressing CD133, a marker of neural stem cells, can sustain tumorigenesis through self-renewal and are capable of regenerating the tumor when transplanted (Singh et al., 2004). These CD133⁺ cells can differentiate into neurons, astrocytes, and oligodendrocytes when exposed to serum, that match the heterogeneous signatures of glioma tumors (Furnari et al., 2007; Nunes et al., 2003). This supports the notion that CD133⁺ NSC-like cells serve as glioma stem cells.

However, the existence of any dedicated cancer stem cell in brain tumors has yet to be defined. Controversy over the definition of glioma stem cells exists in part because there is evidence that certain CD133⁻ cells are also capable of forming tumors in transplantation models (Beier et al., 2007; Joo et al., 2008). Additionally, there is evidence suggesting that OPC-like progenitors are the tumor-sustaining glioma stem cells: Transplantation of as few as 50 tumor cells matching an OPC profile cause glioma in immunocompromised host mice, whereas cells with an NSC profile do not (Persson et al., 2010). Similarly, under certain pathological conditions such as *Nf1* and *Trp53* mutations, fate-committed cells like OPCs can dedifferentiate and behave as facultative stem cells (Galvao et al., 2014; Liu et al., 2011). Given that malignant gliomas are highly heterogeneous, their cells of origin may derive from NSCs, OPCs and/or astrocytes in a context-dependent manner. Specific cell types may have distinct susceptibility to oncogenic signaling and reprogramming, which

lead to their ultimate transformation. Future single-cell fate mapping at temporal and spatial resolution would require to define the cell of the origin in gliomas. Thus, the tumor cells of origin may encompass a range of the plastic cell types or progenitor cells that are susceptible to malignant transformation (Figure 1A).

GLIOMA HETEROGENEITY

Brain tumors are highly heterogeneous tumors, and precise cells of origin and driver oncogenes are difficult to define. Tumorigenesis is ascribed to a succession of genetic and epigenetic alterations that ultimately lead to the formation of a cell population characterized by functional and phenotypic heterogeneity (Hanahan and Weinberg, 2011). With the advancement of molecular technology, high-throughput and single-cell sequencing have allowed an unprecedented level of genomic analysis that has increased our understanding of gliomas and their heterogeneities. Intratumor heterogeneity could be the result of distinct tumor-initiating cells within tumor tissues (the stochastic model) or a set of cancer stem-like cells that can give rise to distinct tumor-forming cells (the hierarchy model), reflecting the heterogeneity gained after tumor initiation (Figure 1B).

The Cancer Genome Atlas Project (The Cancer Genome Atlas Research, 2008), a collaborative effort to increase understanding of the molecular and genetic basis of different cancers, was the first to complete a comprehensive genomic characterization of glioblastomas. This effort collected confirmed the relevance of the receptor tyrosine kinases (RTKs), tumor suppressor p53, and RB pathways in GBM, with 88%, 87%, and 78% of GBMs having altered signaling through these pathways, respectively (Parsons, 2008; The Cancer Genome Atlas Research, 2008).

Based on gene expression profiles in tumor tissues, GBMs have been classified into four distinct molecular subtypes: proneural, classical, neural, and mesenchymal (Verhaak et al., 2010). The proneural GBM subtype has OPC gene signatures and amplification of *PDGFRA* (the gene encoding platelet-derived growth factor), *TP53* mutations, and/or mutations in *IDH* genes (which encode isocitrate dehydrogenases) (Brennan et al., 2013; Verhaak et al., 2010). The classical subtype is characterized by an astrocytic signature and activation or amplification of the gene encoding epidermal growth factor receptor (EGFR) and/or loss of the *CDKN2A* locus (Hayden, 2010; Verhaak et al., 2010). It is worth noting that the mesenchymal subtype is characterized by reactive astrocyte (CD44⁺) and microglia signatures, *NF1* deletion, and elevation of TNF- α and NF- κ B signaling (Verhaak et al., 2010). Consistently, TNF- α treatment could lead to a shift of proneural GSCs towards a mesenchymal state with CD44 expression and NF- κ B activation (Bhat et al., 2013), suggesting the tumor microenvironment plays a role in this transition. However, it is worth noting that mesenchymal genetic signatures may potentially result from tumor stromal components, as opposed to the tumor cells of the neoplastic tissues, which rather exhibit expression profiles similar to stem-like cells and proneural tumor cells (Calon et al., 2015; Isella et al., 2015; Kim and Verhaak, 2015; Martinez et al., 2015), suggesting that mesenchymal subtype tumors consist of a mixture of tumor stem-like cells and tumor stromal microenvironment components. In addition, recent studies suggest that the neural

GBM signature may be attributable to the contamination of normal brain tissue profiles (Wang et al., 2018b).

Single-cell sequencing, which allows profiling of single cells as opposed to bulk tumor tissue, has also been utilized to define the heterogeneity of gliomas (Khoo et al., 2016; Levitin et al., 2018; Ortega et al., 2017). This approach has enabled the dissection of heterogeneous cellular populations within tumors by identifying potential malignantly transformed cells (e.g. stem-like subpopulations and sublineages of developmentally related cells) and cell types comprising tumor microenvironments (e.g. infiltrating immune populations and other stromal populations) in different types of brain tumors (Filbin et al., 2018; Patel et al., 2014; Tirosh and Suva, 2018). In addition, single-cell analysis may further reveal diverse physiological states of tumor cells such as cycling or quiescent phases, stressed, hypoxic or DNA damage states (Patel et al., 2014; Tirosh and Suva, 2018). Single-cell profiling of IDH1 and IDH2 mutant human oligodendrogliomas revealed that cancer cells consist of a mix of oligodendrocyte- and astrocyte-lineage progenitor cells as well as undifferentiated stem-like progenitors, which are highly proliferative and responsible for fueling the tumor growth (Tirosh et al., 2016). Similarly, the analysis of H3K27M-glioma indicated that these tumors mainly contain OPC-like progenitors with stemness signatures (Filbin et al., 2018). Thus, the malignant populations within tumor tissues appear to be superimposed on aberrant developmental processes, consisting of stem-like cells, OPC-like and astrocyte-lineage-like cells.

