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Authors

Ilkhanizadeh, Shirin

Lau, Jasmine

Huang, Miller

et al.

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Glial Progenitors as Targets for Transformation in Glioma

Shirin Ilkanizadeh[1,4], **Jasmine Lau**[1,4,#], **Miller Huang**[1,4,#], **Daniel J. Foster**[1,2,3,#], **Robyn Wong**[1,4,#], **Aaron Frantz**[1,2,3], **Susan Wang**[1,2,3], **William A. Weiss**[1,2,4], and **Anders I. Persson**[1,2,3,*]

[1]Department of Neurology, University of California, San Francisco, CA 94158, USA

[2]Department of Neurological Surgery and Brain Tumor Research Center, University of California, San Francisco, CA 94158, USA

[3]Sandler Neurosciences Center, University of California, San Francisco, CA 94158, USA

[4]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA 94158, USA

Abstract

Glioma is the most common primary malignant brain tumor and arises throughout the central nervous system (CNS). Recent focus on stem-like glioma cells has implicated neural stem cells (NSCs), a minor precursor population restricted to germinal zones, as a potential source of gliomas. In this review, we will focus on the relationship between oligodendrocyte progenitor cells (OPCs), the largest population of cycling glial progenitors in the postnatal brain, and gliomas. Recent studies suggest that OPCs can give rise to gliomas. Furthermore, signaling pathways often associated with NSCs also play key roles during OPC lineage development. Recent advances suggesting that gliomas can undergo a switch from progenitor- to stem-like phenotype after therapy, implicating that an OPC-origin is more likely than previously recognized. Future in-depth studies of OPC biology may shed light on the etiology of OPC-derived gliomas and reveal new therapeutic avenues.

Keywords

brain; cancer; glioma; glioblastoma; neural stem cell; oligodendrocyte progenitor cell

1. Introduction

Gliomas are the most common malignant primary brain tumor and associated with approximately 16,000 cancer-related deaths in United States per year (Louis et al., 2007). Recent advances in the molecular characterization of gliomas have defined subgroups of tumors that are genetically and epigenetically distinct (Noushmehr et al., 2010; H. S. Phillips et al., 2006; Sturm et al., 2012; Verhaak et al., 2010). The temporal and regional specificity

[*]Correspondence: Anders I. Persson, Sandler Neurosciences Center, Department of Neurology, University of California San Francisco, 675 Nelson Rising Lane, NS-270B, San Francisco, 94158, CA, USA, Phone: 415-606-3604, Fax: 415-476-0133, Anders.Persson@ucsf.edu.
[#]These authors have contributed equally.

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of genetically distinct gliomas (Sturm et al., 2012), argue that either several discrete populations of precursor cells may be vulnerable to transformation, or that multiple glioma subgroups share a common cell of origin. Glial cells outnumber neurons by 10-fold in the human brain and are composed mainly of terminally differentiated cells and minor discrete precursor populations. Modeling of glioma in mice has demonstrated that cells at various differentiation stages throughout glial and neuronal lineages have the potential to generate gliomas. In this review, we present recent findings suggesting that the most wide-spread population of cycling cells in the pediatric and adult brain of mammalians, the oligodendrocyte progenitor cells (OPCs), represent a likely origin for large cohorts of gliomas. We propose that more in-depth studies of OPC biology will inform novel preventive measures and therapeutic interventions to reverse the fatal outcome of most glioma patients.

Gliomas can grossly be divided into astrocytic, oligodendrocytic, and ependymal phenotypes. Classification by the World Health Organization (WHO) distinguishes malignancy by grade (I-IV). Based on histological appearance, gliomas of most grades and types are found in children and adults. Recent molecular profiling of grade IV glioblastoma (GBM) exemplifies that subsets of tumors in children, young adults, and adolescents, that are indistinguishable by histology, can be segregated based on genetic alterations, broad-scale gene expression, and methylation patterns. Here, we will present recent experimental advances on the understanding of why humans are diagnosed with a certain type of glioma and where it came from.

Recent advances highlight the cellular heterogeneity in gliomas, the influence of the tumor microenvironment, and that treatment-resistant tumor cells display a high degree of stemness. Emerging research suggest that the failure to target glioma stem cells (GSCs) rather than the inability to debulk tumors through surgical resection, radiation and chemotherapy, explain the poor survival of glioma patients (Huse & Holland, 2010). In this review, we will discuss ways to identify GSCs, their interactions with tumor microenvironment, and therapeutic advances to target GSCs. In 2012, Yanoko Nishiyama and John Gurdon were awarded the Novel Prize in Medicine for identifying factors that can reprogram somatic cells into pluripotent stem cells. Since these factors are also expressed in stem-like cancer cells, it is possible that they arose from more differentiated cells. In fact, viral transduction of oncogenes into mature neurons and astrocytes generate gliomas in mice (Friedmann-Morvinski et al., 2012). Similarly, it is plausible that also OPCs can give rise to more stem-like gliomas.

2. Glial Cell Lineages

Recent advances describe a mosaic organization of neural stem cells (NSCs) and astrocyte precursors in the central nervous system (CNS) that generate neuron, astrocytes, and oligodendrocytes with a high degree of regional specificity of (Merkle, Mirzadeh, & Alvarez-Buylla, 2007; Tsai et al., 2012). The positional identity is an organizing principle underlying cellular subtype diversification in the brain and is controlled by a homeodomain transcriptional code (Hochstim, Deneen, Lukaszewicz, Zhou, & Anderson, 2008). During embryonic development, expansion and cell fate determination of neural precursors is

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controlled by gradients of secreted molecules along rostrocaudal and dorsoventral axes. Radial glia and embryonic NSCs generate neurons, glial cells, and ependymal cells in temporal waves during neural development (Rakic, 1990). As a remnant from fetal development, neurogenesis in mammalians is restricted after birth to the dentate gyrus of the hippocampus and the subventricular zone (SVZ) lining the lateral ventricles (Doetsch, 2003; Eriksson et al., 1998; Sanai et al., 2011). Recent studies suggest that NSCs are lining the third and fourth ventricles as well (S. Weiss et al., 1996; Xu et al., 2005). In the postnatal cerebellum, Bergmann glia express markers associated with NSCs (Koirala & Corfas, 2010; Sottile, Li, & Scotting, 2006). In contrast to rodents, SVZ neurogenesis in humans ceased after 18 months, indicating that few SVZ NSCs are present in the aging human brain (Sanai et al., 2011). Given the extensive self-renewal capacity of NSCs, these cells have been suggested as the cell of origin for gliomas (Figure 1). Considering the low abundance of NSCs and the wide distribution of gliomas throughout the human postnatal brain, it is more likely that an abundantly expressed cell type is susceptible to transform into glioma.

A first wave of oligodendrocyte progenitors arise from the embryonic ventral forebrain, followed by a second wave originating from the lateral and caudal ganglionic eminences, and finally a third wave arises within the postnatal cortex (Kessaris et al., 2006). In the developing mouse brain and spinal cord, the first oligodendrocyte-lineage cells appear around embryonic day 12.5 (E12.5) (Zuo & Nishiyama, 2013). The cells are characterized by expression of the basic helix-loop-helix (bHLH) transcription factors *OLIG1, OLIG2, NKX2.2*, the *Sry-related high mobility group box gene* (*SOX10*), and platelet-derived growth factor receptor alpha (PDGFRA) (Zuo & Nishiyama, 2013). At E14.5 PDGFRA positive cells also express the chondroitin sulfate proteoglycan neuro-glial 2 (NG2) (in humans CSPG4) in the ventral mouse forebrain (Nishiyama, Lin, Giese, Heldin, & Stallcup, 1996). While *OLIG2* is required for generation of oligodendrocyte specification, the bHLH factors *ASCL1* promotes oligodendrogenesis by repressing *DLX1/2*, a transcriptional repressor of *OLIG2* (Ligon et al., 2006; Petryniak, Potter, Rowitch, & Rubenstein, 2007). Other prerequisites for oligodendrogenesis include the SOXE proteins SOX8, SOX9, and SOX10 (C. C. Stolt et al., 2003). In contrast, the SOXD proteins SOX5 and SOX6 inhibit oligodendrocyte specification (C. Stolt et al., 2006). In addition, the developmentally expressed genes *NOTCH-1, wingless* (*WNT*), *and sonic hedgehog* (*SHH*), normally associated with NSCs, block differentiation and maintain an undifferentiated state in OPCs (Zuo & Nishiyama, 2013) (Figure 1B).

As the most widely distributed population of cycling cells in the postnatal brain, OPCs, also referred to as polydendrocytes, represent a fourth major type of glia in the CNS (Zuo & Nishiyama, 2013). In fact, approximately 70% of 5-bromo-2′-deoxyuridine (BrdU)-incorporating cells in the adult rat brain co-expressed NG2 (Dawson, Polito, Levine, & Reynolds, 2003; Lasiene, Matsui, Sawa, Wong, & Horner, 2009). An elegant study by Hughes et al. (2013) show that OPCs are under homeostatic control to ensure generation of appropriate numbers of myelin-producing oligodendrocytes (Hughes, Kang, Fukaya, & Bergles, 2013). As OPCs are recruited to focal injuries, a proliferative burst of OPCs surrounding the injury restore the cell density. It has been debated if all OPCs have the same proliferative capacity or respond to different environment cues. PDGFA acts as a potent

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mitogen of OPCs expressing PDGFRA (Hall, Giese, & Richardson, 1996). Hill et al., (2013) recently demonstrated that in white matter, but not grey matter, OPCs proliferate in response to PDGF by activating WNT and phosphatidylinositol 3-kinase (PI3K) (Hill, Patel, Medved, Reiss, & Nishiyama, 2013). Similar to NSCs, the mitogen epidermal growth factor (EGF) induces symmetrical cell division in adult OPCs (Sugiarto et al., 2011) (Figure 2). Treatment of human OPCs with histone deacetylase (HDAC) inhibitors prevented differentiation into oligodendrocytes, demonstrating the importance of post-translational modification of histones (Conway, O'Bara, Vedia, Pol, & Sim, 2012). In summary, several drivers (*PDGFRA*, *EGFR*, modulation of histone function) of gliomagenesis also play key roles in OPC development, arguing that proliferating OPCs, abundant throughout life, may transform in response to environmental pressure and play a key role in gliomagenesis.

3. Glioma Subgroups and Cell of Origin

Neuropathologists classify gliomas based on grade (I-IV) that includes grade II diffuse gliomas and grade III-IV malignant gliomas. Ependymomas, astrocytomas, oligodendrogliomas, and oligoastrocytomas display fewer mitoses, necrosis, nuclear atypia, and vascular proliferation compared to grade IV GBM (Louis et al., 2007). To develop a more personalized medicine approach and improve survival in patients, research has focused on characterizing subsets of GBM patients. Microarray expression profiling was first able to separate low- versus high-grade gliomas and primary versus recurrent tumors (Godard et al., 2003; Rickman et al., 2001; van den Boom et al., 2003). New technological advances and the Cancer Genome Atlas network (TCGA) have defined subsets of GBMs based on epigenomic, genomic, and transcriptomal signatures (Noushmehr et al., 2010; H. S. Phillips et al., 2006; Verhaak et al., 2010). When Phillips et al. (2006) stratified primary GBMs based on survival, they identified a better prognosis for tumors displaying a proneural gene expression signature. Patients with worse prognosis could be separated into classical and mesenchymal subsets of tumors (H. S. Phillips et al., 2006). When primary GBMs were not classified based on survival, Verhaak et al. (2010) later identified a fourth neural GBM subgroup (Verhaak et al., 2010). A couple of years earlier, approximately 12% of GBM patients displayed isocitrate dehydrogenase (*IDH*) mutations in tumors and showed increased overall survival (Parsons et al., 2008). Verhaak et al. showed that *IDH* mutations were exclusively found in a subset of proneural GBMs (Verhaak et al., 2010). A recent study demonstrated 6 subgroups of GBMs (Sturm et al., 2012). Childhood GBMs showed a strong correlation to histone H3.3 (*H3F3A*) mutations at two critical residues; (K27(M) or G34(R/V), that added two additional GBM subgroups with unique epigenetic and gene expression signatures (Sturm et al., 2012). Interestingly, these *H3F3A* mutations give rise to GBMs in separate anatomic compartments, and in contrast to $IDH1^{R132H}$ mutant tumors, are diagnosed in adolescents (G34) or young children (K27). The authors refer to these 6 GBM subgroups as; IDH1, K27, G34, RTK I ‘PDGFRA’, mesenchymal, and RTK II ‘classic”, since they are associated with unique genetic alterations (Sturm et al., 2012) (Figure 2). Gene expression profiling of diffuse gliomas shows that approximately 75% and 50% of diffuse oligodendrogliomas and astrocytomas, respectively, belong to the proneural subgroup (L. a D. Cooper et al., 2010). Interestingly, the fraction of proneural tumors correlates well with the frequency of *IDH* mutations in diffuse gliomas (Yan et al., 2009). A

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recent study suggests that activity among signal transduction pathways at the protein level can define GBM subclasses (Brennan et al., 2009). However, future advances in proteomics are needed to effectively distinguish glioma patients at the protein level. Progress in subclassification of gliomas is used to develop biomarkers and gene expression signatures that can be used to stratify patients in clinical trials (Olar & Aldape, 2012). In parallel, magnetic resonance imaging (MRI) predictors that associate with GBM subgroups are in development (Gutman et al., 2013). MRI studies show that proneural GBMs had significantly lower levels of contrast enhancement and $IDH1^{R132H}$ mutant GBMs show accumulation of 2-hydroxyglutarate (2HG) (Chaumeil et al., 2013; Gutman et al., 2013). However, decision-making is still governed by genetic alterations as gliomas show regional heterogeneity for MRI parameters and association to GBM subgroups.

