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SYSTEMATIC REVIEWS

Role of glioma stem cells in promoting tumor chemo- and radioresistance: A systematic review of potential targeted treatments

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Abstract

BACKGROUND

Gliomas pose a significant challenge to effective treatment despite advancements in chemotherapy and radiotherapy. Glioma stem cells (GSCs), a subset within tumors, contribute to resistance, tumor heterogeneity, and plasticity. Recent studies reveal GSCs' role in therapeutic resistance, driven by DNA repair mechanisms and dynamic transitions between cellular states. Resistance mechanisms can involve different cellular pathways, most of which have been recently reported in the literature. Despite progress, targeted therapeutic approaches lack consensus due to GSCs' high plasticity.

AIM

To analyze targeted therapies against GSC-mediated resistance to radio- and chemotherapy in gliomas, focusing on underlying mechanisms.

METHODS

A systematic search was conducted across major medical databases (PubMed, Embase, and Cochrane Library) up to September 30, 2023. The search strategy utilized relevant Medical Subject Heading terms and keywords related to including "glioma stem cells", "radiotherapy", "chemotherapy", "resistance", and "targeted therapies". Studies included in this review were publications focusing

on targeted therapies against the molecular mechanism of GSC-mediated re-sistance to radiotherapy resistance (RTR).

RESULTS

In a comprehensive review of 66 studies on stem cell therapies for SCI, 452 papers were initially identified, with 203 chosen for full-text analysis. Among them, 201 were deemed eligible after excluding 168 for various reasons. The temporal breakdown of studies illustrates this trend: 2005-2010 (33.3%), 2011-2015 (36.4%), and 2016-2022 (30.3%). Key GSC models, particularly U87 (33.3%), U251 (15.2%), and T98G (15.2%), emerge as significant in research, reflecting their representativeness of glioma characteristics. Pathway analysis indicates a focus on phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (mTOR) (27.3%) and Notch (12.1%) pathways, suggesting their crucial roles in resistance development. Targeted molecules with mTOR (18.2%), CHK1/2 (15.2%), and ATP binding cassette G2 (12.1%) as frequent targets underscore their importance in overcoming GSC-mediated resistance. Various therapeutic agents, notably RNA inhibitor/short hairpin RNA (27.3%), inhibitors (*e.g.*, LY294002, NVP-BEZ235) (24.2%), and monoclonal antibodies (*e.g.*, cetuximab) (9.1%), demonstrate versatility in targeted therapies. among 20 studies (60.6%), the most common effect on the chemotherapy resistance response is a reduction in temozolomide resistance (51.5%), followed by reductions in carmustine resistance (9.1%) and doxorubicin resistance (3.0%), while resistance to RTR is reduced in 42.4% of studies.

CONCLUSION

GSCs play a complex role in mediating radioresistance and chemoresistance, emphasizing the necessity for precision therapies that consider the heterogeneity within the GSC population and the dynamic tumor microenvironment to enhance outcomes for glioblastoma patients.

Key Words: Glioma stem cells; Chemoresistance; Radioresistance; Molecular pathways; Targeted therapies; Systematic review

Core Tip: The challenge of treating gliomas persists despite advancements in chemotherapy and radiotherapy, with glioma stem cells (GSCs) contributing to resistance and tumor heterogeneity. This systematic literature review, covering 66 studies, underscores the intricate role of GSCs in therapeutic resistance, particularly highlighting their involvement in DNA repair mechanisms and dynamic cellular state transitions. Targeted therapies face challenges due to GSCs' high plasticity, and the review emphasizes the need for precision treatments that account for GSC population heterogeneity and the tumor microenvironment's dynamic nature. Versatile therapeutic agents, including RNA inhibitor/short hairpin RNA, inhibitors (*e.g.*, LY294002, NVP-BEZ235), and monoclonal antibodies (*e.g.*, cetuximab), demonstrate efficacy in overcoming GSC-mediated resistance. Notably, the most common effect on the chemo- and radiotherapy response is a reduction in temozolomide resistance, highlighting the potential for improved outcomes by disrupting GSC-mediated resistance mechanisms in glioblastoma patients.

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INTRODUCTION

Gliomas, one of the most aggressive and prevalent form of primary brain tumors, continues to present a formidable challenge to effective therapeutic intervention[1]. Despite advancements in treatment modalities such as radiotherapy resistance (RTR) and chemotherapy resistance (CTR) with temozolomide (TMZ), the prognosis for glioma patients remains bleak, with a median overall survival of around 15 months[2-4]. A major obstacle in achieving better outcomes is the intrinsic resistance of gliomas to conventional adjuvant treatments[5]. In recent years, the focus has shifted towards understanding the role of glioma stem cells (GSCs) in fostering resistance to adjuvant therapies, unraveling a complex interplay between cancer stem cells and treatment response[4,6].

