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Review

Therapeutic Targets in Glioblastoma: Molecular Pathways, Emerging Strategies, and Future Directions

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Abstract: Glioblastoma (GBM) is the most aggressive primary brain tumor in adults, characterized by rapid growth, invasive infiltration into surrounding brain tissue, and resistance to conventional therapies. Despite advancements in surgery, radiotherapy, and chemotherapy, median survival remains approximately 15 months, underscoring the urgent need for innovative treatments. Key considerations informing treatment development include oncogenic genetic and epigenetic alterations that may dually serve as therapeutic targets and facilitate treatment resistance. Various immunotherapeutic strategies have been explored and continue to be refined for their anti-tumor potential. Technical aspects of drug delivery and blood-brain barrier (BBB) penetration have been addressed through novel vehicles and techniques including the incorporation of nanotechnology. Molecular profiling has emerged as an important tool to individualize treatment where applicable, and to identify patient populations with the most drug sensitivity. The goal of this review is to describe the spectrum of potential GBM therapeutic targets, and to provide an overview of key trial outcomes. Altogether, the progress of clinical and preclinical work must be critically evaluated in order to develop therapies for GBM with the strongest therapeutic efficacy.

Keywords: glioblastoma; molecular pathways; targeted therapy; immunotherapy; epigenetic modulation; tumor microenvironment; blood-brain barrier; nanotechnology; CAR T-Cell therapy; oncolytic viruses; MGMT Promoter Methylation; gene therapy; combination therapies; biomarkers; drug delivery systems

1. Introduction

GBM, classified by the World Health Organization (WHO) as an IDH wild-type grade IV astrocytoma, is the most aggressive primary brain tumor in adults [1]. Originating from glial cells, GBMs are characterized by rapid proliferation, diffuse infiltration into surrounding brain tissue, extensive angiogenesis, and pronounced genomic instability [2]. The heterogeneous nature of these tumors encompasses a wide spectrum of genetic, epigenetic, and phenotypic variations among tumor cells, contributing to their complex biology and resistance to therapy [3].

Globally, GBM represents about 15% of all primary brain and central nervous system (CNS) tumors and about 45% of malignant brain tumors [5]. The annual incidence is about 3.2 per 100,000, making GBM the most common primary brain malignancy in adults [6]. GBM mainly occurs between ages 45 and 70 and is slightly more common in males [7].

The prognosis for GBM remains poor despite aggressive treatment. The median overall survival is approximately 14 to 16 months following standard therapy, with a two-year survival rate of about 26% and a five-year survival rate less than 10% [9]. Factors influencing prognosis include patient age, performance status, extent of surgical resection, and molecular markers such as O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status [10]. The current standard care for GBM is maximal safe resection followed by radiotherapy and chemotherapy [9].

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Despite aggressive multimodal therapy, GBM invariably recurs. Recurrent potential arises from the inability to achieve complete surgical resection, dissemination of tumor cells beyond the primary tumor site [13], resistance to radiotherapy and chemotherapy, the immune-suppressive tumor microenvironment, and the challenge of delivering therapeutic agents across the blood-brain barrier (BBB) [14]. The presence of intra-tumoral heterogeneity, with distinct clonal populations within different regions of the same tumor, poses an additional consideration for treatment efficacy and subsequent resistance due to the potential for clonal selection following treatment.

2. Molecular Pathogenesis of GBM

The distinct molecular profile of GBM contributes to disease pathogenesis. Molecular-level alterations can also serve as important therapeutic targets. GBM is characterized by a complex array of genetic mutations and epigenetic modifications that drive its aggressive phenotype. Key genetic alterations include mutations in TP53, PTEN, and EGFR, each contributing to the disruption of critical cellular processes [26]. TP53 is a key regulator of genomic stability. TP53 mutations, observed in approximately 31–38% of cases, impair DNA repair, cell cycle arrest, and apoptosis [27]. These mutations are more common in secondary GBMs but also occur in primary GBMs [28]. PTEN mutations, present in 24–37% of GBMs, are mainly present in primary GBMs and lead to unchecked activation of the PI3K/AKT signaling pathway, promoting cell growth and survival by inhibiting apoptosis [29]. EGFR amplification and mutations are observed in 36–60% of primary GBMs, with the EGFRvIII variant present in 20–50% of EGFR-amplified cases [30]. This variant results from a deletion in the extracellular domain and produces constitutive receptor activation, leading to downstream proliferation, survival, and angiogenesis [31]. Mutations are detailed in Table 1.

Table 1. Common Genetic Mutations and Epigenetic Modifications in GBM.

Genetic Mutation/Epigenetic Modification	Frequency in GBM (% of Cases)	Impact on Tumor Biology	Potential Approaches under Investigation
TP53 Mutations	31–38% overall; up to 65% in secondary GBMs	Disrupts cell cycle control and apoptosis	Potential for therapies targeting p53 pathways
PTEN Mutations	24–37% (mainly in primary GBMs)	Activates PI3K/Akt signaling, promoting proliferation and survival	Use of PI3K/Akt pathway inhibitors
EGFR Amplification and Mutations	36–60% in primary GBMs; EGFRvIII in 20–50% of amplified cases	Enhances cell growth via receptor activation	EGFR inhibitors and antibodies targeting EGFRvIII variant
NF1 Mutations or Deletions	15–17%	Affects RAS/MAPK signaling pathways	Therapies targeting RAS/MAPK components
PIK3CA and PIK3R1 Mutations	PIK3CA: 7–10%; PIK3R1: 7–8%	Activates PI3K/Akt pathway	PI3K inhibitors
RB1 Mutations	8–13%	Impairs cell cycle	CDK inhibitors

