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REVIEW

Cellular and Molecular Mechanisms of Cancer Drug Resistance

Hunting glioblastoma recurrence: glioma stem cells as retrospective targets

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Abstract

Glioblastoma (GBM) remains one of the most aggressive and treatment-resistant brain malignancies in adults. Standard approaches, including surgical resection followed by adjuvant radio- and chemotherapy with temozolomide (TMZ), provide only transient control, as GBM frequently recurs due to its infiltrative nature and the presence of therapy-resistant subpopulations such as glioma stem cells (GSCs). GSCs, with their quiescent state and robust resistance mechanisms, evade conventional therapies, contributing significantly to relapse. Consequently, current treatment methods for GBM face significant limitations in effectively targeting GSCs. In this review, we emphasize the relationship between GBM recurrence and GSCs, discuss the current limitations, and provide future perspectives to overwhelm the challenges associated with targeting GSCs. Eliminating GSCs may suppress recurrence, achieve durable responses, and improve therapeutic outcomes for patients with GBM.

cancer stem cells; drug resistance; glioblastoma; glioma stem cells; recurrence

INTRODUCTION

Glioblastoma (GBM) represents the most common and aggressive primary malignant brain tumor in adults, characterized by rapid proliferation, and diffuse infiltration into surrounding brain tissue (1). Despite advances in surgery, radiotherapy, and chemotherapy, GBM continues to pose a daunting clinical challenge, with a median survival of only 12–18 mo (2). A primary contributing factor to the poor prognosis of patients with GBM is the high rate of tumor recurrence. This recurrence highlights the urgent need for innovative therapies targeting the mechanisms driving tumor regrowth (3).

The mechanisms underlying GBM recurrence are multifaceted and complex, involving a combination of tumor cell-intrinsic factors, microenvironmental cues, and therapeutic resistance mechanisms (4). Among these mechanisms, emerging evidence suggests that a subpopulation of tumor cells known as glioma stem cells (GSCs) play a critical role in driving tumor recurrence and therapeutic resistance in GBM (5).

GSCs are a distinct subpopulation within the tumor exhibiting self-renewal, multipotency, and resistance to conventional treatments (6). These cells are thought to drive tumor growth, invasion, and recurrence through their ability to evade therapy, repopulate the tumor bulk, and promote tumor heterogeneity (7, 8). Importantly, GSCs exhibit enhanced resistance to conventional therapies such as radiation and chemotherapy, making them a critical therapeutic target for improving GBM outcomes (9).

This review aims to provide a comprehensive overview of the current state-of-the-art in understanding the role of GSCs as retrospective targets in hunting glioblastoma recurrence. We will delve into the molecular mechanisms underlying GSC biology, their contributions to tumor recurrence and therapeutic resistance, and the therapeutic strategies aimed at targeting GSCs to prevent recurrence. In addition, we will discuss the challenges and opportunities associated with translating GSC-targeted therapies, with the ultimate goal of improving outcomes for patients with GBM facing recurrence.

Glioblastoma and Therapy Resistance

Surgical resection serves as the primary therapeutic approach for GBM, with the extent of resection greatly impacting prognosis (10). Despite efforts for complete resection, tumor recurrence near the primary mass limits surgery and radiotherapy effectiveness (11). Innovations such as fluorescence-guided surgery using 5-aminolevulinic acid for tumor cell marking have improved precision (10). However, adjunctive treatments like the implantation of biodegradable carmustine-impregnated wafers into the tumor bed postresection remain controversial, with marginal improvements in median survival compared with radiotherapy alone (12).

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Following surgical resection, the standard treatment protocol involves fractionated localized radiotherapy combined with temozolomide (TMZ) chemotherapy for newly diagnosed patients with GBM (2, 13). Although this combination has shown some efficacy, few patients survive beyond 5 yr, indicating the limitations of conventional therapies (14).

Overall, although conventional methods remain the cornerstone of GBM treatment, their limitations underscore the urgent need for innovative therapeutic approaches to overcome resistance and improve patient survival.

The Role of Glioma Stem Cells in Glioblastoma Recurrence

Recurrence represents a formidable obstacle in conventional glioma treatment strategies, posing significant challenges clinically. Molecular mechanisms underlying glioma recurrence are multifaceted, involving intricate interplays of signaling pathways governing cell proliferation, invasion, and resistance to apoptosis. Reorganization of the tumor microenvironment (15), along with alterations in DNA mismatch repair mechanisms, including mutations in MSH6, contribute significantly to recurrence (16–20). Several studies using whole genome sequencing and transcriptome analysis reveal that therapy can induce hypermutation in receptor tyrosine kinase genes, potentially accelerating recurrence (21). Furthermore, several genes, including Latent Transforming Growth Factor Beta-Binding Protein 4 (*LTBP4*), MutS Homolog 6 (*MSH6*), PR Domain Zinc Finger Protein 2 (*PRDM2*), and Insulin-Like Growth Factor 1 Receptor (*IGF1R*), are uniquely mutated and expressed in recurrent tumors (22).

Following surgical resection, residual cells in the resection cavity serve as the starting point for harboring aforementioned mutations that trigger recurrence. GSCs are thought to be among these pioneering remaining cells, initiating recurrence (23, 24). Residual tumor cells become increasingly resilient to both radiotherapy and chemotherapy, ultimately leading to patient mortality (Fig. 1).

Single-cell transcriptomic analysis has identified unique phenotypic clusters in recurrent tumors, suggesting a shift in cellular composition during recurrence (24–27). These clusters likely represent GSC populations that evade conventional therapies and contribute to therapeutic resistance through unique molecular and epigenetic features, such as increased chromatin accessibility and vascular gene activation (5, 28, 29).

Genetic differences.

GSCs exhibit specific biomarkers that distinguish them from differentiated tumor cells, providing insights into their functional properties and therapeutic vulnerabilities. Key oncogenes such as *SOX2, NANOG, CHRDL1*, and *OCT4* orchestrate GSC self-renewal and tumorigenic potential (26, 30–33). In addition, FOXM1 plays a regulatory role in GSCs via interacting with SOX2 (34), Wnt/β-catenin (35, 36), and STAT3-β-catenin (37) signaling pathways.

In addition to exhibiting distinct expression profiles, GSCs can be categorized into proneural (PN GSCs) and mesenchymal (MES GSCs) subtypes based on their gene signatures (26, 38, 39). Gene expression analysis of GSCs from in vivo models, patient samples, and conventional glioma stem cell lines identified two phenotypes: GSf (full stem) and GSr (restricted stem) (40). The GSf phenotype, resembling the proneural subtype, is characterized by CD133 expression and notable invasiveness. In contrast, the GSr phenotype lacks CD133 expression, grows adherently in vitro, and shows reduced invasiveness (38). Differential analysis of these phenotypes highlights enriched genes on chromosome 19, including Kruppel-type Zinc Finger transcription factors, which are implicated as potential tumor suppressors in several cancers including ovarian carcinoma (41), esophageal squamous cell carcinoma (42), and oropharyngeal carcinoma (43). Moreover, the expression of CD133 in GSf phenotype is associated with active *NOTCH1* and *HER3* and is proposed as a potential target in GBM (44). Notably, among markers overexpressed in patient tumors and GSf lines, C-X-C chemokine receptor type 4 (CXCR4) has been identified as a potential therapeutic target. Studies showed that antagonization of CXCR4 effectively inhibits the highly invasive growth of GS xenografts in vivo and suppressed cell migration in vitro (40). Conversely, the GSr phenotype is marked by the activation of epidermal growth factor receptor (EGFR) and phosphatidylinositol 3-kinase (PI3K)/mTOR pathways (38), indicating a distinct subset of metabolically active GSCs responsible for resistance to chemotherapy and radiotherapy.