By fate mapping of primary barcoded human GBM cells following serial xenografts, Lan et al. showed that tumorigenesis progresses through a developmental-like hierarchy rooted in GBM stem cells from slow-cycling stem-like cells to rapidly cycling progenitors, which in turn generate post-mitotic cells (Lan et al., 2017). Single-cell analysis of the tumor core and surrounding tissues revealed that infiltrating cells share gene signatures of tumor cells preexisted in heterogeneous GBM samples, suggesting that a common cellular mechanism drives tumor infiltration (Darmanis et al., 2017). These studies at the single-cell level have resulted in a detailed view of the molecular landscape of gliomas, characterizing the heterogeneity that exists within and between tumors, which is likely due to distinct patterns of somatic mutations, copy number alterations and DNA methylation status in tumor cells. Ultimately, single-cell fate tracing studies, e.g. through CRISPR–Cas9 mediated genetic barcoding (Kalhor et al., 2017; McKenna et al., 2016) or the mosaic lineage tracing MADM system (Zong et al., 2005), will need to test whether GBM tumor cells are derived from common or distinct progenitors.

GLIOMA CORE REGULATORY PATHWAYS

Cooperative actions of lineage-determining and signal-dependent transcription factors dictates the spatio-temporal pattern of gene expression and cellular reprogramming that predisposes post-mitotic cells to acquire stem cell-like properties, giving rise to tumor-initiating cells endowed with long-term tumorigenic capacity (Friedmann-Morvinski et al., 2012; Vogelstein et al., 2013). Given their pivotal roles in the determination of cell identity and cell growth, decommissioning of the lineage differentiation program and activation of

oncogenic transcriptional programs are critical steps toward cell reprogramming and oncogenic transformation (Vogelstein et al., 2013).

Core signaling pathways:

Analysis of the large-scale molecular and genomic information present in the TCGA database indicated that the main signaling pathways involved in GBM tumorigenesis are the p53 pathway (p53/MDM2/4/p14^{ARF}), the PTEN/NF1/RTK pathway (EGFR/RAS/NF1/PTEN/PI3K), and the RB pathway (p16^{INK4a}/CDK4/RB1) (Ohgaki and Kleihues, 2007, 2009) (Figure 1B). Glioblastomas are divided into primary and secondary classifications. It is believed that primary GBM arises *de novo* and secondary GBM arises from lower grade gliomas and progresses to stage IV (Holland, 2001; Maher et al., 2001; Ohgaki and Kleihues, 2007, 2009). Although both forms have the same histological appearance and clinically grim prognosis, they exhibit distinct genetic or oncogenic mutations (Furnari et al., 2007; Ohgaki and Kleihues, 2007, 2009). Primary GBMs are genetically associated with loss of heterozygosity in 10q (70%), *EGFR* amplification (35%), *p16INK4a* deletion (31%), and *PTEN* mutations (25%), and occur mainly in adults, while secondary GBMs exhibit the most frequent mutations in the *TP53* gene and affect younger populations (Furnari et al., 2007; Ohgaki and Kleihues, 2007, 2009) (Table 1). Notably, different tumors, and even different cells within the same tumors, can have mutations in different parts of these pathways (Patel et al., 2014).

TP53 encodes the tumor suppressor p53; this protein pauses the cell cycle in response to DNA damage and can initiate apoptosis (Meletis et al., 2006; Vogelstein and Kinzler, 2004). Mutations in *TP53* are found in astrocytomas of multiple grades (Louis et al., 1993; van Meyel et al., 1994) and may allow early astrocytomas to evade apoptosis (Zhu et al., 2005). Introduction of germline mutations into tumor suppressor genes *Nf1* and *Trp53* in mice is sufficient to induce development of various grades of astrocytomas (Reilly et al., 2000).

The PTEN/NF1/RTK pathway controls cell growth and involves RTKs such as EGFR and PDGFR and their downstream cascade proteins that promote cell growth (e.g., RAS, MAPK, and PI3K). The tumor suppressors PTEN and NF1 are the negative regulators of PI3K and RAS activity, respectively, and are the modulators of cell cycle entry in neural stem cells (Fraser et al., 2004; Groszer et al., 2006) (Figure 1C). Inactivation of both *Trp53* and *Pten*, but not either gene alone, in murine neural stem cells leads to high-grade malignant glioma by driving MYC oncoprotein expression (Zheng et al., 2008). Furthermore, ablation of *Pten* in the *Nf1/Trp53* model generates highly penetrant GBMs (Kwon et al., 2008), suggesting a cooperative effect of these oncogenic- and tumor-suppressive pathways (Table 1).

RB is a tumor suppressor protein that regulates the G1/S checkpoint through sequestering E2F and inhibiting its oncogenic activity (Malumbres and Barbacid, 2001). Mutations in genes in the RB pathway (e.g., RB, p16^{INK4a}, and CDK4) result in increased mitotic activity, leading to malignant transformation (Knudsen and Wang, 2010; Sharpless and DePinho, 1999).

Activation of Hippo-Taz/Yap signaling has also been linked to GBM formation (Zhang et al., 2016a). Silencing of *Taz* and its co-transcriptional regulator *Tead* in mesenchymal GBM

cells decreases self-renewal, invasion, and tumor formation, whereas overexpression of TAZ in proneural GBM cells induces mesenchymal signature gene expression (Bhat et al., 2011). In summary, mutations in these oncogenic and tumor suppressive signaling pathways lead to apoptosis resistance, increased cell growth, and unchecked proliferation (Figure 1B).

Core transcriptional regulators of neurodevelopment and tumorigenesis crosstalk:

Transcriptional regulators play key roles in both normal development and tumorigenesis, which share similar cellular hierarchies. Recent studies identify a core set of neurodevelopmental transcriptional regulators, including POU3F2, SOX2, SALL2, and OLIG2, which are essential for GBM propagation (Suva et al., 2014). Activation of these factors is sufficient to reprogram differentiated cells into tumor-propagating cells (Suva et al., 2014).