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		regulation via retinoblastoma pathway	targeting cell cycle dysregulation
CDKN2A Deletion (p16^INK4) and p14^ARF)	31–78% in primary GBMs	Loss of cell cycle inhibition, increased proliferation	CDK4/6 inhibitors; restoring cell cycle checkpoints
ATRX Mutations	Common in secondary GBMs and lower-grade gliomas	Involved in telomere maintenance	Targeting telomere elongation mechanisms
TERT Promoter Mutations	58% in primary; 28% in secondary GBMs	Increases telomerase activity (anti-senescence),	Telomerase inhibitors
MGMT Promoter Hypermethylation	36% in primary; 75% in secondary GBMs	Reduces DNA repair capacity; better response to alkylating agents	Predictive biomarker for temozolomide efficacy
Hypermethylation of Tumor Suppressor Genes	RB1: 14% primary, 43% secondary; CDKN2A-p14^ARF: 6% primary, 31% secondary	Silencing of genes critical for cell cycle and apoptosis	Use of demethylating agents to reactivate tumor suppressor genes
Loss of Heterozygosity (LOH) on Chromosome 10	Up to 70% in primary GBMs	Associated with PTEN loss; contributes to tumor progression	Important to target PTEN pathway
Chromosome 9p21 Deletion	31–78% in primary GBMs	Loss of CDKN2A locus, leading to cell cycle dysregulation	Need for therapies targeting cell cycle control

Epigenetic changes, such as DNA methylation and histone modifications, play a crucial role in GBM pathogenesis (34, 35, 36). Methylation of the MGMT promoter reduces the expression of the MGMT enzyme responsible for repairing alkylated DNA [37,38]. Patients with MGMT promoter methylation accordingly exhibit increased sensitivity to the alkylating chemotherapy temozolomide

GBM cells exploit several signaling pathways to support their malignant behavior, providing opportunities for targeted therapeutic interventions [41]. The PI3K/Akt/mTOR pathway is central to regulating cell growth, survival, metabolism, and angiogenesis [42]. Activation occurs through receptor tyrosine kinases (RTKs) like EGFR and PDGFR [43]. In GBM, aberrant activation of this pathway is common due to genetic alterations in PTEN, PIK3CA, or amplification of RTKs, leading to increased protein synthesis, inhibition of apoptosis, and promotion of cell cycle progression [44]. The Mitogen-Activated Protein Kinase (MAPK) pathway is another critical signaling cascade involved in cell proliferation and differentiation [45]. While mutations leading to constitutive activation of this pathway are less common in GBM, they can result from upstream RTK activation, and cross-talk between the PI3K/Akt/mTOR and MAPK pathways contributes to tumor growth and resistance mechanisms [46].

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Additionally, developmental signaling pathways such as Notch, Wnt/β-catenin, and Hedgehog are implicated in maintaining cancer stem cells (CSCs) within GBM, which contribute to tumor development , resistance to therapy, and recurrence [47]. The Notch pathway promotes cell survival and self-renewal, supporting the maintenance of CSCs when overactivated in GBM [48]. Dysregulation of the Wnt/β-catenin pathway leads to increased β-catenin levels and transcription of oncogenic targets [49], while the Hedgehog pathway influences stem cell maintenance and has been associated with GBM aggressiveness [50]. Table 2 provides an overview of some key signaling pathways in GBM and associated targeted therapies.

Table 2. Key Signaling Pathways in GBM and Potential Therapeutic Targets.

Signaling Pathway	Key Components	Role in GBM Progression	Potential Targeted Therapies
p53 Pathway	TP53 gene, MDM2, p21	Regulates cell cycle and apoptosis; mutations lead to uncontrolled cell proliferation and impaired cell death	MDM2 inhibitors (e.g., RG7112), compounds restoring p53 function (e.g., PRIMA-1)
PI3K/AKT/mTOR Pathway	PI3K (PIK3CA), AKT, mTOR, PTEN	Promotes cellular growth, survival, and metabolism; frequently activated due to PTEN loss or PIK3CA mutations	PI3K inhibitors (e.g., BKM120), AKT inhibitors (e.g., perifosine), mTOR inhibitors (e.g., everolimus)
EGFR Pathway	EGFR, EGFRvIII mutant, downstream effectors (RAS, AKT)	Enhances tumor cell proliferation and survival; EGFR amplification/mutation leads to constitutive activation	EGFR tyrosine kinase inhibitors (e.g., erlotinib), monoclonal antibodies, vaccines targeting EGFRvIII
NF-κB Pathway	NF-κB proteins (p65, p50), IκB kinase (IKK) complex	Drives inflammation, promotes tumor growth and resistance to apoptosis	NF-κB inhibitors (e.g., parthenolide, BAY 11-7082)
Wnt Signaling Pathway	Wnt ligands, Frizzled receptors, β-catenin	Regulates cell proliferation and differentiation; aberrant activation contributes to tumor aggressiveness	Wnt pathway inhibitors (under investigation)
TERT Pathway	Telomerase reverse transcriptase (TERT)	Maintains telomere length, allowing unlimited cell division	Telomerase inhibitors, TERT-targeted therapies
CDKN2A/pRB Pathway	CDKN2A gene (p16^INK4A, p14^ARF), RB1 protein	Controls cell cycle progression; loss leads to unchecked proliferation	CDK4/6 inhibitors (e.g., palbociclib), strategies to restore pathway function

