Drug Resistance Updates 42 (2019) 35–45

Contents lists available at ScienceDirect

Drug Resistance Updates

journal homepage: www.elsevier.com/locate/drup

Glioblastoma cancer stem cell biology: Potential theranostic targets

Farzaneh Sharifzad[a,b], Saeid Ghavami[c,d,e], Javad Verdi[a,f], Soura Mardpour[f], Mahsa Mollapour Sisakht[a], Zahra Azizi[g], Adeleh Taghikhani[b,h], Marek J. Łos[i], Esmail Fakharian[j], Marzieh Ebrahimi[b,*], Amir Ali Hamidieh[k,**]

[a] Department of Applied Cell Sciences, Kashan University of Medical Sciences, Kashan, Iran
[b] Department of Stem Cells and Developmental Biology, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran
[c] Department of Human Anatomy & Cell Science, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada
[d] Children's Hospital Research Institute of Manitoba, Winnipeg, MB, Canada
[e] Research Institute of Oncology and Hematology, Cancer Care Manitoba, University of Manitoba, Winnipeg, Canada
[f] Department of Tissue Engineering and Applied Cell Sciences, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran
[g] Heart Rhythm Program, Southlake Regional Health Centre, Toronto ON Canada
[h] Department of Immunology, Faculty of Medical Sciences, Tarbiat Modarres University, Tehran, Iran
[i] Biotechnology Center, Silesian University of Technology in Gliwice, Poland
[j] Department of Neurosurgery, Kashan University of Medical Sciences, Kashan, Iran
[k] Pediatric Stem Cell Transplant Department, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
Glioblastoma
Cancer stem cell
Self-renewal
Chemoresistance
Wnt
Notch

ABSTRACT

Glioblastoma multiforme (GBM) is among the most incurable cancers. GBMs survival rate has not markedly improved, despite new radical surgery protocols, the introduction of new anticancer drugs, new treatment protocols, and advances in radiation techniques. The low efficacy of therapy, and short interval between remission and recurrence, could be attributed to the resistance of a small fraction of tumorigenic cells to treatment. The existence and importance of cancer stem cells (CSCs) is perceived by some as controversial. Experimental evidences suggest that the presence of therapy-resistant glioblastoma stem cells (GSCs) could explain tumor recurrence and metastasis. Some scientists, including most of the authors of this review, believe that GSCs are the driving force behind GBM relapses, whereas others however, question the existence of GSCs. Evidence has accumulated indicating that non-tumorigenic cancer cells with high heterogeneity, could undergo reprogramming and become GSCs. Hence, targeting GSCs as the "root cells" initiating malignancy has been proposed to eradicate this devastating disease. Most standard treatments fail to completely eradicate GSCs, which can then cause the recurrence of the disease. To effectively target GSCs, a comprehensive understanding of the biology of GSCs as well as the mechanisms by which these cells survive during treatment and develop into new tumor, is urgently needed. Herein, we provide an overview of the molecular features of GSCs, and elaborate how to facilitate their detection and efficient targeting for therapeutic interventions. We also discuss GBM classifications based on the molecular stem cell subtypes with a focus on potential therapeutic approaches.

Abbreviations: BMP, bone morphogenic protein; CD, cluster of differentiation; CSC, cancer stem cell; CNS, central nervous system; CTGF, connective tissue growth factor; CSF, colony stimulating factor; Dov, dovitinib; EMT, epithelial-mesenchymal transition; FABP, fatty acid-binding protein; FGF, fibroblast growth factor; GLI, glioma-associated oncogene; GSCs, glioblastoma cancer stem cells; HIF, hypoxia-inducible factor; HO, heme oxygenase; ID, inhibitor of differentiation; IL, interleukin; MDSC, myeloid-derived suppressor cell; MMP, matrix metalloproteinase; NSC, neural stem cell; PcG, polycomb group; PDGF, platelet-derived growth factor; PLAGL, pleomorphic adenoma gene-like; PRC, polycomb repressive complex; RGC, radial ganglion cell; SDF, stromal cell-derived factor; SHH, sonic hedge hog; TAM, tumor-associated macrophage; TMZ, temozolomide; TGF, transforming growth factor; TP, thymidine phosphorylase; TRKA, tyrosine receptor kinase type A; VEGF, vascular endothelial growth factor; ZEB1, zinc finger E-box binding homeobox 1

* Corresponding author at: Department of Stem Cells and Developmental Biology, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran.
** Corresponding author at: Paediatric Stem Cell Transplant, Department of Children's Medical Center, Tehran University of Medical Sciences, P.O. Box: 19395-4644, Tehran, Iran.
E-mail addresses: mebrahimi@royaninstitute.org (M. Ebrahimi), aahamidieh@tums.ac.ir (A.A. Hamidieh).

https://doi.org/10.1016/j.drup.2018.03.003
Received 4 December 2017; Received in revised form 28 February 2018; Accepted 16 March 2018

Introduction

Among the many types of primary tumors, glioblastoma multiforme (GBM) is a highly aggressive and lethal cancer that is considered incurable. The current treatment is limited to gross total resection followed by radical chemo- and radiotherapy. The chemotherapeutics that have been used include alkylating agents such as nitrosoureas, which induce cytotoxicity due to the formation of DNA cross-linking, and temozolomide (TMZ), which promotes apoptosis via generation of single- and double-strand breaks in DNA (Brandes et al., 2016).

Targeted therapies such as the administration of anti-angiogenic agents, anti-epidermal growth factor receptor (EGFR), and phosphoinositide 3-kinase (PI3K) inhibitors as an adjuvant for second line treatment have also been used; however. These approaches have proven to be only marginally effective, and the poor median survival of GBM patients currently being 15 months, has not improved significantly (Schwartzentruber et al., 2012). Despite advances in the current understanding of the molecular and cellular biology of GBM, treatment strategies have not changed considerably. Moreover, the neurotoxicity of the chemotherapy can induce the formation of secondary gliomas (Dimov et al., 2011).

Other treatment complications have arisen owing to the stemness of a rare subpopulation of tumor cells called glioblastoma stem cells (GSCs) or tumor-initiating cells, which have stem cell characteristics but are not necessarily derived from normal stem cells (Pointer et al., 2014). They are able to self-renew, proliferate, and differentiate into various cell types, which underlies the cellular heterogeneity in GBM. GSCs give rise to new tumor cells after therapeutic eradication of the bulk of the tumor (Chen et al., 2012). Although the concept of cancer stem cells (CSCs) is controversial for some types of cancer, accumulating evidence supports this concept, suggesting that GSCs may be a primary contributing factor for tumor recurrence (Akbari-Birgani et al., 2016; Farahani et al., 2014; Hombach-Klonisch et al., 2017; Wasik et al., 2014). Indeed, GSCs harbor capacities for self-renewal, differentiation, and plasticity, as well as increased chemo- and radioresistance (Ahmad and Amiji, 2017; Dey et al., 2010). The mechanisms underlying drug resistance include, drug metabolic inactivation, inhibition of pro-drug to bioactive drug conversion, increased double strand DNA repair, decreased drug influx and enhanced drug efflux. Energy-dependent drug efflux lowers intracellular drug concentration. This mechanism mostly operates via increased expression of the ATP-binding cassette super family (ABC) of transporters (Hiddingh et al., 2014). ABC transporters are commonly ovexpressed in GSC, in particular the ABCG2 (Wee et al., 2016). Many novel approaches have been tested to achieve effective tumor cell targeted therapy. For example, variety of drugs coupled to nano-vehicles have been employed to target specific intra-cellular compartments to enhance tumor cell drug sensitivity. For more details, see reviews (Bar-Zeev et al., 2017; Li et al., 2016; Livney and Assaraf, 2013).

High expression of aldehyde dehydrogenase-I by GSCs is another mechanism underlying GSC chemoresistance. Aldehyde dehydrogenase detoxifies alkylating agents and reduces their reactivity by converting drugs' aldehyde groups into carboxylic acid. O^6 –methyl-guanine DNA-methyl transferase (MGMT), a detoxifier enzyme, is also considered to contribute to chemoresistance (Safa et al., 2015; Soehngen et al., 2014). Finally, high mobility group protein A2 (HMGA2), which is a structural chromatin protein, is overexpressed in GSCs (Yi et al., 2016). These are the most typically discussed topics in the literature. Indeed, GSCs have recently been identified as potential therapeutic targets owing to their roles in tumor initiation and recurrence (McCord et al., 2009; Zhou et al., 2015b). Moreover, glioblastoma tumors exhibit proliferative and hyper-angiogenic phenotypes that can vary substantially depending on patient age and the extent of necrosis and hemorrhage (Barajas et al., 2015; Burger et al., 1985). In the present review, we discuss GBM classifications based on the molecular stem cell subtypes with a focus on potential therapeutic approaches.

Characterization and isolation of GSCs

For characterization of CSCs, technologies such as fluorescence activated cell sorter (FACS) (Ablett et al., 2012; Witt et al., 2016), and magnetic activated cell sorting (MACS) (Torre-Healy et al., 2017) provide data for identification of single CSCs among cell populations. These technologies take advantage of cellular granularity (FACS only), size, and expression of well-defined surface markers (Hasmim et al., 2016; Prestegarden et al., 2010). CD133, CD44, and CD24 are the most common markers used as stemness identification tools, although several studies have not confirmed their reproducibility and accuracy owing to the genetic heterogeneity of CSCs (Dantas-Barbosa et al., 2015; Hiddingh et al., 2014). Furthermore, microenvironmental signals in the *in vivo* niches or during *in vitro* isolation and cultivation impose epigenetic changes, and variations in CSC phenotypes are also possible. Consequently, there are many challenges that still need to be overcome.

To isolate and identify GSCs, specific and precise criteria are needed. Singh et al., described appropriate methods for GSCs characterization based on the functional properties of isolated GSCs. Additionally, neurosphere assays can be applied to assess GSC proliferation *in vitro* (Lathia and Liu, 2017; Singh et al., 2003). In this approach, researchers cultivate cells in an appropriate concentration of growth factors, and the frequencies of GSCs in tumors can be determined (Lathia and Liu, 2017; Singh et al., 2004). Another approach to identify GSCs is the use of specific surface markers to define subpopulations within the tumor that are lineage-specific. For instance, the aberrantly reactivated EGFR pathway, which causes genetic alteration, has been detected in GBM (Flavahan et al., 2016) and results in EGFR promoter alterations which facilitate EGFR overexpression (Erfani et al., 2015; Iacopino et al., 2014). Recently, Erfani et al, developed a method for the isolation of the EGFR + population of tumor cells in which fluorescence-activated cell sorting is used, to select EGFR + cells based on their affinities towards EGF ligands. This further allowed the determination that these cells displayed stemness properties by the functional characterization including a highly proliferative neurosphere, tri-lineage differentiation, as well as the expression of Sox2 and nestin (Erfani et al., 2015) The most common GSC surface markers are listed in Table 1.

GSC tumor microenvironment –the GBM niche

Researchers have started to focus on determining the origin and identity of cells that induce the development of GBM and/or promote metastasis and relapse. Several hypotheses have been proposed, including dedifferentiation of ordinary neural cells, transformation of undifferentiated precursor cells, and proliferation of neural stem cells (NSCs) (Friedmann-Morvinski and Verma, 2014). According to these hypotheses, when genetic mutations in oncogenes accumulate in normal brain cells, dedifferentiation (a process similar to reprogramming) may occur, or accumulation of genetic mutations in NSCs may cause the NSCs to form cancer cells (Campos et al., 2016). The nature and properties of stem cell niche is an important factor in determining the fate of cancer stem cells (Farahani et al., 2014; Plaks et al., 2015).

