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REVIEW

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Stem cell therapies and glioma stem cells in glioblastoma: a systematic review of current challenges and research directions

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Abstract

Background Glioblastoma is the most aggressive tumor of glial origin and the most common, as established by the World Health Organization. GBM has been one of the most intractable tumors with minimal progress in prognosis despite decades of research. Stem cell therapy (SCT) has raised hopes with regard to possibly targeting tumor progression and recurrence. Glioma stem cells (GSCs) are directly involved in gliomagenesis and chemoresistance, thus constituting potential valuable therapeutic targets for improving treatment outcomes.

Objective The objective of this review article is to assess and consider the potential therapeutic benefits, challenges, and prospective research directions for SCTs for glioblastoma with a particular focus on GSCs as key therapeutic targets.

Materials and methods A literature review was performed using search terms and Boolean operators pertinent to SCT and glioblastomas to gather all existing literature. The databases PubMed/MEDLINE, Scopus, and the Cochrane Library were searched in accordance with the standard guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020.

Results and conclusions The review established that the main mesenchymal stem cells (MSCs), neural stem cells (NSCs), induced pluripotent stem cells (iPSCs), and hematopoietic stem cells are the first SCTs evaluated in terms of their potential as a glioblastoma therapy. While SCTs were found to be effective in tumor targeting and immune modulation, they face certain restrictions, including death of stem cells inside the body, tumor heterogeneity, and transformation to malignancy. Research must now focus on the combination of stem cell therapy with molecular-targeted therapy and advanced delivery systems for improved tumor targeting, better overcoming resistance, and enhancing both efficacy and safety for patients undergoing treatment for glioblastoma.

Highlights

- MSCs, NSCs, iPSCs, and HSCs are the primary stem cell types explored in glioblastoma therapy.
- GSCs, as key drivers of tumor initiation, progression, and resistance, are essential therapeutic targets.

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• Ongoing research and clinical trials are needed to optimize stem cell applications and improve outcomes for glioblastoma patients.
• Concerns of both efficacy and safety remain regarding stem cell therapy for the treatment of glioblastoma.

Keywords Glioblastoma, Stem cell, Glioblastoma stem cell, Stem cell therapy

Introduction

Glioblastoma stem cells (GSC) are a subset of cells present in glioblastomas that demonstrate stem-like features, such as tumor self-renewal and differentiation. These cells are crucial for glioblastoma initiation, development, and treatment resistance. GSCs are responsible for the aggression in glioblastoma as they promote tumor growth, invasion, and recurrence while having high resistance to conventional treatments, including chemotherapy and radiotherapy. Targeting GSCs is emerging as an attractive therapeutic strategy aimed at improving treatment outcomes and addressing obstacles posed by tumor heterogeneity and resistance mechanisms.

Glioblastoma (GBM) is the most aggressive brain neoplasm with the poorest prognosis [1–3]. It is a malignant high-grade tumor of astrocytes and the most common central nervous system (CNS) tumor [4]. With its high prevalence, glioblastoma has become a pressing concern in the field of oncology and has been classified as grade IV by the World Health Organization (WHO) [5]. GBM, even in the face of aggressive use of existing therapeutic options, has a median survival of 12–15 months after diagnosis and represents about 60% of all primary brain tumors in adults [1, 2, 5, 6]. GBM is often male predominant and tends to occur more in people aged 45 to 70 years group [1, 2, 5, 6]. The impact extends beyond its physical manifestations, profoundly affecting the livelihood and personal life of affected patients and their families, especially where sequelae of neurological deficit, cognitive decline, and emotional distress ensue.

Due to its capacity to infiltrate cerebral tissue, GBM exhibits an aggressive disposition which makes total surgical resection impossible in virtually all cases. Chemoradiotherapy alongside surgical resection is frequently employed in the standard treatment of GBM. The total survival rate remains depressingly low despite improvements in neuro-oncological intervention, emphasizing the urgent need for innovative therapeutics [7, 8].

Stem cells have enormous potential in the field of regenerative medicine due to their exceptional capacity for self-renewal and cell-type differentiation. These extraordinary cells may repair or replace damaged tissues; this distinct feature of certain metabolic activity encourages the use of stem cells for the treatment of pathological conditions. Stem cell therapy (SCT) has gained considerable attention in recent years, particularly in the context of glioblastoma treatment. The use of stem cells in this setting offers several possibilities, including the capacity to target tumor cells and regenerate healthy brain tissue [2, 5, 9].

Mesenchymal stem cells (MSCs), neural stem cells (NSCs), induced-pluripotent stem cells (iPSCs), and hematopoietic stem cells (HSCs) are four SCT types investigated to treat glioblastoma. Bone marrow, adipose tissue, and umbilical cord blood are just a few of the sources from which MSCs are derived. They are able to migrate to the tumor site, releasing antitumor molecules and immune-modulating agents to relay an antitumor response [10]. NSCs, in contrast, are present in the adult brain naturally and possess the ability to differentiate into various neural cell types. They may be genetically modified to express therapeutic agents and target glioblastoma cells specifically [11]. Adult cells, like that of skin, are reprogrammed to resemble embryonic stem cells (ESCs) to create iPSCs. Once differentiated, they may become different cell types, including neural cells. iPSCs hold promise for the management of glioblastoma as they can become patient-specific, enabling individualized therapy. HSCs, found in bone marrow, may develop into a plethora of varying blood cell lineages, comprising myelocytes, lymphocytes, and erythrocytes. HSCs may be utilized in conjunction with high-dose chemotherapy, but cannot be administered to specifically target the cells of glioblastoma. With this strategy, also known as autologous hematopoietic stem cell transplantation (AHSCT), the patient's blood cell production may be saved while receiving higher chemotherapy doses [12].

