24 The Pivotal Role of Glioma Stem Cells in Promoting Glioma Radio-Cchemoresistance, Progression, and Recurrence is a Topic of Significant Interest and Potential Breakthroughs in Neurosurgery, Oncology, and Molecular Biology. These Potential Breakthroughs Inspire Hope for Improved Treatment Strategies and Patient Outcomes

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24.1 INTRODUCTION

Gliomas, a class of primary brain tumors, pose a formidable challenge in the realm of oncology due to their aggressive nature and propensity for therapeutic resistance (Ostrom et al., 2020). Comprising approximately 80% of all malignant brain tumors, gliomas are notorious for their infiltrative growth, making complete surgical resection nearly impossible. The epidemiological landscape underscores the gravity of the issue, with an annual incidence of gliomas estimated to be 6.6 per 100,000 individuals globally (Louis et al., 2016).

Despite advancements in medical science, gliomas continue to be associated with dismal prognoses. The standard treatment modalities, encompassing surgical intervention, radiotherapy (RTR), and chemotherapy (CTR), have met with limited success. Gliomas often display resistance to conventional therapies, leading to frequent relapses and disease progression. The median survival for patients diagnosed with glioblastoma, the most aggressive form of glioma, hovers around 15 months, underscoring the urgent need for innovative therapeutic strategies (Stupp et al., 2005).

Glioma stem cells (GSCs) are not just a subpopulation within gliomas but the architects of therapeutic resistance and tumor dynamics. Their unique properties and dynamic interplay with the tumor microenvironment make them a critical contributor to therapeutic resistance.

The intricate landscape of gliomas is increasingly unraveled with the identification and characterization of GSCs. Traditionally, tumors were perceived as a homogeneous mass of rapidly dividing cells. However, the discovery of GSCs has reshaped this paradigm, revealing a hierarchical organization within gliomas (Singh et al., 2003). GSCs, often called tumor-initiating cells, contribute to tumor initiation and maintenance and play pivotal roles in tumor heterogeneity and plasticity.

GSCs are recognized as a subpopulation within gliomas endowed with self-renewal capabilities and the capacity to differentiate into various cell types constituting the tumor bulk (Chen et al., 2012). This unique cellular subpopulation has emerged as a critical contributor to therapeutic resistance, attributed to their intrinsic molecular characteristics and dynamic interplay with the tumor microenvironment (Bao et al., 2006). GSCs, by their stem cell-like properties, can evade the effects of CTR and RTR, leading to treatment resistance (Galli et al., 2004).

DOI: 10.1201/9781003464594-24

24.1.1 Epidemiological Overview of Gliomas

To appreciate the gravity of the situation, it is essential to delve into the epidemiological dimensions of gliomas. Globally, gliomas represent a significant burden, with an estimated 296,851 new cases reported in 2022 (Bray et al., 2018). The incidence rate varies by geographical region, with age-adjusted rates ranging from 4.67 per 100,000 in Asia to 6.21 per 100,000 in Europe (Ostrom et al., 2020). Gliomas afflict individuals across a broad age spectrum, with a median age at diagnosis of 64 years (Ostrom et al., 2020). Glioblastoma, the most malignant subtype, accounts for approximately 54% of all gliomas, imposing a bleak prognosis (Ostrom et al., 2020).

24.2 THE MOLECULAR ORCHESTRA: GSCS IN THERAPEUTIC RESISTANCE, RECURRENCE, AND PROGRESSION

Understanding the molecular intricacies orchestrated by GSCs provides a blueprint for comprehending glioma behavior and devising targeted therapeutic interventions. GSCs contribute significantly to therapeutic resistance through diverse mechanisms. These mechanisms include the expression of drug efflux transporters (Spiegl-Kreinecker et al., 2002), activation of DNA damage repair pathways, and evasion of apoptosis (Safa, 2022). Notably, GSCs exhibit a remarkable ability to adapt to therapeutic pressures, leading to treatment resistance and tumor recurrence.

The phenomenon of tumor recurrence in gliomas is intricately linked to the survival and persistence of GSCs following initial treatment (Aramini et al., 2022). These cells, endowed with enhanced DNA repair mechanisms and resistance to apoptosis, fuel the resurgence of tumors even after aggressive therapeutic interventions. Additionally, GSCs contribute to tumor heterogeneity, a phenomenon recognized as a significant impediment to successful treatment strategies (Aramini et al., 2022). Tumor heterogeneity, driven by the diverse molecular profiles of GSCs, results in a dynamic tumor landscape, impeding the efficacy of targeted therapies and fostering disease progression.

24.3 CURRENT THERAPEUTIC LANDSCAPE AND EMERGING CHALLENGES

Efforts to combat gliomas have led to the exploration of targeted therapies explicitly aimed at GSCs. Despite significant strides in understanding GSC biology, a standardized treatment approach remains elusive. Numerous studies have reported promising results with targeted therapies targeting specific molecular pathways and surface markers on GSCs (Hersh et al., 2022). However, the absence of a unified treatment paradigm underscores the need for a comprehensive review to synthesize existing knowledge and identify avenues for future research.

24.3.1 The Objective of the Systematic Literature Review for the Chapter

In light of the emerging role of GSCs in glioma pathogenesis, the current systematic literature review aims to elucidate the molecular mechanisms underpinning CTR and RTR resistance, tumor recurrence, and progression. By synthesizing data from relevant studies, we seek to provide a comprehensive overview of the current understanding of GSCs and their impact on glioma dynamics. Additionally, we aim to critically evaluate the existing targeted therapies designed to counteract GSC-mediated resistance and propose potential directions for future research in this critical field.

24.3.2 Literature Review

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Page et al., 2021), we systematically assessed targeted therapeutics for the molecular mechanisms associated with GSC-mediated resistance to adjuvant therapy. The comprehensive literature search encompassed significant databases, including PubMed, Web of Science, Cochrane, and Embase, and was meticulously executed by two authors (E. A. and A. G.). The initial search transpired on September 10, 2023, with subsequent updates conducted on December 12, 2023.

To construct an effective search strategy, a series of keyword searches were undertaken, employing combinations of AND and OR to extract results for key terms such as “glioma,” “glioma stem cells,” “radiotherapy,” “chemotherapy,” “resistance,” “recurrence,” “progression,” and “targeted therapies.” Utilizing Medical Subject Heading (MeSH) terms and Boolean operators, the search included terms like (“glioma stem cells” OR “GSC” OR “cancer stem cells” OR “CSC”) AND (“chemotherapy” OR “radiotherapy” OR “temozolomide” OR “adjuvant treatments” OR “recurrence” OR “progression”) AND (“resistance” OR “resilience”) AND (“targeted therapy” OR “targeted treatment” OR “targeted strategy”). These search terms were instrumental in retrieving relevant studies.

In addition to the systematic search, a reference analysis of select publications was conducted to uncover further pertinent articles. To narrow the focus, a search filter was applied to exclusively display articles within the specified timeframe of 2000–2023.

24.3.3 Inclusion and Exclusion Criteria

Our selection of studies adhered to specific inclusion criteria: (1) written in English, (2) investigations focusing on the molecular mechanisms of GSC-mediated resistance to RTR, (3) examinations addressing the molecular mechanisms of GSC-mediated resistance to CTR, (4) research exploring the molecular mechanisms of GSC-mediated glioma progression, (5) studies delving into the molecular mechanisms of GSC-mediated glioma recurrence, and

(6) inquiries into targeted therapies against the molecular mechanisms of GSC-mediated resistance to RTR and CTR, glioma progression, and glioma recurrence. Conversely, the following exclusion criteria were applied: (1) editorials, case reports, case series, cohort studies, literature reviews, and meta-analyses; (2) studies lacking clear definitions of methods and results; (3) investigations not reporting data on the molecular mechanisms of GSC-mediated resistance to RTR and CTR, glioma progression, and glioma recurrence, and their targeted treatments; (4) redundantly published research; and (5) unavailability of the full text.

The Endnote X9 software was utilized to import the list of identified studies, and any duplicates were systematically eliminated. To ensure the integrity of the results, two independent researchers (E. A. and P.P.P.) meticulously examined the studies against the stipulated inclusion and exclusion criteria. In cases of disagreement, a third reviewer (M. Z.) intervened to reach a consensus. Subsequently, the eligible articles underwent a comprehensive full-text screening process.

For every investigation, we extracted the following details: authorship, publication year, examination of GSC lines, exploration of GSC pathways, identification of molecular agents and associated mechanisms, observed effects, and conceivable targeted therapeutic interventions. Our principal focus was unraveling the molecular mechanisms behind GSC-mediated resistance to RTR and CTR, glioma progression, and glioma recurrence and exploring targeted treatments designed to counteract these mechanisms.

24.3.4 Risk of Bias Assessment and Statistical Analysis

The assessment of study quality utilized the Newcastle-Ottawa Scale (NOS; Wells et al., 2000) evaluating criteria such as selection, comparability, and outcome assessment. A perfect score of 9 was sought, with higher scores indicative of superior study quality. Studies achieving seven or more points were categorized as high quality. Two authors (E. A. and P.P.P.) conducted the evaluation process independently. In cases of discrepancies, the third author re-examined the papers (Figure 24.1). Descriptive statistics, encompassing ranges and percentages, were presented. The R statistical package v3.4.1 (http://www.r-project.org) was employed for all statistical analyses.

24.3.5 Results

After duplicates were eliminated, 591 papers in total were found. After the title and abstract were analyzed, 332 articles were found for full-text analysis. For 330 articles, eligibility was determined. The following criteria led to the exclusion of the remaining 168 articles: (1) 203 articles that are not pertinent to the research issue; (2) 6 papers that lack technique and results information, and (3) 5 publications that are part of a systematic literature review or meta-analysis.

At least one or more outcome measures were available for all of the studies that were part of the analysis for each patient group under consideration. Figure 24.2 shows the PRISMA statement's flow chart, and Figure 24.3 reports the PRISMA checklist.

24.3.6 Data Analysis

24.3.6.1 GSCs and Glioma Resistance to RTR and CTR

A systematic literature review centered on the data presented in Table 24.1 thoroughly investigated GCSs-mediated mechanisms contributing to glioma radio-chemoresistance. A total of 57 studies were included, covering the period from 2006 to 2023, demonstrating the evolution of research in this field over two decades. Notably, there has been a concentration of studies in recent years, signifying an increased interest and emphasis on understanding GCSs-mediated resistance mechanisms in gliomas.

Several GCS lines were explored across the studies, with U87 and U251 emerging as the most frequently used cell lines, appearing in numerous studies, followed by LN229, T98G, A172, and other cell lines. These cell lines have become prominent models for studying GCS-mediated mechanisms, offering valuable insights into the resistance mechanisms associated with gliomas. Specifically, U87 has been employed in 16 studies (28.1%), U251 in 15 studies (26.3%), T98G in 9 studies (15.8%), and LN18 in 4 studies (7.0%), with other GCSs lines used less frequently.