In the adult mammalian brain, two neurogenic niches have been identified: the subventricular zone (SVZ) located in the forebrain lateral ventricle, and the sub-granular zone (SGZ) located in the hippocampus in the dentate gyrus. Stem cells in both the quiescent and active mitotic states reside in these two regions (Bayin et al., 2015). The tumor niche can be divided into three distinct areas, including the perivascular niche, which is characterized by non-malignant cells such as reactive astrocytes, fibroblasts, pericytes, neural progenitor cells, and a variety of immune cells, as well as malignant cells, including GSCs and tumor cells surrounding disorganized blood vessels (Hambardzumyan and Bergers, 2015). The interactions among these cells promote GSC survival and growth. Angiogenic factors, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-

Table 1
Common surface markers on GSCs.

Marker		Origin	Normal function	Reference
Nestin	Intermediate filament	Mammalian CNS stem cells during development	Proliferation/migration	(Prestegarden et al., 2010)
CD133/Prominin	Member of the pantaspanglycoprotein family	Normal human NSCs, several cancers and brain tumor cells	Effects on cell polarity, migration, stem cell-adjacent cell interactions, and ECM	(Rizzino, 2009; Sun et al., 2016)
Musashi-1	RNA binding protein	Its expression is correlated with the proliferation and grade of malignancy	Inhibition of mRNA translation	(Chen et al., 2017; Kaneko et al., 2000)
SOX2 and HMG box	DNA binding protein	Multipotent NSCs and ESCs	Sustain neural and embryonic stem cell pluripotency	(Rizzino, 2009)
CXCR4	Also known as fusin	Neurons and glial cells during embryogenesis and in the adult brain	Ligand for CXCL12/SDF-1, lymphocyte homing, apoptosis, and stem cell movement	(J Richardson, 2016; Zhu et al., 2002)
CD44	Glycoprotein	Stem cells and CSCs	Moderates homing of stem cells as an adhesion molecule	(Ariza et al., 1995; Pietras et al., 2014; Xu et al., 2010)
L1CAM(CD171)	Glycoprotein	Neural cells	Maintain survival and tumor growth, GSC radiosensitivity and DNA damage response regulation, neuron adhesion molecule	(Jackson et al., 2014; Samatov et al., 2016)
CD15(SSEA-1)	Trisaccharide	Developing brain stem cells and adult SVZ		(Son et al., 2009)
A2B5	Ganglioside	Early stage of gliomagenesis and tumor propagation	Specific progenitor cell marker	(Auvergne et al., 2016; Auvergne et al., 2013; Ogden et al., 2008)

derived growth factor (PDGF), are important mediators of angiogenesis, which affect the oxygen supply to the tumor. These angiogenic factors may be produced by the tumor, especially under hypoxic conditions, and could facilitate the formation of the tumor blood vessels (Calabrese et al., 2007; Farahani et al., 2014; Plaks et al., 2015). Furthermore, VEGF causes pericytes to separate from each other and the vascular basement membrane to be disrupted. The specific role of VEGF in pericyte disintegration leads to the formation of abnormal and leaky blood vessels, which are enlarged and vulnerable to hemorrhage. This phenomenon is phenotypically similar to the process in kidney glomeruli, called glomeruloid microvascular proliferation (GMP), and is a hallmark of GBM (Dvorak, 2015). The leakiness of the GBM vessels has severe consequences on the blood brain barrier (BBB) and disrupts its firm structure (Abbott, 2013).

Following BBB disruption, tumor-derived chemokines/cytokines attract immunomodulatory cells, which can enter the brain and secrete more angiogenic factors, while suppressing immune function. The interaction among these factors, tumor cells, and GSCs results in tumor progression (Hambardzumyan and Bergers, 2015). The major populations of cells involved in this process at the tumor niche are monocytes, myeloid-derived suppressor cells (MDSCs) (Kohanbash and Okada, 2012), and neutrophils (Bergers and Song, 2005; Feng et al., 2015; Liang et al., 2014). Moreover, tumor-associated macrophages (TAM)s are common infiltrating cells in the perivascular niche adjacent to GSCs (Mantovani et al., 2002; Zhou et al., 2015a). These cells promote neovascularization by producing heme oxygenase-1 (HO-1) and thymidine phosphorylase (TP), which are strongly associated with neoangiogenesis (Hirano et al., 2001). High expression of chemo-attractants by TAMs, including VEGF, interleukin (IL)-6, IL-1β, colony stimulating factor (CSF), and stromal cell-derived factor 1α (SDF1α), results in recruitment of polarized macrophages and monocytes. This generates an immunosuppressive phenotype and facilitates tumor progression. TAMs can also induce matrix metalloproteinase 9 (MMP9) expression by releasing transforming growth factor-β (TGF-β), which further promotes GSC proliferation (Badie and Schartner, 2001; Hambardzumyan et al., 2016). In turn, GSCs can release periostin in the aforementioned niche, which acts as another chemoattractant for TAMs (Zhou et al., 2015a).

The perinecrotic or hypoxic niche, which can be identified by cells around the necrosis center (i.e., irregular architecture, blind ends, absence of smooth muscles and high permeability), is created from inefficient blood supply, which causes hypoxia, subsequently induces pseudo-palisading necrosis, and is an important regulator of tumor growth, cell maintenance, stemness induction, and immune surveillance (Ishii et al., 2016; Semenza, 2010; Soeda et al., 2009)

Hypoxia-inducible factors (HIF1 and HIF2) are the main proteins upregulated in response to low oxygen tension. They are strong inducers of VEGF and IL-8, which promote angiogenesis and invasion (Brat, 2011; Filatova et al., 2013; Schito and Semenza, 2016; Zagzag et al., 2006) and also activate genes involved in dedifferentiation and self-renewal. Some studies have found GSCs as an enriched population in the hypoxic niche (Seidel et al., 2010; Uribe et al., 2017). Indeed, hypoxia induces stemness characteristics, which can be measured by increased expression of CD133 and other GSC markers (Bar et al., 2010; Silver and Lathia, 2017; Soeda et al., 2009). Hence, GSCs and tumor cells may be maintained in the hypoxic niche, even after chemo/radiotherapy, and the death of cells in the necrotic area results in release of pro-inflammatory signals, which converts inflammatory cells to immunosuppressive cells (Casazza et al., 2013; Qian and Pollard, 2010; Rivera and Bergers, 2015). These events cause the cells to lose function and induce angiogenesis. Furthermore, hypoxia stimulates the differentiation of GSCs into endothelial cells, which could explain the growth of tumors and GSCs in a direction from the necrotic area towards the neovascular region (Soda et al., 2011).

The invasive niche for GBM has also been identified. GBM tumor cells have the unique ability to use normal blood vessels to migrate, and

Table 2
Genes commonly mutated in GBM.

Gene	Function	Expression status	Reference
EGFR	Regulates processes involved in cell growth, division, and survival	Gain of function/amplification	(Mazzoleni et al., 2010)
IDH1	Produces NADPH	Gain of function/amplification	(Cohen et al., 2013)
PDGFRA	Regulates processes involved in cell growth, division, and survival	Gain of function/amplification	(Furnari et al., 2015; Koschmann et al., 2016; McLendon et al., 2008)
HDM2	Regulates processes involved in cell growth, division, and survival	Gain of function/amplification	(de Toledo et al., 2000; Lathia and Liu, 2017; Noushmehr et al., 2010)
PIK3CA	Regulates processes involved in cell growth, division, and survival	Gain of function/amplification	(Gallia et al., 2006; Zhao et al., 2017)
TERT	Induces EGFR expression/involved in cell renewal	Gain of function/amplification	(Beck et al., 2011)
PIK3R1	Regulates processes involved in cell growth, division, and survival	Gain of function/amplification	(McLendon et al., 2008; Zhao et al., 2017)
PTEN	Regulates cell signaling involved in cell proliferation and survival	Loss of function/deletion	(Benitez et al., 2017; Zheng et al., 2008)
TP53	Check point protein involved in apoptosis	Loss of function/deletion	(Daniele et al., 2014)
CDKN2A	Cell cycle regulation/retinoblastoma activation	Loss of function/deletion	(Faiq et al., 2015; Parsons et al., 2008)
NF1	Regulates cell signaling involved in cell proliferation and survival	Loss of function/deletion	(Verhaak et al., 2010)
ATRX	Regulates cell division	Loss of function /deletion	(Cottini et al., 2013; Schwartzentruber et al., 2012)
RB	Regulation of cell cycle	Loss of function/deletion	(Cenciarelli et al., 2016)

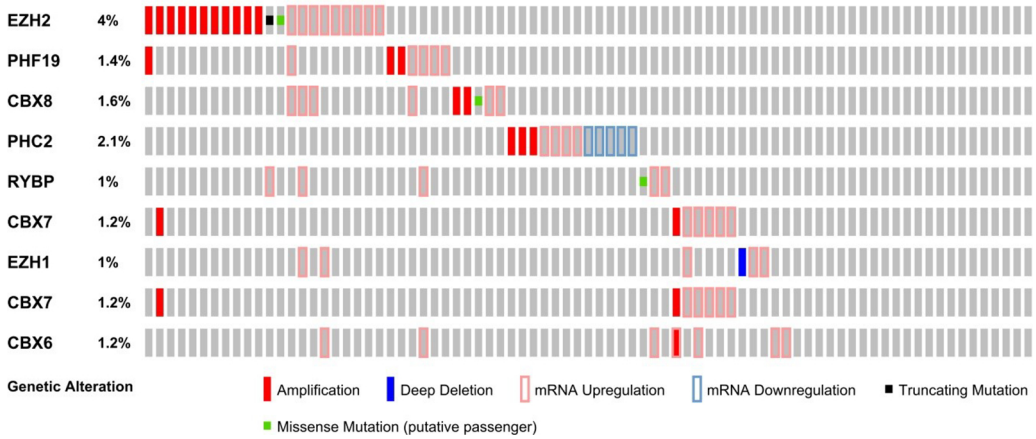

Fig. 1. TCGA analysis of PcGs in GBM patients. Due to the lack of a GSC database, the diagram shows PcG alterations with special consideration of the occurrence frequency and type of mutation.

they invade the normal brain parenchyma in this manner (Cuddapah et al., 2014). Complete deletion of MMP2 and MMP9 can enhance perivascular invasiveness and reduce angiogenesis, in contrast to the aforementioned niches (Du et al., 2008; Silver and Lathia, 2017). Astrocytes are the key cells in this niche. Exchange of ions and metabolites between blood vessels and the brain occurs via direct contact between astrocyte-end feet and pericytes and/or endothelial cells (Mathiisen et al., 2010; Silver and Lathia, 2017). The invasive niche of glioma cells can also induce astrocyte proliferation and migration by paracrine interaction. These reactive astrocytes can release connective tissue growth factor (CTGF), which binds to tropomyosin receptor kinase type A (TRKA) and integrin-1β that are located on the surface of GSCs. This leads to tumor cell infiltration via induction of zinc finger E-box binding homeobox-1 (ZEB1), a transcription factor involved in the epithelial-mesenchymal transition (EMT) (Abbott, 2013; Edwards et al., 2011).

Studies have shown that astrocytes, which are reactive to growth factors, cytokines, and metabolites, express sonic hedgehog (SHH); SHH is attached to the membrane protein Patch1, leading to activation of GLI and promoting stemness properties. Thus, astrocytes are important cells in the maintenance of GSCs and invasiveness of tumors (Becher et al., 2008). On the basis of these findings, larger tumors are expected to have expanded invasive niches, resulting in induction of neo-angiogenesis through hypoxia.