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c-Met Pathway	c-Met receptor, hepatocyte growth factor (HGF)	Promotes cell growth, invasion, and angiogenesis	c-Met inhibitors (e.g., crizotinib, cabozantinib), monoclonal antibodies (e.g., onartuzumab)
FGFR Pathway	FGFR receptors, FGF ligands	Involved in cell proliferation and survival; less commonly altered in GBM	FGFR inhibitors (e.g., futibatinib, pemigatinib)
BRAF Pathway	BRAF kinase (V600E mutation)	Activates MAPK/ERK pathway, promoting growth	BRAF inhibitors (e.g., dabrafenib, vemurafenib)
Src Pathway	Src family kinases	Facilitates proliferation and invasion	Src inhibitors (e.g., dasatinib)
RAS/MAPK Pathway	RAS proteins, RAF, MEK, ERK	Controls cell proliferation and differentiation; overactivation leads to tumor growth	MEK inhibitors, oncolytic viruses targeting RAS pathway
MGMT	O6-Methylguanine-DNA methyltransferase	Repairs DNA damage from alkylating agents;	MGMT inhibitors,
VEGF Signaling	Vascular endothelial growth factor (VEGF), VEGF receptors	Stimulates angiogenesis, supporting tumor vascularization	Anti-VEGF therapies (e.g., bevacizumab)
TGF-β Pathway	Transforming growth factor-beta (TGF-β)	Promotes invasion and immunosuppression	TGF-β inhibitors (e.g., galunisertib)
HDAC Pathway	Histone deacetylases	Epigenetic regulation; overactivity leads to aberrant gene expression	HDAC inhibitors (e.g., vorinostat, panobinostat)
Notch Pathway	Receptors (Notch1–4), Ligands (Dll1, Dll3, Dll4, Jagged1–2), γ-secretase, RBPJK	Maintains GSCs, promotes treatment resistance, drives tumor growth, angiogenesis, and stemness under hypoxia.	GSIs (DAPT, RO4929097), ASIs (INCB3619), miRNAs (miR-34a, miR-181c), Arsenic trioxide, Tipifarnib, CB-103
Hedgehog pathway	Sonic Hedgehog (SHH), Patched (PTCH1/2), Smoothened (SMO), GLI1/2/3	Regulates tumor growth, stem cell maintenance, drug resistance, and promotes angiogenesis and invasion.	SMO inhibitors (e.g., Vismodegib, Sonidegib), GLI inhibitors (e.g., GANT-61), combination therapies to overcome resistance.

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MAPK Pathway	EGFR, PDGFRA, BRAF, MAPK kinases	Promotes cell proliferation, survival, and therapy resistance via pathway hyperactivation (High MAPK activity correlates with poor survival and increased tumor aggressiveness)	MAPK inhibitors (e.g., BRAF inhibitors); potential for combination therapies targeting MAPK and PI3K/AKT pathways.

The GBM tumor microenvironment (TME) also plays an important role in disease pathogenesis. The TME contains a complex network of cellular, molecular, and biochemical interactions that can facilitate tumor growth and resistance to therapy [51], but also shape many of the key signaling pathways implicated in GBM progression. Consequently, understanding how the TME influences aberrant signaling within tumor cells is essential for identifying effective therapeutic targets. Hypoxia within tumors results from rapid cell proliferation outpacing new blood vessel development [52]. Stabilization of hypoxia-inducible factors (HIFs) under low oxygen conditions leads to upregulation of vascular endothelial growth factor (VEGF), stimulating angiogenesis and creating abnormal, leaky vasculature that contributes to tumor growth and invasion [53]. GBM also alters the TME composition through immunoevasive strategies , including the secretion of immunosuppressive cytokines like transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10) [54], upregulation of programmed death-ligand 1 (PD-L1) on tumor cells to inhibit T-cell function [55], and recruitment of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) to suppress anti-tumor immunity [56]. Interactions with surrounding stroma support tumor growth. Astrocytes can provide metabolic support and survival factors [57], microglia and macrophages can be co-opted to a tumor-promoting phenotype [58], and matrix metalloproteinases (MMPs) can degrade the extracellular matrix to facilitate invasion [59].

3. Emerging Therapeutic Targets Under Investigation

3.1. Targeting Growth Factor Receptors

Targeting growth factor receptors, such as the epidermal growth factor receptor (EGFR), has been an important focus of investigation due to the relatively high incidence of alterations in GBM [30]. Monoclonal antibodies like cetuximab are designed to bind to the extracellular domain of EGFR, blocking ligand binding and receptor activation [60]. However, their efficacy is limited by effective BBB penetration and the heterogeneity of EGFR mutations across different tumor regions [61]. Small molecule tyrosine kinase inhibitors like erlotinib inhibit EGFR activity by competing with ATP binding [62]. However, clinical trials have shown limited success due to insufficient central nervous system (CNS) drug delivery and resistance mechanisms like PTEN loss [45,79].

3.2. Signal Transduction Pathway Inhibitors

Inhibitors targeting the frequently activated PI3K/Akt/mTOR pathway are under exploration [42]. Agents such as rapamycin analogs (e.g., everolimus) can reduce cell proliferation and induce autophagy [64]. However, their clinical efficacy is often limited due to feedback activation loops and incomplete pathway inhibition [65]. To overcome resistance mechanisms, dual PI3K/mTOR inhibitors are being studied [66]. MEK and ERK inhibitors, like trametinib, are also under evaluation, particularly in tumors with specific mutations or as part of combination therapies [67].

3.3. Epigenetic Modulators

Epigenetic modulators have emerged as promising therapeutic agents in GBM treatment [37]. Histone deacetylase (HDAC) inhibitors like vorinostat modify chromatin structure to alter gene expression, reactivating tumor suppressor genes and inducing apoptosis [68]. These agents are

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attractive due to their ability to cross the BBB [69]. DNA methyltransferase (DNMT) inhibitors such as azacitidine aim to demethylate DNA and restore normal gene function [70]. Clinical trials are ongoing to determine their efficacy and safety in patients with GBM.

3.4. Immunotherapy

Immunotherapy represents a rapidly evolving frontier in GBM treatment. While no immunotherapy has achieved regulatory approval for GBM to date, numerous approaches are under active investigation, including immune checkpoint inhibitors (ICIs), chimeric antigen receptor (CAR) T-cell therapies, therapeutic vaccines, oncolytic viruses, cytokine-based strategies, and agents targeting the immunosuppressive tumor microenvironment, such as tumor-associated macrophages (TAMs) [71].