To develop subgroup-specific therapies in glioma, improved pre-clinical models are needed. Traditionally, researchers have studied therapeutics using cultures or xenografts of human GBM cell lines. Passaging of primary human GBM tumors in immunocompromised mice is an improved model system that better preserves tumor cell heterogeneity (Hodgson et al., 2009). However, the strong influence of the tumor microenvironment and the importance of blood-brain barrier permeability for drugs have led to generation of several genetically-engineered murine models (GEMM) of glioma (Table 1). These models are also useful for studies of premalignant events and the cell of origin for different types of gliomas. Although these models have been highly informative, a discrepancy of previously developed GEMM of glioma is the failure to recapitulate the genetic alterations observed in human counterparts. For example, whole-genome sequencing studies have identified $B\text{-}RAF^{V600E}$, *FGFR1, MYB1, MYBL1, H3F3A, and ATRX* mutations in pediatric gliomas (J. Zhang et al., 2013). However, recent progress has employed $BRAF^{V600E}$ mutation and neurofibromin 1 (NF1) loss to generate pilocytic gliomas and high-grade GBMs (J. Chen et al., 2012; Robinson et al., 2011). Modeling of *H3F3A* and $IDH1^{R132H}$ mutations in murine GEMM will be useful tools to develop new therapeutics against larger cohorts of childhood and adult glioma patients.

4. H3F3A Mutations Drive Gliomagenesis in Separate Brain Regions

For NSCs and progenitor cells to achieve production of different types of neurons and glia at appropriate times and places during development, they must integrate cell-intrinsic programs and environmental cues. These developmental dynamics are reflected in changes in gene expression, which is regulated by transcription factors and at the epigenetic level. Methylation and acetylation of histones function as epigenetic modulators of differentiation in NSCs and progenitors (X.-L. Hu, Wang, & Shen, 2012). However, mutations of epigenetic sites on histones can block differentiation and transformation of cells into cancers. In this section of the review, we will discuss recent findings demonstrating mutations at two distinct residues (K27(M) or G34(R/V)) of *H3F3A* in childhood GBMs. Interestingly, K27 and G34 mutant pediatric GBMs are associated with distinct anatomical locations, have subgroup-specific gene expression signatures, and occur at different ages, suggesting that different precursor cells may represent the cell of origin for K27 and G34 mutant GBMs.

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Whole-genome and whole-exome sequencing studies independently identified recurrent mutations in the gene *H3F3A* in pediatric glioma (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 (Figure 3). 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). This may be reflective of their prognosis as patients with K27 mutant tumors typically have lower overall survival rates compared to G34 mutant and *H3F3A* wildtype (WT) tumors, while patients with *IDH* mutant tumors had better prognosis compared to patients with tumors containing either *H3F3A* mutation (Sturm et al., 2012). Consistent with these findings, Wu et al identified 78% of patients with the lethal pediatric tumor, diffuse intrinsic pontine glioma (DIPG), contained the K27 mutation while no DIPG samples had a mutation at G34 (Wu et al., 2012). A separate study by Khuong-Quang et al. found a similar trend where K27 mutations were identified in 71% of DIPG samples, while none had G34 or *IDH* mutations (Khuong-Quang et al., 2012). Both K27 and G34 mutations frequently co-occur with other genetic mutations and associate with the expression of developmentally regulated genes. For example, 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). One of the initial studies that identified these recurrent *H3F3A* mutations also found mutations in the chromatin remodeling protein, ATRX, and the tumor suppressor *TP53* (Schwartzentruber et al., 2012). *ATRX* mutations were 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). *TP53* mutations were also consistently found in tumors with G34 mutations, which may represent an alternate mechanism of p53 inactivation, as *OLIG2*, commonly lost in G34 tumors, has been shown to block p53 function (Mehta et al., 2011). Conversely, this may also explain why K27 mutant tumors (which are OLIG2+) do not need to correlate as strongly with *TP53* mutations (although a high percentage (∼70%) of K27M mutant tumors do co-express mutant *TP53*). The frequent association of *TP53* and *H3F3A* mutations in pediatric GBM is reminiscent with the strong link between *TP53* and $IDH1^{R132H}$ mutations in adult GBM. To summarize, these studies suggest that *H3F3A* mutant GBMs may arise from regionally distinct *OLIG2*-expressing glial progenitors.

4.1 Regulation of DNA methylation by K27 and G34 *H3F3A* mutations

DNA is condensed in the nucleus by wrapping around histones and multiple histones assemble to form a nucleosome, which consists of nine histone subunits (two of each core histone [H2A, H2B, H3, H4] and the linker histone H1). In addition to compacting DNA, histones contribute to the epigenetic regulation of the genome via substitution of various histone isoforms and posttranslational modifications. These alterations that regulate gene expression are largely due to acetylation and methylation of lysine and arginine residues.

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Although methylation is generally associated with repression of gene expression, methylation can indicate active transcription depending on the residue that is methylated as well as the amount of methyl groups added at that site (mono-, di- and tri-methylation). This is illustrated with Histone H3 where tri-methylation of lysine 4 and 36 (K4, K36) associate with active transcription, while tri-methylation of K9 and K27 suggest gene silencing (Chi, Allis, & Wang, 2010). While di- and tri-methylation of K27 are linked to inhibition of gene expression, mono-methylated K27 is localized at highly expressed genes, as is acetylated K27 (Creyghton et al., 2010; Steiner, Schulz, Maksimova, Wong, & Gallagher, 2011).

Two DIPG K27 mutant cell lines demonstrated a reduction in tri-methylation (me3) and di-methylation (me2) status at K27 while not impacting the acetylation levels of K27 (H3K27ac) compared to normal NSCs (Chan et al., 2013). Similarly, another study found suppressed H3K27me3 levels in 6 GBMs containing K27 mutations (Venneti et al., 2013). Ectopic expression of *H3F3A* K27 in 293T cells, human astrocytes and mouse embryonic fibroblasts, decreased di-and tri-methylation of K27 on endogenous *H3F3A* proteins and the exogenously expressed mutant without affecting the methylation status of K36, a post-translationally modified site near G34 (Chan et al., 2013; Lewis et al., 2013). The mechanism for reduced methylation at K27 may be due to *EZH2*, the catalytic subunit of polycomb repressive complex 2 (PRC2), which is a methyltransferase that targets Histone 3.3 K27. Since the expression levels of EZH2 is not altered between patient samples expressing either WT *H3F3A* or the K27 mutation, the mutation may act in a dominant negative fashion to block *EZH2* function (Venneti et al., 2013). This was supported by the finding that a K27 peptide demonstrated a higher affinity for EZH2 compared to wildtype *H3F3A* and inhibited PRC2 activity via interaction with *EZH2* (Chan et al., 2013; Lewis et al., 2013). In K27 mutant DIPG cells, the sites which retained H3K27me3 had increased levels of trimethylation, as well as *EZH2*, and were genes associated with cancer pathways, such as the tumor suppressor *CDKN2A* (Chan et al., 2013). Although overexpression of mutant K27 lowered the methylation status of both the endogenous and exogenous K27, mis-expression of an *H3F3A* G34 mutant only decreased tri-methylation of K36 on the exogenous peptide, while not affecting the endogenous *H3F3A* K36 (Chan et al., 2013; Lewis et al., 2013). This would suggest that the G34 site would need to be mutated on both alleles to have a tumorigenic effect while the K27 mutation on only one allele may be sufficient for transformation. The requirement for an additional hit on G34 may explain why these tumors appear later in life than K27 mutant tumors. Sturm et al. found global hypomethlation of genomic DNA in G34 mutant tumors, which stands in contrast to global hypermethylation in $IDH1^{R132H}$ mutant tumors (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 (Schwartzentruber et al., 2012; Sturm et al., 2012).

4.2 Chromosome and Myc aberrations in *H3F3A* mutant glioblastoma

Chromosomal aberrations have been investigated between *H3F3A* WT and K27 mutant DIPG tumors (Khuong-Quang et al., 2012). As expected due to the role histones play in chromatin remodeling, K27 mutant tumors exhibit different chromosomal aberrations compared to tumors with *H3F3A* WT. *H3F3A* WT samples exhibited gains of 2p and 7p as

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well as losses in 9p and 12q. K27 tumors harbored losses of 5q, 6q, 17p and 21q and gains in 19p. Focal recurrent gains were also observed in 4q12 (containing *PDGFRA*), and 8q24.21 (*MYC/PVT1* locus). Intriguingly, while *MYC* is amplified in K27 tumors, chromosome 2p24.3 (which includes *MYCN*) is significantly gained in *H3F3A* wildtype tumors. Although amplification of *MYCN* has not been observed in G34 mutant samples, overexpression of the G34 mutation induces expression of MYCN in normal human astrocytes and fetal glial cells (Bjerke et al., 2013; Khuong-Quang et al., 2012). This implies that amplification and overexpression of *MYC* and *MYCN* appear to segregate based on the *H3F3A* mutations. MYC proteins are known to promote apoptosis via activation of *TP53* (Chesler et al., 2008; Elson, Deng, Campos-Torres, Donehower, & Leder, 1995) and a number of cancer models utilize overexpression of *MYC* in combination with loss of *TP53* function (Kawauchi et al., 2012; Pei et al., 2012; Schmitt et al., 2002; Yu & Thomas-Tikhonenko, 2002). Since MYC is also known to promote proliferation and block differentiation, the combination of amplified *MYC*, mutant *TP53* and K27 may provide insight to the genetic etiology of DIPG.

4.3 Delineating the cell of origin for K27 and G34 *H3F3A* mutant glioblastoma

Neural stem cells, astrocyte precursors, and OPCs are all abundant at birth in humans and represent possible targets for transformation by K27 mutation. In mice, viral transduction of Nestin-expressing precursors with mutant *TP53* and K27 failed to induce gliomagenesis in the newborn murine brainstem, but did induce proliferating ectopic cell clusters (Lewis et al., 2013). In humans, Nestin and OLIG2 are co-expressed in the ventral pons around 6 years of age, the peak for DIPG occurrence (Monje et al., 2011). In contrast to K27 mutant GBMs, G34 mutant tumors express the forebrain marker *FOXG1* and other forebrain development-related transcription factors such as *ARX, DLX5, FOXA1, NR2E1, POU3F2,* and *SP8* (Bjerke et al., 2013). Although NSC are not abundant in the forebrain in adolescents when most G34 mutant GBMs are diagnosed, these tumors express the NSC-associated genes Musashi-1 (*MSI1*), eyes absent homolog 4 (*EYA4*), and *SOX2* under control of the active transcription marker, H3K36me3 (Bjerke et al., 2013). High expression of *MYCN* in G34 mutant GBMs may enable more restricted forebrain precursors to dedifferentiate into a NSC phenotype. Using a mosaic mouse model, Liu et al. (2011) elegantly demonstrated that even when combined loss of *TP53* and *NF1* were introduced in Nestin positive NSCs, transformation only occurred after NSCs had differentiated into OPCs (C. Liu et al., 2011). A similar approach can be used to delineate the cell of origin for K27 and G34 mutant GBMs.

5. Gliomagenesis and Mutations in Isocitrate Dehydrogenase Genes

In humans, five genes encode three isoforms of the metabolic enzyme *IDH* that are involved in the citric acid cycle. IDH1 is found both in the cytoplasm and peroxisomes while IDH2 and IDH3 are localized to the mitochondria. IDH1 and IDH2 are closely related and catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG) while reducing nicotinamide adenine dinucleotide phosphate ($NADP^+$) to NADPH (Figure 4). The unrelated multisubunit enzyme, IDH3, reduces NAD^+ to NADH and is thought to play a central role in aerobic energy production in the tricarboxylic acid (TCA) cycle. A critical residue, involved

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in the binding of isocitrate, is arginine 132 (R132), found within the active site of human *IDH1* and is evolutionary conserved in the functionally analogous R172 of *IDH2*. $IDH1^{R132H}$ results in an 80% reduction in enzyme activity. The R132 mutation abolishes normal catalytic activity by preventing the protein to bind to isocitrate. In normal cells, *IDH* genes mediate epigenetic changes that maintain cellular homeostasis. Yet, in cancer cells these epigenetic modifications represent a key hallmark of tumorigenesis. Interestingly, *IDH* mutations are generally mutually exclusive and occur uniquely on these arginine residues, which are conserved across species and malignancies.