Genetic events involved in GSC biology

To obtain basic knowledge for targeting GSCs and efficient treatment of GBM, the genetic and epigenetic alterations in these cells must be well defined, and the molecular pathways and cellular interactions between GSCs and the tumor microenvironment as well as normal cells must be evaluated. Seventy-four genetic mutations have been detected using accessible data in The Cancer Genome Atlas (TCGA) via the c bio portal (Table 2). This database has been used to categorize mutations, and the most frequently identified signaling pathways are discussed below, and listed in Table 4.

The most common pathways involved in maintenance of GSCs

Notch signaling pathway

Notch signaling plays important roles in cell fate, proliferation and migration, also it is involved in maintaining cellular quiescence and regulating neural (NSC) differentiation (Saito et al., 2017). The cleavage of notch receptor by γ-secretase by the jagged family or delta ligands binding, leads to the translocation of Notch intracellular domain (NICD) to the nucleolus; this results in the formation a complex with RBPJ and MAML in the nucleus and activation of the hairy and enhancer of split (HES) and HEY genes, thereby promoting the

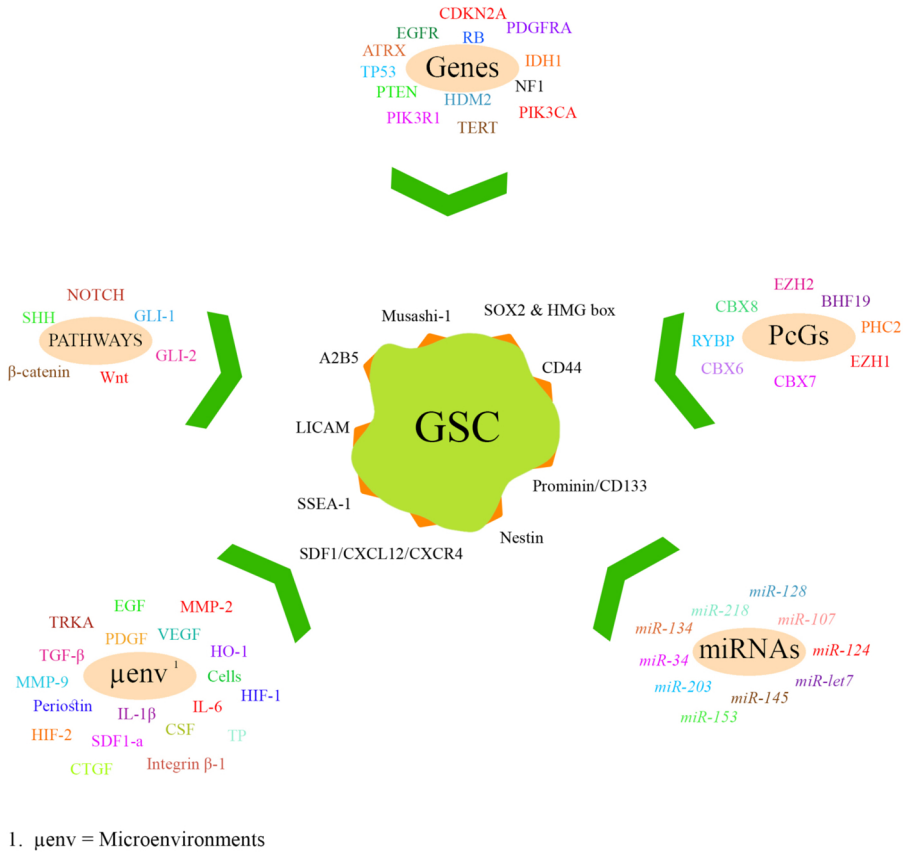

Fig. 2. Molecular interactions among GSCs and aforementioned factors. A brief graphical explanation is provided for the intracellular and extracellular factors that promote or inhibit stemness.

Table 3
miRNAs involved in the regulation of GBM fate.

miRNA	Gene targeted	Changed Expression in GBM	Function	Reference
miR-218	BMI1, LEF1, IKBKB, ECOP, CDK6	downregulated	Inhibits glioma stem-like cells	(Liu et al., 2012; Mathew et al., 2014; Zhang et al., 2011)
miR-107	Notch-2, SLLA4, CDK6	downregulated	Downregulation of Nestin and CD133	(Chen et al., 2013; He et al., 2013)
miR-128	P70S6K1, SUZ12, BMI1, PDGFRα, EGFR, E2F3a, WEE1, MSI1	downregulated	Suppresses PRC activity, early events in gliomagenesis	(Ciafre et al., 2005; Papagiannakopoulos et al., 2012; Rooj et al., 2016; Zhang et al., 2009)
miR-134	KRAS, STAT5B	downregulated	Stimulates differentiation	(Zhang et al., 2014)
miR-153	BCL2, MCL1, IRS1	downregulated	Impairs self-renewal and differentiation	(Xu et al., 2011; Zhao et al., 2013)
miR-203	PLD2, SNAI	downregulated	Inhibits stemness and glioma cell migration	(Deng et al., 2016; Liao et al., 2015)
miR-let-7	NRAS, KRAS, CCND1	downregulated	Possible anti-tumorigenic effects	(Guo et al., 2013; Wang et al., 2013)
miR-124	SNAI1, PIM3, NRAS, SOS	downregulated	Decreases self-renewal and migration	(Lv and Yang, 2013; Xia et al., 2012)
miR-34	MET, NOTCH1, NOTCH2,	downregulated	Induces apoptosis and inhibit invasion	(Guessous et al., 2010; Li et al., 2009)
miR-145	Sox2	downregulated	Contributes to silencing of c-Myc	(Speranza et al., 2012)

maintenance of multipotency (Bayin et al., 2017; Dantas-Barbosa et al., 2015).

CD133-positive GSCs overexpress Notch signaling pathway activators, including inhibitor of differentiation 4 (ID4) and a cellular chaperon; fatty acid-binding protein 7 (FABP7), which directly affect radial ganglion cell (RGC) migration. High expression of these genes promotes infiltrating potential of GBM tumors (Kaloshi et al., 2007); thus, the Notch signaling pathway is thought to promote migration. The activation mechanisms of oncogenic signaling in GSCs by Notch, remain unclear, however it had been shown that an extracellular matrix protein Tenascin-C, increased Notch activation in GSCs (Sarkar et al., 2017). Notch signaling activation is also involved in maintaining the stemness of GSCs, and determining glial cell fate. Thus, inactivation of this pathway may be an effective method for blocking GSCs and limiting tumor growth.

Sonic hedgehog (SHH)/glioma-associated oncogene (GLI) signaling pathway

During embryonic development, SHH plays a critical role in organogenesis and especially neural progenitor regulation. However, this is not the case in quiescent adult tissues, with the exception of repair and tissue maintenance. Hence, this is an important pathway affecting the self-renewal and tumorigenicity of GSCs (Clement et al., 2007; Honorato et al., 2018). The majority of GSCs have activated the SHH/GLI-pathway and it also causes the up-regulation of drug efflux P-glycoprotein (ABCB1), ABCG2/BCRP, ABCC1/MRP1 MGMT, BMI, (Hombach-Klonisch et al., 2017; Shahi et al., 2016). Recently, studies have shown that SHH/GLI activity is crucial for Nanog regulation, and

Table 4
Surface markers and other potential molecular targets in GSCs.

	Marker Identifier	Agent	Mechanism	In vivo	In vitro	Clinical trial	Reference
Cell Surface Marker	CD133	Carbon nanotube-conjugated anti-CD133(CD133-SWNT)	Directly targets GSCs, kills them synergistically with photothermolysis	+	+	Not yet	(Wang et al., 2011)
	CD44/Osteopontin	CD44 antagonist	Decreases GSC survival by enhancing Hippo signalling, inhibiting growth signalling from ErbB/c-Met RTKs	+	+	Not yet	(Xu et al., 2010)
Signalling pathways	NOTCH	NOTCH siRNA	Downregulation of NANOG, N-cadherin, CD133, and Oct-4	+	+	Not yet	(Wang et al., 2012)
	NOTCH/NOTCH ligand	OMP-59R5 (Tarextumab), BMS-906024		+	+	Solid tumors other than GBM	(Dragu et al., 2015)
	TGFβR1 inhibitor	LY2109761	Induces radiosensitivity, reduces microvessels	+	+	Not yet	(Mengxian et al., 2011)
	Targeting Wnt pathway	Celcoxib	Inhibits invasiveness and induce apoptosis	+	+	NCT00112502	(Kardosh et al., 2008; McCord et al., 2009; Sareddy et al., 2013)
		SEN461	Inhibits GBM growth by protecting against Axin degradation and βcatenin loss.	+	+	Not yet	(De Robertis et al., 2013)
		XAV939	Inhibits GBM growth viaβ-catenin phosphorylation and stabilization of Axin.	+	+	Not yet	(Huang et al., 2009; Lee et al., 2016)
MicroRNAs	*miR-34-a*		Induction of GSC differentiation	+	+	Not yet	(Guessous et al., 2010; Li et al., 2009)
	miR-145		Suppression of anti-apoptotic genes, increases sensitivity to chemo/radiotherapy	+	+	Not yet	(Speranza et al., 2012)
	miR-128		RTKs, EGFR, PDGFR-α targeting, NSC differentiation	+	+	Not yet	(Ciafre et al., 2005)

binding of SHH/GLI1/GLI2 to the Nanog promoter leads to activation of Nanog expression. The transcription factor Nanog is one of the 'master regulators' of the expression of several stemness factors. Conversely, p53 downregulates Nanog expression by decreasing GLI1 expression and activity. Furthermore, loss of p53 leads to activation of SHH signaling, upregulation of Nanog, and maintenance of stemness properties (Abou-Antoun et al., 2017; Ma et al., 2017; Zbinden et al., 2010). In contrast, bone morphogenic protein (BMP), which may also act as a growth factor and have pro-differentiation activities in stem cells, is downregulated by GLI. Piccirillo et al., showed that this pathway blocked the proliferation of GSCs (Piccirillo et al., 2006; Shahi et al., 2016). Furthermore, inhibition of SHH could potentiate the therapeutic effect of TMZ, one of the key drugs employed to treat glioblastoma. Hence, the aforementioned studies affirm the contribution of this pathway to GSCs chemoresistance and its targeting could potentially increase chemotherapy efficacy (Honorato et al., 2018).

The Wnt/β-catenin signaling pathway

During CNS development, the Wnt signaling pathway is a crucial player in self-renewal, differentiation, and NSC development specifically in axis patterning and the differentiation of posterior and interior structure of CNS. (Kalani et al., 2008; Zuccarini et al., 2018). However, aberrant activation of this pathway in the CNS leads to transformation into brain tumors. The regulatory association between the Wnt pathway and maintenance of GSCs involves genetic and epigenetic mechanisms (Pulvirenti et al., 2011). With regard to genetic regulation, overexpression of pleomorphic adenoma gene-like2 (PLAGL2) results in upregulation of Wnt components such as frizzled (FZD) 2, FZD9, and Wnt6, thereby activating the canonical Wnt pathway (Zheng et al., 2010; Zuccarini et al., 2018). The other genetic event affecting Wnt is FoxM1, which directly binds to the Sox2 promoter and induces stemness programming and maintenance of GSCs (Lee et al., 2015).

Epigenetic factors affect Wnt signaling; the transmembrane protein Evi, which is overexpressed in GBM, is regulated via epigenetic mechanisms and alters the canonical and non-canonical Wnt pathways (Ahmad and Amiji, 2017; Augustin et al., 2012; Bartscherer et al., 2006). Moreover, a Wnt family member; Wnt5A promotes endothelial differentiation of GSCs which is associated with neovascularization, hence providing environment that facilitates tumor cell growth and invasion (Binda et al., 2017; Hu et al., 2016).

