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Glioblastoma and resistance to radiotherapy: role of cancer stem cells subpopulations, hypoxia and therapeutic strategies

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ABSTRACT

Glioblastoma is the most aggressive primary brain tumor in adults, characterized by rapid progression, resistance to therapy, and inevitable recurrence. Despite standard treatment—surgical resection, X-ray radiotherapy, and temozolomide chemotherapy—prognosis remains poor. Growing evidence indicates that glioma stem cells (GSCs) and hypoxia drive this resistance and recurrence.

This review examines distinct GSC subtypes: mesenchymal GSCs, the most aggressive and invasive; proneural GSCs, which are more radiosensitive but highly proliferative and contribute to recurrence; and slow-cycling GSCs, which, though less well understood, are of growing interest due to their activation and deactivation during radiotherapy or through as-yet-unknown mechanisms. Hypoxia, a hallmark of the glioblastoma microenvironment, maintains these stem cells in a dedifferentiated state. As a key regulator, hypoxia orchestrates radioresistance mechanisms and promotes stem-like cell persistence through processes such as epithelial-mesenchymal transition-like (EMT-like), proneural-mesenchymal transition (PMT), or the reprogramming of differentiated cancer cells into GSCs.

The review concludes by highlighting therapeutic strategies under development to overcome radioresistance, including targeting GSCs, hypoxia, or employing alternative irradiation modalities beyond X-ray radiotherapy.

Introduction

Glioblastoma (GBM) is the most aggressive brain tumor in adults. The standard treatment consist of surgical resection followed by X-ray radiotherapy (RT) delivered in 30 fractions of 2 Gy combined with temozolomide chemotherapy, and adjuvant therapy with tumor treating fields [1,2]. Despite this multimodal protocol, prognosis remains poor with a median survival is 15 months and a 5-year survival rate of <2.7% [1].

The poor prognosis can be attributed to GBM pathophysiology, characterized by highly invasive and rapidly proliferating cells, a hypoxic tumor microenvironment that promotes angiogenesis, and additional adaptive mechanisms favoring tumor progression. These features contribute to near-universal recurrence, underscoring the presence of resistant cell populations and the limitations of current treatments.

Surgical resection, although essential, cannot achieve complete tumor removal due to presence of infiltrative tumor cells. Chemotherapy efficacy, is frequently compromised by MGMT promoter unmethylated status in about 60% of patients, which preserves MGMT expression, enhances DNA mismatch repair, and reduces the benefit of temozolomide [3]. Finally, RT, a cornerstone of standard treatment, faces similar limitations: most recurrence occur within the irradiated field and its efficacy is significantly diminished under hypoxic conditions [4].

In light of GBM's resistance to conventional treatments, a particularly resilient cell population has been identified: glioma stem cells (GSC). These cells drive tumor recurrence and employ specific mechanisms to survive radiation therapy. This review focuses on GSC, their characteristics, and their role in resistance to ionizing radiation resistance.

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Hypoxic microenvironment and GSC subtypes in GBM

GBM microenvironment

Tumors can be modeled as multi-compartment systems, comprising a tumor microenvironment with diverse cell types. This review focuses on the hypoxic microenvironment in glioblastoma (GBM) and its role in tumor survival, progression, and aggressiveness. Understanding these mechanisms is critical for elucidating GBM radioresistance.

Tumor microenvironment

Hypoxia – Hypoxia is a hallmark of the GBM microenvironment, defined by reduced oxygen partial pressure (<10 mmHg) relative to normal brain tissue. Hypoxia allows the activation of the transcriptional Hypoxia-Inducible Factors (HIF, Fig. 1). HIF is a heterodimer comprising α and β subunits with three α isoforms: HIF-1α (encoded by *HIF1A* gene), HIF-2α (also known as Endothelial PAS domain-containing protein (EPAS-1), encoded by *EPAS1* gene), and HIF-3α (encoded by *HIF3A* gene). Under normoxia, the α subunit undergoes rapid degradation *via* prolyl hydroxylation and von Hippel-Lindau (VHL) mediated ubiquitination. Under hypoxia, the degradation of the α subunit is inhibited since prolyl hydroxylase domain enzymes (PHDs), which require oxygen, cannot hydroxylate proline residues, preventing VHL-mediated ubiquitination. This leads to α subunit stabilization and its nuclear translocation, where it dimerizes with the β subunit, HIF-1β (also known as Aryl Hydrocarbon Receptor Nuclear Translocator (ARNT), encoded by *ARNT* gene) [5]. The resulting heterodimer, termed as HIF1, HIF2 or HIF3 according to the subunit α isoform, binds to hypoxia response elements, promoting expression of HIF-target genes involved in cell survival, proliferation, angiogenesis, metabolic switch, immunity, invasion and metastases, stemness, extracellular matrix modification, processes that collectively drive treatment resistance (Table 1).

The advent of CRISPR/Cas9 technology enables specific and stable inhibition of the expression of HIF-1 and/or HIF-2 factors. Using this approach, Wang et al. revealed the complex interplay between HIF-1 and HIF-2 in maintaining GBM stem cell characteristics and tumor progression. In this study, they demonstrated that the HIF-1/HIF-2/hsa-miR-210-3p network drives malignant progression of GBM *via* a positive feedback loop with EGF. Notably, inhibiting a single factor has limited effects, whereas simultaneous inactivation, reduced stem cell markers and impaired the formation of gliospheres [6]. Further cell cycle analysis revealed a shift toward the G2/M + S phase, with accelerated proliferation but significantly reduced stemness and invasive character [7]. Additionally, the knockout of both factors sensitized cells to chemotherapy [8].

More recently, hypoxia has also been shown to induce microRNAs expression, with over 130 identified as hypoxia-inducible. The most well-studied, hsa-miR-210-3p, enhances HIF transcriptional activity, upregulates target genes such as vascular endothelial growth factor-A (*VEGF-A*) and carbonic anhydrase 9 (*CA9*), while also promoting hypoxic survival and chemoresistance in GBM cells [6].

Cell heterogeneity

Differentiated tumor cells – These cells represent the majority of tumor cells and are characterized by rapid proliferation and invasion. They consume large quantities of nutrients and oxygen supplied by the blood vessels and can be identified by the expression of GFAP or NeuN markers. They also exhibit a transcriptional signature, including increased activation of the YAP/TAF/TEAD pathway, with the CC1 protein enabling macrophage recruitment of [9].