Central to the enigma of glioma resistance is the discovery that GSCs, a subpopulation within the heterogeneous tumor mass, contribute not only to tumor initiation and maintenance but also to tumor heterogeneity and plasticity. It is now known that GSCs, characterized by their self-renewal capacity and multilineage differentiation potential, are emerging as key players in the intricate landscape of glioma progression[4,5]. The ability of GSCs to generate different cellular states, driven by intrinsic and extrinsic factors, results in a dynamic equilibrium of heterogeneous cell populations within the tumor microenvironment[2,3].

Therapeutic resistance in gliomas is a multifaceted challenge. Gliomas possess an innate ability to adapt to therapies, and, as postulated by recent studies, this resistance is attributed in part to GSCs[5]. The traditional understanding of resistance mechanisms involves the activation of DNA repair mechanisms, especially in the context of TMZ and ionizing radiation[6]. However, recent studies proposed a spectrum of recurrence patterns, suggesting that resistance can stem from preexisting chemo-resistant clones or treatment-induced changes in cell populations[5]. Indeed, GSCs, equipped with efficient DNA damage repair systems, exhibit heightened resistance to chemotherapy, particularly TMZ, and RTR [2]. The cytotoxic effects of RTR and TMZ, mediated through O6-methylguanine-methyltransferase, are mitigated in GSCs due to increased expression of O6-methylguanine-methyltransferase and other anti-apoptotic proteins. This resistance is further compounded by the ability of GSCs to transition between different cellular states, confounding the efficacy of conventional therapies[4,5].

Despite significant strides in understanding the role of GSCs in therapeutic resistance, there is a lack of consensus on targeted therapeutic approaches[6]. The high plasticity of GSCs and their dynamic transitions between cellular states present a formidable challenge for devising curative strategies[5]. TMZ exposure, while stimulating the conversion of differentiated tumor cells into GSCs, underscores the need for tailored therapeutic interventions that specifically target GSCs[2,3].

In this context, a systematic literature review becomes imperative to consolidate the diverse findings and discern a common line of treatment against GSC-mediated resistance. This systematic literature review aims to analyze the current landscape of targeted therapies addressing chemo- and radioresistance in gliomas, with a specific focus on the mechanisms underlying GSC-mediated resistance to adjuvant treatments.

MATERIALS AND METHODS

Literature review

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria[7], a systematic evaluation of targeted therapeutics targeting the molecular mechanism of GSC-mediated resistance to adjuvant therapy was conducted[8]. A methodical and thorough literature search of the PubMed, Web of Science, Cochrane, *Reference Citation Analysis* (*RCA*) (https://www.referencecitationanalysis.com) and Embase databases was conducted by two authors (Agosti E and Ghidoni M). On September 30, 2023, the initial literature search was carried out; on December 10, 2023, the search was updated. To create a search strategy, many keyword searches were conducted. Combinations of AND and OR were employed to find results for the search terms "glioma stem cells", "radiotherapy", "chemotherapy", "resistance", and "targeted therapies". The Medical Subject Heading terms and Boolean operators ("glioma stem cells" OR "GSC" OR "cancer stem cells" OR "CSC") AND ("chemotherapy" OR "radiotherapy" OR "temozolomide" OR "adjuvant treatments") AND ("resistance" OR "resilience") AND ("targeted therapy" OR "targeted treatment" OR "targeted strategy"). These terms were used to retrieve studies. A reference analysis of a few chosen publications revealed other relevant articles. A search filter was applied to display only articles from the specified time frame of 2000-2023. Following that, a further search on https://clinicaltrials.gov/ was conducted to find active clinical studies that target the biological mechanism underlying GSC-mediated resistance to adjuvant therapy.

Inclusion and exclusion criteria

The selection of papers was based on the following inclusion criteria: (1) English language; (2) Studies on targeted therapies against the molecular mechanism of GSC-mediated resistance to RTR; and (3) Studies on targeted therapies against the molecular mechanism of GSC-mediated resistance to CTR. The following exclusion criteria were applied: (1) Case series, case reports, editorials, meta-analyses, literature reviews, and cohort studies; (2) Studies in which the methods and/or results were imprecisely stated or poorly defined; (3) Studies that left out details regarding certain target treatments; (4) Repeatedly published research; and (5) unavailability of the full text.

Before the qualified studies were imported into Endnote X9, duplicates were removed. Two separate researchers, Panciani PP and Agosti E analyzed the data in compliance with the conditions for inclusion and exclusion. A third reviewer, Zeppieri M, resolved all disputes. Afterwards, the qualifying articles underwent full-text screening.

Data extraction

The data extracted for each study included: Authors, year of publication, glioma cell lines studies, GSCs pathway, therapeutic target and agents, molecular effects and impact on radio- and chemoresistance.

Outcomes

The molecular mechanism of GSC-mediated resistance to radiation therapy and/or chemotherapy, as well as targeted therapeutics that target the molecular mechanism of GSC-mediated resistance to adjuvant treatments, were our primary outcomes.

