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REVIEW

Stem Cell-Based Delivery of Immunomodulators for Overcoming Glioblastoma Immune Evasion

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ABSTRACT

Glioblastoma (GBM) is the most aggressive primary brain tumour in adults, characterised by rapid progression, extensive heterogeneity, and poor outcomes despite surgery, radiotherapy, and temozolomide (TMZ). A subpopulation of glioblastoma stem cells (GSCs) with self-renewal and multi-lineage differentiation capabilities drives tumour initiation, progression, recurrence, and therapeutic resistance. GSCs evade conventional treatments via enhanced DNA repair, multidrug efflux, activation of survival pathways, epigenetic reprogramming, and entry into quiescent states. Moreover, these cells utilise key immune escape

Abbreviations: ABC, ATP Binding Cassette; ABCG2/BCRP1, ATP-binding cassette subfamily G member 2/breast cancer resistance protein 1; AHSCT, autologous haematopoietic stem cell transplantation; AKT, protein kinase B; APC, astrocyte progenitor cell; AR, androgen receptor; ASCL1, achaete-scute family BHLH transcription factor 1; ATM, ataxia telangiectasia mutated; ATR, ATM- and Rad3-related; BBB, blood–brain barrier; BAD, BCL2-associated agonist of cell death; BAX, BCL2-associated X protein; BCL-2, B-cell lymphoma 2; BCL2L1a, Bcl-XL isoform; BH3, BCL-2 homology 3; BIM/BCL2L11, BCL2-like 11; BMP, bone morphogenetic protein; CAR-T, chimeric antigen receptor T cell; CDC2/CDK1, cyclin-dependent kinase 1; CDC25C, cell division cycle 25C; CDK2, cyclin-dependent kinase 2; CD133, prominin-1; CD34+ HSCs, cluster of differentiation 34 positive haematopoietic stem cells; CD, cytosine deaminase; CHK1/CHK2, checkpoint kinase 1/2; CSC, cancer stem cell; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, C-X-C chemokine receptor type 4; DCs, dendritic cells; DDR, DNA damage response; DIAPH3, diaphanous-related formin 3; DSB, double-strand break; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EGFRvIII, variant III of epidermal growth factor receptor; ESCs, embryonic stem cells; EVs, extracellular vesicles; EZH2, enhancer of zeste homologue 2; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FOXM1, forkhead box protein M1; FOXG1, forkhead box G1; FOXO, forkhead box O; GBM, glioblastoma multiforme; GSCs, glioblastoma stem cells; HES1, hairy and enhancer of split-1; HGF, hepatocyte growth factor; HIF, hypoxia-inducible factor; HSCs, haematopoietic stem cells; HSPCs, haematopoietic stem and progenitor cells; HDAC/HDAC6, histone deacetylase/histone deacetylase 6; hiPSCs/iPSCs, human induced pluripotent stem cells/induced pluripotent stem cells; HSV-TK, Herpes Simplex Virus Thymidine Kinase; ID, intradermal; IKKα, IκB kinase alpha; IV, intravenous; JAK/STAT, Janus kinase/signal transducer and activator of transcription; LAK cells, lymphokine-activated killer cells; MAPK, mitogen-activated protein kinase; MCL1, myeloid cell leukaemia 1; MES-like, mesenchymal-like; MGMT, O6-methylguanine-DNA methyltransferase; MDR, multidrug resistance; MDM2, mouse double minute 2; MSCs, mesenchymal stem cells; mTOR/mTORC1/mTORC2, mammalian target of rapamycin/complex 1/complex 2; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NOTCH, NOTCH signalling pathway; NPCs, neural progenitor cells; NSCs, neural stem cells; Olig2, oligodendrocyte transcription factor 2; OPCs, oligodendrocyte precursor cells; PARP1, poly (ADP-ribose) polymerase 1; PBSCs, peripheral blood stem cells; PDGF, platelet-derived growth factor; PDK1, 3-phosphoinositide-dependent protein kinase 1; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PI3KCA/PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PRC2, polycomb repressive complex 2; PTEN, phosphatase and tensin homologue; RAS, rat sarcoma viral oncogene; RGCs, radial glial cells; RT, radiotherapy; RTK, receptor tyrosine kinase; SHH, sonic hedgehog; SOX2, SRY-Box transcription factor 2; STAT, signal transducer and activator of transcription; SVZ, subventricular zone; TACC, transforming acidic coiled-coil proteins; TGF/TGF-β, transforming growth factor/transforming growth factor beta; TMZ, temozolomide; TNF, tumour necrosis factor; WNT/Wnt-β-catenin, wingless-type signalling pathway.

mechanisms, such as downregulation of major histocompatibility complex molecules and the secretion of immunosuppressive factors, to escape detection and destruction by the immune system. Evidence suggests that transformed neural stem cells are a likely source of GSCs, with key survival networks including EGFR, FGFR, HGFR, and PI3K/AKT/mTOR signalling. Their phenotypic plasticity and adaptability to the tumour microenvironment further complicate eradication. Stem cell-based strategies utilising NSCs, MSCs, haematopoietic stem/progenitor cells, or induced pluripotent stem cells can effectively deliver immunomodulators to counteract these immune evasion mechanisms, exploiting tumour tropic migration to deliver therapeutic payloads into hypoxic and infiltrative niches. Approaches such as suicide gene therapy, oncolytic virus delivery, and CXCL12—CXCR4 axis modulation aim to target both proliferative and dormant GSCs. Preclinical studies demonstrate promising efficacy, yet challenges remain, including safety concerns, variability in outcomes, and the limited translational relevance of current models. This review provides a concise overview of GSC biology, resistance mechanisms, and emerging stem cell-based interventions, highlighting opportunities and obstacles in developing effective therapies for GBM.

1 | Introduction

Glioblastoma stem cells (GSCs) represent a specialised population within glioblastomas that exhibit stem cell-like properties, including the capacity for tumour self-renewal and multi-lineage differentiation. These cells are integral to the initiation, progression, and therapeutic resistance of glioblastoma. By sustaining tumour growth, enhancing invasion, and driving recurrence, GSCs contribute significantly to the aggressive nature of the disease. Their notable resistance to standard interventions like chemotherapy and radiotherapy (RT) has established them as a promising therapeutic target for enhancing clinical outcomes and addressing challenges associated with tumour heterogeneity and resistance mechanisms [1, 2].

GBM is the most malignant and rapidly progressing primary brain tumour, characterised by its dismal prognosis. Classified by the World Health Organization as the grade IV astrocytic neoplasm, GBM is the most common tumour of the central nervous system in adults [3]. Despite intensive treatment approaches including surgical resection, RT, and chemotherapy, median survival remains about 12–15 months after diagnosis, with tumours accounting for around 60% of all primary brain malignancies in adults. The disease indicates a higher incidence in males and mostly affects individuals aged 45 to 70 years. Beyond its physical impact, GBM imposes a deep burden on patients and their families, often causing severe neurological deficits, cognitive determinations, and emotional distress [4, 5].