The pathways implicated in GCSs-mediated resistance mechanisms encompass a diverse array, including Notch, Akt , SHH/Gli1, MMR, PI3K/AKT/mTOR, and Wnt/β-catenin (Aldea et al., 2014; Yu et al., 2015; Yang et al., 2018, Maciaczyk et al., 2017).

The MMR pathway appears frequently, indicating its crucial role in glioma resistance (Yip et al., 2009; Sørensen et al., 2015; McCord et al., 2022). The distribution is as follows: MMR in 15 studies (26.3%), Notch in 8 studies (14.0%), Akt in 8 studies (14.0%), SHH/Gli1 in 4 studies (7.0%), PI3K/Akt /mTOR in 4 studies (7.0%), and other pathways with varied frequencies. Various molecular agents have been explored in the context of GCSs-mediated resistance, with MGMT, PARP-1, and ABCG2 being the most frequently investigated. The distribution is as follows: MGMT in 12 studies (21.1%), PARP-1 in 11 studies (19.3%), ABCG2 in 8 studies (14.0%), Chk1/Chk2 in 4 studies (7.0%; Wu et al., 2012), ATM in 3 studies (5.3%), and other agents with varied frequencies. The molecular mechanisms underlying GCSs-mediated resistance are diverse, encompassing processes such as repairing DNA damage, inhibiting apoptosis, and inducing drug efflux (Staberg et al., 2018; Salaroglio et al., 2018). Repairing DNA damage is a recurring theme in the reported studies, often involving MMR proteins, MGMT, and PARP-1 (Johannessen et al.,

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 24.1 **Overview of the study quality**. The assessment of study quality utilized the Newcastle-Ottawa Scale (NOS). The Figure was generated criteria such as selection, comparability, and outcome assessment based om the publication by Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000

2008; Sarkaria et al., 2008; Beier et al., 2008; Golding et al., 2009; Beier et al., 2011; Siebzehnrubl et al., 2013). The inhibition of apoptosis is notably associated with Akt, BMI1, and NF-kB pathways (Bhat et al., 2013). The drug efflux mechanism is explored in studies targeting MRP1, ABCG2, and P-glycoprotein (Bleau et al., 2009; Shahi et al., 2016; Zhang et al., 2023), while metabolic plasticity is mentioned in studies involving ALDH-1A1, PPP, and ALDH1A3 (Schäfer et al., 2012; Wu et al., 2020).

BER: base excision repair system; BMX: bone marrow tyrosine kinase on chromosome X; CAXII: carbonic

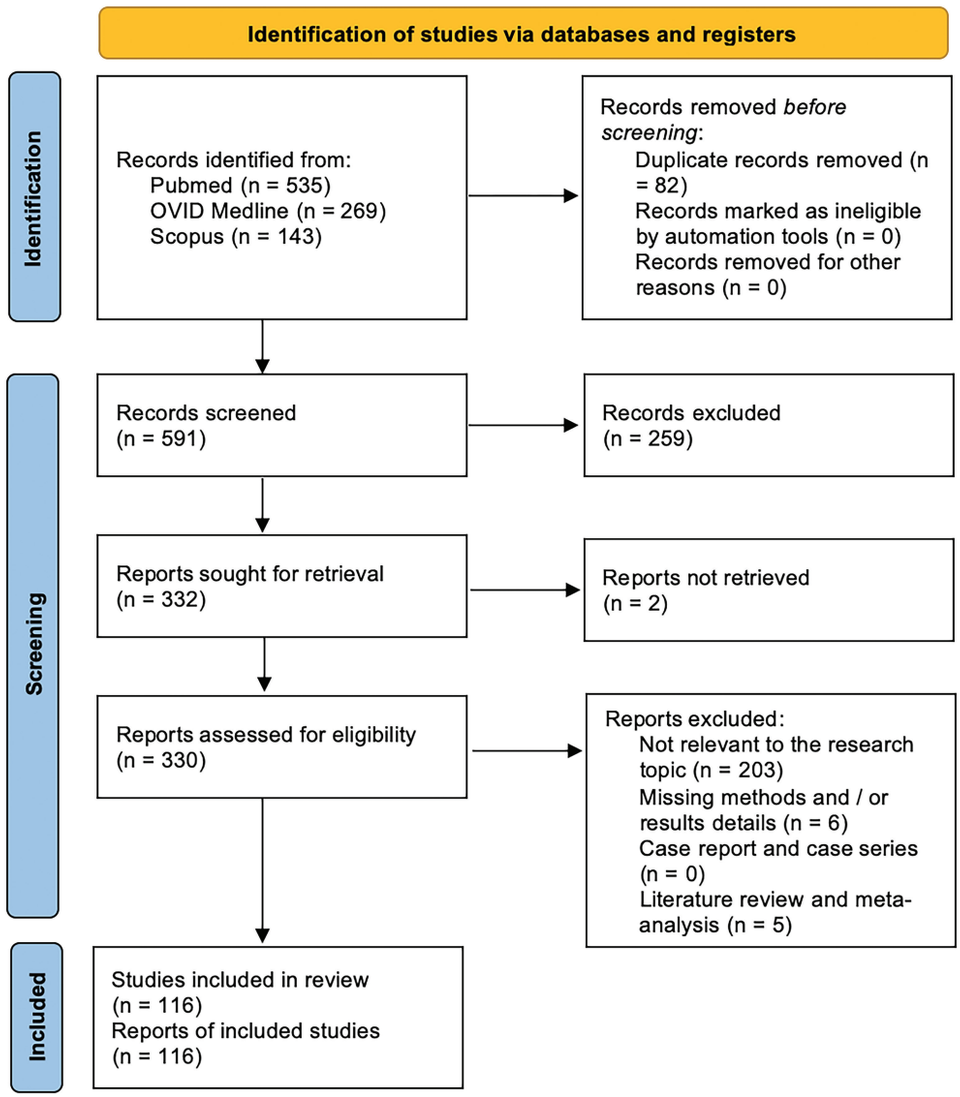

FIGURE 24.2 Assessment of studies using Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). The systematically assessment of studies on targeted therapeutics for the molecular mechanisms associated with GSC-mediated resistance to adjuvant therapy. The Figure was generated following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines in the publication by Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:71

anhydrase XII; CQ= chloroquine; CTX: chemotherapy; DBH: debromohymenialdisine;DEAB:4-diethylaminobenzaldehyde; DGAT1: diacylglycerol acyl-transferase 1; DSBs: double stranded breaks; FN: fibronectin; FTC: fumitremorgin C; GBM: glioblastoma; GSCs: glioblastoma stem cells; GSIs: γ-secretase inhibitors; HN: humanin; ID4: inhibitor of differentiation 4; KDMs: histone lysine demethylase genes; MBD3: methyl CpG binding domain 3 protein; MDR1: multiple drug resistance 1 gene; MGMT: O6-methylguanine-DNA methyltransferase; 6-MP: 6-mercaptopurine; MMR: mismatch repair; O6-BG: O6-benzylguanine; MRP1: multidrug resistance protein 1; PARP-1: poly(ADP-ribose) polymerase-1; PEI–SNAs: poly-ethylenimine-wrapped spherical nucleic acid nanoparticles; Pgp: P-glycoprotein; PKM2: M2 isoform of pyruvate kinase; PPP: pentose phosphate pathway; Pyr-Pam: pyrvinium pamoate; RT: radiotherapy; sgRNA: single guide RNA; Shh: sonic hedgehog; shRNA: short hairpin RNA; siRNA: small interference ribonucleic acid; Sp1: specificity protein 1; TMZ: temozolomide; YY1: yin yang 1; ZEB1: zinc finger E-box binding homeobox 1.

The effects of GCSs-mediated resistance manifest in chemoresistance, radioresistance, increased oncogenic potential, and altered metabolic plasticity (Shi et al., 2018). Chemoresistance and repairing DNA damage emerge as the predominant effects observed in the studies (Yin et al., 2023; Li et al., 2023b). The distribution is as follows: chemoresistance in 28 studies (49.1%), repairing DNA damage in 22 studies (38.6%), radioresistance in 14 studies (24.6%), increased oncogenic potential in 13 studies (22.8%), altered metabolic plasticity in 9 studies (15.8%; Facchino et al., 2010). Chemoresistance

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2,3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	4-6
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	7
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	7,8
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	7
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	7
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	7
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	9
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	9
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	9
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	9
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	9
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	9-16
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	9-16
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	9-16
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	16-30
Limitations	20	Discuss the limitations of the scoping review process.	30
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	31
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	NA

FIGURE 24.3 Checklist in preforming the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). The checklist was based on the systematically assessment of studies on targeted therapeutics for the molecular mechanisms associated with GSC-mediated resistance to adjuvant therapy. The Figure was generated following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines in the publication by Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:71

is frequently associated with repair mechanisms (MMR, MGMT, BER; Agnihotri et al., 2012; Nadkarni et al., 2012), inhibition of apoptosis (Akt, BMI1, NF-kB; Carra et al., 2013; Liu et al., 2006), and drug efflux (MRP1, ABCG2, P-glycoprotein; Li et al., 2010; Munoz et al., 2015; Yu et al., 2018).

Radioresistance is predominantly linked to repair mechanisms (MMR, ATM), inhibition of apoptosis (Akt, Notch; De Bacco et al., 2016; Purow et al., 2005), and protective autophagy (Notch, ATG4B; Natsumeda et al., 2016a; Ma et al., 2017).