The first observations of *IDH1/2* mutations were identified in metastatic colon cancer. These mutations are also found in sarcomas, leukemias, and gliomas. Traditionally, oncogenic events are known to induce aberrant changes that lead to rapid cell cycle progression. However, pioneering studies in leukemia demonstrated that *IDH* mutation leads to a block in differentiation in hemapoietic precursor cells (Chaturvedi et al., 2013). The ability of *IDH* mutation to disrupt normal differentiation into defined cell lineages has also been demonstrated in murine forebrain NSCs (C. Lu et al., 2013). This block in differentiation was attributed to prevention in histone demethylations required for NSCs to terminally differentiate. Although the differentiation program was compromised in the NSCs, the authors found no indication of transformation, suggesting that *IDH* mutations may transform glial progenitor or dedifferentiated terminally differentiated glial cells. Parsons et al. (2008) sequenced over 20,000 protein coding genes in order to identify genetic alterations in GBMs and found that 12% of the samples analyzed harbored a recurrent point mutation in the active site of *IDH1/2* (Parsons et al., 2008). Specifically, 5% of primary gliomas and 60-90% of secondary gliomas had *IDH1/2* mutations. Further, they observed that $IDH1^{R132H}$ mutations occurred in a large fraction of young patients and that most patients with secondary GBMs were associated with increased overall survival. Mutations in *IDH2* are much less common and mutually exclusive with $IDH1^{R132H}$ as mentioned before. Virtually all tumors with *IDH* mutations are of the proneural subtype. Other studies found *IDH* mutations in 80% grade II and grade III gliomas as well as in secondary GBMs. Importantly, Yan et al. (2009) reported that $IDH1^{R132H}$ is a favorable prognostic marker for glioma patients (Yan et al., 2009).

Hypoxia-inducible factor 1α (HIF-1α) is a transcription factor that facilitates tumor growth under conditions of low oxygen and its stability is regulated by α-ketoglutarate. Human gliomas with $IDH1^{R132H}$ mutation express higher levels of HIF-1α compared to *IDH* wildtype tumors. Additionally, expression of IDH1 in cultured cells reduces α-KG and increases HIF-1α levels (S. Zhao et al., 2009). These results indicate that $IDH1^{R132H}$ mutations may contribute to tumorigenesis in part through the HIF-1 pathway.

As previously mentioned, mutations occur at a single amino acid residue of the $IDH1^{R132H}$ active site. Interestingly, in tumors, only a single copy of the gene is mutated and the expression of a wildtype *IDH1* allele is critical for the formation of a heterodimer with the mutated allele. Cancer-associated $IDH1^{R132H}$ mutations have been found to resulting in the production of 2-HG instead of α-KG. Remarkably, levels of 2-HG are elevated in human gliomas harboring $IDH1^{R132H}$ mutations. These findings indicate that the production of the

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oncometabolite 2-HG in *IDH1*^{R132H} mutated tumors may contribute to glioma initiation and malignant progression.

The accumulation of 2-HG has been associated with increased histone methylation and decreased 5-hydroxylmehtylcytosine (5hmC), resulting in genome-wide histone and DNA methylation alterations (Figure 4). Furthermore, it has been demonstrated that a large number of loci in *IDH1*^{R132H} mutant gliomas display hypermethylation (Noushmehr et al., 2010). Together, these findings suggest that *IDH* mutations may alter the expression of a large number of genes rather than a few specific genes. Reportedly, mutations of *IDH1*^{R132H} occur at an early stage during gliomagenesis (Watanabe, Nobusawa, Kleihues, & Ohgaki, 2009) and may contribute to tumor initiation by globally changing the epigenetic landscape and control cellular state and fate. In fact, glioma samples with *IDH* mutations and increased histone methylation display a gene expression profile enriched for neural progenitor genes. In summary, 2-HG producing *IDH* mutations inhibit histone demethylation and can thereby block cell differentiation.

It is established that acquired alterations in the methylation landscape cause dysregulation and can thereby be involved in onconenesis (Jones & Baylin, 2007). A distinct subclass of human glioblastomas has the CpG island methylator phenotype (CIMP) and is associated with the proneural subgroups of tumors and *IDH* mutation (Noushmehr et al., 2010). The fact that both *IDH* mutation and the CIMP phenotype occur in glioblastomas raises the question of cause and effect. Turcan et al. (2013) demonstrate elegantly that *IDH1*^{R132H} mutation is the cause of CIMP, and establishes the CIMP phenotype by remodeling the epigenome (Turcan et al., 2013). Importantly, primary human astrocytes introduced with *IDH1*^{R132H} mutation display epigenomic alterations mirroring low-grade gliomas positive for the CIMP phenotype. These observations further our mechanistic understanding of the role of *IDH* mutation and CIMP in gliomanenesis, providing targets for development of novel therapies.

5.1 Models of *IDH*-mutant gliomas

Studying *IDH*-mutant gliomas has been obstructed by the lack of models of *IDH*-mutant glioma-producing mice. With respect to the effects of *IDH* mutations on tumorigenesis Sasaki et al. (2012) generated brain-specific *IDH1*^{R132H} knock-in (IDH1-KI) mice (Sasaki et al., 2012). These mice are embryonically lethal, display brain hemorrhage and elevated 2-HG levels but decreased reactive oxygen species (ROS). Interestingly, the increased levels of 2-HG stabilize HIF-1α proteins and upregulate HIF-target gene transcription. Moreover, an ER stress response is triggered which causes intrinsic cell death. These effects may increase vascular endothelial growth factor (VEGF) levels, leading to aberrant blood vessel formation and ultimately resulting in brain hemorrhage.

Cell lines with *IDH1*^{R132H} mutation can only be maintained transiently in vitro, as the mutation does not persist in non-immortalized cells. Furthermore, primary *IDH*-mutant gliomas from patient tumors do not grow well in vitro (Piaskowski et al., 2011). In contrast to normal cells, introduction of *IDH* mutations into glioma cells decreases the proliferation rate, which may ultimately cause a selection pressure against cultured glioma cells harboring *IDH* mutations (Bralten et al., 2011). Despite these challenges, at least one group has

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reported the isolation of a glioma cell line with an endogenous R132H mutation in *IDH1*^{R132H} (Luchman et al., 2012). The researchers established neurosphere cultures from an *IDH1*^{R132H} mutant anaplastic oligoastrocytoma sample and confirmed retention of the mutation over passages. These cells were also used in orthotopic xenografts of non-obese diabetic/severe combined immune deficiency (NOD/SCID) mice. Mass spectroscopy experiments were performed to confirm production of 2-HG by glioma cells with endogenous *IDH1*^{R132H} mutations both in vivo and in vitro. In summary, there is a great need for glioma models with *IDH* mutations to interrogate the roles of IDH mutations during gliomagenesis since efforts to model IDH mutant gliomas have failed and the ability to grow primary *IDH* mutant tumors has been challenging.

5.2 Glial progenitor-origin for *IDH*-mutant gliomas

Development of *IDH*-mutant sarcoma or leukemia-models, have allowed researcher to search for drugable targets up- or down-stream of IDH in a cell-type specific context (Sasaki et al., 2013). To date, most studies of *IDH*-mutations in glioma have relied on overexpression in different glioma cell lines (Rohle et al., 2013). However, genes important for terminal differentiation present in OPCs are lacking in these artificial cell lines and without those genes in place methylation inhibition cannot be studied. Since *IDH* mutations are most common in oligodendroglioma, development of *IDH*-mutant oligodendroglioma models and the ability to xenograft/culture *IDH*-mutant human oligodendrogliomas will generate excellent tools to better understand the earliest transformation events and to perform pre-clinical studies. As *IDH* mutations are found in 12% of all gliomas, much effort is currently focused on defining the molecular events following *IDH* mutations to find drugable targets. To improve the survival of patients diagnosed with glioma, defining the cell of origin and the first molecular events that initiate transformation will be fundamental for development of new therapies. *IDH1*^{R132H} mutant oligodendrogliomas are thought to arise in white matter regions of the cerebral hemispheres. Oligodendrocyte progenitor cells represent the most widely spread population of cycling cells in the adult brain. OPCs in adults are scattered throughout the brain, while NSCs mainly reside in the subventricular zone and the hippocampus. The genetics and location of *IDH1*^{R132H} gliomas suggest that OPCs may be susceptible to transformation. This raises the question if *IDH1*^{R132H} mutation is sufficient to transform OPCs? Oligodendroglioma show distinct histological features including fried-egg morphology that distinguish them from other gliomas. Co-deletion of chromosomal arms 1p and 19q is a well-known prognostic marker found frequently (>60%) in grade II-III oligodendrogliomas. Recent exomic sequencing has identified tumor suppressor genes: homolog of Drosophila *capicua* (*CIC*) and *far-upstream binding protein 1* (*FUBP1*) in 53% and 15% of oligodendrogliomas, respectively (Yip et al., 2011). Since CIC and FUBP1 are located on chromosomal arm 19q and 1p, respectively, loss of these regions inactivates the genes and could potentially contribute to oligodendroglioma development. A strong association between *IDH1*^{R132H} mutation and 1p/19q co-deletion is found in grade II-III oligodendrogliomas, suggesting that these genetic alterations are important for gliomagenesis. While a subfraction of oligodendrogliomas display *IDH1*^{R132H} and *TP53* mutations, it is more commonly observed in astrocytic tumors.

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The reason for the favorable prognosis of *IDH1*^{R132H} mutant patients is still unknown. Several studies have suggested that *IDH1*^{R132H} mutation and 2-HG block cell differentiation (Chaturvedi et al., 2013; Figueroa et al., 2010; C. Lu et al., 2013). The reduced aggressiveness in IDH-mutant tumors may be a result of inhibited differentiation, rather than regulation of cell cycle genes. Alternatively, the better prognosis for *IDH*-mutant patients may reflect an OPC origin. Mutant *IDH1*^{R132H} accelerate onset of myeloproliferative disease (MPD)-like myeloid leukemia in mice in cooperation with Homeobox protein Hox-A9 (*HOX9A*) (Chaturvedi et al., 2013). Further, mutant *IDH1*^{R132H} accelerated cell cycle transition through repression of cyclin-dependent-kinase inhibitors CDKN2A and CDKN2B, and reduced activation of MAPK signaling. Interestingly, a complex transcriptional regulatory network of *HOX* genes specify neural progenitor cell identity during early development (Gavalas, Trainor, Ariza-McNaughton, & Krumlauf, 2001; Lumsden & Krumlauf, 1996; Trainor & Krumlauf, 2001) Further, it has been reported that sustained activation of MAPK activation in oligodendrocytes stimulates oligodendrocyte progenitor expansion (Ishii, Furusho, & Bansal, 2013). Together, these data may support the idea that OPC are the cells of origin of *IDH1*^{R132H} mutant cancers.

In contrast to classical and mesenchymal GBMs that express gene expression profiles reminiscent of NSCs, *IDH*-mutant gliomas display a proneural phenotype (Verhaak et al., 2010). Interestingly, Verhaak et al. (2010) found that the transcriptomal signature of proneural GBMs were closely associated with oligodendrocytes rather than astrocytes, neurons, or NSCs (Verhaak et al., 2010). Due to low activity of NADPH-producing dehydrogenases in rodent versus human brain, it was suggested that rodents are unsuitable to model gliomas (Atai et al., 2011). However, no studies have demonstrated expression of *IDH* isoforms at high resolution and in defined cell populations, why the cell-specific role of this gene family is still unclear. In the Verhaak et al. study, many genes that are normally found in OPCs, such as NKX2.2, PDGFRA, and OLIG2, were overexpressed in *IDH*-mutant proneural GBMs (Verhaak et al., 2010). Support from GEMMs show that proneural gliomas can derive from OPCs (Lindberg, Kastemar, Olofsson, Smits, & Uhrbom, 2009; Persson et al., 2010). The regional association of *IDH1*-mutant GBMs to frontal cortex and white matter regions, argue that OPCs, rather than NSCs, represent a likely origin for *IDH*-mutant gliomas.

6. Proneural-to-Mesenchymal Transition (PMT) in Glioma

Epithelial-to-mesenchymal transition (EMT) occurs during critical stages during development, such as gastrulation and neural crest formation (Kalluri & Weinberg, 2009; Thiery, 2002). As epithelial cancer cells undergo EMT, they become invasive, metastasize, and become drug-resistant (Craene & Berx, 2013; A. Singh & Settleman, 2010). In many cancers, including breast cancer, the mesenchymal phenotype is associated with increased activation of transforming growth factor beta (TGFβ) signaling, leading to increased expression of the transcription factor families of *SNAIL*, *SLUG* and *TWIST*, and down-regulation of *E-cadherin* (Craene & Berx, 2013; Mallini, Lennard, Kirby, & Meeson, 2013).

Transcriptomal profiling of gliomas, displaying a neuroepithelial origin, show that the mesenchymal phenotype is associated with stemness, invasiveness, and poor survival (H. S.

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Phillips et al., 2006; Sturm et al., 2012; Verhaak et al., 2010) (Figure 5). Although in a small cohort of patients, recurrent tumors shifted from a proneural to mesenchymal phenotype, reminiscent of EMT (Lai et al., 2011; H. S. Phillips et al., 2006). In this section, we will review new exciting data suggesting that expression of a single gene or changes in the tumor microenvironment can shift gliomas between proneural and mesenchymal phenotypes, which we will refer to as a proneural-to-mesenchymal transition (PMT). Since recurrent gliomas tend to have a mesenchymal phenotype (Lai et al., 2011), these findings have implications for therapy and suggest that even more stem-like gliomas can arise from OPCs.