GSCs are also implicated in epithelial-mesenchymal transitioning (36, 45, 46). They drive epithelial-mesenchymal transition (EMT) by downregulating epithelial markers such as E-cadherin and upregulating mesenchymal markers like vimentin and N-cadherin. Not only glioma stem cells themselves but also their cell products can be targeted as a novel diagnostic and therapeutic approach. For example, exosomes released by GSCs carry elevated levels of miR-155-5p, which downregulates acetyl-CoA thioesterase 12, a tumor suppressor, while promoting mesenchymal transition in recipient glioma cells (47).

Notably, specific biomarkers like CD133, CD44, and Nestin are frequently enriched in GSCs and associated with glioma recurrence (48). The expression profile of recurrent glioblastomas often reflects the molecular signature of GSCs, suggesting their contribution to tumor relapse. Targeting these GSC-specific biomarkers and alterations in gene expression changes offers promise for eradicating the tumor-initiating cell population and preventing recurrence (32, 49).

Preclinical studies demonstrated that targeting GSCs via Hedgehog, NOTCH, and PI3K/AKT signaling inhibition blocks tumor growth, and significantly prolongs survival (50–56). Similarly, the expression of Laminin-411 in the glioma microenvironment is linked with cancer stem cell markers presenting an opportunity for targeted intervention through a novel nanobioconjugate strategy (57). In addition, LASS2 reduces GSC migration and invasion by promoting tumor cell apoptosis and inhibiting EMT, suggesting its potential as a therapeutic target (45). Using GSC-specific biomarkers in targeted therapy approaches will lead to more precise and efficient treatment strategies tailored to individual patients, ultimately improving outcomes in glioma management.

Epigenetic factors.

Histone modifications regulate chromatin structure and gene accessibility. These modifications contribute to differential gene expression profiles between GBM and GSCs (58).

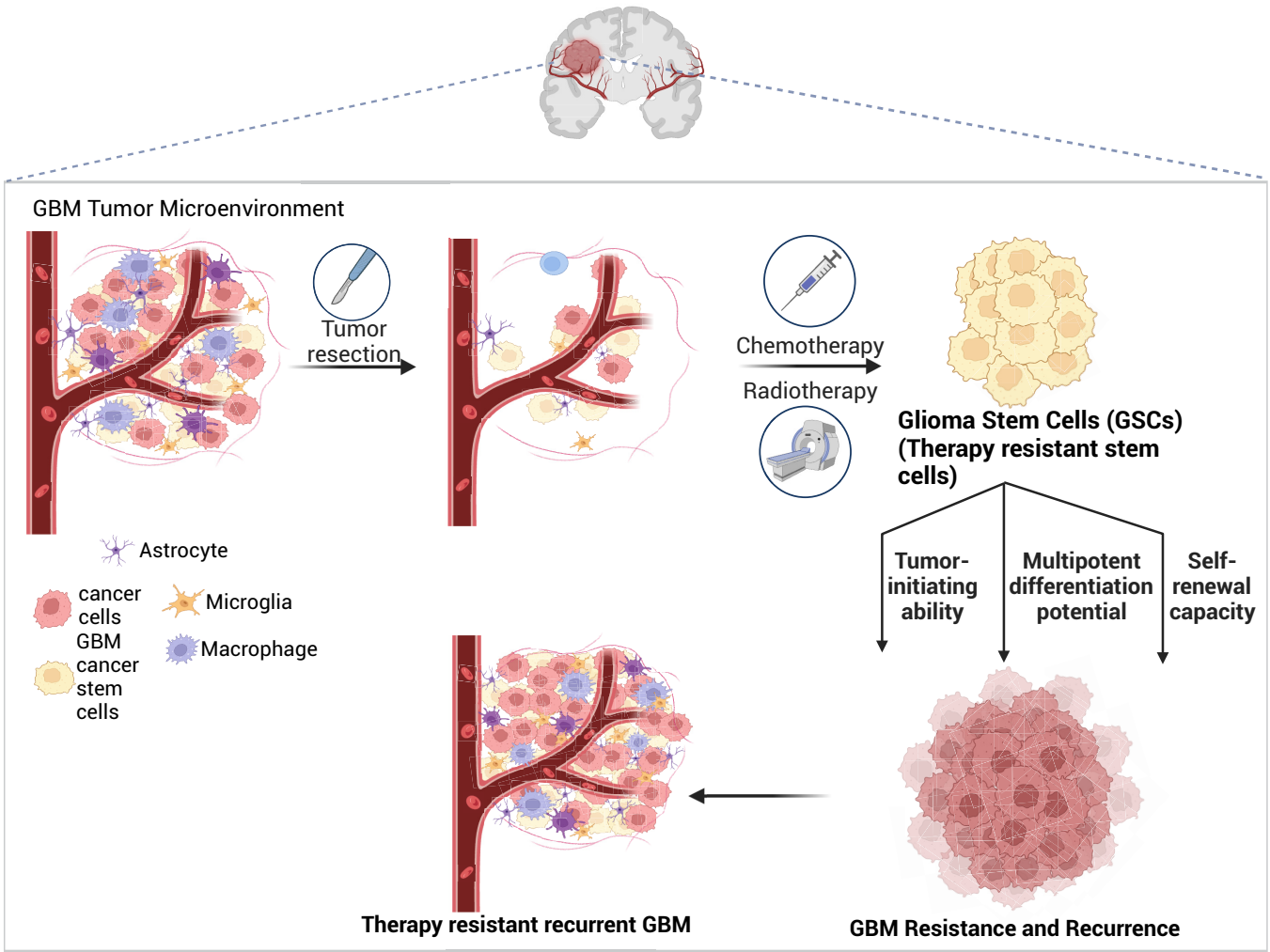

Figure 1. The role of therapy-resistant glioma stem cells (GSCs) in glioblastoma (GBM) recurrence. Schematic representation of targeting GSCs to improve treatment outcomes and prevent disease relapse. GSCs within the tumor niche serve as a reservoir for tumor recurrence due to cancer stem cell characteristics and therapy-resistant profile.

For instance, GSCs display higher levels of histone acetylation at enhancer regions of stemness-related genes. Histone deacetylases (HDACs), particularly HDAC6, play a crucial role in preserving GSC characteristics, such as radioresistance and stemness. Inhibiting HDACs demonstrates significant antitumor effects (59).

Studies showed that methylation of the O^6-methylguanine-DNA methyltransferase (MGMT) promoter predicts GBM response to alkylating agents. Dysregulated Polycomb group (PcG) proteins, key epigenetic regulators, contribute to GSC tumorigenicity by maintaining repressive chromatin states (60). Differential methylation in GSCs—particularly hypermethylation of genes targeted by the Polycomb Repressive Complex 2 (PRC2)—is crucial for preserving GSC stemness and linking these epigenetic patterns to broader contexts in stem cell biology and cancer (61). GBM exhibits upregulation of enhancer of zest homolog 2 (EZH2), a key Polycomb repressor, which is critical for maintaining GSCs. EZH2 dysfunction in the bone morphogenetic protein (BMP) pathway converts cytostatic signals into proproliferative signals, contributing to GSC tumorigenicity (62). Specific genes like serine peptidase inhibitor (SPINT2), a putative tumor suppressor silenced in GSCs through promoter hypermethylation, highlight the role of epigenetic alterations in disrupting cancer cell signaling (63). In addition, noncanonical DNA demethylation at the sixth position of adenine bases [N6-methyladenine (N6-mA)], regulated by the demethylase AlkB homolog 1 (ALKBH1), plays a significant role in maintaining GSC properties (64). Lysine demethylase 2B (KDM2B), another GSC-specific DNA demethylase, acts as an epigenetic remodeler for glioma initiator cells, further underscoring the importance of precise DNA methylation regulation (65). Epigenetic regulation of differentiation capacity in GSCs involves factors such as Achaete-Scute family BHLH transcription factor 1 (ASCL1), a pioneer transcription factor and master regulator of neuronal lineage differentiation. ASCL1's role becomes particularly critical in the context of Notch inhibitor treatments, emphasizing its therapeutic relevance (66).