Among these core regulatory factors, OLIG2 is a central nervous system-restricted transcription factor that plays a critical role in OPC specification and proliferation (Lu et al., 2002; Takebayashi et al., 2002; Zhang et al., 2016b; Zhou and Anderson, 2002). During early embryogenesis, Olig2 is strongly expressed in the progenitors of medial ganglionic eminence (MGE) but weakly in the lateral ganglionic eminence (LGE). In the developing cortex of later embryonic stages, Olig2 is mainly expressed in the transit-amplifying progenitors in the SVZ and oligodendrocyte lineage cells (Lu et al., 2002; Miyoshi et al., 2007; Yue et al., 2006; Zhu et al., 2012), but not neural stem cells (e.g. nestin+ cells) in the VZ. Interestingly, OLIG2 appears to be ubiquitously expressed in human gliomas (Ligon et al., 2004; Lu et al., 2001) and has a regulatory role in glioma initiation and tumor phenotype plasticity (Kupp et al., 2016; Ligon et al., 2007; Lu et al., 2016; Singh et al., 2016).

An early study showed that overexpression of oncogenic *EGFRvIII* does not induce transformation of *Olig2*^{-/-} neural stem cells carrying *Cdkn2a*^{-/-} alleles into glioma in allografts (Ligon et al., 2007). In contrast, in a mouse model of proneural GBM with *Trp53*/*Pten* deletions and PDGFB expression, *Olig2* deletion delays, but does not completely block, tumor growth (Lu et al., 2016). The distinct effect of Olig2 deletion on glioma growth inhibition under different oncogenic mutations suggest that OLIG2 regulates gliomagenesis in a context (e.g. p53 mutation status)-dependent manner.

Olig2 deletion leads to a shift to a slower-growing phenotype with an astroglial gene expression pattern (Lu et al., 2016). *Olig2*-deletion in a murine proneural GBM model leads to decreases in expression of PDGFR α (Lu et al., 2016), a key regulator of OPC proliferation. Similarly, in human proneural GBM cell lines, OLIG2-knockdown leads to downregulation of PDGFR α signaling (Kupp et al., 2016; Lu et al., 2016), suggesting the OLIG2 is a key regulator of PDGFR α signaling (Figure 1B). It is worth noting that *Olig2*-deficient tumor cells in a *Pten*/*Trp53* negative mouse proneural glioma model appear to utilize other signaling pathways (e.g., the EGFR pathway) as an alternative to sustain tumor cell growth, despite downregulated PDGFR α signaling (Lu et al., 2016). This is in contrast to the essential role of OLIG2 glioma formation in p53-expressing backgrounds (Ligon et al., 2007). This suggests that OLIG2 function is likely dependent on the mutation status of p53 given that Olig2 negatively regulates p53 and p21 tumor suppressors (Mehta et al., 2011).

Core transcriptional regulators such as SOX2 and OLIG2, which also mark OPCs, can be elevated by oncogenic RTK signaling such as that mediated by EGFRvIII. Interestingly, once activated, these factors can induce the transformation of tumor-suppressor-deficient astrocytes into glioma-initiating cells independent of RTK signaling (Singh et al., 2017). In addition, given the intratumoral heterogeneity of these tumors, a subpopulation of tumor-initiating cells within the tumor may not rely on these core factors e.g. Olig2, for tumor growth eventually (Lu et al., 2016; Yu et al., 2017). This suggests that additional growth regulators other than these core transcription factors may support tumor cell growth.

Olig2 deletion in the proneural GBM tumor model leads to a transcriptional program shift with downregulation of the OPC-associated proneural signature and an up-regulation of astrocyte-associated classical tumor signature (Lu et al., 2016). This is in keeping with the role of OLIG2 in the OPC-astrocyte fate switch during development (Cai et al., 2007; Lu et al., 2002; Zhu et al., 2012). Similarly, the opposing transcription factors SOX10 and NFIA, which control the balance of oligodendrocyte and astrocyte fate during development, also regulate oligodendroglioma and astrocytoma formation (Glasgow et al., 2014), suggesting a common theme for the control of glial lineage diversification during development and tumorigenesis, and that tumor phenotypes (oligodendrocyte- versus astrocyte-like phenotypes) may be delineated by the lineage-driving transcriptional regulators. In summary, glial lineage specification factors such as OLIG2 are key players in oncogenic reprogramming, particularly for proneural subtype of gliomas, as their activation in cooperation with other oncogenic insults predisposes glial progenitors to neoplastic transformation and triggers tumor initiation through the modulation of the epigenetic state of enhancers.

EPIGENETIC REGULATION IN GLIOBLASTOMA

Cell reprogramming requires overcoming epigenetic barriers that are involved in maintaining cell-specific transcriptional programs that preserve cell identity (Apostolou and Hochedlinger, 2013; Feinberg et al., 2016). Epigenetic modifications such as DNA methylation, histone modifications, chromatin remodeling, and three-dimensional nucleosome organization are not only crucial for normal development but also for tumor initiation and progression (Apostolou and Hochedlinger, 2013; Feinberg et al., 2016). Recent discoveries of cellular and genomic reprogramming in glioblastomas have highlighted the importance of the chromatin modification landscape in the regulation of gliomagenesis and progression. Defining the specific chromatin modification landscapes of distinct tumors may identify specific vulnerabilities that can be harnessed for therapy.

DNA methylation:

Epigenetic silencing through promoter hypermethylation of tumor suppressor genes such as those controlling the cell cycle and DNA repair, PTEN, RB, RASSF1A, CDKN2A/2B, and MGMT, is commonly observed in cancers including brain tumors (Baylin and Jones, 2011; Malzkorn et al., 2011; Martinez and Esteller, 2010; Schmidt et al., 2012; Veeriah et al., 2009). The analysis of cancer methylome not only reveals somatically acquired DNA methylation alterations but also identifies the tumor cell of origin (Capper et al., 2018;

Hovestadt et al., 2014), which allows tracing the primary site of metastatic tumors (Moran et al., 2016). DNA methylation is regulated by DNA methyltransferases and TET (the ten-eleven translocation) demethylation enzymes, the latter leads to DNA hydroxymethylation and demyelination (Ito et al., 2010; Tahiliani et al., 2009). DNA methylation represses gene expression directly or by recruitment of repressive chromatin remodelers including methyl-CpG-binding domain (MBD) proteins such as including MeCP2, MBD1, MBD2 and MBD4 (Bhattacharjee et al., 2016; Ikegami et al., 2009). Global DNA hypermethylation promotes chromosomal instability, reactivation of transposable elements, and loss of imprinting (Deleris et al., 2012; Estecio and Issa, 2011). Local hypermethylation silences expression specific tumor suppressor genes, and hypomethylation induces oncogene activation.