This systematic review aims to explore the current state of knowledge regarding SCTs for patients with glioblastoma, assessing the benefits, disadvantages, and potential directions for future research. SCTs are increasingly being investigated for the management of glioblastoma. There are several types of SCTs considered for patients with this severe, common form of brain tumor. There currently exists some debate on which SCT should be utilized for patients with GBM, thereby warranting a review of the recent literature to provide additional input for the management of glioblastoma.

Materials and methods

A review of the literature was conducted with Boolean operators and relevant search terms: "Stem Cell Therapy AND Glioblastoma"; "Neural Stem Cells

AND Glioblastoma"; "Cord Blood AND Glioblastoma". The electronic databases searched were PubMed/MEDLINE with MeSH terms focusing on stem cell therapy and glioblastoma, Scopus with relevant subheadings such as stem cells and neuro-oncology, and the Cochrane Library. The literature was extracted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) format (See Fig. 1). The selected literature consisted of studies from the past 5 years. Incomplete or ongoing trials, systematic reviews, study protocols, and animal models were excluded. Following the removal of duplicates, titles, and abstracts was screened for studies reporting various SCTs for GBM. Data entry, removal of duplicates, and screening were completed with the Zotero reference management software package. The methodological quality of each study was assessed using Cochrane Collaboration's risk of bias tool (RoB2) [13]. Ratings of low, unclear, or high risk of bias will be assigned to each domain by two independent reviewers. Any disagreements regarding the risk of bias was discussed until a decision is made. In case a decision cannot be reached, the piece of literature in question was discussed by a third reviewer. After the inclusion, exclusion, and deletion of duplicates, 64 articles were included in the final study. This review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [14] (See Fig. 1). This research was also registered in PROSPERO under the number CRD42022322907. A title and abstract screening was performed according to PRISMA standards (the link below): https://www.crd.york.ac.uk/prospero/display_record.php? RecordID=322907.

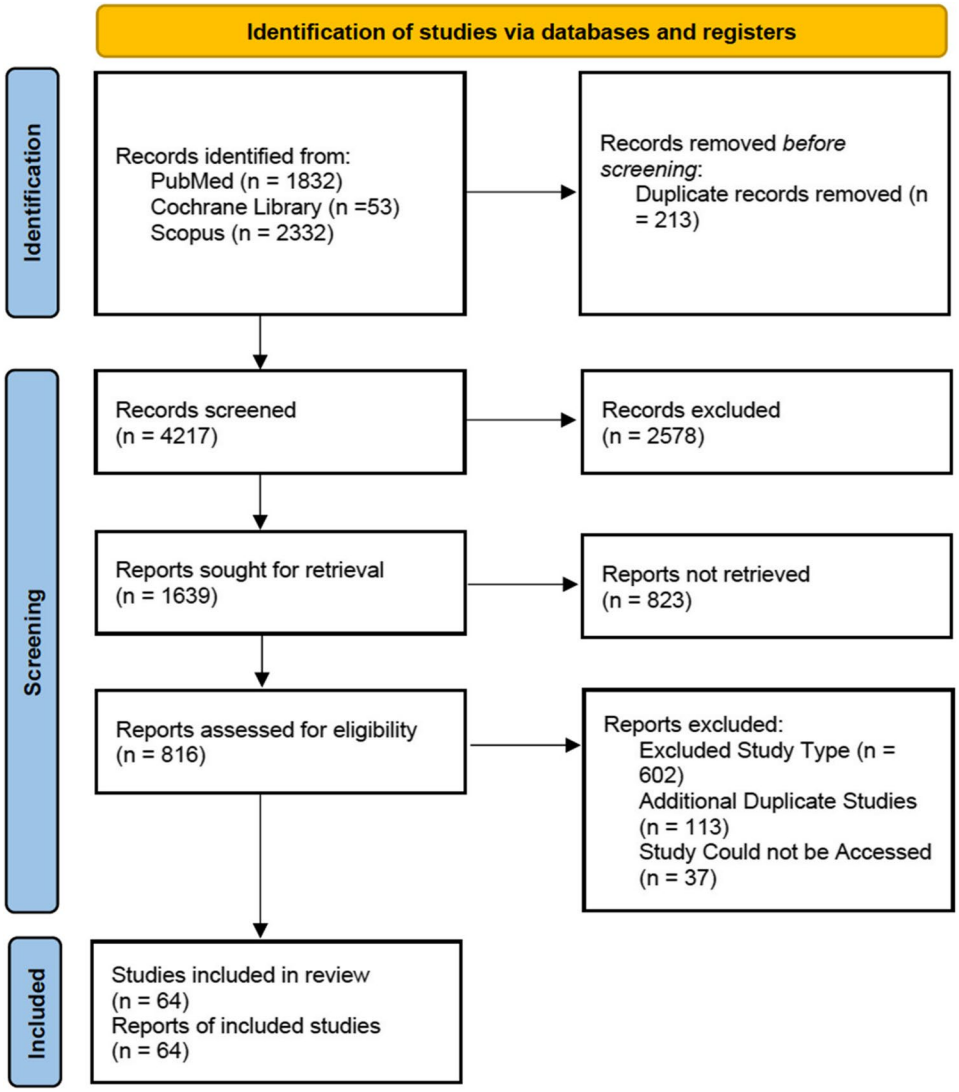

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA, 2020)

Results

The results of the systematic review revealed several key findings regarding SCT for patients with GBM. A total of 64 studies from 5 years prior were included in the final analysis, following the PRISMA guidelines.

Types of stem cell in use

Different stem cell types have been investigated for their therapeutic potential in targeting GB tumors and delivering therapeutic agents. This section discusses the types of stem cells that have been utilized in GBM therapy based on the literature search (see Table 1).

