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Predictive molecular biomarkers of radiosensitivity in adult glioma: a narrative review

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Abstract

Gliomas are the most common malignant primary brain tumors in adults, yet their prognosis remains poor despite advances in treatment. Radiotherapy is a cornerstone of glioma management; however, its efficacy is often limited by tumor radioresistance. Understanding the molecular mechanisms underlying this resistance is critical for improving therapeutic outcomes. Recent research has identified key biomarkers and molecular pathways, including immune modulation, hypoxia, cell cycle regulation, apoptosis, and stress responses that influence tumor radiosensitivity and prognosis. This review explores predictive molecular biomarkers for radiosensitivity in gliomas, highlighting the latest advancements in preclinical studies and available clinical data, as well as their potential to inform future personalized radiotherapy strategies. Incorporating these biomarkers into clinical decision-making may facilitate patient stratification, guide combined modality approaches, and improve treatment precision and outcomes in glioma care.

Keywords Glioma, Molecular biomarkers, Radiosensitivity, Tumor radioresistance

Introduction

Gliomas are the most common malignant primary brain tumors in adults [1, 2]. The classification of gliomas has evolved from histological frameworks to the molecularly driven WHO 2021 classification [3]. Before, the grading was based on cellular morphology and mitotic activity, categorizing gliomas into grades I-IV based on aggressiveness (2007 WHO classification) [4]. The 2016 update introduced molecular markers such as isocitrate dehydrogenase (IDH) mutations and chromosomal 1p/19q co-deletion, allowing for more precise prognostic and therapeutic distinctions [5]. The 2021 revision emphasized molecular

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diagnostics, defining glioblastomas (GBMs) as IDH-wild-type grade 4 tumors and incorporating additional markers such as telomerase reverse transcriptase (TERT) promoter mutations or epidermal growth factor receptor (EGFR). This molecular refinement has not only improved diagnostic precision but also highlighted critical pathways influencing treatment response [6].

Despite advancements in treatment modalities, including radiotherapy (RT), which remains a cornerstone in glioma management, the prognosis of higher-grade gliomas remains poor [7]. Most treatment failures are caused by recurrence in the previously irradiated high-dose volume, mainly in the site of the residual gross tumor, surgical cavity or their vicinities. Thus, radioresistance is the prime suspect of most treatment failures in high-grade gliomas, especially GBM [8]. The growing understanding of glioma molecular biology now provides a framework to investigate these resistance mechanisms. Recent studies have identified key biomarkers that influence tumor cell survival, prognosis, and therapeutic response. These factors are implicated in diverse pathways, including immune-related mechanisms, hypoxia [9], cell cycle [10], apoptosis [11] and stress response [12]. This article explores the complex paradigm of predictive molecular biomarkers for glioma radiosensitivity and offers a comprehensive review of recent advancements in this field. Throughout the manuscript, radioresistance refers to the tumor's ability to survive and proliferate despite radiation treatment, while radiosensitivity reflects how susceptible a tumor is to the damage caused by radiation.

Methods

We conducted a literature search through PubMed, Scopus, and Google Scholar, focusing on studies published from 2000 to 2024 that assessed various molecular markers and mechanisms related to RT response in glioma. Clinical and studies evaluating predictors of RT sensitivity in glioma were included based on the presence of keywords "glioma", "radiosensitivity", "radiotherapy response", and "molecular biomarkers". The main findings of each study were summarised to detect potential biomarkers that could guide treatment approaches and improve outcomes.

Predictive molecular biomarkers of radiosensitivity in glioma

The key molecular markers and a brief explanation of their mechanism in response to RT are summarized in following paragraphs and illustrated in Fig. 1, and a short report on the impact of each marker is presented in Table 1.

Integrating radiosensitivity gene signatures

The development of gene signatures of glioma radiosensitivity has shown potential for clinical stratification of patients benefiting from adjuvant radiation after glioma surgery. Using large glioma patient cohorts from TCGA and CGGA, studies have validated and compared predictive indexes such as the radiosensitivity index (RSI) and also the 31-gene signature (31-GS), with the latter showing higher predictive potential. Integration of these signatures with glioma-specific characteristics has contributed to the new predictive models, including a 12-gene signature (PI12). Additionally, in this study, a nomogram combining PI12 with clinical features outperformed the traditional WHO grading system in prognostic accuracy and highlighted its potential for clinical application in treatment decision-making, improving the identification of radiosensitive patients and personalized radiotherapy planning [72]. The following sections will explore the key molecular pathways that influence glioma response to radiotherapy.

Immune-related mechanisms

The most common immune-related pathways are the cytokine-cytokine receptor interaction and tumor necrosis factor (TNF) signaling pathways. When autocrine growth factor ligands, such as transforming growth factor alpha (TGF-α) and TNF-α, are expressed, they can augment the MAPK pathways and act as critical mediators in the cell's response to radiation [73].

PD-1/PD-L1 axis

The programmed death-1/programmed death ligand 1 (PD-1/PD-L1) axis is a key in modulating glioma responses to RT. High PD-L1 expression is associated with worse overall survival (OS) in lower-grade gliomas (LGGs) receiving RT, suggesting its potential as a predictive marker [13]. Elevated baseline soluble PD-L1 (sPD-L1) levels correlate with higher tumor grade, shorter progression-free survival (PFS), and OS. RT further increases sPD-L1, especially in IDH-1-mutant gliomas. Preclinical models show that combining RT with anti-PD-L1 antibodies improves outcomes, underscoring the therapeutic potential of targeting this axis [14]. Additionally, RT significantly upregulates PD-L1 expression at protein and mRNA levels, partly via the EGFR/JAK2 pathway. Inhibition of EGFR blocks RT-induced PD-L1 upregulation, and combining RT with EGFR inhibitors as well as anti-PD-L1 agents enhances antitumor immune response [15].

RGS4

Regulator of G protein signaling 4 (RGS4) strongly correlates with immune infiltration and its regulators (Fig. 1, immune-related section). RGS4 can induce the invasion,