Noncoding RNAs (ncRNAs), including microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), regulate gene expression posttranscriptionally. Aberrant expression of ncRNAs influences key processes like apoptosis, metastasis, and proliferation in GSCs. For instance, LINC00461 promotes cell

cycle progression, whereas Integrative Hepatocyte Growth Factor Signaling Enhancer Gene (INHEG) enhances GSC self-renewal and tumorigenicity by regulating rRNA modifications (67, 68). The long noncoding RNA, nuclear enriched abundant transcript 1 (NEAT1) has an essential role in EGFR-driven glioblastomas, especially GSC, triggering β-catenin in WNT signaling by controlling the EZH2. Recent studies show that some noncoding RNA, like lncRNA *Metastasis Associated Lung Adenocarcinoma Transcript 1* (MALAT1), and miR-129, can be worked for maintaining the expression of SOX2, and is a potential biomarker for GSCs (29808528). The other lncRNA difference between GBM and GSC is glioma stem cell association long noncoding RNA (GSCAR; ENSG00000250377), which is a 676-bp lncRNA that is significantly increased in glioma malignant tissues and cell lines, particularly in GSCs, and has been linked with poor clinical outcomes (69).

Tumor microenvironment and niche qualities.

The microenvironment of GSCs plays a crucial role in tumor progression and therapeutic resistance. A key component of this microenvironment is the tumor vascular niche, which supports GSC self-renewal and survival (70). Conversely, GSCs also exert influence on the tumor vasculature, promoting tumor angiogenesis and vasculogenesis (71). GBM vasculature is structurally abnormal, exhibiting irregular architecture, high permeability, and severe hypoxia (72). Unlike normal vessels, GBM vasculature forms through unique processes, including vascular co-option and vasculogenic mimicry (73).

GSCs secrete proangiogenic factors like vascular endothelial growth factor (VEGF) and hepatoma-derived growth factor (HDGF), which promote endothelial cell migration and tube formation (74, 75).

They can also transdifferentiate into endothelial cells, contributing directly to tumor vasculogenesis and vessel-like network formation through vasculogenic mimicry (76, 77). In addition, GSCs differentiate into pericytes, stabilizing tumor blood vessels and facilitating tumor growth. Recruitment and differentiation of GSCs into pericytes are mediated by signaling pathways such as the stromal cell-derived factor 1 (SDF-1)/CXCR4 axis and transforming growth factor β (TGF-β) secretion (8).

High Mobility Group AT-Hook 2 (HMGA2), expressed in GSCs and pericytes, regulates self-renewal and differentiation into pericytes, highlighting its dual role in GSC maintenance and vascular niche stabilization (78). Overall, GSCs shape the tumor vascular niche by driving angiogenesis, vasculogenesis, and pericyte differentiation. Understanding these interactions provides critical insights for developing therapies that target the tumor microenvironment to combat GBM.

Immune system.

GBM has distinctive features, including a suppressive tumor microenvironment, the presence of tumor-associated microglia and macrophages (TAMs), and dysfunctional T cell populations (79–82). GSCs contribute to immunosuppression, preventing effective immune-modulating therapies (83). GSCs secrete soluble modulators such as TGF-β, interleukin-10 (IL-10), and prostaglandin E2 (PGE-2), which exert immunosuppressive effects and evade immune surveillance (84–86).

IL-10 modulates immune cell activity, downregulating antigen-presenting molecules in TAMs and impairing CD4+ T cell activation (87, 88). In addition, IL-10 promotes the differentiation of Treg cells, inducing a suppressive immune phenotype (89). Similarly, TGF-β drives the conversion of CD4+ T cells into Tregs while inhibiting cytotoxic gene expression and downregulating activating receptors like NKG2D on CD8+ T and natural killer (NK) cells (90–92). GSCs also express immune checkpoint molecules like PDL-1, which interact with PD-1 on T cells, leading to T cell exhaustion and suppression of immune responses (93, 94). This interaction increases resistance to T cell-mediated killing, further contributing to GSC-mediated immune evasion.

Targeted Therapy Strategies for Glioma Stem Cells

Targeting GBM is challenging due to its chemo-resistant nature and high recurrence rates. Therapeutic efforts focus on targeting GSCs, the key drivers of recurrence and cancer persistence. Approaches include molecular pathway inhibition, biomarker-targeted therapies, chronotherapy, immunotherapies, and stem cell-based delivery systems.

Blocking of glioma stem cell-related molecular pathways.

Several GSC markers and related signaling pathways have been identified as therapeutic targets, including Wnt, Notch, Hedgehog (Hh), JAK/STAT, EGFR, and circadian clock genes (Fig. 2).

Blocking of the following pathways may lead to target GCSs at the molecular level.

Wnt signaling. Dysregulated Wnt signaling plays a crucial role in GSC self-renewal, tumor invasion, and therapy resistance (95). This pathway facilitates interactions between GSCs and the tumor microenvironment, enhancing their invasiveness and survival under stress conditions. The Semaphorin 3C (Sema3C) pathway acts as an alternative activator of canonical Wnt signaling by promoting the nuclear translocation of β-catenin, bypassing upstream Wnt pathway blockages. Sema3C expression is elevated in ∼85% of GBM cases and enhances GSC invasion, self-renewal, and survival through the Sema3C/plexinD1/rac1/β-catenin/Wnt signaling axis (96, 97). These findings suggest that dual inhibition strategies, such as blocking the Wnt pathway with LGK974 (a Porcupine inhibitor) and suppressing Sema3C using shRNA, significantly reduce GSC self-renewal and gliomagenesis (98). A connection between β-catenin and the transcription factor FoxM1 has also been identified, where FoxM1 regulates GSC self-renewal and stemness. FoxM1 is upregulated in several cancers, including GBM, and contributes to fatty acid synthesis (FAS), which supports GSC survival and reduces the expression of stemness markers. Targeting FoxM1, alongside inhibiting FAS, offers a promising strategy for reducing GSC-driven tumor progression.

Notch signaling. In both normal neural stem cells (NSCs) and GSCs, the Notch signaling system is essential for regulating differentiation, preserving cellular quiescence, increasing proliferation, and promoting metastasis. Activation of the Notch pathway triggers transcription-dependent processes by releasing the intracellular domains of Notch