Glioma stem cells – Since the 1960s, the presence of cancer stem cells has been demonstrated in numerous tumors [10] including GBM [11]. These cells can be identified by specific markers, such as CD133, CD44, CD15, LICAM, SOX-2, NANOG, OLIG2, NESTIN, ID1 or A2B5 [12] and are often located in specific niches (*see "Locations of GSC" for details*), which protect them from the effects of radiotherapy and chemotherapy [13]. GSC have the capacity of self-renewal, indefinite proliferation, tumor initiation, and differentiation into heterogeneous tumor cell populations. *In vitro*, these cells can form spheroids, called gliospheres, due to their clustering and suspension in a dedifferentiation medium (serum- depleted and enriched in growth factors such as EGF and FGF-2), which enables them to survive RT treatments [13] and relapse [14]. *In vivo*, GSC have been described as capable of initiating new tumors [11]. They represent a highly heterogeneous population, which

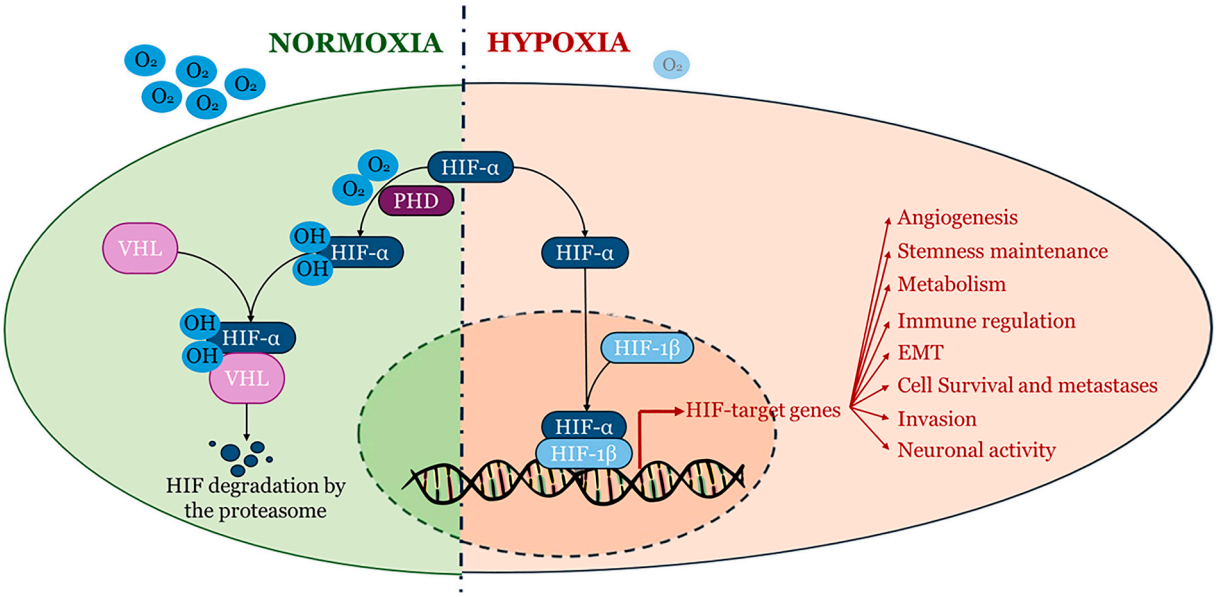


Fig. 1. HIF regulation under normoxia and hypoxia Schematic representation of the cellular regulation of hypoxia-inducible factors (HIF) according to oxygen availability. Under normoxic conditions, Prolyl Hydroxylase Domain enzyme (PHD) hydroxylate the α subunit of HIF, allowing recognition by the Von Hippel–Lindau protein (VHL) and subsequent ubiquitination and proteasomal degradation. Under hypoxic conditions, hydroxylation is inhibited by the lack of oxygen, leading to α subunit stabilization and nuclear translocation. The α subunit then heterodimerizes with HIF-1β, binds to Hypoxia-Responsive Elements (HRE) in target gene promoters, and activates the transcription of genes involved in a cancer progression and resistance to treatments.

Table 1
Hypoxia Target Genes in *homo sapiens*.

Signaling pathway	Official gene symbol	NCBI GeneID	Full name	Role	HIF-1 or HIF-2 activation	Pro-oncogenic action	References
Metabolism	*GLUT1*	38109	Glucose Transporter 1	Glucose transporter that increases glucose uptake	HIF-1	Induces Warburg Effect	Wolf et al., 2011 https://doi.org/10.1084/jem.20101470
	GLUT3	6515	Glucose Transporter 3	Glucose transporter that increases glucose uptake	HIF-1	Induces Warburg Effect	Yu et al., 2012 https://doi.org/10.1016/j.brainres.2011.10.046
	HKII	3099	Hexokinase II	Enzyme that phoshorylates gluocse to create glucose-6 phosphate for the initiale step of glycolysis	HIF-1	Enables aerobic glycolytic metabolism, leading to therapeutic resistance and promoting tumor growth	Wolf et al., 2011 https://doi.org/10.1084/jem.20101470
	CA9	768	Carbonic Anhydrase-9	Regulates pH by converting CO_2 to bicarbonate and protons	HIF-1	Identifies CA-IX expression as an independent factor associated with poor survival in patients with GBM	Said et al., 2013 & Proescholdt et al., 2012 https://doi.org/10.1016/j.bmc.2013.03.068 & https://doi.org/10.1093/neuonc/nos216
	PGK1	5230	Phosphoglycerate Kinase 1	Key enzyme in glycolysis	HIF-1	Inhibits the conversion of pyruvate to acetyl-CoA through the upregulation of PDK1	Guo et al., 2024 https://doi.org/10.1038/s41467-024-51,232-w
	PDK1	5163	Pyruvate Dehydrogenase Kinase	Mitochondrial enzyme	HIF-1	Selectively inhibits pyruvate dehydrogenase, promoting increased cytosolic glycolysis and lactate production	Velpula et al., 2013 https://doi.org/10.1158/0008-5472.CAN-13-1868
	GAPDH	2597	Glyceraldehyde-3-phosphate dehydrogenase	Glycolytic enzyme	HIF-1	Promotes anaerobic glycolysis and participates in the regulation of apoptosis	Velpula et al., 2013 https://doi.org/10.1158/0008-5472.CAN-13-1868
	G6PD	2539	Glucose-6-phosphate dehydrogenase	Glycolytic enzyme	HIF-1	Provides NADPH for biosynthesis and antioxidant defense	Chettimada et al., 2015 https://doi.org/10.1152/ajplung.00229.2014
	MCT4	9122	Solute carrier family 16 member 4	Lactate transporter produced by anaerobic glycolysis	HIF-1	Maintains glycolysis by removing excess lactate and acidifying the tumor microenvironment	Dimmer et al., 2000 PMC1221245
	LDH-A	3939	Lactate Dehydrogenase A	Converts pyruvate to lactate to sustain glycolysis	HIF-1	Promotes lactate accumulation under hypoxia, leading to stabilization of HIF-1α	Li et al., 2025 https://doi.org/10.1186/s12964-025-02366-x
Invasion, metastasis	*MMP2*	4313	Matrix Metalloproteinase 2	Degrades ECM to facilitate invasion	HIF-1	Promotes tumor invasion, cell migration, and metastasis formation.	Fujiwara et al., 2007 https://doi.org/10.3892/ijo.30.4.793
	MMP9	4318	Matrix Metalloproteinase 9	Degrades ECM to facilitate invasion	HIF-1	Promotes tumor invasion, cell migration, and metastasis formation.	Fujiwara et al., 2007 https://doi.org/10.3892/ijo.30.4.793
	PAI-1 (SERPINE1)	5054	Plasminogen Activator Inhibitor type 1	Inhibitor of uPA system, a cancer suppressor	HIF-1	Is upregulated under hypoxic conditions. Depends on ROS to facilitate migration and invasion	Zhang et al., 2023 https://doi.org/10.1631/jzus.B2200269
	ANGPTL4	51129	Angiopoietin-Like 4 protein	Secreted glycoprotein, regulates angiogenesis and lipid metabolism	HIF-1	Facilitates wound healing, modulates vascular permeability, and regulates ROS levels	Chedeville et al., 2020 https://doi.org/10.3390/biomedicines8090310
Stemness	*OCT3/4*	5460	POU class 5 homeobox 1	Transcription factors	HIF-1 & HIF-2	Maintains CSC state	Zeng et al., 2018 https://doi.org/10.3892/ol.2018.9442
	NANOG	79923	Nanog homeobox	Transcription factor	HIF-2	Contributes to the induction of malignancy in CSCs	Yuan et al., 2020 & Petruzzlli et al., 2014 https://doi.org/10.2741/4907 & https://doi.org/10.1371/journal.pone.0108309
	PROM1	8842	Prominin 1	Membrane glycoprotein	HIF-1 & HIF-2	Acts as a cancer stem cell marker and promotes self-renewal	Ohnishi et al., 2013 https://doi.org/10.1371/journal.pone.0066255