Adipose-derived stem cells (ASCs), ESCs, and iPSCs have been studied for their potential therapeutic use in GBM management [15]. Abadi et al. [1] highlighted the diagnostic potential of stem cells in GBM and discussed the pitfalls associated with SCT, including the possibility of stem cell malignant transformation [15]. These findings suggest that ASCs, ESCs, and iPSCs have been considered diagnostic tools and potential therapeutic agents in GBM treatment. Glioma stem cells (GSCs), HSCs, and NSCs have also been explored in the context of GBM therapy [16]. Glioma stem cells (GSCs) and normal neural stem cells (NSCs) share many characteristics, including self-renewal, multipotency, and the expression of key stemness markers (e.g., Nestin, SOX2). However, GSCs are pathologically reprogrammed versions of NSCs or their progeny that drive glioblastoma (GBM) growth, resistance to therapy, and recurrence.

Induced pluripotent stem cells recreate adult reprogrammed cells that resemble embryonic stem cells and thus may offer a patient-specific treatment. The work of Abadi et al. [1] cites iPSCs diagnostic and therapeutic potential in clinical management of GBM see Table 1).

According to Akindona et al. [2], it is essential to address the tumor microenvironment in future SCT approaches for GBM. The study posits that GSCs, HSCs, and NSCs are not only instrumental in the formation and advancement of GBMe rationale for these interventions is that such cells are thought to help in the onset of tumors, in the resistance to therapies, and in the recurrence of the tumor, which is a crucial factor in reaching durable treatment response.

MSCs represent an attractive therapeutic option for GBM since they migrate to tumor sites, promote tissue repair, and are involved in immune modulation, hence supporting targeted therapy and favorable outcome in GBM patients. Al-Kharboosh et al. [3] highlighted the tropism of MSCs to sites of injury, their immunomodulatory effects on solid tumors, and their hypoimmunogenic nature [17]. These properties make MSCs attractive candidates for the targeted delivery of therapeutic agents to GBM tumors. Sources like umbilical cord blood, bone marrow, and adipose tissue have provided human mesenchymal stem cells (hMSCs) that have special attraction to tumors and which have shown immunomodulatory effects, making these hMSCs promising therapeutic agents for GBM tumor delivery. Al-Kharboosh et al. [3] touched on the low immunogenic nature of the MSCs and their ability to modulate the tumor microenvironment. On the other hand, the drawbacks include low survival rates following my own transplantation, inducing anoikis-type apoptosis, and in some cases, promoting tumor growth. To minimize the dangers, biodegradable scaffolds or genetic modifications are suggested. These strategies are aimed at enhancing cell adhesion, increasing stem cell survival, and decreasing tumor promotion—essential objectives for the success and safety of stem cell therapy for treating glioblastoma (see Table 1).

Attia et al. [4] explored the potential of NSCs for delivering therapeutic agents to GBM sites [18]. The study suggests that NSCs can migrate toward GBM tumors, offering a targeted approach to delivering therapeutic interventions. Stem cells associated with cancer have also been investigated in the context of GBM therapy. According to Bahmad et al. [5] in their study on the repurposing of anticancer drugs with the aim of targeting stem cells for treatment of brain tumors, emphasis had been placed on the effects of these drugs on cancer stem cells [18]. Targeting these cells may be crucial for effective GBM therapy. While the use of these various stem cell types shows promise in GBM treatment, it is important to acknowledge the limitations and potential risks associated with SCT. The provided studies indicate a low risk of bias, suggesting a good level of reliability in the findings. However, further research and clinical studies are needed to fully understand the efficacy, safety, and long-term effects of stem cell-based therapies in GBM. NSCs are the natural kinds of cells that are found in the brain. They have the ability to differentiate into various types

Table 1 Summary table: stem cell types in glioblastoma therapy

Stem Cell Type	Mechanisms of Action	Therapeutic Benefits	Limitations	Key References
MSCs	Tumor homing, immunomodulation, therapeutic agent delivery	Hypoimmunogenic, accessible sources	Low survival, anoikis, potential tumor-promoting effects	Al-Kharboosh et al. [3]
NSCs	Migration to tumor sites, differentiation into neural cell types	Targeted drug delivery	Limited availability, genetic modification required, malignant transformation risks	Attia et al. [4]
iPSCs	Patient-specific reprogramming, differentiation into neural cell types	Personalized therapies	Tumorigenicity, genetic instability	Abadi et al. [1]

of neural cells and migrate towards GBM tumors. Attia et al.[4] says that the NSCs have come out as probable candidates with regard to targeted delivery using these cells due to having these properties with the capacity to migrate and homing to a tumor site. However, the potential has some problems, which include limited availability, genetic modification to improve therapeutic effects, and malformation risk (see Table 1).

Molecular insights and therapeutic targets in glioblastoma

Recently, investigations have been directed at studies through which researchers would understand how the dissemination of stem cells affects glioblastoma. The major concern has been molecular mechanisms acting within glioblastoma stem cells (GSC) leading to their maintenance, tumor progression, and therapeutic resistance which impacts neurocognitive functions as well as recurrence and prognosis in a patient suffering from glioblastoma.

According to Peng et al., transforming growth factor beta-induced (TGFBI), a protein secreted from tumor-associated macrophages (TAMs), has been implicated in supporting GSC survival and tumor growth via integrin αvβ5-Src-Stat3 signaling in malignant glioblastoma. TGFBI was significantly linked with glioma WHO grades and poor prognosis of patients [15]. Other immune cell clusters, like CD8 + T cells, which are transformed into exhausted phenotypes in the tumour microenvironment, can interact with TAM. According to certain research, this process might be connected to the Tim3 signalling pathway and PD-1/PD-L1. The serum or CSF levels of TGFBI were diagnostic/prognostic markers [15]. Therefore, therapeutic results against GSC-driven tumor progression with TGFBI signaling intervention might promise [15].

Gander and colleagues have analyzed primary glioblastoma stem cell cultures (pGSC's) highlighting key stem cell markers: MSI1, Notch1, nestin, Sox2, Oct4, FABP7, and ALDH1A3, which associated directly with radio resistance and matrix invasion capability [17]. PGSCs demonstrated the mesenchymal mRNA signatures to be positively correlated with multifocal tumor recurrence as well as poor survival when compared to those showing a proneuronal signature [17]. The findings shed light on the targeting of mesenchymal markers and pathways as a strategy to overcome radio resistance induced by GSC and make therapeutic success possible towards more personalized treatment approaches [18].