GBM's highly infiltrative growth pattern makes complete surgical removal almost unattainable even with advanced neurosurgical techniques. Standard of care therapy usually involves maximal safe resection followed by chemo RT; however, survival rates stay unacceptably low. This shows the pressing need for innovative therapeutic methods that can address both the infiltrative nature and intrinsic resistance mechanism of GBM [6–8]. Stem cells hold exceptional promises in regenerative medicine because of their unique ability to self-renew and differentiate into many cell types. This regeneration potential has led researchers to explore its use in the treatment of pathological conditions, including malignant brain tumours. In GBM therapy, stem cells offer an opportunity not only for targeted delivery of antitumor agents but also for helping the regeneration of healthy neural tissues [9]. Several stem cell-based approaches have been studied for GBM management, including MSCs, NSCs, induced pluripotent stem cells iPSCs and haematopoietic stem cells HSCs. MSCs obtainable from bone marrow adipose tissue or umbilical cord blood can home to tumour sites and secret antitumor compounds and immunomodulatory factor [10].

NSCs, which naturally live in the adult brain, can differentiate into many neural cell types and can be genetically engineered to deliver a therapeutic agent directly to GBM cells. iPSCs are made by reprogramming adult somatic cells like skin fibroblasts into a pluripotent state similar to embryonic stem cells; when differentiated, they can give neural cells and may be customised for patient-specific therapy [2]. HSCs are found in bone marrow. They can differentiate into various blood cell lineages. HSCs are mainly used along with high-dose chemotherapy to restore haematopoiesis. This is common in processes like autologous haematopoietic stem cell transplantation AHSCT. However, they do not directly target glioblastoma GBM cells [11]. The purpose of this review is to examine the current evidence about the use of stem cell-based therapies in GBM, highlighting their potential advantage, limitations, and future prospects. In alignment with the review focus, we will summarise GSC-driven resistance mechanisms, discuss the immune microenvironment and immune evasion in GBM, and examine stem cell-based strategies, particularly those for the delivery of immunomodulatory agents. This comprehensive approach aims to inform therapeutic decision-making in this very challenging disease and identify promising ways for future research.

2 | Origin and Role of GSCs

Recent advances in molecular profiling have enabled GBM to be classified into the distinct molecular subtypes at both the bulk tissue and single-cell levels. Despite this advancement, the mechanisms behind the early phases of glioma genesis are still not completely clear. This uncertainty mainly stems from challenges in detecting tumours in the initial stage and the limited availability of early-stage specimens. Increasing evidence supports the cancer stem cell (CSC) model, which proposes that a subset of tumour cells possesses heightened self-renewal, proliferative, and differentiation capacities [12]. Originally identified in acute myeloid leukaemia, leukaemia stem cells were found to drive disease initiation and

progression. Subsequently, CSC populations have also been detected in various solid tumours, including ones of the breast, prostate, colon, and pancreas. In GBM GSCs isolated from patient-derived tumours display potent tumorigenicity, evidenced by their ability to form neurospheres in culture, a hallmark of self-renewal [13].

Historically, GBM was thought to arise through dedifferentiation of mature neural cells into progenitor-like states that are sustaining tumour progression. This view gradually shifted with the discovery of adult NSCs and the recognition of molecular and signalling parallels between NSCs and GSCs. Such similarities have led to the hypothesis that GBM originates from NSCs undergoing malignant transformation into GSCs, which then propagate neoplastic growth [14]. Supporting this, platelet-derived growth factor (PDGF) activation inside NSCs of the subventricular zone (SVZ) has been shown to trigger hyperplasia and early tumour formation. Moreover, molecular classifications of high-grade gliomas indicate that tumour progression mirrors specific stages of normal neurogenesis, further linking gliomagenesis with developmental programmes [15]. GSCs have been identified by using NSC markers such as CD133, and these cells, when cultured, differentiate into tumour cells phenotypically similar to the patient's original tumour. High-resolution technologies such as single-cell RNA sequencing and RNA velocity analyses have clarified cellular trajectories of tumour initiation, revealing that GBM evolution recapitulates conserved neurodevelopmental processes [15]. Rapidly proliferating cancer cells are emerging as the most tumorigenic and therapy-resistant populations. Additionally, studies in patient samples and genome-edited mouse models have detected low-frequency GBM driver mutations in histologically normal SVZ tissue distant from the primary tumour. These mutations, present at high levels in corresponding tumours, suggest that mutated NSCs can migrate from the SVZ to other brain regions for seeding malignant lesions [15, 16].

The transformation of NSCs into GSCs may involve tumour suppressor loss, such as p53 inactivation, together with activation of mitogenic signalling pathways. Mutant p53 in NSCs accelerates oncogenic mutation accumulation, promoting expansion of Olig2-positive progenitor-like cells and glioma initiation [17]. Dysregulation of genes that govern cell cycle control and mitotic progression in neural progenitors, such as Aurora kinase A, Forkhead Box M1 FOXM1, and Diaphanous related formin 3 DIAPH3, can induce chromosomal instability and predispose to malignant transformation [15]. Multiple experimental lines are converging on the idea that glioma genesis depends on activation of proliferative pathways like Ras and AKT in neural progenitors but not in differentiated astrocytes to generate high-grade gliomas that resemble human GBM [18]. Furthermore, signalling axes including AKT and NOTCH are influencing prognosis, while GSCs often show elevated WNT activity, enhanced neurosphere formation, and upregulated SOX2 expression. Aberrant Wnt β-catenin signalling promotes invasiveness and therapy resistance partly through epithelial-mesenchymal transition that is driven by FOSL1 upregulation. Spatial transcriptomics has further demonstrated that NOTCH signalling is enriched in mesenchymal-like GBM cells infiltrating the surrounding brain tissue (Figure 1) [19].

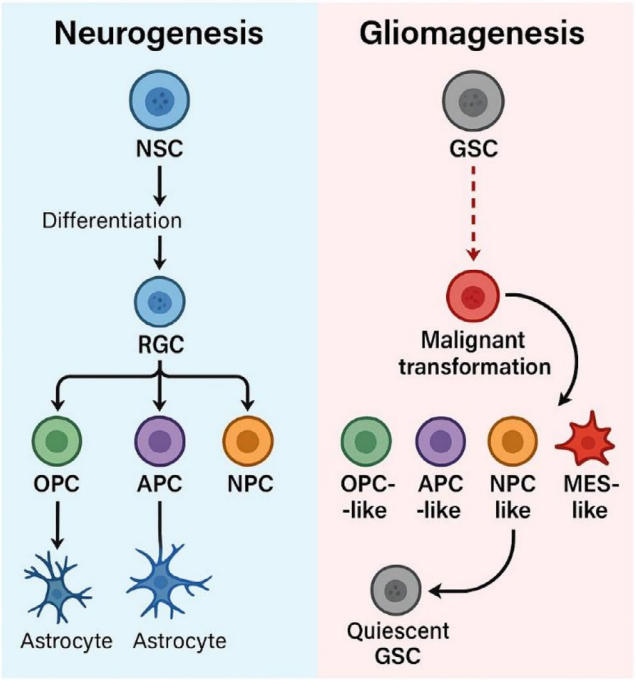

FIGURE 1 | Parallel representation of neurogenesis (left) and gliomagenesis (right), illustrating the relationship between GBM cell states and their cells of origin. Solid black arrows indicate normal differentiation from NSCs through radial glia cells (RGCs) into lineage specific progenitors, oligodendrocyte progenitor cells (OPCs), astrocyte progenitor cells (APCs), and neural progenitor cells (NPCs), which further mature into their respective cell types. Dashed red arrows represent malignant transformation from normal progenitors to GBM like counterparts, OPC like, APC like, NPC like, and MES like, supported by single cell RNA seq data. The MES like state shows a more distant similarity to RGCs compared to the other states.