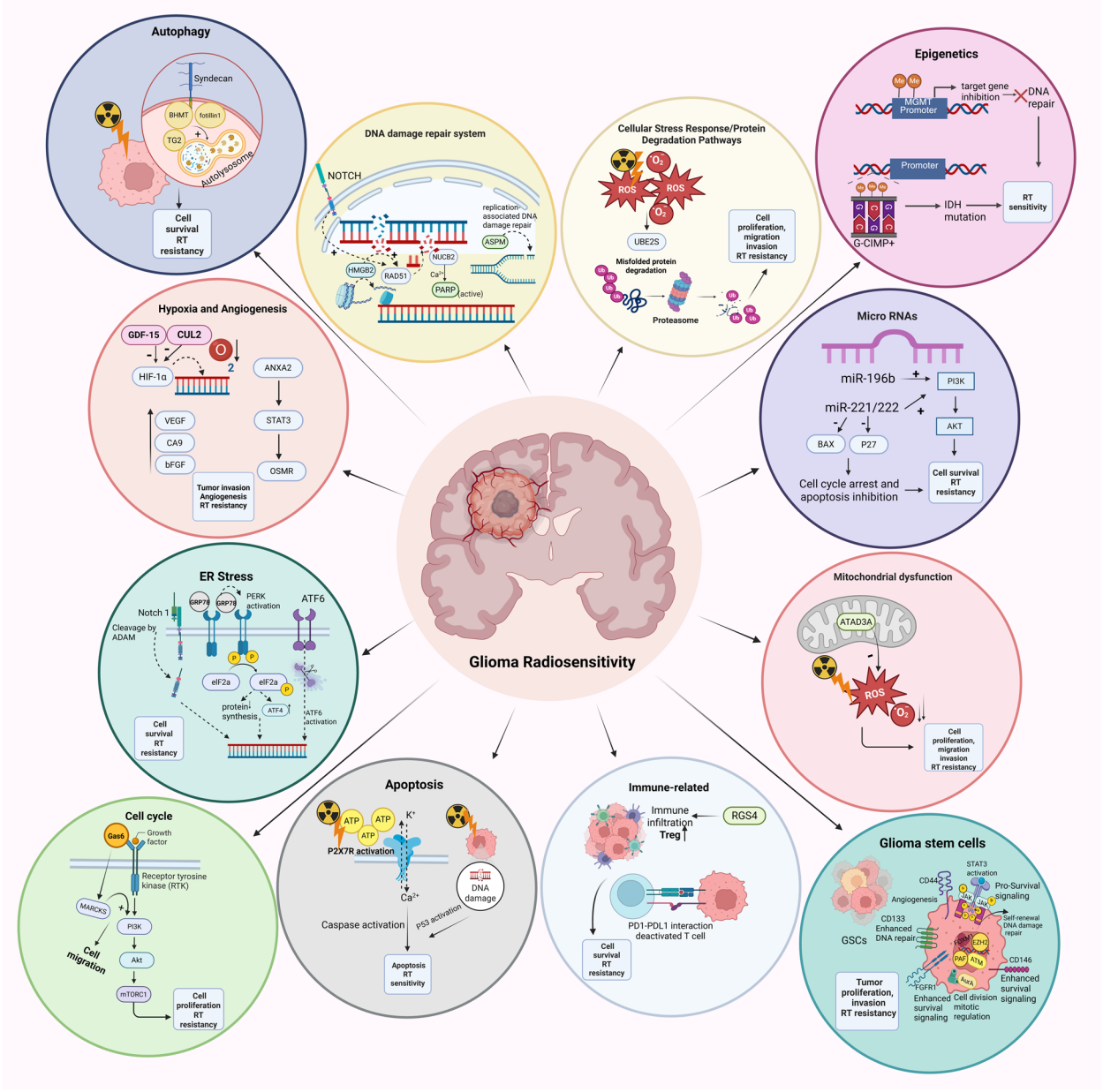

Fig. 1 A summary of predictive molecular pathways of radiosensitivity in glioma Legend: Autophagy: Syndecan and related proteins contribute to cell survival and RT resistance DNA Damage Repair System: NOTCH signaling and repair proteins like RAD51 may repair RT-induced DNA damage Proteasome function in response to reactive oxygen species (ROS) and accumulation of misfolded proteins contribute to RT resistance MGMT promoter methylation, IDH mutation, and G-CIMP status modulate RT sensitivity Dysregulation of miRNAs like miR-196b and miR-221/222 leads to apoptosis inhibition, cell survival, and RT resistance Mitochondrial dysfunction: ATAD3A mitigates mitochondrial dysfunction and ROS accumulation and can drive RT resistance Glioma stem cell functions and signaling pathways promote RT resistance Immune-related mechanisms: PD-1/PD-L1 interaction and immune infiltration contribute to RT resistance Apoptosis: Caspase activation and pathways like P2X7R determine RT-induced apoptosis and increase RT sensitivity Cell cycle: Receptor tyrosine kinase (RTK) pathway promotes cell proliferation and RT resistance ER stress: Pathways such as PERK and ATF6 mediate cell survival under RT-induced stress Hypoxia and angiogenesis: Factors like VEGF and HIF-1α contribute to tumor invasion, angiogenesis, and RT resistance

migration, and proliferation of glioma cells. However, the inhibition of RGS4 expression increases cancer sensitivity to chemoradiotherapy. RGS4 is associated with the markers (such as matrix metalloproteinase-2 (MMP2)) that are negatively involved in glioma stem cell (GSC) invasion and migration. It also induces the apoptosis of GSCs, which is a therapeutic target in GBM [16]. It has been shown that RGS4 knockdown may inhibit cell proliferation and migration, leading to chemoradiotherapy sensitivity [17].

Table 1 Biomarkers and molecular mechanisms associated with radioresistance in gliomas. The table summarizes the expression trends, evidence levels, potential therapeutic strategies, and supporting references for each biomarker categorized by biological mechanisms

Mechanism	Biomarker	Expression Trend in RT Resistance	Evidence Level	Associated Therapy	Reference
Immune-related	PD-L1	Upregulated after RT at tumor (mRNA/protein) and plasma (sPD-L1) levels; correlated with EGFR activation; high levels associated with RT resistance and worse OS/PFS	Clinical trials + Preclinical (in vitro and in vivo)	Anti-PD-1/PD-L1 inhibitors	[13–15]
	RGS4	Upregulated in RT/chemoradiotherapy-resistant glioma	Preclinical (in vitro)	-	[16, 17]
Hypoxia	HIF-1	Increased expression of HIF-1α is linked to enhanced radioresistance in glioma cells through the transcriptional activation of long noncoding RNAs that interfere with DNA damage repair mechanisms. Low HIF-1 expression in adjacent tumor and peripheral edge regions is associated with longer OS and PFS.	Preclinical (in vitro and in vivo) + Prospective clinical study	-	[9, 18, 19]
	OSMR	High expression of OSMR in GBM stem cells is associated with radioresistance.	Preclinical (in vitro and in vivo)	-	[20]
	NASP	High expression of NASP correlates with poor prognosis and radioresistance in GBM.	Preclinical (in vitro and in vivo) + Clinical retrospective study	-	[21]
	CA9	High expression of CA9 in hypoxic glioma cells is associated with increased radioresistance. Knockdown of CA9 improves radiosensitivity by inducing ferroptosis.	Preclinical (in vitro and in vivo)	-	[22]
Angiogenesis	VEGF	Contributes to radioresistance by enhancing angiogenic potential and reducing oxidative stress.	Preclinical (in vitro) + Clinical trials (Phase II-III)	Bevacizumab (anti-VEGF); mixed clinical results	[23–26]
	CUL2	Elevated CUL2 expression is associated with reduced levels of HIF-1α, EGFR, and Cyclin B1, increased radiosensitivity, and improved survival in GBM.	Retrospective clinical study	-	[27]
	GDF 15	Radiation-induced GDF15 secretion from brain endothelial cells enhances VEGFA expression in GBM cells via MAPK1/SP1 signaling, promoting angiogenesis and radioresistance.	Preclinical (in vitro and in vivo)	-	[28]
Cell cycle	MARCKS	High MARCKS expression increases radiosensitivity and improves survival.	Preclinical (in vitro and in vivo) + Retrospective clinical study	-	[29]
Mitochondrial dysfunction	ATAD3A	ATAD3A high expression is associated with radioresistance through the maintenance of mitochondrial integrity.	Preclinical (in vitro) + Retrospective clinical study + Ex vivo human tissue analysis	-	[30]
Energy metabolism	UBE2S	Increases resistance to chemo-radiotherapy via Akt phosphorylation, correlates with PTEN mutations	Preclinical (in vitro) + Retrospective clinical study + Ex vivo human tissue analysis	-	[31]
	Metabolites	Glycolysis associated with radioresistance, oxidative phosphorylation enhances radiosensitivity	Preclinical (in vitro and in vivo)	Dichloroacetate (DCA) combined with radiotherapy, enhances the radiosensitivity	[32]
	Purines	Strong correlation with radiation resistance; high expression of GTP synthesis enzyme linked to shorter survival	Preclinical (in vitro and in vivo) + Retrospective clinical study	Inhibition of GTP synthesis using FDA-approved inhibitors (e.g., mycophenolate mofetil (MMF))	[33]
Endoplasmic reticulum (ER) stress	ATF6	Upregulated after radiation, contributes to radioresistance.	Preclinical (in vitro)	-	[34]
	GRP78	Upregulated with ATF6 activation after radiation, contributes to radioresistance.	Preclinical (in vitro)	-	[34, 35]
	NOTCH1	Upregulated with ATF6 activation after radiation, contributes to radioresistance.	Preclinical (in vitro)	-	[34]
Apoptosis	P2X7 purinergic receptor	High P2X7R expression enhances radiosensitivity and survival probability.	Preclinical (in vivo) + Retrospective clinical study	-	[11]
	E2F1	Overexpression of E2F1 enhances radiosensitivity regardless of p53 status	Preclinical (in vitro)	-	[36, 37]

Table 1 (continued)

Mechanism	Biomarker	Expression Trend in RT Resistance	Evidence Level	Associated Therapy	Reference
Autophagy	PI3K/Akt/mTOR pathway Syndecan 1, Transglutaminase 2,	Increased autophagic flux promotes cell survival and radioresistance. Syndecan 1 and Transglutaminase 2 were overexpressed in the radioresistant GBM cells.	Preclinical (in vitro)	Inhibition of autophagy (e.g., bafilomycin A1), targeting PI3K/Akt/mTOR pathway	[38–40]
DNA damage repair	HGF/MET pathway	This pathway could play a role in the radioresistance of GBM.	Preclinical (in vivo)	Combining RT with MET inhibition prolongs survival in GBM	[41]
	HMGB2	High HMGB2 expression correlates with poor prognosis, increased glioma cell proliferation, and enhanced radioresistance.	Preclinical (in vitro) + Retrospective clinical study + Ex vivo human tissue analysis	-	[42]
	NUCB2	High NUCB2 expression is associated with increased GBM recurrence and promotes cell proliferation, invasion, and tumor growth	Preclinical (in vitro and in vivo) + Ex vivo human tissue analysis	-	[43]
	RAD51	High RAD51 expression in GSCs contributes to DNA damage repair and radioresistance.	Preclinical (in vitro and in vivo) + Retrospective clinical study + Ex vivo human tissue analysis	-	[44]
	ASPM	Down-regulation of ASPM by siRNA enhanced radiosensitivity	Preclinical (in vitro)	-	[45]
	Notch	Upregulated in radioresistant GSCs	Preclinical (in vitro and in vivo)	Inhibition of Notch pathway with γ-secretase inhibitors (GSIs) renders the glioma stem cells more sensitive to radiation at clinically relevant doses	[46]
Differentiation	PDPN	Upregulated in radioresistant glioma cells	Preclinical (in vitro and in vivo) + Retrospective clinical study + Ex vivo human tissue analysis	-	[47]

Table 1 (continued)