These studies have shown that canonical and non-canonical Wnt signaling pathways are involved in maintenance and gliomagenesis of GSCs. Furthermore, Wnt signaling induces TMZ resistance through promotion of O^6-methylguanine-DNA methyltransferase (MGMT) expression, which protects the genome from anticancer therapeutics like TMZ, that act as alkylating agents (Lee et al., 2016; Wickström et al., 2015). Broad and unspecific targeting of the Wnt signaling pathway is not a viable option because of its key role in the aforementioned physiologic functions in the brain and in other tissues and organs. The blockade of such a crucial signaling system, which controls vital functions will certainly cause serious side effects in patients. Though, it would be essential to design strategies based on targeting the Wnt axis at the tumor level (Zuccarini et al., 2018).

Epigenetic changes in GSCs

Epigenetic heterogeneity is involved in regulation of GSCs. Epigenetic mechanisms are considered a dynamic interface between physical, social and metabolic signals of the external world, allowing changes in gene expression in response to the environment (Herman and Baylin, 2003). Indeed, GBM harbors not only genetic- but also epigenetic alterations, which in concert regulate cancer cell gene expression (Mack et al., 2016).

Epigenetic changes may involve: (*i*) DNA methylation especially within gene-promotor area (CpG islands), hence affecting gene

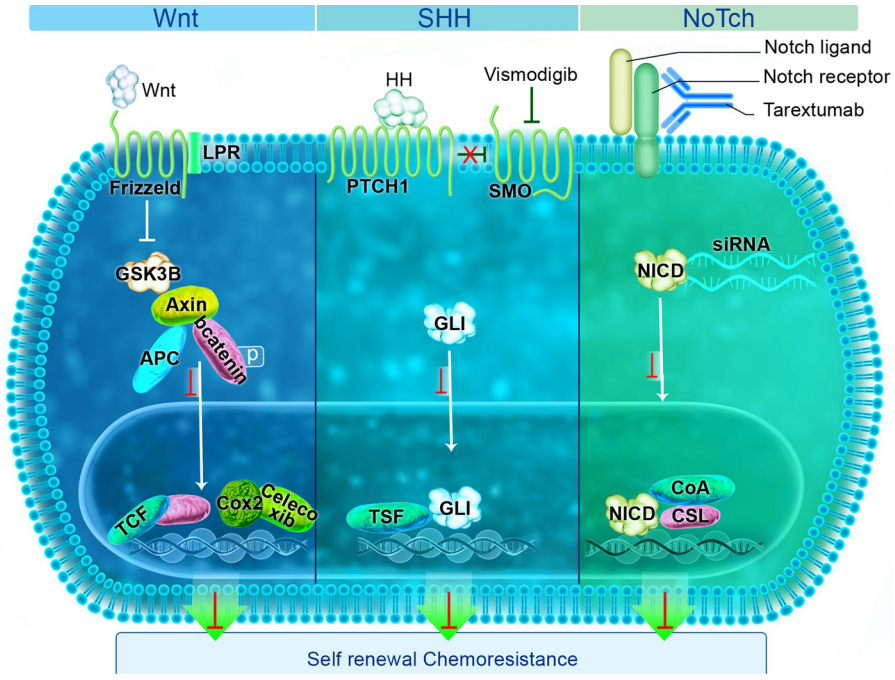

Fig. 3. Schematic diagram of the signaling pathways most involved in GSC maintenance and their components, which are already used as targets of most commonly used drugs. *Wnt signaling:* Binding of wnt proteins with the Frizzled and low density lipoprotein receptor-related protein/α2 macroglobulin receptor (LRP) families as their receptor results in disassembling of Axin, adenomatous polyposis coli (APC), and formation of the GSK3β complex through stabilization of βcatenin. This produces a signal to the β-catenin to migrate to the nucleus and make a connection with T cell factor (TCF) to activate their target gene, which is involved in stem cell maintenance. Celecoxib, a member of the non-steroidal anti-inflammatory drug (NSAID) family, targets the cyclooxygenase2 (COX2) gene and XAV939 and SEN461, two small molecules that have shown therapeutic promise for the treatment of Wnt-induced gliomas by stabilizing Axin, such that the amount of cytoplasmic phosphorylated β-catenin increases and then β-catenin cannot move to the nucleolus. *SHH pathway:* Binding of HH ligands to 12 transmembrane patched homologue1 (PTCH1) causes 7-transmembrane protein smoothened homologue (SMO) release. Thus, GLI is activated via a multistep process and moves to the nucleolus to induce transcription and regulate genes while stimulating cell proliferation, self-renewal, and chemoresistance. Vismodegib binds to SMO and blocks the rest of the pathway. *Notch pathway:* The interaction between notch ligand and the notch receptor initiates Notch signaling, which proceeds by the sequential cleavage of Notch; therefore, Notch intracellular domain (NICD) is released from the membrane and moves toward the nucleolus. There, it forms a transcriptional activating complex with the nuclear transcription factor CSL and the co activator (CoA). This complex induces target genes involved in self-renewal and chemoresistance. Tarextumab is a monoclonal antibody (Ab) that targets Notch receptors and blocks the whole pathway. Blockade of this pathway appears to restrict self-renewal.

expression. Specifically, promoter hypermethylation (addition of methyl groups to cytosine residues in DNA) results in gene silencing. Hypermethylation of tumor-suppressor genes, such as *TP53*, can promote cancer development (Noushmehr et al., 2010). Conversely, hypomethylation (decreased methylation) causes activation of genes that are normally silenced or suppressed, such as oncogenes (Feinberg and Vogelstein, 1983; Noushmehr et al., 2010). (*ii*) Post-translational modifications of histones, i.e., methylation, acetylation, phosphorylation, sumoylation, and ubiquitylation, affect the chromatin architecture and result in epigenetic changes in the regions around enhancers, promoters, and other regulatory elements. Mutations in the histone modification pathway can promote and enhance GBM formation (Tessarz and Kouzarides, 2014). (*iii*) Polycomb group proteins (PcGs) play a crucial role in embryonic development and can cause gene silencing through chromatin remodeling (Fig. 1). Dysregulation of these proteins leads to tumor progression, invasion, and metastasis (Koppens and Van Lohuizen, 2016). The TCGA database, reveals a numbers of PcGs with altered expression in GBM versus the normal brain as shown in Fig. 2. Among the listed proteins, BMI1, one of the members of polycomb repressive complex1 (PRC1), prevents GSCs from differentiating into mature neurons and also inhibits apoptosis (Abdouh et al., 2009). EZH2, a component of the polycomb repressive complex2 (PRC2), is also thought to be involved in sustaining GSCs through the activation of STAT3 (Kim et al., 2013). Owing to intricate interactions among these proteins, they are thought to also be involved in inducing GBM progression and invasion. (*iv*) Modifications in microRNAs (miRNA), which are non-coding functional RNAs that have crucial effects on post-transcriptional regulation (Table 3). miRNA expression is greatly altered in GSCs versus the normal brain (Nagarajan and Costello, 2009). Moller et al., demonstrated altered expression of 351 miRNAs in GBM, with 256 overexpressed and 95 under-expressed (Møller et al., 2013).

Conclusions and perspectives regarding therapeutic agents for eradication of GSCs

Despite major advances in research, treatment of GBM continues to be a major challenge. Surgical resection followed by radical chemoradiotherapy is a standard treatment protocol in patients with GBM (Tome-Garcia et al., 2017). However, the only benefit that these treatments can achieve is shrinking the tumor size by killing active cancer cells. Tumor metastasis or recurrence is common after such treatments owing to molecular heterogeneity and the unique tumor microenvironment in GMB (McCord et al., 2009). Therefore, it is crucial to design strategies that focus on targeting GSCs and their microenvironment components to eradicate GSCs in combination with traditional therapies, which may lead to more effective treatment. Other available treatment approaches include specific chemotherapeutic agents, immunotherapies, radiotherapies, gene therapies, and induction of GSC differentiation to normal cells; these treatment modalities may have applications in the targeting of GSCs with the goal of eradicating minimal residual disease and blocking tumor recurrence (Cho et al., 2013).

Currently, many studies are underway to target GSCs for more effective treatment. For example, Thanasupawat et al., tested a small molecule inhibitor, dovitinib (Dov; TK1258, CHIR258) (Thanasupawat et al., 2017). Dov is a benzimidazole-quinolinone compound that acts as a receptor tyrosine kinase inhibitor and down-regulates HMGA2. Considering the special function of HMGA2 protein in self-renewal, its down-regulation should reduce the size of GB tumors. Dov also causes reduced expression of MGMT, which is an important enzyme that plays an important role in the repair of DNA damage caused by the alkylating activity of TMZ (as shown above), and is a potential chemoresistance determinant. Dov damages DNA by its localization in the minor groove, and it targets topoisomerase I and II. Combinatorial treatment of TMZ with Dov enhances DNA damage and apoptosis in GB cells (Thanasupawat et al., 2017). The pathway blockers demonstrated in Fig. 3 are other examples of these stemness-targeted drugs. Selected,

potential targets for GMB-therapy have been listed in Table 4.

Salinomycin is another potentially promising experimental drug that preferentially kills GSCs as well as other types of CSCs (Jangamreddy et al., 2013, 2015; Xipell et al., 2016). While phase I clinical trials testing the potential use of salinomycin in glioblastoma yet await to be published, the drug and its derivatives, are currently being intensively explored as an anti-CSCs agent for several types of malignancies.

In the current review, we highlighted the molecular markers that can be utilized to isolate GSCs from normal stem cells. These promising therapeutic targets may afford a systematic, well-organized approach for cancer treatment and prevent further exposure of patients to the severe side effects of chemoradiotherapies and more invasive approaches. Further laboratory and clinical investigations are needed to identify the appropriate selection of targets for promising treatments.

Acknowledgements

The authors would like to acknowledge Mr. Hamidreza Abolkheir and Mr. Javad Firouzi, scientists researchers at the Royan Institute, for their support for the completion of this study. Saeid Ghavami has been supported by a Health Science Centre General Operating Grant and Research Manitoba New Investigator Operating Grant. MJŁ kindly acknowledges the support from NCN grant #: 2016/21/B/NZ1/02812, the supported by LE STUDIUM Institute for Advanced Studies (region Centre-Val de Loire, France) through its Smart Loire Valley General Program, co-funded by the Marie Sklodowska-Curie Actions, grant # 665790. Marzieh Ebrahimi has been supported by Iranian council for stem cell sciences and technologies, grant# Rep 218 and Royan institute, grant# 94000197.