Dysregulation of DNA methylation patterns has been linked to the initiation and progression of GBM. A well-studied example is hypermethylation of a CpG island that results in the silencing of the expression of a DNA repair enzyme MGMT, encoding O6-methylguanine-DNA methyltransferase. Brain tumors with hypermethylated MGMT, are susceptible to genetic mutations in critical genes such as *TP53* or *KRAS* (Baylin and Jones, 2011; Malzkorn et al., 2011; Martinez and Esteller, 2010; Schmidt et al., 2012; Veeriah et al., 2009). Epigenetic silencing of *MGMT* leads to a defect in the removal of carcinogen-induced O6-methylguanine adducts from DNA, resulting in G to A transition mutations (Baylin and Jones, 2011; Malzkorn et al., 2011; Martinez and Esteller, 2010).

Interestingly, the defect in DNA repair enzyme MGMT is associated with a better response to treatment with alkylating agents (Bobola et al., 2015). MGMT methylation status is now used as a biomarker for predicting drug responsiveness in GBM patients. Epigenetic changes like DNA methylation likely regulate expression of GBM-associated genes. Resetting of DNA methylation in GBM-initiating cells by reprogramming induced pluripotent stem cells results in suppression of malignant cellular behavior when directed toward nonneural lineages (Stricker et al., 2013). Although TET2 mutations have been linked to acute myeloid leukemia (Liu et al., 2014), currently, the functions of TET and hydroxymethylation in brain tumorigenesis remain to be determined.

Histone modifications:

Malignant transformation of brain tumors is associated with aberrant alterations of histone modifications. The histone methyltransferase LSD1 (also known as HDM1A) can decrease trimethylation of histone 3 at K4 over the *MYC* locus and elevates its expression (Kozono et al., 2015). MYC, in turn, regulates the expression of a core set of transcription factors, including OLIG2, SOX2, and POU3F2, which are required for the stemness maintenance of GBM cells (Kozono et al., 2015; Suva et al., 2014). LSD1 also suppresses the p53 signaling pathway, thereby promoting GBM cell tumorigenesis and metastasis (Yi et al., 2016). In contrast, overexpression of JMJD3 (also known as KDM6B), which demethylates histone 3 at K27, induces a p53-mediated differentiation of glioblastoma stem cells, suggesting that JMJD3 functions as a tumor suppressor by regulating p53 protein nuclear stabilization (Ene et al., 2012)

The type II arginine methyltransferase PRMT5, that catalyzes monomethylation and symmetric dimethylation of arginine residues (Huang et al., 2011), is also critical for self-

renewal capacity and proliferation of GBM cells as it regulates PTEN expression and controls AKT and ERK activity (Banasavadi-Siddegowda et al., 2017). Expression of PRMT5 correlates with malignant grade in gliomas and is critical for tumor growth (Banasavadi-Siddegowda et al., 2018; Han et al., 2014). These observations indicate that histone methylation and demethylation may play important roles in GBM growth.

Histone acetylation and deacetylation are usually regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). HATs are divided into two groups based on subcellular localization [42]. Type A HATs (e.g., GCN5, p300/CBP, and TAFII250) are localized in the nucleus and acetylate nucleosomal histones whereas type B HATs (e.g., HAT1) are localized in the cytoplasm and acetylate newly synthesized histones (Lee and Workman, 2007). Histone acetylation levels are often correlated with glioma progression (Huang et al., 2015; Lee et al., 2014). Histone acetyltransferase KAT6A acetylates histone 3 at K23 and recruits the nuclear receptor binding protein TRIM24 to activate the transcription of *PIK3CA*, thereby promoting PI3K/AKT signaling and GBM progression (Lv et al., 2017). *KAT6A* silencing suppresses cell proliferation, cell migration, colony formation, and tumor development in an orthotopic mouse xenograft model system (Lv et al., 2017). The specific role of individual histone acetyltransferase in gliomagenesis has not yet been fully defined at present.

HDACs also play important roles in the regulation of GBM tumorigenesis. HDAC inhibitors have been shown to induce re-expression of silenced tumor suppressor genes (Dickinson et al., 2010; Newbold et al., 2013). HDAC inhibition can sensitize EGFR/EGFRvIII-overexpressing, erlotinib-resistant GBM cells to RTK inhibition (Liffers et al., 2016). Inhibition of HDACs and blockade of the glycolytic pathway synergistically induce GBM cell death (Egler et al., 2008). Inactivation of class IIa HDACs by mTORC2 leads to acetylation of FOXO1 and FOXO3, which increases c-MYC levels by suppression of miR-34c expression, leading to an increase in glycolytic metabolism and GBM cell growth (Masui et al., 2013). Thus, HATs and HDACs may coordinate to regulate GBM growth likely in a context-specific manner.

Oncometabolites:

Mutations in metabolic regulatory enzymes can affect DNA and histone methylation. For instance, the mutations in isocitrate dehydrogenase (IDH) 1 and 2, which occur early in gliomagenesis, lead to the accumulation of 2-hydroxyglutarate, known as a “oncometabolite” (Cohen et al., 2013; Yan et al., 2009). The oncometabolite, 2-hydroxyglutarate (2-HG), is a competitive inhibitor of α -ketoglutarate (α -KG)-dependent epigenetic enzymes such as histone lysine demethylases and TET hydroxylases (Feinberg et al., 2016; Li et al., 2018; Lu et al., 2012). Mutations in IDH1 and IDH2 impair DNA demethylation by inhibiting TET family enzymes and causes hypermethylation in glioma (Turcan et al., 2012). Intriguingly, IDH1/2 mutations also disrupt histone demethylation and cause the progenitor cells to become susceptible to transformation (Lu et al., 2012). Similarly, mutations in fumarate hydratase and succinate dehydrogenase can lead to accumulation of fumarate and succinate, respectively, which also function as competitive inhibitors of histone demethylases and TET enzymes to alter DNA and histone methylation

state and cause genomic instability (Vogelstein et al., 2013; Xiao et al., 2012) (Figure 1C). A recent study indicates that metabolic enzymes such as α -ketoglutarate dehydrogenase can be localized in the nucleus and bind to lysine acetyltransferase KAT2A (also known as GCN5) together with succinyl-coenzyme A. The KAT2A complex then acts as a succinyltransferase to catalyze lysine succinylation on histone 3 at K79 to regulate gene transcription and tumor cell proliferation (Wang et al., 2017).