Assessment of risk of bias

The Newcastle-Ottawa Scale was used to assess the quality of the listed studies[8]. The quality was conducted by analyzing the study's outcome evaluation, comparability, and selection criteria. The ideal score was nine. Higher scores corresponded with higher-quality studies. Studies with a seven or above were considered to be of very high caliber. Panciani PP and Agosti E carried out the quality evaluation independently. When discrepancies surfaced, the third

author went back and reviewed the papers (Figure 1).

Statistical analysis

The offered descriptive data contained ranges and percentages. All statistical analyses were performed using R statistical software, version 3.4.1 (http://www.r-project.org).

RESULTS

Literature review

A total of 452 publications were found after duplicates were removed. 203 publications were identified for full-text analysis after the abstracts and titles were analyzed. Qualified articles included 201 papers. A total of 168 items were excluded based on the following criteria: Meta-analysis or systematic literature review (4 papers), lack of details about results and/or results (5 articles), and studies unrelated to the research issue (159 papers). All the studies included in the analysis had one or more outcome measures available for each of the patient categories under consideration. Figure 2 shows the flow chart for the PRISMA statement.

Data analysis

The systematic literature review focused on targeted therapies against GSCs to address resistance to RTR and CTR. The analysis of data from Table 1 provides a comprehensive understanding of the trends and frequencies associated with key parameters, including the year of publication, target GSCs models, GSCs pathways, therapeutic targets, therapeutic agents, molecular effects, and the impact on adjuvant treatment responses.

The studies span from 2005 to 2022, showcasing a gradual increase in research over time. Notably, there is a clustering of publications in recent years, suggesting a heightened interest and focus on developing targeted therapies against GSC-mediated resistance in glioma. The distribution of publications is as follows: (1) 2005-2010: 11 studies (33.3%); (2) 2011-2015: 12 studies (36.4%); and (3) 2016-2022: 10 studies (30.3%). This breakdown provides a temporal perspective on the evolving landscape of research in this field.

The most frequently used GSC models are crucial indicators of their relevance in research. The distribution of target GSC models in descending order of frequency is as follows: (1) U87: 11 studies (33.3%); (2) U251: 5 studies (15.2%); (3) T98G: 5 studies (15.2%); and (4) Other cell lines: 6 studies (18.2%). In some studies, the GCLs used were not specified (11, 33.3%). The prominence of U87, U251, and T98G underscores their significance in GSC research, likely due to their representativeness of glioma characteristics.

The pathways involved in GSC-mediated resistance exhibit distinct frequencies, highlighting the emphasis on specific molecular targets. The distribution of GSCs pathways, from most to least frequent, is as follows: (1) Phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR): 9 studies (27.3%); (2) Notch: 4 studies (12.1%); (3) Ataxia telangiectasia and Rad3-related/checkpoint kinase 1/protein 53 (ATR/Chk1/p53) or ataxia telangiectasia mutated (ATM)/CHK2/p53: 3 studies (9.1%); (4) Nuclear factor κB (NF-κB): 3 studies (9.1%); (5) Rat sarcoma/rapidly accelerated fibrosarcoma/mitogen activated protein kinase (RAS/RAF/MAPK): 2 studies (6.1%); and (6) Others: 11 studies (33.3%). The predominance of PI3K/AKT/mTOR and Notch pathways suggests their critical roles in the development of resistance, guiding therapeutic strategies.

The targeted molecules across various studies demonstrate a diverse range of therapeutic approaches. The distribution of therapeutic targets, from most to least frequent, is as follows: mTOR: 6 studies (18.2%); CHK1/2: 5 studies (15.2%); ATP binding cassette G2 (ABCG2): 4 studies (12.1%); epidermal growth factor receptor (EGFR): 2 studies (6.1%); and others: 19 studies (57.6%). The high frequency of mTOR and CHK1/2 as therapeutic targets underscores their significance in overcoming GSC-mediated resistance.

Different classes of therapeutic agents exhibit varying frequencies, indicating preferences and efficacies. The distribution of therapeutic agents, from most to least frequent, is as follows: RNA inhibitor (RNAi)/short hairpin RNA (shRNA): 9 studies (27.3%); inhibitors (*e.g.*, LY294002, NVP-BEZ235): 8 studies (24.2%); cannabidiol (CBD): 3 studies (9.1%); monoclonal antibodies (*e.g.*, cetuximab): 3 studies (9.1%); and others: 8 studies (24.2%). The prevalence of RNAi/shRNA and inhibitors highlights the versatility of these agents in targeted therapies against GSC-mediated resistance.