TABLE 24.1
Overview of GCSs-mediated Mechanisms to Promote Glioma Radio-chemoresistance to Adjuvant Treatments and Potential Targeted Therapies

Author, Year	GSCs Model	Pathway	Molecular Agent	Mechanism	Effect	Targeted Therapy
Spiegl-Kreinecker et al. (2002)	GBM cell lines	N/A	MRP1	MRP1 has efflux pump activity exporting	Through drug efflux, it causes chemoresistance	PRO
Bao et al. (2006)	GBM cell lines	Chk	Chk1, Chk2	Chk1 Chk2 allow the repair of DNA damaged by RT	Repairing DNA damage, resulting in radioresistance	DBH+ RT
Liu et al. (2006)	GBM cell lines	N/A	BCRP1, MGMT, FLIP, BCL-2, BCL-XL, IAPs	Inhibition of apoptosis and drug efflux caused by CTX	Inhibition of apoptosis and repairing DNA damage, resulting in chemoresistance	N/A
Johannessen et al. (2008)	GBM cell lines	MMR, BER	MMR proteins, MGMT, BER proteins, PARP-1	Repairing DNA damage caused by CTX	Repairing DNA damage, resulting in chemoresistance	O^6-BG+CTX; INO-1001, ABT-888 + TMZ
Sarkaria et al. (2008)	GBM cell lines	MMR, BER	MMR proteins, MGMT, BER proteins, PARP-1	Repairing DNA damage caused by CTX and RT	Repairing DNA damage, resulting in chemoresistance and radioresistance	O^6-BG+CTX; AG-14361, AG-014699 + TMZ
Beier et al. (2008)	GBM cell lines	N/A	MGMT	MGMT allows GCSs to survive and repair DNA damage caused by CTX	Repairing DNA damage, resulting in chemoresistance	O^6-BG+TMZ
Bleau et al. (2009)	U87	PTEN/ PI3K/ Akt	Akt	Akt induces ABCG2 activation	Through drug efflux, it causes chemoresistance	FTC
Yip et al. (2009)	U251	MMR	MSH6	N/A	MSH6 mutation causes chemoresistance	Wild-type MSH6+ TMZ
Golding et al. (2009)	U87, U1242, U1242	AKt	ATM	ATM allows DNA damage response	Repairing DNA damage, resulting in radioresistance	KU-60019
Wang et al. (2010)	GBM cell line	Notch	Notch1, Notch2	Notch1 and Notch2 allow radiation-induced Akt activation	Inhibition of apoptosis, resulting in radioresistance	GSIs + RT
Facchino et al. (2010)	GBM cell lines	N/A	BMI1	BMI1 controls DNA DSB response and repair	Repairing DNA damage, resulting in radioresistance	shBMI1+ RT
Li et al. (2010)	GBM cell lines	N/A	ABCG2	miRna-328 downregulation causes ABCG2 upregulation	Through drug efflux, it causes chemoresistance	miRNA-328
Ulasov et al. (2011)	U87	Notch, SHH	NOTCH1, NCOR2, GLI1	NOTCH 1, NCOR2, GLI1 are upregulated	Inhibition of apoptosis, resulting in chemoresistance	GSI-1, cyclopamine; + TMZ
Jeon et al. (2011)	A172, A1207, LN18, and LN229	SOX	ID4	ID4-mediated SOX2 induction enhances ABCC3 and ABCC6 expression	Through drug efflux, it causes chemoresistance	shID4+ BCNU
Beier et al. (2011)	GBM cell lines	MMR	MGMT, MDR1, MSH6, PARP	Repairing DNA damage caused by CTX	Repairing DNA damage, resulting in chemoresistance	N/A
Agnihotri et al. (2012)	A172 and T98G	BER	APNG	It repairs the cytotoxic lesions N3-methyladenine and N7-methylguanine	Repairing DNA damage, resulting in chemoresistance	APNG siRNA + TMZ
Wu et al. (2012)	GBM cell lines	Chk	Chk1, Chk2	Chk1 Chk2 allow the repair of DNA damaged by RT	Repairing DNA damage, resulting in radioresistance	Chk1-shRNA + RT
Hardee et al. (2012)	U251, U87MG	TGF-β	TGF-β	TGF-β promotes effective DNA damage response	Repairing DNA damage, resulting in radioresistance	LY364947 + RT

(*Continued*)

TABLE 24.1 (Continued)

Author, Year	GSCs Model	Pathway	Molecular Agent	Mechanism	Effect	Targeted Therapy
Schäfer et al. (2012)	GBM cell lines	N/A	ALDH-1A1	ALDH-1A1 increases cellular detoxification	Increased metabolic plasticity, resulting in chemoresistance	DEAB, ALDH1A1 shRNA; + TMZ
Nadkarni et al. (2012)	U251 and U87	MMR	ATM	ATM allows the repair of DNA DSBs induced by TMZ	Repairing DNA damage, resulting in chemoresistance	KU-55933+TMZ
Martín et al. (2013)	A172, U87 and U373	Akt, NF-kB	ABCG2	ABCG2 is upregulated	Through drug efflux, it causes chemoresistance	Melatonin + CTX
Siebzehnrubl et al. (2013)	GBM cell lines	ZEB1	ZEB1	MGMT is a downstream effector of ZEB1	Repairing DNA damage, resulting in chemoresistance	N/A
Bhat et al. (2013)	GBM cell lines	NF-kB	TNF-α	NF-kB mediates antiapoptotic effects and DNA damage repair	Repairing DNA damage, resulting in radioresistance	N/A
Venere et al. (2014b)	GBM cell lines	SSBR	PARP-1	PARP allows GSCs to tolerate DNA damage induced by RT	Repairing DNA damage, resulting in radioresistance	PARPi + RT
Aldea et al. (2014)	GBM cell lines	PI3K/ Akt /mTOR, RAS/ RAF/ MAPK	mTOR, RAF	Reduction of differentiation, increasing proliferation, and efflux pump activity	Through drug efflux, it causes chemoresistance	Metformin and/or Sorafenib
Tentori et al. (2014)	GBM cell lines	SSBR	PARP-1	PARP allows GSCs to tolerate DNA damage induced by CTX	Repairing DNA damage, resulting in chemoresistance	PARPi + TMZ
Sørensen et al. (2015)	GBM cell lines	MMR, BER	MGMT, MDRs, BER, MMR	Repairing DNA damage caused by CTX	Repairing DNA, resulting in chemoresistance	N/A
Yu et al. (2015)	U87 and U251	PI3K-Akt -mTOR	Akt	Akt activation induced by TMZ reduces differentiation and increases proliferation	Inhibition of apoptosis, resulting in chemoresistance	Metformin+ TMZ
Munoz et al. (2015)	U87 and T98G	MDR1	Pgp	Pgp inactivates TMZ thanks to its drug efflux pump activity	Through drug efflux, it causes chemoresistance	Reversan, PSC833, CP-100356 + TMZ
Banelli et al. (2015)	GBM cell lines	N/A	KDM5A	KDM5a allows the genomic stability of GSCs	Repairing DNA, resulting in chemoresistance	HDACi
Wickström et al. (2015)	GBM cell lines	Wnt/β-catenin	MGMT	Wnt pathway increases MGMT expression	Repairing DNA, resulting in chemoresistance	O^6-BG+TMZ
Natsumeda et al. (2016b)	GBM cell lines	Notch	LC3B	Notch blockade induces protective autophagy	Protective autophagy causes chemoresistance	MRK003 + CQ
De Bacco et al. (2016)	U251, SNB19	Akt	MET	MET through Akt activates DNA repair and the antiapoptotic protein p21	Repairing DNA and inhibition of apoptosis, resulting in radioresistance	JNJ38877605 + RT
Shahi et al. (2016)	U87MG, LN405, and LN18	Shh-Gli1-BMI1	MRP1	Shh-Gli1-BMI1 signaling increases MRP1 expression	Through drug efflux, it causes chemoresistance	BMI1 siRNA, GANT61; +/or not TMZ
Ma et al. (2017)	U87 and U251	N/A	miR-26a	miR-26a inhibits GSK3β, and so inhibits the degradation of Mcl1	Protective autophagy causes chemoresistance	lncRNA AC023115.3 + CTX
Marampon et al. (2017)	U87 and U251	DSBR	HDAC4, HDAC6	HDAC4 and HDAC6 sustain DNA double-strand break repair	Repairing DNA and inhibition of apoptosis, resulting in radioresistance	HDAC4 shRNA, HDAC6 shRNA

(*Continued*)

TABLE 24.1 (Continued)

Author, Year	GSCs Model	Pathway	Molecular Agent	Mechanism	Effect	Targeted Therapy
Valtorta et al. (2017)	U251 and T98G	N/A	Bax/Bcl-2	A low Bax/Bcl-2 ratio inhibits apoptosis	Inhibition of apoptosis, resulting in chemoresistance	Metformin + TMZ
Huang et al. (2017)	GBM cell lines	ERK, Akt	ATG4B	ATG4B activated by MST4 stimulates autophagy in GSCs	protective autophagy causes radioresistance	NSC185058 + RT
Staberg et al. (2018)	GBM cell lines	N/A	KDM2B	KDM2B allows the genomic stability of GSCs	Repairing DNA, resulting in chemoresistance	siKDM2B-1, siKDM2B-2; + CTX
Yang et al. (2018)	GBM cell lines	SHH/Gli1	HDAC6	Inhibition of differentiation and apoptosis of GSCs via activation of SHH/Gli1	Inhibition of apoptosis, resulting in radioresistance	HDAC6i
Jalota et al. (2018)	U87 and LN229	HIF	COX-2	COX-2 and its pathway promote epithelial-mesenchymal transition	Increased oncogenic potential, resulting in chemoresistance	NS-398 + BCNU
Yu et al. (2018)	U87	FAK/ Paxillin/ Akt	FN	FN upregulates Pgp expression	Through drug efflux, it causes chemoresistance	Cilengitide + CTX
Shi et al. (2018)	GBM cell lines	STA3	BMX	BMX activates STAT3	Increased oncogenic potential, resulting in radioresistance	Ibrutinib
Melamed et al. (2018)	U87	HH	Gli1	Inhibition of differentiation and apoptosis of GSCs	Inhibition of apoptosis, resulting in chemoresistance	Gli1 PEI–SNAs +/or not TMZ
Salaroglio et al. (2018)	GBM cell lines	N/A	CAXII	CAXII is necessary for the Pgp efflux of TMZ	Through drug efflux, it causes chemoresistance	Psammaplin C + TMZ
Jia et al. (2019b)	GBM cell lines	N/A	YY1	YY1 enhances stemness in GSCs	Increased oncogenic potential, resulting in chemoresistance	MiR-7-5p + TMZ
Wu et al. (2020)	LN229, U87, T98G	N/A	ALDH1A3	ALDH1A3 detoxifies lipid peroxidation	Increased metabolic plasticity, resulting in chemoresistance	PX458 with ALDH1A3 sgRNA
Moon et al. (2020)	LN229, U118, U87, U251, T98G	N/A	CK1A	CK1A binds MBD3 to BTRCP E3 ubiquitin ligase causing degradation of MBD3	Increased oncogenic potential, resulting in chemoresistance	Pyr-Pam
McCord et al. (2022)	GBM cell lines	MMR	MSH6	MSH6 mutation causes increased cellular tolerance of base mismatches	MSH6 mutation causes chemoresistance	N/A
Kang et al. (2023)	U87	N/A	DGAT1	RT-induced DGAT1 increases triglyceride formation	Increased metabolic plasticity, resulting in radioresistance	DGAT1 shRNA, Cladribine
Zhang et al. (2023)	U87	Akt/PTEN	P-glycoprotein	PI3K signaling pathway causes the activation of P-glycoprotein	Through drug efflux, it causes chemoresistance	Resveratrol
Li et al. (2023b)	U251, A172, U87, and T98G	NF-kB	IRAK1	IRAK1 prevents ubiquitination and degradation of PRDX1	Inhibition of autophagic cell death, resulting in radioresistance	H-151
Bailleul et al. (2023)	GBM cell lines	PPP	PKM2	Radiation-induced inhibition of PKM2 increases PPP activity to harness its antioxidant power.	Increased metabolic plasticity, resulting in radioresistance	TEPP46 + RT