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Table 1 (*continued*)

Signaling pathway	Official gene symbol	NCBI GeneID	Full name	Role	HIF-1 or HIF-2 activation	Pro-oncogenic action	References
	SOX2	6657	Sex determining region Y-box 2	Maintain stem cell-like characteristics	HIF-1 & HIF-2	Induces pluripotent stem cell traits and promotes glioma cell chemoresistance	Wang et al., 2022 https://doi.org/10.7150/jca.54
	VEGF-A	7422	Vascular Endothelial Growth Factor A	Stimulates blood vessel formation	HIF-1 & HIF-2	Promotes glioma growth and tumoral angiogenesis	Jensen et al., 2006 https://doi.org/10.1007/s11060-005-9103-z
	PDGFRB	5159	Platelet derived growth factor	Regulate cell growth and division	HIF-1	Activates PI3K/AKT and MAPK/RAS signaling pathways, promoting tumor aggressiveness	Xiu-Ying et al., 2024 & Schito et al., 2012 https://doi.org/10.1038/s41598-024-54,801-7 & https://doi.org/10.1073/pnas.1214019109
	EPO	2056	Epythropoietin	Hormone that stimulates erythropoiesis	HIF-2	Activates the ERK pathway, promoting angiogenesis and tumor growth	Pérès et al., 2015 & Sena et al., 2014 https://doi.org/10.1016/j.yexcr.2011.06.011 & https://doi.org/10.1158/1541-7786.MCR-13-0607
	ADM	133	Adrenomedullin	Induces vasodilation and promotes angiogenesis	HIF-1 & HIF-2	Ameliorates the EMT	Kitamuro et al., 2000 & Sena et al., 2014 https://doi.org/10.1046/j.1471-4159.2000.0751826.x & https://doi.org/10.1158/1541-7786.MCR-13-0607
Vasocontrol/ Angiogenesis	*ENG*	2022	Endoglin	Integral membrane glycoprotein	HIF-1	Functions as an accessory component of the TGF-β receptor complex, contributing to the distinction between normal vessels and malignant neovascularization	Clara et al., 2014 https://doi.org/10.1111/neup.12111
	ANGTP2	285	Angiopoietin-2	Regulates vascular permeability and angiogenesis	HIF-1	Promotes tumoral angiogenesis and invasiveness	Simon et al., 2008 https://doi.org/10.1002/jcp.21558
	NOS2	4843	Nitric oxide synthase 2	Produces nitric oxide, regulating vasodilation, cell signaling and immunity.	HIF-1	Promotes angiogenesis, tumor survival, and invasion by modulating HIF-1α, cell migration, and immune escape	Heunecke et al., 2014 https://doi.org/10.1073/pnas.1401799111
	ET1	1906	Endothelin 1	Vasoactive peptide secreted by endothelial cells	HIF-1	Promotes proliferation, angiogenesis, invasion, and resistance to apoptosis through activation of the MAPK and PI3K/AKT pathways	Bagnato et al., 2008 https://doi.org/10.1139/Y08-058
	FN1	2335	Fibronectin 1	Protein of extracellar matrix	HIF-1	Mediates EGFR phosphorylation	Mao et al., 2023 https://doi.org/10.1038/s41419-023-05788-y
	Snail	6615	Snail Family Transcriptional Repressor 1	Transcription factor	HIF-1	Stabilizes mesenchymal markers *via* HIF and recruits the Notch intracellular domain	Zhu et al., 2021 33,575,089
Epithelial Mesenchymal Transition & Proneural Mesenchymal Transition	*Twist*	7291	Twist Family bHLH transcription factor 1	Transcription factor	HIF-1	Stabilizes mesenchymal markers *via* HIF, stimulates EMT, and limits E-cadherin synthesis	Yang et al., 2023 https://doi.org/10.1002/tox.23785
	CXCR4	7852	C-X-C Motif Chemokine Receptor 4	Receptor of CXCL12 play a role in immunity	HIF-1	Enhances tumor cell migration	Zagzag et al., 2006 https://doi.org/10.1038/labinvest.3700482
	LOX	4015	Lysyl Oxidase	Enzyme involved in the remodeling of the extracellular matrix	HIF-1	Induces tumor neovascularization and promotes metastasis	Kore et al., 2018 https://doi.org/10.1016/j.bbrep.2018.03.008
	BCL2	596	B-Cell Lymphoma 2	Anti-apoptotic protein of the Bcl-2 family	HIF-1	Confers resistance to apoptosis	Freeland et al., 2001 & Chen et al., 2009 https://doi.org/10.1016/s0169-328x(01)00158-9 & https://doi.org/10.1631/jzus.B2200269
Cell survival	*BCLXL*	1057	B-Cell Lymphoma extra long	Anti-apoptotic protein of the Bcl-2 family	HIF-1	Confers resistance to apoptosis and therapeutic agents by inhibiting Bax and Bak activation	Chen et al., 2009 https://doi.org/10.1074/jbc.M805997200

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Table 1 (*continued*)

Signaling pathway	Official gene symbol	NCBI GeneID	Full name	Role	HIF-1 or HIF-2 activation	Pro-oncogenic action	References
	BNIP3	664	Bcl-2/adenovirus E1B19 kDa interacting protein 3	Regulated pro-apoptotic protein, autophagy inducer	HIF-1	Activates autophagy, promoting survival and resistance to metabolic stress	Sowter et al., 2001 11,559,532
	Survivin	332	Survivin	Member of the Inhibitor of Apoptosis (IAP)	HIF-1	Confers resistance to apoptosis	Yang et al., 2004 https://doi.org/10.1038/sj.gt.3302280
	VSIR	64115	V-domain Ig suppressor of T-cell activation	B7 family negative checkpoint modulator	HIF-1	Inhibits T-cell function and proliferation	Deng et al., 2019 https://doi.org/10.1158/2326-6066.CIR-18-0507
	CD47	961	Cluster of differenciation 47	Integrin-associated protein Transmembrane immuno checkpoint protein	HIF-1	Induces immune escape by preventing tumor cell phagocytosis	Liu et al., 2024 https://doi.org/10.1007/s12672-023-00836-7
	CD70	970		Ligand expressed on activated lymphocytes	HIF-2	Promotes immune escape when overexpressed in tumors	Kitajima et al., 2018 10.18632/oncotarget.24919
	CD73	4907	Ecto-5′-nucleotidase	Enzyme that converts extracellular AMP to adenosine	HIF-1	Promotes tumor growth and immune resistance	Synnestvedt et al., 2002 https://doi.org/10.1172/JCI15337
	TNFRSF9	3607	TNF receptor superfamily member 9	Co-stimulatory receptor expressed on activated T lymphocytes	HIF-1 & HIF-2	Drive proliferation, IL-2 production, and increased cytolytic activity	Phan et al., 2015 https://doi.org/10.1016/j.molimm.2015.08.004
Immunity	*HLA-G*	3135	Human leukocyte antigen G	Immune checkpoint marker HLA-G Gene of the major histocompatibility complex	HIF-1	Blocks CD94/NKG2 receptors on activated T cells, preventing recognition by $CD8^+$ T cells	Sasaki et al., 2016 & Garziera et al., 2017 https://doi.org/10.1002/eji.201545835 https://doi.org/10.1155/2017/4587520
	CTLA4	1493	Cytotoxic T-lymphocyte associated protein 4	Member of the immunoglobulin superfamily and is expressed by activated T cells	HIF-1	Increases tumor immune escape	Hu et al., 2021 https://doi.org/10.7717/peerj.11306
	LAG3	3902	Lymphocyte activation gene-3	Inhibitory receptor expressed on activated T cells/NK cells	HIF-1 & HIF-2	Contributes to lymphocyte depletion and immune evasion	Hu et al., 2021 / Veliça et al., 2021 https://doi.org/10.7717/peerj.11306 / https://doi.org/10.1158/2326-6066.CIR-20-0561
	PD-L1	29126	Programmed death ligand 1	Immune checkpoint marker HLA-G Up-regulated on MDSC	HIF-1 & HIF-2	Mediates MDSC-dependent T-cell suppression by modulating cytokine production, including IL-6 and IL-10	Norman et al., 2014 https://doi.org/10.1084/jem.20131916