Mechanism	Biomarker	Expression Trend in RT Resistance	Evidence Level	Associated Therapy	Reference
Stemness	CD133	CD133 + tumors are associated with shorter PFS, indicating a role of CD133 in promoting radioresistance through facilitating more efficient DNA damage repair caused by radiation.	Preclinical (in vitro and in vitro) + Retrospective clinical study + Ex vivo human tissue analysis	Cathepsin L inhibition with radiotherapy (in vitro) suppresses tumor angiogenesis and overcomes the radioresistance of CD133-positive GSCs in GBM.	[48–50]
	CD146	CD146 increased resistance to RT by enhancing cell survival via the downregulation of p53 and activation of NF-κB. Increased CD146 expression correlated with higher glioma grades and progression rates.	Preclinical (in vitro and in vivi) + Retrospective clinical study	-	[44, 51]
	CD44	CD44 enhances the properties of CSCs, promotes angiogenesis, and ultimately contributes to radioresistance.CD44 overexpression is linked to aggressive tumor phenotype and Survival outcomes are mixed.	Retrospective clinical study + Ex vivo human tissue analysis	-	[52–55]
	CHRDL1	CHRDL1 promotes GSC stemness and radioresistance via BMP pathway inhibition; associated with poor glioma survival.	Preclinical (in vitro) + Retrospective clinical study	-	[56]
	STAT3	Activated in resistant glioma; correlated with poor prognosis and shorter survival.	Preclinical (in vitro and in vivo) + Retrospective clinical study	STAT3/Slug inhibition synergistically enhances the efficacy of radiosensitivity and improves survival in (preclinical target)	[57, 58]
	FoxM1	FoxM1 regulates GSC maintenance via Sox2. FoxM1 overexpression promotes growth and radioresistance.	Preclinical (in vitro and in vivo)	-	[59]
	EZH2	EZH2 upregulation in GSCs plays a critical role in GBM tumor propagation and radioresistance	Preclinical (in vitro)	-	[60]
	FGFR1	Upregulated in radioresistant GSCs; positively associated with poor RT response and shorter survival	Preclinical (in vitro and in vivo) + Retrospective clinical study	-	[61, 62]
	AurA	Aura A contributes to radioresistance via the maintenance of stem cell phenotype	Preclinical (in vitro)	-	[63]
	PAF	Increased activity during replication stress; supports radioresistance	Preclinical (in vitro)	-	[64]
	ATM	Increased ATM phosphorylation in GSCs after RT leads to radioresistance	Preclinical (in vitro)	KU55933 as an ATM specific inhibitor (in vitro)	[65]
Epigenetic	G-CIMP	IDH1 mutation and G-CIMP + phenotype associated with better survival	Retrospective clinical study	-	[66]
	MGMT promoter methylation	Methylated MGMT promoter is associated with better prognosis and lower progression, enhanced radiosensitivity	Preclinical (in vitro) + Retrospective clinical study	Temozolomide	[67–69]
	Micro RNAs	miR-196b downregulation promotes glioma cell sensitivity to temozolomide and RT. High expression of miR-221/222 correlated with shorter survival and poor prognosis.	Preclinical (in vitro) + Retrospective clinical study		[70, 71]

Abbreviations:RT Radiotherapy, *OS* Overall survival, *PFS* Progression-free survival, *GBM* Glioblastoma multiforme, *GSCs* Glioma stem cells, *CSCs* Cancer stem cells, *PD-L1* Programmed death-ligand 1, *sPD-L1* Soluble PD-L1, *RGS4* Regulator of G protein signaling 4, *HIF-1α* Hypoxia-inducible factor 1-alpha, *OSMR* Oncostatin M receptor, *NASP* Nuclear autoantigenic sperm protein, *CA9* Carbonic anhydrase, *VEGF* Vascular endothelial growth factor, *EGFR* Epidermal growth factor receptor, *GDF 15* Growth/differentiation factor-15, *MAPK* Mitogen-activated protein kinase, *UBE2S* Ubiquitin conjugated enzyme E2S, *SP1* Specificity protein 1, *MARKS* Myristoylated alanine-rich C-kinase substrate *PI3K/Akt/mTOR* Phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin, *HGF/MET* Hepatocyte growth factor/Mesenchymal-epithelial transition factor, *HMGB2* High mobility group box 2, *NUCB2* Nucleobindin-2, *RAD51* DNA repair protein RAD51 homolog, *ASPM* Abnormal spindle-like microcephaly-associated protein, *PDPN* Podoplanin, *CHRDL1* Chordin-like 1, *STAT3* Signal transducer and activator of transcription 3, *FoxM1* Forkhead box protein M1, *EZH2* Enhancer of zeste homolog 2, *FGFR1* Fibroblast growth factor receptor 1, *PAF* PCNA-associated factor, *AurA* Aurora kinase A, *ATM* Ataxia-telangiectasia mutated kinase, *G-CIMP* Glioma CpG island methylator phenotype, *IDH1* Isocitrate dehydrogenase 1, *MGMT* O6-methylguanine-DNA methyltransferase, *miR* MicroRNA

Hypoxia

HIF-1

Research has demonstrated that hypoxia-inducible factor (HIF)–1α is activated in hypoxic environments, subsequently controlling many genes involved in proliferation and cell survival. For instance, Kessler et al. showed that knocking down HIF-1α in glioma cells increased cell radiosensitivity, suggesting that HIF-1α promotes radioresistance by supporting the survival pathways of cells under low oxygen levels [9]. Moreover, increased expression of specific genes involved in the cell cycle and DNA repair regulation has also been linked to HIF-1α activation, further influencing the radiation response. According to Zhang, HIF-1α mediates radioresistance through the transcriptional activation of long noncoding RNAs that interfere with DNA damage repair mechanisms [74]. Hsieh et al. reported that cycling hypoxia increases levels of reactive oxygen species, thus prolonging HIF-1 signaling and increasing ionizing radioresistance [18]. Translational clinical observations also indicated that HIF-1 expression did not predict survival when assessed across the whole tumor. However, low HIF-1 expression in the adjacent tumor region was associated with longer OS and PFS. Additionally, low HIF-1 expression in the peripheral edge region predicted longer PFS [19]. Specifically, a hypoxic environment diminishes the efficacy of RT by lowering the reactive oxygen species, which are essential for DNA damage brought on by radiation. Cell cycle arrest, reduced apoptosis, enhanced autophagy, increased antioxidant responses, maintaining cancer stem cell populations, and other cellular pathways are also regulated by hypoxia. These adaptations contribute to a robust defence against radiation damage [75]. These data indicate that interfering with HIF-1 activation or its downstream consequences may increase tumor radiosensitivity by inhibiting radiation-induced protective responses, as illustrated in Fig. 1 (hypoxia section).

OSMR

The oncostatin M receptor (OSMR) is a significant target of Annexin A2 (ANXA2) in GBM. In hypoxic conditions, GBM cells can trigger the ANXA2–STAT3–OSMR signaling pathway, which mediates tumor invasion, angiogenesis, and cell growth which is illustrated in Fig. 1 (Hypoxia and Angiogenesis section). The ANXA2–STAT3–OSMR pathway modulates changes in malignant phenotypic and mesenchymal transition in GBM [76]. In a preclinical study, researchers found that the OSMR in mitochondria helps GSCs resist radiation by enhancing energy production. Removing OSMR made the cells more sensitive to radiation and improved survival in mouse models. Targeting OSMR could enhance GBM treatment [20].

NASP

Another activator of the ANXA2/STAT3 pathway is the nuclear autoantigenic sperm protein (NASP). NASP is significantly expressed in GMB, and NASP expression is negatively correlated with the promotion of GBM. Functionally, NASP promotes GBM cell proliferation, migration, invasion, and radioresistance; interacts directly with ANXA2; and promotes its nuclear localization. The NASP/ANXA2 axis has a role in DNA damage repair after RT; NASP overexpression significantly activates the activator and signal transducer and activator of transcription 3 (STAT3) pathway, which has a role in tumor survival and aggressiveness. As a result, GBM cells that express more NASP acquire higher radioresistance [21].

CA9

Carbonic anhydrase IX (CA9) is associated with the response to hypoxia and cellular pH regulation. Its expression is linked to hypoxic conditions within gliomas, contributing to radioresistance (Fig. 1, Hypoxia and Angiogenesis section) [77]. In a preclinical experiment with glioma cells, X-ray exposure induced lipid peroxidation and the activation of ferroptosis markers in U251 and GL261 glioma cells. Silencing CA9 in hypoxic glioma cells led to significant changes in iron-regulating proteins, which boosted both ferroptosis and radiosensitivity. Ferroptosis inhibitors increased cell survival after X-ray treatment, while inducing ferroptosis heightened the X-ray-induced cell death. These results suggest that targeting CA9 to enhance ferroptosis could improve the radiosensitivity of glioma cells [22].

Angiogenic factors

Angiogenesis plays a key role in the treatment response and progression of GBM (Fig. 1, Hypoxia and Angiogenesis section).

VEGF

In preclinical studies, vascular endothelial growth factor (VEGF) was shown to promote radioresistance in glioma through different mechanisms. One study found that irradiation increased VEGF secretion in glioma cell lines, with higher VEGF levels linked to greater resistance [78]. Another study showed that VEGF reduced oxidative stress and protected cells from radiation by decreasing mitochondrial oxygen consumption [23]. These findings suggest that VEGF contributes to radioresistance via both angiogenesis and metabolic regulation. Bevacizumab (BEV) is an anti-VEGF drug, in an early-phase II trial [24] showed encouraging outcomes, but phase III trials [25, 26] failed to demonstrate a clear survival benefit; thus, the effectiveness of combining anti-VEGF therapy with other treatments is still uncertain.