References

Abbott, N.J., 2013. Blood–brain barrier structure and function and the challenges for CNS drug delivery. J. Inherit. Metab. Dis. 36, 437–449.
Abdouh, M., Facchino, S., Chatoo, W., Balasingam, V., Ferreira, J., Bernier, G., 2009. BMI1 sustains human glioblastoma multiforme stem cell renewal. J. Neurosci. 29, 8884–8896.
Ablett, M.P., Singh, J.K., Clarke, R.B., 2012. Stem cells in breast tumours: are they ready for the clinic? Eur. J. Cancer 48, 2104–2116.
Abou-Antoun, T.J., Hale, J.S., Lathia, J.D., Dombrowski, S.M., 2017. Brain cancer stem cells in adults and children: cell biology and therapeutic implications. Neurotherapeutics 14, 372–384.
Ahmad, G., Amiji, M.M., 2017. Cancer stem cell-targeted therapeutics and delivery strategies. Expert Opin. Drug Deliv. 14, 997–1008.
Akbari-Birgani, S., Paranjothy, T., Zuse, A., Janikowski, T., Cieslar-Pobuda, A., Likus, W., Urasinska, E., Schweizer, F., Ghavami, S., Klonisch, T., Los, M.J., 2016. Cancer stem cells, cancer-initiating cells and methods for their detection. Drug Discov. Today 21, 836–842.
Ariza, A., López, D., Mate, J.L., Isamat, M., Musulen, E., Pujol, M., Ley, A., Navas-palacios, J., 1995. Role of CD44 in the invasiveness of glioblastoma multiforme and the noninvasiveness of meningioma: an immunohistochemistry study. Hum. Pathol. 26, 1144–1147.
Augustin, I., Goidts, V., Bongers, A., Kerr, G., Vollert, G., Radlwimmer, B., Hartmann, C., Herold-Mende, C., Reifenberger, G., von Deimling, A., 2012. The Wnt secretion protein Evi/Gpr177 promotes glioma tumourigenesis. EMBO Mol. Med. 4, 38–51.
Auvergne, R.M., Sim, F.J., Wang, S., Chandler-Militello, D., Burch, J., Al Fanek, Y., Davis, D., Benraiss, A., Walter, K., Achanta, P., 2013. Transcriptional distinctions between normal and glioma-derived A2B5+ progenitor cells identify a core set of genes dysregulated at all stages of gliomagenesis. Cell Rep. 3, 2127.
Auvergne, R., Wu, C., Connell, A., Au, S., Cornwell, A., Osipovitch, M., Benraiss, A., Dangelmajer, S., Guerrero-Cazares, H., Quinones-Hinojosa, A., 2016. PAR1 inhibition suppresses the self-renewal and growth of A2B5-defined glioma progenitor cells and their derived gliomas in vivo. Oncogene 35, 3817.
Badie, B., Schartner, J., 2001. Role of microglia in glioma biology. Microsc. Res. Tech. 54, 106–113.
Bar, E.E., Lin, A., Mahairaki, V., Matsui, W., Eberhart, C.G., 2010. Hypoxia increases the expression of stem-cell markers and promotes clonogenicity in glioblastoma neurospheres. Am. J. Pathol. 177, 1491–1502.
Barajas Jr., R.F., Phillips, J.J., Vandenberg, S.R., McDermott, M.W., Berger, M.S., Dillon, W.P., Cha, S., 2015. Pro-angiogenic cellular and genomic expression patterns within glioblastoma influences dynamic susceptibility weighted perfusion MRI. Clin. Radiol. 70, 1087–1095.
Bartscherer, K., Pelte, N., Ingelfinger, D., Boutros, M., 2006. Secretion of Wnt ligands requires Evi, a conserved transmembrane protein. Cell 125, 523–533.
Bar-Zeev, M., Livney, Y.D., Assaraf, Y.G., 2017. Targeted nanomedicine for cancer therapeutics: towards precision medicine overcoming drug resistance. Drug Resist. Updates 31, 15–30.
Bayin, N.S., Modrek, A.S., Placantonakis, D.G., 2015. Brain tumor stem cells. Molecular Pathology of Nervous System Tumors. Springer, pp. 23–34.
Bayin, N.S., Frenster, J.D., Sen, R., Si, S., Modrek, A.S., Galifianakis, N., Dolgalev, I., Ortenzi, V., Illa-Bochaca, I., Khahera, A., Serrano, J., Chiriboga, L., Zagzag, D., Golfinos, J.G., Doyle, W., Tsirigos, A., Heguy, A., Chesler, M., Barcellos-Hoff, M.H., Snuderl, M., Placantonakis, D.G., 2017. Notch signaling regulates metabolic heterogeneity in glioblastoma stem cells. Oncotarget 8, 64932–64953.
Becher, O.J., Hambardzumyan, D., Fomchenko, E.I., Momota, H., Mainwaring, L., Bleau, A.-M., Katz, A.M., Edgar, M., Kenney, A.M., Cordon-Cardo, C., 2008. Gli activity correlates with tumor grade in platelet-derived growth factor–induced gliomas. Cancer Res. 68, 2241–2249.
Beck, S., Jin, X., Sohn, Y.-W., Kim, J.-K., Kim, S.-H., Yin, J., Pian, X., Kim, S.-C., Nam, D.-H., Choi, Y.-J., 2011. Telomerase activity-independent function of TERT allows glioma cells to attain cancer stem cell characteristics by inducing EGFR expression. Mol. Cells 31, 9–15.
Benitez, J.A., Ma, J., D'Antonio, M., Boyer, A., Camargo, M.F., Zanca, C., Kelly, S., Khodadadi-Jamayran, A., Jameson, N.M., Andersen, M., 2017. PTEN regulates glioblastoma oncogenesis through chromatin-associated complexes of DAXX and histone H3. 3. Nat. Commun. 8, 15223.
Bergers, G., Song, S., 2005. The role of pericytes in blood-vessel formation and maintenance. Neurooncology 7, 452–464.
Binda, E., Visioli, A., Giani, F., Trivieri, N., Palumbo, O., Restelli, S., Dezi, F., Mazza, T., Fusilli, C., Legnani, F., 2017. Wnt5a drives an invasive phenotype in human glioblastoma stem-like cells. Cancer Res. 77, 996–1007.
Brandes, A.A., Bartolotti, M., Tosoni, A., Franceschi, E., 2016. Nitrosoureas in the management of malignant gliomas. Curr. Neurol. Neurosci. Rep. 16, 13.
Brat, D.J., 2011. Glioblastoma: biology, genetics, and behavior. American Society of Clinical Oncology Educational book/ASCO. American Society of Clinical Oncology. Meeting. pp. 102–107.
Burger, P.C., Vogel, F.S., Green, S.B., Strike, T.A., 1985. Glioblastoma multiforme and anaplastic astrocytoma pathologic criteria and prognostic implications. Cancer 56, 1106–1111.
Calabrese, C., Poppleton, H., Kocak, M., Hogg, T.L., Fuller, C., Hamner, B., Oh, E.Y., Gaber, M.W., Finklestein, D., Allen, M., 2007. A perivascular niche for brain tumor stem cells. Cancer Cell 11, 69–82.
Campos, B., Olsen, L.R., Urup, T., Poulsen, H., 2016. A comprehensive profile of recurrent glioblastoma. Oncogene 35, 5819–5825.
Casazza, A., Laoui, D., Wenes, M., Rizzolio, S., Bassani, N., Mambretti, M., Deschoemaeker, S., Van Ginderachter, J.A., Tamagnone, L., Mazzone, M., 2013. Impeding macrophage entry into hypoxic tumor areas by Sema3A/Nrp1 signaling blockade inhibits angiogenesis and restores antitumor immunity. Cancer Cell 24, 695–709.
Cenciarelli, C., Marei, H.E., Felsani, A., Casalbore, P., Sica, G., Puglisi, M.A., Cameron, A.J., Olivi, A., Mangiola, A., 2016. PDGFRα Depletion Attenuates Glioblastoma Stem Cells Features By Modulation of STAT3, RB1 and Multiple Oncogenic Signals.
Chen, J., Li, Y., Yu, T.-S., McKay, R.M., Burns, D.K., Kernie, S.G., Parada, L.F., 2012. A restricted cell population propagates glioblastoma growth after chemotherapy. Nature 488, 522–526.
Chen, L., Chen, X.-R., Zhang, R., Li, P., Liu, Y., Yan, K., Jiang, X.-D., 2013. MicroRNA-107 inhibits glioma cell migration and invasion by modulating Notch2 expression. J. Neurooncol. 112, 59–66.
Chen, H.-Y., Lin, L.-T., Wang, M.-L., Laurent, B., Hsu, C.-H., Pan, C.-M., Jiang, W.-R., Chen, P.-Y., Ma, H.-I., Chen, Y.-W., 2017. Musashi-1 enhances glioblastoma cell migration and cytoskeletal dynamics through translational inhibition of Tensin3. Sci. Rep. 7, 8710.
Cho, D.-Y., Lin, S.-Z., Yang, W.-K., Lee, H.-C., Hsu, D.-M., Lin, H.-L., Chen, C.-C., Liu, C.-L., Lee, W.-Y., Ho, L.-H., 2013. Targeting cancer stem cells for treatment of glioblastoma multiforme. Cell Transplant. 22, 731–739.
Ciafre, S., Galardi, S., Mangiola, A., Ferracin, M., Liu, C.-G., Sabatino, G., Negrini, M., Maira, G., Croce, C., Farace, M., 2005. Extensive modulation of a set of microRNAs in primary glioblastoma. Biochem. Biophys. Res. Commun. 334, 1351–1358.
Clement, V., Sanchez, P., De Tribolet, N., Radovanovic, I., i Altaba, A.R., 2007. HEDGEHOG-GLI1 signaling regulates human glioma growth, cancer stem cell self-renewal, and tumorigenicity. Curr. Biol. 17, 165–172.
Cohen, A.L., Holmen, S.L., Colman, H., 2013. IDH1 and IDH2 mutations in gliomas. Curr. Neurol. Neurosci. Rep. 13, 345.
Cottini, F., Anderson, K.C., Tonon, G., 2013. Cancer Genomics: From Bench to Personalized Medicine. Elsevier Inc.
Cuddapah, V.A., Robel, S., Watkins, S., Sontheimer, H., 2014. A neurocentric perspective on glioma invasion. Nat. Rev. Neurosci. 15, 455–465.
Daniele, S., Taliani, S., Da Pozzo, E., Giacomelli, C., Costa, B., Trincavelli, M.L., Rossi, L., La Pietra, V., Barresi, E., Carotenuto, A., 2014. Apoptosis therapy in cancer: the first single-molecule co-activating p53 and the translocator protein in glioblastoma. Sci. Rep. 4, 4749.
Dantas-Barbosa, C., Bergthold, G., Daudigeos-Dubus, E., Blockus, H., Boylan, J.F., Ferreira, C., Puget, S., Abely, M., Vassal, G., Grill, J., Geoerger, B., 2015. Inhibition of the NOTCH pathway using gamma-secretase inhibitor RO4929097 has limited antitumor activity in established glial tumors. Anticancer Drugs 26, 272–283.
De Robertis, A., Valensin, S., Rossi, M., Tunici, P., Verani, M., De Rosa, A., Giordano, C., Varrone, M., Nencini, A., Pratelli, C., 2013. Identification and characterization of a small-molecule inhibitor of Wnt signaling in glioblastoma cells. Mol. Cancer Ther. 12, 1180–1189.
de Toledo, S.M., Azzam, E.I., Dahlberg, W.K., Gooding, T.B., Little, J.B., 2000. ATM