3.5. Immune Checkpoint Inhibitors (ICIs)

The immunosuppressive tumor microenvironment of GBM blunts effective antitumor immune responses by various mechanisms, including the upregulation of immune checkpoints. Common inhibitory receptors such as programmed cell death-1 (PD-1), programmed cell death-ligand 1 (PD-L1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), lymphocyte-activation gene 3 (LAG-3), and T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) play pivotal roles in dampening T-cell activity within GBM [72].

3.5.1. PD-1/PD-L1 Blockade

Agents like nivolumab and pembrolizumab block PD-1, restoring T-cell function and potentially improving tumor cell clearance. Despite encouraging efficacy in other solid tumors, trials in GBM have been disappointing. For example, phase III trials combining nivolumab with standard therapy did not improve overall survival compared to historical controls. The lack of success highlights the formidable immunosuppressive milieu and the necessity of careful patient selection, rational combination therapies, and novel trial designs [73].

3.5.2. CTLA-4 Inhibition

Ipilimumab, a CTLA-4 blocking antibody, has shown limited efficacy in GBM. Unlike PD-1 blockade, CTLA-4 inhibition often leads to more global immune activation and higher rates of immune-related adverse events. Combinations of PD-1 and CTLA-4 inhibitors, though potentially more efficacious, also face toxicity and tolerability challenges [74].

3.5.3. Next-Generation Checkpoints (LAG-3, TIM-3, and Others)

Targeting emerging checkpoints, including LAG-3, TIM-3, and others currently under exploration (e.g., TIGIT, VISTA), may overcome resistance to PD-1/CTLA-4 blockade. Early-phase trials are ongoing, evaluating whether simultaneous blockade of multiple inhibitory receptors can more effectively penetrate GBM's robust immune defenses [75].

3.6. Chimeric Antigen Receptor (CAR) T-Cell Therapy

CAR T-cell therapies genetically engineer patient-derived T cells to recognize specific antigens on GBM cells. The success of CAR T-cells in hematological malignancies has spurred interest in solid tumors, including GBM.

Established Targets

Early CAR T-cell trials focused on EGFR variant III (EGFRvIII), which is frequently mutated in GBM, as well as on interleukin-13 receptor α2 (IL13Rα2). While clinical responses have been

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observed, durable remissions are rare, likely due to heterogeneous antigen expression, T-cell exhaustion, and the highly immunosuppressive GBM microenvironment [76].

3.7. Vaccines and Peptide-Based Immunotherapies Under Investigation Vaccines Aim to Induce or Enhance an Endogenous, Tumor-Specific Immune Response

3.7.1. Peptide-Based Vaccines

Peptide vaccines targeting tumor-associated antigens (TAAs) or neoantigens unique to GBM cells (e.g., EGFRvIII) represent a promising strategy. By focusing on mutations not found in normal tissue, these vaccines minimize the risk of off-target effects and maximize tumor specificity [78].

3.7.2. Dendritic Cell (DC) Vaccines

DC vaccines involve loading patient-derived DCs with tumor peptides, lysates, or mRNA to present TAAs to T cells. Clinical trials have shown that dendritic cell (DC) vaccines can induce robust immune responses and may prolong survival in select patient populations [79]. Notably, a recent phase 3 prospective, externally controlled trial of an autologous tumor lysate-loaded DC vaccine (DCVax-L) in newly diagnosed and recurrent glioblastoma reported significantly improved median overall survival compared to matched external controls. In newly diagnosed patients, median overall survival was extended to 19.3 months from randomization (22.4 months from surgery), compared to 16.5 months in controls, and in recurrent disease median overall survival was 13.2 months vs 7.8 months in controls. These findings highlight the potential of DC-based immunotherapy to improve outcomes in malignant brain tumors [79]. Ongoing research optimizes antigen selection, DC maturation protocols, and combination strategies with ICIs or radiotherapy to enhance vaccine efficacy.

3.7.3. Cell-Penetrating and Tumor-Targeting Peptides

Beyond classic vaccines, tumor-targeting peptides can selectively bind receptors overexpressed on GBM cells, serving as vehicles for diagnostics or targeted drug delivery. Cell-penetrating peptides (CPPs) offer an avenue for enhancing drug or gene therapy delivery directly into malignant cells, potentially improving therapeutic index [80].

3.8. Oncolytic Virus Therapies

Oncolytic viruses (OVs) are engineered to preferentially infect, replicate within, and lyse tumor cells. This not only causes direct oncolysis but also exposes TAAs to the immune system, potentially converting an immunosuppressive "cold" tumor into an "immunologically hot" one.

3.8.1. Virus Platforms

Genetically modified herpes simplex viruses (e.g., G207, G47Δ), adenoviruses (e.g., DNX-2401), and poliovirus derivatives (e.g., PVSRIPO) have demonstrated safety and suggested efficacy in early-phase clinical trials [81].

3.8.2. Mechanistic Synergies

OVs can be combined with ICIs or CAR T cells to enhance antitumor immunity. As OVs disrupt the tumor extracellular matrix and local immunosuppression, T cells and immune effector cells may gain improved access to cancer cells, leading to synergistic therapeutic effects [82].

3.9. Cytokine-Based Therapies

Cytokines can modulate the immune system's capacity to recognize and eliminate tumor cells. Interleukin-2 (IL-2) can activate and expand T-cell populations, while interferon-alpha (IFN-α) can

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exert antiproliferative effects and enhance antigen presentation [83]. However, cytokine therapies can be limited by systemic toxicity and the complexity of delivering these agents into the CNS. Investigational approaches include localized delivery methods, engineered cytokines with improved specificity, and combinations with other immunotherapies to reduce off-target effects.