will be described thereafter.

Non tumor cells – GBM are not limited to tumor cells and also includes various cells, such as astrocytes, neurons, oligodendrocytes, microglia, endothelial cells, and immune cells. These cells can also participate in tumor progression; for example, active astrocytes secrete cytokines (IL-6, TGF-β) and matrix metalloproteinases (MMP-2, MMP-9) in the presence of the tumor, promoting GBM cell proliferation and invasion of [15]. Microglia are heavily recruited in GBM and acquire a pro-tumoral M2 phenotype [16]. Neurons also participate in tumor progression through the secretion of neuroligin-3 [17].

The heterogeneity of GBM cells and their microenvironment is well pronounced and explains tumor's aggressiveness. However, this heterogeneity must be considered not only at the tissue level but also at a molecular one. This review focuses on GSC, which are not a single entity but a collection of different subpopulations.

Different subtypes of GSC

Distinguishing between GSC subpopulations is becoming an increasingly important consideration to improve the treatments. Indeed, GSC are highly involved in GBM plasticity since they are present in different population subtypes, each with specific properties that influence tumor progression and therapeutic response to a greater or lesser extent (Table 2).

Slow-cycling GSC

GSC, like differentiated cells, can be categorized into two groups: slow-cycling and fast-cycling cells. Slow-cycling cells include both GSC and differentiated cells and are characterized by their low proliferative rate, meaning that they divide much more slowly than the bulk of tumor cells. Their doubling time is approximately three times longer than that of fast-cycling cells in GBM patient-derived cell lines [18]. In a model of mouse embryonic fibroblasts, quiescent cells exhibit increases tricarboxylic acid cycle flux and mitochondrial respiration compared to proliferating cells [19]. Despite their quiescence, slow-cycling cells are believed to play a major role in GBM progression through their stem cell-like properties, contributing to tumor invasiveness, therapy resistance, and recurrence [20]. When isolated using PKH-26 membrane labeling dye, only the dye-retaining cells (slow-cycling cells) preserve long-term self-renewal capacity after serial *in vitro* passaging, whereas the fast-dividing cells eventually lose this potential. Importantly, slow-dividing cells comprise a relatively homogeneous stem cell population *in vitro* and *in vivo* [21].

Recently, Yang et al. investigated the stemness profile of slow-

Table 2
Characterization of cancer stem cells (CSC) in glioblastoma.

	Proneural (PN) CSC	Mesenchymal (MES) CSC	Slow-cycling CSC
Specific Markers	CD15 MAP2 OLIG2 SOX-2 CD133 (Wang et al. 2021)	CD44 YLK-40 ALDH1A3 EGFR (Mahabir et al. 2014; Wang et al. 2021; Mao et al. 2013)	MAP17 (Aghamiri et Amin 2025)
Signaling pathway's activation	Notch pathways (Saito et al. 2014; Rajakulendran et al. 2019) Wnt pathways (Rajakulendran et al. 2019) Glycolysis (Wang et al. 2021)	TGF-β (Lottaz et al. 2010; Bentaberry-Rosa et al. 223) STAT3 (Lau et al. 2015) NF-κB (Bhat et al. 2013) Glycolysis + Oxidative phosphorylation (Wang et al. 2021)	TCA cycle (Kang et al. 2024)
Localization	Perivascular niche (Jin et al. 2017)	Hypoxic and necrotic niche (Jin et al. 2017)	Not found
Oncogenic features	Proliferation (Fedele et al. 2019)	Invasion (Mao et al. 2013; Conroy et al. 2018) & Radioresistance (Minata et al. 2019)	Recurrence (Puig et al. 2018)

cycling cells and demonstrated that these cells exhibit characteristics specific to mesenchymal GSCs [22]. A potential marker for slow-cycling GSC, PDZK1-interacting protein 1 (PDZK1IP1, also known as MAP17), has been associated with stem-like phenotypes, immune modulation, and an immunosuppressive tumor microenvironment [23].

The tumor microenvironment supports the maintenance of slow-cycling GSC by providing regulatory signals that promotes dormancy, with hypoxia being a key factor. While the exact mechanisms remain unclear, it has been shown that HIF-mediated activation of protein phosphatase 2 A (PP2A) can induce cellular quiescence in GBM tumors [24].

It is important to note that these slow-cycling cells are not permanently inactive. Their reactivation can be triggered by environmental stimuli such as physiological stress, immune system interactions, or chemotherapy as shown in different preclinical cancer models such as GBM, carcinoma, melanoma, colorectal cancer, or non-small-cell lung cancer [25,26]. In a preclinical model of GBM, Hoang-Minh et al. show that slow-cycling cells have critical roles in GBM invasion and chemoresistance, and thus in tumor recurrence [27].

Overall, it is essential to understand that while slow-cycling cells may exhibit phenotypic and functional traits of cancer stem cells, not all slow-cycling cells are cancer stem cells. Likewise, not all cancer stem cells are slow-cycling cells [28].

Proneural (PN) GSC

The profile of PN GSC is similar to that of differentiated neuronal cells, but they express specific markers such as CD15, CD133, MAP-2, Oligo2 and SOX-2, which reflect their stem origin and their ability to maintain a partially differentiated state [29]. This partial differentiation appears to render them more sensitive to treatments [30]. Moreover, PN GSC rely on glycolysis (as the Warburg effect) and thus require glucose supplied by blood vessels. They are primarily located in perivascular niches and are therefore sensitive to hypoxia [29]. Nevertheless, they retain the ability to self-renew, proliferate extensively, and initiate tumors by activating the Notch and Wnt pathways [31]. Additionally, stress conditions such as hypoxia, or anticancer treatments as RT, can promote their transition to more aggressive phenotypes, increasing their capacity for invasion and resistance to treatments [32].