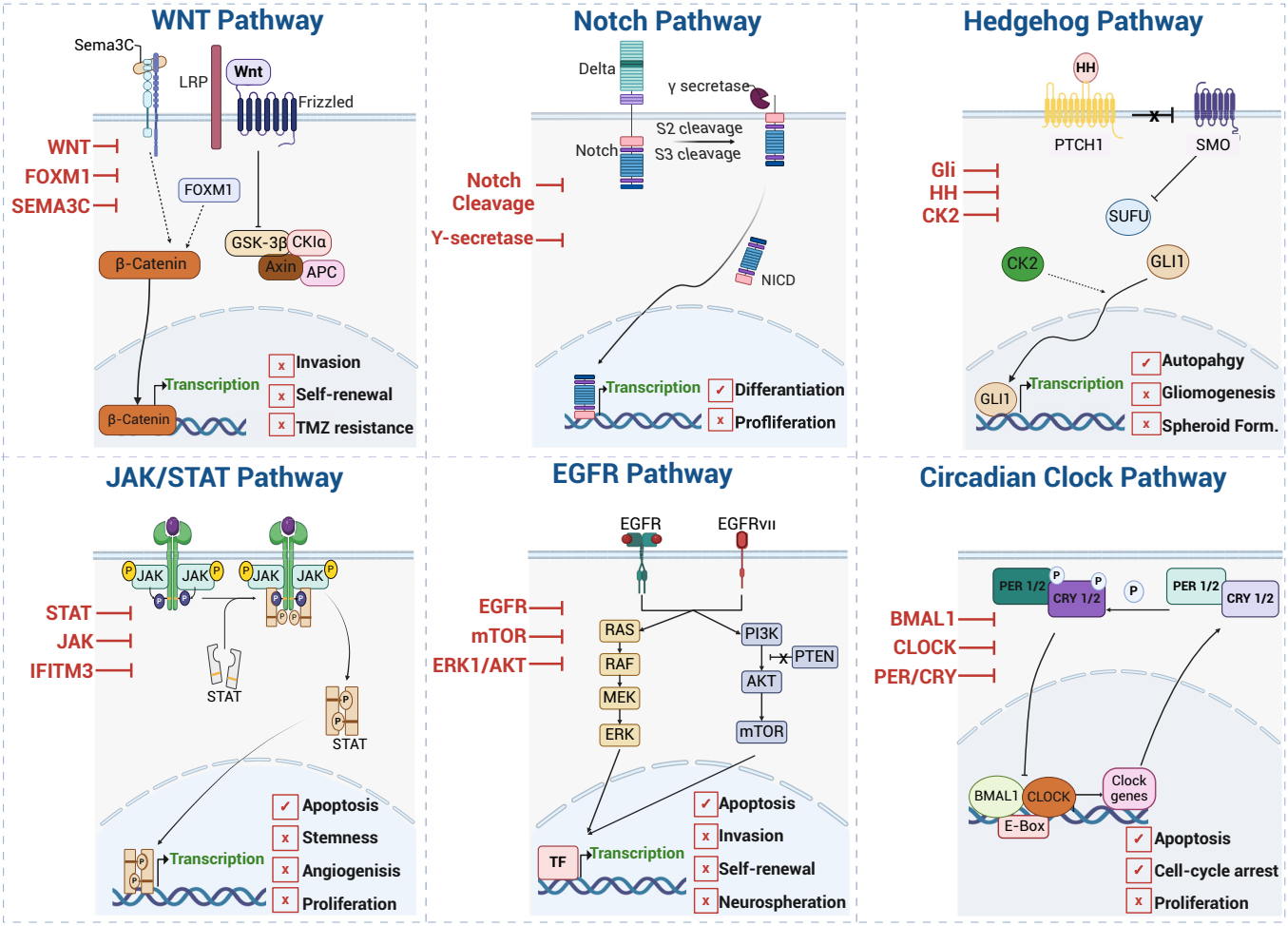

Figure 2. Glioma stem cell (GSC) targeting strategies at the molecular level. Schematic representation of molecular pathways for targeting GSCs, including Wnt, Notch, Hedgehog, JAK/STAT, epidermal growth factor receptor (EGFR), and circadian clock pathways. Black lines show normal activities, whereas the red lines indicate targets that have the ability to reduce or block the activity of related pathways. Red boxes represent inhibition (x) or activation (✓) of certain pathways upon GSC targeting. CK2, casein kinase 2; CLOCK, circadian locomotor output cycles kaput; IFITM3, interferon-induced transmembrane protein 3; mTOR, mammalian target of rapamycin; NICD, intracellular domains of Notch receptors; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; Sema3C, semaphorin 3C.

receptors (NICDs), which mediate downstream signaling (99). Compounds like RO4929097 effectively inhibit Notch1 by targeting the γ-secretase complex, which performs the final proteolytic step required for NICD release (100). γ-Secretase inhibitors block Notch cleavage, disrupting GSC maintenance and differentiation. The proneural GSC subtype, which expresses higher levels of Notch pathway genes, shows significantly reduced viability following treatment with RO4929097 (101). Furthermore, *N*-[*N*-(3,5-difluorophenacetyl-L-alanyl)]-*S*-phenylglycine *t*-butyl ester (DAPT), another γ-secretase inhibitor, enhances the therapeutic efficacy of temozolomide (TMZ). By suppressing Notch1 signaling, combined DAPT and TMZ treatment reduces tumorsphere proliferation and recurrence, underscoring the therapeutic potential of targeting the Notch pathway in glioblastoma (102). Other studies highlight the broader significance of Notch signaling in GSC biology. For example, Lim domain only 2 (LMO2), a gene prominently expressed in GSCs, plays an oncolytic role by maintaining stem cell properties through Notch pathway activation (103).

Hedgehog signaling. The Hedgehog (Hh) signaling system assumes a crucial role in the comprehension and management of glioblastoma, as it is essential for embryonic development, cell differentiation, proliferation, and tissue patterning. Key components of this pathway include patched (Ptch) and smoothened (Smo), which regulate a cascade that activates the glioma-associated oncogene (Gli) transcription factors, promoting GSC tumorigenesis (104). Abnormal activation of Hh-Gli signaling is strongly linked to GSC aggression and enhanced self-renewal capacity. Studies show that overexpression of Gli1 in the central nervous system of model organisms, such as tadpoles, induces brain tumor formation. Conversely, Hh signaling inhibitors like cyclopamine effectively suppress glioma cell proliferation and prevent primary tumor regrowth (105). LDE225, a Smo antagonist, disrupts Gli protein activation, induces autophagic cell death in GSCs, and reduces tumor spheroid formation more effectively in GSCs than in non-GSCs (106). Casein kinase 2 (CK2) also supports Hh/Gli signaling and GSC maintenance through β-catenin activation. CX-4945, a selective CK2 inhibitor, reduces MGMT

expression and increases the sensitivity of tumor cells to temozolomide (TMZ), highlighting its therapeutic potential (107). Combining Hh pathway inhibitors with other therapies has shown synergistic effects; for example, coadministration of cyclopamine, Notch inhibitors (GSI), and TMZ significantly enhances cytotoxicity against CD133-positive GSCs (108).

JAK/STAT pathways. The JAK/STAT pathway is crucial for cell survival, proliferation, and tumorigenesis in GSCs (6). Targeting this pathway has shown therapeutic potential in glioblastoma. STAT3 inhibitors, such as STX-0119 and WP1066, reduce GSC proliferation in vitro and inhibit tumor growth in vivo. STX-0119 has demonstrated efficacy in subcutaneous xenograft models, significantly reducing GSC marker expression, including CD44, NANOG, Nestin, CD133, and SOX2. It also downregulates STAT3 target genes, such as MMP9, TGFB1, VEGF, c-Myc, survivin, and cyclin D1, effectively curtailing tumor progression (109). Similarly, WP1066 inhibits both JAK2 and STAT3, improving survival in GBM xenograft models and reducing tumor burden (110). Arsenic trioxide (ATO), another JAK/STAT pathway inhibitor, decreases STAT3 activation, inducing apoptosis and reducing GSC stemness. However, clinical translation has proven challenging; a phase II trial combining ATO with radiation and temozolomide did not show significant survival benefits (NCT: 28510787). GSC-derived interferon-inducible transmembrane protein 3 (IFITM3) stimulates JAK2/STAT3 signaling, driving angiogenesis through robust release of basic fibroblast growth factor (bFGF). A multitargeted approach combining anti-VEGF drugs with IFITM3 inhibition could effectively reduce angiogenesis and therapy resistance in GBM (111). Other small-molecule inhibitors, such as ODZ10117 and Napabucasin, target STAT3-related mechanisms. ODZ10117 inhibits the SH2 domain of STAT3, whereas Napabucasin disrupts nuclear factor-κB heterodimer formation. Both significantly reduce tumor growth and compromise GSC stemness in preclinical models (112). Recent studies highlight the role of X-linked nonreceptor tyrosine kinase BMX in STAT3 activation. BMX bypasses suppressor of cytokine signaling 3 (SOCS3)-mediated regulation, enabling GSCs to maintain malignant phenotypes. BMX inhibitor ibrutinib disrupts GSC viability and decreases GBM tumor growth with minimal effects on normal brain progenitor cells, representing a promising therapeutic strategy (113). In addition, ribosomal S6 protein kinase 4 (RSK4) contributes to EZH2 inhibitor resistance in GBM. RSK4 phosphorylates EZH2, activating the EZH2/STAT3 pathway and promoting drug resistance. RSK4 knockdown restores sensitivity to EZH2 inhibitors and reduces GSC marker expression. Combining RSK4 inhibitors, such as BI-D1870, with EZH2 inhibitors has shown significant efficacy in preventing GBM progression in vivo and in vitro (114).