complexes with HDM2 and promotes its rapid phosphorylation in a p53-independent manner in normal and tumor human cells exposed to ionizing radiation. Oncogene 19, 6185.
Deng, Y., Zhu, G., Luo, H., Zhao, S., 2016. MicroRNA-203 As a stemness inhibitor of glioblastoma stem cells. Mol. Cells 39, 619.
Dey, M., Ulasov, I.V., Lesniak, M.S., 2010. Virotherapy against malignant glioma stem cells. Cancer Lett. 289, 1–10.
Dimov, I., Tasic-Dimov, D., Conic, I., Stefanovic, V., 2011. Glioblastoma multiforme stem cells. Sci. World J. 11, 930–958.
Dragu, D.L., Necula, L.G., Bleotu, C., Diaconu, C.C., Chivu-Economescu, M., 2015. Therapies targeting cancer stem cells: current trends and future challenges. World J. Stem Cells 7, 1185.
Du, R., Petritsch, C., Lu, K., Liu, P., Haller, A., Ganss, R., Song, H., Vandenberg, S., Bergers, G., 2008. Matrix metalloproteinase-2 regulates vascular patterning and growth affecting tumor cell survival and invasion in GBM. Neurooncology 10, 254–264.
Dvorak, H.F., 2015. Tumors: wounds that do not heal—redux. Cancer Immunol. Res. 3, 1–11.
Edwards, L.A., Woolard, K., Son, M.J., Li, A., Lee, J., Ene, C., Mantey, S.A., Maric, D., Song, H., Belova, G., 2011. Effect of brain-and tumor-derived connective tissue growth factor on glioma invasion. J. Natl. Cancer Inst. 103, 1162–1178.
Erfani, P., Tome-Garcia, J., Canoll, P., Doetsch, F., Tsankova, N.M., 2015. EGFR promoter exhibits dynamic histone modifications and binding of ASH2L and P300 in human germinal matrix and gliomas. Epigenetics 10, 496–507.
Faiq, N., Chmielecki, J., Goldberg, M., Stephens, P., Kurzrock, R., Kesari, S., Piccioni, D.E., 2015. Analysis of BRAF Alterations and Molecular Profiling in Glioblastoma and Astrocytoma. American Society of Clinical Oncology.
Farahani, E., Patra, H.K., Jangamreddy, J.R., Rashedi, I., Kawalec, M., Rao Pariti, R.K., Batakis, P., Wiechec, E., 2014. Cell adhesion molecules and their relation to (cancer) cell stemness. Carcinogenesis 35, 747–759.
Feinberg, A.P., Vogelstein, B., 1983. Hypomethylation of ras oncogenes in primary human cancers. Biochem. Biophys. Res. Commun. 111, 47–54.
Feng, X., Szulzewsky, F., Yerevanian, A., Chen, Z., Heinzmann, D., Rasmussen, R.D., Alvarez-Garcia, V., Kim, Y., Wang, B., Tamagno, I., 2015. Loss of CX3CR1 increases accumulation of inflammatory monocytes and promotes gliomagenesis. Oncotarget 6, 15077.
Filatova, A., Acker, T., Garvalov, B.K., 2013. The cancer stem cell niche (s): the crosstalk between glioma stem cells and their microenvironment. Biochim. Biophys. Acta (BBA)-Gen. Subjects 1830, 2496–2508.
Flavahan, W.A., Drier, Y., Liau, B.B., Gillespie, S.M., Venteicher, A.S., Stemmer-Rachamimov, A.O., Suva, M.L., Bernstein, B.E., 2016. Insulator dysfunction and oncogene activation in IDH mutant gliomas. Nature 529, 110–114.
Friedmann-Morvinski, D., Verma, I.M., 2014. Dedifferentiation and reprogramming: origins of cancer stem cells. EMBO Rep., e201338254.
Furnari, F.B., Cloughesy, T.F., Cavenee, W.K., Mischel, P.S., 2015. Heterogeneity of epidermal growth factor receptor signalling networks in glioblastoma. Nat. Rev. Cancer 15, 302.
Gallia, G.L., Rand, V., Siu, I.-M., Eberhart, C.G., James, C.D., Marie, S.K., Oba-Shinjo, S.M., Carlotti, C.G., Caballero, O.L., Simpson, A.J., 2006. PIK3CA gene mutations in pediatric and adult glioblastoma multiforme. Mol. Cancer Res. 4, 709–714.
Guessous, F., Zhang, Y., Kofman, A., Catania, A., Li, Y., Schiff, D., Purow, B., Abounader, R., 2010. microRNA-34a is tumor suppressive in brain tumors and glioma stem cells. Cell Cycle 9, 1031–1036.
Guo, Y., Yan, K., Fang, J., Qu, Q., Zhou, M., Chen, F., 2013. Let-7b expression determines response to chemotherapy through the regulation of cyclin D1 in glioblastoma. J. Exp. Clin. Cancer Res. 32, 41.
Hambardzumyan, D., Bergers, G., 2015. Glioblastoma: defining tumor niches. Trends Cancer 1, 252–265.
Hambardzumyan, D., Gutmann, D.H., Kettenmann, H., 2016. The role of microglia and macrophages in glioma maintenance and progression. Nat. Neurosci. 19, 20–27.
Hasmim, M., Bruno, S., Azzi, S., Gallerne, C., Michel, J.G., Chiabotto, G., Lecoz, V., Romei, C., Spaggiari, G.M., Pezzolo, A., Pistoia, V., Angevin, E., Gad, S., Ferlicot, S., Messai, Y., Kieda, C., Clay, D., Sabatini, F., Escudier, B., Camussi, G., Eid, P., Azzarone, B., Chouaib, S., 2016. Isolation and characterization of renal cancer stem cells from patient-derived xenografts. Oncotarget 7, 15507–15524.
He, J., Zhang, W., Zhou, Q., Zhao, T., Song, Y., Chai, L., Li, Y., 2013. Low-expression of microRNA-107 inhibits cell apoptosis in glioma by upregulation of SALL4. Int. J. Biochem. Cell Biol. 45, 1962–1973.
Herman, J.G., Baylin, S.B., 2003. Gene silencing in cancer in association with promoter hypermethylation. N. Engl. J. Med. 349, 2042–2054.
Hiddingh, L., Tannous, B.A., Teng, J., Tops, B., Jeuken, J., Hulleman, E., Boots-Sprenger, S.H., Vandertop, W.P., Noske, D.P., Kaspers, G.J., Wesseling, P., Wurdinger, T., 2014. EFEMP1 induces gamma-secretase/Notch-mediated temozolomide resistance in glioblastoma. Oncotarget 5, 363–374.
Hirano, H., Tanioka, K., Yokoyama, S., Akiyama, S.-i., Kuratsu, J.-i., 2001. Angiogenic effect of thymidine phosphorylase on macrophages in glioblastoma multiforme. J. Neurosurg. 95, 89–95.
Hombach-Klonisch, S., Mehrpour, M., Shojaei, S., Harlos, C., Pitz, M., Hamai, A., Siemianowicz, K., Likus, W., Wiechec, E., Toyota, B.D., Hoshyar, R., Seyfoori, A., Sepehri, Z., Ande, S.R., Khadem, F., Akbari, M., Gorman, A.M., Samali, A., Klonisch, T., Ghavami, S., 2017. Glioblastoma and chemoresistance to alkylating agents: involvement of apoptosis, autophagy, and unfolded protein response. Pharmacol. Ther.
Honorato, J., de Faria Lopes, G.P., Basile, G., Moura-Neto, V., Spohr, T., 2018. Sonic Hedgehog Inhibition in Glioblastoma Potentializes Temozolomide Effect? CLINICAL CANCER RESEARCH, AMER ASSOC CANCER RESEARCH 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA 19106-4404 USA, pp. 91.
Hu, B., Wang, Q., Wang, Y.A., Hua, S., Sauvé, C.-E.G., Ong, D., Lan, Z.D., Chang, Q., Ho, Y.W., Monasterio, M.M., 2016. Epigenetic activation of WNT5A drives glioblastoma stem cell differentiation and invasive growth. Cell 167, 1281–1295 e1218.
Huang, S.-M.A., Mishina, Y.M., Liu, S., Cheung, A., Stegmeier, F., Michaud, G.A., Charlat, O., Wiellette, E., Zhang, Y., Wiessner, S., 2009. Tankyrase inhibition stabilizes axin and antagonizes Wnt signalling. Nature 461, 614–620.
Iacopino, F., Angelucci, C., Piacentini, R., Biamonte, F., Mangiola, A., Maira, G., Grassi, C., Sica, G., 2014. Isolation of cancer stem cells from three human glioblastoma cell lines: characterization of two selected clones. PLoS One 9, e105166.
Ishii, A., Kimura, T., Sadahiro, H., Kawano, H., Takubo, K., Suzuki, M., Ikeda, E., 2016. Histological characterization of the tumorigenic "Peri-Necrotic Niche" harboring quiescent stem-like tumor cells in glioblastoma. PLoS One 11 e0147366.
Jackson, M., Hassiotou, F., Nowak, A., 2014. Glioblastoma stem-like cells: at the root of tumor recurrence and a therapeutic target. Carcinogenesis p. bgu243.
Jangamreddy, J.R., Ghavami, S., Grabarek, J., Kratz, G., Wiechec, E., Fredriksson, B.A., Rao Pariti, R.K., Cieslar-Pobuda, A., Panigrahi, S., Los, M.J., 2013. Salinomycin induces activation of autophagy, mitophagy and affects mitochondrial polarity: differences between primary and cancer cells. Biochim. Biophys. Acta 1833, 2057–2069.
Jangamreddy, J.R., Jain, M.V., Hallbeck, A.L., Roberg, K., Lotfi, K., Los, M.J., 2015. Glucose starvation-mediated inhibition of salinomycin induced autophagy amplifies cancer cell specific cell death. Oncotarget 6, 10134–10145.
Kalani, M.Y.S., Cheshier, S.H., Cord, B.J., Bababeygy, S.R., Vogel, H., Weissman, I.L., Palmer, T.D., Nusse, R., 2008. Wnt-mediated self-renewal of neural stem/progenitor cells. Proc. Natl. Acad. Sci. 105, 16970–16975.
Kaloshi, G., Mokhtari, K., Carpentier, C., Taillibert, S., Lejeune, J., Marie, Y., Delattre, J.-Y., Godbout, R., Sanson, M., 2007. FABP7 expression in glioblastomas: relation to prognosis, invasion and EGFR status. J. Neurooncol. 84, 245–248.
Kaneko, Y., Sakakibara, S., Imai, T., Suzuki, A., Nakamura, Y., Sawamoto, K., Ogawa, Y., Toyama, Y., Miyata, T., Okano, H., 2000. Musashi1: an evolutionally conserved marker for CNS progenitor cells including neural stem cells. Dev. Neurosci. 22, 139–153.
Kardosh, A., Golden, E.B., Pyrko, P., Uddin, J., Hofman, F.M., Chen, T.C., Louie, S.G., Petasis, N.A., Schönthal, A.H., 2008. Aggravated endoplasmic reticulum stress as a basis for enhanced glioblastoma cell killing by bortezomib in combination with celecoxib or its non-coxib analogue, 2, 5-dimethyl-celecoxib. Cancer Res. 68, 843–851.
Kim, E., Kim, M., Woo, D.-H., Shin, Y., Shin, J., Chang, N., Oh, Y.T., Kim, H., Rheey, J., Nakano, I., 2013. Phosphorylation of EZH2 activates STAT3 signaling via STAT3 methylation and promotes tumorigenicity of glioblastoma stem-like cells. Cancer Cell 23, 839–852.
Kohanbash, G., Okada, H., 2012. Myeloid-derived suppressor cells (MDSCs) in gliomas and glioma-development. Immunol. Invest. 41, 658–679.
Koppens, M., Van Lohuizen, M., 2016. Context-dependent actions of Polycomb repressors in cancer. Oncogene 35, 1341–1352.
Koschmann, C., Zamler, D., MacKay, A., Robinson, D., Wu, Y.-M., Doherty, R., Marini, B., Tran, D., Garton, H., Muraszko, K., 2016. Characterizing and Targeting PDGFRA Alterations in Pediatric High-grade Glioma.
Lathia, J.D., Liu, H., 2017. Overview of Cancer stem cells and stemness for community oncologists. Target. Oncol. 12, 387–399.
Lee, Y., Kim, K.H., Kim, D.G., Cho, H.J., Kim, Y., Rheey, J., Shin, K., Seo, Y.J., Choi, Y.-S., Lee, J.-I., 2015. FoxM1 promotes stemness and radio-resistance of glioblastoma by regulating the master stem cell regulator Sox2. PLoS One 10, e0137703.
Lee, Y., Lee, J.-K., Ahn, S.H., Lee, J., Nam, D.-H., 2016. WNT signaling in glioblastoma and therapeutic opportunities. Lab. Investig. 96, 137–150.
Li, Y., Guessous, F., Zhang, Y., DiPierro, C., Kefas, B., Johnson, E., Marcinkiewicz, L., Jiang, J., Yang, Y., Schmittgen, T.D., 2009. MicroRNA-34a inhibits glioblastoma growth by targeting multiple oncogenes. Cancer Res. 69, 7569–7576.
Li, W., Zhang, H., Assaraf, Y.G., Zhao, K., Xu, X., Xie, J., Yang, D.-H., Chen, Z.-S., 2016. Overcoming ABC transporter-mediated multidrug resistance: molecular mechanisms and novel therapeutic drug strategies. Drug Resist. Updates 27, 14–29.
Liang, J., Piao, Y., Holmes, L., Fuller, G.N., Henry, V., Tiao, N., de Groot, J.F., 2014. Neutrophils promote the malignant glioma phenotype through S100A4. Clin. Cancer Res. 20, 187–198.
Liao, H., Bai, Y., Qiu, S., Zheng, L., Huang, L., Liu, T., Wang, X., Liu, Y., Xu, N., Yan, X., 2015. MiR-203 downregulation is responsible for chemoresistance in human glioblastoma by promoting epithelial-mesenchymal transition via SNAI2. Oncotarget 6, 8914.
Liu, Y., Yan, W., Zhang, W., Chen, L., You, G., Bao, Z., Wang, Y., Wang, H., Kang, C., Jiang, T., 2012. MiR-218 reverses high invasiveness of glioblastoma cells by targeting the oncogenic transcription factor LEF1. Oncol. Rep. 28, 1013–1021.
Livney, Y.D., Assaraf, Y.G., 2013. Rationally designed nanovehicles to overcome cancer chemoresistance. Adv. Drug Deliv. Rev. 65, 1716–1730.
Lv, Z., Yang, L., 2013. MiR-124 inhibits the growth of glioblastoma through the down-regulation of SOS1. Mol. Med. Rep. 8, 345–349.
Ma, Y., Yu, W., Shrivastava, A., Alemi, F., Lankachandra, K., Srivastava, R.K., Shankar, S., 2017. Sanguinarine inhibits pancreatic cancer stem cell characteristics by inducing oxidative stress and suppressing sonic hedgehog-Gli-Nanog pathway. Carcinogenesis 38, 1047–1056.
Mack, S.C., Hubert, C.G., Miller, T.E., Taylor, M.D., Rich, J.N., 2016. An epigenetic gateway to brain tumor cell identity. Nat. Neurosci. 19, 10–19.
Mantovani, A., Sozzani, S., Locati, M., Allavena, P., Sica, A., 2002. Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. Trends Immunol. 23, 549–555.
Mathew, L.K., Skuli, N., Mucaj, V., Lee, S.S., Zinn, P.O., Sathyan, P., Imtiyaz, H.Z., Zhang, Z., Davuluri, R.V., Rao, S., 2014. miR-218 opposes a critical RTK-HIF pathway in mesenchymal glioblastoma. Proc. Natl. Acad. Sci. 111, 291–296.
Mathiisen, T.M., Lehre, K.P., Danbolt, N.C., Ottersen, O.P., 2010. The perivascular