Guadagno et al. also identified two subgroups within the PN population based on the expression levels of the transcriptional regulator PATZ1 [33]. The PATZ1^{high} population is correlated with a longer survival. PATZ1 appears to downregulate the G protein-coupled receptor CXCR-4 [33], which is an inducer of the mesenchymal phenotype in GBM [34].

Mesenchymal (MES) GSC

MES GSC represent the most aggressive stem cell subpopulation in tumors. These cells express specific markers including CD44, YKL-40, ALDH1A3, and EGFR [29,35] and are characterized by their high invasive capacity, increased resistance to treatments [36] and central role in tumor progression. These characteristics are regulated by signaling pathways activated by MES GSCs: TGF-β, NF-κB, STAT3 or the glycolysis-mediated metabolism pathways [35].

The metabolism of MES GSC is another key factor underlying their aggressiveness. Unlike PN GSC, which rely solely on glycolysis and glucose utilization, MES GSC can switch between glycolysis and oxidative phosphorylation. They can also activate glutamine and lipid metabolism, which contribute to therapy resistance to [37]. Thus, they have an advantage in severe hypoxia and adapt readily to it, explaining their prevalence in necrotic and hypoxic areas [29].

Clinically, MES GSC in GBM are associated with a poor prognosis [29], due to their strong resistance to RT and chemotherapy treatments [30,36] as well as their active role in remodeling the tumor microenvironment to enhance their proliferation and migration [38].

In summary, GBM is a complex entity characterized by cellular heterogeneity that contributes to its progression, treatment resistance and recurrence. Characterization of the different subtypes of GSC has enabled the definition of four clinically relevant gliomas subgroups by The Cancer Genome Atlas (TCGA) Network [39]: proneural (TCGA-PN), mesenchymal (TCGA-MES), classical (TCGA-CL) and neural (TCGA-NL). Among all malignant gliomas, the most common subtypes are TCGA-PN (32.73%) and TCGA-MES (32.4%), followed by TCGA-CL (19.77%) and TCGA-NL (15.09%) [40,41]. These subtypes are associated with distinct prognoses. The TCGA-PN subtype is associated with a better prognosis and is more frequently observed in lower grade such as diffuse astrocytoma and anaplastic astrocytoma [42], whereas the TCGA-MES and TCGA-CL subtypes are associated with poor clinical prognosis. Slow-cycling GSC, however, remain a poorly quantified and uncategorized population.

It is also important to recognize that GSC heterogeneity is not limited to static categories. Recent findings emphasize a high degree of phenotypic plasticity, including the existence of hybrid proneural-mesenchymal states that further enhance global treatment resistance [43].

Locations of GSC

GSC subtypes are distinguished by their specific characteristics. They have distinct needs and are located in different tumor areas, called niches, to promote their survival and self-renewal.

Perivascular niches

Endothelial cells, which line blood vessels, constitute the perivascular niches of GBM, also called invasive niche and actively participate in tumor progression, treatment resistance, and the maintenance and enrichment of GSCs. Endothelial cells express VEGFR2 and angiopoietins (such as Ang-2) which participate in vascular remodeling and the structuring of perivascular niches [44]. These interactions are associated with an increase in the GSC population and the stabilization of their self-renewal properties, promoting tumor invasion, progression, and recurrence [45]. Furthermore, nitric oxide produced by endothelial cells activates the Notch signaling pathway in GSC, which is essential for their survival and self-renewal. In these perivascular niches, endothelial

cells secrete basic fibroblast growth factor (FGF-2), which promotes the reprogramming of tumor cell into GSC [46]. This is not the only reprogramming phenomenon that can occur, GSCs can also undergo an endothelial transdifferentiation process, acquiring markers such as CD144 and VEGFR2, thereby contributing to tumor neovascularization and resistance to anti-angiogenic therapies [47].

Hypoxic and necrotic niches

Hypoxic and necrotic niches, characterized by oxygen partial pressure below 10 mmHg and distant from the oxygen supply, represent another key location for GSCs, particularly MES GSC. In these regions, hypoxia is thought to activate numerous factors and pathways in favor of GSCs. For example, TGF-β1 is activated and promotes epithelial-mesenchymal transition (EMT), leading to an increase in GSC number and poor outcomes for GBM patients [48]. CBF-1, a key transcriptional modulator of the Notch signaling pathway, is also activated in the hypoxic niche and promotes GSC proliferation by accelerating EMT [49]. Similarly, VEGFA, a target gene of HIF, is activated by hypoxia, promoting GSC self-renewal. These hypoxic niches provide a favorable environment for GSC, supporting not only their maintenance in the stem state but also for their increased resistance to treatments.

Immune niches

Immune niches also support GSCs. Indeed, GSCs interact with tumor-associated macrophages, creating an immunosuppressive environment and modulating the activity of T cells [50]. These interactions allow GSC to escape immune control while supporting their growth and invasion.

It is essential to note that all these niches are not always strictly distinct and that the location of GSC is not fixed. These cells can migrate and adapt in response to changing microenvironmental conditions and treatments such as RT.

Radioresistance: Focus on GSC

RT by X-rays: Principle and effects

RT uses electromagnetic radiation, mainly X-rays, typically emitted by a linear particle accelerator. Directed at the tumor, X-rays penetrate the skin to reach the tumor cells and induce multiple DNA damage. This damage arises in two ways: one-third results from direct effect *via* immediate electron-DNA interaction while two-thirds arise from indirect effects, through water radiolysis, generating Reactive Oxygen Species (ROS) capable of damaging tumor cells. These lesions ultimately cause the death of irradiated tumor cells.

Given that RT's indirect effect are mediated by ROS, oxygen plays a fundamental role in RT efficacy by increasing ROS production, thereby causing more DNA breaks in tumor cells. However, GBM develops under hypoxic conditions, with oxygen partial pressure of 1 to 10 mmHg compared to 25 to 45 mmHg in healthy brain tissue. Contrary to common assumptions, hypoxia does not necessarily reduce ROS production. Some studies have shown increased ROS, particularly mitochondrial H_20_2, through HIF-1α stabilization, notably in GBM [51], suggesting that hypoxia-induced ROS are exclusively mitochondrial. This would explain the low ROS level at the DNA and the lack of effect on the nucleus due to the absence of DNA damage. Other studies challenge this hypothesis by observing a reduction in ROS production in isolated mitochondria under hypoxia [52]. These contradictory observations may be explained by the measurement methods (which typically reflect the balance between ROS production and elimination), experimental conditions often *in vitro* rather than *in vivo*, and ROS variability across different cellular compartments.

GSC resistance to RT

In the Stupp protocol, X-ray RT is the most effective conventional treatment for GBM after surgery [53]. However, as discussed above, the different cell types in the tumor, do not respond uniformly to this treatment. Differentiated tumor cells are generally the most sensitive to RT. Their high metabolic activity and proliferation rate make them vulnerable to damage by ROS generated during irradiation [13]. Conversely, MES GSC, particularly the MES subtype, exhibit increased resistance to RT [54]. Slow-cycling GSC escape RT because their cell cycle is arrested in the G0 phase. Furthermore, RT can activate slow-cycling cell GSCs, ensuring tumor persistence and promoting recurrence [55]. PN GSC are considered the most sensitive GSC to irradiation due to their relatively higher proliferation rate compared to quiescent cells. Indeed, after irradiation, a decrease in Oligo2 and SOX-2 expression, markers of PN GSC, is observed within tumor cells from patients with GBM [56].