CUL2

Another gene pathway related to angiogenesis is CUL2, which can predict survival rates and progression in GBM. Cullin2 proteins negatively correlate with several angiogenic markers, such as VEGF-A, EGFR, HIF-1α, and Cyclin B1. Increased CUL2 expression is associated with radiosensitivity and decreased signal intensities in imaging [27].

GDF15

Growth/differentiation factor-15 (GDF15) regulates tumor angiogenesis by increasing the cross-talk between brain GBM cells and endothelial cells (ECs). Radiation-induced GDF15 secretion activates the transcriptional promoter VEGFA through p-MAPK1/SP1 signaling in human GBM cells. Consequently, VEGF upregulation in GBM cells causes angiogenic activity and radioresistance [28].

Cell cycle

MARCKS

In GBM, the myristoylated alanine-rich C-kinase substrate (MARCKS) protein is a key modulator of cell cycle dynamics and radiosensitivity. Intracerebral tumor growth rates and GBM cell proliferation are negatively associated with MARCKS expression. In vitro, MARCKS silencing increased radiation resistance and proliferation, while its overexpression reduced tumor growth and aging. Clinically, high MARCKS expression was associated with improved survival, especially in proneural GBM with unmethylated MGMT promoters. Furthermore, after MARCKS knockdown, cells recovered more rapidly from radiation-induced cell cycle arrest, revealing a reduction in apoptosis rates, which collectively contribute to radioresistance (Fig. 1, Cell cycle section) [29].

Mitochondrial dysfunction

ATAD3A

Cells expressing high levels of ATAD3A exhibit increased resistance to radiation-induced cell death, as demonstrated in in vitro experiments using GBM cell lines. Clinically, high ATAD3A expression was correlated with worse prognosis in GBM patient samples, suggesting its potential as an independent biomarker for radioresistance. Mechanistically, in vitro studies showed that ATAD3A mitigates radiation-induced mitochondrial dysfunction, which alters nuclear ATM signaling pathways. Furthermore, ATAD3A plays a crucial role in maintaining mitochondrial integrity, thereby contributing to increased radioresistance (Fig. 1, Mitochondrial dysfunction section) [30].

Energy metabolism

UBE2S

Another protein expressed in gliomas is ubiquitin conjugated enzyme E2S (UBE2S). High UBE2S expression is negatively associated with 1p19q deletion and IDH1 mutation, which contributes to glioma radioresistance, and it is positively associated with PTEN mutation and EGFR amplification. Specifically, in GBM, UBE2S is linked to Akt phosphorylation, and through controlling the proteasomal breakdown (Fig. 1, Protein degradation pathways) of von Hippel–Lindau (VHL), UBE2S is vital for HIF-1a stabilization. UBE2S leads to the FAK phosphorylation at Tyr397, which is critical for multiple signaling pathways that regulate cell proliferation, migration, and invasion [31, 79]. These processes are critical for tumor growth and response to therapy, further underscoring the potential role of UBE2S in glioma biology.

Metabolites

In an astrocytoma mouse model, specific metabolites, such as fumarate and glucose-1,6-bisphosphate, were identified as potential biomarkers of response to RT. Fumarate levels were positively correlated in treated mice, distinguishing the RT group from the control group. Metabolic profiling of tumor tissues revealed that RT disrupted key metabolic pathways [80]. In another study, authors explored how metabolic modulation can enhance the effectiveness of RT in GBM. They found that high glycolysis in GBM cells contributes to radioresistance, suggesting that targeting tumor metabolism could help overcome this resistance. The study focused on dichloroacetate (DCA), a pyruvate dehydrogenase kinase 1 inhibitor that shifts GBM cells from glycolysis to oxidative phosphorylation. Although DCA alone showed modest antitumor effects, combining it with RT significantly improved treatment outcomes. In vitro, DCA enhanced radiation sensitivity by inducing G2–M cell cycle arrest, increasing oxidative stress, and amplifying DNA damage. In vivo, the combination of DCA and RT improved survival in mice with GBM. This study demonstrates the potential of combining metabolic targeting with RT to improve treatment efficacy in GBM [32].

Purines

By correlating intracellular metabolite levels with radiation resistance across several genomically distinct GBM models, a study demonstrated that high purine metabolite levels, especially guanylate, strongly correlated with reduced radiation sensitivity. Inhibiting GTP synthesis using FDA-approved inhibitors, such as mycophenolate mofetil (MMF), radiosensitized GBM cells and patient-derived neurospheres by impairing DNA repair processes. Interestingly, exogenous purine nucleosides protected radiation-sensitive GBM models by promoting

DNA repair, indicating that purine metabolism plays a crucial role in mediating radiation resistance. The study also found that high expression of the rate-limiting enzyme of de novo GTP synthesis was associated with poor prognosis and shorter survival in GBM patients. These findings suggest that targeting purine metabolism, particularly GTP synthesis, could be a promising strategy to overcome therapy resistance in GBM [33].

Stress response

Endoplasmic reticulum (ER) stress is induced when proteins are misfolded and start to accumulate. The unfolded protein response (UPR) uses mechanisms that attempt to regain homeostasis via the temporary shutdown of protein translation and increasing the folding ability of the ER. As shown in Fig. 1.

ER Stress

The UPR process is a cellular process that helps maintain the burden of stress from misfolded or accumulated proteins and promotes cell survival under stressful conditions. In glioma, either the cell survival-promoting effect or an apoptosis-inducing effect can be mediated by the UPR, depending on the extent and duration of stress [81]. The PERK-eIF2α route is one of these crucial ER stress response pathways, and it is linked to regulating radiosensitivity in various cancers, such as head and neck tumors [12]. An in vitro study revealed that radiation causes ER stress in GBM cells, increasing downstream signaling attributed to the stress response in GBM, linked to changes in the reactive oxygen species balance. Furthermore, ATF6 was shown to be a main regulator of the UPR/ER stress pathway and to maintain the viability of GBM cells under stress conditions. Knocking down ATF6 increased cell death, indicating that it caused radioresistance in glioma. ATF6, activated in response to radiation, upregulates the proteins GRP78 and NOTCH1. NOTCH1 signaling is linked to cell survival and proliferation, and GRP78 protects cells from stress. When exposed to radiation, glioma cells have a higher chance of surviving when these proteins are upregulated, indicating that these proteins are part of stress response mechanisms contributing to radioresistance [34]. One study reported that radiation potently induces the UPR in GSCs. When 2-deoxy-D-glucose (2-DG) was combined with radiation, the UPR response was potentiated, increasing the degree of stress in glioma cells. This increased stress further lowered their potential to survive following radiation; thus, increasing their radiosensitivity. Through a stress response brought on by overexpression of the UPR, 2-DG may make GSCs more delicate to radiation [82]. GRP78 is overexpressed in GBM and is an ER chaperone implicated in the UPR. GRP78 overexpression has a major role in glioma cells' ability to survive and withstand various stresses, such as RT and chemotherapy. One study revealed that the inhibition of caspase-7 activation, one of the key constituents of the apoptotic pathway for survival, was mediated by GRP78 in glioma cells. This antiapoptotic effect promotes the radioresistance of glioma cells, allowing them to survive after RT. Suppression of the GRP78 expression increases glioma cells' susceptibility to RT and chemotherapy, leading to increased cell death rates [35].

Apoptosis

P2X7 purinergic receptor

Activation of the P2X7 purinergic receptor (P2X7R) by high concentrations of extracellular ATP induces apoptosis in glioma cells. This receptor triggers cytotoxicity caused by ATP, facilitating RT-mediated cell death. High expression of P2X7R is related to intense apoptosis (Fig. 1, Apoptosis section); therefore, P2X7R is considered an important marker for predicting radiosensitivity in glioma cells [83]. In an in-vivo study, mice lacking functional P2X7Rs developed radioresistance and consequently had a smaller reduction in tumor volume than mice with functional P2X7Rs following RT. Additionally, patients with elevated P2X7R levels in human glioma samples were more radiosensitive and lived longer than those with lower P2X7R levels [11].

P53

The p53 status influences radiosensitivity and the apoptotic response in glioma cells (Fig. 1, Apoptosis section). However, even in p53-deficient tumors, alternative pathways can trigger apoptosis after irradiation. Ceramide is a naturally occurring lipid generated through acid sphingomyelinase activation and was found to be the main executor of p53-independent apoptosis following gamma irradiation in glioma cells. A significant build-up of ceramide illegitimately induced apoptosis in p53-deficient glioma cells, which indicated that ceramide acts in a pro-apoptotic manner in response to radiation. In cells with functional p53, acid ceramidase is an upregulated enzyme that breaks down ceramide into smaller components, thereby reducing intracellular ceramide levels and promoting increased cell survival following radiation exposure [36]. Inhibiting ceramidase may increase radiosensitivity through targeting some glioma cells. Regardless of whether p53 was wild-type or mutant, a different study found that E2F1 caused cell death in glioma cell lines. The effect is further enhanced when p53 is combined with ionizing radiation; this discovery implies that the apoptotic pathway may be independent of p53 and could be leveraged to enhance radiosensitivity. GSCs are generally immune to primary apoptosis induced by radiation. This resistance may contribute to the low control of gliomas observed in patients treated with radiation

and indicates that strategies to induce apoptosis should be implemented as part of the treatment regimen. E2F1 induces apoptosis without inducing the proapoptotic protein BAX, which is a common inducer of p53-dependent pathways of apoptosis. These findings further support the role of a p53-independent pathway of apoptosis in glioma cells. This study suggests that therapies directed toward the activation of E2F1 or similar mechanisms could enhance glioma cell radiosensitivity by promoting apoptosis, thereby overcoming intrinsic tumorradioresistance [37].