EGFR signaling. GSC regulation relies heavily on the epidermal growth factor receptor (EGFR), whose overexpression drives self-renewal and tumorigenicity. The most common EGFR mutation in GBM is EGFR variant III (EGFRvIII), found in 25%–33% of cases. Targeted therapies using bispecific antibodies against EGFRvIII and CD133 have demonstrated increased cytotoxicity toward EGFRvIII/CD133-positive GSCs, highlighting their therapeutic potential (6). EGFR inhibitors offer a promising strategy for halting GSC growth and promoting apoptosis. However, first-generation EGFR inhibitors, such as erlotinib and gefitinib, have shown limited efficacy, with less than 20% of patients responding favorably when these agents are used as initial therapy for glioma (115). Despite this, EGFR blockade sensitizes glioma GSCs to radiation and chemotherapy, suggesting its value in combination therapies. The tumor suppressor phosphatase and tensin homolog (PTEN), often lost or mutated in gliomas, is thought to underlie the limited response to EGFR inhibitors. PTEN is essential for maintaining neural precursor cells through mTOR pathway activation. Promising results from rapamycin clinical trials indicate that combining rapamycin with EGFR inhibitors may overcome TMZ resistance in GBM cells (116). ZR2002, a novel "combi-molecule," irreversibly blocks EGFR tyrosine kinase activity and induces DNA damage via its chlorethyl moiety. In preclinical studies, ZR2002 exhibited potent antiproliferative effects on GSCs while sparing healthy astrocytes. It significantly reduced EGFR, Erk1/2, and AKT phosphorylation and improved survival in mice bearing intracranial mesenchymal TMZ-resistant GSC lines (117).

Biomarker discovery.

Although ongoing studies present several GSC-related molecular markers, further research is needed to understand the molecular basis of GSC biology and its connection to tumor recurrence. Such insights could drive the discovery of novel biomarkers and therapeutic targets.

Long noncoding RNA INHEG: a guardian of GSC self-renewal. Long noncoding RNAs (lncRNAs) are key regulators in various malignancies, including GBM. INHEG, a lncRNA, has been shown to enhance GSC self-renewal and gliomagenesis. CRISPR/Cas9-mediated overactivation of INHEG in GSC cell lines increases their proliferative capacity, making INHEG a potential therapeutic target for halting GBM progression (68).

MEIS1 and CREB5: important roles in GSC function. Myeloid ecotropic viral integration site 1 (MEIS1) is upregulated in gliomas and is critical for cellular proliferation and growth. Silencing MEIS1 reduces GSC proliferation and correlates with improved patient outcomes, making it a potential biomarker and therapeutic target (118). Similarly, cAMP response element-binding protein (CREB5) is highly expressed in undifferentiated GSCs and associated with poor prognosis. Suppression of CREB5 limits GSC proliferation and self-renewal, presenting another viable therapeutic target (119).

NRF2 signaling: a double-edged sword in cancer stemness. Nuclear factor E2-related factor 2 (NRF2) enhances cancer stem cell traits, including treatment resistance, in various cancers. In GSCs, NRF2 silencing reduces stemness markers and GSC numbers. Targeting NRF2, particularly its interactions with mitochondrial NIX and the hypoxia-induced VEGF-GSC axis, offers a promising therapeutic approach (120).

IL-6: a glioma development catalyst. Interleukin-6 (IL-6), a senescence-associated secretory phenotype (SASP) factor, plays a key role in GSC-driven glioma progression, especially after chemotherapy and radiation. Targeting IL-6 or its receptors using short hairpin RNAs reduces GSC development and neurosphere-forming ability, providing a potential

strategy to slow GBM progression and improve patient survival (121).

miRNA therapeutics: a tool for control of cancerous gene expression. Micro RNA (miRNA) based therapeutics have great potential, as evidenced by the finding of miRNAs like miR-17-3p, miR-222, and miR-340 that are linked to poor survival. These miRNAs may be targets for various treatment approaches intended to prevent the formation of tumors and impair the viability of GBM stem cells (122).

Chronotherapy.

Mammal physiology and behavior are regulated by the circadian rhythm, which orchestrates various biological functions across organs, tissues, and cells, including tumor cells. Central clock proteins, such as aryl hydrocarbon receptor nuclear translocator-like protein 1 (BMAL1) and circadian locomotor output cycles kaput (CLOCK), form heterodimers that bind to E-box sequences in the promoter regions of circadian genes, such as PER1, PER2, PER3 (period genes) and CRY1, CRY2 (cryptochrome genes), initiating their transcription (123). Variations in clock gene expression influence glioma biology. According to the Cancer Genome Atlas, BMAL1 is upregulated in high-grade gliomas but is downregulated in patient-derived GSCs. Reduced BMAL1 expression decreases mitochondrial metabolic activity and tricarboxylic acid cycle (TCA) enzyme levels, leading to cell-cycle arrest and apoptosis in GSCs (124). In mouse models, BMAL1 knockdown inhibited tumor formation, extended lifespan, and suppressed GSC proliferation without affecting normal neural stem cell growth. This suggests that BMAL1 is essential for GSC survival and a promising therapeutic target. Its role in regulating metabolic processes like glycolysis and the TCA cycle demonstrates how GSCs adapt their metabolism via circadian and epigenetic alterations (124). CLOCK is another critical circadian regulator. Depleting CLOCK impairs GSC renewal, reduces glycolysis and TCA cycle enzyme expression, and induces apoptosis and cell-cycle arrest, further supporting its role in GSC metabolism and survival (125). PER2, a circadian protein, also plays a key role in gliomagenesis. GSCs exhibit reduced PER2 mRNA and protein levels. Overexpression of PER2 inhibits GSC growth by arresting cells in the G0/G1 phase of the cell cycle. PER2 downregulates proteins linked to GSC invasiveness and stemness, such as Wnt7b, β-catenin, MMP2, MMP9, and c-Myc, through targeting the Wnt/β-catenin signaling pathway (126). Therapeutic approaches targeting circadian proteins have shown promise. KL001 and its derivative SHP656 stabilize CRY1/2 levels and exhibit antitumor effects in GSCs. Administration of KL001 enhances GSC apoptosis and reduces migration and proliferation. In addition, SR9009, a circadian rhythm-modulating drug, alters tumor metabolism by increasing lipid droplet size in T98G cells and reducing the expression of genes involved in glycolysis, the TCA cycle, and lipid metabolism in GSCs (127, 128).

Immunotherapy.

Cancer's ability to suppress the immune response is a key hallmark, and GBM exemplifies this through its immunosuppressive tumor microenvironment. Although the brain possesses immune surveillance mechanisms that activate under pathogenic conditions, brain tumors like GBM actively suppress these responses (129–131). GBM is classified as a "cold" tumor due to its limited immune response, enriched with cells that inhibit antitumor immunity by reducing T cell and dendritic cell migration and activity. These adaptations allow GBM to escape immune detection and develop resistance (132). Among GBM cells, GSCs exhibit unique features, including self-renewal, tumor progression, and resistance to standard treatments, making them particularly challenging therapeutic targets (133–135). The pathways driving GSC resistance and tumorigenesis vary among patients, complicating the development of universal treatment strategies. These challenges have spurred interest in next-generation cancer therapies like immunotherapy, which offers a promising alternative for targeting GSCs by leveraging the immune system.