A research group from Slovenia showed that the TRIM28-selective nanobody (NB237) dramatically inhibited glioblastoma cells and showed some reductions in zebrafish models for GSC invasiveness and dissemination [18]. However, TRIM28 was not found to be a direct prognostic marker, but TRIM28 inhibition has therapeutic potential for reducing GSC-driven tumor spread [18]. Results are indicative of possible efficacy of TRIM28 targeting as a strategy toward reduced metastasis and recurrence in glioblastoma [18].

Research into glioblastoma's molecular mechanisms and therapeutic targets have yielded many critical insights into the drivers of resistance and recurrence, especially concerning glioblastoma stem cells (GSCs). Such targets include TGFBI, TRIM28, ALKBH2, and ALKBH5 and constitute promising opportunities for targeting the survival of tumor-propagating GSCs. Inclusion of these applications into current combined modality therapies with SCT, immunotherapy, or molecular-targeted therapies should potentiate therapeutic efficacy to improve outcomes for glioblastoma patients. More research to validate these approaches and to discover new interventions specifically against GSCs is necessary.

The results of the reviewed literature were summarized below (Table 2).

Summary of key findings

The last five years have witnessed several studies on the roles of each stem cell type in the management of glioblastoma (GBM): mesenchymal stem cells (MSCs), neural stem cells (NSCs), induced pluripotent stem cells (iPSCs), hematopoietic stem cells (HSCs), adipose-derived stem cells (ASCs), embryonic stem cells (ESCs), glioblastoma stem cells (GSCs), cancer stem cells. Whereas certain stem cell types including ASCs, ESCs, and iPSCs have been investigated for therapeutic utility, others like GSCs, HSCs, and NSCs are believed to contribute to the pathophysiology of the disease (see Table 2). The potential of MSCs has been interesting in the management of GBM because of their ability to migrate into the tumors, alter the immune system, and carry the therapeutic agents. In the same way, NSCs can also find their way to GBM tumors, thereby enabling the delivery of treatment to the focus.

Even if those results are encouraging some obstacles exist which prevent the effective translation of the preclinical outcomes into successful therapies in a clinical setting. For instance, there has been a concern over tumor risk, cell death rates are inconsistent, and therapeutic effects are not guaranteed within a patient population. In addition, concerns regarding safety and improvement of stem cell administration techniques warrant the conducting of more vigorous clinical depending on the indication of treatment. In order to realize the full benefit of SCT in treatment of GBM, these limitations will have to be overcome. In relation to the molecular mechanism of stem cells, a range of therapeutic targets have been identified by researchers, among them being TGFBI. TGFBI plays a role in GSC maintenance and malignant growth promotion, making it a promising candidate as a biomarker for

Table 2 Summary of relevant findings and types of stem cells

References number	Authors	Year	Title	Type of Stem-cell	Summary of effects or relevant findings	Risk of Bias
[1]	Abadi B, Ahmadi-Zeidabadi M, Dini L, et al.	2021	Stem cell-based therapy treating glioblastoma multiforme.	ASCs, ESCs, iPSCs	This study shows SC as a diagnostic tool and pitfalls of SC-therapy including SC malignant transformation.	Low
[2]	Akindona FA, Frederico SC, Hancock JC, et al.	2022	Exploring the origin of the cancer stem cell niche and its role in anti-angiogenic treatment for glioblastoma.	GSCs, HSCs, NSCs	This study shows current understanding of the GBM CSC niche formation which should be targeted by future SC therapies.	Low
[3]	Al-Kharboosh R, ReFaey K, Lara-Velazquez M, et al.	2020	Inflammatory Mediators in Glioma Microenvironment Play a Dual Role in Gliomagenesis and Mesenchymal Stem Cell Homing: Implication for Cellular Therapy	MSCs	This study shows the potential of MSC-based therapies due to its tropism to sites of injury, immunomodulation of solid tumors, and hypo immunogenic nature.	Low
[4]	Attia N, Mashal M, Pemminati S, et al.	2021	Cell-Based Therapy for the Treatment of Glioblastoma: An Update from Preclinical to Clinical Studies.	MSCs, NSCs	This study shows the potential of MSCs for delivering therapeutic agents to GB.	Low
[5]	Bahmad HF, Daher D, Aljamal AA, et al.	2021	Repurposing of Anticancer Stem Cell Drugs in Brain Tumors	CSCs	This study shows the drug repurposing process for targeting CSCs.	Low
[6]	Bakhshinyan D, Savage N, Salim SK, et al.	2021	The Strange Case of Jekyll and Hyde: Parallels Between Neural Stem Cells and Glioblastoma-Initiating Cells.	GSCs, NSCs	This study shows the extensive overlap between NSCs and GSCs in function, but their distinct genetic differences which can be targeted in SC-based therapy.	Low
[7]	Benmelouka AY, Munir M, Sayed A, et al.	2021	Neural Stem Cell-Based Therapies and Glioblastoma Management: Current Evidence and Clinical Challenges	NSCs	This study shows the potential of NSCs, due to their migratory and tumor homing features, to be exploited to provide an important drug delivery source that may help in targeting malignant cells with a reduced toxicity.	Low
[8]	Biserova K, Jakovlevs A, Uljanovs R, et al.	2021	Cancer Stem Cells: Significance in Origin, Pathogenesis and Treatment of Glioblastoma.	CSCs, GSCs	This study shows the challenges in targeting GSCs due to their chemotherapy and radiotherapy resistant properties.	Low
[9]	Boyd NH, Tran AN, Bernstock JD, et al.	2021	Glioma stem cells and their roles within the hypoxic tumor microenvironment.	GSCs	This study shows added emphasis on targeting these microenvironments during therapeutic design may lead to desirable improvements in standard of care.	High
[10]	Bryukhovetskiy I.	2022	Cell-based immunotherapy of glioblastoma multiforme	CSCs, HSCs	This study shows HSC transplantation should be performed directly after chemoradiation treatment.	Some Concerns
[11]	Buccarelli M, Beninati S, Tabolacci C	2023	Editorial: Cancer stem cell differentiation: A realistic potential therapeutic option?	CSCs	This study shows the use of organoids to study CSC differentiation requires further study.	Low
[12]	Calinescu AA, Kauss MC, Sultan Z, et al.	2021	Stem cells for the treatment of glioblastoma: a 20-year perspective	MSCs, NSCs	This study shows several new discoveries that can be used to make stem cell therapies for glioblastoma more effective to prolong the life of patients with brain tumors.	Low
[13]	Chang X, Ma Z, Zhu G, et al.	2021	New perspective into mesenchymal stem cells: Molecular mechanisms regulating osteosarcoma	MSCs	This study shows the effects of MSCs on the components of the TME and cellular communication and the prospects for clinical applications of MSCs.	Low
[14]	Chen J, Huang L, Yang Y, et al.	2023	Somatic cell reprogramming for nervous system diseases: techniques, mechanisms, potential applications, and challenges.	ASCs, HSCs	This study shows the potential benefits of somatic cell reprogramming for neurological disease research and therapy.	Low
[19]	Choi BD, Maus MV, June CH, et al.	2019	Immunotherapy for glioblastoma: adoptive t-cell strategies	HSCs	This study shows GBM poses a unique set of challenges that must be addressed before the full potential of immunotherapy can be realized.	Low