GSC heterogeneity is not the only cause of resistance to RT. The tumor microenvironment plays an important role in this response. Perivascular niches, rich in endothelial cells and angiogenic factors, provide a refuge for GSCs, enabling their survival and regeneration after treatment [57]. Hypoxic niches protect them indirectly through oxygen deprivation, which limits RT efficacy of *via* HIF pathway activation, thereby maintaining the stem-like phenotype [58].

However, the effects of RT extend far beyond a simple dichotomy between cell death and survival. Irradiation also triggers mechanisms within the tumor that profoundly alter the behavior of the remaining cells. These mechanisms include MES transition and the reprogramming of differentiated tumor cells into GSC, rendering the tumor even more aggressive and treatment-resistant.

Radiation-induced cellular reprogramming of differentiated tumor cells into GSC

Epithelial-mesenchymal transition-like (EMT-like) and Proneural-mesenchymal transition (PMT)

EMT is a well-described process in which some epithelial cells transform into MES cancer cells. This mechanism, although complex, has been well characterized for several years and occurs in many cancers including GBM, despite the absence of a basement membrane [59]. Epithelial cells near the tumor exhibit decreased expression of cell adhesion proteins, such as E-cadherin, leading to a cleavage of adherent junctions and a loss of polarity. These cells then acquire motile characteristics through overexpression of N-cadherin and Vimentin, which are MES markers. Several known signaling pathways drive EMT, such as the Notch, Wnt, TGF-β, EGFR, and AKT [48,60]. Hypoxia also promotes EMT through the activation of HIF-1 and HIF-2 transcription factors, which regulate genes involved in EMT [61], as well as migration and invasion. In GBM, In GBM, the term EMT-like is used, as the brain lacks a typical epithelium, EMT-like involves the activation of molecular programs analogous to EMT, including SNAI1, TGF-β, Twist, N-cadherin and Vimentin, which contribute to cellular plasticity and highlight the highly infiltrative nature of GBM [62].

EMT has also been shown to be activated by irradiation [63]. Indeed, RT is the precursor of tumor cell invasion. This is due, in particular, to the RT-induced ROS, which activate EMT through several mechanisms. Firstly, ROS activates MAPK3 and MAPK1 (also known as ERK-1 and ERK-2) [60] to upregulate the SNAI1 protein which, in part, enables inhibition of E-cadherin. Secondly, the redox imbalance induced by ROS leads to the activity of the metalloproteinases, which degrade the ECM and trigger EMT [64]. In addition, Kesenakurti et al. demonstrate the translocation of PAK-4, a key regulator of nuclear signaling and transcription, to the nucleus, along with PPAR-γ, another regulator of transcription. In response to irradiation, this PAK-4/PPAR-γ complex binds to the *NOX1* promoter to induce EMT transition [65]. More generally, irradiation increases the likelihood of EMT in glioma.

This EMT, caused in part by RT, strengthening the tumor's ability to resist treatment and cause recurrence.

Following RT, PN GSC can transform into MES GSCs [56]. This EMT-like process involving PN cells is called Proneural-Mesenchymal

transition (PMT) and is associated with increase tumor aggressiveness and treatment-resistance (Fig. 2). PMT can be explained by the activation of various molecular mechanisms and signaling pathways. Among these, RT-induced downregulation of PATZ1 and Oligo2 leads to CXCR4 overactivation, promoting the transition of PN GSC to a MES state [34,66]. Transient activation of STAT3 by RT also contributes to the establishment of a durable PMT [67]. Furthermore, CD109 regulated by YAP/TAZ has been identified as a key player and a marker in the induction of PMT after irradiation [30]. Bhat et al. revealed that the activation of the NF-κB pathway, associated with the activity of immune cells in the tumor microenvironment, contributes also significantly to the plasticity and aggressiveness of MES cells [54].

RT-promoted reprogramming of PN GSC into MES GSC, increases tumor aggressiveness and treatment resistance.

Tumor cell reprogramming into GSC

Alongside EMT-like and PMT, another transformation mechanism has been more recently identified. Dahan et al. demonstrated the dedifferentiation of GBM tumor cells to a stem-like phenotype after X-ray irradiation [68]. Although the reprogramming of tumor cells into GSC has been little studied, it has also been observed following chemotherapy [69] and induction of HIF factors [70]. Indeed, Auffinger et al. demonstrated that temozolomide-based chemotherapy promotes the conversion of differentiated tumor cells into GSC [69]. This process involves a phenotypic reorganization of differentiated tumor cells, both *in vitro* and *in vivo*, enabling them to acquire GSC characteristics, such as the expression of pluripotency markers such as CD133, SOX-2, Oct-4, and Nestin. Once converted, these cells adopt invasive and treatment-resistant behaviors similar to those of pre-existing GSC. Lee et al. implicated hypoxia signaling pathway to the process of reprogramming tumor cells into GSC. Indeed, after chemotherapy, increased the expression of HIF-1α and HIF-2α subunits appears to induce reprogramming, as their inactivation by shRNA blocks dedifferentiation [70]. This was confirmed by Wang et al. who demonstrated that knockdown of HIF-1α or HIF-2α decreased the expression of the stem cell markers CD133 and CD15 and inhibited gliosphere formation under hypoxic conditions [71]. Using models of differentiated primary GBM lines exposed to subtoxic irradiation of 3 Gy, Dahan et al. also demonstrated that RT induces the reprogramming of tumor cells into GSC. This phenomenon was also demonstrated on *in vivo* models in nude xenograft mice orthotopically transplanted with irradiated cells, showing an increase in the expression of stem cell markers [68]. This study also highlighted the involvement of survivin, an anti-apoptotic protein that appears to be upregulated after irradiation but these reprogramming mechanisms remain unclear and require further investigation.

Therapeutic strategies to overcome RT-induced changes in GSC

Among the various therapeutic strategies used in the treatment of GBM, those targeting RT-induced resistance and recurrence mechanisms may represent promising therapies (Fig. 3).

Clinical-stage evidences

Targeting hypoxia

Given the involvement of hypoxia in GBM, targeting this mechanism is one of the most advanced strategies. Some studies have aimed to reoxygenate hypoxic niches. For example, Hyperbaric Oxygen Therapy enhances irradiation efficacy by intermittently oxygenating the patient with pure medical oxygen. Hyperbaric oxygen therapy appears to be an effective chemosensitizer both *in vitro* and *in vivo* [7] and a phase II clinical trial demonstrated an increase in overall survival [72]. However, this therapy has not shown any new clinical trials in patients with GBM probably due to the emergence of nanoparticles which specifically reoxygenate hypoxic niches. Amedlous et al. used zeolites that enable for high oxygen release without toxic effects in a GBM model [73].