Autophagy

Autophagy can be a double-edged sword: it can facilitate cell survival under stress conditions by degrading damaged organelles and proteins, while it may also cause autophagy-mediated cell death when cellular stress is too high. According to a study by Daido et al., autophagy is triggered when the DNA-dependent catalytic subunit of protein kinase is inhibited, leading to radiosensitization of GBM cells, hence suggesting that autophagic processes can impact overall sensitivity to RT [38].

PI3K/Akt/mTOR

One crucial cell survival mechanism linked to carcinogenesis is the PI3K/Akt/mTOR. Its suppression induces autophagy instead of apoptosis, thereby increasing radiosensitivity in GBM. This pathway presents a potential therapeutic target to modulate autophagy for improved treatment outcomes [39]. One study reported that irradiation significantly increases autophagic flux in the radioresistant GBM cell lines U251R and U87, whereas the radiosensitive cell line U251 does not show increased autophagic flux. Inhibiting autophagy with bafilomycin A1 reduced radioresistance in GBM cells, indicating that autophagy is a cell survival-promoting mechanism when exposed to radiation. Syndecan 1 and transglutaminase 2 are among the key proteins that are overexpressed in radioresistant cells. This indeed reflects their role in maintaining a high level of autophagy, hence contributing to radioresistance. Syndecan 1 and transglutaminase 2 confer radioresistance by facilitating the fusion of lysosomes with autophagosomes, thereby preserving the autophagic flux to ensure cell survival following irradiation (Fig. 1, Autophagy). A new protein complex mediated by Syndecan 1, transglutaminase 2, flotillin 1, and betaine homocysteine methyltransferase has been identified, executing the fusion of autophagosomes and lysosomes. This complex, via high levels of autophagy in irradiated GBM cells, promotes radioresistance [40].

DNA damage and repair

As shown in Fig. 1, DNA damage response systems can lead to radiosensitivity via different molecular pathways [42].

HGF/MET pathway

One significant pathway is the hepatocyte growth factor (HGF)/MET pathway. Research has demonstrated that this pathway could play a role in GBM radioresistance via preinvasive and DNA damage response mechanisms. Inhibition of MET results in the inhibition of proinflammatory cytokines, which have been shown to synergistically suppress experimental syngeneic glioma growth along with irradiation. This process requires MET expression in the tumor and an intact immune system. Combining RT with MET inhibition prolongs survival in GBM. It has been mentioned that MET inhibition decreases the induction of immunomodulatory, proinflammatory, and proangiogenic pathways by RT, thereby increasing the efficacy of RT [41].

High mobility group box 2

High mobility group box 2 (HMGB2) is linked to poor prognosis in GBM due to its role in promoting cell proliferation, viability, DNA damage repair, and invasion. It induces radioresistance, partly through colony formation. These findings suggest HMGB2 as a potential biomarker and prognostic factor for OS in GBM [42].

Nucleobindin-2

Nucleobindin-2 (NUCB2) plays an important role in glioma progression and prognosis in GBM. Also, with its established functions in energy homeostasis, NUCB2 promotes tumor cell survival, migration, invasion, and enhanced DNA damage repair following RT. Its expression is strongly correlated with poor prognosis in GBM patients [43].

RAD51

GSCs rely heavily on RAD51-mediated repair. Inhibiting RAD51 in GSCs impaires robust DNA repair mechanisms. Resistance to RT is thought to be due to efficient DNA double-strand break (DSB) repair and the nonhomologous end joining (NHEJ) repair pathway, which is also essential for fixing DSBs. The RAD51, a DSB repair protein, is high in GSCs and contributes to DSB repair after RT. Small-molecule RAD51 inhibitors prevent RAD51 focus formation, reduce DNA DSB repair, and cause significant radiosensitization [44]. Inhibition of RAD51 can also inhibit homologous recombination (HR) function, which increases the replication-specific radiosensitizing effects of poly (ADP-ribose) polymerase (PARP) inhibition [84]. Inhibition of PARP promotes the

radiosensitivity of human GBM cells and triggers DNA breaks that are repaired via HR [85].

ASPM

ASPM expression plays a key role in cell proliferation, invasion, and migration and causes the G0/G1 phase to stop. There are binding sites in the ASPM promoter for the transcription factor FoxM1. Increased FoxM1 is positively correlated with ASPM and promotes the migration and proliferation of glioma cells [86]. Inhibition of ASPM increases the number of abnormal chromosomes, indicating that ASPM is involved in preserving genomic stability in the DNA repair process. ASPM is required for efficient NHEJ, and its function appears to involve a DNA-PK-dependent pathway. This is a radioresistance mechanism of GBM cells [45].

Notch

Inhibition of the Notch pathway renders GSCs more sensitive to radiation at relevant doses. The expression of Notch1 or Notch2 protects GSCs against RT. Notch inhibition reduces Mcl-1 levels and Akt activity and also sensitizes GSCs to RT [46].

Differentiation

Podoplanin (PDPN) has been identified as an independent biomarker across different studies in both low- and high-grade gliomas. Research has shown that the PDPN potential mechanism is probably involved in cell differentiation. The PDPN expression on the cancer cells is associated with tumor aggressiveness and radioresistance, and its knockdown can prolong patient survival [47].

Stemness

Cancer stem cells (CSCs) are crucial in tumor formation, progression, metastasis, and also treatment resistance. They share the characteristics of signaling pathways of stem cells and self-renewal capabilities, highlighting their unique importance in cancer biology. GSCs are distinct cells within tumors contributing to treatment challenges, poor outcomes, and tumor recurrence [87]. Research has focused on identifying GSCs using specific markers to understand their mechanisms and predict radioresistance. Notably, a 12-gene-derived stemness score has been associated with key clinicopathological features and proposed as a novel prognostic indicator; gliomas with a low stemness score appear more responsive to chemotherapy, highlighting its potential role in guiding treatment stratification [88].

CD133

CD133, identified as a marker of CSCs, has been linked to radioresistance in multiple types of cancers [89]. Compared to CD133- cells, CD133 + glioma cells show more efficient DNA damage repair via activation of DNA damage checkpoint proteins, Chk1 and Chk2, after RT exposure (Fig. 1, "Glioma stem cells" section) [90]. CD133 + tumors are associated with shorter PFS, indicating a role of CD133 in promoting radioresistance [48]. In orthotopic models, Jamal et al. found that CD133 + GBM stem cell-like cells (CSCLs) were more radioresistant than CD133 – negative cells, showing reduced radiation-induced DNA DSBs [49]. Conversely, no notable change was observed between CD133- and CD133 + cells in vitro, highlighting the importance of brain microenvironmental factors in leading to the radioresistance of CD133 + GSCs [49]. Tamura et al. conducted a study to evaluate CD133 + expression across different glioma grades and assess its impact on the effectiveness of RT. They found that RT increased CD133 + expression and Ki-67 indices in high-grade and de novo GBMs, but not in LLGs, suggesting that CD133 + cells may drive post-RT proliferation, invasiveness, and recurrence in de novo GBM [91]. Cathepsin L, a lysosomal protease overexpressed in many cancers, promotes invasion by degrading the extracellular matrix [92]. Wang et al. reported its co-expression with CD133 in malignant gliomas and showed that Cathepsin L knockdown reduced stemness, impaired self-renewal, and increased radiosensitivity by limiting checkpoint activation, DNA repair, and induced apoptosis. They also confirmed in vivo that inhibiting Cathepsin L reduced GSC stemness and decreased blood vessel formation [50]. As an upstream regulator of NF-κB, its inhibition also induces G2/M arrest [93]. Alongside other cathepsins (B, D, Z/X), Cathepsin L may serve as a prognostic marker of glioma radioresistance [94].

CD146

As shown in Fig. 1 ("Glioma stem cells" section), CD146 is a cell adhesion molecule overexpressed in GSCs and promotes GBM aggressiveness and stemness. Liang et al. showed that high CD146 levels correlate with increased invasion, tumor grade, and upregulation of stem cell factors such as Oct-4 and SOX2. Moreover, CD146 increases radioresistance by enhancing cell survival via the downregulation of p53 and activation of NF-κB [51, 95, 96]. Also, Liang et al. found that CD146 upregulates Yes-associated protein (YAP) through the Hippo pathway, a mechanism recently correlated with radioresistance in other cancers as well [51].