Table 2 (continued)

References number	Authors	Year	Title	Type of Stem-cell	Summary of effects or relevant findings	Risk of Bias
[20]	Ciechomska IA, Wojnicki K, Wojtas B, et al.	2023	Exploring novel therapeutic opportunities for glioblastoma using patient-derived cell cultures	GSCs	This study shows that GBM-derived cell cultures mimic the considerable tumor heterogeneity, and that identifying patient-specific signaling vulnerabilities can assist in overcoming therapy resistance, by providing personalized combinatorial treatment recommendations.	Low
[21]	Corbet C, Prieur A	2020	Editorial: therapeutic targeting of cancer stem-like cells (Csc)– the current state of the art	CSCs	This study shows how the specific permissive microenvironment can be therapeutically exploited.	High
[22]	Dai X, Ye L, Li H, et al.	2023	Crosstalk between microglia and neural stem cells influences the relapse of glioblastoma in GBM immunological microenvironment.	NSCs	This study shows the underlying mechanisms of tumor microenvironment in the pathogenesis of glioma.	Low
[15]	Dwivedi S, Sharma P	2023	Cancer stem cells: future possibilities for cancer therapy	CSCs	This study shows many CSC clinical trials for cancer treatment have shown promise.	Low
[16]	Fares J, Ahmed AU, Ulasov IV, et al.	2021	Neural stem cell delivery of an oncolytic adenovirus in newly diagnosed malignant glioma: a first-in-human, phase 1, dose-escalation trial	NSCs	It is implied that immunological and histopathological findings support continued investigation of NSC-CRAd-S-pk7 in a phase 2/3 clinical trial.	Low
[17]	Geribaldi-Doldán N, Fernández-Ponce C, Quiroz RN, et al.	2021	The Role of Microglia in Glioblastoma.	GSCs, NSCs	This study shows the similarities tumor microenvironment could be important to clarify some mechanisms involved in GB malignancy and to support the discovering of new therapeutic targets for the development of more effective glioblastoma treatments.	Low
[18]	Ghasemi Darestani N, Gilmanova AI, Al-Gazally ME, et al.	2023	Mesenchymal stem cell-released oncolytic virus: an innovative strategy for cancer treatment	MSCs	It is implied that MSCs exhibit tumor-trophic migration characteristics, allowing them to be used as delivery vehicles for successful, targeted treatment of isolated tumors and metastatic malignancies.	Low
[23]	Ghasempour E, Hesami S, Movahed E, et al.	2022	Mesenchymal stem cell-derived exosomes as a new therapeutic strategy in the brain tumors	MSCs	This study shows potential applications of MSC and their produced exosomes in the treatment of brain tumors.	Low
[24]	Gisina A, Kholodenko I, Kim Y, et al.	2022	Novel Data Obtained by Single-Cell Sequencing.	CSCs	It is implied that inconsistencies in earlier glioma stem cell research and also provides insight into the development of more effective targeted therapy.	Low
[25]	Hersh AM, Gaitsch H, Alomari S, et al.	2022	Molecular Pathways and Genomic Landscape of Glioblastoma Stem Cells: Opportunities for Targeted Therapy	GSCs	This study shows continued investigation into the molecular pathways of GSCs and candidate therapeutics is needed to discover new effective treatments for GBM and improve survival.	Low
[26]	Ho NTT, Rahane CS, Pramanik S, et al.	2021	FAM72, Glioblastoma Multiforme (GBM) and Beyond	NSCs	This study shows NSCs may transform into cancer stem cells and generate brain tumor cells responsible for brain cancer such as glioblastoma multiforme (GBM).	Low
[27]	Jiapaer S, Furuta T, Tanaka S, et al.	2018	Potential Strategies Overcoming the Temozolomide Resistance for Glioblastoma	GSCs	This study shows current knowledge of different resistance mechanisms, novel strategies for enhancing the effect of temozolomide, and emerging therapeutic approaches to eliminate GSCs.	Low
[28]	Khamis ZI, Sarker DB, Xue Y, et al.	2023	Modeling Human Brain Tumors and the Microenvironment Using Induced Pluripotent Stem Cells	iPSCs	This study shows iPSC-derived isogenic cells and three-dimensional (3D) brain cancer organoids combined with patient-derived xenografts will enhance future compound screening and drug development for these deadly human brain cancers.	Low
[29]	Kwon S, Yoo KH, Sym SJ, et al.	2019	Mesenchymal stem cell therapy assisted by nanotechnology: a possible combinational treatment for brain tumor and central nerve regeneration	MSCs	This study shows the homing and nerve regenerative abilities of MSCs in order to provide a better understanding of potential cell therapeutic applications of non-genetically engineered MSCs with the aid of nanotechnology.	Low