3.10. Targeting the Tumor Microenvironment: Tumor-Associated Macrophages (TAMs)

GBM is characterized by a highly immunosuppressive microenvironment containing abundant TAMs, often skewed towards an M2-like, pro-tumorigenic phenotype that promotes angiogenesis, invasion, and resistance to therapy. Colony-stimulating factor-1 receptor (CSF-1R) inhibitors (e.g., PLX3397) target macrophage survival and polarization. Reducing the population of M2-like macrophages or reprogramming them towards an M1-like, antitumor state can enhance the efficacy of T-cell-based therapies and improve patient outcomes [84]. Strategies to combine TAM-targeting agents with CAR T cells, vaccines, or ICIs may yield synergistic effects, altering the overall tumor ecosystem to favor an effective antitumor immune response.

3.11. Targeting Tumor Metabolism

Targeting tumor metabolism offers a new therapeutic avenue. Glutaminolysis, the process by which glutamine is converted into glutamate and subsequently into α-ketoglutarate in the tricarboxylic acid (TCA) cycle, supports the bioenergetic and biosynthetic needs of rapidly proliferating tumor cells. Inhibiting glutaminase (GLS), the enzyme catalyzing the first step of glutaminolysis, has shown potential in suppressing tumor growth. Studies indicate that GBM tissues can be categorized into glycolytic-dominant and mitochondrial-dominant types, with the latter also being glutaminolysis-dominant. Therefore, targeting the glutaminolysis pathway may be particularly effective for mitochondrial-dominant GBMs. [85]. Additionally, metabolic reprogramming in GBM involves alterations in lipid metabolism, which contribute to tumor growth and survival. Targeting enzymes involved in fatty acid synthesis and oxidation pathways offers another avenue for therapeutic intervention. For instance, inhibitors of fatty acid synthase (FASN) have demonstrated efficacy in preclinical models by disrupting lipid biosynthesis essential for tumor cell membranes and signaling molecules. The researchers observed that treating GSCs with 20 μM cerulenin, a FASN inhibitor, led to a significant reduction in cell proliferation and invasiveness. Specifically, de novo lipogenesis decreased by approximately 40%, and the invasiveness of GSCs was reduced by 40–50% following cerulenin treatment. Additionally, the expression of stemness markers such as nestin, Sox2, and FABP7 decreased, while the differentiation marker GFAP increased [86]. Furthermore, ketogenic metabolic therapy (KMT) has been proposed as a potential treatment strategy for GBM. KMT aims to exploit the metabolic flexibility of GBM cells by restricting glucose availability and providing ketone bodies as alternative energy sources, thereby inhibiting glycolysis and glutaminolysis pathways. This approach may enhance the efficacy of existing treatments and improve patient outcomes [87].

GBM cells exhibit high glycolytic rates, leading to increased lactate production. Monocarboxylate transporters (MCTs) facilitate the export of lactate from tumor cells, maintaining intracellular pH balance and supporting continued glycolysis. Inhibiting MCTs can disrupt this process, leading to intracellular acidification and reduced tumor growth. Research has shown that targeting MCTs with inhibitors like α-cyano-4-hydroxycinnamic acid (CHC) effectively impairs GBM cell proliferation [88]. Also, isoform 2 of pyruvate kinase (PKM2) is a glycolytic enzyme that plays a pivotal role in tumor metabolism by regulating the final step of glycolysis. In cancer cells, PKM2 expression promotes aerobic glycolysis and supports anabolic processes essential for rapid cell proliferation. Silencing PKM2 increases apoptosis and promotes differentiation in both rat and human glioma spheroids. Mechanistically, PKM2 interacts with Oct4, a pivotal regulator of self-renewal and differentiation in stem cells, and this interaction influences glioma stemness. Treatment with the pyruvate dehydrogenase kinase inhibitor dichloroacetate (DCA) augments the formation of PKM2/Oct4 complexes, thereby inhibiting Oct4-dependent gene expression. Taken together, these findings highlight a molecular pathway in which PKM2 governs gliomagenesis by regulating

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stemness via Oct4, underlining the therapeutic potential of targeting PKM2 to disrupt cancer cell metabolism and tumor growth [89,90].

3.12. Bypassing Blood-Brain Barrier

Despite these promising metabolic targets, effective treatment of GBM also requires overcoming a major hurdle in neuro-oncology: the restrictive nature of the blood-brain barrier (BBB). Focused ultrasound (FUS) combined with circulating microbubbles has been developed to temporarily disrupt the BBB, allowing enhanced delivery of therapeutic agents into the brain. This method has shown promise in preclinical models and is currently being tested in clinical trials. For instance, low-intensity FUS with microbubbles can increase the intracranial concentration of chemotherapeutic agents, leading to significant tumor volume reduction and extended survival in patient-derived xenograft models. In situ and intranasal delivery of therapeutics are other approaches to bypass the BBB [91]. Convection-enhanced delivery (CED) allows for direct infusion of drugs into the tumor site [92], while the intranasal route offers a non-invasive method to deliver drugs directly to the CNS via the olfactory and trigeminal nerves [93].

3.13. Drug Repurposing and Combination Therapies

Drug repurposing involves using existing drugs with known safety profiles for new therapeutic indications [94]. Agents like metformin and statins have shown potential in inhibiting GBM cell proliferation and inducing apoptosis [95]. Combination therapies that target multiple pathways simultaneously are being explored to overcome resistance mechanisms [96]. For example, combining metformin with temozolomide has demonstrated effectiveness in enhancing the chemotherapeutic response [97].

3.14. Oncolytic Viruses and Gene-Based Approaches

Gene therapy offers another promising approach for GBM treatment [98]. By delivering genetic material and regulatory elements to target cells through delivery vehicles, gene therapy can circumvent the BBB [99]. Oncolytic viruses (OVs) have garnered considerable interest for their dual action in glioma therapy: they can selectively infect and lyse tumor cells while simultaneously triggering robust anti-tumor immunity. However, it is increasingly recognized that their immunostimulatory capacity may be even more critical than their direct cytolytic effects. By replicating within tumor cells and causing immunogenic cell death, OVs release tumor antigens in an inflammatory context that promotes dendritic cell activation and T cell priming. This cascade enhances both innate and adaptive immune responses, effectively transforming the immunosuppressive tumor microenvironment into one more conducive to tumor clearance. As a result, OVs serve as powerful in situ vaccines, mobilizing the patient's immune system against residual glioma cells and potentially establishing long-term immunologic memory, an effect that is often more pivotal for durable therapeutic outcomes than the immediate oncolytic killing itself. Various oncolytic viruses, including adenoviruses and herpes simplex viruses, have shown promising anticancer activity in preclinical and clinical studies [100].