3 | Therapeutic Opportunities Targeting GSCs

GBM remains one of the most challenging malignancies to treat, with curative strategies still out of reach. The standard of care regimen consists of maximal safe surgical resection, adjuvant RT, and chemotherapy with the alkylating agent temozolomide. Although this multimodal approach modestly extends survival, it is often accompanied by considerable systemic toxicity and diminished quality of life [20]. Moreover, intrinsic and acquired resistance to treatment is common. Anti-angiogenic therapies, such as the vascular endothelial growth factor (VEGF) targeting antibody bevacizumab, have improved progression-free survival in some cases but failed to extend overall survival [21]. Treatment challenges are compounded by GBM's infiltrative nature, which precludes complete tumour removal, and by the blood–brain barrier, which restricts delivery of many systemic agents [6]. To address these obstacles, current research is focused on:

1. Elucidating the molecular mechanisms driving tumour growth, recurrence, and resistance.
2. Developing approaches to selectively target tumour cells while sparing normal brain tissue.
3. Translating molecular insights into innovative surgical and oncological strategies.

4. Refining preclinical models to better predict clinical outcomes.
5. Advancing personalised medicine in clinical trials.

A promising area of investigation involves targeting GSCs through the manipulation of genetic and molecular pathways. Dysregulated signalling cascades that promote proliferation, survival, and migration present opportunities for therapeutic intervention, while tumour suppressive pathways may be harnessed to inhibit GSC function. Receptor tyrosine kinases (RTKs), a family of transmembrane receptors, play central roles in regulating cell growth, differentiation, motility, and metabolism [22]. Ligands such as epidermal growth factor (EGF), fibroblast growth factor (FGF), VEGF, platelet-derived growth factor (PDGF), transforming growth factor (TGF), and hepatocyte growth factor (HGF) activate RTKs, triggering dimerization or oligomerization and subsequent autophosphorylation. These events initiate downstream signalling through pathways including PI3K/AKT/mTOR, RAS/MAPK, and JAK/STAT, ultimately promoting tumour cell proliferation and invasion [23].

RTK activity is normally controlled by mechanisms such as autoinhibition and tyrosine phosphatase activity; however, in GBM, mutations, overexpression, or copy number alterations can shift the balance towards oncogenesis [24]. Consequently, numerous RTK inhibitors have been developed and tested in GBM, with varied success. While certain agents, such as anlotinib and regorafenib, have shown moderate benefits, many, including dasatinib, pazopanib, and ponatinib, have demonstrated limited efficacy in extending survival. Multi-target RTK inhibitors remain under evaluation, often in combination with other modalities, as researchers seek to optimise strategies for disrupting RTK-mediated GSC proliferation and survival [15, 25].

3.1 | Targeting GSCs via Growth Factor Receptor Signalling

Among the growth factor receptors implicated in GBM, epidermal growth factor receptors (EGFRs) are the most frequently altered, with approximately 60% of cases showing driver mutations, rearrangements, alternative splicing events, or gene amplifications. Consequently, EGFR inhibition has long been a central focus of therapeutic development in GBM [26]. Monoclonal antibodies such as cetuximab and nimotuzumab, as well as small-molecule tyrosine kinase inhibitors including gefitinib, erlotinib, dacomitinib, osimertinib, and depatuxizumab mafodotin, have undergone extensive evaluation. Despite early promise, most agents have demonstrated limited clinical benefit. For example, depatuxizumab mafodotin did not improve overall survival in newly diagnosed patients with EGFR amplified tumours. Gefitinib, the first EGFR inhibitor approved by the FDA, failed to show clinical efficacy either alone or in combination regimens. Erlotinib, when used alongside RT and temozolomide (TMZ), produced mixed results in newly diagnosed GBM, though some studies reported modest benefit in recurrent disease. Dacomitinib, a second-generation inhibitor, showed preclinical efficacy but lacked a significant clinical impact [27, 28]. The third-generation inhibitor osimertinib has greater potency against EGFR, with case reports and retrospective studies suggesting limited but notable benefit, particularly when combined with bevacizumab. Overall, monotherapy with EGFR inhibitors has yielded suboptimal outcomes, prompting interest in combinatorial approaches [29]. One emerging strategy involves cotargeting EGFR and the androgen receptor (AR), given evidence that AR activation can occur independently of hormonal ligands through EGFR signalling. AR expression correlates positively with EGFR in GBM, and preclinical studies have shown that the AR inhibitor enzalutamide, especially when combined with afatinib, reduces GSC populations and improves survival in animal models [30].

Fibroblast growth factor receptors (FGFRs) are altered in only about 3% of GBM cases, yet specific rearrangements, such as fusions between FGFR1 or FGFR3 and transforming acidic coiled coil (TACC) proteins, produce constitutively active kinases that drive tumorigenesis. FGFR3 is the most commonly affected receptor through amplification or fusion events, while FGFR2 alterations are less frequent and often result in nonfunctional chimeric proteins [19]. Nevertheless, rare cases of FGFR2 amplification with oncogenic fusion have been documented in aggressive GBM. Development of FGFR inhibitors has been slower than that of EGFR or VEGFR inhibitors, though several multitarget tyrosine kinase inhibitors (e.g., erlotinib, sorafenib, lapatinib, ponatinib, lucitanib, nintedanib) have shown some FGFR activity. Selective FGFR inhibitors such as erdafitinib, pemigatinib, and infigratinib are under investigation, with erdafitinib demonstrating tumour growth suppression in FGFR3 TACC3 fusion-positive GBM and pemigatinib inducing partial responses in individual cases [31, 32]. The hepatocyte growth factor receptor (HGFR, also known as c-Met) is activated by hepatocyte growth factor/scatter factor and plays a key role in GSC biology, despite amplification occurring in fewer than 5% of GBM cases [15]. Selective inhibitors such as capmatinib have shown minimal efficacy as monotherapy in PTEN-deficient GBM but are being tested in combination with bevacizumab. Crizotinib has shown encouraging results in early phase studies, with improved progression-free and overall survival when added to standard chemoradiotherapy, and synergistic effects when combined with EGFR inhibitors in preclinical models [33].