6.1 Mesenchymal phenotype as a function of glioma subgroup

Mesenchymal GBMs are associated with genes expressed in immune cells, vasculature, invasive cells, but also markers expressed in mesenchymal stem cells and NSCs (H. S. Phillips et al., 2006; Sturm et al., 2012; Verhaak et al., 2010). In contrast, *IDH* mutant GBMs are strictly proneural (Lai et al., 2011; Sturm et al., 2012). *IDH* mutations are frequent in secondary (60-90%) GBMs and grade II-III gliomas compared to primary (5%) GBMs (Balss et al., 2008; Bleeker et al., 2009; Hartmann et al., 2009; Kang et al., 2009; Sanson et al., 2009; Watanabe et al., 2009; Yan et al., 2009). In Phillips et al., (2006), *IDH* wildtype, but not mutant, underwent PMT as they underwent recurrence (Lai et al., 2011; H. S. Phillips et al., 2006). This raises the question if methylation of target genes is required for PMT in gliomas. In epithelial cancers, EMT is associated with increased invasion, resistance to therapy, and acquisition of a ‘cancer stem cell’-like phenotype (Mani et al., 2008; Polyak & Weinberg, 2009). It becomes increasingly clear, that anti-angiogenic treatments and radiotherapy enrich for GSCs and generate highly invasive mesenchymal tumors (Bao et al., 2006; Diehn et al., 2009; Kraus et al., 2002; K. V Lu et al., 2012). Therefore, as we learn more about the mechanisms that drive PMT in glioma, a future goal should be to design therapies that block PMT and improve outcome in patients.

6.2 Transcriptional master regulators of PMT in glioma

In epithelial cancers, *SNAIL, TWIST, ZEB1* and *TGFB1* are known master regulators of EMT (Kalluri & Weinberg, 2009; Thiery, 2002). *In vitro* studies suggest that ZEB1 and TWIST also regulate tumor invasion, chemoresistance and stemness in GBM cell lines (Mikheeva et al., 2010; Siebzehnrubl et al., 2013). In an attempt to identify other drivers of the mesenchymal phenotype in GBMs, Carro et al. (2009) used a bioinformatics approach to contrast gene expression signatures between GBM subgroups (Carro et al., 2009). The top six transcription factors that distinguished GBM subgroups (signal transducer and activator of transcription 3 (*STAT3*), *C/EBPβ, bHLH-B2, RUNX1, FOSL2* and *ZNF238*) regulated >74% of the mesenchymal gene expression signature. They identified *C/EBPβ* and *STAT3* as the main master regulators of mesenchymal transcription networks. During development, *C/EBPβ* and *STAT3* have opposing roles on neurogenesis (Gu et al., 2005; Ménard et al., 2002). While *C/EBPβ* promotes neurogenesis and opposes gliogenesis, *STAT3* promotes astrocytic differentiation and inhibits neurogenesis (Ménard et al., 2002; Nakashima, 1999; Paquin, 2005). As *C/EBPβ* and *STAT3* were transduced into human fetal NSCs, the authors observed reduced neurogenesis and induction of a program towards a mesenchymal phenotype. In primary human GBM cells, *C/EBPβ* and *STAT3* were essential for the mesenchymal phenotype and tumorigenicity when xenografted into immunocompromised

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mice. Other studies show that *C/EBPβ* and *STAT3* can individually regulate glioma biology. For example, downregulation of *C/EBPβ* in glioma cells inhibited proliferation, invasion and tumorigenicity in mice (Aguilar-Morante, Cortes-Canteli, Sanz-Sancristobal, Santos, & Perez-Castillo, 2011; Homma et al., 2006), consistent with findings demonstrating that increased mRNA and protein levels of *C/EBPβ* are associated with a worse prognosis (Homma et al., 2006). Similarly, *STAT3* is known to promote tumor growth in glioma. Recent findings suggest that *STAT3* is required for maintenance of GSCs (Garner et al., 2013; Priester et al., 2013; Sherry, Reeves, Wu, & Cochran, 2009).

To identify additional master regulators of the mesenchymal phenotype in glioma, Bhat et al. employed a regulatory network analysis of GBM microarray data sets (Bhat et al., 2011). Compared to mesenchymal GBMs, the authors found lower expression of the *transcriptional coactivator with PDZ-binding motif* (*TAZ*) in proneural GBMs and lower-grade gliomas. Expression of *TAZ* correlated well with the degree of CpG island hypermethylation of its promoter. Silencing of *TAZ* in mesenchymal GSCs decreased mesenchymal marker expression, invasion, self-renewal, and tumor formation. Conversely, overexpression of *TAZ* in proneural GSCs as well as murine NSCs induced expression of mesenchymal markers, through a binding with co-activator TEAD. Interestingly, *TAZ* cooperates with PDGF-B to induce high-grade mesenchymal gliomas in the RCAS/Nestin-tv-a model, suggesting that aberrant RAS activation may be a prerequisite for mesenchymal transition by *TAZ* (Bhat et al., 2011). In other cancers, the TAZ-TEAD nuclear complex has previously been shown to play important roles in EMT, cell growth, and organ development (Hong & Yaffe, 2006; Q.-Y. Lei et al., 2008; Heng Zhang et al., 2009; B. Zhao, Li, Lei, & Guan, 2010).

As master regulators of the mesenchymal phenotype, *STAT3*, *C/EBPβ* and *TAZ* represent future therapeutic targets. The ability to inhibit these transcriptional nodes may lead to a collapse of the mesenchymal phenotype, reduced treatment-resistance, and improved survival in GBM patients. Pharmacological *STAT3* inhibitors are currently being evaluated in clinical trials against solid tumors. A future challenge will be to identify therapeutics that target *C/EBPβ* and *TAZ*. A small molecule inhibitor screen identified the porphyrin family such as verteporfin (a macular degeneration drug) as inhibitors of *YAP/TEAD*-dependent transcription (Liu-Chittenden et al., 2012). As mediators of the Hippo pathway, YAP and *TAZ* are paralogs and display 50% homology (Q.-Y. Lei et al., 2008). Furthermore, Rho, ROCK, and WNT inhibitors inhibit *YAP/TAZ* activities (Piccolo, Cordenonsi, & Dupont, 2013). Lastly, since increasing data supports that proneural gliomas arise from OPCs rather than NSCs, future studies should address if introduction of *TAZ* or other mesenchymal master regulators into OPCs can give rise to mesenchymal gliomas.

Future studies should confirm *STAT3*, *C/EBPβ* and *TAZ* as master regulators of PMT in gliomas. Interestingly, gene networks regulated by *TAZ* were non-overlapping compared to those regulated by *STAT3* or *C/EBPβ* (Bhat et al., 2011). Is it possible that an up-stream effector gene regulates *TAZ, STAT3*, and *C/EBPβ* in gliomas? TCGA analyses revealed that the mesenchymal GBM subgroup were enriched in nuclear factor kappa-light-chain-enhancer of activated B cells (*NFκB*) and tumor necrosis factor (*TNF*) superfamily of genes (Verhaak et al., 2010). Supporting data show that TNFα treatment induced NFκB activation

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in patient-derived proneural human GBM cells, leading to PMT and increased radioresistance (Bhat et al., 2013). Interestingly, activated NFκB signaling increased the activation of all three master regulators: *STAT3*, *C/EBPβ* and *TAZ*. Inhibition of NFκB activation via a mutant *IκB* blunted the mesenchymal switch, and the authors also showed that minocycline, as an anti-inflammatory inhibitor that targets NFκB pathway, effectively reduce tumor proliferation of mesenchymal GBMs. This elegant study suggests that NFκB blockade can block the mesenchymal gene network. Future studies should demonstrate if NFκB inhibition combined with standard of care can improve outcome in human glioma patients.

Pathway enrichment analysis of proneural and mesenchymal GBMs revealed that genes involved in glycolysis and gluconeogenesis were enriched in mesenchymal GBM cells. At the protein level, glycolytic activity was also increased in mesenchymal cells. The authors identified aldehyde dehydrogenase ALDH1A3 as the most highly expressed metabolic enzyme in mesenchymal GBM cells. Blockade of ALDH1 activity reduced proliferation of mesenchymal, but not proneural, GBM cells (Mao et al., 2013). Interestingly, radiation of proneural GBM cells induced an increased expression of mesenchymal markers and a concomitant down-regulation of proneural genes, a shift that was reversed by ALDH1A3 inhibition. Results from this study suggest that an upregulation of the glycolysis pathway occurs when glioma cells need to maintain their energy requirement in low nutrient conditions, also observed in mesenchymal tumors in a harsh microenvironment, or in proneural tumors that undergo a stress such as radiotherapy. The importance of glycolysis in tumorigenesis was confirmed by another study that associated expression of glucose transporter, type 3 (GLUT3) with tumorigenicity of GSCs (Flavahan et al., 2013). This highlights the adaptation of GSCs to survive in a nutrient-depleted environment and respond to stress following therapy.

Other genes that are associated with the mesenchymal phenotype in gliomas include the inhibitor of differentiation (*ID*) genes *ID1* and *ID2*, two bHLH factors that promote tumorigenicity in mesenchymal high-grade murine gliomas. In this mouse model, murine hippocampal NSCs were transduced with lentiviruses for $H\text{-}Ras^{V12}$ and short-hairpin RNAs against *TP53* (Niola et al., 2013). RNA interference experiments showed that down-regulation of ID proteins reduced stem cell-associated markers such as ITGA6, Nestin and SSEA-1 *in vitro* and the number of perivascular glioma stem-like cells expressing SSEA-1 *in vivo* (Niola et al., 2013). Furthermore, *c-MET* has been linked to the mesenchymal phenotype in epithelial cancers. When overexpressed *c-MET* induced an EMT-like transition and stemness in GSCs (De Bacco et al., 2012). Similarly, incubation of GBM cells with the c-MET ligand HGF induced a mesenchymal phenotype (Yunqing Li, 2011). It is still unclear if these genes only play a role in existing mesenchymal tumor cells, or alternatively can induce PMT in proneural GBM cells

6.3 Influence of the tumor microenvironment on the mesenchymal phenotype

A tight relationship exists between tumor microenvironment and EMT during tumor progression (Finger & Giaccia, 2010; Kalluri & Weinberg, 2009; Polyak & Weinberg, 2009). As mentioned above, mesenchymal GBMs were found to be enriched in genes of the

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TNF superfamily and NFκB, reflecting a high level of necrosis and a prominent immune infiltration compared to proneural GBMs (H. S. Phillips et al., 2006; Verhaak et al., 2010). This was confirmed with histopathological analyses reflecting high levels of necrosis, hypoxia, and inflammation in mesenchymal specimens compared to other transcriptional subtypes (L. A. D. Cooper et al., 2012; Engler et al., 2012). Further, several mesenchymal network genes identified by Carro et al. (e.g. *C/EBPβ*, *C/EBPδ*, *FOSL2* and *STAT3*) were amongst the highest ranked genes that positively correlated with the extent of necrosis, and C/EBPβ and C/EBPδ proteins were expressed in hypoxic perinecrotic regions in GBMs (L A. D. Cooper et al., 2012). As GBMs, in contrast to lower-grade gliomas, are associated with necrosis and more extensive inflammation, it is plausible that necrosis contributes to the mesenchymal phenotype (L. a D. Cooper et al., 2010).

In 2009, bevacizumab was approved for use in recurrent GBM patients. However, a number of studies in patients and preclinical models have demonstrated that the beneficial effects of anti-VEGF therapy are transient as the tumors become highly invasive in nature to circumvent the blockade of the vasculature (Keunen et al., 2011; K. V Lu et al., 2012; Pàez-Ribes et al., 2009). Anti-VEGF therapy and radiotherapy are known to induce HIF1α levels, leading to increased transcription of VEGF and stromal-cell derived factor 1 (SDF-1), and recruitment of myeloid cells. Ultimately, this cascade of events lead to increased vasculogenesis and recurrent tumors displaying a high degree of stemness and expression of mesenchymal markers (Kioi et al., 2010; Piao et al., 2012, 2013). Inhibition of C-X-C chemokine receptor 4 (CXCR4) activity or blockade of HIF1α effectively depleted influx of inflammatory myeloid cells following radiation of mice xenografted with human GBM cells (Kioi et al., 2010). Future studies should identify more specific immune targets and employ GEMM of glioma, displaying an intact immune system, to effectively study changes in the tumor microenvironment following radiotherapy or anti-angiogenic treatment.

As an important target in GBM therapy, recent studies have identified molecular interactions between VEGF and other RTKs. In a GEMM model of glioma, Lu et al. (2012), found that VEGF recruits tyrosine phosphatase PTP1B to prevent c-MET activation (K. V Lu et al., 2012). Hence, anti-VEGF therapy induced VEGFR2 and c-MET heterodimerization followed by HGF-induced phosphorylation of c-MET. The VEGFR2/c-MET complex produced a switch from T-cadherin to N-cadherin, increased invasion and induction of a mesenchymal phenotype. Surprisingly, these effects were independent on hypoxia, suggesting that recruitment of CXCR4-expressing myeloid cells did not contribute to the mesenchymal phenotype in this mouse model.