(*Continued*)

TABLE 24.1 (Continued)

Author, Year	GSCs Model	Pathway	Molecular Agent	Mechanism	Effect	Targeted Therapy
Liu (X) et al. (2023b)	U87, T98G, M059K and U251	DSBR	Sp1	Sp1 activates the DNA-PKcs promoter	Repairing DNA, resulting in radioresistance	Sp1 shRNA
Cescon et al. (2023)	GBM cell lines	PI3K/Akt	COL6	COL6 causes the activation of the ATR/ATM axis	Repairing DNA, resulting in chemoresistance	COL6A1 siRNAs
Agudelo et al. (2023)	GL26 and U251-MG	N/A	HN	HN improves GSC's capacity to induce endothelial cell migration and proliferation.	Increased oncogenic potential, resulting in chemoresistance	HN shRNA
Yin et al. (2023)	U87, T98G, LN18, U251	N/A	HPRT1	HPRT1 converts AICA to AICAR	Repairing DNA, resulting in chemoresistance	6-MP + TMZ
Li (s) et al. (2023a)	U251	N/A	FBXO7	FBXO7 controls Rbfox2-mediated splicing of mesenchymal genes	Increased oncogenic potential, resulting in chemoresistance	FBXO7 shRNAs + TMZ

Various targeted treatments have been explored to counter GCSs-mediated resistance, including O6-BG, TMZ, RT, and specific inhibitors targeting pathways and molecular agents. O6-BG, TMZ, and RT emerge as the most frequently investigated treatments. The distribution is as follows: O6-BG in 15 studies (26.3%), specific inhibitors in 10 studies (17.5%), and others with variable frequencies. O6-BG+CTX and O6-BG+TMZ are used in studies targeting MMR and MGMT pathways (Wickström et al., 2015). GSIs + RT is explored as a combination therapy targeting Notch pathways. PARPi + RT and PARPi + TMZ are investigated for targeting PARP-1 (Venere et al., 2014a; Tentori et al., 2014). Metformin + TMZ is explored in studies targeting metabolic pathways (Valtorta et al., 2017; Gao et al., 2013). HDACi is studied in the context of inhibiting HDAC4 and HDAC6 (Banelli et al., 2015). The main inhibitors of specific pathways described are LY364947 + RT targeting TGF-β (Hardee et al., 2012), NSC185058 + RT targeting ERK/Akt (Huang et al., 2017), and TEPP46 + RT targeting PPP (Bailleul et al., 2023).

24.3.6.2 GSCs and Glioma Progression

A systematic literature review focusing on the data presented in Table 24.2 thoroughly investigated GSCs-mediated mechanisms contributing to glioma progression and potential targeted therapies. This analysis, which included 50 studies from 2005 to 2023, showcases the evolution of research in this field over nearly two decades. The concentration of recent studies indicates a heightened interest and emphasis on understanding GSCs-mediated progression mechanisms in gliomas, providing a solid and reliable foundation for further research. Several GSC lines were explored across the studies. U87, U251, and A172 emerged as the most frequently used cell lines, appearing in numerous studies, followed by T98G, U373, U387, LN229, U138, U118, U1242, GOS3, SHG44, and GL26 cell lines. These cell lines have become prominent models for studying GSCs-mediated mechanisms, providing valuable insights into the progression mechanisms associated with gliomas. In detail, from most to least frequent, U87 has been used in 14 studies (28.0%), U251 in 12 studies (24.0%), A172 in 6 studies (12.0%), T98G in 5 studies (10.0%), U373 in 3 studies (6.0%), U387 in 3 studies (6.0%), LN229 in 2 studies (4.0%), and other GSCs lines used with lower frequency.

The pathways implicated in GSCs-mediated progression mechanisms include a diverse array, such as Wnt/β-catenin, Notch, HIF2α, Akt , SHH/Gli1, JAK/STAT, PI3K/Akt , TGF-β, and more (Heddleston et al., 2009; Molina et al., 2010; Man et al., 2018). Notably, the Wnt/β-catenin and Notch pathways appear frequently, indicating their crucial roles in glioma progression (Kahlert et al., 2012).

The distribution is as follows: Wnt/β-catenin 11 studies (22.0%), Notch 9 studies (18.0%), HIF2α 4 studies (8.0%), Akt 4 studies, SHH/Gli1 3 studies (6.0%), JAK/STAT 2 studies (4.0%), PI3K/Akt 2 studies (4.0%), TGF-β 2 studies (4.0%), and other pathways with varied frequencies (Jalota et al., 2018).

Several molecular agents have been explored in the context of GSCs-mediated progression, with HIF1α, GLI1, MMP-13, STAT3, and YY1 being the most frequently investigated. The distribution appears as follows: HIF1α 7 studies (14.0%), GLI1 5 studies (10.0%), MMP-13 4 studies (8.0%), STAT3 4 studies (8.0%), YY1 4 studies (8.0%), VEGF 2 studies (4.0%), Shh ligand 2 studies (4.0%), and other agents with varied frequencies.

The molecular mechanisms underlying GSCs-mediated progression are not a single, straightforward process but a

TABLE 24.2
Overview of GCSs-mediated Mechanisms to and Potential Targeted Therapies

Author, Year	GSCs Lines	Pathway	Molecular Agent	Mechanism	Effects	Targeted Therapy
Purow et al. (2005)	U87, U251, T98G, U373, U387, and A172	Notch	Notch-1, Delta-like-1, Jagged-1	They increase proliferation and inhibit differentiation and apoptosis in GSCs	Inhibition of differentiation and apoptosis, resulting in GBM progression	Notch-1 siRNA, Delta-like-1 siRNA, Jagged-1 siRNA, Delta-like-1 Fusion protein
Zagzag et al. (2006)	U87	HIF-1, VEGF/ VEGFR	HIF-1α, VEGF	They increase the expression of CXCR4.	Enhanced invasive ability, resulting in GBM progression	HIF-1α shRNA, AMD3100
Piccirillo et al. (2006)	GBM cell lines	Smad	Smad proteins	The reduction of the Smad signaling cascade increases the proliferation and inhibits the differentiation of GSCs	Inhibition of differentiation and increasing proliferation, resulting in GBM progression	BMP4
Clement et al. (2007)	U87	HH-GLI	GLI1	Increases self-renewal and stemness in GSCs	Inhibition of differentiation, resulting in GBM progression	Cyclopamine
Bar et al. (2007)	GBM cell lines	Shh	Shh ligand	Shh ligand increases the expression of Gli1	Increasing proliferation, resulting in GBM progression	Cyclopamine
Du et al. (2008)	GBM cell lines	HIF-1α	SDF1α, MMP-9	HIF-1α through SDF1α increases tumor angiogenesis	Increased oncogenic potential, resulting in GBM progression	EDTA
Silber et al. (2008)	U87 and U251	EGF, FGF	miR-124, miR-137	miR-124 and miR-137 downregulation causes inhibition of GSC differentiation	Inhibition of differentiation, resulting in GBM progression	miR-124, miR-137
Gal et al. (2008)	GBM cell lines	SMAD	miR-451	miR-451 downregulation inhibits GSC differentiation	Inhibition of differentiation, resulting in GBM progression	SMAD3, SMAD4, miR-451+ Imatinib mesylate
Yeh et al. (2009b)	GBM cell lines	NF-kβ	Leptin	Leptin induces migration and invasion of GSCs through MMP-13 production	Enhanced invasive ability, resulting in GBM progression	MMP-13-shRNA
Golding et al. (2009)	U87, U1242, U1242	Akt	ATM	ATM, through Akt , controls GSC proliferation and invasion	Enhanced invasive ability, resulting in GBM progression	KU-60019
Heddleston et al. (2009)	GBM cell lines	Notch	HIF2α	HIF2α reduces the differentiation of GSCs	Inhibition of differentiation, resulting in GBM progression	N/A
Riolfi et al. (2010)	LN229, LN18, U138, U118	STAT 3, Akt	leptin/ObR	Leptin inhibits Rb, and through STAT3, Akt increases GSC proliferation	Increasing proliferation, resulting in GBM progression	N/A
Ernst et al. (2010)	GBM cell lines	Wnt/b--catenin	miR-17-92	CTGF repression caused by miR-17-92 reduces the differentiation of GSCs	Inhibition of differentiation, resulting in GBM progression	Anti-miR-17-92
Zheng et al. (2010)	GBM cell lines	Wnt	PLAGL2	Enhanced PLAGL2 expression suppresses the differentiation of GSCs	Inhibition of differentiation, resulting in GBM progression	DKK1
Molina et al. (2010)	U251	Erk, Akt	Akt	Akt activation increases tumorigenicity, stemness, and invasiveness	Increased oncogenic potential, resulting in GBM progression	Rapamycin

(*Continued*)

TABLE 24.2 (Continued)