3.2 | Targeting GSCs via the PI3K/AKT/mTOR Pathway

The PI3K/mTOR signalling axis integrates extracellular cues such as nutrient availability, growth factors, and hormones to regulate proliferation, survival, and metabolism. Upon activation, PI3K catalyses the production of PIP3, which recruits and activates downstream kinases including PDK1 and AKT [34]. Activated AKT influences numerous cellular processes:

- Suppression of proapoptotic transcription factors (FOXO family) and proteins (BAD, BAX, caspases 3/9) [35].
- Promotion of cell cycle progression via MDM2 mediated p53 degradation and stabilisation of cyclin D1/D3 through p27 and p21 regulation [36].
- Inhibition of glycogen synthase kinase 3β [37].
- Activation of IKKα and Tpl2, leading to NF-κB signalling [38].

AKT also activates mTORC1, a major regulator of tumour growth. Given that over 80% of GBM harbour alterations in RTK/PI3K signalling, this pathway is a major therapeutic target. Inhibitors fall into several classes: dual PI3K/mTOR inhibitors, pan PI3K inhibitors, isoform-selective PI3K inhibitors, and mTOR-specific inhibitors [19]. Dual inhibitors such as dactolisib, voxtalisib, and paxalisib have been evaluated in both preclinical and clinical settings. Dactolisib, when combined with chemoradiotherapy, showed antitumor activity in vitro and in animal models, though monotherapy in mice was ineffective and toxicities remain a challenge. Clinical trials for dactolisib and voxtalisib have shown limited benefit, whereas paxalisib has demonstrated more encouraging results in early trials for both newly diagnosed and recurrent GBM [15, 39]. Pan PI3K inhibitors, including buparlisib, pilaralisib, pictilisib, and sonolisib, have largely shown limited clinical efficacy, with toxicity frequently limiting their use. Isoform-specific inhibitors, such as the p110β selective agent GSK2636771, are in early clinical evaluation, particularly for PTEN-deficient tumours [39]. mTOR inhibition began with rapamycin, followed by its analogues everolimus, temsirolimus, sirolimus, and ridaforolimus. Despite good tolerability, these agents have generally failed to improve survival, likely due to incomplete pathway blockade and lack of mTORC2 inhibition. Newer ATP competitive inhibitors targeting both mTORC1 and mTORC2, such as vistusertib and torin derivatives, are under preclinical study [40] (Figure 2).

3.3 | Epigenetic Mechanisms in GSC Regulation

Epigenetic dysregulation in GBM includes altered DNA methylation, histone modifications, and chromatin remodelling, all of which can promote oncogenesis or therapy resistance. Global hypomethylation can activate oncogenes and destabilise the genome, whereas promoter hypermethylation can silence tumour suppressors, as observed with BCL2L11 (BIM) in EGFR inhibitor-resistant GBM [41]. Methylation of the MGMT promoter is a favourable prognostic factor and predicts better response to TMZ. DNA methyltransferase inhibitors such as decitabine and 5-azacytidine have shown the capacity to alter methylation patterns, enhance immune recognition, and suppress tumour growth in preclinical models [42]. Histone modifications also regulate GSC biology. EZH2, a histone methyltransferase within the PRC2 complex, represses tumour suppressor genes and is implicated in GBM progression. Histone deacetylases (HDACs), particularly HDAC6, influence GSC proliferation and drug resistance by modulating EGFR trafficking, cytoskeletal organization, and downstream signalling. HDAC inhibitors, including belinostat, panobinostat, and vorinostat, have been tested clinically, but most failed to demonstrate significant benefit as monotherapy or in combination regimens [43]. Notably, valproic acid, a selective class I/IIa HDAC inhibitor, has been associated with prolonged survival when used with standard chemoradiotherapy,

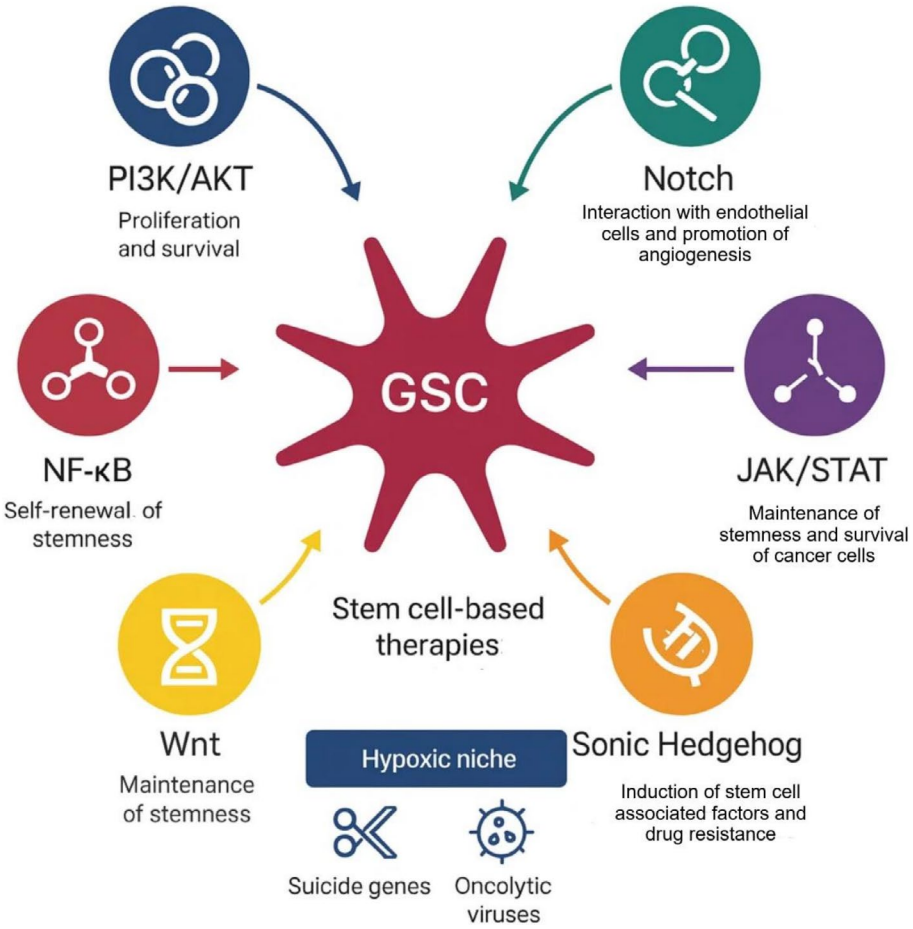

FIGURE 2 | Key signalling pathways in glioma stem cells (GSCs) and their roles in tumour progression, stemness maintenance, angiogenesis, invasion, and drug resistance. The diagram illustrates six major pathways: PI3K/AKT, Notch, Wnt, Sonic Hedgehog, NF κB, and JAK/STAT, each contributing to the survival and aggressive behaviour of GSCs, highlighting their importance as potential therapeutic targets in GBM treatment.

potentially by enhancing TMZ efficacy. Ongoing studies are evaluating isoform-selective HDAC inhibitors for GBM (Table 1) [44–47].