Immunotherapy reduces and eliminates the immunosuppressive effects of GSCs through approaches such as monoclonal antibodies (mAbs) or by stimulating the patient's immune response. Rather than directly targeting tumor cells, immunotherapy enhances the immune system's specificity and strength against cancer cells (136). Numerous clinical trials have demonstrated the potential of immunotherapeutic approaches in GBM treatment. These include monoclonal antibodies, cytokines, vaccines, immune checkpoint inhibitors, oncolytic viruses, and cell-based delivery systems. Their effectiveness may stem from enhanced suppression of GSCs and the targeted engagement of stem cell antigens to bolster antitumor immunity (137–139). Immunotherapeutic strategies for glioblastoma have been extensively examined in previous literature (140, 141). In this review, we concentrate on studies and trials specifically targeting cancer stem cells and GSCs (Table 1).

T and NK cell-based therapies. Adoptive immunotherapy involves manipulating a patient's immune cells ex vivo to target glioma antigens before reintroducing them into the patient. This strategy leverages the body's immune system to combat GSCs and prevent tumor growth and progression (142, 143). The use of cytotoxic T lymphocytes (CTLs) has shown promise in targeting tumor-associated antigens. CTLs are isolated from the patient, selected for antitumor specificity, expanded ex vivo, and then reintroduced into the patient to attack cancer cells (Fig. 3). However, the effectiveness of CTL-mediated GSC targeting has not yet been evaluated in a large-scale clinical trials (144, 145). NK cell-based therapies are less common but hold significant promise due to NK cells' ability to recognize transformed cells without the need for specific antigens. This broad recognition minimizes damage to healthy cells (146). CAR-NK cells, which are genetically engineered to target cancer-specific antigens like chimeric antigen receptor-T (CAR-T) cells (Fig. 3), represent an emerging strategy to combat chemotherapy-resistant GSC populations (147–149).

Chimeric antigen receptor (CAR)-T cell therapy has been intensively studied in cancer immunotherapy in recent years (150). This strategy involves engineering T cells with CARs to recognize specific antigens, enhancing their ability to bind and destroy cancer cells. CARs combine antigen-binding and T cell-activating properties, enabling precise targeting of tumor cells (151). CAR-T cell therapy works by increasing the interaction between malignant cells and T cells and regulating the secretion of various interleukins (ILs) in the tumor

Table 1. *Recent clinical trials focusing on targeting glioma stem cells*

Category	Intervention	ROA	Disease	Phase	Trial Number
Mapping tumor stem cells	Glioma stem cell marker GlioStem	N/A	High-grade glioma	Obs.	NCT 05556486
Vaccine	Dendritic cells loaded with brain tumor stem cells	Intradermal	Recurrent gioblastoma, ependymoma, or medulloblastoma	Phase I	NCT 01171469
	Dendritic cell vaccine	Intradermal	Newly diagnosed or recurrent glioblastoma	Phase I	NCT 02010606
	Dendritic cells transfected with mRNA from autologous tumor stem cells	Intradermal	Glioblastoma	Phase II/III	NCT 03548571
	Dendritic cell vaccine with mRNA from tumor stem cells	Intradermal	Glioblastoma	Phase I/II	NCT 00846456
	Dendritic cell vaccine with mRNA from tumor stem cells	Intradermal	Glioblastoma	Phase I	NCT 00890032
	Dendritic cell vaccine with mRNA from tumor stem cells	Intradermal	Glioblastoma	Phase I/II	NCT 00846456
	Dendritic vaccine, allogeneic hematopoietic stem cells, cytotoxic lymphocytes	DC: subcutaneous HSC: intervertal CTL: intrathecal	Glioblastoma	Phase II/III	NCT 01759810
Immunotherapy + vaccine	PD-1 antibody (Carilizumab) + autologous glioblastoma stem-like cell antigens-primed dentiritic cell vaccines	N/A	Glioblastoma	Phase II	NCT 04888611
Chemotherapy	Liposomal encapsulated Ara-C (DepoCyt)	Intraventricular	Glioblastoma	Phase I/II	NCT 01044966
	Diagnostic ChemoID assay + chemotherapy	Intravenous	Glioblastoma	Phase III	NCT 03632135
	Cancer stem cell high-throughput drug screening + combination drug therapy	N/A	Glioblastoma	Phase I	NCT 02654964
	Cancer stem cell high-throughput drug screening + combination drug therapy	N/A	Newly diagnosed glioblastoma	Early Phase I	NCT 05380349
	Cancer stem cell high-throughput drug screening + combination drug therapy	N/A	Glioblastoma	Early Phase I	NCT 05043701

CTL, cytotoxic T lymphocytes; DC, dendritic cells; HSC, hematopoietic stem cell; ROA, route of administration.

microenvironment (152). Extensive research over many years has led to modification and improvement of the CAR structure. These modifications aim to strengthen signaling pathways and promote targeted cytokine release. Each CAR-T generation contains different stimulatory components that can elicit different cytokine responses (153).

Due to the high incidence of hematological malignancies and their specific cell surface markers (CD19), these malignancies have become the focus of CAR-T cell therapy. Although initial CAR-T clinical trials focused on hematological malignancies, recent studies have explored CAR-T therapy in solid tumors like glioblastoma. There are many CAR-T cell therapy clinical trials performed on solid tumors, including glioblastoma (154), hepatocarcinoma (155), gastric cancer (156), lung cancer (157), renal cancer (158), and prostate cancer (159).

In CAR-T cell therapy for solid tumors, many antigens such as human epidermal growth factor receptor 2 (HER2), interleukin-13 receptor subunit α-2 (IL-13Rα2), GD2, ROR1, EGFR, EGFRvIII, CEA, CD133, and MUC1 have been targeted in clinical studies (154, 160–162). Targeted studies of CAR-T cell therapy specifically for glioblastoma have revealed promising results on the targetability of brain tumors. This therapy targets glioblastoma-specific antigens, including EGFR wt, EGFRvIII, and interleukin-13 receptor subunit α-2 (IL-13Rα2) (163, 164). CAR-T cells can infiltrate glioblastoma, become activated in the glioblastoma microenvironment, and activate a variety of adaptive cellular responses in patients. However, due to the heterogeneity of glioblastoma, loss of tumor antigens during tumor progression, exhaustion of CAR-T cells in the TME, activation of compensatory adaptive resistance mechanisms, and upregulation of immunosuppression, CAR-T cells need to be combined with other treatments. In addition to CAR-T therapy being given in combination with other treatments, CAR-T cells targeting multiple different antigens also offer an improved treatment option. Preclinical studies show that trivalent CAR-T cells that together target human epidermal growth factor receptor 2 (HER2), IL-13Rα2, and EPH receptor A2 (EphA2) are more effective than bivalent or monovalent CAR-T cells (165–167).

Stem cell-based therapies.