Targeting inflammatory cells in the tumor microenvironment has yielded some success in preclinical models. As mentioned previously, NFκB activation induces a PMT in proneural glioma cells. The authors also demonstrated that TNFα from microglia/macrophages in the tumor microenvironment is a contributing source of NFκB activation, and dual targeting of NFκB in tumors and immune cell activation via minocycline was effective in decreasing tumor growth and radioresistance only in the mesenchymal and not proneural tumors (Bhat et al., 2013). In another recent study, a colony stimulating factor 1 receptor (CSF1R) inhibitor BLZ945 that targets the tumor-associated myeloid cells was effective in causing the regression of tumors in a proneural model of GBM and increased survival of tumor-

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bearing mice (Pyonteck et al., 2013). Analyses of tumors revealed that myeloid numbers was unchanged, but the expression of tumor-promoting M2 markers was significantly reduced in these cells. This suggests a reeducation of the immune cells that was sufficient to cut off growth support of tumor cells. It will be interesting if CSF1R inhibition will be effective in gliomas of other subclasses, especially mesenchymal tumors that have high inflammatory signature, and in conjunction with standard of care such as irradiation or chemotherapy.

Reactive astrocytes represent another stromal component of the tumor microenvironment in gliomas. Similar to peripheral tumors where fibroblasts respond to tumor growth and injury, astrocytes become reactive in response to pathological conditions. In glioma, the reactive state and the abundance of reactive astrocytes increase with grade. A recent report show that reactive astrocytes is a major component of the tumor microenvironment in a PDGF-driven GEMM of glioma, surrounding the tumor at the periphery and in the perivascular niche, a region suggested to harbor GSCs (Katz et al., 2012). Less is known about the role of reactive astrocytes propagating tumor growth and promoting treatment-resistance in the GSC compartment.

It becomes increasingly clear that radiotherapy and anti-angiogenic treatments effectively target the tumor bulk, but leave behind subpopulations of tumor cells that become treatment-resistant and form invasive recurrent tumors. Additional investigations are needed to fully understand mechanisms underlying PMT in human glioma. As future studies try to prevent PMT or target the mesenchymal phenotype, it is important to appreciate the extensive intratumoral heterogeneity found in human GBMs. Sottoriva et al. (2013) found that multiple regions form a single GBM show proneural, classical, and mesenchymal gene expression signatures (Sottoriva et al., 2013). This finding parallels recent progress demonstrating intratumoral heterogeneity for RTK amplifications in human GBMs. Intratumoral GBM heterogeneity in the tumor microenvironment and genetic alterations represent a major challenge for future therapies.

7. Relationship Between Glioma Stem Cells and Glial Progentiors

All tumor cells within a tumor tissue must be eliminated to cure the disease. Traditional cancer therapies have been directed to eliminating tumor cells based on their susceptibility to genotoxic therapies such as radiation and DNA alkylating agents. However, cancer stem cells, also referred to as tumor-initiating or tumor-propagating cells, represent small subpopulations of cells within the bulk tumor that are resistant to genotoxic chemotherapies (Dick, 2008; Reya, Morrison, Clarke, & Weissman, 2001). Considerable research effort is being directed to the identification and characterization of cancer stem cells for determining properties that can be exploited for therapeutic eradication. To date, the identification and isolation of cancer stem cells have relied on differential uptake of cell-permeable dyes or expression of cell-surface antigens.

The first report identifying cancer stem cells in glioma, was based on expression of glycosylated CD133 protein on the cell surface of GBM cells (S. K. Singh et al., 2003). CD133-expressing GSCs co-expressed NSC proteins, showed high self-renewal capacity

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and, in contrast to CD133 negative tumor cells, established tumors in xenografted mice (S. K. Singh et al., 2003). Subsequent reports showed that CD133-expressing GBM cells undergo asymmetric cell division (a prerequisite for tumor regrowth), are resistant to treatment with the alkylating agent temozolomide, and display increased radioresistance (Bao et al., 2006; Deleyrolle et al., 2011; J D Lathia et al., 2011; G. Liu et al., 2006). Additional, and perhaps more provocative findings suggest that CD133+ GSCs regenerate endothelial cells, as well as pericytes, allowing tumors to reestablish the microenvironmental niche required for regrowth (Ricci-Vitiani et al., 2010; R. Wang et al., 2010). More recent reports suggest a large number of alternative GSC markers, many of which show partial or no overlap with CD133+ cells (Anido et al., 2010; Bao et al., 2008; He et al., 2011; Kim et al., 2012; Justin D Lathia et al., 2010; Y. Li et al., 2011; Mazzoleni et al., 2010; Rasper et al., 2010; S. K. Singh et al., 2003; Son, Woolard, Nam, Lee, & Fine, 2009; Tchoghandjian et al., 2010) (Table 2). Interestingly, CD133, A2B5, CD44, c-Met, PDGFRβ and EGFR are also expressed on OPCs (Bouvier-Labit, Liprandi, Monti, Pellissier, & Figarella-Branger, 2002; Moransard, Sawitzky, Fontana, & Suter, 2010; Raff, Miller, & Noble, 1983; Verhaak et al., 2010; J. Wang, O'Bara, Pol, & Sim, 2013). Is it possible that GSC-rich gliomas can arise from OPCs? In fact, we and other groups have demonstrated that the proneural tumor oligodendroglioma can arise from OPCs (Lindberg et al., 2009; C. Liu et al., 2011; Persson et al., 2010). As oncogenic events were introduced into NSCs and OPCs, mosaic analysis with double markers found that transformation only occurred after NSCs had differentiated into OPCs (C. Liu et al., 2011). As A2B5-expressing GSCs become more mesenchymal with grade (Auvergne et al., 2013), it is possible that cell-surface proteins on GSCs change during the disease progression or following therapy (Bhat et al., 2011, 2013; K. V Lu et al., 2012; Mao et al., 2013). In comparison to lower-grade tumors, GBMs display a transcriptional gene expression signature reminiscent of embryonic stem (ES) cells (Ben-Porath et al., 2008). Higher expression of reprogramming factors in GBM (the same factors used by Yamanaka and colleagues to reprogram somatic cells (Takahashi & Yamanaka, 2006), suggest that dedifferentiation of OPCs or more differentiated cells can produce gliomas with a high degree of stemness. In this section, we will discuss gene families that are normally associated with stem cells, but also play important roles during OPC lineage development.

7.1 Polycomb gene family

Proneural genes are expressed in a timely and regional fashion during neocortical development (Wilkinson, Dennis, & Schuurmans, 2013). As one example, the Polycomb group (PcG) gene family regulates cell fate during development. PcG proteins function as complexes known as polycomb repressive complexes (PRC) and work by repressing transcription with methylation altering chromatin structure (Simon & Kingston, 2009). Expression of PRCs maintain stemness in ES and repress developmental genes active during differentiation (T. I. Lee et al., 2006). The PRCs play a similar role in various cancers (Easwaran et al., 2012). As the catalytic component of PRC, *Enhancer of Zeste homolog 2* (*EZH2*), a histone-lysine N-methyltransferase, is downregulated as NSCs differentiate into astrocytes (Sher et al., 2008). Induced overexpression of *EZH2* in astrocytes partially dedifferentiates them back towards NSCs (Sher, Boddeke, & Copray, 2011). Interestingly, when NSCs differentiate into OPCs, *EZH2* expression remains high (Sher, Boddeke, Olah, & Copray, 2012). Down-regulation of *EZH2* in OPCs resulted in derangement of the

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oligodendrocytic phenotype, due to re-expression of neuronal and astrocytic genes, and ultimately apoptosis (Sher et al., 2012). *EZH2* catalyzes the methylations of lysine 27 on histone H3 (H3K27) (R. Cao et al., 2002). As stated above, the *K27M* mutant has a higher affinity for *EZH3* compared to wild type. So it is clear that oncogenic event such as the *K27M* mutation could disregulate *EZH2* leading to cancer. Inhibition of *EZH2* with drugs or shRNA has been used as a treatment and has been shown to impair the self-renewal of GBM cancer stem cells (Suvà et al., 2009).

7.2 NOTCH

NOTCH is an important pathway in CNS development and tissue patterning. However, NOTCH is also active in adult NSC keeping them in a quiescent state, and preventing differentiation (Ables, Breunig, Eisch, & Rakic, 2011). In addition, NOTCH functions in OPCs as a repressor of differentiation (Sim et al., 2011; S. Wang et al., 1998) (Figure 2). In glioma, NOTCH-1 and its ligands DELTA-LIKE-1 (DLL1) and JAGGED-1 are overexpressed (Purow et al., 2005; Hongbing Zhang et al., 2007). Furthermore, NOTCH is expressed in several GBM subgroups (Verhaak et al., 2010), where it forms transcriptional networks with *GLI1*, *Myc*, *BMP2*, and *RUNX2* (L. a D. Cooper et al., 2010). Several studies suggest that NOTCH-1 activity is essential for survival of GSCs (Ables et al., 2011; Saito et al., 2013; Hongbing Zhang et al., 2007). For example, expression of the active form of NOTCH-1 in human glioma cell lines increase proliferation and self-renewal (Hongbing Zhang et al., 2007). RNA interference experiments showed that *DLL1* and *JAGGED-1* knockdown reduce survival of GSCs (Purow et al., 2005). *In vitro* studies suggest cooperative effects of pharmacological inhibition using the γ-secretase inhibitor and γ-irradiation as they target GSCs and non-GSCs, respectively (Ables et al., 2011; Saito et al., 2013). The NOTCH pathway represents an attractive target for future therapies trying to eliminate GSCs.

7.3 Sonic hedgehog (SHH)

Sonic hedgehog is essential for survival of postnatal NSCs (Machold et al., 2003). In addition, As SHH down-stream targets, expression of members of the *GLI* family is associated with proliferative regions during neural development (Dahmane et al., 2001). In GBMs, *GLI-1* is necessary for survival of GSCs and induced by oncogenic drivers (Clement, Sanchez, De Tribolet, Radovanovic, & Ruiz I Altaba, 2007; Dahmane et al., 2001; Santoni et al., 2013). Treatment with the pharmacological SHH inhibitor cyclopamine effectively depleted CD133+ GSCs (Clement et al., 2007). Interestingly, similar to NOTCH-1 inhibition, cyclopamine and temozolomide cooperates to target GSCs and non-GSCs, respectively (Clement et al., 2007). As a downstream target of *GLI* genes, *NANOG* is known to promote stemness and is expressed in GBMs (Clement et al., 2007; Mitsui et al., 2003). Interestingly, *NANOG* is able to reprogram *TP53*-deficient mouse astrocytes into high-grade gliomas (Moon et al., 2011). SHH also stimulates proliferation of OPCs and is necessary during OPC lineage development (Ferent, Zimmer, Durbec, Ruat, & Traiffort, 2013; Lelievre et al., 2006; Tekki-Kessaris et al., 2001), suggesting that *SHH-GLI1* signaling may also drive tumor growth in more progenitor-like gliomas (Figure 2).

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7.4 Wingless (WNT)

Wingless (WNT) has been extensively studied as a developmental pathway regulating cell fate specification, migration, and proliferation. The WNT pathway also plays a role in self-renewal of adult NSCs (Kalani et al., 2008). A WNT antagonists increased the numbers of immature OPCs in spinal cord explants (Shimizu et al., 2005), demonstrating that endogenous WNT signaling controls oligodendrocyte development. Isolation of OPCs from the human fetal brain based on CD140a (PDGFRA) expression showed that 12/15 WNT target genes were highly expressed in CD140a+ versus CD140- cell fractions (Sim et al., 2011). The authors concluded that WNT and NOTCH are essential for survival of OPCs. A comparison of development pathways, show that the WNT pathway is more dysregulated than NOTCH or SHH in GSCs compared to human adult NSCs (Sandberg et al., 2013). The authors show that the WNT inhibitor secreted frizzled-related protein 1 (SFRP1) effectively reduced proliferation and self-renewal of GSCs (Sandberg et al., 2013). Furthermore, WNT components are more prominently expressed in A2B5+ cells isolated from GBM versus lower-grade gliomas (Auvergne et al., 2013). During normal development, WNT influence the timing and efficacy of OPC generation in the telencephalon (Langseth et al., 2010). As a target of WNT transcriptional activation, AXIN2 is expressed in OPCs and is essential for normal kinetics of remyelination (Fancy et al., 2011). Interestingly, *SOX17* is a down-stream target of the WNT pathway in both OPCs and human oligodendroglioma cells (H.-L. Chen, Chew, Packer, & Gallo, 2013; Chew et al., 2011), exemplifying how in-depth knowledge of OPCs can increase our understanding of glioma biology (Figure 2).