Furthermore, given the role of HIF transcriptional factors in the reprogramming of differentiated tumor cells into GSC, therapeutic strategies targeting hypoxia signaling pathway to improve the efficacy of treatments on GSC should not be overlooked, especially HIF-2, which

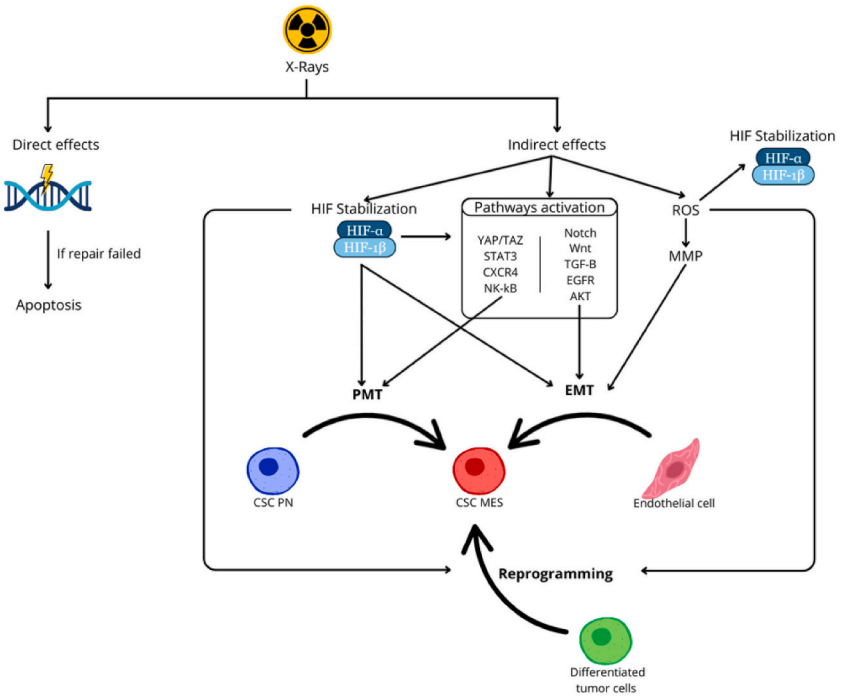


Fig. 2. Effects of radiotherapy on glioblastoma stem cells Diagram showing the direct and indirect effects of radiation therapy. Direct effects lead to apoptosis of cancer cells when their DNA repair system has been compromised. Indirect effects are more numerous; despite the induction of reactive oxygen species (ROS), the stabilization and activation of numerous metabolic pathways promotes the reprogramming of cancer cells into stem cells, as well as epithelial-mesenchymal transition (EMT) and proneural-mesenchymal transition (PMT).

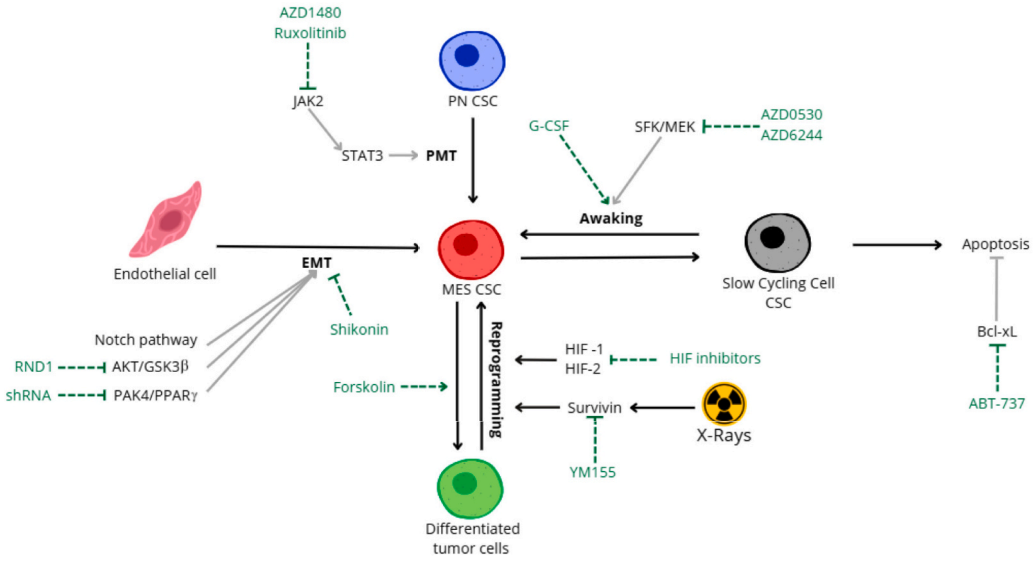


Fig. 3. Therapeutic strategies to overcome radiotherapy-induced changes in glioma stem cell Summary diagram of therapeutic strategies to counteract glioma stem cell (GSC) changes. Prevent epithelial-mesenchymal transition (EMT), proneural-mesenchymal transition (PMT), reprogramming, or the reactivation of slow-cycling cells GSC.

is predominantly localized in niches with large GSC populations [74]. Numerous HIF inhibitors are being widely tested to elucidate the mechanisms of activation of this pathway or to provide new therapeutic perspectives in hypoxic cancers (Table 3). PT-2385, a specific inhibitor of HIF-2, binds to a cavity within the PAS-B domain of HIF-2α, preventing its heterodimerization with HIF-1β. The use of this inhibitor as monotherapy did not affect the viability of GBM cells *in vitro* [75], which has been recently confirmed in a mouse GBM cell line [76]. Nevertheless, Espinoza et al. demonstrated a favorable reduction in tumor volume after treatment, as well as a reshaping of the infiltrating microglia and macrophages in immunocompetent mice [76]. Clinical studies for GBM (NCT03216499) have also begun, showing its acceptable safety and highly variable effects as a single agent, suggesting the need to evaluate its effects in combination with RT and chemotherapy [77]. Moreover, the development of its analogue PT-2977, also known as belzutifan, aims to overcome the limitations of PT-2385 by improving its pharmacokinetic profile. Belzutifan is currently under clinical evaluation for renal cell carcinoma (NCT04846920) [78] and remains investigational for GBM. Targeting HIF-1 is at preclinical stage. Gauthier et al. observe that HIF-1α knockdown by siRNA limits radiation-induced migration of GSCs in GBM demonstrating a radiosensitizing effect of HIF-1 inhibition *in vitro* and *in vivo* [79].

Preclinical-stage observations

Preventing PMT and EMT

Targeting the PMT and the EMT represents emerging strategies for limiting the aggressiveness and resistance of tumor cells, particularly after RT. One study showed in murine proneural high grade gliomas cells that inhibition of JAK-2, a key activator of STAT3, by molecules such as AZD1480 or ruxolitinib, combined with RT, prevented PMT and reduced cell aggressiveness [67]. These results are supported in a preclinical GBM model, where mice transplanted with human proneural glioma cells treated with AZD1480 in combination with RT showed significantly improved survival compared with those given RT alone [80]. Ruxolitinib is currently being studied in human GBM (NCT03514069). This observation highlights the interest in targeting STAT3, which plays a central role in PMT-dependent cellular plasticity and tumor aggressiveness.

There is also growing evidence that Notch pathway inhibitors act as radiosensitizers by blocking the EMT mechanisms associated with radioresistance. Indeed, Kesanakurti et al. showed *in vitro* and *in vivo* that irradiation increases the recruitment of the PAK-4/PPAR-γ complex to the *NOX1* promoter by up-regulating PAK-4. Inhibition of PAK-4 by shRNA reduces radio-induced activation of the complex, suggesting a potential therapeutic efficacy of targeting PAK-4 to overcome radioresistance in GBM [65]. More recently, a natural naphthoquinone derivative, Shikonin, has shown promise for inhibiting EMT in GBM. Indeed, Zhang et al. show *in vitro* and *in vivo* that Shikonin upregulates p53 and hsa-miR-361-5p, thereby suppressing *ZEB1* expression and reducing the levels of MES markers such as N-cadherin, Vimentin, and SNAI1 [81]. Similarly, restoration of Rnd1 expression attenuated EMT and reduced temozolomide resistance through inhibition of the AKT/GSK-3β pathway, decreasing cell migration and invasiveness in the GBM [82]. Targeting the TGF-β pathway also remains an important axis. Inhibition of Cathepsin S by *Z*-FL-COCHO preserved tight junction integrity and prevented TGF-β-induced EMT in GBM cells, thus limiting invasion [83].