Stem cell-based therapies are emerging as innovative and promising strategies, particularly for solid tumors like GBM. These therapies aim to overcome the limitations of conventional treatments by combining targeted therapeutic approaches with cell-based delivery systems to enhance clinical outcomes (168). Using genetic engineering tools—

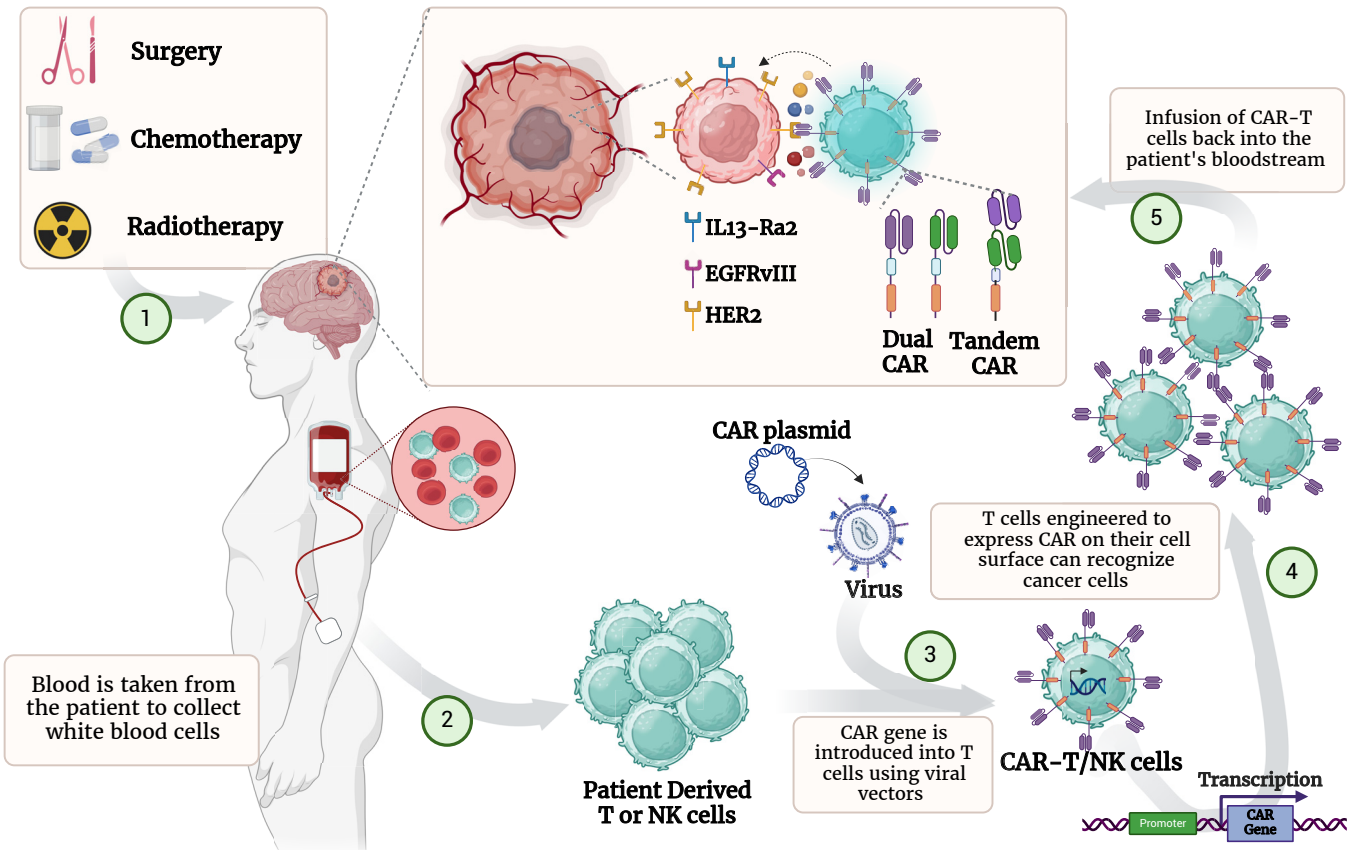

Figure 3. Potential chimeric antigen receptor-T (CAR-T)/natural killer (NK) cell therapy route to target glioma stem cells (GSCs). Chimeric antigen receptor-T/NK cell therapy is a treatment method in which T/NK cells obtained from the patient are genetically modified in a laboratory environment to bind to certain antigens on cancer cells and kill them. The pioneering approach can be adapted to target GSCs. Therapy schedule composed of subsequent procedures. Primarily, standard treatment methods including surgery, chemotherapy, and radiotherapy are applied to the patients (*1*). Blood is taken from the patient to collect white blood cells (*2*). CAR gene is introduced into T cells using viral vectors (*3*). T cells engineered to express CAR (variable) on their cell surface can recognize cancer cells (*4*). Infusion of CAR-T cells back into the patient's bloodstream (*5*).

such as viral or nonviral delivery of targeted therapeutics, shRNA/miRNA regulation, CRISPR/Cas gene editing, oncolytic virotherapy, nanoparticles, and photodynamic therapy—this approach seeks to reduce tumor burden and improve survival of patients with GBM, either directly or as an adjuvant therapy (Fig. 4).

In this context, stem cell-based therapies may potentially be effective to address challenges hard to treat GSCs due to the feasible properties of stem cells such as tumor tropism, multimodality, and continuous onsite microfabrication of therapeutics.

Stem cells can be modified and served as a vehicle to target GSCs in several ways such as anti-GSC micro RNA (miRNA) delivery. One possible candidate is miR-302-367 cluster to decrease tumors. Primary glioma cells have been modified to express miR-302-367 consistently under cancer-against-cancer approaches. Surprisingly, these cells changed the expression of stemness markers, the proliferation, and the tumorigenicity of nearby glioblastoma cells in a paracrine-dependent manner. Additional analysis of the secretome produced by cells expressing miR-302-367 revealed that a significant portion of the protein was encased in exosomes, which the nearby glioblastoma cells ingested. Targets of miR-302-367, including CXCR4/SDF1, SHH, cyclin D, cyclin A, and E2F1, were inhibited as a result of this cell-to-cell transfer. Mice brain tumor development was effectively redirected by an orthotopic xenograft of glioblastoma stem-like cells coexpressing miR-302-367 (169).

Bone morphogenetic protein 4 (BMP4), a pivotal factor during embryogenesis, has demonstrated efficacy in suppressing GSC tumorigenicity. Direct delivery of BMP4 into the tumor microenvironment using BMP4-coated acrylic beads improved survival in glioma-bearing animals. In one study, more than 75% of tumor-bearing mice became tumor-free after systemic injection of human adipose-derived mesenchymal stem cells (hAMSCs) transduced with a retroviral vector expressing BMP4 (170).

Recent approaches focus on engineering stem cells to deliver bacterial toxin fusions that disrupt cellular translation machinery. Pseudomonas exotoxin (PE)-fused recombinant proteins have been explored as treatments for GBM, but systemic toxicity, short therapeutic half-life, and off-target effects have hindered clinical translation. To address these challenges, toxin-resistant human neural stem cells were engineered to secrete PE-cytotoxins targeting EGFR (Nb-PE) or IL13Rα2 (IL13-PE), which are expressed on GBM cells, including GSCs. Stem cell-based delivery of IL13-PE significantly improved long-term survival in a GBM resection mouse model compared with direct infusion of recombinant IL13-PE. This strategy effectively