The outcomes at the molecular level show distinct frequencies, indicating the varied impacts of therapeutic interventions. The distribution of molecular effects, from most to least frequent, is as follows: Inhibition of key signaling molecules: 32 studies (97.0%); modulation of cellular processes (*e.g.*, autophagy): 3 studies (9.1%); and others: 2 studies (6.1%). The impact of therapeutic agents on adjuvant treatment responses is crucial for assessing overall efficacy. The distribution of effects on CTR response (in total described in 20 studies, 60.6%), from most to least frequent, is as follows: Reduction in TMZ resistance: 17 studies (51.5%); reduction in carmustine (BCNU) resistance: 3 studies (9.1%); and reduction in doxorubicin (DOXO) resistance: 1 study (3.0%). The reduction of resistance to RTR was reported in 14 studies (42.4%).

The effectiveness of therapeutic agents in reducing resistance to specific adjuvant treatments provides valuable insights into their clinical potential[1,9-39] (Table 1). A summary of the ongoing clinical trials focusing on targeted therapies against the molecular mechanism of GSC-mediated resistance to adjuvant treatments is available in Table 2.

Table 1 Summary of the studies included in the systematic literature review

Ref.	GCLs	GSCs pathway	Therapeutic target	Therapeutic agent	Effects	
					Molecular	Adjuvant treatments response
Eller *et al*[9], 2005	Ros57, Jon52, Mor56	RAS/RAF/MAPK	EGFR	Cetuximab	EGFR inhibition	RTR reduction
Bao *et al*[1], 2006	A172	ATR/Chk1/p53, ATM/Chk2/p53	Chk1, Chk2	DBH	Chk1/2 inhibition	RTR reduction
Clement *et al* [10], 2007	U87	HH-GLI	GLI1, GLI2, GLI3R	Cyclopamine	GLI1,2 inhibition and GLI3R activation	CTR to TMZ reduction
Bleau *et al*[11], 2009	U87	PI3K/AKT/mTOR	PI3Kα/δ, Akt PHD	LY294002, perifosine	ABCG2 inhibition	CTR to TMZ reduction
Li *et al*[12], 2009	U373MG	NF-κB	LRRFIP1	miR-21	LRRFIP1 inhibition	CTR to VM-26 reduction
Wang *et al*[13], 2010	T3359, T3691, T4105, T4202, T4592	Notch	NOTCH1, NOTCH2	GSIs, Notch1/2-specific shRNA	NOTCH1/2 inhibition	RTR reduction
Facchino *et al* [14], 2010	Not specified	PRC1	BMI1	RNAi (shBMI1)	BMI1 inhibition	RTR reduction
Li *et al*[15], 2010	Not specified	PI3K/Akt/mTOR	ABCG2	miRNA-328	ABCG2 inhibition	CTR to TMZ reduction
Ulasov *et al*[16], 2011	U87MG	Notch, SHH	NOTCH1, SMO	GSI-1, cyclopamine	Notch and SHH inhibition	CTR to TMZ reduction
Wu *et al*[17], 2010	Not specified	ATR/CHK1/p53	CHK1	RNAi (shCHK1)	CHK1 inhibition	RTR reduction
Squatrito *et al* [18], 2012	Not applicable	ATM/CHK2/p53	CHK2	RCAS/PDGF	CHK2 inhibition	RTR reduction
Zhu *et al*[19], 2011	HSR-GBM1/2/3	Notch	JAG1, DLL4	RNAi (shJAG1, shDLL4)	JAG1 and DLL4 inhibition	CTR to TMZ and RTR reduction
Nadkarni *et al* [20], 2012	U251, U87	PIKK	ATM	KU-55933	ATM inhibition	CTR to TMZ reduction
Nabissi *et al* [21], 2013	U87MG	PI3K/Akt/mTOR	TRPV2	CBD	TRPV2 inhibition	CTR to TMZ, BCNU and DOXO reduction
Wang *et al*[22], 2013	SU-2	PI3K/Akt/mTOR	mTORC1/2	NVP-BEZ235	mTORC1/2 inhibition	RTR reduction
Martín *et al*[23], 2013	A172, U87, U373	ABC	ABCG2/BCRP	Melatonin	ABCG2/BCRP inhibition	CTR to TMZ reduction
Bhat *et al*[24], 2013	Not specified	TNF-α/NF-κB	NF-κB	IkB-SR	NF-κB inhibition	RTR reduction
Aldea *et al*[25], 2014	Not specified	PI3K/AKT/mTOR RAS/RAF/MAPK	mTOR, RAF	Metformin, sorafenib	mTOR and RAF, inhibition	CTR to TMZ reduction
Nabissi *et al* [26], 2015	Not specified	PI3K/AKT/mTOR TRPV2	Aml-1a	CBD	Aml-1a inhibition	CTR to BCNU reduction
Yu *et al*[27], 2015	U87, U251, T98G, SHG44	PI3K/AKT/mTOR	mTORC1/2	NVP-BEZ235	mTORC1/2 inhibition	CTR to TMZ reduction
Natsumeda *et al* [28], 2016	HSR-GBM1, JHH520	Notch	HES1, HES5, HEY1, autophagy	MRK003 + CQ	Notch inhibition	CTR reduction
Venugopal *et al* [29], 2015	Not specified	Wnt/β-catenin	CK1α	Pyrvinium	CK1α inhibition	CTR to TMZ and RTR reduction
Yi *et al*[30], 2016	U87	Autophagic PCD	Autophagy, Bcl-2, Caspase-3	CQ	Bcl-2 inhibition and Caspase-3 activation	RTR reduction
Marampon *et al* [31], 2017	U87MG, U251MG	HDAC	HDAC4, HDAC6	shRNAs (HDAC4-shRNA,	HDAC4/6 inhibition	RTR reduction