Table 3. 1: EGFR Inhibitors for GBM.

Agent	Mechanism	Clinical Phase / Population	Findings
Gefitinib	1st-generation EGFR tyrosine kinase inhibitor (TKI)	Phase II (Recurrent GBM) (e.g., NCT01520870)	- Poor BBB penetration - EGFR alterations in GBM are heterogeneous; not all tumors rely on EGFR signaling

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Dacomitinib	Pan-EGFR TKI (inhibits EGFR, HER2, HER4)	Phase II (Recurrent GBM) (e.g., NCT02447419)	- Still challenged by BBB penetration - Broader than gefitinib, but GBM evolves alternate pathways
Osimertinib	3rd-generation EGFR TKI, better BBB permeability	Early-Phase / Preclinical (Recurrent GBM)	- Promising in preclinical models due to improved BBB penetration - Further phase I/II trials needed to determine safety & efficacy
Nimotuzumab	Anti-EGFR monoclonal antibody (mAb)	Phase II / III (Various GBM populations)	- Mixed results: some modest improvements in specific subgroups - Reduced toxicity vs. other anti-EGFR mAbs because of intermediate affinity
Depatux-M (ABT-414)	Antibody–drug conjugate targeting EGFR; delivers cytotoxic agent	Phase II/III (EGFR-amplified GBM) (e.g., NCT02573324)	- Some efficacy in EGFR-amplified GBM - Ocular toxicity reported; highlights the need for careful dosing and patient selection
Challenges: • Poor BBB penetration. • Intratumoral heterogeneity and EGFR pathway redundancy. • Adaptive resistance (GBM cells switch to alternative pathways).			

Table 3. 2: Other Receptor Tyrosine Kinase (RTK) Inhibitors for GBM.

Agent	Mechanism	Clinical Phase / Population	Findings
Cabozantinib	Inhibits MET & VEGFR2 (angiogenesis)	Phase II (Recurrent GBM) (e.g., NCT00704288)	- Modest activity in heavily pretreated patients - Notable toxicities (hypertension, fatigue, etc.)
Capmatinib (INC280)	Selective MET inhibitor	Phase II (Recurrent GBM) (e.g., NCT01870726)	- Limited efficacy overall

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			- Possible benefit in tumors with MET amplification or alterations
Erdafitinib	Pan-FGFR inhibitor (incl. FGFR3-TACC3 fusions)	Phase II (Recurrent GBM) (e.g., NCT01703481)	- Partial responses in some patients with FGFR alterations - Ongoing trials with biomarker selection
Challenges: • Overlapping growth pathways (GBM can activate PI3K, PDGF, or EGFR). • BBB penetration and systemic toxicity. • Small subsets of GBM harbor these specific driver alterations.			

Table 3. 3: Cell Cycle (CDK4/6) Inhibitors for GBM.

Agent	Mechanism	Clinical Phase / Population	Findings
Palbociclib	CDK4/6 inhibitor; blocks G1→S phase transition	Phase II (Recurrent GBM) (e.g., NCT01227434)	- No significant efficacy as monotherapy - Ongoing combos with radiation or targeted agents
Ribociclib	CDK4/6 inhibitor	Phase I/II (Recurrent GBM) (e.g., NCT02345824)	- Limited single-agent benefit - Potential synergy with other pathways (e.g., mTOR inhibitors)
Challenges: • GBM often has **multiple** genetic alterations (RB, p53, PTEN), so simply blocking CDK4/6 is not enough. • Tumors may develop resistance to CDK4/6 inhibitors, reducing their effectiveness over time. • Identifying patients who would benefit most from these therapies is challenging due to the lack of reliable biomarkers.			

Table 3. 4: MET/ALK/Multiple RTK Inhibitors for GBM.

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Agent	Mechanism	Clinical Phase / Population	Findings
Bortezomib / Marizomib	Proteasome inhibitors (alter proteostasis)	Bortezomib: Phase I/II; Marizomib: Phase III (e.g., NCT03345095)	- Bortezomib limited by BBB & toxicity - Marizomib under combination trials (TMZ + RT), hoping synergy
Bevacizumab	Anti-VEGF mAb (angiogenesis blockade)	Approved for Recurrent GBM	- Improves progression-free survival, less proven benefit in overall survival - Combined with chemo or RT
Challenges: • Many agents, like bortezomib, face difficulty effectively reaching brain tumor sites due to the BBB. • Agents such as bortezomib are limited by systemic toxicity, reducing their feasibility for long-term use or high dosing • Bevacizumab shows improved progression-free survival but limited evidence of extending overall survival in patients.			

Table 4. 1: CAR T Cells for GBM.

Agent	Target	Clinical Phase / Population	Key Findings & Rationale
EGFRvIII-targeted CAR T Cells	EGFRvIII mutation (common in GBM)	Early-phase (e.g., NCT02209376)	- Safe but limited efficacy due to antigen loss and immunosuppressive microenvironment
IL13Rα2-targeted CAR T Cells	IL13Rα2 (overexpressed in GBM)	Phase I (Case reports)	- Dramatic regression in a single case report - Studies ongoing to confirm broad efficacy and overcome tumor heterogeneity
HER2-targeted CAR T Cells	HER2 receptor	Early-phase	- Preliminary safety established; potential

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			synergy with other immunotherapies
Challenges: • GBM's antigen heterogeneity (tumors can downregulate the target). • T cell trafficking into the brain. • Immunosuppressive environment (TAMs, MDSCs, Tregs).			