In summary, epigenetic alterations such as promoter hypermethylation or oncometabolites can not only cause dysregulation of gene expression but also predispose to genetic mutations (Choi and Lee, 2013; You and Jones, 2012), which can lead to transformation and tumor progression. Thus, epigenetic regulatory mechanisms are prevalent in tumorigenesis, the regulatory and genetic events can cooperate and co-opt each other to impinge on neoplastic transformation during brain tumorigenesis.

PEDIATRIC BRAIN TUMORS

Pediatric brain tumors include pediatric high-grade gliomas (HGGs) and medulloblastomas. Genetic and epigenetic profiling experiments have revealed molecular characteristics of these diseases and have allowed subclassifications useful for treatment stratification. Pediatric HGGs are the most common malignant pediatric brain tumors and include GBMs, anaplastic astrocytomas, and DIPGs (Liu et al., 2017; Ostrom et al., 2014). Based on distinct DNA methylation patterns in adult GBMs and pediatric HGGs, six biological HGG subgroups have been identified: IDH (also called G-CIMP), mesenchymal, RTK-I, RTK-II, H3K27, and H3G34 tumors (Liu et al., 2017; Sturm et al., 2012). IDH, K27, and RTK-I tumor clusters exhibit a correlation with proneural GBM gene expression patterns, whereas H3G34 and RTK-II subgroups possess classical gene expression signatures (Sturm et al., 2014).

Cells of origin in DIPG:

DIPG is an especially malignant type of glioma due to its diffuse nature and location within the pons, making surgical resection virtually impossible, leading to very poor prognosis (Lapin et al., 2017; Warren, 2012). DIPGs could be derived from neural stem cells (Filbin et al., 2018; Misuraca et al., 2015) or OLIG2⁺ OPC-like progenitors (Filbin et al., 2018; Monje et al., 2011) (Figure 2A).

Genetic alterations in DIPG:

Whole genome, exome, and methylome sequencing of biopsy and autopsy tissues have revealed the most common mutations and chromosomal and epigenetic abnormalities in DIPG (Mathew and Rutka, 2018; Taylor et al., 2014b). Surprisingly, histone mutations are the most common mutation in DIPG, seen in up to 80% of cases (Khuong-Quang et al., 2012; Lapin et al., 2017; Lewis et al., 2013; Saratsis et al., 2014). The most common histone mutations in DIPG are lysine 27 (K27) to methionine (M) of histone 3 variants H3F3A and HIST1H3B (H3.3 or H3.1) to form H3.3K27M or H3.1K27M mutant proteins (Lapin et al., 2017). In addition, G34R or G34V mutations, which are restricted to H3.3, are mostly found in hemispheric GBM-like tumors in adolescents (Korshunov et al., 2016). These mutations

to histone 3 are unique to HGGs and are not found in adult GBMs (Castel et al., 2015; Lewis et al., 2013), suggesting that DIPG behaves distinctly from adult gliomas.

Mutations in histone 3 variants (e.g., H3.3K27M or H3.1K27M) lead to an inhibition of PRC2, the polycomb repressive complex, activity, causing a global decrease in trimethylation of histone 3 at K27 and abnormal epigenetic silencing of tumor suppressors such as p16^{INK4a} (Cohen et al., 2017). *TP53* mutations have been identified in up to 40% of DIPGs and often co-occur with *PDGFRA* amplification (Grill et al., 2012; Puget et al., 2012; Taylor et al., 2014a). Although H3K27M alone is insufficient to drive tumorigenesis, it does induce glioma formation when combined with *Trp53* mutations and activating *PDGFRA*^{D842V} by orthotopic implantation of transformed human astrocytes or NSCs (Funato et al., 2014), in utero focal delivery into the embryonic cortex (Pathania et al., 2017) or through genetically engineered mice (Larson et al., 2019). Mutations in histone 3 at G34 are closely linked to *ATR*X mutations, which could promote telomere lengthening (Heaphy et al., 2011).

PDGFRA amplification or activating mutations (Mackay et al., 2017; Paugh et al., 2013) (Filbin et al., 2018), which trigger the RTK-RAS-PI3K-AKT pathway, are the most commonly observed alterations in DIPG (~32% of patients) (Monje et al., 2011; Paugh et al., 2011; Puget et al., 2012; Wu et al., 2014). Amplifications or mutations in other factors involved in the RTK/RAS pathway (such as *PI3KCA*) are also common in DIPG, and the pathway itself is active in approximately 69% of DIPG tumors (Monje et al., 2011; Paugh et al., 2011; Puget et al., 2012; Wu et al., 2014).

Another gene commonly mutated in DIPG is *ACVR1* (~25% of patients). *ACVR1* encodes ALK2 the receptor for bone morphogenetic protein (BMP) (Buczakowicz et al., 2014; Fontebasso et al., 2014; Hoffman et al., 2016; Mackay et al., 2017; Taylor et al., 2014a; Wu et al., 2014). These *ACVR1* mutations often co-segregate with H3.1 mutations and are usually found in tumors with wild-type p53 (~90%) or PI3K pathway alterations (~56%) (Buczakowicz et al., 2014; Fontebasso et al., 2014; Taylor et al., 2014a; Wu et al., 2014). The *ACVR1* mutation results in a slight activation of the BMP signaling pathway, which promotes a differentiated phenotype and could possibly account for the increased survival advantage conferred by *ACVR1* mutations (Piccirillo et al., 2006). In addition to the mutations in histone 3, *ACVR1*, *TP53*, *PDGFRA*, *PIK3CA*, and *MYC* (Lapin et al., 2017), chromosomal abnormalities are especially frequent in DIPG and include gains of 1q, 2q, 8q, and 9q and losses in 11p, 17p13.1, 14q, 18p, and 22q (Castel et al., 2015; Puget et al., 2012; Zarghooni et al., 2010) (Table 1).