8. Targeted Therapy in Glioma

During development, receptor tyrosine kinases (RTKs) signaling mediate effects of growth factors and regulate expansion and differentiation programs in specific neural precursor populations (Forsberg-Nilsson, Behar, Afrakhte, Barker, & McKay, 1998; Hébert & Fishell, 2008; Kilpatrick & Bartlett, 1995). In the brain, members of the fibroblast growth factor receptor (FGFR), epidermal growth factor (EGFR), and platelet-derived growth factor (PDGFR) families are expressed in distinct NSCs and more differentiated progenitor populations. In GBM, amplifications or somatic mutations in *EGFR*, *PDGFRA*, *FGFR1*, or *c-MET* often correlate with transcriptomal subgroups (Verhaak et al., 2010). Approximately 88% of GBMs display genetic amplifications of RTKs and genetic alterations of down-stream effector genes. Towards developing a personalized medicine approach and improve outcome for GBM patients, clinical studies increasingly include only subsets of GBM patients that show distinct genetic alterations (Noushmehr et al., 2010; H. S. Phillips et al., 2006; Verhaak et al., 2010). Intra-tumoral heterogeneity of *EGFR*, *PDGFRA*, and *c-MET* in GBMs suggest that future approaches should target several RTKs or common down-stream effectors to benefit GBM patients (Snuderl et al., 2011; Stommel, Kimmelman, & Ying, 2007; Szerlip et al., 2012). Furthermore, pharmacological studies show that monotherapy with either *EGFR* or *PDGFR* inhibitors is not sufficient to prevent recurrence in patients (Lo, 2010; Morris & Abrey, 2010). In this section, we will discuss the expression of RTKs in glioma, why inhibition of RTKs or down-stream targets has failed in patients, and their roles in OPC lineage development.

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8.1 Epidermal growth factor gene family

As the most commonly amplified RTK in GBMs, EGFR is a member of the ErbB family of membrane-bound receptor tyrosine kinases, of which the other members are ErbB2/HER2/Neu, ErbB3/HER3, and ErbB4/HER4 (Mineo et al., 2007; Verhaak et al., 2010). In addition, approximately 50% of *EGFR* amplified GBMs express a constitutively active mutation, called EGFRvIII, lacking the extracellular domain (Gan, Kaye, & Luwor, 2009). Other point mutations in the extracellular ligand binding domain of EGFR have been described (J. C. Lee et al., 2006; Vivanco et al., 2012). Over the years, much effort has focused on development of small molecule inhibitors against EGFR inhibitors or vaccines against EGFRvIII (Sampson et al., 2010). To date, EGFR inhibition in patients has largely failed (Table 3). Association of poor response in patients displaying *EGFRvIII* mutation and *PTEN* loss suggest that improved stratification of enrolled patients will improve future response rates (Haas-Kogan et al., 2005; Mellinghoff et al., 2005). Furthermore, development of type II that also bind to the inactive conformation of EGFR or irreversible inhibitors may more effectively block down-stream signaling and produce a better response in patients (Barkovich et al., 2012; Vivanco et al., 2012). However, redundant expression of EGFR family members that also contributes to treatment resistance. For example, proneural GBMs express high levels of ErbB3, functionally active in heterodimers with other ErbB family members (Verhaak et al., 2010).

ErbB3 is highly expressed on both human OPCs and proneural glioma cells expressing A2B5 (Auvergne et al., 2013; Sim et al., 2011; Verhaak et al., 2010). *ErbB3* and *EGFR* regulate survival in OPCs (Flores et al., 2000; Ivkovic, Canoll, & Goldman, 2008) (Figure 2). In fact, we and others have shown that proneural gliomas can arise from OPCs (Lai et al., 2011; Lindberg et al., 2009; Persson et al., 2010). Introduction of human *EGFRvIII* into OPCs produced hyperplasia in postnatal white matter in mice (Ivkovic et al., 2008). Moreover, we showed that a constitutively active avian form of *EGFRvIII*, *v-erbB*, generates oligodendroglioma in mice (Persson et al., 2010). In conclusion, EGFR signaling remains an important therapeutic target as research generates better pharmacological tools and identifies molecular characteristics in glioma subgroups for stratification of patients.

8.2 Targeting the proneural subgroup by PDGFR inhibition

Platelet-derived growth factor isoform α and β forms homo- or heterodimers upon ligand binding. Amplification of *PDGFRA* was identified in 11% of patients (The Cancer Genome Atlas Research Network, 2008). Increased PDGF pathway activity, however, has been reported in up to 33% of adult GBM (Brennan et al., 2009). However, a more recent paper suggests that not only focal, but also low-level, amplifications of *PDGFRA* are frequent in pediatric (29%) and adult (20%) GBM patients (J. J. Phillips et al., 2013). The authors show that in GBM patients displaying $IDH1^{R132H}$ mutations, *PDGFRA* amplification was a negative prognostic marker (J. J. Phillips et al., 2013). Recent studies suggest that PDGFRB is expressed on subsets of GSCs and can cross-talk with EGFR in GBMs (Akhavan et al., 2013; Kim et al., 2012).

As one of the first successful small molecule kinase inhibitors, Imatinib effectively inhibited kinase activity of the fusion gene *BCR-ABL* (Druker et al., 2001). However, Imatinib also

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inhibits kinase activity for PDGFRA, tyrosine-protein kinase Kit (c-KIT), and fms-like tyrosine kinase 3 (FLT-3). To inhibit PDGFRA signaling in human GBMs, Imatinib reduced phosphorylated AKT levels in 4/11 patients but had no effect on overall survival benefit (Razis et al., 2009) (Table 3). However, since enrolled patients were not stratified based on *PDGFA* amplification, it is unclear if Imatinib will increase the survival in subsets of GBM patients (Figure 2).

In patients, approximately 35% of proneural GBMs display focal amplifications of *PDGFRA* (Verhaak et al., 2010). These proneural GBMs express genes associated with OPCs, including PDGFRA commonly used to isolate murine or human OPCs (Sim et al., 2011). PDGFB ligand transforms murine OPCs into gliomas (Lindberg et al., 2009). In postnatal mice, PDGF ligand increases proliferation of NG2+ OPCs in white matter, but not grey matter, an effect that was largely dependent on WNT and PI3K signaling (Hill et al., 2013). In summary, *PDGFRA* represents a relevant future therapeutic target in proneural gliomas, in particular *PDGFRA* amplified gliomas.

8.3 Targeting the mesenchymal phenotype through c-MET inhibition

As hepatocyte growth factor (HGF) binds to the c-mesenchymal-epithelial transition factor (c-MET) it can stimulate proliferation of NSCs and OPCs in the postnatal brain (Ohya, Funakoshi, Kurosawa, & Nakamura, 2007; T.-W. Wang, Zhang, Gyetko, & Parent, 2011). Expression of HGF and c-MET at the boundaries between epithelial and mesenchymal cells regulate normal organogenesis; epithelial cells expressing c-MET, and mesenchymal cells secreting the HGF ligand. In glioma, c-MET and HGF expression levels correlate with grade (Koochekpour et al., 1997). Amplification of c-MET is present in approximately 5% of GBMs (Dunn et al., 2012). In a study comparing 19 paired primary and recurrent patient biopsies, overexpression of c-MET has was reported in over 30% of newly diagnosed primary GBM and was much more common (>75%) in relapse cases (W. Liu et al., 2011). Importantly, c-MET overexpression is a key feature of the mesenchymal subclass (H. S. Phillips et al., 2006; Verhaak et al., 2010) and associated with worse prognosis across GBM subgroups (Abounader & Laterra, 2005). Mesenchymal GBMs are associated with high expression of immune-related genes and dense vasculature (Verhaak et al., 2010).

Pre-clinical and clinical studies show that anti-angiogenic therapy in GBMs results in a more invasive phenotype (Gerstner et al., 2010; K. V Lu et al., 2012) (Table 3). In an elegant study by Lu et al., HGF-dependent MET phosphorylation and tumor cell migration were suppressed by a direct interaction between the protein tyrosine phosphatase 1B (PTP1B) and a MET/VEGFR2 heterocomplex, implicating VEGF as a negative regulator of tumor cell invasion (K. V Lu et al., 2012). Concordantly, the dual c-MET and VEGFR inhibitor Cabozantinib (XL184) reduced proliferation GBM cells *in vitro* and *in vivo*, potently reducing phosphorylated c-MET, pAKT, and pERK1/2 levels (Navis et al., 2013; Yakes et al., 2011). Cabozantinib is currently used in clinical trials against newly diagnosed or recurrent GBMs (Table 3).

Several studies show that c-MET signaling induces a reprogramming network and support the GSC phenotype (Joo et al., 2012; Y. Li et al., 2011). Expression of c-MET has even been suggested as a functional marker of GSCs (De Bacco et al., 2012). Experiments in an

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orthotopic xenograft model show that c-MET inhibition reduces growth by selectively targeting the GSC compartment in GBMs (Rath et al., 2013). Future studies should characterize the response of rare GSCs expressing c-MET to radiotherapy and temozolomide treatment in glioma patients.

8.4 Treatment-resistance associated with RTK inhibition

RTK Cooperativity—Cooperativity between multiple RTKs drive tumor growth in GBMs (Stommel et al., 2007). Combined inhibition of MET, PDGFRA, and EGFR was needed to effectively inhibit proliferation in human primary GBM cultures. This is consistent with findings demonstrating intra-tumoral GBM heterogeneity of RTKs in vivo (Snuderl et al., 2011). Furthermore, significant cross-talk occurs between different RTKs. For example, cross-talk has been observed between c-MET and EGFR (Jo et al., 2000; Reznik et al., 2008), c-MET and VEGFR2 (K. V Lu et al., 2012) IGFR1 and PDGFRA (Bielen et al., 2011), and EGFR and PDGFRB (Akhavan et al., 2013).

Redundant Activation of PI3K/mTOR—Ligand binding of the EGFR, PDGFR and c-MET promotes activation of down-stream phosphatidylinositol 3-kinase (PI3K) and mammalian target of rapamycin (mTOR) signaling. Activating mutations in PI3K, observed in 15% of GBMs and missense mutation or deletion of PTEN, seen in more than a third of GBMs, effectively uncouple this pathway from upstream RTK control (The Cancer Genome Atlas Research Network, 2008). Monotherapy with either PI3K inhibitors alone are unlikely to yield any clinical benefit, as PI3K inhibitors yield a cytostatic effect (Cheng, Fan, & Weiss, 2009). As mTOR kinase is a key effector molecule downstream of PI3K, much effort has focused on development of specific mTOR kinase inhibitors. However, the canonical allosteric mTOR kinase; rapamycin/sirolimus, increased phosphorylation of AKT through a feedback loop (Akhavan, Cloughesy, & Mischel, 2010). Furthermore, rapamycin/sirolimus and subsequent “rapalogs”, including temsirolimus/CCI-779 and everolimus/RAD-001, showed limited efficacy in clinical trials. Instead, second generation mTOR inhibitors bind the active site of mTOR kinase, block downstream signaling from both mTORC1 and mTORC2, and are currently being evaluated in clinical trials.

Combined inhibition of PI3K and mTOR potently reduce survival and proliferation of cancer cells. PI-103 is a p110α isoform (catalytic subunit of PI3K) and mTOR kinase dual inhibitor that potently blocks phosphorylation of mTOR targets and induce a robust G_0G_1 arrest (Fan et al., 2006). The clinical compound, NVP-BEZ235 (Maira et al., 2008) demonstrated robust anti-proliferative activity in many cancer types (Baumann, Mandl-Weber, Oduncu, & Schmidmaier, 2009; P. Cao, Maira, García-Echeverría, & Hedley, 2009; Chapuis et al., 2010; Chiarini et al., 2010; Santiskulvong et al., 2011), including glioma (T.-J. Liu et al., 2009). However, NVP-BEZ235 fails to cross the BBB and therefore is of limited use in GBM patients. Combined inhibition of EGFR effectively cooperated with PI3K/mTOR inhibitors (Fan et al., 2007). These studies exemplify that often combined inhibition of key survival pathways is needed.

Feedback Loops—Blockade of mTOR can paradoxically lead to activation of MAPK (Carracedo et al., 2008) and AKT (O'Reilly et al., 2006; Hongbing Zhang et al., 2007).

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Similarly, blockade of MAPK (MEK-ERK pathway) can increase phosphorylation of EGFR (X. Li, Huang, Jiang, & Frank, 2008). To avoid the negative effects of feedback loops, researchers use a strategy based on combined inhibition of RTKs and down-stream effectors (Rao et al., 2005; Ronellenfitsch, Steinbach, & Wick, 2010; M. Y. Wang et al., 2006). This strategy has also been evaluated in a clinical setting in GBM patients (Doherty et al., 2006; Kreisl, Lassman, et al., 2009; Nghiemphu, Lai, Green, Reardon, & Cloughesy, 2012; David A Reardon et al., 2006, 2010). Combined treatment regimens were well-tolerated and patients receiving dual inhibitors showed a slight survival benefit (De Witt Hamer, 2010).

Activation of Alternative Survival Pathways—Combined or single treatment with PI3K and mTOR inhibitors induces autophagy in human GBM cells as a survival mechanism (Fan & Weiss, 2010). Interestingly, blockade of autophagy sensitizes GBM cells to radiotherapy, chemotherapy, and RTK inhibition (Kanzawa et al., 2004; Lin et al., 2012; Paglin et al., 2001; Shingu et al., 2009). Preliminary studies in GBM patients suggest that blockade of autophagy in combination with standard of care is a promising strategy (Briceño, Calderon, & Sotelo, 2007; Sotelo, Briceño, & López-González, 2006).