				HDAC6-shRNA)		
Huang *et al*[32], 2017	Not specified	MST4/ATG4B	ATG4B	NSC185058	ATG4B inhibition	RTR reduction
Dai *et al*[33], 2017	T98G, U87, U251, U343, MGR2, Hs683	AKT/GSK3β/β-catenin	SCD1	siRNA (SCD1-siRNA)	SCD1 inhibition	CTR to TMZ reduction
Minata *et al*[34], 2019	U87, TS528	PTEN/PI3K/AKT	pY240-PTEN	PD173074	FGFR2 inhibition	CTR to TMZ and RTR reduction
Yuan *et al*[35], 2019	T98G-R, U118-R	FUS/MDM2	FUS domains (RRM, Znf_BP2)	ADAMTS9-AS2	FUS domains inhibition	CTR to TMZ reduction
Moon *et al*[36], 2020	T98G, LN229, U118MG, U87MG, U251MG	CK1A/BTRCP/MBD3/NuRD	CK1A	Pyr-Pam	MBD3 pathway inhibition by activating CK1A	CTR to TMZ reduction
Huang *et al*[37], 2021	Not specified	CK2α/PRMT6/RCC1	PRMT6	EPZ020411	PRMT6 inhibition	RTR reduction
Chen *et al*[38], 2022	T98G, LN229	PI3K/AKT/mTOR, NF-κB	EPHB3, TNFAIP3	YTHDF2	EPHB3 and TNFAIP3, inhibition	CTR to TMZ reduction
Chang *et al*[39], 2023	Not specified	USP36/ALKBH5	USP36	shRNA	Chk1 inhibition	RTR reduction

ABCG2/BCRP: ATP binding cassette G2/breast cancer resistance protein; ADAMTS9-AS2: Antisense RNA 2 to ADAMTS9; Aml-1a: Acute myeloid leukemia; ATR/Chk1/p53: Ataxia telangiectasia and Rad3-related/checkpoint kinase 1/protein 53; ATM: Ataxia telangiectasia mutated; Bcl-2: B-cell lymphoma 2; BTRCP/MBD3/NuRD: Beta transducin repeat-containing protein/methyl-CpG binding domain protein 3/nucleosome remodeling and deacetylase; BCNU: Carmustine; BER: Base excision repair; BMI1: B lymphoma Mo-MLV insertion region 1; CBD: Cannabidiol; CQ: Chloroquine; CTR: Chemotherapy resistance; DBH: Debromohymenialdisine; DLL4: Delta-like 4; DOXO: Doxorubicin; EGFR: Epidermal growth factor receptor; EPHB3: Eph receptor B3; FGFR2: Fibroblast growth receptor 2; FUS/MDM2: Fused in sarcoma/mouse double minute 2; GCL: Glioma cell line; GLI3R: Glioma associated oncogene homolog 3 repressor; GSI: Gamma secretase inhibitor; GSK3β: Glycogen synthase kinase 3 beta; HES: Hairy and enhancer of split; HDAC: Histone deacetylase; HH-GLI: Hedgehog-glioma-associated oncogene; IkB-SR: IkB super repressor; JAG1: Jagged 1; LRRFIP1: Leucin rich repeat flightless-interacting protein 1; miRNA: MicroRNA; miR-21: MicroRNA 21; MST4/ATG4B: Macrophage stimulation 1/autophagy related protein 4B; NF-κB: Nuclear factor κB; PARPi: Poly(ADP-ribose) polimerase; PHD: Prolyl hydroxylase; PI3K/AKT/mTOR: Phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin; PIKK: Phosphoinositide 3-kinase related kinase; PCD: Programmed cell death; PRC1: Polycomb repressive complex 1; PRMT6/RCC1: Protein arginine methyltransferase 6/regulator of chromosome condensation 1; pY240-PTEN: Phosphorylated tyrosine 240 in the phosphatase and tensin homolog; Pyr-Pam: Pyrvinium pamoate; RAS/RAF/MAPK: Rat sarcoma/rapidly accelerated fibrosarcoma/mitogen activated protein kinase; RCAS/PDGF: Replication-competent avian sarcoma-leukosis virus/platelet derived growth factor; RNAi: RNA inhibitors; RRM: RNA recognition motif; RTR: Radiotherapy resistance; SHH: Sonic hedgehog; shRNA: Short hairpin RNA; SCD1: Stearoyl-CoA desaturase 1; SMO: Smoothened protein; TNFAIP3: Tumor necrosis factor alpha-induced protein 3; TNF-α: Tumor necrosis factor α; TMZ: Temozolomide; TRPV2: Transient receptor potential cation channel subfamily V member 2; USP36/ALKBH5: Ubiquitin-specific protease 36/AlkB homolog 5, RNA demethylase; VM-26: Teniposide; YTHDF2: YTH N(6)-methyladenosine RNA binding protein 2; ZNF_BP2: Zinc finger domain binding protein 2.