Table 2 (continued)

References number	Authors	Year	Title	Type of Stem-cell	Summary of effects or relevant findings	Risk of Bias
[30]	Lakis NS, Brodsky AS, Karashchuk G, et al.	2022	Stem cell phenotype predicts therapeutic response in glioblastomas with MGMT promoter methylation.	GSCs	This study shows that the presence of a high stem cell phenotype in GBM, as marked by expression of SOX2 or CD133, may be associated with the clinical response to treatment.	Low
[31]	Miyaguchi K, Wang H, Black KL, et al.	2023	Activated T cell therapy targeting glioblastoma cancer stem cells	GSCs	This study shows synthetic peptide pool showed significantly increased IFN-γ secretion and increased cytotoxicity towards target cells.	Low
[32]	Moosavi MA, Djavaheri-Mergny M.	2023	Exploring the complex link between autophagy, regulated cell death, and cell fate pathways in cancer pathogenesis and therapy.	CSCs	This study shows potential clinical relevance, as the evaluation of UPR, autophagy and apoptosis markers could be used both therapeutically and diagnostically.	Low
[33]	Nowak B, Rogujski P, Janowski M, et al.	2021	Mesenchymal stem cells in glioblastoma therapy and progression: How one cell does it all	MSCs	This study shows previously shown contradictory data and provides a realistic, current clinical perspective on MSCs' potential in GBM treatment.	Low
[34]	Oraee-Yazdani S, Akhlaghpasand M, Rostami F, et al.	2023	Case report: Stem cell-based suicide gene therapy mediated by the herpes simplex virus thymidine kinase gene reduces tumor progression in multifocal glioblastoma	MSCs	This study shows the gliomatous focus (frontal) treated with bone marrow-derived MSCs carrying the HSV-TK gene had a different pattern of growth and recurrence compared with the non-treated one (parietal).	Some Concerns
[35]	Piper K, DePledge L, Karsy M, et al.	2021	Glioma Stem Cells as Immunotherapeutic Targets: Advancements and Challenges.	CSCs, GSCs	This study shows multiple treatment strategies have been suggested targeting GCSs, including immunotherapy, posttranscriptional regulation, modulation of the tumor microenvironment, and epigenetic modulation.	Low
[36]	Ramanathan A, Lorimer IAJ.	2022	Engineered cells as glioblastoma therapeutics	NSCs	This study shows clinical trials have established the feasibility and safety of engineered cell therapies for glioblastoma and show some evidence for activity.	Low
[37].	Robertson FL, Marqués-Torrejón MA, Morrison GM, et al.	2019	Experimental models and tools to tackle glioblastoma.	NSCs, hPSCs, GSCs	This study shows the recent convergence of two key technologies: human stem cell and cancer stem cell culture, as well as CRISPR/Cas tools for precise genome manipulations.	Low
[38]	Rodriguez SMB, Staicu GA, Sevastre AS, et al.	2022	Glioblastoma Stem Cells-Useful Tools in the Battle against Cancer.	GSCs	This study shows significant results in oncology, researchers are still developing novel strategies, of which one could be targeting the GSCs present in the hypoxic regions and invasive edge of the glioblastoma.	Low
[39]	Sadanandan N, Shear A, Brooks B, et al.	2021	Treating Metastatic Brain Cancers With Stem Cells	MSCs	This study shows using stem cell therapy to interrupt inflammation secondary to this leaky BBB represents a paradigm-shifting approach for brain cancer treatment.	Low
[40]	Satterlee AB, Dunn DE, Valdivia A, et al.	2022	Spatiotemporal analysis of induced neural stem cell therapy to overcome advanced glioblastoma recurrence.	NSCs	This study shows NSC delivery strategies that increased spatiotemporal TRAIL coverage and significantly decreased GBM volume throughout the brain, reducing tumor burden 100-fold as quantified in live ex vivo brain slices.	Low
[41]	Schiffer D, Annovazzi L, Casalone C, et al.	2018	Glioblastoma: Microenvironment and Niche Concept	GSCs, NSCs	This study shows interaction between GSCs and endothelial cells (ECs) is basically conceived as responsible for tumor growth, invasion and recurrence.	Low
[42]	Smiley SB, Zarrinmayeh H, Das SK, et al.	2022	Novel therapeutics and drug-delivery approaches in the modulation of glioblastoma stem cell resistance	GSCs	This study shows a rationale for multidrug therapy using a targeted nanotechnology approach that preferentially target GSCs is proposed with discussion and examples of drugs, nanomedicine delivery systems, and targeting moieties.	Low
[43]	Song CG, Zhang YZ, Wu HN, et al.	2018	Stem cells: a promising candidate to treat neurological disorders.	ESCs, iPCs MSCs, NSCs	This study shows use of tracing techniques for transplanted SCs will lead to important discoveries about stem cell survival, migration, retention, and therapy monitoring.	Low

Table 2 (continued)