4 | GBM Is Extremely Challenging to Overcome

Despite extensive research and numerous clinical trials, therapeutic advances in GBM remain limited. Barriers include:

1. The infiltrative nature of GBM and the sensitivity of brain tissue prevent complete surgical resection [19].
2. The restrictive blood-brain barrier limits drug delivery [6].
3. A lack of early detection tools and biomarkers [6].
4. The adaptability of GBM cells, which enables them to evade therapy through molecular and phenotypic changes [7].

4.1 | Heterogeneity and Plasticity in GSCs

GBM is highly heterogeneous at genetic, transcriptional, and phenotypic levels, with GSCs serving as key drivers of this diversity. Molecular subtypes, classical, proneural, and mesenchymal, are defined by distinct driver mutations and exhibit different biological behaviours and prognoses. Advances in single-cell sequencing have refined this classification, revealing malignant cell states resembling neural progenitor-like, oligodendrocyte precursor-like, astrocyte-like, and mesenchymal-like phenotypes [48]. GSCs also display significant plasticity, transitioning dynamically between cellular states in response to microenvironmental cues, therapies, transcriptional programmes, and epigenetic changes. This flexibility enables therapy resistance and complicates targeting strategies. Epigenetic modifications, such as methylation changes induced by stressors like hypoxia or irradiation, can drive state transitions. Transcriptomic shifts, mediated by transcription factors including ASCL1, HES1, OLIG2, and SOX2, further sustain stemness or promote differentiation, depending on expression patterns [15, 49].

4.2 | Quiescence and Therapy Resistance

A subset of GSCs can survive in hypoxic, nutrient-deprived regions by entering a quiescent, reversible G0 state. These dormant cells evade therapies that target rapidly dividing populations and can later re-enter the cell cycle to drive recurrence. Quiescent GSCs exhibit distinct molecular profiles and often adopt a mesenchymal-like, migratory phenotype, facilitating tumour repopulation. Targeting pathways that regulate quiescence, such as FOXG1/Wnt β-catenin or BMP signalling, may improve treatment efficacy. Strategies under investigation include forcing quiescent cells to re-enter the cell cycle for subsequent elimination or maintaining them in a permanent dormant state [49, 50].

4.3 | Resistance to Therapy

4.3.1 | Resistance to Chemotherapy

Temozolomide (TMZ) remains the first-line chemotherapeutic for GBM and has contributed to improved patient survival. Nonetheless, resistance to TMZ is widespread and a major cause of tumour relapse and treatment failure. TMZ acts by methylating guanine at the O6 position during DNA replication, creating mismatches that lead to G2/M arrest and apoptosis [51]. Resistance frequently arises from elevated activity of the DNA repair enzyme O6 methylguanine DNA methyltransferase (MGMT), which removes the methyl group from alkylated guanine, restoring DNA integrity and negating the drug's cytotoxicity. MGMT is markedly upregulated in GSCs, conferring a strong innate resistance and rendering these cells highly refractory to therapy. Within the tumour core, hypoxic conditions cause fluctuating MGMT expression, further enhancing protection against TMZ [52].

Chemoresistance in GSCs can also involve cell-cycle modulation, with extended G2/M arrest mediated by CHK1, CDC25C, and CDC2, allowing additional time for DNA repair. Some cells adopt a quiescent state under therapeutic stress, avoiding cytotoxic damage; upon repair, they can re-enter the cell cycle through activation of growth regulatory proteins such as CDK2 and E2F. Furthermore, TMZ-resistant GSC clones express higher levels of antiapoptotic genes, including MCL1, BCL2, and BCL2L1a, compared with differentiated tumour cells [53, 54]. Multidrug resistance (MDR) is another hallmark of GSCs, primarily driven by overexpression of ATP-binding cassette (ABC) transporters, which actively expel chemotherapeutic agents, lowering their intracellular concentration [55]. ABCG2 (BCRP1) is strongly expressed in GSCs and associated with a 'side population' phenotype characterised by high efflux capacity and the ability to survive therapy. MDR1 (Pglycoprotein) is also elevated in GSCs, conferring resistance to agents such as doxorubicin and etoposide. Combining chemotherapy with MDR inhibitors, such as melatonin or perifosine, can enhance drug sensitivity and therapeutic efficacy [13]. GSC chemoresistance is further reinforced by the activation of signalling pathways, including NOTCH and Sonic Hedgehog (SHH), in response to TMZ. This activation increases the expression of downstream effectors like NOTCH1 and GLI1. Pharmacological inhibition of these pathways with agents such as cyclopamine or γsecretase inhibitors markedly enhances TMZ-induced cytotoxicity, offering a potential route to improve treatment outcomes [19].

4.3.2 | Resistance to Radiotherapy

RT is a mainstay in GBM management, yet radioresistance is a frequent and formidable obstacle. Factors influencing tumour cell survival after radiation include cell intrinsic properties, radiation dose, and the surrounding microenvironment [56]. GSCs play a pivotal role in mediating resistance, enabling tumour persistence, renewed proliferation, and recurrence. These cells demonstrate preferential activation of DNA damage checkpoints and superior DNA damage repair (DDR) capacity, mediated by kinases such as CHK1 and CHK2. A delayed cell cycle progression further enhances survival by allowing efficient repair before cell division resumes [54]. This enhanced DDR capacity presents a therapeutic vulnerability; inhibition of key regulators such as ATM, ATR, CHK1, CHK2, and PARP1 can sensitise GSCs to radiation. Overexpression of RAD51, another critical DDR protein, facilitates repair of RT-induced double-strand breaks in GSCs. Targeting RAD51 with inhibitors like RI-1 or B02 impairs DNA repair, depletes GSC populations, and increases radiosensitivity (Table 2) [48, 58–65].

TABLE 1 | Therapeutic strategies targeting GSCs: Pathways, agents, and clinical status.