DISCUSSION

The radioresistance and chemoresistance promoted by GSCs poses a significant challenge in the effective treatment of gliomas, and understanding the molecular mechanisms underlying this resistance is crucial for developing targeted therapies[2,3,5,6]. Several studies have identified key signaling pathways implicated in GSC-mediated resistance. For instance, Eller *et al*[9] highlighted the involvement of the RAS/RAF/MAPK pathway and its therapeutic targeting through EGFR inhibition with Cetuximab. This finding aligns with other studies, such as that by Bao *et al*[1] emphasizing the importance of ATR/Chk1 and ATM/Chk2 pathways in GSC resistance, which was effectively targeted by Chk1/2 inhibition[5]. Moreover, the PI3K/AKT/mTOR pathway has been implicated in GSC-mediated resistance[11,12], and its inhibition, as demonstrated by Nabissi *et al*[21] led to a reduction in TMZ resistance[5]. These results collectively underscore the complexity of GSC-associated signaling networks and the need for a multifaceted therapeutic approach[2,3].

Beyond signaling pathways, studies have explored the role of specific molecules and proteins in GSC-mediated resistance[4]. For instance, the transcription factor B lymphoma Mo-MLV insertion region 1, a key component of the polycomb repressive complex 1, was targeted through RNAi in a study by Facchino *et al*[14] resulting in a reduction in radioresistance. Additionally, the involvement of NOTCH and sonic hedgehog signaling was addressed by Ulasov *et al*[16] where inhibition of NOTCH1 and Smoothened protein led to decreased resistance to TMZ. These findings indicate the importance of understanding the intricate molecular interactions within GSCs to develop targeted interventions[2]. The study by Zhu *et al*[19] focused on the Notch pathway by specifically targeting Jagged 1 and delta-like 4, resulting in reduced resistance to both TMZ and radiotherapy. This aligns with the work of Nadkarni *et al*[20] who targeted ATM through phosphoinositide 3-kinase related kinase inhibition, effectively reducing resistance to TMZ. The diversity of molecular targets identified in these studies emphasizes the heterogeneity of GSCs and the need for personalized therapeutic strategies[2,3].

Table 2 Summary of the ongoing clinical trials focusing on targeted therapies against the molecular mechanism of glioma stem cell-mediated resistance to adjuvant treatments

Trial name	Year	Title	Trial phase	Therapeutic agent
NCT00916409	2014	A prospective, multicenter trial of NovoTTF-100 A together with TMZ compared to TMZ alone in patients with newly diagnosed GBM	III	NovoTTF-100A device
NCT01474239	2016	Randomized noncomparative phase II trial with bevacizumab and FOT in the treatment of recurrent GBM	II	Bevacizumab
NCT02698280	2018	Phase II study of bevacizumab and ACNU in patients with recurrent high-grade glioma	II	Bevacizumab
NCT04396860	2020	Randomized noncomparative phase II trial with bevacizumab and FOT in the treatment of recurrent GBM	II/III	Ipilimumab, nivolumab, NovoTTF-100 A device
NCT01310868	2021	An evaluation of the tolerability and feasibility of combining 5-ALA with BCNU wafers (Gliadel®) in the surgical management of primary GBM	II	5-ALA Gliadel® wafers
NCT01290939	Ongoing	Phase III trial exploring the combination of bvacizumab and CCNU in patients with first recurrence of a GBM	III	Bevacizumab
NCT00884741	Ongoing	Phase III double-blind placebo-controlled trial of conventional concurrent chemoradiation and adjuvant TMZ plus bevacizumab versus conventional concurrent chemoradiation and adjuvant TMZ in patients with newly diagnosed GBM	III	Bevacizumab
NCT02017717	Ongoing	A randomized phase III open-label study of nivolumab versus bevacizumab and multiple phase I safety cohorts of nivolumab or nivolumab in combination with ipilimumab across different lines of GBM	III	Nivolumab, bevacizumab, ipilimumab
NCT00753246	Ongoing	Phase III study of standard radiotherapy plus concomitant and adjuvant OSAG 101 (Theraloc®) plus TMZ versus standard radiotherapy plus concomitant and adjuvant TMZ patient with newly diagnosed, histologically confirmed GBM multiforme grade IV	III	Nimotuzumab

GBM: Glioblastoma; TMZ: Temozolomide.