References number	Authors	Year	Title	Type of Stem-cell	Summary of effects or relevant findings	Risk of Bias
[44]	Stevanovic M, Kovacevic-Grujicic N, Mojsin M, et al.	2021	SOX transcription factors and glioma stem cells: Choosing between stemness and differentiation.	GSCs	This study underlines the key aspect relevant to such refinements, that is, multimodal therapeutic strategies in targeting more than one hallmark of cancer cells in the overall battle against GBM.	Low
[45]	Strepkos D, Markouli M, Klonou A, et al.	2020	Insights in the immunobiology of glioblastoma.	CSCs, GSCs	This study shows novel therapies that modulate the phenotype of microglial and astrocyte cells to a pro-inflammatory state show promising results for GB management.	Low
[46]	Sun N, Meng X, Liu Y, et al.	2021	Applications of brain organoids in neurodevelopment and neurological diseases.	hPSCs, GSCs, NSCs	This study shows the current state of brain organoid differentiation strategies, summarize current progress and applications in the medical domain, and discuss the challenges and prospects of this promising technology.	Low
[47]	Tang X, Zuo C, Fang P, et al.	2021	Targeting Glioblastoma Stem Cells: A Review on Biomarkers, Signal Pathways and Targeted Therapy	GSCs	This study shows targeting GSCs provides a tremendous opportunity for revolutionary approaches to improve the prognosis and therapy of GBM, despite a variety of challenges.	Low
[48]	Tong L, Jiménez-Cortegana C, Tay AHM, et al.	2022	NK cells and solid tumors: therapeutic potential and persisting obstacles	iPSCs	This study shows potential strategies to circumvent such obstacles towards superior therapeutic activity.	Low
[49]	Tsibulnikov S, Drefs NM, Timashev PS, et al.	2022	To Explore the Stem Cells Homing to GBM: The Rise to the Occasion	MSCs, NSCs	This study shows proteins and lipid molecules that are released by GBM to attract stem cells.	Low
[50]	Vaidya M, Sreerama S, Gonzalez-Vega M, et al.	2023	Coculture with neural stem cells may shift the transcription profile of glioblastoma multiforme towards cancer-specific stemness.	GSCs, NSCs	This study shows cell-secreted signaling molecules and extracellular vesicles (EVs) are likely involved in reciprocal communication between NSCs and GBM, causing transcription modification	Low
[51]	Valor LM, Hervás-Corpión I	2020	The epigenetics of glioma stem cells: a brief overview.	GSCs	This study shows multiple epigenetic activities can be involved in glioma malignancy in a complex manner; therefore, the simultaneous modulation of various epigenetic activities may be highly effective.	Low
[52]	Verdugo E, Puerto I, Medina MÁ.	2022	An update on the molecular biology of glioblastoma	GSCs	This study shows there are clinical trials focused on the PI3K/Akt/mTOR axis, angiogenesis, and tumor heterogeneity for developing molecular-targeted therapies against GBM.	Low
[53]	Vieira de Castro J, Gonçalves CS, Hormigo A, et al.	2020	Exploiting the Complexities of Glioblastoma Stem Cells: Insights for Cancer Initiation and Therapeutic Targeting	GSCs	This study shows none of these cell-surface markers is, per se, sufficiently robust to distinguish GSCs from normal stem cells.	Low
[54]	Wang G, Wang W.	2022	Advanced Cell Therapies for Glioblastoma.	ESCs, iPSCs, NSCs, UCB	This study shows allogeneic stem cell therapies provide the possibility of controllable, continuous, and consistent cell therapy production and significantly reduce the waiting time for GBM patients to receive advanced treatment.	Some Conerns
[55]	Wang Y, Xu H, Liu T, et al.	2018	Temporal DNA-PK activation drives genomic instability and therapy resistance in glioma stem cells	CSCs	This study shows a time-sensitive mechanism controlling CSC resistance to DNA-damaging treatments and suggests DNA-PK/Rad50 as promising targets for CSC eradication.	Low
[56]	Wang Z, Zhang H, Xu S, et al.	2021	The adaptive transition of glioblastoma stem cells and its implications on treatments	GSCs, NSCs	This study shows neural stem cells were also hypothesized to participate in glioblastoma stem cells mediated tumor resistance to radio chemotherapies.	Low
[57]	Wen PY, Reardon DA, Armstrong TS, et al.	2019	A Randomized Double-Blind Placebo-Controlled Phase II Trial of Dendritic Cell Vaccine ICT-107 in Newly Diagnosed Patients with Glioblastoma.	CSCs	This study shows promising results for, CT-107, an autologous dendritic cell (DC) immunotherapy targeting six antigens on both tumor and cancer stem cells.	Low

Table 2 (continued)

References number	Authors	Year	Title	Type of Stem-cell	Summary of effects or relevant findings	Risk of Bias
[58]	Wu H, Liu J, Wang Z, et al.	2021	Prospects of antibodies targeting CD47 or CD24 in the treatment of glioblastoma	CSCs, GSCs	This study shows the feasibility of CD47/CD24 antibody treatment, either individually or in combination, to target the tumor stem cells.	Low
[59]	Yao Y, Luo F, Tang C, et al.	2018	Molecular subgroups and B7-H4 expression levels predict responses to dendritic cell vaccines in glioblastoma: an exploratory randomized phase II clinical trial	GSCs	This study shows a Dendritic Cell Vaccine loaded with GSC antigens has shown promising results in clinical trials.	Low
[60]	Yuan E, Liu K, Lee J, et al.	2022	Modulating glioblastoma chemotherapy response: Evaluating long non-coding RNA effects on DNA damage response, glioma stem cell function, and hypoxic processes	GSCs	This study shows maintenance of GSC identity is a mechanism of TMZ resistance.	Low
[61]	Zanders ED, Svensson F, Bailey DS.	2019	Therapy for glioblastoma: is it working?	GSCs	This study shows models based on pluripotent stem cells, complemented by advances in single-cell imaging and gene editing technologies.	Low
[62]	Zeng J, Zeng XX	2023	Systems medicine for precise targeting of glioblastoma.	MSCs, NSCs	This study shows NSCs and MSCs acting as potential vehicles carrying therapeutics via the intranasal route, avoiding the risks of invasive methods in order to reach the GBM cells.	Low
[63]	Zhang Q, Xiang W, Yi DY, et al.	2018	Current status and potential challenges of mesenchymal stem cell-based therapy for malignant gliomas.	MSCs	This study shows challenges for MSC-treatments of GBM including: no clear conclusion on whether MSCs themselves support or suppress the progression of glioma, glioma associated MSCs, malignant transformation of MSCs, and MSC-mediated immunosuppression.	Low
[64]	Zhu K, Xie V, Huang S.	2020	Epigenetic regulation of cancer stem cell and tumorigenesis	CSCs, GSCs	This study shows epigenetic modifications confer to tumor cells including CSCs reversible and inheritable genomic changes and affect gene expression without alteration in DNA sequence.	Low

Results of viewed literature

diagnosing and prognosticating GBMs. Hence, targeting these molecules appears to be a potential approach for tackling resistance to TMZ in GBM. Furthermore, studies on TRIM28 selective nanobody (NB237) suggested hopeful prospects in terms of therapeutic modalities mitigating GBM as it hinders the invasiveness and spread of glioblastoma cells and GSCs.