Target pathway/mechanism	Key molecular drivers	Representative agents	Preclinical/clinical outcomes	Limitations/challenges	References
Growth factor receptor signalling—EGFR	EGFR amplification, EGFRvIII mutation, rearrangements	Cetuximab, Nimotuzumab, Gefitinib, Erlotinib, Dacomitinib, Osimertinib, Depatuxizumab Mafodotin, Afatinib + Enzalutamide	Limited benefit as monotherapy; some combinational regimens show survival extension; AR–EGFR co targeting reduces GSCs in models	Rapid resistance; BBB penetration; heterogeneity of EGFR alterations	[15, 44]
Growth factor receptor signalling—FGFR	FGFR3 TACC3 fusions, FGFR1/2/3 amplification	Erdafitinib, Pemigatinib, Infigratinib, Sorafenib, Lapatinib, Nintedanib	Partial responses in FGFR3-TACC3+ GBM; tumour suppression in preclinical models	Rare alterations; limited patient population; need biomarker-guided trials	[45]
Growth factor receptor signalling—HGFR/c-Met	c-Met overexpression, PTEN-deficiency	Capmatinib, Crizotinib, Cabozantinib	Crizotinib + EGFR inhibitors show synergy in preclinical studies; improved PFS in early trials	Monotherapy efficacy low; pathway redundancy; toxicity in combinations	[32]
PI3K/AKT/mTOR Pathway	RTK activation, PTEN loss, PI3KCA mutations	Dactolisib, Voxtalisib, Paxalisib, Buparlisib, GSK2636771, Rapamycin analogues, Vistusertib	Paxalisib shows promising early-phase results; dual PI3K/mTOR blockade inhibits GSC proliferation	Dose-limiting toxicities; incomplete pathway inhibition; adaptive resistance	[40]
Epigenetic regulation—DNA methylation	MGMT promoter methylation, BIM promoter methylation	Decitabine, 5-Azacytidine	Alters methylation patterns, sensitises to therapy, enhances immune recognition in preclinical models	Global demethylation risk; limited clinical translation	[46]
Epigenetic regulation—histone modification	EZH2 overexpression, HDAC6 activity	Belinostat, Panobinostat, Vorinostat, Valproic acid	Valproic acid prolongs survival with chemoradiotherapy; HDAC inhibitors modulate EGFR trafficking and GSC stemness	Monotherapy often ineffective; toxicity; resistance via compensato	[43]

TABLE 2 | Key barriers and resistance mechanisms in glioblastoma multiforme (GBM) and GSCs.

Category	Mechanism	Key molecular drivers	Therapeutic opportunities	References
Major clinical barriers in GBM	Infiltrative growth and delicate brain tissue	N/A	Limits surgical resection; requires targeted and localised therapies	[57]
	Blood–brain barrier (BBB)	Tight junction proteins, efflux pumps	Use of BBB permeable drugs, nanoparticles, focused ultrasound	[58]
	Lack of early biomarkers	N/A	Develop sensitive detection assays (e.g., liquid biopsy, imaging tracers)	[48]
	Cellular adaptability	Genetic/epigenetic reprogramming	Multi target therapies, adaptive treatment protocols	[59]
Heterogeneity and plasticity in GSCs	Inter and intra tumoral diversity	Subtypes: Classical, Proneural, Mesenchymal; TFs: ASCL1, HES1, OLIG2, SOX2	Subtype specific targeted therapy, epigenetic modulators	[60]
	Dynamic state transitions	Hypoxia, irradiation induced methylation changes	Inhibit plasticity via microenvironmental modulation	
Quiescence driven resistance	Dormancy in hypoxic niches	FOXG1/Wnt β catenin, BMP signalling	Force re entry into cycle for eradication; permanent dormancy induction	[61]
Chemoresistance in GSCs	DNA repair enzyme overexpression	MGMT upregulation	MGMT inhibitors (O6 benzylguanine)	[54]
	Cell cycle modulation	CHK1, CDC25C, CDC2	Target checkpoint kinases (CHK inhibitors)	[53]
	Anti apoptotic signalling	MCL1, BCL 2, BCL2L1a	BH3 mimetics (venetoclax, navitoclax)	[15]
	Multidrug resistance (MDR)	ABCG2, MDR1	ABC transporter inhibitors (elacridar, tariquidar)	[62]
	Pro survival signalling	NOTCH1, GLI1 (SHH pathway)	γ secretase inhibitors, cyclopamine	[63]
Radioresistance in GSCs	Enhanced DDR capacity	ATM, ATR, CHK1, CHK2, RAD51	DDR inhibitors (ATM/ATR inhibitors, PARP inhibitors, RAD51 blockers)	[64]
	Delayed cell cycle progression	G2/M arrest	Cell cycle disruptors (CDK inhibitors)	[65]

5 | A Comprehensive Overview of Current Clinical Trials

A variety of innovative approaches are being explored to enhance treatment options for GBM, particularly focusing on immunotherapies and advanced therapeutic techniques. One promising strategy involves using bispecific antibodies combined with white blood cells to locate and destroy tumour cells while sparing normal cells. A Phase I trial is currently assessing the effectiveness of this combination for patients with recurrent or refractory glioblastoma multiforme [1, 66, 67]. Another experimental treatment, referred to as TVI Brain 1, aims to harness 'killer' white blood cells to target cancer cells. Previous Phase I studies have shown that this treatment is safe and has prolonged survival in some patients. This has led to a Phase II study designed to identify the most effective vaccine components, utilising dendritic cells treated with tumour lysate obtained during surgery [2, 68]. Additionally, a single-centre Phase I study is investigating the safety of administering autologous dendritic cells combined with tumour-derived stem cells to patients with recurrent brain tumours. Positive results could pave the way for a Phase II efficacy trial [3, 69, 70].

In another approach, patients are being randomised to receive nivolumab, either alone or in combination with dendritic cell vaccine therapy, prior to surgical intervention. After surgery, both groups will continue receiving DC vaccines and nivolumab until disease progression is confirmed [4, 71, 72]. An open-label Phase I study is also underway, examining the safety of combining EGFRvIII-targeted CAR T cells with pembrolizumab, a PD-1 inhibitor, for patients newly diagnosed with GBM. This study aims to improve outcomes for this high-risk population [5]. Moreover, researchers are evaluating a novel strategy involving the use of oncolytic adenovirus delivered through neural stem cells in conjunction with radiation and chemotherapy, seeking enhanced efficacy without increasing toxicity for newly diagnosed malignant gliomas [6, 73]. A Phase I/II trial is also focusing on the effects of combining temozolomide with stem cell transplantation for newly diagnosed GBM patients, targeting the stopping of cancer cell growth while preparing for transplantation. Research continues to determine the effectiveness of high-dose versus intermediate-dose chemotherapy followed by autologous stem cell transplantation, with some trials also looking into the addition of isotretinoin to prevent recurrence [7, 74, 75].

Finally, a clinical trial is exploring the use of genetically modified neural stem cells that convert 5-fluorocytosine into fluorouracil directly at tumour sites, presenting a targeted approach to treating high-grade gliomas [8]. Chemotherapy drugs like carboplatin, thiotepa, and etoposide operate through various mechanisms to halt tumour cell division, ultimately leading to cancer cell death. Combining chemotherapy with autologous stem cell transplantation may enable doctors to administer higher doses of these drugs, thereby increasing tumour cell kill rates. Additionally, isotretinoin has shown potential in preventing glioma recurrence, but it remains unclear which chemotherapy regimen, alone or combined with isotretinoin, is most effective for treating recurrent high-grade glioma [9]. Furthermore, genetically modified NSCs that can convert 5-fluorocytosine into the chemotherapy agent fluorouracil directly at tumour sites may represent a promising treatment avenue. This approach is being explored in clinical trials involving patients undergoing surgery for recurrent high-grade gliomas [10] (Table 3).