These complex interactions highlight the importance of targeting key EMT and PMT pathways to counter tumor plasticity and improve RT.

Emerging concepts

Targeting slow-cycling GSC

Given the ability of slow-cycling GSC to resist to RT, inducing their awakening could sensitize them to treatment and prevent recurrence. To this end, Santos-de-Frutos and Djouder have recently reviewed and discussed three types of therapeutic strategies to eliminate dormant cells: to wake up these dormant cells, to maintain these cells in a quiescent state or to eliminate the cells while they are quiescent [84]. These strategies have emerged in non-brain tumors but it is still less studied in GBM. However, Harmine, a potent inhibitor of quiescence cells state, seems to be effective by inhibiting the ATP binding to the kinase pocket of DYRK1A which is involved in the regulation of G0-G1 transition [20]. Another strategy involves targeting FABP7, a fatty acid transport in slow-cycling GSC which may be a viable therapeutic strategy because. Its inhibition, combined with glycolysis inhibition, sensitizes GSCs to metabolic stress and to increase overall survival [27]. These therapeutic strategies targeting slow-cycling GSCs do not appear to be sufficiently studied in GBM. Further research is therefore needed.

Preventing cell reprogramming

An emerging therapeutic strategy involves blocking radiation- and/or hypoxia-induced reprogramming of differentiated tumor cells into GSCs. Specific down-regulation of survivin has been shown to block radiation-induced plasticity and thus represents an interesting avenue for preventing reprogramming. This protein is already known to be associated with poor prognosis and short survival in several tumor types, including as renal cell carcinoma [85]. A survivin inhibitor, YM155, significantly reduced gliospheres formation and reprogramming after irradiation of GBM cells [68]. This inhibitor has been evaluated in numerous clinical trials in melanoma (NCT00281541), breast cancer (NCT01038804), and non-small cell lung cancer (NCT01100931), but does not appear to promote any improvement, although its safety is guaranteed [86]. Very recently, an innovative preclinical strategy demonstrated on a syngeneic GL261 glioma mouse model that combining irradiation with forskolin, an established agent for neuronal differentiation, can transiently reprogram glioma cells into neuron-like or microglia-like phenotypes, significantly depleting the GSC pool and slowing tumor growth [87]. However, studies aiming at of blocking reprogramming after irradiation are limited and require further attention.

Optimizing RT modalities

Targeting GSC is an emerging and promising strategy for circumventing GBM resistance mechanisms of. However, it cannot overcome the many limitations of X-ray irradiation, such as its lack of ballistic precision and accuracy for radiation delivery. X-ray RT does not spare healthy tissue. and its effectiveness is greatly diminished in hypoxia [88]. Moreover, as highlighted in this review, X-ray irradiation can promote recurrence notably through cellular reprogramming mechanisms leading to numerous deleterious effects for the patient. To overcome these limitations, hadrontherapy, a form of RT using charged particles instead of X-rays, is increasingly explored. Among the available hadrontherapies, proton therapy offers better dose distribution than X-rays, allowing maximal energy deposition within the tumor while sparing surrounding healthy tissues [89]. Moreover, proton beam irradiation appears to have higher efficacy in treating GSCs in GBM than conventional X-rays *in vitro* [90]. Cliniclally, a prospective phase II randomized trial reported reduced normal tissue toxicity and patient reported less fatigue compared to intensity-modulated radiation therapy [91]. However, current clinical data for protontherapy do not establish superior progression-free or overall survival in GBM patients [92]. Early-phase clinical trials are now evaluating dose-escalated proton therapy in combination with standard chemoradiation (NCT05768087, NCT04752280), with the aim of improving both efficacy and tolerability in GBM patients.

Another hadrontherapy approach, carbon ion RT (CIRT), is increasingly being studied and favored for radioresistant cancers such as GBM. CIRT has better ion ballistics, twice the biological efficacy of X-rays [93] and allows for the safer use of radiosensitizers such as PARPs with a more pronounced effect in CIRT than X-ray [90]. In addition, CIRT reduces migration [94], invasion, and hypoxia-induced radioresistance *in vitro* and *in vivo* [4,95]. Valable et al. showed consistent lineage-dependent efficacy under hypoxic or normoxic conditions. The U-251 MG human GBM cell line exhibited greater cell death l compared to X-rays regardless of oxygen levels. However, this was not the case for the GL15 GBM cell line, which still exhibited some radioresistance to CIRT under hypoxia [4]. The results demonstrate that, although CIRT is more efficient than X-rays in both GBM cells, hypoxia can still limit CIRT efficacy in a cell-type-specific manner. This highlights the need to combine CIRT with hypoxia -targeting strategies. Other studies have used CIRT to target GSCs. For example, Kumar et al. showed *in vitro* on the U-251 MG and LN-229 lines a reduction in the formation of gliospheres post-CIRT in contrast to X-rays [96]. In addition, Chiblak et al. demonstrated *in vitro* and *in vivo* that CIRT effectively eradicates radioresistant patient-derived GSCs, leading to growth inhibition and prolonged survival [97]. Based on physical rational and preclinical evidences, the use of hadrontherapy by carbon ions instead of X-ray RT to target radioresistant cancers and cancer stem cells is promising. However, it is not yet established as a standard of care. It should also be stressed that CIRT remains strictly investigational for GBM, with only two clinical studies without published results (NCT01165671, NCT04536649). CIRT is not accessible for all tumors due to its high cost and very limited geographical availability.

Conclusion and emerging therapeutic approaches

Although X-ray RT remains the standard irradiation technique in the Stupp protocol for GBM, tumor-resistance mechanisms, particularly those driven by the hypoxic microenvironment and GSCs, considerably limit its efficacy. This review highlights the central role of GSC in tumor resistance and recurrence, whether MES, proliferative or slow cycling cells, all of which are influenced by hypoxia and capable of adapting their phenotype after exposure to irradiation. Through HIF factors, hypoxia helps maintain the stem state, promotes cellular plasticity and supports processes such as EMT, PMT or reprogramming of differentiated cancer cells into GSC.

To counteract radioresistance, several systemic therapeutic approaches are emerging including reducing hypoxia, inhibiting HIF, or blocking of reprogramming mechanisms into the stem phenotype. In addition, proton and carbon ion approaches are promising investigational strategies that require prospective validation, particularly in molecularly defined GBM cohorts and in combination with systemic therapies. These approaches provide testable therapeutic hypotheses and may improve treatment strategies if validated in clinically relevant models and prospective trials.

CRediT authorship contribution statement

Elsa Sarrazin: Conceptualization, Writing – original draft, Writing – review & editing. **Samuel Valable:** Conceptualization, Writing – review & editing, Supervision. **Elodie A. Pérès:** Writing – review & editing. **Nathalie Colloc'h:** Writing – review & editing. **Evelyne Emery:** Writing – review & editing. **Paul Lesueur:** Writing – review & editing. **Arthur Leclerc:** Writing – review & editing. **Myriam Bernaudin:** Conceptualization, Writing – review & editing, Supervision. **Juliette Aury-Landas:** Conceptualization, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2026.103198.

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