Author, Year	GSCs Lines	Pathway	Molecular Agent	Mechanism	Effects	Targeted Therapy
Inoue et al. (2010)	U251	N/A	MMP-13	MMP-13 allows GSCs migration and invasion	Enhanced invasive ability of GSCs, resulting in GBM progression	MMP-13 shRNA
Cheng et al. (2011)	GBM cell lines	N/A	L1CAM	High expression of LICAM promotes tumor invasion	Enhanced invasive ability of GSCs, resulting in GBM progression	N/A
Kahlert et al. (2012)	GBM cell lines	WNT/β-catenin	ZEB1	Wnt through ZEB1 activates epithelial-to-mesenchymal transition	Enhanced invasive ability of GSCs, resulting in GBM progression	β-catenin shRNAs
Kaur et al. (2013)	GBM cell lines	Wnt/β-catenin	Wnt3a, Wnt1	Wnt3a increases cell proliferation and cell migration	Increased oncogenic potential, resulting in GBM progression	Wnt3a shRNAs, Wnt1 shRNAs
Kanno et al. (2013)	U87	JAK/STAT	STAT3	STAT3 allows the proliferation and self-renewal of GSCs	Increasing proliferation, resulting in GBM progression	VHL
Carra et al. (2013)	GBM cell lines	pI3K/Akt, MAPK	Mcl-1	Expression of antiapoptotic factor Mcl-1	Inhibition of apoptosis, resulting in GBM progression	Sorafenib
Cheng et al. (2013)	GBM cell lines	TGF-β	SDF-1/CXCR4	The SDF-1/CXCR4 axis via TGF-β enables GSC differentiation into pericytes	Increased oncogenic potential, resulting in GBM progression	AMD3100
Rheinbay et al. (2013)	GBM cell lines	Wnt	ASCL1	ASCL1 activates Wnt signaling by repressing the negative regulator DKK1	Inhibition of differentiation, resulting in GBM progression	N/A
Gao et al. (2013)	U251	N/A	Fibulin-3	Fibulin-3 increases the expression of MMP-2	Enhanced invasive ability of GSCs, resulting in GBM progression	Metformin
Siebzehnrubl et al. (2013)	GBM cell lines	ZEB1	ZEB1	ZEB1 promotes invasion by different distribution of N-cadherins on GSCs	Enhanced invasive ability of GSCs, resulting in GBM progression	N/A
Gong et al. (2014)	U251	PTEN/PI3K/Akt	ABCG2	ABCG2 regulates the invasion and spread of GSCs through MMP-9 activity	Enhanced invasive ability of GSCs, resulting in GBM progression	ABCG2 siRNA
Hu et al. . (2016)	GBM cell lines	Akt	WNT5A	WNT5A allows Endothelial Lineage Differentiation of GSC	Enhanced invasive ability of GSCs, resulting in GBM progression	BOX5
Madan et al. (2016)	U87, U373 and GOS3	EGFR/Akt	FAT1	FAT1 through HIF1α increases the invasiveness of GSCs	Enhanced invasive ability of GSCs, resulting in GBM progression	FAT1 siRNA (HSS103567)
Adamo et al. (2017)	U87, AM38 and U251	Wnt/β-catenin	RYK	RYK activates the WNT/β-catenin pathway and allows the cell migration	Inhibition of differentiation, resulting in GBM progression	RYK siRNA
Cenciarelli et al. (2017)	GBM cell lines	NOTCH, STAT3/5	Notch1	Notch1 inhibits differentiation and increases the invasiveness of GSCs	Increased oncogenic potential, resulting in GBM progression	shHes1
Clark et al. (2017)	U87	Akt	P53	Akt phosphorylation causes P53 inhibition	Increased oncogenic potential, resulting in GBM progression	Resveratrol
Maciaczyk et al. (2017)	GBM cell lines	Notch	CBF1	CBF1 promotes the activation of invasive programs through epithelial-to-mesenchymal transition	Enhanced invasive ability of GSCs, resulting in GBM progression	CBF1 shRNA

(*Continued*)

TABLE 24.2 (Continued)

Author, Year	GSCs Lines	Pathway	Molecular Agent	Mechanism	Effects	Targeted Therapy
Yu et al. (2017)	GBM cell lines	N/A	SOX2, OLIG2, SALL2, POU3F2	These transcription factors cause GBM growth.	Increasing proliferation, resulting in GBM progression	SOX2 siRNA, OLIG2 siRNA, SALL2 siRNA, POU3F2 siRNA
Man et al. (2018)	GBM cell lines	Notch	Vasorin, HIF1α/STAT3	Stabilization of Notch-1 and save it from lysosomal degradation	Inhibition of apoptosis, resulting in GBM progression	N/A
Yang et al. (2018)	GBM cell lines	SHH/Gli1	HDAC6	Inhibition of differentiation and apoptosis of GSCs via inactivation of SHH/Gli1	Inhibition of differentiation and apoptosis, resulting in GBM progression	HDAC6i
Jalota et al. (2018)	U87 and LN229	HIF	COX-2	COX-2 and its pathway promote epithelial-mesenchymal transition	Increased oncogenic potential, resulting in GBM progression	NS-398 + BCNU
Yu et al. (2018)	U87	FAK/Paxillin/Akt	FN	FN increases MMP-2 and MMP-9 expression and inhibits p53-mediated apoptosis.	Enhanced invasive ability of GSCs, resulting in GBM progression	Cilengitide + CTX
Shi et al. (2018)	GBM cell lines	STA3	BMX	BMX activates STAT3	Increased oncogenic potential, resulting in GBM progression	Ibrutinib
Melamed et al. (2018)	U87	HH	Gli1	Inhibition of differentiation and apoptosis of GSCs	Inhibition of apoptosis, resulting in GBM progression	Gli1 PEI–SNAs
Jia et al. (2018)	GBM cell lines	N/A	YY1	YY1 enhances stemness in GSCs	Increased oncogenic potential, resulting in GBM progression	MiR-7-5p + TMZ
MacLeod et al. (2019)	GBM cell lines	SOX	SOCS3, USP8, DOT1L	They allow the stemness, proliferation, and self-renewal capacity of GSCs	Increased oncogenic potential, resulting in GBM progression	SOCS3 gRNAs, Ubv8, EPZ-5676
Huang et al. (2019)	U251, U87, A172, SHG44	JAK2/STAT3	AP-2α	AP-2α downregulation inhibits the suppression of Nanog and enhances the proliferation, migration, and invasion of GSCS.	Increased oncogenic potential, resulting in GBM progression	N/A
Panza et al. (2020)	U87 and T98G	Notch	Leptin, Notch-1	Leptin-mediated upregulation of the Notch-1 receptor and the activation of its downstream effectors	Increased oncogenic potential, resulting in GBM progression	GSIs, LFDI peptide, dominant-negative of mastermind-like-1
Mitchell et al. (2023)	GBM cell lines	Wnt/β-catenin	WDR5	WDR5 allows the assembly of the WRAD complex and increases the expression of GSC-related oncogenic pathways	Increased oncogenic potential, resulting in GBM progression	MM-102, C16
Jiang et al. (2023)	U87, U251, A172	Wnt	GSCAR (lncRNA ENSG00000250377)	GSCAR, through SOX2 stabilization, increases the proliferation, migration, and self-renewal ability of GSCs	Increased oncogenic potential, resulting in GBM progression	GSCAR shRNAs
Liu, Y. et al. (2023)	GBM cell lines	N/A	GALNT2, STAT3	GALNT2, through the expression of CD44 increases GSCs proliferation, self-renewal, and invasion	Increased oncogenic potential, resulting in GBM progression	GSK343

(*Continued*)

TABLE 24.2 (Continued)

Author, Year	GSCs Lines	Pathway	Molecular Agent	Mechanism	Effects	Targeted Therapy
Yun et al. (2023)	A172, U87, and LN229	Wnt/β-catenin	NLGN3	NLGN3 plays a role in maintaining stem cell-like properties	Increased oncogenic potential, resulting in GBM progression	DAB2IP
Cescon et al. (2023)	GBM cell lines	PI3K/Akt	COL6	COL6 causes the activation of the ATR/ATM axis	Inhibition of differentiation, resulting in GBM progression	COL6A1 siRNAs
Agudelo et al. (2023)	GL26 and U251	N/A	HN	HN improves GSC's capacity to induce endothelial cell migration and proliferation.	Increased oncogenic potential, resulting in GBM progression	HN shRNA
Li et al. (2023a)	U251	N/A	FBXO7	FBXO7 controls Rbfox2-mediated splicing of mesenchymal genes	Increased oncogenic potential, resulting in GBM progression	FBXO7 shRNAs + TMZ

Abbreviations: BER: base excision repair system; BMPs: bone morphogenetic proteins; CBF1: RBPJ: recombination signal binding protein for immunoglobulin kappa J; FN: fibronectin; GBM: glioblastoma; GSCs: glioblastoma stem cells; GSIs: γ-secretase inhibitors; HIF2α: hypoxia-inducible factor-2α; HN: humanin; MMP: matrix metalloproteinase; NLGN3: synaptic proteins neuroligin 3; PEI–SNAs: poly-ethylenimine-wrapped spherical nucleic acid nanoparticles; Shh: sonic hedgehog; shRNA: short hairpin RNA; siRNA: small interference ribonucleic acid; VHL: von Hippel-Lindau protein; YY1: yin yang 1; ZEB1: zinc finger E-box binding homeobox 1.

diverse range, encompassing the promotion of invasion, inhibition of differentiation, inhibition of apoptosis, and increased stemness (Rheinbay et al., 2013). The reported studies' promotion of invasion and inhibition of differentiation are recurring themes, adding to the complexity. The distribution is as follows: promotion of invasion in 18 studies (36%), inhibition of differentiation in 16 studies (32.0%), inhibition of apoptosis in 10 studies (20.0%), increased stemness in 6 studies (12.0%), and other mechanisms with varied frequencies. Promotion of invasion is frequently associated with pathways like Wnt/β-catenin, Akt, HIF-1α, and MMP-9. Inhibition of differentiation is predominantly linked to pathways such as Notch, Wnt/β-catenin, and STAT3 (Piccirillo et al., 2006).

The effects of GSCs-mediated progression manifest in increased oncogenic potential, enhanced invasive ability, inhibition of differentiation, and increased stemness. Increased oncogenic potential and enhanced invasive ability emerge as the predominant effects observed in the studies. The distribution is as follows: increased oncogenic potential in 22 studies (44.0%), enhanced invasive ability in 20 studies (40.0%), inhibition of differentiation in 16 studies (32%), and increased stemness in 6 studies (12.0%). Increased oncogenic potential is frequently associated with pathways like Wnt/β-catenin, Notch, and JAK/STAT. Enhanced invasive ability is predominantly linked to pathways such as Wnt/β-catenin, Akt, HIF-1α, and MMP-9.

Various targeted treatments have been explored to counter GSCs-mediated progression, offering various potential solutions, including GSIs, specific inhibitors, siRNAs, shRNAs, and peptides targeting pathways and molecular agents. GSIs and specific inhibitors, in particular, have emerged as the most frequently investigated treatments, providing a promising outlook. The distribution is as follows: GSIs 11 studies (22.0%), specific inhibitors ten studies (20.0%), shRNAs seven studies (14.0%), siRNAs five studies (10.0%), and other treatments with varied frequencies. GSIs are often used in studies targeting Notch and Wnt/β-catenin pathways. Specific inhibitors are explored in the context of inhibiting HIF1α, STAT3, MMP-9, and other targets (Yun et al., 2023; Liu et al., 2023a; Jiang et al., 2023)

24.3.6.3 GSCs and Glioma Recurrence

A comprehensive investigation into GCSs-mediated mechanisms contributing to glioma recurrence and potential targeted therapies has been undertaken through an exhaustive systematic literature review, primarily focusing on the data outlined in Table 24.3. Nine studies were incorporated into this analysis, spanning from 2011 to 2022, providing a nuanced perspective on the evolution of research over the past decade in understanding GCS-mediated recurrence mechanisms in gliomas.

Several GSC lines were explored across the studies, with U87 and U251 being the most frequently utilized cell lines appearing in multiple studies. The detailed breakdown, from most to least frequent, reveals that U87 was used in 3 studies (33.3%), followed by U251 in 3 studies (33.3%), and other GSC lines were used with lower frequency. These cell lines have emerged as pivotal models for unraveling GCSs-mediated mechanisms, offering critical insights into the recurrence mechanisms associated with gliomas.