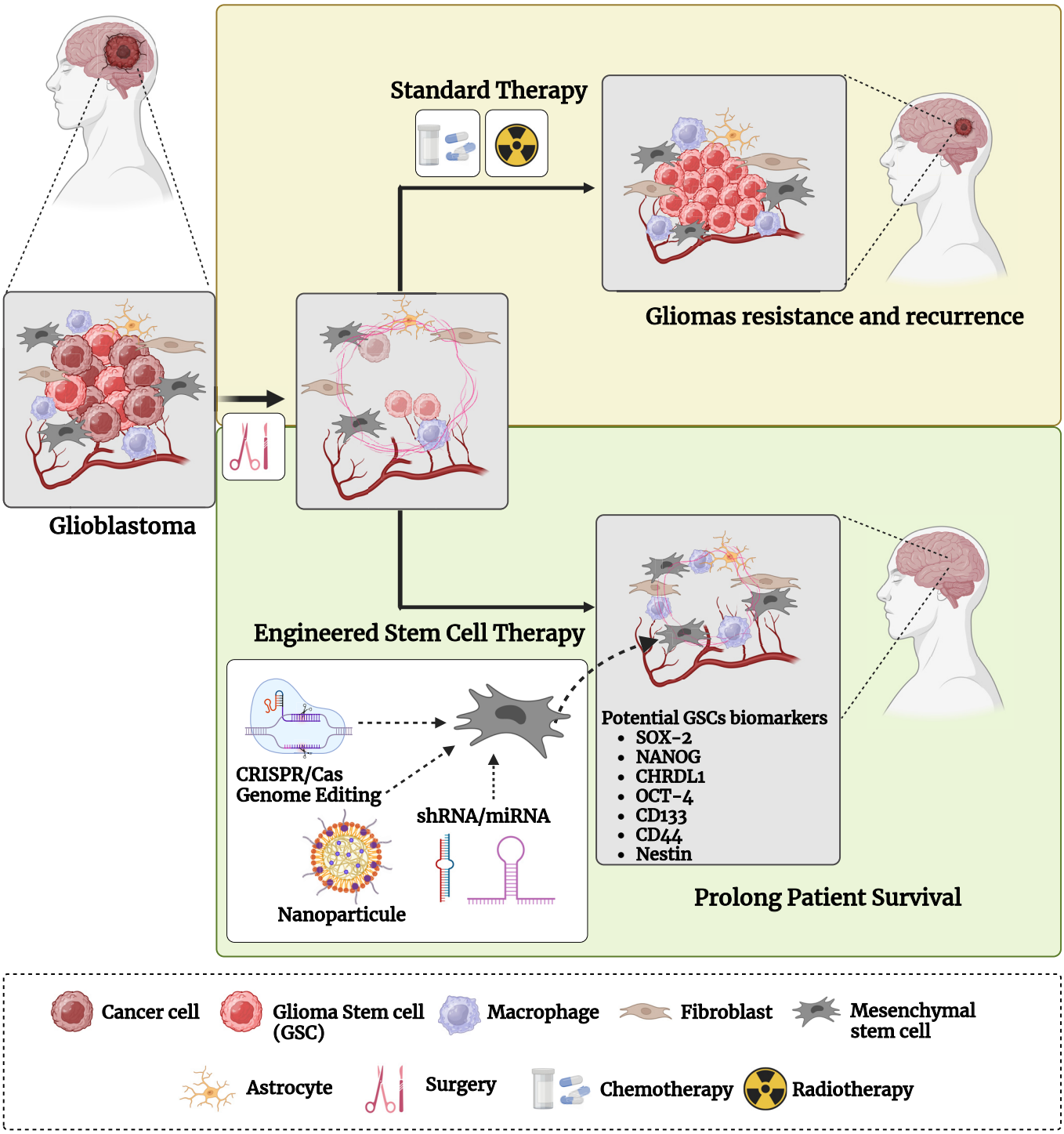

Figure 4. Stem cell-based glioma stem cell (GSC) targeting therapy approach. Stem cells can be engineered to target GSCs using several technical tools such as CRISPR/Cas gene editing, shRNAs, miRNAs, nanoparticles etc., which may block or lower the rate of tumor relapse and result in prolonged patient survival.

targets residual GSC populations responsible for tumor recurrence, highlighting its clinical potential (171).

DISCUSSION

Conventional GBM treatments often fail to achieve durable outcomes, particularly regarding recurrence and long-term survival. Despite initial responses to surgery, radiation, and chemotherapy, GBM frequently recurs, resulting in a dismal prognosis. This recurrence is largely driven by GSCs, which possess unique cellular and molecular characteristics that confer therapy resistance and promote tumor regrowth. GSCs contribute to recurrence through enhanced DNA repair mechanisms, activation of prosurvival signaling pathways

(e.g., PI3K/AKT and Notch), and evasion of apoptosis. In addition, their ability to exploit the tumor microenvironment and undergo epithelial-mesenchymal transition (EMT) enables invasion and resistance to conventional treatments.

Targeting GSCs is pivotal for improving GBM outcomes by addressing the root cause of recurrence. Developing therapies that specifically disrupt GSC survival and signaling pathways could significantly enhance survival rates.

Several innovative approaches have been explored to combat GBM recurrence. For instance, a prospective biomedical study (NCT01872221) demonstrated that magnetic resonance spectroscopy imaging can identify metabolic tumor regions likely to recur, marked as Choline-to-N-Acetylaspartate Index (CNI)+ areas. Biopsies from CNI+ areas generated GSC-enriched neurospheres faster than those from CNI− regions and were associated with poorer patient outcomes. This study underscores the importance of detecting glioma stem cell burden and tailoring treatments accordingly (172).

Similarly, a randomized phase III clinical trial (NCT03632135) evaluated the ChemoID assay, a clinically validated personalized tool for identifying CSC-targeted cytotoxic therapies. This assay enhances survival by identifying optimal chemotherapeutic agents or combinations targeting both bulk tumor cells and GSCs. Additional studies have corroborated the utility of ChemoID in improving survival outcomes in recurrent and advanced gliomas (173–176).

Other clinical trials (NCT02654964, NCT05380349, and NCT05043701) have investigated Cancer Stem Cell High-Throughput Drug Screening (CSC-HTS), which facilitates personalized drug combinations to target CSCs and delay tumor progression. Personalized approaches revealed by HTS could serve as a critical step in precision medicine, addressing patient-specific drug sensitivities (177–179).

FUTURE PERSPECTIVES

Future research should focus on multitargeted therapies to address the interconnected and redundant signaling pathways within GSCs. Simultaneous suppression of multiple pathways could enhance therapeutic efficacy and circumvent resistance mechanisms. Moreover, integrating targeted therapies with standard treatments like radiation and chemotherapy may yield synergistic effects, improving patient outcomes.

Overcoming the blood-brain barrier (BBB) remains a significant challenge in delivering effective drugs to GSCs. Innovative strategies to improve BBB penetration, such as nanoparticle-based delivery systems, could enhance therapeutic efficiency. In addition, the development of noninvasive biomarkers for early detection and monitoring treatment response will play a crucial role in optimizing GBM management.

Emerging therapies targeting circadian clock genes, such as those involving miR-302-367, BMP4, and stem cell-mediated delivery of Pseudomonas exotoxin (PE)-cytotoxins, show substantial promise. These approaches have demonstrated potential not only for slowing tumor progression but also for improving survival rates. Their practical implementation could transform current treatment paradigms into more focused, less toxic strategies.

Personalized medicine is crucial for tackling the heterogeneity of GBM and GSC biomarkers. Molecular profiling has revealed significant variability in genetic alterations and signaling pathways among patients. Techniques such as transcriptomics, immunophenotyping, and epigenetic profiling expand the scope of precision medicine beyond traditional genomic approaches. These innovations enable the development of therapies tailored to individual patient profiles, improving efficacy while minimizing off-target effects.

In addition, CAR-T/NK immunotherapy models and stem cell-based delivery options offer new avenues for combating GBM recurrence. CAR-engineered immune cells can directly or indirectly target GSCs, whereas stem cells can serve as multimodal delivery vehicles. Used as adjuvant therapies, these strategies may significantly enhance primary treatments, paving the way for improved survival rates.

In conclusion, advancing basic research and clinical trials focused on GSCs will provide innovative solutions to overcome GBM recurrence. These efforts have the potential to transform glioblastoma management, offering patients more effective, tailored treatment options that address the underlying molecular drivers of this challenging disease.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

S.M.E., B.S.K., and N.K. conceived and designed research; S.M.E., B.S.K., R.K., and H.B.Ş. prepared figures; S.M.E., B.S.K., R.K., H.B.Ş., B.S., and N.K. drafted manuscript; S.M.E., B.S.K., R.K., H.B.Ş., and N.K. edited and revised manuscript; S.M.E., B.S.K., R.K., H.B.Ş., B.S., and N.K. approved final version of manuscript.

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