6 | Exploration of Future Strategies for GSC Targeted Therapies

Identifying specific biomarkers associated with GSCs is crucial for improving both diagnostic accuracy and therapeutic targeting. These biomarkers can be instrumental in personalising treatment plans, allowing clinicians to select therapies tailored to the molecular profile of individual tumours. Research into extracellular vesicles (EVs) offers a promising avenue for biomarker discovery [76, 77]. EVs, which contain proteins, lipids, and nucleic acids released by cells, can reflect the state of the tumour microenvironment and the molecular profile of GSCs. Analysing the content of EVs in bodily fluids, such as blood or cerebrospinal fluid, could yield non-invasive biomarkers for early detection, monitoring treatment response, and predicting outcomes [76, 77]. Furthermore, understanding the interactions between GSCs and the tumour microenvironment might reveal new pathways that influence tumour behaviour and treatment resistance [78]. For instance, components of the microenvironment, such as specific cytokines or metabolic byproducts, could act as indicators of GSC activity and provide additional therapeutic targets [79, 80].

The advent of CRISPR technology for gene editing opens up innovative possibilities in targeted therapies for GBM. By specifically modifying GSC characteristics such as their proliferation rate, tumorigenicity, or resistance to existing treatments, researchers can develop a deeper understanding of GSC biology [79, 80]. For example, CRISPR can be employed to silence oncogenic pathways that are critical for GSC survival and proliferation. By knocking out genes responsible for maintaining GSC properties, researchers can explore how these cells adapt and whether targeted therapies can be developed to exploit any newfound vulnerabilities [80, 81]. Moreover, CRISPR technology facilitates the creation of more accurate preclinical models of GBM. By genetically engineering GSCs to mimic patient-specific characteristics, researchers can test new drugs and combinations in a more representative setting. Such models can yield valuable insights into which therapies may be most effective in real-world scenarios. Integrating artificial intelligence (AI) and machine learning into GBM research has the potential to revolutionise drug discovery and treatment strategies [82, 83].

AI can analyse large datasets, including genomic, proteomic, and clinical data, to uncover patterns that may not be immediately apparent through traditional analysis methods. By leveraging AI algorithms, researchers can predict which compounds are likely to interact effectively with GSCs [82, 83]. For instance, machine learning models can sort through vast chemical libraries to identify candidates that target specific biomarkers or pathways relevant to GSCs, thereby streamlining the development of targeted therapies [84, 85]. Furthermore, AI can assess patient data to identify subgroups that may respond uniquely to certain treatments, enabling personalised approaches that optimise efficacy and minimise side effects [84, 85]. This predictive capacity

TABLE 3 | Summary of clinical trials for GBM treatments.

Cellular intervention	Phase	Participants	Cell type	Cell dose	Cell delivery route	Start date	End date	Status	References
Lymphokine-activated killer cells	I	13	Monocytes/ WBCs	Not specified	IT	Mar 1997	Jan 2003	Completed	[66]
Activated white blood cells + cancer vaccine+ immune adjuvant activated WBCs	I/II	14	Activated WBCs	N/A	IV infusion	Apr 2010	Mar 2011	Completed	[67]
Autologous tumour lysate pulsed DC vaccination	II	60	DCs	1, 5, or 10×10^6 DCs	ID	Oct 2010	Jan 2023	Active	[68]
DCs	I	8	DCs	5, 10 or 15×10^6 DCs	ID	Sep 2010	Jun 2012	Completed	[69]
DCs	I	6	DCs	Not specified	ID	Jan 2016	Dec 2019	Completed	[70]
CART EGFRvIII T cells	I	7	T lymphocytes	Not specified	IV Infusion	Mar 2019	Feb 2021	Completed	[71]
Neural stem cells loaded with an oncolytic adenovirus	I	13	NSCs	First cohort 5×10^7 NSCs, second cohort 1×10^8 NSCs, third cohort 1.5×10^6 NSCs	Injected into the walls of the resection cavity	Apr 2017	Dec 2021	Active	[72]
In vitro transfected (Phoenix RD114 pseudotype vector) peripheral blood stem cell transplant	I/II	12	CD34+ HSCs	Not specified	IV Infusion	Feb 2009	Jan 2021	Completed	[73]
Transplantation of autologous PBSCs	III	1	PBSCs	Not specified	IV Infusion	Oct 2004	Sep 2006	Completed	[74]
NSC/enzyme prodrug	Phase I	15	NSCs	Not specified	Intracerebral	Feb 2010	Jan 2017	Completed	[75]

enhances the likelihood of successful treatment outcomes and can inform clinical decisions more effectively than traditional methods (Table 4).

7 | Perspectives and Future Directions

GSCs remain a formidable therapeutic target due to their heterogeneity, adaptability, and capacity to occupy hypoxic, invasive niches. Their ability to adopt quiescent states enables survival under conventional therapies. Stem cell-based strategies have emerged as a promising avenue to circumvent these challenges. Engineered NSCs, MSCs, and haematopoietic stem and progenitor cells are among the most widely investigated platforms [13, 86]. A key advantage of these cell types is their inherent ability to home to sites of injury or tumour growth, including hypoxic and deeply infiltrative regions inaccessible to many therapies [87]. This tumour tropism is mediated by growth factors, chemokines, and inflammatory cues within the glioma microenvironment. MSCs and NSCs can cross the blood–brain barrier and integrate into tumour-associated vasculature, enabling perivascular migration and sustained intratumoral presence. This targeting capability allows these cells to reach quiescent GSCs in otherwise inaccessible niches and may overcome the challenges posed by GBM heterogeneity [49].

Engineered stem cells also serve as versatile vehicles for gene therapy, offering immune evasion and amenability to genetic modification. Suicide gene therapy, in which stem cells are engineered to express prodrug-activating enzymes such as herpes simplex virus thymidine kinase (HSV TK), allows localised conversion of prodrugs like ganciclovir into cytotoxic metabolites. This approach induces tumour-specific cell death, with a bystander effect extending toxicity to adjacent tumour cells. Dual suicide gene systems, such as HSV TK combined with cytosine deaminase (CD), generate synergistic cytotoxic effects, reduce the risk of resistance, and enhance safety by enabling self-elimination of therapeutic cells after treatment [88, 89].