Table 4. 2: Vaccines Under Investigation for GBM.

Agent	Mechanism	Clinical Phase / Population	Key Findings & Rationale
Rindopepimut	Peptide vaccine targeting EGFRvIII	Phase III (ACT IV; NCT01480479)	- Did not improve OS vs. control - Trial halted; underscores how GBM escapes single-target therapies
DCVax®-L	Dendritic cell vaccine with autologous tumor lysate	Phase III (NCT00045968)	- Interim data suggest possible survival benefit - Full results pending; likely works best in low tumor burden
Challenges: • Antigen loss / tumor heterogeneity. • GBM's robust immune evasion mechanisms.			

Table 5. Oncolytic Viruses for GBM.

Agent	Virus Type / Target	Clinical Phase / Population	Key Findings & Rationale
PVSRIPO	Engineered poliovirus targeting CD155	Phase I/II (Recurrent GBM)	- Demonstrated safety; some patients have prolonged survival - Requires strong anti-tumor immune response
DNX-2401	Oncolytic adenovirus selectively replicating in GBM	Phase I (Recurrent GBM) (NCT00805376)	- Induces immune response; some durable remissions

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			- Combining with other immunotherapies is under investigation
G47Δ	Genetically engineered herpes simplex virus	Phase II (Japan)	- Conditional approval in Japan for recurrent GBM - Showed improved survival vs. historical controls
Challenges: • Achieving uniform virus distribution in a large, heterogeneous tumor. • Success depends heavily on eliciting a strong and targeted anti-tumor immune response, which can vary significantly between patients.			

Table 6. Epigenetic Modulators for GBM.

Agent	Mechanism	Clinical Phase / Population	Key Findings & Rationale
Vorinostat	HDAC inhibitor; alters gene expression, induces apoptosis	Phase II	- Limited efficacy as monotherapy - Combining with RT or chemo being explored
Azacitidine	DNMT inhibitor; demethylates DNA to restore tumor suppressor genes	Phase II (NCT03666559)	- Ongoing; rationale is that epigenetic changes in GBM may re-sensitize to therapy
Challenges: • Both HDAC and DNMT inhibitors often show limited effectiveness as standalone treatments. • Tumor cells can develop resistance to these agents, limiting their long-term utility. • Many GBMs show epigenetic dysregulation. Reversing some of these changes might re-open tumor sensitivity to immunotherapy or chemo.			

3.15. Nanotechnology and Drug Delivery Systems

Nanoparticles are colloidal particles ranging from 1 to 100 nanometers in size, designed to carry drugs, genes, or imaging agents [101,102]. Their small size allows for enhanced permeation and retention within tumor tissues due to the leaky vasculature characteristic of GBM [87]. Researchers at Yale and the University of Connecticut have developed bioadhesive nanoparticles that adhere to tumor sites, enabling sustained and localized drug release. For instance, a study from Yale and the University of Connecticut introduced nanoparticles that, upon adhering to GBM tissues, gradually release therapeutic agents, enhancing treatment precision and minimizing systemic side effects [103].

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Piezoelectric nanoparticles, such as barium titanate nanoparticles (BTNPs), have been investigated for their ability to generate electric stimulation upon exposure to ultrasound. Functionalized with antibodies targeting GBM cells, these nanoparticles can induce anti-proliferative effects and enhance sensitivity to chemotherapy. In vitro studies have demonstrated that ultrasound-mediated piezo-stimulation using BTNPs can significantly reduce GBM cell proliferation and promote apoptosis [104].

Exosome-like nanovesicles (ELNs) have been engineered to mimic natural exosome properties, serving as biocompatible carriers for drug delivery. These synthetic vesicles can be tailored to deliver therapeutic oligonucleotides, proteins, or chemotherapeutic agents directly to GBM cells, potentially enhancing treatment specificity and reducing off-target effects [105]. Research has shown that brain-targeted ELNs loaded with therapeutic oligonucleotides can elicit anti-tumor effects in GBM animal models [106]. Furthermore, marine-derived compounds have been utilized to create nanocarriers for drug delivery in GBM treatment. These nanocarriers offer biocompatibility and the ability to encapsulate a variety of therapeutic agents. Recent research has highlighted the potential of these systems to enhance drug delivery efficiency and therapeutic outcomes in GBM models [107].

Innovative DNA-based nanostructures, such as DNA nanotubes, have been engineered to deliver therapeutics directly to GBM tumors. These nanotubes can be functionalized with targeting ligands and therapeutic agents, facilitating precise delivery. Studies have shown that DNA nanotubes can effectively penetrate tumor tissues and deliver payloads, inhibiting tumor growth in experimental models [108]. Advancements in nanotechnology have facilitated the development of nanocarrier systems for gene therapy applications in GBM. These systems are designed to deliver genetic material, such as siRNA or plasmid DNA, to tumor cells, modulating gene expression to inhibit tumor growth. Recent studies have demonstrated the potential of these nanocarriers to enhance the efficacy of gene therapies in GBM treatment [109].

Surface modifications can exploit endogenous transport mechanisms across the BBB; for instance, coating nanoparticles with ligands targeting transferrin receptors or low-density lipoprotein receptors facilitates receptor-mediated transcytosis into the CNS [110]. nanoparticles employed in GBM research include liposomes, solid lipid nanoparticles, dendrimers, and polymeric nanoparticles. Liposomal formulations can encapsulate chemotherapeutic agents like temozolomide or doxorubicin, protecting them from degradation and enhancing CNS penetration [111]. Additionally, nanoparticles can be loaded with multiple agents, facilitating delivery of combination therapies that target different tumor pathways simultaneously [96]. Magnetic nanoparticles offer dual functions of drug delivery and diagnostic imaging [112]. Superparamagnetic iron oxide nanoparticles can be guided to the tumor site using external magnetic fields and monitored through magnetic resonance imaging (MRI) [113]. Moreover, these nanoparticles can induce hyperthermia upon exposure to alternating magnetic fields, causing localized tumor cell death [114].