The pathways implicated in GCSs-mediated recurrence mechanisms showcase a diverse array, including JAK/STAT3, TGF-b, NOTCH, Akt /mTOR, WNT, and HIF1α/HIF2α. Notably, the JAK/STAT3 and TGF-b pathways appear frequently, indicating their significant roles in glioma recurrence (Kanno et al., 2013). The distribution is as follows: JAK/STAT3 in 3 studies (33.3%), TGF-b in 2 studies (22.2%), NOTCH in 1 study (11.1%), Akt /mTOR in 1 study (11.1%),

TABLE 24.3
Overview of GCSs-mediated Mechanisms to Promote Glioma Recurrence and Potential Targeted Therapies

Author, Year	GSCs Lines	Pathway	Molecular Agent	Mechanism	Effects	Targeted Therapy
Cheng et al. (2011)	GBM cell lines	N/A	L1CAM	High expression of LICAM promotes tumor invasion	Enhanced invasive ability of GSCs, resulting in recurrence	N/A
Han et al. (2013)	U87 and U251	JAK/ STAT3	Leptin	leptin serves to link the accumulation of adipokine to the invasion	Enhanced invasive ability of GSCs, resulting in recurrence	Ob-R siRNAs, siSTAT3
Wang et al. (2016)	U87 and U251	TGF-b	LTBP4	LTBP4 mutation causes activation of TGF-b	Increases the cell proliferation, causing the recurrence	LTBP4 shRNA
Yu et al. (2016)	GBM cell lines	NOTCH	Notch1	Notch1 enhances the self-renewal capacity of GSCs	Promotion of GBM cell stemness and proliferation, resulting in recurrence	Notch1 siRNA
Hu et al. (2016)	GBM cell lines	Akt / mTOR	WNT5A	WNT5A allows Endothelial Lineage Differentiation of GSC	Enhanced invasive ability of GSCs, resulting in recurrence	BOX5
Lee et al. (2016)	U87 and U251	N/A	HIF1α, HIF2α	HIFs reduce the differentiation of GSCs	Promotion of GBM cell stemness, resulting in recurrence	HIFs shRNA, Calbiochem 400088
Moon et al. (2020)	LN229, U118, U87, U251, T98G	N/A	CK1A	CK1A binds MBD3 to BTRCP E3 ubiquitin ligase causing degradation of MBD3	Promotion of GBM cell stemness, resulting in recurrence	Pyr-Pam
Knudsen et al. (2022)	GBM cell lines	WNT, NOTCH, Akt	PTN	PTN Induces the GSC Program in GBM Tumor Cells	Promotion of GBM cell stemness, resulting in recurrence	N/A
Muthukrishnan et al. (2022)	GBM cell lines	N/A	P300	H3K27 acetylation by P300 causes the conversion of GSC into vascular-like cells	Enhanced invasive ability of GSCs, resulting in recurrence	C646 + RT

Abbreviations: GBM=: glioblastoma; GSCs=: gGlioblastoma stem cells; HIF2α:= hypoxia-inducible factor-2α; MBD3:= methyl CpG binding domain 3 protein; PTN:= pleiotrophin; Pyr-Pam:= pyrvinium pamoate; RT:= radiotherapy; shRNA:= short hairpin RNA; siRNA=: sSmall interference ribonucleic acid.The molecular mechanisms underlying GCSs-mediated recurrence are diverse, encompassing processes such as the promotion of invasion, enhancement of stemness, and inhibition of differentiation. Notably, the reported studies' promotion of invasion and enhancement of stemness are recurring themes. The distribution is as follows: promotion of invasion in three studies, enhancement of stemness in three studies, and inhibition of differentiation in one study, with other mechanisms demonstrating varied frequencies. Promotion of invasion is frequently associated with pathways like JAK/STAT3, TGF-b, WNT, HIF1α/HIF2α, and CK1A (Moon et al., 2020). Stemness enhancement is predominantly linked to pathways such as WNT5A, HIF1α/HIF2α, CK1A, PTN, and P300.

WNT in 1 study (11.1%), and HIF1α/HIF2α in 1 study (11.1%), with other pathways demonstrating varied frequencies.

Several molecular agents were explored in the context of GCSs-mediated recurrence, with Notch1, LTBP4, WNT5A, HIF1α, HIF2α, CK1A, PTN, and P300 being the most frequently investigated (Panza et al., 2020). The distribution is one study each (11.1% each) for Notch1, LTBP4, WNT5A, HIF1α/HIF2α, CK1A, PTN, P300, and other agents demonstrating varied frequencies.

The effects of GCS-mediated recurrence manifest in enhanced invasive ability and promotion of GBM cell stemness. Enhanced invasive ability and promotion of GBM cell stemness emerge as the predominant effects observed in the studies. The distribution is as follows: enhanced invasive ability in four studies (44.4%) and promotion of GBM cell stemness in four studies (44.4%). Enhanced invasive ability is frequently associated with pathways like JAK/STAT3, TGF-b, WNT, HIF1α/HIF2α, CK1A, and PTN. Promoting GBM cell stemness is predominantly linked to pathways such as WNT5A, HIF1α/HIF2α, CK1A, PTN, and P300.

Various targeted treatments have been explored to counter GCSs-mediated recurrence, including siRNAs and shRNAs targeting specific pathways and molecular agents (Adamo et al., 2017; Yu et al., 2017). The targeted therapies encompass Ob-R siRNAs, siSTAT3, LTBP4 shRNA, Notch1 siRNA, BOX5, HIFs shRNA, Calbiochem 400088, Pyr-Pam, N/A, and C646 + RT. The distribution is as follows: siRNAs in three studies (33.3%), shRNAs in two studies (22.2%), and other treatments demonstrating varied frequencies. SiRNAs are often used in studies targeting Notch1, Ob-R, and WNT5A pathways, while shRNAs are explored in targeting LTBP4, HIFs, and CK1A.

24.3.6.4 Summary of Results

The study comprehensively examines GSC-mediated mechanisms in GBM, revealing intricate pathways and molecular players. Noteworthy findings include the identification of critical pathways, such as Notch, Wnt/β-catenin, and JAK/STAT3, contributing to chemoresistance, radioresistance, progression, and recurrence (Mitchell et al., 2023; Wang et al., 2010; Cheng et al., 2011). The study highlights the multifaceted nature of GSCs, with specific molecular agents, like miR-124 and miR-137, influencing differentiation and contributing to tumor progression (Silber et al., 2008). Furthermore, potential targeted therapies, including siRNAs and small molecules, are introduced to counteract these mechanisms. The results underscore the complexity of GSC-mediated processes, emphasizing the need for targeted interventions to improve treatment outcomes.

24.3.6.5 GSCs and the Tumor Microenvironment

The intricate interplay between GSCs and the tumor microenvironment (TME) is a dynamic and multifaceted relationship that profoundly influences the pathobiology of glioblastoma (GBM). GSCs are considered the driving force behind GBM aggressiveness, as they actively engage with various components of the TME, contributing to tumor progression, therapy resistance, and immune evasion.

The TME provides a nurturing niche for GSCs, sustaining their stemness and promoting self-renewal. Studies by Lathia et al. (2011) demonstrated that endothelial cells within the TME release interleukin-6 (IL-6), a crucial factor in supporting GSC maintenance and self-renewal. This intricate signaling interaction indicates indicative' dependency of GSCs on the TME for their survival and propagation (Lathia et al., 2011). Beyond receiving signals, GSCs actively shape the TME to create a supportive milieu. One pivotal aspect is the modulation of immunosuppression. GSCs have been implicated in evading immune recognition through various mechanisms. Yamashita et al. identified the upregulation of programmed cell death-ligand 1 (PD-L1) on GSCs, highlighting their role in establishing an immunosuppressive TME. GSCs create a shield against immune surveillance by inhibiting T-cell activity, contributing to their immune escape strategies.

The interaction between GSCs and the TME extends to the vasculature, with GSCs actively participating in angiogenesis, a hallmark of GBM pathology. The secretion of pro-angiogenic factors by GSCs stimulates endothelial cells to form new blood vessels, facilitating tumor growth and progression (Bao et al., 2006). Additionally, GSCs contribute to maintaining and remodeling the extracellular matrix (ECM), fostering an environment conducive to invasion. By producing matrix metalloproteinases (MMPs), GSCs actively degrade the ECM, promoting their infiltrative behavior and contributing to the highly invasive nature of GBM (Bao et al., 2006). Understanding this bidirectional interplay between GSCs and the TME is crucial for developing targeted therapies. Disrupting the cross talk between GSCs and their microenvironment holds promise for mitigating GBM aggressiveness. For instance, targeting IL-6 signaling, as identified by Lathia et al. (2011), could disrupt the supportive signals provided by endothelial cells, hindering GSC maintenance. Similarly, strategies to inhibit PD-L1 expression on GSCs might unleash the immune system to recognize and eliminate these tumorigenic cells.

Moreover, the role of GSCs in angiogenesis opens avenues for anti-angiogenic therapies. Targeting the pro-angiogenic factors released by GSCs or disrupting their interaction with endothelial cells could impede the formation of new blood vessels, limiting the nutrient supply to the tumor and hampering its growth (Bao et al., 2006). Additionally, considering the ECM remodeling by GSCs, inhibitors of MMPs may represent a strategy to attenuate the invasive potential of GSCs and hinder tumor spread (Bao et al., 2006)

24.3.7 Mechanisms of Tumoral Immunologic Escaping

GSCs play a pivotal and multifaceted role in orchestrating tumoral immunologic escape within gliomas, actively contributing to establishing an immunosuppressive microenvironment that shields them from immune recognition and destruction. Understanding the intricate mechanisms GSCs employ in immune evasion is crucial for developing effective therapeutic strategies against gliomas.

One key aspect of GSC-mediated immunosuppression involves the modulation of checkpoint molecules, particularly PD-L1. GSCs have been identified as potent inducers of PD-L1 expression, creating a shield against immune recognition. Studies by Yamashita et al. demonstrated elevated PD-L1 levels in GSCs, facilitating their ability to evade immune surveillance. The interaction between PD-L1 on GSCs and programmed cell death protein 1 (PD-1) on T cells inhibits T-cell activation, preventing an effective antitumor immune response. This GSC-driven upregulation of immune checkpoints contributes significantly to the immunosuppressive microenvironment within gliomas.

Furthermore, GSCs actively engage with various immune cell populations within the TME, influencing their phenotype and function. Regulatory T cells (Tregs) are critical orchestrators of immunosuppression, and GSCs have been shown to promote the recruitment and activation of Tregs within gliomas (Wei et al., 2010). The increased presence of Tregs creates an immunosuppressive milieu by dampening the activity of effector T cells and inhibiting antitumor immune responses. Additionally, GSCs contribute to the recruitment of myeloid-derived suppressor cells (MDSCs), another immunosuppressive cell population, further reinforcing the inhibitory environment within gliomas (Raychaudhuri et al., 2015). This orchestrated recruitment and activation of immunosuppressive cells by GSCs highlight their role in shaping the TME to favor immune escape.