Different proteins and factors can be implicated in GSC-mediated resistance. For instance, Wang *et al*[22] highlighted the role of transient receptor potential cation channel subfamily V member 2 in resistance to TMZ, BCNU, and DOXO, which was effectively targeted using CBD. Similarly, the inhibition of ABCG2/breast cancer resistance protein by Melatonin, as demonstrated by Martín *et al*[23] resulted in reduced resistance to TMZ. These studies shed light on the potential of targeting specific proteins to overcome GSC-mediated resistance[4,5].

The modulation of autophagy has emerged as a promising therapeutic avenue in overcoming GSC resistance. Venugopal *et al*[29] demonstrated that inhibiting Notch through MRK003 + chloroquine effectively reduced GSC resistance, highlighting the crosstalk between autophagy and GSC-mediated resistance. Additionally, Yi *et al*[30] targeted CK1α to reduce resistance to TMZ and radiotherapy, emphasizing the intricate network of pathways involved in GSC-mediated resistance. The study by Alhaddad *et al*[40] delves into the role of autophagy induction in promoting M2-like macrophage polarization, thereby contributing to radioresistance[41]. This contrasts with Li *et al*[42] where PI3Kγ inhibition suppresses microglia/TAM accumulation in the glioma microenvironment by inhibiting autophagy, ultimately promoting an exceptional response to TMZ[2]. The dual role of autophagy in GSC-mediated resistance mechanisms highlights the need for a nuanced understanding of context-dependent responses to therapeutic interventions[4].

The inclusion of studies by Zhang *et al*[43] and Wu *et al*[44] in the systematic review underscores the relevance of long non-coding RNAs (lncRNAs) in GSC-mediated chemoresistance. Zhang *et al*[43] shed light on the exosomal transfer of lncRNA SBF2-AS1, enhancing chemoresistance to TMZ[6]. In parallel, Wu *et al*[44] demonstrate the role of lnc-TALC in promoting O6-methylguanine-DNA methyltransferase expression, a key contributor to TMZ resistance[17]. These findings resonate with the growing body of evidence highlighting the regulatory role of lncRNAs in glioma progression [42].

The role of epigenetic regulators in GSC resistance emerged. Huang *et al*[32] targeted HDAC4/6 using shRNAs, resulting in a reduction in radioresistance. Dai *et al*[33] employed siRNA against SCD1, revealing its role in TMZ resistance. These findings underscore the importance of epigenetic modifications in GSC resistance and the potential of epigenetic therapies.

The contribution of hypoxia-driven mechanisms to GSC-mediated radioresistance, as discussed by Alhaddad *et al*[40] resonates with the findings of Hsieh *et al*[45] NADPH oxidase subunit 4, identified as a mediator of cycling hypoxia-promoted radiation resistance in glioblastoma multiforme, underscores the intricate relationship between the tumor microenvironment and resistance mechanisms. The role of hypoxia in shaping the GSC phenotype adds a layer of complexity to the design of targeted therapies, necessitating strategies that account for the dynamic nature of the tumor microenvironment[2,6,46].

Moreover, the manuscript the interplay between GSCs and the tumor microenvironment seems to play a pivotal role in the development of glioma resistance. Moon *et al*[36] targeted CK1A/BTRCP/MBD3/NuRD pathway using pyrvinium pamoate, illustrating the complex interaction between GSCs and their microenvironment in mediating resistance. The study by Huang *et al*[37] further emphasized the role of CK2α/PRMT6/RCC1 pathway, which was targeted using

Modified Newcastle-Ottawa Quality Assessment Scale

Selection

(1) Representativeness of the exposed cohort
- (a) Consecutive eligible participants were selected, participants were randomly selected, or all participants were invited to participate from the source population
- (b) Not satisfying requirements in part (a), or not stated

(2) Selection of the non-exposed cohort
- (a) Selected from the same source population
- (b) Selected from a different source population
- (c) No description

(3) Ascertainment of exposure
- (a) Medical record
- (b) Structured interview
- (c) No description

(4) Demonstration that outcome of interest was not present at the start of the study
- (a) Yes
- (b) No or not explicitly stated

Comparability

(1) Were there clearly defined inclusion and exclusion criteria?
- (a) Yes
- (b) No or not explicitly stated

Outcome

(1) Assessment of outcome
- (a) Independent or blind assessment stated, or confirmation of the outcome by reference to secure records
- (b) Record linkage (*e.g.*, identified through ICD codes on database records)
- (c) Self-report with no reference to original structured injury data or imaging
- (d) No description

(2) Was follow-up long enough for outcomes to occur?
- (a) Yes (≥ 12 months)
- (b) No (< 3 months)

(3) Adequacy of follow up
- (a) Complete follow up-all participants accounted for
- (b) Subjects lost to follow up unlikely to introduce bias (< 20% lost to follow up or description provided of those lost)
- (c) Follow up rate < 85% and no description of those lost provided
- (d) No statement

Figure 1 Modified Newcastle-Ottawa Scale. ICD: International Classification of Diseases.