Controlled release systems aim to maintain therapeutic drug concentrations at the tumor site over extended periods, reducing systemic toxicity and improving efficacy [115]. These systems can be engineered to release their payload in response to specific stimuli within the tumor microenvironment, such as pH changes, enzymatic activity, or temperature variations [116]. Biodegradable polymers like polylactic-co-glycolic acid (PLGA) are commonly used to fabricate nanoparticles or implants that gradually degrade, releasing the encapsulated drug [117]. The Gliadel® wafer is a notable example of an implantable polymeric device approved for the treatment of high-grade glioma. The device delivers carmustine directly into the resection cavity post-surgery, bypassing the BBB and minimizing systemic exposure [118]. Hydrogel-based systems offer another approach to controlled drug release [119]. Injectable hydrogels can conform to the shape of the resection cavity and provide a sustained release of therapeutics [120]. These hydrogels can be loaded with chemotherapeutic agents, growth factor inhibitors, or even nanoparticles carrying genetic material [121]. Smart delivery systems are being developed to respond dynamically to the tumor environment [122]. For instance, pH-sensitive nanoparticles can release their cargo in the acidic conditions typical of tumor tissues [123], while enzyme-responsive systems utilize enzymes

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overexpressed in GBM to trigger drug release [124]. These advanced delivery platforms hold promise for enhancing the specificity and effectiveness of GBM treatments.

3.16. Molecular Profiling and Biomarkers

Molecular profiling involves analyzing tumors for genetic mutations, gene expression patterns, and other molecular characteristics [16]. This information is crucial for identifying patients most likely to benefit from specific therapies [125]. For instance, EGFR amplification or mutation status can influence the response to EGFR inhibitors [63]. Advancements in next-generation sequencing and bioinformatics have made comprehensive molecular profiling more accessible [126]. Integrating these techniques into clinical practice enables the stratification of patients in clinical trials, increasing the likelihood of detecting treatment effects in responsive subgroups [127].

Predictive biomarkers indicate the likelihood of response to a particular therapy, while prognostic biomarkers provide information about overall disease outcome regardless of treatment [128]. MGMT promoter methylation is a predictive biomarker for responsiveness to temozolomide; patients with methylated MGMT derive greater benefit from alkylating agents due to reduced DNA repair capability [38]. Elevated PD-L1 levels on tumor cells may predict responsiveness to immune checkpoint inhibitors, although the correlation is not absolute in GBM [55]. Incorporating biomarker assessment into clinical trials enhances the ability to evaluate therapeutic efficacy accurately and facilitates the development of personalized treatment strategies [129].

3.17. Combination Therapies

Given the complexity of GBM pathogenesis and the redundancy of signaling pathways, combination therapies targeting multiple pathways simultaneously are hypothesized to produce synergistic effects [96]. Combining agents can overcome resistance by targeting alternative pathways that tumor cells may utilize to evade single-agent therapies, enhance efficacy through simultaneous inhibition of complementary pathways, and reduce doses to minimize toxicity while maintaining efficacy [130]. Examples include the Stupp protocol, which combines temozolomide with radiotherapy to leverage the radiosensitizing effects of temozolomide [9], and trials combining EGFR inhibitors with temozolomide to block survival pathways activated by DNA damage [131]. Immunotherapy combinations, such as combining immune checkpoint inhibitors with vaccines or oncolytic viruses, may enhance immune activation against tumor cells [132]. Angiogenesis inhibitors combined with other therapies may normalize tumor vasculature, improving drug and oxygen delivery [133]. Optimizing combination regimens requires careful consideration of pharmacodynamics, potential overlapping toxicities, and scheduling to maximize synergistic effects while minimizing adverse events [134].

4. Challenges and Future Directions

GBM exhibits significant intra-tumoral heterogeneity, with distinct subpopulations of tumor cells harboring different genetic and epigenetic alterations [17, 65, 125]. This diversity complicates treatment, as cells within the same tumor can respond differently to therapy and rapidly develop resistance to targeted agents. Resistance often arises through genetic mutations, the activation of alternative signaling pathways, and phenotypic shifts that allow tumor cells to evade existing treatments [65,135]. Efforts to counteract resistance include combination therapies aimed at multiple pathways, sequential treatment strategies, and synthetic lethality approaches targeting vulnerabilities in resistant cells [136].

Despite increased understanding of GBM biology, therapeutic gains remain limited. Even newer therapies can still produce side effects that compromise patients' quality of life. Combination regimens, targeting multiple pathways, and leveraging advanced technologies are among the strategies under investigation to address these persistent challenges [143]. Emerging "omics" technologies, genomics, transcriptomics, and proteomics, continue to shed light on the molecular

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diversity of GBM, offering more precise targets for intervention [142,153]. Integrating these massive datasets with artificial intelligence and machine-learning approaches has led to the discovery of novel biomarkers and therapeutic targets [140], laying the groundwork for more personalized treatment strategies [141,154,155].

Immunotherapies such as immune checkpoint inhibitors, CAR T-cell therapy, and cancer vaccines show promise, with the potential for durable responses in some patients. Yet, the adaptability of GBM and immunosuppressive tumor microenvironment remain formidable obstacles. Advancements in nanotechnology also hold potential: designing nanoparticles that cross the blood-brain barrier and deliver agents directly to tumor sites could enhance drug specificity and reduce systemic toxicity.

5. Conclusions

Despite intensive efforts and technological advances, meaningful clinical breakthroughs in GBM remain elusive. Ongoing research focusing on personalized medicine, combination therapies, and emerging modalities such as immunotherapy and nanotechnology underscores the need for continued innovation. Addressing GBM's complexity will require a multidisciplinary push to develop more effective, tolerable, and accessible treatments that finally offer patients tangible improvements in survival and quality of life.

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