8.5 Therapeutic targeting of IDH-mutant gliomas

Several studies have shown that *IDH1*^{R132H} mutations in glioma are associated with better survival (Gravendeel et al., 2010; Ichimura et al., 2009; Labussière et al., 2010; Nobusawa, Watanabe, Kleihues, & Ohgaki, 2009; Parsons et al., 2008; Sanson et al., 2009; S. Zhao et al., 2009). However, there is still controversy over the use of *IDH* mutations as a prognostic indicator. In low-grade glioma patients, Houillier et al. (2010) found that *IDH1*^{R132H} mutation and 1p-19q co-deletion were associated with prolonged overall survival and a better response to temozolomide treatment (Houillier et al., 2010). Unlike 1p-19q co-deletion, *IDH1*^{R132H} mutation was not associated with prolonged progression-free (PFS) survival. The data indicate that *IDH1*^{R132H} mutation may be a significant prognostic indicator independently of 1p-19q status. Similarly, Hartman and colleagues found that IDH status was the most important predictor of progression-free and overall survival only in patients receiving adjuvant therapy (Hartmann et al., 2009). In contrast, van den Bent et al. reported that the presence of *IDH1*^{R132H} mutation was an indicator of improved prognosis independent of adjuvant therapy (van den Bent et al., 2010). Taken together, these results emphasize the need for more in-depth studies in order to determine the prognostic versus predictive role of IDH status in human glioma.

Reduced expression of *IDH1*^{R132H} inhibited cell proliferation and clone formation *in vitro* (Jin et al., 2012), suggesting that direct targeting of the mutation is a viable strategy. Rohle and colleages identified a selective *IDH1*^{R132H} inhibitor (AGI-5198) through a high throughput screen that effectively reduced tumor growth in a GBM xenograft model (Rohle et al., 2013). The inhibitor blocked the ability of *IDH1*^{R132H} mutation to produce 2-HG, demethylation of histone H3K9me3, and changes in global methylation signatures. The SHH pathway has been proposed as a possible target downstream of *IDH1*^{R132H} mutation (Valadez et al., 2013). Since IDH1^{R132H} mutation is associated with a CIMP phenotype, researchers are evaluating hypomethylating agents or epigenetic modifiers (Fathi & Abdel-Wahab, 2012).

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In summary, the discovery of *IDH* mutations has been pivotal for furthering our understanding of how tumorigenesis may occur in gliomas. These findings have led scientists to identify molecular targets in glioma patients diagnosed with *IDH*-mutant tumors. Future studies should aim to extend histological identification of *IDH*-mutant tumors to non-invasive imaging correlates in patients.

9. Concluding Remarks and Future Perspectives

The wide-spread distribution and life-long proliferative capacity of OPCs match the temporal and regional occurrence of gliomas, and therefore represent targets for transformation (Figure 6). Genetically distinct gliomas displaying *PDGFRA* amplifications, $IDH1^{R132H}$ mutations, and *H3F3A* mutations express the OPC-related genes OLIG2, NKX2.2, PDGFRα and SOX10, implicating a common cell of origin (Sturm et al., 2012; Verhaak et al., 2010). Even mesenchymal gliomas may arise from OPCs as novel data suggest that defined intrinsic factors and influence from the tumor microenvironment enable gliomas to toggle between proneural and mesenchymal phenotypes (Bhat et al., 2013; Mao et al., 2013). An emerging focus on OPCs in gliomagenesis will provide critical information to researchers studying etiology, tumor microenvironment, and therapeutic intervention in glioma.

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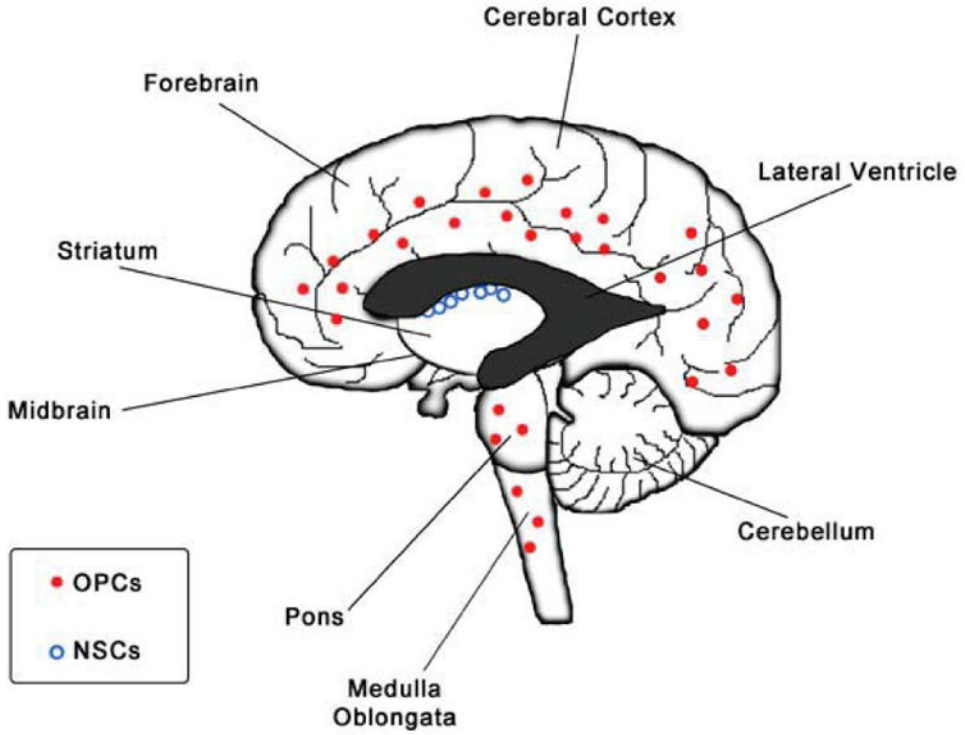

Figure 1.

OPCs are the most widely distributed population of cycling cells in forebrain and hindbrain regions. In contrast, a discrete population of NSCs is found in the SVZ lining the lateral ventricles.

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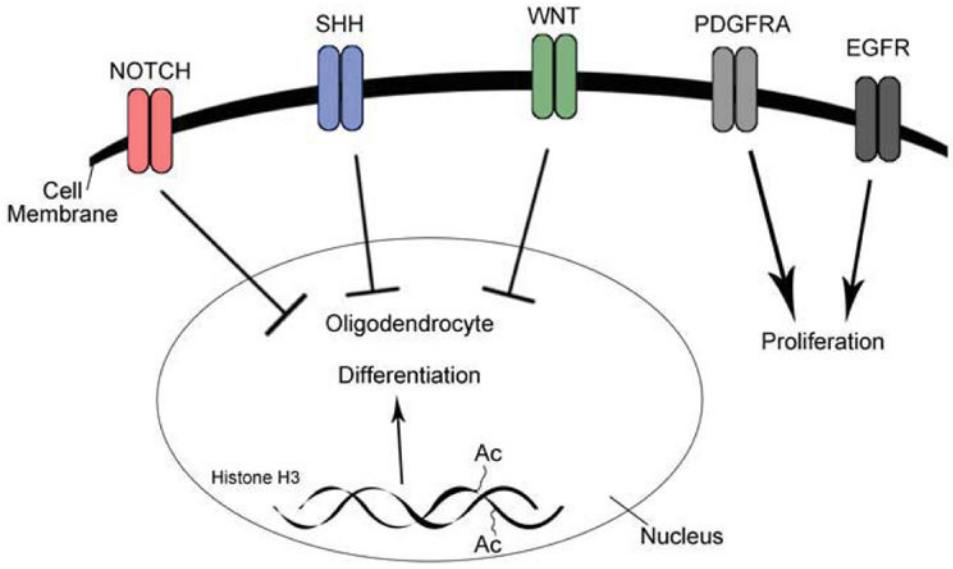

Figure 2.

Activation of NOTCH, SHH, and WNT signaling inhibits OPC differentiation into oligodendrocytes. On the contrary, acetylation of histone H3 promotes differentiation of OPCs. Growth factor-mediated activation of PDGFRA or EGFR increases proliferation in OPCs.

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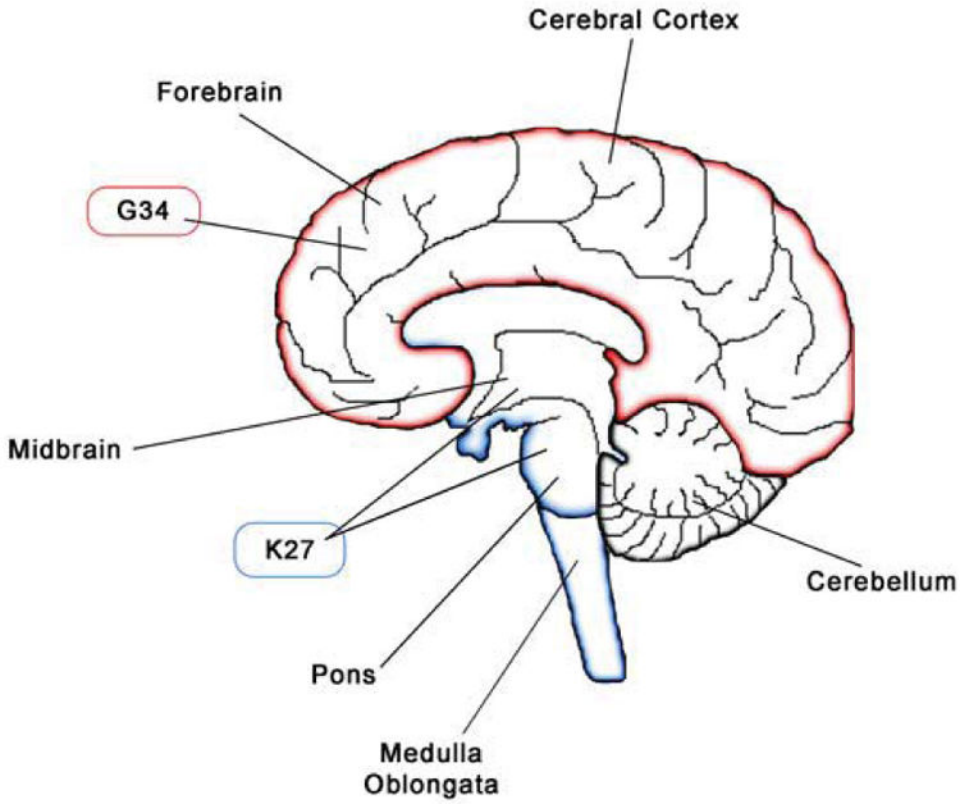

Figure 3.
GBMs displaying G34 and K27 in the *H3F3A* mutations localize to forebrain and hindbrain regions, respectively.

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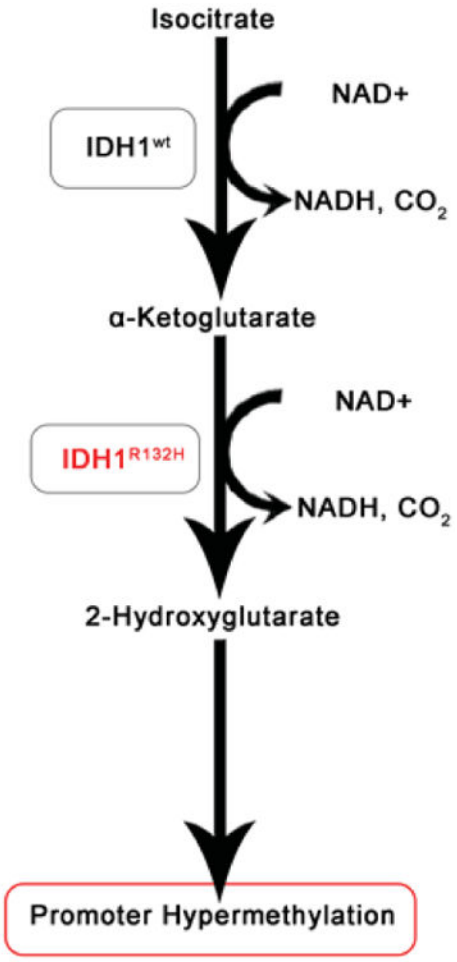

Figure 4.

$IDH1^{R132H}$ mutant gliomas show reduced levels of α-ketoglutarate and overproduction of 2-hydroxyglutarate (2-HG) that leads to a hypermethylated phenotype.