Moreover, GSCs modulate the release of soluble factors that exert immunosuppressive effects. Transforming growth factor-beta (TGF-β), a potent immunosuppressive cytokine, is actively secreted by GSCs, it inhibits T-cell activation and

promotes Treg differentiation (Platten et al., 2014a). The secretion of TGF-β by GSCs adds another layer to their immunomodulatory capabilities, establishing an unfavorable microenvironment for effective antitumor immune responses.

GSCs also influence the expression and activity of immunosuppressive enzymes within the TME. Indoleamine 2,3-dioxygenase (IDO), an enzyme associated with immune tolerance, is upregulated by GSCs, leading to the depletion of tryptophan and the generation of immunosuppressive kynurenine metabolites (Wainwright et al., 2012). This metabolic reprogramming driven by GSCs creates a hostile environment for immune cells, impairing their function and promoting immune evasion.

The cross talk between GSCs and the immune system extends to modulating the inflammatory milieu. GSCs promote the secretion of pro-inflammatory cytokines, such as IL-6 and interleukin-8 (IL-8), which contribute to the recruitment of immunosuppressive cell populations and the establishment of an immune-tolerant microenvironment (Wei et al., 2010). This pro-inflammatory signature further supports GSC-mediated immune evasion, creating a self-sustaining loop that hampers effective antitumor immune responses.

Understanding the central role played by GSCs in orchestrating tumoral immunologic escape provides a foundation for developing targeted therapeutic strategies. Strategies that disrupt the PD-L1/PD-1 axis, such as immune checkpoint inhibitors, have shown promise in restoring T-cell function and overcoming GSC-mediated immunosuppression. Additionally, targeting the recruitment and activation of Tregs and MDSCs by GSCs represents a viable approach to alleviate the immunosuppressive burden within gliomas (Wei et al., 2010; Raychaudhuri et al., 2015).

24.3.8 GSC-Mediated Mechanisms to Promote Glioma Radio-Chemoresistance and Potential Targeted Therapies

24.3.8.1 Chemoresistance

GSCs have emerged as central players in promoting glioma chemoresistance through a myriad of mechanisms that collectively contribute to the survival and recurrence of these aggressive brain tumors. The intricate interplay between GSCs and CTR agents poses a significant challenge in achieving durable treatment responses. This discussion explores the GCSs-mediated mechanisms underlying glioma chemoresistance and evaluates potential targeted therapies informed by the findings from the systematic review (Peña Agudelo et al., 2023).

24.3.8.1.1 Multidrug Efflux Transporters

One of the primary mechanisms by which GSCs confer chemoresistance is through the overexpression of ATP-binding cassette (ABC) transporters, such as ABCG2 and ABCB1, which actively pump chemotherapeutic agents out of the cells, preventing their intracellular accumulation (Gong et al., 2014; Martin et al., 2013). This efflux-mediated resistance has been implicated in various glioma cell lines, including U251 and U87 (Gong et al., 2014). Targeting these efflux transporters has shown promise in overcoming chemoresistance. For instance, ABCG2 inhibition through small interfering RNA (siRNA) has been demonstrated to sensitize GSCs to CTR, providing a potential strategy for improving treatment outcomes (Gong et al., 2014).

24.3.8.1.2 DNA Repair Mechanisms

GSCs exhibit enhanced DNA repair capabilities, allowing them to counteract the DNA damage induced by chemotherapeutic agents efficiently. The upregulation of DNA repair enzymes, such as O6-methylguanine-DNA methyltransferase (MGMT), has been associated with resistance to alkylating agents like temozolomide (TMZ) (Gong et al., 2014). The silencing of MGMT through siRNA or small molecules has been explored to sensitize GSCs to alkylating agents, presenting a potential avenue to overcome this resistance mechanism (Gong et al., 2014; Madan et al., 2016).

24.3.8.1.3 Activation of Survival Pathways

GSCs activate pro-survival signaling pathways, including the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, in response to chemotherapy-induced stress. This activation promotes cell survival and inhibits apoptosis, contributing to chemoresistance (Jia et al., 2019a). Targeting the PI3K/Akt pathway has been proposed to enhance chemotherapeutic efficacy. For instance, the use of Ibrutinib, an inhibitor of Bruton's tyrosine kinase (BTK), which intersects with the PI3K/Akt pathway, has demonstrated promising results in overcoming GSC-mediated chemoresistance (Melamed et al., 2018; Cescon et al., 2023; Clark et al., 2017).

24.3.8.1.4 TME Interactions

As underlined, the dynamic interaction between GSCs and the TME plays a crucial role in chemoresistance. GSCs actively communicate with stromal cells, creating a supportive niche that shields them from the cytotoxic effects of CTR. The secretion of growth factors, such as TGF-β, by GSCs, contributes to the immunosuppressive TME, promoting chemoresistance (Cheng et al., 2013). Disrupting these interactions presents an opportunity for therapeutic intervention. Targeting TGF-β signaling has been explored as a strategy to alter the TME and enhance the sensitivity of GSCs to CTR (Cheng et al., 2013).

24.3.8.1.5 Metabolic Reprogramming

GSCs undergo metabolic reprogramming, favoring glycolysis over oxidative phosphorylation, providing a survival advantage and contributing to chemoresistance (Huang et al., 2019). The overexpression of glycolytic enzymes, such as lactate dehydrogenase-A (LDHA), has been associated with chemoresistance in GSCs (Huang et al., 2019). Targeting glycolytic pathways or LDHA inhibition represents a potential strategy to sensitize GSCs to CTR, disrupting their metabolic advantage and enhancing treatment response.

24.3.8.2 Epigenetic Alterations

Epigenetic modifications, including changes in microRNA expression, contribute to GSC-mediated chemoresistance. For instance, miR-451 downregulation in GSCs has been associated with resistance to CTR (Silber et al., 2008). Strategies aimed at restoring or mimicking the expression of these microRNAs hold promise in overcoming chemoresistance. Anti-miR-17-92, targeting the miR-17-92 cluster, has been explored to enhance chemosensitivity by reversing the miRNA-mediated resistance mechanism (Zheng et al., 2010; Ernst et al., 2010).

24.3.8.2.1 Radio Resistance

GSCs play a pivotal role in developing glioma radioresistance, contributing to the challenges in achieving effective therapeutic outcomes. The mechanisms underlying GSC-mediated radioresistance are multifaceted, involving various signaling pathways and molecular alterations. This discussion delves into the GCS-mediated mechanisms that promote glioma radioresistance and explores potential targeted therapies, drawing insights from the systematic review's findings (Kang et al., 2023; Marampon et al., 2017).

24.3.8.2.2 DNA Repair Machinery

One key contributor to GSC-mediated radioresistance is the enhanced DNA repair capacity exhibited by these cells. The upregulation of DNA repair proteins, including MGMT, allows GSCs to repair radiation-induced DNA damage efficiently, promoting cell survival (Gong et al., 2014). Strategies aimed at inhibiting DNA repair mechanisms, such as MGMT silencing through siRNA or pharmacological inhibitors, have shown promise in sensitizing GSCs to RTR (Gong et al., 2014).

24.3.8.2.3 Activation of Survival Pathways

In response to radiation-induced stress, GSCs activate pro-survival signaling pathways, including the phosphatidylinositol 3-kinase (PI3K)/Akt pathway. This activation enhances cell survival and inhibits apoptosis, contributing to radioresistance (Jia et al., 2019a). Targeting the PI3K/Akt pathway has been explored to sensitize GSCs to RTR. Inhibitors such as Ibrutinib, which intersects with the PI3K/Akt pathway, have demonstrated potential in overcoming GSC-mediated radioresistance (Melamed et al., 2018).

24.3.8.2.4 TME Interactions

The dynamic interplay between GSCs and the TME significantly influences radioresistance. GSCs actively communicate with stromal cells, creating a supportive niche that shields them from the cytotoxic effects of radiation. The secretion of growth factors, such as TGF-β, by GSCs, contributes to the immunosuppressive TME, promoting radioresistance (Cheng et al., 2013). Disrupting these interactions presents an opportunity for therapeutic intervention. Targeting TGF-β signaling has been explored as a strategy to alter the TME and enhance the sensitivity of GSCs to radiation therapy (Cheng et al., 2013).

24.3.8.2.5 Notch Signaling Pathway

Notch signaling, a crucial pathway in stem cell maintenance, has been implicated in GSC-mediated radioresistance. Notch1 enhances the self-renewal capacity of GSCs and promotes radioresistance (Hu et al., 2016). Inhibiting Notch signaling through Notch1 siRNA has been proposed as a potential strategy to sensitize GSCs to radiation therapy, disrupting the molecular mechanisms contributing to their radioresistance (Hu et al., 2016).

24.3.8.2.6 Metabolic Reprogramming

Metabolic alterations in GSCs, favoring glycolysis over oxidative phosphorylation, contribute to radioresistance. The overexpression of glycolytic enzymes, such as LDHA, has been associated with radioresistance in GSCs (Huang et al., 2019). Targeting glycolytic pathways or LDHA inhibition represents a potential strategy to sensitize GSCs to radiation therapy, disrupting their metabolic advantage and enhancing treatment response.

24.3.8.2.7 Hypoxia-Inducible Factors

GSCs thrive in the hypoxic microenvironment of gliomas, and the activation of hypoxia-inducible factors (HIFs) contributes to radioresistance. HIFs reduce the differentiation of GSCs and promote their stemness, fostering resistance to radiation therapy (Lee et al., 2016). Strategies aimed at targeting HIFs or modulating the hypoxic response present avenues for enhancing the radiosensitivity of GSCs.

24.4 GSC-MEDIATED MECHANISMS TO PROMOTE GLIOMA PROGRESSION AND POTENTIAL TARGETED THERAPIES

GSCs influence glioma progression differently, orchestrating mechanisms that enhance oncogenic potential and invasive ability. This intricate process involves critical molecular players, including Akt, HIF-1α, and MMP-9, each contributing significantly to the aggressive nature of gliomas (Cheng et al., 2011; Melamed et al., 2018; Du et al., 2008; Zagzag et al., 2006). Du et al. (2008) unravel the impact of cyclopamine in elevating Gli1 expression, thereby fostering uncontrolled proliferation and progression, a finding consistent with the existing literature demonstrating the association between Gli1 and heightened oncogenic potential (Inoue et al., 2010). Cheng et al. (2011) shed light on L1CAM's role in promoting tumor invasion, unveiling a critical aspect of GSC-mediated glioma progression.