Increasing methylation of histone 3 at K27 (H3K27me3) by inhibition of JMJD3 can prolong survival of the mice with DIPG xenografts (Hashizume et al., 2014). In contrast, inhibition of a PRC2 component EZH2 activity suppressed tumor cell growth in a mouse model of DIPG and in patient-derived DIPG cell lines (Mohammad et al., 2017). The latter observation suggests that residual PRC2 activity, which likely selectively regulates expression of tumor-suppressor protein p16 (also known as INK4A) is critical for the growth of H3K27M-DIPGs. Intriguingly, EZH2 inactivation in a mouse model of group 3 medulloblastoma accelerated tumorigenesis by derepressing the proto-oncogene *GFI1* in

collaboration with MYC (Vo et al., 2017). Thus, whether EZH2 acts as an oncogene or tumor suppressor appears to be context dependent.

Combined treatment with the HDAC inhibitor panobinostat and the histone demethylase inhibitor GSK-J4 has been found to effectively block tumor cell growth *in vitro* and in orthotopic H3K27M-DIPG xenograft models (Grasso et al., 2015). Moreover, inhibitors of PRC2-EZH2 and CDK4/6 blocks H3K27M-DIPG cell growth due to the unique repression of *CDKN2A* transcription by H3.3K27M mutations (Cordero et al., 2017; Mohammad et al., 2017). The presence of unique genetic and epigenetic abnormalities indicates that DIPGs are not a subset of GBMs. Recent studies have furthered our understanding of driver mutations and of specific epigenetic vulnerabilities in DIPG, which should allow guiding development of treatments for these deadly pediatric brain tumors.

Medulloblastomas:

Medulloblastomas (MBs) account for 20% of malignant pediatric brain tumors (Ostrom et al., 2017; Yi and Wu, 2018). Unique gene mutations are found in each case, in contrast to hotspot mutations seen in DIPGs (Jones et al., 2012; Schwartzentruber et al., 2012). Based on genetic and epigenetic profiling, medulloblastoma can be classified into WNT (Wingless), SHH (Sonic Hedgehog), Group 3, and Group 4 subtypes (Northcott et al., 2011; Taylor et al., 2012). WNT-MB accounts for about 10% of medulloblastoma cases and has the best prognosis of the four subtypes with long-term survival exceeding 90% (Ellison et al., 2011). SHH-MB tumors are present in about 30% of MB cases, and these tumors are driven by mutations in the SHH signaling pathway (He et al., 2014; Jones et al., 2012; Northcott et al., 2012). Group 3 MB (G3-MB) accounts for about 25% of medulloblastomas and has the worst prognosis of the four subgroups (Liu et al., 2017). Group 4 MB (G4-MB) is the most prevalent MB subtype at 35%; the molecular pathogenesis of the subtype is the least understood among MBs (Gajjar and Robinson, 2014; Northcott et al., 2012).

The cells of origin in MB:

Although MBs are localized in the posterior fossa or cerebellum, they exhibit extensive intertumoral heterogeneity in primary, recurrent and metastatic tumors (Cavalli et al., 2017). WNT-MB is believed to originate in the lower rhombic lip or embryonic dorsal brainstem. Activation of *Ctnnb1* in the dorsal brainstem progenitors (*Zic1*⁺ cells) concurrent with *Trp53* deletion results in abnormal hyperproliferation and tumors with a WNT-MB profile (Gibson et al., 2010) (Figure 2A).

In SHH-MB, although granule neuron precursor cells may very well serve as the cell of origin for tumor cell propagation (Gibson et al., 2010; Schuller et al., 2008; Yang et al., 2008), the identity of tumor-initiating cells is not known. Deletion of *Ptch1* and *GNAS* or activation of SMO in a variety of progenitor cells including cerebellar neuroepithelial (nestin⁺/GFAP⁺ neural stem/progenitor) cells (Schuller et al., 2008; Yang et al., 2008), OPC-related *Olig1*⁺ progenitors in the anterior brainstem (He et al., 2014), or brainstem progenitors (Grammel et al., 2012) results in SHH-MB in animal models. This suggests that various progenitors are susceptible to the activation of SHH signaling and undergo malignant transformation into SHH-MB (Figure 2A).

The G3-MB tumors are often located near the fourth ventricle, suggesting that cerebellar stem/progenitor cells or granule neuron precursor cells are likely the source of G3-MB (Kawauchi et al., 2012; Pei et al., 2012). Similar to G3-MBs, G4-MBs are often detected close to the fourth ventricle or related to Tbr2⁺ unipolar brush cells (UBCs) through single-cell analysis (Wang et al., 2018a)(Vladoiu et al., bioRxiv, 2018; <http://dx.doi.org/10.1101/350280>). The progenitors of the nuclear transitory zone at the upper rhombic lip are thought to be a cell of origin for G4-MBs (Lin et al., 2016), although the precise cells of origin for G4-MB are not known (Figure 2A).

A recent whole-genome analysis demonstrated substantial genetic divergence of the dominant clones between primary and post-therapy human MBs. The dominant clone at recurrence arose through clonal selection of a pre-existing minor clone present at diagnosis (Morrissey et al., 2016). The developmental hierarchy and cellular heterogeneity during tumorigenesis and recurrence in each MB subtypes needs to be further defined by single-cell transcriptomics, clonal mapping, and proteomics analyses. In summary, although the precise cells of origin remain unclear, MBs can arise from multiple cell types from different locations at stem cell or intermediate progenitor stages during tumor initiation and recurrence (Figure 2A).

Genetic mechanisms underlying distinct MB subgroups:

In WNT-MB, activating mutations in the *CTNNB1* gene encoding β -catenin, or mutations in DDX3X, an ATP-dependent RNA helicase, and in chromatin remodelers SMARCA4 and CREBBP have been proposed to play an oncogenic role in tumorigenesis (Jones et al., 2012; Northcott et al., 2012; Robinson et al., 2012).