CD44

Liu et al. demonstrated that CD44 enhances CSC properties, promotes angiogenesis, and contributes to radioresistance in GBM following optimal RT (Fig. 1, "Glioma stem cells" section) [52]. Its expression also correlates with nestin, a stem cell marker [53]. Conversely, CD44 knockdown reduces differentiation markers, impairs

sphere formation, and increases CD133 levels [97]. In a study analyzing both primary and recurrent GBM cases, CD44 expression was higher in more aggressive tumor subtypes. Interestingly, despite indicating less aggressive features, lower CD44 levels were unexpectedly associated with reduced survival. The authors proposed that this paradox may reflect the complex, context-dependent role of CD44; notably, lower CD44 expression has been linked to resistance to alkylating agents such as temozolomide (TMZ). Thus, tumors with lower CD44 may be more chemoresistant and prone to recurrence, contributing to poorer outcomes [54]. In contrast, another study analyzing 62 newly diagnosed GBM patients found that high CD44 expression was significantly associated with shorter OS (3.5 vs. 18.5 months) and was an independent poor prognostic factor in multivariate analysis. CD44 overexpression correlated with more extensive tumor invasion but not with recurrence, suggesting that high CD44 may reflect a more intrinsically aggressive tumor phenotype in treatment-naïve GBM [55]. These discrepancies may stem from differences in patient cohorts (treatment-naïve vs. recurrent) and the need to assess CD44 as an independent prognostic factor, as the context of treatment and tumor progression can alter its role. This highlights the complex role of CD44 in GBM and emphasizes the necessity for extended research to ascertain its function in GSCs and its diagnostic and prognostic potential.

CHRDL

The Chordin-like (CHRDL) protein family, including Chordin-like 1 and 2 (CHRDL1 and CHRDL2), promotes differentiation in GBM by inhibiting bone morphogenic protein 4 (BMP4) and reducing their tumorigenic potential [98]. Burglar et al. demonstrated that CHRDL1 depletion reduces GBM stemness's functional and molecular features, ultimately enhancing radiosensitivity through BMP4 signaling pathway [56]. The Chordin family appears significant in facilitating radioresistance in GSCs; however, further research is required to validate this association.

STAT3

The signal transducer and activator of transcription 3 (STAT3) is an oncogene and also a transcription factor that promotes cancer progression by remaining active in various tumors. It supports metastases formation, growth, and CSC maintenance, though it also influences the tumor microenvironment and immune responses [99]. Lin et al. also discovered that the STAT3/Slug axis promotes tumor invasion and CSCL properties in radioresistant GBM cells [57]. The phosphorylation of STAT3 at serine 727 (pS727-STAT3) is correlated with poor prognosis and reduced survival in GBM patients, and its inhibition has been shown to enhance the radiosensitivity of GSCs (Fig. 1, "Glioma stem cells" section) [58]. These findings suggest that STAT3 can serve as a biomarker of radioresistance in GSCs.

FoxM1

Forkhead box M1 (FoxM1) is one of the crucial transcription factors for malignant gliomas. It promotes progression and development by supporting cell invasion, proliferation, angiogenesis, and CSC self-renewal (Fig. 1, "Glioma stem cells" section) [100]. Lee et al. found that FoxM1 mediates Sox2 in GBM cells, playing a role in maintaining stemness and promoting radioresistance. They confirmed their findings by showing that Sox2 expression was reduced in cells with FoxM1 knockdown, which amplified the sensitivity of GBM cells [59]. Additionally, FoxM1 interacts with maternal embryonic leucine-zipper kinase (MELK) to form a complex that enhances FoxM1 phosphorylation and activation. This complex regulates essential mitotic genes in GSCs and the proliferation of GSCs [101]. Inhibiting MELK kinase with Compound 1 and OTSSP167 causes mitotic catastrophe and apoptosis in GSCs, decreases tumor growth, and makes cells more sensitive to RT [102].

EZH2

EZH2 is a polycomb group protein that supports the maintenance of GSCs and promotes tumor progression (Fig. 1, "Glioma stem cells" section). Inhibition of EZH2 disrupts self-renewal, reduces proliferation, and suppresses the expression of oncogenes such as Akt and c-Myc [103]. Kim et al. demonstrated that the MELK-FoxM1-EZH2 signaling is vital for radioresistance. Their analysis revealed that MELK/FoxM1 enhances EZH2 signaling, promoting tumorigenesis and progression after RT [60]. Wang et al. discovered that NIMA-related kinase 2 (NEK2) is a protein-binding of EZH2, which has a crucial role in the post-translational regulation of EZH2 in GSCs. They observed that NEK2 is vital for conserving GSCstemness and promoting growth, while its kinase activity regulates EZH2, contributing to radioresistance in GSCs. The study confirmed that NEK2 expression is higher in recurrent GBM tissues compared to naive patients, indicating its role in therapy resistance. Finally, they exhibited a novel NEK2 inhibitor, CMP3a, which has shown promise in attenuating GBM growth and inhibiting tumor proliferation, thereby enhancing the effectiveness of RT [104]. It can be concluded that EZH2 and NEK2 play key roles in GSC-mediated radioresistance and may serve as potential biomarkers in future studies.

FGFR1

Fibroblast growth factor receptor 1 (FGFR1) is amplified and highly expressed across multiple cancer types.

Noncanonical FGFRs are involved in cell adhesion and extracellular matrix proteins, having a role in the migration and invasion of cancer cells [105]. Andersson et al. found that inhibiting FGFR1 increased the tumor sensitivity to radiation (Fig. 1, "Glioma stem cells" section). This inhibition reduced FoxM1 levels and increased FOXN3 levels. Additionally, knocking down FoxM1 or FGFR1 decreased the epithelial-to-mesenchymal transition (EMT) genes associated with tumor resistance. In this way, the FGFR1/FoxM1/EMT gene axis may predict GBM relapse [61]. Additionally, it has been previously established that FGFR1 signaling has a role in this resistance via activating the PLCγ/HIF1α pathway [62].

AurA

Aurora A (AurA) is a serine/threonine kinase involved in cell division, centrosome maturation, mitotic entry, spindle formation, and cytokinesis (Fig. 1, "Glioma stem cells" section) [106]. Inhibiting AurA has been shown to enhance chemo- and radiosensitivity in GBM. Hsu et al. demonstrated that AurA promotes GSC stemness via the FGF1/FGFR pathway, while its inhibition reduced the GSC population [63]. These findings suggest that AurA has a crucial role in increasing GSC characteristics and contributes to radioresistance and may serve as a potential marker.

PAF

Proliferating cell nuclear antigen (PCNA)-associated factor (PAF) is a DNA damage protein overexpressed in GSCs. It controls the DNA translesion synthesis (TLS) enzymes, easing error-free DNA synthesis (Fig. 1, "Glioma stem cells" section). This, in turn, supports GSC self-renewal, tumorigenicity, and stemness, ultimately contributing to radioresistance [64]. These findings indicate that PAF might be a maintenance factor for GSCs, highlighting the need to validate its role further.

ATM

Ataxia-telangiectasia mutated (ATM) plays a crucial role in preserving genome stability (Fig. 1, "Glioma stem cells" section). The gene initiates cellular stress responses, regulating DNA repair, apoptosis, cell cycle arrest, and oxidative sensing [107]. Zhou et al. demonstrated that GSCs exhibit higher radioresistance than GBM cells, attributed to their elevated expression of phosphorylated cell cycle checkpoint proteins [65]. Subsequently, they found that inhibiting ATM in GSCs leads to increased G2 phase arrest and a higher apoptosis rate following irradiation, enhancing the radiosensitivity of GSCs [108]. Another study found that GSCs exhibit significantly higher radioresistance due to the efficient repair of DSBs. Interestingly, this effect is reversed by inhibiting ATM [109]. These findings indicate the use of ATM as a marker for radioresistance in GSCs.

Epigenetic mechanisms

DNA methylation is one of the key epigenetic mechanisms in glioma development, where aberrant hypermethylation and hypomethylation of specific genes contribute to tumor formation and progression. Irregular gene methylation alters DNA repair, cell proliferation, and cell cycle regulation, influencing tumor sensitivity to radiation and affecting patient survival and treatment outcomes [110]. For example, a CGGA-based study on 288 glioma cases identified a nine-gene risk model based on m6A methylation regulators significantly associated with OS in glioma. The risk score correlated with key clinical features, including RT status. Notably, high-risk patients with high-grade glioma showed greater sensitivity to RT and TMZ, suggesting m6A-related gene expression may serve as a biomarker of radiosensitivity [111].

Glioma-Cytosine-phosphate-Guanine (CpG) island methylator phenotype (G-CIMP)

CpG islands are regions rich in G-C content and typically found near or within the gene promoters. Abnormal methylation of these regions has a critical role in cancer development [112]. Noushmehr et al. identified a distinct subtype of gliomas, the glioma-CpG island methylator phenotype (G-CIMP). This subtype is explained by extensive hypermethylation across various genetic loci and is associated with mutations of IDH1, earlier age at diagnosis, and improved patient outcomes (Fig. 1, Epigenetics section) [113]. IDH-mutant gliomas with a G-CIMP + phenotype share molecular features with LGGs and are associated with better outcomes. Guan et al. demonstrated that proneural G-CIMP +, IDH1-mutant gliomas II/III (LGGs) have significantly better survival rates than other molecular subtypes. Although this subtype is not common, it holds considerable significance [66]. In contrast, the G-CIMP-low subtype showed the lowest OS among IDH-mutant gliomas. Meanwhile, IDH-wildtype G-CIMP – LGGs display features that resemble GBMs more closely [114].