To fully grasp the potential of stem cells in the fight against glioblastoma, more research is warranted in this field. SCT has the potential to be a useful tool when mitigating GBM development and resistance. To appreciate further the capabilities and applications of stem cells, we advise conducting more experimental study on the many kinds of stem cells and their critical role in the treatment of glioblastoma alongside other varying neoplasms. It is recommended to pursue additional molecular investigations to provide clarity on the diverse roles of stem cells and their possible use in the treatment of glioblastoma.

Rather, there is a need for future studies in the field of glioblastoma therapy to focus more specifically on the pathways involved in GSC maintenance, proliferation, and resistance to therapies, such as Notch, Hedgehog, and Wnt signaling within glioma stem cells. Further exploration of pathways would also lead to disrupting basic patterns that sustain GSC-driven tumor progression and recurrence in favor of more precise and effective therapeutic opportunities. Blending stem cell therapies into established treatments similar to immunotherapy and chemoradiotherapy makes a promising road forward.

Such combinational approaches would confront the diversity of glioblastoma at the same time by targeting multiple pathways so as to overcome all potential resistance mechanisms and provide enhanced overall efficacies. One example could be the utilization of stem cells as delivery vehicles for immunomodulatory agents or chemotherapeutic drugs to synergize with traditional therapies delivering better outcomes.

Moreover, methods of advanced delivery still require further refinement. Advanced methods such as biodegradable scaffolds and nanotechnology-based platforms promise to improve the precision and efficacy of stem cell-based treatments. Such systems could be expected to offer well-protected transplanted cells with better viability and help them reach targeted sites with fewer chances of affecting healthy cells. Personalized therapies, supported by the nuclear and genetic characteristics of patients, can also help in refining the application of stem cell therapies to achieve effective and optimal benefits.

Concerns and debates in stem cell therapy for the treatment of glioblastoma

The possibility of tumor formation in SCT as a form of antineoplastic treatment is a worry to the scientific community. An incidence of spontaneous malignant transformation has been observed to be 45.8% in the long-term culture of MSCs obtained from bone marrow [19]. Oxygen tension and culture conditions have a profound impact on such changes. Compared to pluripotent properties exhibited by the likes of ESCs and iPSCs, multipotent stem cells like that of NSCs, MSCs, and HSCs are thought to be more stable and appropriate for therapeutic uses [19].

MSC transplantation has been considered safe and effective for various therapeutic applications. MSCs rely on cell communication and adhesion for their viability, however, peri-isolation and transplantation, these mechanisms are disrupted, precipitating apoptosis via anoikis [20]. Anoikis, is cell death caused by detachment from the extracellular matrix (ECM). It limits mesenchymal stem cell (MSC) survival after transplantation but aids cancer metastasis when resisted. Strategies like scaffolds and enhanced adhesion improve MSC therapy, making anoikis a key focus in glioblastoma treatment. It is apoptosis due to loss of cell-ECM or cell-cell adhesion, leads to poor engraftment of MSCs. Strategies to improve cell retention and inhibit anoikis, such as using biodegradable biomaterials, may enhance the efficacy of MSC therapy. While transplantation is important, delivering MSCs temporarily may reduce the risks associated with a long-term presence in the tissue [20]. MSCs are believed to have a transient therapeutic effect on resident cells rather than a long-lasting one. When utilizing MSC therapy, various factors like isolation methods, expansion techniques, administration route, cell concentration, and synthetic modifications need to be carefully evaluated to maximize potential benefits [20].

In addition, the effects of stem cells, specifically MSCs, have displayed inconsistencies across different experimental settings. A study by Klopp et al. examined these discrepancies and found contradictory results in the literature [21]. They attribute these differences to the varying types of MSCs used, with adult MSCs having a stronger tumor-promoting effect compared to fetal MSCs [21]. The timing of MSC injection also played a role, with studies showing a growth-promoting effect when MSCs were injected simultaneously with tumor cells, while inhibitory effects were observed when MSCs were introduced at a later stage of tumor activity. These findings suggest that the phase of tumor growth, whether early or late, may significantly influence the effects of MSCs [21, 22].

In conclusion, it is imperative to understand the substantial differences between animal models and human glioblastomas, as this will influence the preclinical efficacy of these models. While animal models have offered much insight, their limited resemblance to human glioblastoma with respect to vascularization and genetic heterogeneity just adds gems to the difficulty in transforming such experimental knowledge into clinical practice. Such

difficulties are reminders of the importance of research into bridging the gap between such animal models and human clinical trials for ultimate improvement in the treatment of patients suffering from glioblastoma.

Abbreviations

GBM	Glioblastoma multiforme
SCT	Stem cell therapy
GSCs	Glioma stem cells
MSCs	Mesenchymal stem cells
NSCs	Neural stem cells
iPSCs	Induced pluripotent stem cells
ESCs	Embryonic Stem Cells
ECM	Extracellular matrix
CNS	Nervous system
ASCs	Adipose-derived stem cells
NSCs	Neural Stem Cells
HSCs	Hematopoietic Stem Cells
TGFBI	Transforming growth factor, beta-induced
TMZ	Temozolomide
TAMs	Tumor-associated macrophages

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