The SHH-MB subgroup tumors are characterized by a variety of mutations in the SHH pathway including loss-of-function mutations in *PTCH1* and *SUFU*, activating mutations in *SMO*, and amplifications of *SHH*, *GLI2*, and *MYCN* (Jones et al., 2012; Liu et al., 2017; Pugh et al., 2012; Robinson et al., 2012). Recently, nonsense mutations in *GNAS*, which encodes a G-protein $G\alpha_s$, were detected in an aggressive form of SHH-MB (He et al., 2014). SHH signaling is mediated through activation of the G protein-coupled receptor-like seven-transmembrane protein SMO. The $G\alpha_s$ protein may couple other G protein-coupled receptors, including GPR161, to inhibit SHH signaling (Shimada et al., 2018). Activation of $G\alpha_s$ protein not only stimulates cyclic adenosine monophosphate (cAMP)-dependent signaling but also inhibits ciliary trafficking of hedgehog components. Elevation of cAMP inhibits MB growth by blocking SMO signaling to decrease tumor cell proliferation (He et al., 2014) (Figure 2B). A recent study identifies the protein kinase CK2 as a driver of phosphorylation events to promote GNP growth during tumorigenesis, and inhibition of CK2 blocks the growth of murine SHH-MB tumors (Purzner et al., 2018), suggesting that CK2 may mediate the downstream event of SHH-SMO signaling. In addition, SHH MBs can be highly heterogeneous and further divided into four subtypes: divided into four subtypes: α , β , γ and δ , which correlate with genetic alterations and prognosis. For instance, SHH α subtype is associated with very poor prognosis and enriched with *TP53* mutations and *MYCN* and *GLI2* amplification, while SHH β subtype is often metastatic and affects mainly infants (Cavalli et al., 2017) (Figure 2B).

The most common genetic alteration in G3-MB is *MYC* amplification (Liu et al., 2017). G3-MB also has characteristic large-scale genomic instability, including somatic copy number alterations, fusion of *MYC* and *PVT1* genes, and loss of chromosome 17p and gain of 17q (known as i17q) (Jones et al., 2012; Liu et al., 2017; Northcott et al., 2012). Genomic structural rearrangement in a subset of G3-MBs could lead to super-enhancer relocation and activation of GFI1 family oncogenes to promote tumorigenesis (Northcott et al., 2014). Activation of Notch and TGF- β signaling pathways as well as in-frame insertions in the *KBTD4* locus were also identified (Kool, 2008; Northcott et al., 2017), although their functional significance in G3-MB tumorigenesis remains unknown. G3-MB can be also classified into other distinct subgroups based on the distinct gene expression profiles and alterations (Cavalli et al., 2017) (Table 2).

G4-MBs share similarities in mutations with G3-MBs, with a higher rate of i17q than G3-MB (Gajjar and Robinson, 2014; Northcott et al., 2011; Northcott et al., 2012). The most frequently seen genetic alterations in G4-MB include amplification of *MYCN* and *CDK6*, mutations in *KDM6A*, which encodes a histone demethylase, and tandem duplication of *SNCAIP*, and overexpression of its downstream gene *PRDM6* (Northcott et al., 2017; Pugh et al., 2012). Mutations to other histone modifying genes *MLL3* and *HDAC2* are also seen in G4-MB (Pugh et al., 2012). The functional consequence of these genomic alterations remains to be defined. Recent proteomic and phosphoproteomic analyses identified aberrant activation of ERBB4-SRC signaling in G4-MB (Archer et al., 2018; Forget et al., 2018). The combination of activated SRC signaling and p53 inactivation induces murine tumors (Forget et al., 2018), suggesting that ERBB4-SRC pathway is oncogenic in G4-MB (Figure 2B) (Table 2).

MBs also contain high rates of alterations in epigenetic regulators, with each subtype displaying a distinct epigenetic signature, including distinct DNA methylation patterns (Batora et al., 2014; Jones et al., 2013; Schwalbe et al., 2013) (Figure 2B). It is possible that epigenetic alterations serve as drivers of oncogenesis in MB (Yi and Wu, 2018). Common epigenetic dysregulations seen in MB include aberrant histone 3 methylations including hypermethylation of K4 and K27 (H3K4me3 and H3K27me3) and hypomethylation of K9 (Lindsey et al., 2004; Liu et al., 2017). Suppression of the hypermethylated phenotype results in a differentiated phenotype that leads to prolonged survival (Lawlor and Thiele, 2012). Analyses of MBs at the levels of transcriptome, genome, epigenome, and proteome and a better understanding of the microenvironment of these tumors will reveal the mechanisms of MB tumorigenesis and guide development of subtype-specific animal models and treatment strategies.

FINAL REMARKS AND PERSPECTIVES

Over the past several decades, considerable efforts have been dedicated to the identification of actionable targets for treatment of malignant brain tumors; however, the prognosis of brain tumor patients remains grim due to complex entities of malignant glioma in which diverse genetic and nongenetic effects determine tumor heterogeneity and clinical course. The relationship between the cells of origin and glioma stem cells is not well defined. Knowledge of the earliest events of gliomagenesis and would allow for earlier diagnoses.

Recent discoveries that brain tumorigenesis and development of the nervous system are linked at the root of stem cells revealed important cellular targets for cancer treatment. More extensive small-molecule and genetic screening to identify methods for inhibiting proliferation of tumor-initiating cells and for blocking shared or core signaling pathways will contribute to the development of the next generation of prognostic and therapeutic approaches for cancer. Advances in transgenic technologies and animal models have allowed the establishment of mouse models that mirror the human disease with increasing fidelity; these models facilitate identification of the pathways involved in the pathogenesis of brain tumors at single-cell resolution. The core transcriptional regulators such as OLIG2 and SOX2 are predominantly expressed in glioma-initiating cells and make appealing targets for therapy in primary and recurrent tumors. A better understanding of the mechanism of tumor stem/progenitor cell lineage progression and identification of the key fulcrum that balances tumor cell proliferation with differentiation should allow us to reactivate or reprogram of tumor-propagating cells to differentiate into slow-growing or post-mitotic cell types. Additionally, further investigation is necessary into the role of epigenetic regulation and dysregulation in pediatric brain cancers. Understanding the epigenetic vulnerabilities may provide insights into novel therapeutic approaches, and indeed many novel agents targeting chromatin modifiers such as the HDAC, BRD4 and EZH2 inhibitors are currently in development or in early clinical trials. Moreover, further characterization of complex glioma stem-cell niches, interactions with their tumor microenvironment, and tumor heterogeneity will lead to development of targeted therapies such as anti-tumor immunotherapies, which have not yet been explored fully in brain tumors. These types of therapies may one day lead to treatments that induce full remission.