Advanced strategies include MSCs engineered to produce anti-angiogenic proteins and radiation-activated proteins for combined vascular disruption and targeted elimination. HSCs have been modified to deliver TGFβ inhibitors selectively to the GBM microenvironment, augmenting the effects of RT and stimulating durable immune responses [90]. Additionally, MSCs can deliver oncolytic viruses to restore tumour suppressors such as p53 and PTEN, improving viral replication and distribution within tumours. NSCs delivering replicating oncolytic adenoviruses have shown potential in both newly diagnosed and recurrent GBM [48]. The CXCL12–CXCR4 axis is a critical regulator of tumour cell migration, dormancy, and therapeutic resistance in GBM. Elevated CXCL12 in necrotic and angiogenic niches attracts CXCR4-expressing stem cells, guiding their migration towards invasive and hypoxic tumour zones. Engineering MSCs to overexpress CXCR4 enhances tumour tropism [91]. Notably, under TMZ stress, CXCL12–CXCR4 signalling modulates GSC quiescence and reactivation, contributing to recurrence. Targeting this axis with agents such as plerixafor has shown success in mobilising dormant stem cells in other cancers, suggesting dual utility in disrupting protective niches and guiding therapeutic stem cells to resistant GSC populations [92, 93]. Human induced pluripotent stem cells (hiPSCs) offer an alternative platform with unlimited self-renewal, patient-specific compatibility, and greater genetic engineering flexibility compared to MSCs and NSCs. Neural progenitors derived from hiPSCs, when engineered with suicide genes, have demonstrated superior efficacy against GSCs compared to MSC-based approaches (Figure 3) [94].

TABLE 4 | Summary of strategies for improving treatment outcomes in GBM.

Strategy	Description	Potential benefits	References
Novel biomarkers	Identification of specific biomarkers associated with GSCs, focusing on extracellular vesicles and tumour microenvironment interactions.	Improved diagnostic accuracy Personalised treatment plans non invasive monitoring of tumour progression and response to therapy	[78]
CRISPR technology	Utilisation of CRISPR for gene editing to modify GSC characteristics or silence oncogenic pathways and create accurate preclinical models.	Enhanced understanding of GSC biology Development of therapies targeting key pathways More representative models for drug testing	[80, 81]
Artificial intelligence	Integration of AI and machine learning to analyse large datasets and uncover patterns in drug discovery related to GSCs.	Streamlined identification of effective compounds Personalised treatment approaches through predictive analytics Improved patient outcomes	[82, 83]
Combination therapies	Exploration of synergistic effects between emerging therapies and existing treatment modalities, such as immunotherapy and chemotherapy.	Enhanced treatment efficacy Overcoming resistance mechanisms Potential reduction in tumour recurrence and improvement in survival rates	[84]

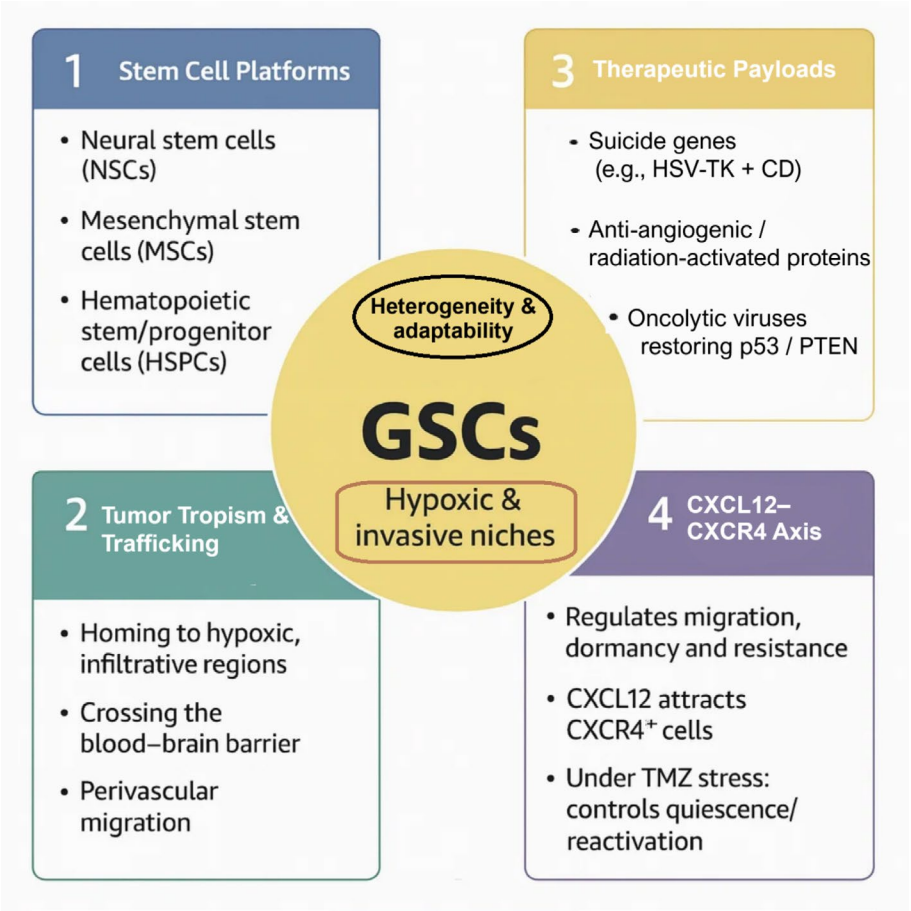

FIGURE 3 | Overview of GSC traits and targeted therapeutic strategies in GBM.

8 | Discussion

The potential for tumorigenesis in stem cell-based therapies remains a significant concern. Malignant transformation has been observed in long-term cultures of bone marrow-derived MSCs, with environmental factors such as oxygen tension influencing transformation risk. Multipotent stem cells like NSCs, MSCs, and HSCs are generally considered more stable and safer for therapeutic use than pluripotent cells, including embryonic stem cells (ESCs) and iPSCs [95]. MSC viability depends on cell adhesion and communication, which are often disrupted during isolation and transplantation. This disruption can trigger anoikis, apoptosis resulting from detachment from the extracellular matrix, reducing cell engraftment and persistence [96]. Enhancing adhesion through biodegradable scaffolds or biomaterials may improve MSC retention and efficacy. MSCs likely exert transient rather than permanent therapeutic effects, and limiting their persistence could reduce long-term risks. Treatment outcomes depend on factors such as cell source, expansion protocols, administration route, dosing, and genetic modifications [97].

The effects of MSCs on tumours vary across studies, influenced by cell source and timing of administration. Some data suggest adult MSCs may promote tumour growth when administered concurrently with tumour cells, while delayed administration may inhibit progression. This indicates that the stage of tumour development is a critical determinant of MSC effects [98]. Finally, significant differences between preclinical models and human GBM, particularly in vascularization and genetic heterogeneity, complicate the translation of laboratory findings to clinical benefit. Bridging this gap requires more representative models to improve the predictive value of preclinical research and ultimately enhance treatment outcomes in patients with GBM [99]. GSCs play a central role in therapeutic resistance due to their heterogeneity, adaptability, and ability to occupy inaccessible niches. Targeting GSCs is crucial for overcoming immune evasion and enhancing treatment efficacy in GBM. Stem cell-based delivery systems, such as engineered neural stem cells and mesenchymal stem cells, show great promise in this area. However, challenges remain, including potential tumorigenesis, variable effects depending on the tumour stage, and the need for more representative preclinical models. Addressing these limitations will be essential for translating these strategies into effective therapies for GBM patients.

Author Contributions

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