EPZ020411, resulting in a reduction in radioresistance. The study by Alhaddad *et al*[40] provides insights into GSC-mediated reprogramming of the tumor microenvironment, specifically in the context of macrophages and microglia. The creation of GSC niches at the tumor border, as reported by Hide *et al*[47] emphasizes the dynamic interplay between oligodendrocyte progenitor cells, macrophages/microglia, and the GSC microenvironment. This aligns with the findings of Li *et al*[42] where PI3Kγ inhibition suppresses microglia/TAM accumulation in the glioblastoma microenvironment. The intercellular crosstalk between GSCs and immune components suggests a complex landscape that contributes to therapy resistance. The study by Alhaddad *et al*[40] emphasizes the broader influence of GSCs on the tumor microenvironment and therapy response. The creation of GSC niches at the tumor border, as demonstrated by Hide *et al*[47] signifies the role of GSCs in orchestrating the cellular composition of the microenvironment. This resonates with the findings of Liu *et al*[48], where ADAM8 causes tumor infiltration of tumor-associated macrophages and overcomes TMZ chemosensitization. The interplay between GSCs and the microenvironment emerges as a critical determinant of therapy response and poses challenges for designing targeted interventions[49,50]. These findings highlight the need for a holistic approach considering the tumor microenvironment in developing therapeutic strategies[2,5,6].

CONCLUSION

In conclusion, the role of GSCs in mediating radioresistance and chemoresistance is a complex and multifaceted phenomenon. Versatile therapeutic agents, including RNAi/shRNA, inhibitors (*e.g.*, LY294002, NVP-BEZ235), and monoclonal antibodies (*e.g.*, cetuximab), demonstrate efficacy in overcoming GSC-mediated resistance. The diverse mechanisms discussed in the literature highlight the need for precision therapies that account for the heterogeneity within the GSC population and the dynamic nature of the tumor microenvironment. As research in this field progresses, a deeper understanding of the molecular intricacies will pave the way for targeted interventions that can disrupt GSC-

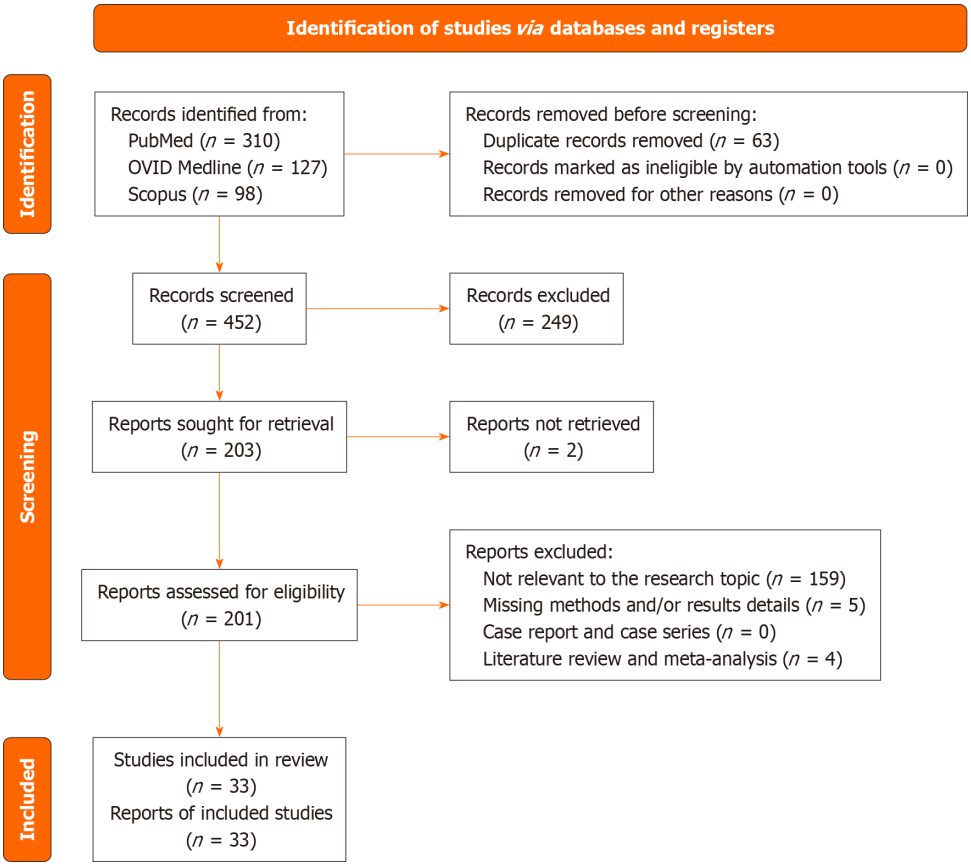

Figure 2 Flow chart according to the PRISMA statement.

mediated resistance mechanisms, ultimately improving the outcomes for glioblastoma patients.

FOOTNOTES

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