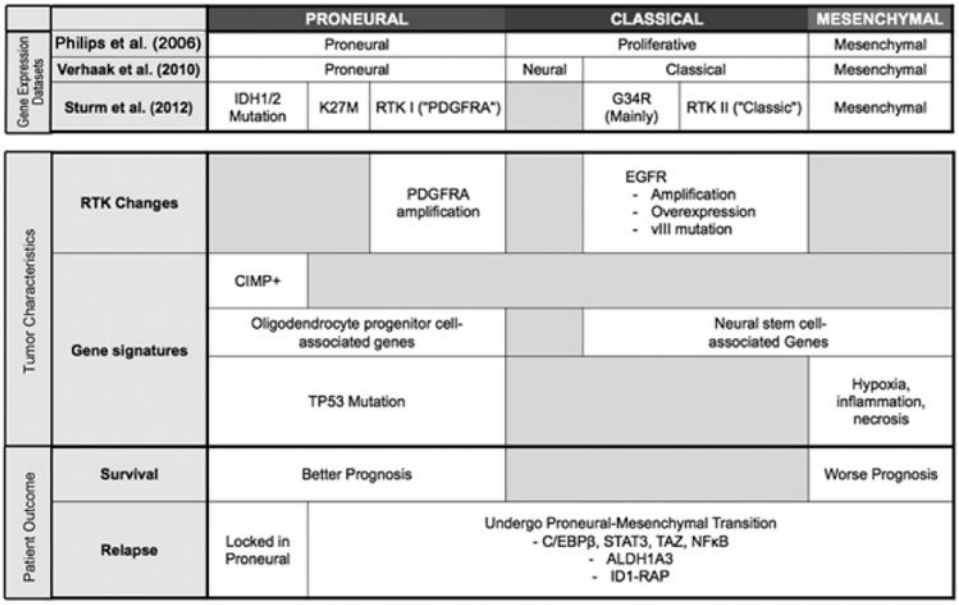

Figure 5.

Transcriptomal profiling of human GBMs identified a proneural subgroup of patients with better overall survival compared to proliferative or mesenchymal subgroups. With no stratification based on survival, Verhaak et al. identified four subgroups and found that approximately 35% of proneural GBMs displayed *IDH1/2* mutations along with a hypermethylated (CIMP+) phenotype. Sturm et al. extended these observations to also include childhood GBMs and found that hotspot mutations in *H3F3A* and *IDH1* defined distinct epigenetic and biological subgroups. While proneural GBMs are associated with OPC-like gene expression signature, more aggressive GBMs express genes known to drive mesenchymal transcriptional networks.

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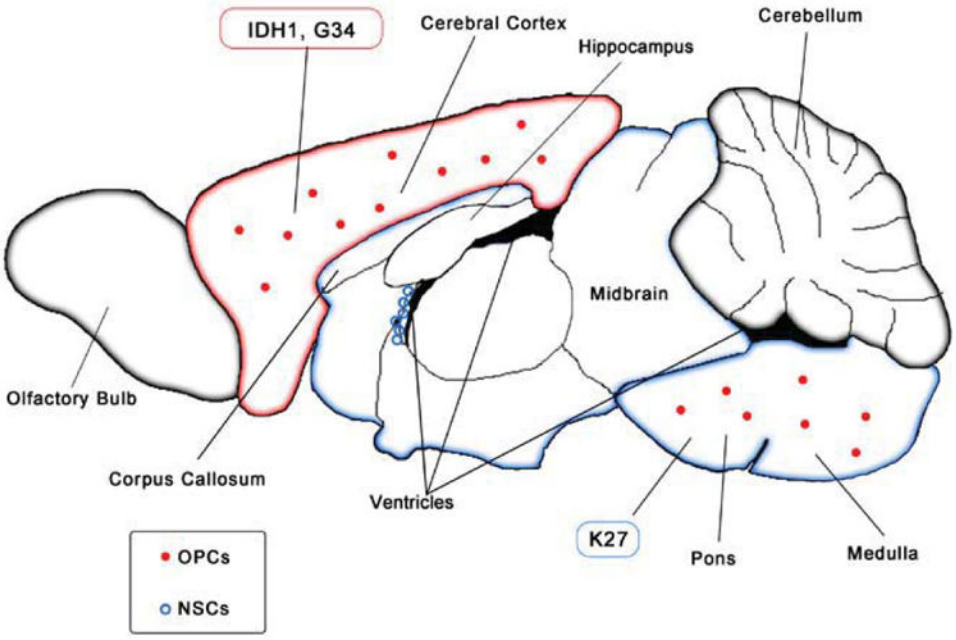

Figure 6.

OPCs, but not NSCs, are highly abundant in regions where *IDH1*^{R132H} mutant and *H3F3A* K27 mutant tumors arise in GBM patients, implicating their role in gliomagenesis.

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Table 1.1

Murine glioma models

Cancer genes	Cell of Origin	Mechanism	Reference
Astrocytoma models (II—III)			
c-myc	GFAP	Transgenic	Jensen et al. (2003)
K-ras	GFAP	Cre	Abel et al. (2009)
H-Ras	GFAP	Transgenic	Shannon et al. (2005)
H-Ras/Pten$^{loxp/loxp}$	GFAP	Cre	Wei et al. (2006)
EGFR/Ink4a/Arf$^{-/-}$	Nestin	RCAS	Holland, Hively, DePinho, and Varmus (1998)
Oligodendroglioma models			
H-ras/EGFRvlll	GFAP	Transgenic	Ding et al. (2003)
v-ErbB/Ink4a/Arf$^{+/-}$	S100β	Transgenic	Weiss et al. (2003)
v-ErbB/Trp53$^{-/-}$	S100β	Transgenic	Persson et al. (2010)
PDGFB/Ink4a/Arf$^{-/-}$	Nestin	RCAS	Dai et al. (2001)
PDGFB/Akt	Nestin	RCAS	Dai et al. (2005)
PDGFB	CNP	RCAS	Lindberg, Kastemar, Olofsson, Smits, and Uhrbom (2009)
PDGFA$_L$	GFAP	Transgenic	Nazarenko et al. (2011)
Glioblastoma (GBM) models			
PDGFB	Nestin	RCAS	Shih et al. (2004)
PDGFB/Trp53$^{-/-}$	GFAP	Transgenic	Hede et al. (2009)
K-Ras/Akt	Nestin	RCAS	Holland et al. (2000)
K-Ras/Ink4a/ArT$^{-/-}$	GFAP, Nestin	RCAS	Uhrbom et al. (2002)
K-Ras/Akt/Pten$^{loxp/loxp}$	Nestin	RCAS/Cre	Hu et al. (2005)
Nfl$^{loxp/+}$/Trp53$^{+/-}$	GFAP	Cre	Zhu et al. (2005)
Pten$^{loxp/+}$/Trp53$^{loxp/loxp}$	GFAP	Cre	Zheng et al. (2008)
Pten$^{loxp/+}$/Nfl$^{loxp/+}$/Trp53$^{loxp/-}$	GFAP	Cre	Kwon et al. (2008)
Pten$^{loxp/+}$/Nfl$^{loxp/+}$/Trp53$^{loxp/loxp}$	SVZ, Nestin	CreER	Alcantara Llaguno et al. (2009)
Akt/H-Ras/Trp53$^{+/-}$	SVZ, HC, GFAP	Lentiviral/Cre	Marumoto et al. (2009)
Pten$^{loxp/loxp}$/Trp53$^{loxp/loxp}$/Rb$^{loxp/loxp}$	SVZ, GFAP	Adenoviral/Cre	Jacques et al. (2010)
NfI$^{+/-}$/Trp53$^{loxp/loxp}$	GFAP	Transgenic/Cre	Wang et al. (2009)
PDGFB/Pten$^{loxp/loxp}$/Trp53$^{loxp/loxp}$	Subcortical WM	Retroviral/Cre	Lei et al. (2011)
Ptcn$^{loxp/loxp}$/Trp53$^{loxp/loxp}$Rbl$^{loxp/loxp}$	Astrocyte (GFAP)	CreER	Chow et al. (2011)
NfI$^{-/-}$/Trp53$^{-/-}$	OPC (NG2), NSCs (GFAP/ Nestin)	MADM/Cre	Liu, Sage, et al. (2011)
EGFRvlll/Ink4a/Arf$^{-/-}$	NSC, Astrocyte	Transplant	Bachoo et al. (2002)

As a useful tool for pre-clinical studies and the delineation of cell of origins for different types of glioma, GEMMs of glioma generate tumors resembling grade II-IV human counterparts.

NSC, neural stem cell; OPC, oligodendrocyte progenitor cell; SVZ, subventricular zone; WM, white matter; HC, hippocampus.

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Table 1.2

Examples of cell-surface antigens expressed on GSCs and the corresponding expression in NSC and OPC populations, respectively

GSC marker	Reference	NSC marker	OPC marker
CD133	Singh et al. (2003)	Yes	Yes
A2B5	Tchoghandjian et al. (2010)	No	Yes
CD15/SSEA-1	Son et al. (2009)	Yes	No
ALDH1	Rasper et al. (2010)	Yes	No
CD44	Anido et al. (2010)	Yes	Yes
c-Met	Li et al. (2011)	Yes	Yes

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Table 1.3

Association of pediatric H3F3A (G24 and K27) mutant high-grade gliomas to distinct brain regions

Subgroup	Target	Inhibitor	Other Targets	Clinical Trials	Reference
Classical					
	EGFR	Gefitinib (Iressa/ZD1839)	–	Yes	Reardon et al. (2006)
		Erlotinib (Tarceva/OSI-779)	–	Yes	Raizer and Abrey (2010)
		Cetuximab (Erbitux, C225)	–	Yes	Eller, Longo, Kyle, and Bassano (2005) and Combs et al. (2006)
		Panitumumab (Vectibix)	–	Yes	Gajadhar, Bogdanovic, Munñoz, and Guha (2012)
		AG1478	–	No	Nagane et al. (2001)
		BIBU-1361	–	No	Ghildiyal, Dixit, and Sen (2013)
		EKI-785	–	No	Rao et al. (2005)
		EtDHC	–	No	Han (1997)
		F90	–	No	Liu et al. (2008)
		NSC56452	–	No	Yang, Yang, Pike, and Marshall (2010)
		Lapantinb (GW572016)	HER2	Yes	Vivanco et al. (2012)
		AEE788	VEGF	Yes	Reardon et al. (2012)
		Vandetanib (Zactima/ZD6474)	VEGFR, RET	Yes	Drappatz et al. (2010) and Shen et al. (2013)
		GW2947	HER2	No	Wang, Wei, et al. (2013)
Proneural					
	PDFGR	α/β: Imatinib (Gleevec, imatinib mesylate, STI571	VEGF, bcr-abl	Yes	Reardon et al. (2009) and Dong et al. (2011)
		α: Sunitinib (Sutent, SU11248, sunitinib malate)	VEGFR2, c-KIT	Yes	Neyns et al. (2011)
		Vatalanib (PTK787, ZK222584)	VEGFR, c-kit	Yes	Gerstner et al. (2011)
		Pazopanib (GW786034)	VEGFR, c-Kit	Yes	Iwamoto (2010)
		β: Dasatinib (Sprycel, BMS-354825)	Src. bcr-abl, c-KIT, EPHA2	Yes	Lu-Emerson et al. (2011)
		β: Sorafenib (Nexavar,)	VEGFR2, Raf	Yes	Lee et al. (2012)
		α/β: Tandutinib (MLN0518)	FLT3, c-KIT	Yes	Boult, Terkelsen, Walker-Samuel, Bradley, and Robinson (2013)
		Leflunomide (SU101)	–	Yes	Vlassenko, Thiessen, Beattie, Malkin, and Blasberg (2000) and Shawver et al. (1997)
		Nintedanib (BIBF-1120)	VEGFR, FGFR	Yes	Muhic, Poulsen, Sorensen, Grunnet, and Lassen (2013)

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Subgroup	Target	Inhibitor	Other Targets	Clinical Trials	Reference
		CP-673,451		No	Roberts et al. (2005)
	IDH1R132H	AGI-5198	IDH1R132H	No	Rohle et al. (2013)
Mesenchymal					
	VEGF	Bevacizumab	–	Yes	Kreisl, Kim, et al. (2009)
		Cediranib (Recentin, AZD2171)	–	Yes	Batchelor et al. (2010) and Wachsberger et al. (2011)
		CT322 (BMS-844203)	–	Yes	Waters et al. (2012)
		Sunitinib (Sutent, SU11248, sunitinib malate)	PDGFRα, c-KIT	Yes	Neyns et al. (2011)
		Vatalanib (PTK787, ZK222584)	PDGFR, c-Kit	Yes	Gerstner et al. (2011)
		Pazopanib (GW786034)	PDGFR, c-Kit	Yes	Iwamoto (2010)
		Vandetanib (Zactima/ZD6474)	EGFR, RET	Yes	Broniscer et al. (2013)
		Sorafenib (Nexavar)	PDGFRβ, Raf	Yes	Lee et al. (2012)
	MET	Cabozantinib (XL184)	RET, KIT, VEGFR2	Yes	Yakes et al. (2011) and De Groot et al. (2009)
		SU11274	–	No	Stommel et al. (2007) and Joshi et al. (2012)

Receptor tyrosine kinases have been a major therapeutic target in GBMs. As the most commonly amplified RTK, EGFR represent has been an attractive target in clinical trials. Since subsets of GBMs show PDGFRA amplifications and overexpression, Imatinib and other PDGFR inhibitors have been evaluated in patients. Other clinical trials have inhibited VEGF and c-MET signaling in GBMs. For future clinical trials, whole-genome sequencing and transcriptomal studies will be valuable to stratify glioma patients into defined subgroups.