CpG methylation signatures

CpG methylation signatures refer to specific DNA methylation patterns at CpG sites and have a crucial role in cancer progression and development. Yin et al. identified an 8-CpG signature linked to immune-related gene expression in non-G-CIMP GBMs. This signature is independently linked to poorer outcomes and potential resistance to standard therapies like RT due to the immune-suppressive tumor environment [115]. A recent study detected a 64-CpG methylation panel, focusing specifically on a 10-CpG risk signature, through

a genome-wide methylation analysis of non-G-CIMP GBM with an unmethylated MGMT promoter. Patients categorized as "low-risk" based on this signature exhibited significantly better survival rates when treated with a combination of TMZ and RT compared to high-risk patients. This OS advantage was especially pronounced with the combined therapy compared to RT alone [116]. Li et al. set a risk-score signature based on the methylation of pseudogenes in non-G-CIMP GBMs. Their findings indicate that a higher score predicts better outcomes for patients treated with RT alone than those receiving both RT and TMZ. This pseudogene methylation has the potential to be a novel biomarker, guiding the choice between solo and combination therapy in non-G-CIMP GBMs. However, this signature relies on microarray data that is not widely accessible in routine clinical settings and requires further validation using pyrosequencing or targeted methylation assays to facilitate its potential translation into practice [117].

MGMT promoter methylation

The MGMT gene encodes a repair enzyme for the DNA responsible for removing alkyl groups from the O6 position of guanine. MGMT promoter methylation silences the gene, reducing enzyme activity and limiting DNA repair, which increases tumor sensitivity to chemotherapy. This methylation is particularly associated with heightened sensitivity to alkylating agents like TMZ and improved OS rates in GBM [118]. Additionally, in vitro studies have shown the TMZ radiosensitizing effect in glioma cells [67]. A study by Rivera et al. has revealed that GBM with a methylated MGMT promoter that underwent RT without chemotherapy experienced a significantly lower progression rate of 29%, compared to 58% for those with an unmethylated promoter. This indicates that a methylated MGMT promoter may serve as a prognostic factor for radiosensitivity (Fig. 1, Epigenetics section) [68]. Conversely, a randomized trial involving elderly patients with grade 2 to 4 gliomas, found no difference in OS between patients with methylated and unmethylated MGMT promoters when treated with RT alone [119], possibly due to age-related comorbidities contributing to mortality. Tini et al. observed that in grade 4 glioma patients with unmethylated MGMT promoters, a higher dose of RT (70 Gy) significantly improved OS and PFS compared with the standard RT dose of 60 Gy. Notably, both groups received TMZ along with the RT [69]. Roszkowski et al. found that glioma with an MGMT promoter methylation and IDH1 mutation had a significantly better prognosis, showing a median OS of 40 months compared to patients with MGMT promoter methylation but wild-type IDH1. This finding suggests MGMT promoter hypermethylation and the IDH1 p.R132H mutation may enhance radiosensitivity. Together, these results indicate that MGMT promoter methylation is an advantageous prognostic factor. Additionally, the co-occurrence of promoter methylation of MGMT with the IDH1 mutation may significantly enhance patient survival, leading to a more favorable prognosis https://www.mdpi.com/1422-0067/17/11/1876. In summary, the interaction between G-CIMP methylation, MGMT promoter methylation, and IDH mutations is crucial in influencing the effectiveness of RT and chemoradiotherapy in glioma patients [120].

MicroRNA

MicroRNAs (miRNAs) play a critical role in glioma by modulating genes and influencing disease progression [121]. A study identified 34 differentially expressed miRNAs post-RT, with hsa-miR-208b-3p and hsa-miR-6731-5p upregulated and hsa-miR-2116-3p downregulated, implicating the p53 signaling [122]. Furthermore, a five-microRNA signature has classified patients into high-risk or low-risk groups based on survival outcomes. It was more effective than the IDH mutation in predicting OS, with higher microRNA expression linked to shorter lifespans and higher mortality [123].

MiR-196b, an oncogene in glioma, promotes proliferation via the PI3K/AKT pathway (Fig. 1, Micro RNAs section). Its downregulation increases sensitivity to TMZ and RT by enhancing apoptosis [70].

Additionally, 37 differentially expressed long non-coding RNAs (lncRNAs) were identified, with subsequent analysis demonstrating their remarkable enrichment in cancer-related pathways, including the PI3K-Akt and MAPK signaling pathways. Gene Ontology analysis showed that the activation of processes related to cell proliferation and the DNA damage response has a role in radioresistance. Following these findings, researchers created a risk signature based on three specific DElncRNAs, which functioned as independent indicators for patient outcomes in LGG after RT prediction [124].

A study identified lncRNA DRAIC as a biomarker for predicting patient outcomes. It showed that high DRAIC expression is linked to better OS and PFS, including improved survival after RT. Analyses revealed its association with the ribosome pathway but found no link to MGMT methylation in LGG. However, DRAIC expression was associated with 1p19q codeletion and IDH mutation [125].

A recent study identified several miRNAs as important prognostic markers for primary GBM after receiving RT. Loss of miR-221/222, a microRNA that plays an anti-apoptotic role by inhibiting p27 [126], was associated with a better prognosis, while high expression of miR-221/222 correlated with shorter OS. Additionally, multivariate analysis confirmed miR-19b, miR-18a, and miR-17-5p as independent prognostic indicators [71].

The biology of brain tumors is highly complicated, with epigenetic modifications, tumor heterogeneity, and the surrounding microenvironment critically influencing both tumor progression and therapeutic response. Addressing treatment resistance, particularly radioresistance, requires a more comprehensive understanding of these molecular and epigenetic pathways. However, insights into the epigenetic dynamics within its heterogeneous and complex microenvironment in GBM remain limited. Epigenetic therapies, such as histone deacetylase (HDAC) inhibitors and histone methyltransferase (HMT) inhibitors, have demonstrated potential in other malignancies by enhancing radiosensitivity or mitigating radiation-induced toxicity. Nonetheless, further targeted research is essential to optimize drug delivery and improve therapeutic outcomes in neuro-oncology [127].

Future directions

Despite advances in GBM research, treatment outcomes remain poor, highlighting the need for novel therapeutic strategies. To address this, future research must take a two-pronged approach: [1] identifying promising radiosensitivity biomarkers by integrating genomic, molecular, and imaging technologies and [2] optimizing treatment strategies targeting multiple markers to enable precision medicine approaches tailored to the unique biology of GBM. The following sections briefly discuss recent and ongoing research efforts that exemplify these directions. A recent analysis of multiple GBM datasets, including tumor and blood samples combined with whole-exome sequencing, revealed significant mutations in the OBSCN and AHNAK2 genes involved in cytoskeletal organization, survival, migration, and oncogenic signaling. These mutations influence glioma progression, underscoring the need for comprehensive, multi-gene assessments in large patient cohorts. Future research should build upon these comprehensive methods to identify biomarkers that can predict radiosensitivity and inform tailored treatment strategies [128]. Moreover, advancements in radiogenomics, combining molecular markers with imaging phenotypes, offer promising insights for predicting treatment response and prognosis in GBM. Integrating techniques such as diffusion imaging, perfusion, and spectroscopy with genomic data could enhance our ability to characterize tumor radiosensitivity. Future studies should focus on leveraging these technologies, alongside automated tumor segmentation, to refine RT planning and develop precision treatment strategies informed by molecular and imaging-based biomarkers [129].

On the other hand, optimizing postoperative RT administration may help reduce relapse risk and improve patient outcomes. However, the lack of a radiobiological framework tailored to GBM limits the ability to enhance radiation response, largely due to an incomplete understanding of the tumor's underlying genetic and biomolecular mechanisms. A radiobiological model that corresponds with clinical data indicates a moderate value for the GBM doubling time (Td: 15.4 days), alongside an extended kick-off time for accelerated repopulation (Tk: 37 days). Notably, tumor control probability (TCP) appears to depend more on the total radiation dose (up to a biologically effective dose (BED) of ~92 Gy) rather than on shortening the overall treatment duration, with models predicting a TCP exceeding 0.85 at this dose threshold [130]. Emerging evidence suggests that moderate hypofractionation has been associated with lower toxicity and improved median survival compared to conventional fractionation. Thus, increasing BED through optimized hypofractionation protocols warrants further investigation as a strategy to enhance local control and OS in GBM [131–133].

Additionally, an ongoing clinical trial (NCT05235737) is evaluating treatment strategies for newly diagnosed GBM, including neoadjuvant and adjuvant pembrolizumab, focusing on immune and molecular pathways. Using Immuno-PET imaging with 89Zr-DFO-Atezolizumab, the study tracks PD-L1 expression dynamics and its modulation by radiation and immunotherapy. This dual focus on molecular and imaging biomarkers to predict RT response may guide personalized treatment strategies in GBM.