astroglial sheath provides a complete covering of the brain microvessels: an electron microscopic 3D reconstruction. Glia 58, 1094–1103.
Mazzoleni, S., Politi, L.S., Pala, M., Cominelli, M., Franzin, A., Sergi, L.S., Falini, A., De Palma, M., Bulfone, A., Poliani, P.L., 2010. Epidermal growth factor receptor expression identifies functionally and molecularly distinct tumor-initiating cells in human glioblastoma multiforme and is required for gliomagenesis. Cancer Res. 70, 7500–7513.
McCord, A.M., Jamal, M., Williams, E.S., Camphausen, K., Tofilon, P.J., 2009. CD133+ glioblastoma stem-like cells are radiosensitive with a defective DNA damage response compared with established cell lines. Clin. Cancer Res. 15, 5145–5153.
McLendon, R., Friedman, A., Bigner, D., Van Meir, E.G., Brat, D.J., Mastrogianakis, G.M., Olson, J.J., Mikkelsen, T., Lehman, N., Aldape, K., 2008. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature 455, 1061–1068.
Mengxian, Z., Kleber, S., Roehrich, M., Timke, C., Han, N., Tuettenberg, J., Martin-Villalba, A., Debus, J., Peschke, P., Wirkner, U., 2011. Blockade of TGF-beta signaling by the TGFβR-I kinase Inhibitor LY2109761 enhances radiation response and prolongs survival in glioblastoma. Cancer Res p. canres. 1212.2011.
Møller, H.G., Rasmussen, A.P., Andersen, H.H., Johnsen, K.B., Henriksen, M., Duroux, M., 2013. A systematic review of microRNA in glioblastoma multiforme: micro-modulators in the mesenchymal mode of migration and invasion. Mol. Neurobiol. 47, 131–144.
Nagarajan, R.P., Costello, J.F., 2009. Epigenetic mechanisms in glioblastoma multiforme. Seminars in Cancer Biology. Elsevier, pp. 188–197.
Noushmehr, H., Weisenberger, D.J., Diefes, K., Phillips, H.S., Pujara, K., Berman, B.P., Pan, F., Pelloski, C.E., Sulman, E.P., Bhat, K.P., 2010. Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. Cancer Cell 17, 510–522.
Ogden, A.T., Waziri, A.E., Lochhead, R.A., Fusco, D., Lopez, K., Ellis, J.A., Kang, J., Assanah, M., McKhann, G.M., Sisti, M.B., 2008. Identification of A2B5+ CD133− tUMOR-iNITIATING cells in adult human GLIOMAS. Neurosurgery 62, 505–515.
Papagiannakopoulos, T., Friedmann-Morvinski, D., Neveu, P., Dugas, J., Gill, R., Huillard, E., Liu, C., Zong, H., Rowitch, D., Barres, B., 2012. Pro-neural miR-128 is a glioma tumor suppressor that targets mitogenic kinases. Oncogene 31, 1884–1895.
Parsons, D.W., Jones, S., Zhang, X., Lin, J.C.-H., Leary, R.J., Angenendt, P., Mankoo, P., Carter, H., Siu, I.-M., Gallia, G.L., 2008. An integrated genomic analysis of human glioblastoma multiforme. Science 321, 1807–1812.
Piccirillo, S., Reynolds, B.A., Zanetti, N., Lamorte, G., Binda, E., Broggi, G., Brem, H., Olivi, A., Dimeco, F., Vescovi, A.L., 2006. Bone morphogenetic proteins inhibit the tumorigenic potential of human brain tumour-initiating cells. Nature 444, 761–765.
Pietras, A., Katz, A.M., Ekström, E.J., Wee, B., Halliday, J.J., Pitter, K.L., Werbeck, J.L., Amankulor, N.M., Huse, J.T., Holland, E.C., 2014. Osteopontin-CD44 signaling in the glioma perivascular niche enhances cancer stem cell phenotypes and promotes aggressive tumor growth. Cell Stem Cell 14, 357–369.
Plaks, V., Kong, N., Werb, Z., 2015. The cancer stem cell niche: how essential is the niche in regulating stemness of tumor cells? Cell Stem Cell 16, 225–238.
Pointer, K.B., Clark, P.A., Zorniak, M., Alrfaei, B.M., Kuo, J.S., 2014. Glioblastoma cancer stem cells: biomarker and therapeutic advances. Neurochem. Int. 71, 1–7.
Prestegarden, L., Svendsen, A., Wang, J., Sleire, L., Skaftnesmo, K.O., Bjerkvig, R., Yan, T., Askland, L., Persson, A., Sakariassen, P.Ø., 2010. Glioma cell populations grouped by different cell type markers drive brain tumor growth. Cancer Res. 70, 4274–4279.
Pulvirenti, T., Van Der Heijden, M., Droms, L.A., Huse, J.T., Tabar, V., Hall, A., 2011. Dishevelled 2 signaling promotes self-renewal and tumorigenicity in human gliomas. Cancer Res. 71, 7280–7290.
Qian, B.-Z., Pollard, J.W., 2010. Macrophage diversity enhances tumor progression and metastasis. Cell 141, 39–51.
Richardson, P.J., 2016. CXCR4 and glioblastoma, Anti-Cancer Agents in Medicinal Chemistry. Formerly Current Medicinal Chemistry-Anti-Cancer Agents) 16, 59–74.
Rivera, L.B., Bergers, G., 2015. Intertwined regulation of angiogenesis and immunity by myeloid cells. Trends Immunol. 36, 240–249.
Rizzino, A., 2009. Sox2 and Oct-3/4: a versatile pair of master regulators that orchestrate the self-renewal and pluripotency of embryonic stem cells. Wiley Interdiscip. Rev. Syst. Biol. Med. 1, 228–236.
Rooj, A.K., Mineo, M., Ricklefs, F., Bronisz, A., Chiocca, E., Godlewski, J., 2016. The Novel Role of microRNA-128 in Proneural to Mesenchymal Subtype Transition in Glioblastoma Stem Cells by Targeting Components of Pro-oncogenic Polycomb Repressor Complex. AACR.
Safa, A.R., Saadatzadeh, M.R., Cohen-Gadol, A.A., Pollok, K.E., Bijangi-Vishehsaraei, K., 2015. Glioblastoma stem cells (GSCs) epigenetic plasticity and interconversion between differentiated non-GSCs and GSCs. Genes Dis. 2, 152–163.
Saito, N., Aoki, K., Hirai, N., Fujita, S., Iwama, J., Ikota, M., Nakayama, H., Hayashi, M., Ito, K., Sakurai, T., 2017. Notch Pathway Activation Predicts Resistance to Bevacizumab Therapy in Glioblastoma. AACR.
Samatov, T.R., Wicklein, D., Tonevitsky, A.G., 2016. L1CAM: cell adhesion and more. Prog. Histochem. Cytochem. 51, 25–32.
Sareddy, G.R., Kesanakurti, D., Kirti, P.B., Babu, P.P., 2013. Nonsteroidal anti-inflammatory drugs diclofenac and celecoxib attenuates Wnt/β-catenin/Tcf signaling pathway in human glioblastoma cells. Neurochem. Res. 38, 2313–2322.
Sarkar, S., Mirzaei, R., Zemp, F.J., Wei, W., Senger, D.L., Robbins, S.M., Yong, V.W., 2017. Activation of NOTCH signaling by Tenascin-C promotes growth of human brain tumor-initiating cells. Cancer Res. 77, 3231–3243.
Schito, L., Semenza, G.L., 2016. Hypoxia-inducible factors: master regulators of cancer progression. Trends Cancer 2, 758–770.
Schwartzentruber, J., Korshunov, A., Liu, X.-Y., Jones, D.T., Pfaff, E., Jacob, K., Sturm, D., Fontebasso, A.M., Quang, D.-A.K., Tönjes, M., 2012. Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. Nature 482, 226–231.
Seidel, S., Garvalov, B.K., Wirta, V., von Stechow, L., Schänzer, A., Meletis, K., Wolter, M., Sommerlad, D., Henze, A.-T., Nistér, M., 2010. A hypoxic niche regulates glioblastoma stem cells through hypoxia inducible factor 2α. Brain 133, 983–995.
Semenza, G.L., 2010. Defining the role of hypoxia-inducible factor 1 in cancer biology and therapeutics. Oncogene 29, 625–634.
Shahi, M.H., Farheen, S., Mariyath, M.P., Castresana, J.S., 2016. Potential role of Shh-Gli1-BMI1 signaling pathway nexus in glioma chemoresistance. Tumour Biol. 37, 15107–15114.
Silver, D.J., Lathia, J.D., 2017. Revealing the glioma Cancer stem cell interactome, one niche at a time. J. Pathol.
Singh, S.K., Clarke, I.D., Terasaki, M., Bonn, V.E., Hawkins, C., Squire, J., Dirks, P.B., 2003. Identification of a cancer stem cell in human brain tumors. Cancer Res. 63, 5821–5828.
Singh, S.K., Hawkins, C., Clarke, I.D., Squire, J.A., Bayani, J., Hide, T., Henkelman, R.M., Cusimano, M.D., Dirks, P.B., 2004. Identification of human brain tumour initiating cells. nature 432, 396–401.
Soda, Y., Marumoto, T., Friedmann-Morvinski, D., Soda, M., Liu, F., Michiue, H., Pastorino, S., Yang, M., Hoffman, R.M., Kesari, S., 2011. Transdifferentiation of glioblastoma cells into vascular endothelial cells. Proc. Natl. Acad. Sci. 108, 4274–4280.
Soeda, A., Park, M., Lee, D., Mintz, A., Androutsellis-Theotokis, A., McKay, R., Engh, J., Iwama, T., Kunisada, T., Kassam, A., 2009. Hypoxia promotes expansion of the CD133-positive glioma stem cells through activation of HIF-1α. Oncogene 28, 3949–3959.
Soehngen, E., Schaefer, A., Koeritzer, J., Huelsmeyer, V., Zimmer, C., Ringel, F., Gempt, J., Schlegel, J., 2014. Hypoxia upregulates aldehyde dehydrogenase isoform 1 (ALDH1) expression and induces functional stem cell characteristics in human glioblastoma cells. Brain Tumor Pathol. 31, 247–256.
Son, M.J., Woolard, K., Nam, D.-H., Lee, J., Fine, H.A., 2009. SSEA-1 is an enrichment marker for tumor-initiating cells in human glioblastoma. Cell Stem Cell 4, 440–452.
Speranza, M.C., Frattini, V., Pisati, F., Kapetis, D., Porrati, P., Eoli, M., Pellegatta, S., Finocchiaro, G., 2012. NEDD9, a novel target of miR-145, increases the invasiveness of glioblastoma. Oncotarget 3, 723–734.
Sun, H., Zhang, M., Cheng, K., Li, P., Han, S., Li, R., Su, M., Zeng, W., Liu, J., Guo, J., 2016. Resistance of glioma cells to nutrient-deprived microenvironment can be enhanced by CD133-mediated autophagy. Oncotarget 7, 76238.
Tessarz, P., Kouzarides, T., 2014. Histone core modifications regulating nucleosome structure and dynamics. Nat. Rev. Mol. Cell Biol. 15, 703–708.
Thanasupawat, T., Natarajan, S., Rommel, A., Glogowska, A., Bergen, H., Krcek, J., Pitz, M., Beiko, J., Krawitz, S., Verma, I.M., 2017. Dovitinib enhances temozolomide efficacy in glioblastoma cells. Mol. Oncol.
Tome-Garcia, J., Tejero, R., Nudelman, G., Yong, R.L., Sebra, R., Wang, H., Fowkes, M., Magid, M., Walsh, M., Silva-Vargas, V., 2017. Prospective isolation and comparison of human germinal matrix and glioblastoma EGFR+ populations with stem cell properties. Stem Cell Rep. 8, 1421–1429.
Torre-Healy, L.A., Berezovsky, A., Lathia, J.D., 2017. Isolation, characterization, and expansion of cancer stem cells. Adult Stem Cells: Methods Protocols 133–143.
Uribe, D., Torres, Á., Rocha, J.D., Niechi, I., Oyarzún, C., Sobrevia, L., San Martín, R., Quezada, C., 2017. Multidrug resistance in glioblastoma stem-like cells: role of the hypoxic microenvironment and adenosine signaling. Mol. Aspects Med. 140–151.
Verhaak, R.G., Hoadley, K.A., Purdom, E., Wang, V., Qi, Y., Wilkerson, M.D., Miller, C.R., Ding, L., Golub, T., Mesirov, J.P., 2010. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. Cancer Cell 17, 98–110.
Wang, C.-H., Chiou, S.-H., Chou, C.-P., Chen, Y.-C., Huang, Y.-J., Peng, C.-A., 2011. Photothermolysis of glioblastoma stem-like cells targeted by carbon nanotubes conjugated with CD133 monoclonal antibody. Nanomed. Nanotechnol. Biol. Med. 7, 69–79.
Wang, J., Wang, C., Meng, Q., Li, S., Sun, X., Bo, Y., Yao, W., 2012. siRNA targeting Notch-1 decreases glioma stem cell proliferation and tumor growth. Mol. Biol. Rep. 39, 2497–2503.
Wang, X.-R., Luo, H., Li, H.-L., Cao, L., Wang, X.-F., Yan, W., Wang, Y.-Y., Zhang, J.-X., Jiang, T., Kang, C.-S., 2013. Overexpressed let-7a inhibits glioma cell malignancy by directly targeting K-ras, independently of PTEN. Neurooncology 15, 1491–1501.
Wasik, A.M., Grabarek, J., Pantovic, A., Cieslar-Pobuda, A., Asgari, H.R., Bundgaard-Nielsen, C., Rafat, M., Dixon, I.M., Ghavami, S., Los, M.J., 2014. Reprogramming and carcinogenesis–parallels and distinctions. Int. Rev. Cell Mol. Biol. 308, 167–203.
Wee, B., Pietras, A., Ozawa, T., Bazzoli, E., Podlaha, O., Antczak, C., Westermark, B., Nelander, S., Uhrbom, L., Forsberg-Nilsson, K., 2016. ABCG2 regulates self-renewal and stem cell marker expression but not tumorigenicity or radiation resistance of glioma cells. Sci. Rep. 6.
Wickström, M., Dyberg, C., Milosevic, J., Einvik, C., Calero, R., Sveinbjörnsson, B., Sandén, E., Darabi, A., Siesjö, P., Kool, M., 2015. Wnt/β-catenin pathway regulates MGMT gene expression in cancer and inhibition of Wnt signalling prevents chemoresistance. Nat. Commun. 6.
Witt, A., Lee, C., Lee, T., Azzam, D., Wang, B., Caslini, C., Petrocca, F., Grosso, J., Jones, M., Cohick, E., 2016. Identification of a cancer stem cell-specific function for the histone deacetylases, HDAC1 and HDAC7, in breast and ovarian cancer. Oncogene.
Xia, H., Cheung, W.K., Ng, S.S., Jiang, X., Jiang, S., Sze, J., Leung, G.K., Lu, G., Chan, D.T., Bian, X.-W., 2012. Loss of brain-enriched miR-124 microRNA enhances stem-like traits and invasiveness of glioma cells. J. Biol. Chem. 287, 9962–9971.
Xipell, E., Gonzalez-Huarriz, M., Martinez de Irujo, J.J., Garcia-Garzon, A., Lang, F.F., Jiang, H., Fueyo, J., Gomez-Manzano, C., Alonso, M.M., 2016. Salinomycin induced ROS results in abortive autophagy and leads to regulated necrosis in glioblastoma. Oncotarget 7, 30626–30641.
Xu, Y., Stamenkovic, I., Yu, Q., 2010. CD44 attenuates activation of the hippo signaling

