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Review

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

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ABSTRACT

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

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Introduction

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

The incidence of histologically and genetically distinct brain tumors peaks in defined time windows during childhood and in adults. In this review, we will focus on medulloblastoma and glioma, the most common primary malignant brain tumors in childhood and adults, respectively. Current therapies for medulloblastomas and gliomas include surgical resection, radiation and chemotherapy (Huse and Holland, 2010). Traditional histological classification defines

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

Brain tumors that harbor stem cell-like tumor cells and display stemness signatures are found in highly malignant childhood and adult brain tumors of patients characterized by a poor prognosis (Ben-Porath et al., 2008; Clement et al., 2007; Hemmati et al., 2003; Laks et al., 2009; Singh et al., 2003). Subpopulations of these so-called BTSCs survive current therapies which is why considerable efforts aim to identify therapeutic approaches that also target these cells. Studies by Yamanaka et al. have elegantly demonstrated a small set of reprogramming genes that generate iPS cells from terminally differentiated somatic cells. Studies by Yamanaka et al. have elegantly demonstrated a small set of reprogramming genes like iPS cells from terminally differentiated somatic cells (Takahashi and Yamanaka, 2006). Such reprogrammed iPS cells resemble embryonic stem cells and have implications for how we think about brain tumor heterogeneity. In fact iPS cells like embryonic stem cells are similar to cancer cells and form teratoma or sometimes even malignant teratocarcinoma (Okita et al., 2007; Shih et al., 2007) when injected in immunodeficient mice (Knoepfler, 2009).

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

Table 1
Abbreviations.

Abbreviation	Word
ATRX	Alpha thalassemia/mental retardation syndrome X-linked
bHLH	Basic helix–loop–helix
BMI1	BMI1 polycomb ring finger oncogene
BTSC	Brain tumor stem cell
C/EBPβ	CCAAT-enhancer-binding protein β
CIC	Homolog of the *Drosophila* gene *capicua*
CNS	Central nervous system
CTNNB1	β-catenin
DAXX	Death domain associated protein
DIPG	Diffuse intrinsic pontine glioma
EGF	Epidermal growth factor
EZH2	Enhancer of zeste homologue 2
FGF	Fibroblast growth factor
GBM	Glioblastoma
GEM	Genetically-engineered mouse
GNP	Granule neuron precursor
HES	Hairy and enhancer of split
HGF	Hepatocyte growth factor
HIF2α	Hypoxia inducible factor 2α
ID4	Inhibitor of differentiation 4
IDH1/2	Isocitrate dehydrogenase 1/2
iPS	Induced pluripotent stem
MAD	Mitotic arrest deficient
MADM	Mosaic analysis with double marker
MAPK	Mitogen-activated protein kinase
MAX	Myc-associated factor X
MGMT	Methylated-DNA–protein–cysteine methyltransferase
MLL	Myeloid/lymphoid or mixed-lineage leukemia
NF1	Neurofibromatosis type 1
NG2	Neuron–glial antigen 2
NSC	Neural stem cell
OLIG	Oligodendrocyte transcription factor
OPC	Oligodendrocyte progenitor cell
OTX2	Orthodenticle homeobox 2
PA	Pilocytic astrocytoma
PDGFRA	Platelet-derived growth factor α
PI3K	Phosphatidylinositide 3-kinase
PTCH1	Patched homolog 1 or rather: Patched 1
PTEN	Phosphatase and tensin homolog
REST/NRSF	Repressor element-1 silencing transcription factor/ neuron-restrictive silencer factor
SHH	Sonic hedgehog
SMO	Smoothened homolog or rather: smoothened, frizzled family receptor
SOX	SRY-related HMG box
STAT3	Signal transducer and activator of transcription 3
SVZ	Subventricular zone
TAM	Tumor-associated macrophage
TAPs	Transit-amplifying progenitors
TAZ	Transcriptional coactivator with PDZ-binding motif
TLX	Transcription of nuclear receptor tailess
WNT	Wingless or rather: Wingless-type MMTV integration site

Table legend: abbreviations.

Signals that drive cellular expansion in forebrain and hindbrain regions

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