These advancements emphasize the importance of integrating genomic, molecular, and imaging technologies to enhance our understanding of GBM radiosensitivity. This integration can drive the development of precision medicine approaches and improve the efficacy of RT and patient survival.

Conclusion

This article investigated various pathways or biomarkers of radiosensitivity in glioma based on the supporting evidence across preclinical and clinical studies.

Among immune-related markers, PD-L1 is consistently upregulated following RT and is associated with resistance. Its modulation through immune checkpoint inhibitors offers an immediately actionable clinical target.

Markers of hypoxia, such as HIF-1α, OSMR, NASP, and CA9, are also crucial. Hypoxic microenvironments contribute to impaired DNA damage response and survival signaling, which are mostly assessed in preclinical settings. Targeting these pathways in translational and further clinical studies could sensitize tumors to radiation. VEGF has been linked to resistance through enhanced vascularization and stress adaptation; although anti-VEGF therapies have yielded mixed clinical outcomes, they remain an area of active investigation.

High expression of MARCKS has been linked to increased radiosensitivity based on preclinical, in vitro,

and in vivo studies. Clinical dataset analysis suggested improved survival in GBM, suggesting its potential as a target for enhancing RT effectiveness. In contrast, elevated levels of ATAD3A are associated with radioresistance through the maintenance of mitochondrial integrity, with evidence from preclinical, in vitro, and clinical data analyses.

Alterations in energy metabolism contribute to GBM radioresistance. UBE2S promotes resistance to chemoradiotherapy through Akt/phosphorylation and is associated with PTEN mutations. Metabolic reprogramming also plays a key role, with glycolysis linked to resistance, while enhanced oxidative phosphorylation has improved radiosensitivity in preclinical models. Additionally, elevated purine metabolism is correlated with poor survival and radiation resistance, with preclinical and clinical dataset analyses supporting the potential of targeting this pathway using FDA-approved inhibitors like MMF.

Preclinical in vitro studies suggest that the ER stress response influences glioma radiosensitivity. Radiation activates the UPR pathway, particularly via ATF6, GRP78, and NOTCH1, promoting radioresistance through enhanced survival signaling. However, combining RT with 2-DG enhances ER stress and amplifies the UPR in GSCs, pushing them beyond their adaptive capacity. This heightened stress disrupts survival mechanisms and increases radiosensitivity. These findings from preclinical in vitro models highlight the dual role of the ER stress response in glioma radiosensitivity and suggest therapeutic opportunities in this pathway.

High expression of the apoptosis-related factors like P2X7R has been linked to enhanced radiosensitivity and improved survival probability in GBM, suggesting its potential as a therapeutic target. Additionally, overexpression of E2F1 has increased radiosensitivity, independent of p53 status, highlighting its role in modulating the apoptotic response to radiation.

Increased autophagic flux via the PI3K/Akt/mTOR pathway promotes cell survival and radioresistance in GBM. Overexpression of syndecan 1 and transglutaminase 2 is observed in radioresistant GBM cells. Targeting autophagy in preclinical in vitro studies, with bafilomycin A1, has enhanced radiosensitivity.

DNA repair pathways present some of the most promising targets for radiosensitization. The HGF/MET pathway contributes to GBM radioresistance, with MET inhibition improving survival when combined with RT in the preclinical setting. High HMGB2 expression correlates with poor prognosis and enhanced radioresistance. NUCB2 promotes glioma recurrence and tumor growth. Notably, RAD51 and ATM are upregulated in glioma stem-like cells and contribute directly to enhanced DNA repair capacity following radiation. Inhibition of these molecules has shown preclinical success in restoring radiosensitivity.

Differentiation-related markers like PDPN are upregulated in resistant cells, mostly based on preclinical models. Retrospective clinical cohort analysis has linked this to poor outcomes.

Stemness-related markers contribute to GBM radioresistance by sustaining glioma stem-like cells and enhancing DNA repair. CD133, CD146, and CHRDL1 are associated with poor prognosis and promote tumor survival and angiogenesis, although clinical data on CD44 remain mixed. Key regulators such as STAT3, FoxM1, EZH2, FGFR1, and AurA support stemness and treatment resistance, while ATM and PAF enhance DNA repair under stress. Most of these markers were identified in preclinical models or through retrospective cohort data analysis. Targeting these pathways may improve radiosensitivity and therapeutic outcomes.

Epigenetic markers also provide valuable insights into treatment responsiveness. MGMT promoter methylation remains a strong predictor of RT and TMZ response, while the G-CIMP + phenotype is associated with improved survival. These features support their inclusion in patient stratification frameworks for clinical trials.

Identifying radiosensitivity and radioresistance biomarkers in glioma has important translational potential. Radioresistant features may justify RT dose escalation or the use of sensitizers, while radiosensitive profiles could support dose de-escalation to minimize toxicity. Such biomarker-guided strategies, though needing validation, may pave the way for personalized RT in glioma. However, translating these findings into clinical practice remains challenging due to tumor heterogeneity, intricate interplay between genetic alterations and phenotypic expressions, and dynamic evolution of GSCs [134]. GBM is characterized by marked heterogeneity, both between tumors (inter-tumor) and within a single tumor (intra-tumor), challenging accurate biomarker identification, molecular diagnosis, and treatment planning, as single-biopsy approaches may fail to reflect the whole tumor landscape [135]. Intra-tumor heterogeneity also extends to radiosensitivity, with some tumor regions responding differently to radiation than others, depending on their genetic makeup. To address these challenges, multi-regional sampling for molecular characterization is essential, along with integrated diagnostic and therapeutic approaches, involving personalized treatment combinations targeting multiple pathways [136]. Additionally, advancements in imaging modalities, such as multi-parametric MRI, PET imaging, and radiogenomic models, have enhanced the non-invasive identification of genetically distinct tumor subregions. Techniques like texture analysis and machine learning algorithms further facilitate the detection of intratumoral genetic

and physiological variability, offering promising tools to improve biopsy targeting, RT planning, and treatment response assessment [137]. Ultimately, interdisciplinary collaboration will be critical to translating these discoveries into practice.

Abbreviations

IDH	Isocitrate dehydrogenase
TERT	Telomerase reverse transcriptase
EGFR	Epidermal growth factor receptor
RT	Radiotherapy
RSI	Radiosensitivity index
TNF	Tumor necrosis factor
TGF	Transforming growth factor
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
sPD-L1	Soluble PD-L1
PFS	Progression-free survival
RGS4	Regulator of G protein signaling 4
HIF	Hypoxia-inducible factor
OSMR	Oncostatin M receptor
ANXA2	Annexin A2
NASP	Nuclear autoantigenic sperm protein
STAT3	Signal transducer and activator of transcription 3
CA9	Carbonic anhydrase IX
VEGF	Vascular endothelial growth factor
BEV	Bevacizumab
GDF15	Growth/differentiation factor-15
MARCKS	Myristoylated alanine-rich C-kinase substrate
UBE2S	Ubiquitin conjugated enzyme E2S
VHL	Von hippel–lindau
DCA	Dichloroacetate
MMF	Mycophenolate mofetil
ER	Endoplasmic reticulum
UPR	Unfolded protein response
2-DG	2-deoxy-D-glucose
HGF	Hepatocyte growth factor
GBM	Glioblastoma
HMGB2	High mobility group box 2
NUCB2	Nucleobindin-2
DSB	Double-strand break
NHEJ	Nonhomologous end joining
HR	Homologous recombination
PARP	Poly (ADP-ribose) polymerase
PDPN	Podoplanin
CSCs	Cancer stem cells
CSCLs	Cancer stem cell-like cells
LLG	Low-grade glioma
CHRDL1	Chordin-like 1
CHRDL2	Chordin-like 2
STAT3	Signal transducer and activator of transcription 3
pS727-STAT3	Phosphorylation of STAT3 at serine 727
FoxM1	Forkhead box M1
MELK	Maternal embryonic leucine-zipper kinase
NEK2	NIMA-related kinase 2
FGFR1	Fibroblast growth factor receptor 1
EMT	Epithelial-to-mesenchymal transition
AurA	Aurora A
PCNA	Proliferating cell nuclear antigen
PAF	PCNA-associated factor
ATM	Ataxia-telangiectasia mutated
GSCs	Glioma stem cells
CpG	Cytosine-phosphate-Guanine
G-CIMP	glioma-CpG island methylator phenotype
TMZ	Temozolomide
miRNAs	MicroRNAs
lncRNAs	Long non-coding RNAs
HDAC	Histone deacetylase
HMT	Histone methyltransferase
Td	Doubling time
Tk	Kick-off time
BED	Biologically effective dose
TCP	Tumor control probability

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S.B. conducted the investigation, gathered resources, and drafted the manuscript. R.A. contributed to validation, investigation, manuscript drafting, review, editing, and visualization. S.M., S.M.Z., and S.F. provided resources and contributed to manuscript drafting. P.A.J. and A.F. reviewed, edited, and validated the manuscript. R.G. conceptualized the study, supervised the project, administered the methodology, validated the findings, and reviewed and edited the manuscript. All authors reviewed the manuscript.

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