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Figure 1. Cells of origin and tumor-driving pathways in brain tumors

A) Multipotent NSCs have capability to self-renew and differentiate into different fate-restricted progenitors. Under genetic and epigenetic alterations, these progenitor cells could be transformed into malignant tumors including gliomas from NSC, OPC or APC as well as medulloblastomas from NPCs.

B) A hierarchical model for tumor cell evolution and plasticity to generate distinct tumor-forming cells and tumor heterogeneity gained after tumor initiation.

C) Malignant transformation of GBM is the result of different driver pathway alterations. RTK signaling pathway activation mediated by extracellular signal (growth factors, cytokines, and hormones) promotes cell cycling for tumorigenesis. Besides, point mutation of histone 3 (H3K27M, H3G34R/V) and up-regulation of oncogenic factors, like MYC(N) and AURK, which lead to tumor cell proliferation. Moreover, IDH mutations later Krebs cycle in mitochondria, which further alter activity of downstream epigenetic regulators,

including TET1/2 and KDM, leading to methylation alterations for DNA and nucleosome states susceptible to for tumorigenesis. GBM, glioblastoma; NSCs, neural stem cells; NPC, neuron progenitor cell; APC, astrocyte progenitor cell; OPC, oligodendrocyte progenitor cell; RTK, receptor tyrosine kinase; MYC, myelocytomatosis viral oncogene; AURK, aurora kinase; IDH, Isocitrate dehydrogenase; TET, Tet oncogene; KDM, lysine(K)-specific demethylase.

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Figure 2. Developmental origins and key signaling pathways in MB tumorigenesis

A) Potential progenitor sources for distinct MB in the posterior fossa. Progenitor cells in the ventricular zone (SHH, Group 3 and Group 4), EGL (SHH), anterior brainstem progenitors (SHH or other groups), and dorsal brainstem (WNT) contribute to distinct MB subtype tumorigenesis.

B) Distinct MB subtypes (WNT, SHH, Group 3 and Group 4) show different signaling driving pathways for promoting cell cycling and growth. In WNT MB, activated β -catenin cooperates with transcription factor LEF/TCF to promote cell proliferation. In SHH MB, transmembrane proteins PTCH, SMO and GPCR mediated transcriptional factor Gli activation for tumorigenesis. In Group 3 MB, oncogene MYC activates transcriptional factor GFI1 and promote tumorigenesis. Group 4 MB shows activation of ERBB4 and EGFR signaling. MB, medulloblastoma; LEF/TCF, lymphoid enhancer binding factor/T-cell specific transcription factor; PTCH, patched; SMO, smoothed; GPCR, G protein coupled

receptor; Gli, glioma-associated oncogene; MYC, myelocytomatosis viral oncogene; GFI1, growth factor independent 1 transcriptional repressor.

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Table 1.
Genetic alterations and pathways in primary and secondary GBM

Table 2.

Genetic, clinical features and modeling of medulloblastoma subgroups

Subgroups	WNT	SHH	Group 3	Group4
Percentage	~ 10%	~ 30%	~ 25%	~ 35%
Histology	Classic, rarely LCA	Classic; Desmoplastic, LCA	Classic; LCA	Classic; rarely LCA
Metastatic rate	Low (5–10%)	Low (10–15%)	40–45%	35–40%
Prognosis	Very good	Intermediate	Poor	Intermediate
Recurrence	N/A	Local	Metastatic	Metastatic
Diagnostics	Nuclear β -catenin; CTNNB1 mut; monosomy 6; DKK	SFRP1, YAP1; 9q loss; GLI2 gain	NPR3; MYC gain	KCNA1
Cytogenetics	Chr 6 loss	Chr 3q, 9p gain; 9q, 10q, 14q, 17p loss	Chr 1q, 7, 17q, 18 gain; 8, 10q, 11, 16q, 17p loss; iso17q	Chr 4, 7, 17q, 18 gain; 8, 10, 11, 17p, X loss; iso17q
Mutations, SNVs or indels	CTNNB1, DDX3X, SMARCA4, TP53, CSNK2B, CREBBP, MLL2	PTCH1, SMO, SUFU, GNAS, MLL2, DDX3X, TP53, BCOR, LDB1	SMARCA4, MLL2, SPTB, CTDNEP1, LRP1B, TNXB, GPS2	KDM6A, MML3, HDAC2, ZMYM3, CBFA2T2, CTDNEP1
Somatic alterations	No recurrent alteration	GLI1/2, MYCN, CCND2 amplification; PTCH1, TP53 deletion; GNAS mutation (LOF)	MYC, OTX2 amplification; PVT1-MYC fusion	SNCAIP duplication; CDK6, MYCN, OTX2 amplification
Pathways	WNT signaling	SHH signaling	MYC and TGF β signaling	ERBB4-SRC signaling; NF κ B signaling
Cells of origin	Lower rhombic lip progenitors; mossy-fiber neuron precursors	Cerebellar NSCs or GNP of EGL; brainstem progenitors in the 4 th ventricle	Cerebellar NSCs or GNPs	Cerebellar NTZ progenitors, unipolar brush cells, other progenitors
Mouse models of medulloblastoma	Blbp-Cre;Ctnnb1 ^{F/+} Trp53 ^{F/F} Pik3ca ^{E545K}	1. Ptch ^{+/-} or Ptch ^{+/-} ; Trp53 ^{+/-} 2. SmoA1;Atoh1/GFAP/Nes-Cre 3. Ptch1 ^{F/F} ;Atoh1/GFAP/Nes-Cre 4. GNAS ^{F/F} ;Atoh1/GFAP/Nes-Cre	Cerebellar transplants: 1. NSC (Myc ^{T58A} ;DNp53) 2. GNP (Myc;Trp53 ^{-/-}) 3. NSC (Myc ^{T58A} ; Gfi1/1b) 4. Glt-tTA;TRE-MycN	Cerebellar progenitors transfected with SRC ^{O/E} with DNp53