pathway and is a prime therapeutic target for glioblastoma. Cancer research 70, 2455–2464.
Xu, J., Liao, X., Lu, N., Liu, W., Wong, C.W., 2011. Chromatin-modifying drugs induce miRNA-153 expression to suppress Irs-2 in glioblastoma cell lines. Int. J. Cancer 129, 2527–2531.
Yi, G.-z., Liu, Y.-w., Xiang, W., Wang, H., Chen, Z.-y., Qi, S.-t., 2016. Akt and β-catenin contribute to TMZ resistance and EMT of MGMT negative malignant glioma cell line. J. Neurol. Sci. 367, 101–106.
Zagzag, D., Lukyanov, Y., Lan, L., Ali, M.A., Esencay, M., Mendez, O., Yee, H., Voura, E.B., Newcomb, E.W., 2006. Hypoxia-inducible factor 1 and VEGF upregulate CXCR4 in glioblastoma: implications for angiogenesis and glioma cell invasion. Lab. Investig. 86, 1221–1232.
Zbinden, M., Duquet, A., Lorente-Trigos, A., Ngwabyt, S.N., Borges, I., i Altaba, A.R., 2010. NANOG regulates glioma stem cells and is essential in vivo acting in a cross-functional network with GLI1 and p53. EMBO J. 29, 2659–2674.
Zhang, Y., Chao, T., Li, R., Liu, W., Chen, Y., Yan, X., Gong, Y., Yin, B., Qiang, B., Zhao, J., 2009. MicroRNA-128 inhibits glioma cells proliferation by targeting transcription factor E2F3a. J. Mol. Med. 87, 43–51.
Zhang, J., Sun, C., Yu, S., Wang, Q., An, T., Li, Y., Kong, Y., Wen, Y., 2011. Relationship between miR-218 and CDK6 expression and their biological impact on glioma cell proliferation and apoptosis. Zhonghua bing li xue za zhi Chin. J. Pathol. 40, 454–459.
Zhang, Y., Kim, J., Mueller, A., Dey, B., Yang, Y., Lee, D., Hachmann, J., Finderle, S., Park, D., Christensen, J., 2014. Multiple receptor tyrosine kinases converge on microRNA-134 to control KRAS, STAT5B, and glioblastoma. Cell Death Differ. 21, 720–734.
Zhao, S., Deng, Y., Liu, Y., Chen, X., Yang, G., Mu, Y., Zhang, D., Kang, J., Wu, Z., 2013. MicroRNA-153 is tumor suppressive in glioblastoma stem cells. Mol. Biol. Rep. 40, 2789–2798.
Zhao, H.-f., Wang, J., Shao, W., Wu, C.-p., Chen, Z.-p., To, S.-s.T., Li, W.-p., 2017. Recent advances in the use of PI3K inhibitors for glioblastoma multiforme: current pre-clinical and clinical development. Mol. Cancer 16, 100.
Zheng, H., Ying, H., Yan, H., Kimmelman, A.C., Hiller, D.J., Chen, A.-J., Perry, S.R., Tonon, G., Chu, G.C., Ding, Z., 2008. p53 and Pten control neural and glioma stem/progenitor cell renewal and differentiation. Nature 455, 1129–1133.
Zheng, H., Ying, H., Wiedemeyer, R., Yan, H., Quayle, S.N., Ivanova, E.V., Paik, J.-H., Zhang, H., Xiao, Y., Perry, S.R., 2010. PLAGL2 regulates Wnt signaling to impede differentiation in neural stem cells and gliomas. Cancer Cell 17, 497–509.
Zhou, W., Ke, S.Q., Huang, Z., Flavahan, W., Fang, X., Paul, J., Wu, L., Sloan, A.E., McLendon, R.E., Li, X., 2015a. Periostin secreted by glioblastoma stem cells recruits M2 tumour-associated macrophages and promotes malignant growth. Nat. Cell Biol. 17, 170–182.
Zhou, W., Ke, S.Q., Huang, Z., Flavahan, W., Fang, X., Paul, J., Wu, L., Sloan, A.E., McLendon, R.E., Li, X., Rich, J.N., Bao, S., 2015b. Periostin secreted by glioblastoma stem cells recruits M2 tumour-associated macrophages and promotes malignant growth. Nat. Cell Biol. 17, 170–182.
Zhu, Y., Yu, T., Zhang, X.-C., Nagasawa, T., Wu, J.Y., Rao, Y., 2002. Role of the chemokine SDF-1 as the meningeal attractant for embryonic cerebellar neurons. Nat. Neurosci. 5, 719–720.
Zuccarini, M., Giuliani, P., Ziberi, S., Carluccio, M., Iorio, P.D., Caciagli, F., Ciccarelli, R., 2018. The role of wnt signal in glioblastoma development and progression: a possible new pharmacological target for the therapy of this tumor. Genes 9, 105.