The study underscores the potential of siRNAs as targeted therapies in the pursuit of effective therapeutic strategies against GSC-mediated progression. Specifically, Ob-R siRNAs and LTBP4 shRNA emerge as promising candidates, offering avenues to counteract GSC-mediated progression (Table 24.2). Targeting these pathways becomes crucial for impeding the aggressive nature of GSCs and slowing glioma progression.

24.4.1 Oncogenic Potential and Invasive Ability

24.4.1.1 Role of Cyclopamine in Glioma Progression

The study by Du et al. (2008) delineates the pivotal role of cyclopamine in Gli1 expression, a component of the Sonic Hedgehog (Shh) pathway. Shh signaling is implicated in glioma progression, and inhibiting this pathway, as demonstrated by cyclopamine, emerges as a potential therapeutic strategy. Inoue et al. (2010) support these findings, highlighting Gli1's central role in enhancing oncogenic potential. This emphasizes the need for targeted therapies against Gli1 or upstream regulators within the Shh pathway to curb uncontrolled growth facilitated by GSCs (Bar et al., 2007; Clement et al., 2007).

24.4.1.2 L1CAM as a Promoter of Invasion

Cheng et al. (2011) illuminate the significance of L1CAM overexpression in promoting tumor invasion. L1CAM, a cell adhesion molecule, plays a critical role in glioma invasion, providing a molecular basis for GSCs' aggressive behavior. Targeting L1CAM through specific interventions could be instrumental in curtailing GSCs' invasive capacity, thereby slowing down the progression of gliomas.

24.4.1.3 siRNAs as Targeted Therapies

Exploring siRNAs as targeted therapies introduces a paradigm shift toward precision medicine in glioma treatment. Ob-R siRNAs, designed to target the leptin receptor and LTBP4 shRNA, inhibiting latent TGF-β-binding protein 4, present targeted strategies to disrupt signaling pathways associated with GSC-mediated progression. These siRNAs offer a nuanced approach to intervene in specific molecular pathways that contribute to the aggressive nature of GSCs, showing promise in impeding the relentless progression of gliomas (Han et al., 2013; Yeh et al., 2009a; Riolfi et al., 2010).

24.5 INHIBITION OF DIFFERENTIATION

24.5.1 Role of miR-124 and miR-137 in Differentiation Inhibition

GSCs ability to inhibit differentiation emerges as a critical aspect of glioma progression. Silber et al. (2008) identify miR-124 and miR-137 downregulation as contributors to this process. This finding aligns with previous research highlighting the pivotal role of miRNAs in GSC-mediated differentiation (Gal et al., 2008). The study introduces glioma stem-like cells (GSLCs) and siRNAs targeting critical pathways like Notch and Wnt/β-catenin as potential avenues to counter differentiation inhibition and impede glioma progression.

24.5.2 GSIs as Potential Therapies

The study proposes using gamma-secretase inhibitors (GSIs) to counteract the inhibition of differentiation mediated by GSCs. These inhibitors target the Notch signaling pathway, a key player in maintaining GSC stemness. The potential therapeutic efficacy of GSIs highlights the importance of unraveling the intricate molecular mechanisms governing GSC behavior and differentiation inhibition.

24.5.3 siRNAs Targeting Notch and Wnt/β-catenin Pathways

In addition to GSIs, siRNAs targeting critical pathways like Notch and Wnt/β-catenin emerge as potential therapies to counter differentiation inhibition. The targeted disruption of these pathways offers a precise intervention to impede GSC-mediated glioma progression. The findings underscore the need for a comprehensive understanding of differentiation inhibition's molecular intricacies, paving the way for more effective targeted therapies.

24.6 GSC-MEDIATED MECHANISMS TO PROMOTE GLIOMA RECURRENCE AND POTENTIAL TARGETED THERAPIES

GSCs intricately orchestrate glioma recurrence by activating key pathways, including Notch, TGF-β, JAK/STAT3, and the Wnt/β-catenin pathway. Understanding these molecular intricacies is pivotal for developing targeted therapeutic strategies to counteract GSC-mediated recurrence.

24.6.1 Notch, TGF-β, and JAK/STAT3 Pathways in Recurrence

24.6.2 LTBP4 Mutation and TGF-β Activation

Wang et al. (2016) shed light on the critical role of LTBP4 mutation in activating TGF-β and subsequently promoting glioma cell proliferation, culminating in recurrence. This finding aligns seamlessly with existing literature emphasizing the significance of TGF-β in glioma recurrence (Cheng et al., 2013). TGF-β, a multifunctional cytokine, has promoted glioma progression and recurrence by fostering an immunosuppressive microenvironment and facilitating GSC-mediated mechanisms (Cheng et al., 2013; Huang et al., 2019).

24.6.3 Notch1 as a Central Player in the Recurrence

Notch1 emerges as a central player in glioma recurrence, exerting its influence by enhancing the self-renewal capacity of GSCs (Yu et al., 2016; MacLeod et al., 2019). The activation of Notch signaling pathways has been previously associated with glioma progression and recurrence (Cenciarelli et al., 2017). The study by Yu et al. (2016) introduces a potential therapeutic strategy against recurrence through siRNAs targeting Notch1, offering a nuanced and targeted approach to disrupt this pathway (Ulasov et al., 2011).

24.6.4 Wnt/β-Catenin Pathway in Recurrence

Mitchell et al. (2023) delve into the intricate involvement of the Wnt/β-catenin pathway in glioma progression and

recurrence. WDR5, identified as a critical player, facilitates the assembly of the WRAD complex and enhances the expression of GSC-related oncogenic pathways. The dual role of the Wnt/β-catenin pathway in both progression and recurrence is highlighted by comparative analysis with existing literature (Kaur et al., 2013). The study introduces potential interventions like MM-102 and C16 targeting WDR5, presenting a targeted and precise approach against Wnt/β-catenin-mediated recurrence.

24.7 COMPARATIVE ANALYSIS AND FUTURE DIRECTIONS

24.7.1 Comparative Analysis of GSC-Mediated Mechanisms

The reviewed literature consistently underscores the pivotal role of specific molecular pathways in mediating glioma aggressiveness. Notably, pathways such as Notch, TGF-β, JAK/STAT3, Wnt/β-catenin, Akt, and HIF-1α emerge as recurrent players across various studies. GSCs, through these pathways, drive radio-chemoresistance, progression, and recurrence. For instance, the intricate interplay of GSCs with the TME, highlighted by studies like Yang et al. (2018) and Knudsen et al. (2022), significantly influences glioma pathobiology.

The chapter identified specific molecular agents and pathways in the context of radio-chemoresistance, including those targeted by small molecules, siRNAs, and inhibitors. Integrating multiple targeted therapies represents a promising approach to overcome the heterogeneity of GSC-driven gliomas. Studies by Cheng et al. (2013), Muthukrishnan et al. (2022), and others provide a nuanced understanding of the molecular underpinnings of resistance and offer potential interventions.

Glioma progression, characterized by enhanced oncogenic potential and invasive ability, involves vital molecules such as Akt, HIF-1α, and MMP-9. The studies by Du et al. (2008), Cheng et al. (2011), and Melamed et al. (2018) collectively contribute to delineating the molecular landscape driving progression. SiRNAs targeting Ob-R and LTBP4 shRNA represent potential therapies to counter GSC-mediated progression.

For glioma recurrence, the activation of pathways like Notch, TGF-β, and JAK/STAT3, as highlighted by Wang et al. (2016), Yu et al. (2016), and Mitchell et al. (2023), plays a central role. Targeted therapies, including siRNAs against Notch1, provide avenues for combating recurrence. The Wnt/β-catenin pathway, implicated in progression and recurrence, introduces potential interventions like MM-102 and C16 targeting WDR5 (Mitchell et al., 2023).

24.8 FUTURE DIRECTIONS IN GSC RESEARCH

As we reflect on the findings, it becomes evident that there is a need for further exploration in several key directions. The heterogeneity within GSC populations demands a deeper understanding of the specific subsets driving distinct aspects of glioma pathobiology. Emerging technologies, such as CRISPR-based gene editing and single-cell RNA sequencing, present exciting opportunities to unravel this heterogeneity and identify novel therapeutic targets.

Combinatorial therapeutic strategies hold promise in addressing the intricate molecular landscape of GSC-driven gliomas. Future research could focus on developing synergistic interventions targeting multiple pathways simultaneously to enhance treatment efficacy. Collaborative efforts between researchers and clinicians are paramount for translating these discoveries from bench to bedside, bringing about more personalized and effective treatment strategies.

Integrating advanced imaging techniques and biomarkers for GSC identification and monitoring holds significant potential in refining diagnostic approaches and facilitating early intervention. This could lead to a more precise understanding of the disease and its progression. Moreover, gaining deeper insights into the mechanisms of tumoral immunologic escaping orchestrated by GSCs, as discussed in the chapter, could open avenues for immunotherapeutic interventions tailored to glioma patients.

Understanding the temporal dynamics of GSC-mediated processes is a crucial aspect of future research. Longitudinal studies, tracking the evolution of GSC populations during treatment and disease progression, would provide valuable information for designing dynamic and adaptive treatment strategies. This underscores the need for long-term studies to inform treatment strategies.

24.9 CONCLUSIONS

This chapter, based on a comprehensive systematic review, has meticulously examined numerous studies spanning several years to unravel the intricate molecular mechanisms governing glioblastoma progression and recurrence orchestrated by GSCs. The findings underscore the pivotal roles played by diverse signaling pathways, transcription factors, and molecular agents in fostering the aggressive behavior of GSCs, contributing to the relentless growth, invasion, and therapeutic resistance characteristic of glioblastoma.

The chapter identified critical pathways such as Notch, Wnt/β-catenin, PI3K/Akt , and JAK/STAT3, each wielding a profound influence on GSCs behavior. The modulation of these pathways involves an array of molecular players, including specific proteins, microRNAs, and transcription factors, all interconnected in a complex network that orchestrates GSC stemness, proliferation, and invasion. Notably, interventions targeting these pathways and molecular agents emerge as potential therapeutic strategies, offering a glimpse of hope in the quest to combat glioblastoma.

Moreover, the chapter shed light on the heterogeneity of GSCs and the dynamic interplay between various components within the glioblastoma microenvironment.

Understanding these intricate relationships is paramount for devising effective therapeutic interventions that address the multifaceted nature of glioblastoma progression and recurrence. The documented synergies and cross talk among different molecular entities emphasize the need for a holistic and personalized approach to glioblastoma treatment.

While elucidating these molecular mechanisms provides a foundation for potential targeted therapies, the chapter also underscores the challenges and gaps in current knowledge. Further research must delve deeper into GSC biology's complexities and translate these insights into clinically viable treatment options. The continuous evolution of research in this field holds promise for developing innovative therapies that can disrupt glioma's relentless progression and recurrence, ultimately improving patient outcomes and quality of life.

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