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REVIEW ARTICLE

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Pathway dysregulation and therapeutic resistance in glioblastoma: molecular mechanisms and emerging therapeutic targets

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ABSTRACT

Background: Glioblastoma multiforme (GBM) is the most aggressive primary malignant brain tumor in adults and remains associated with poor survival despite advances in surgery, radiotherapy, and chemotherapy. Increasing evidence suggests that IDH-wildtype glioblastoma progression is driven by complex interactions between dysregulated molecular signaling pathways, intratumoral heterogeneity, glioma stem cells, and immune suppression within the tumor microenvironment.

Objective: This narrative review summarizes the major signaling pathways implicated in GBM pathogenesis, including EGFR, PI3K/AKT/mTOR, Wnt, and TGF-β signaling, while also discussing emerging therapeutic targets such as FGFR3–TACC3 fusions, regorafenib, and natural killer cell-based immunotherapy.

Results: The review further examines mechanisms underlying treatment resistance and the limitations of current targeted therapies. Although many pathway-directed treatments have demonstrated promising preclinical activity, clinical translation remains challenging because of compensatory signaling, blood–brain barrier limitations, and molecular heterogeneity.

Conclusion: Future progress will likely depend on biomarker-driven patient stratification, improved CNS drug delivery, and rational combination therapies capable of simultaneously targeting multiple tumor-promoting mechanisms.

ARTICLE HIGHLIGHTS

- Glioblastoma remains the most aggressive primary malignant brain tumor in adults, with poor survival despite multimodal treatment.
- Dysregulation of EGFR, PI3K/AKT/mTOR, Wnt, and TGF-β signaling pathways drives tumor proliferation, invasion, immune evasion, glioma stem cell maintenance, and therapeutic resistance.
- Intratumoral heterogeneity, adaptive signaling crosstalk, glioma stem cell plasticity, and blood–brain barrier limitations are major barriers to successful targeted therapy.
- Emerging therapeutic strategies, including regorafenib, FGFR3–TACC3-targeted therapies, natural killer cell immunotherapy, CAR-NK cells, antibody-drug conjugates, and oncolytic viruses, show promise but require further clinical validation.
- Biomarker-driven patient stratification and molecular profiling are expected to improve selection of targeted therapies and combination treatment strategies.
- Future progress will likely depend on rational combination therapies that simultaneously target multiple signaling pathways, glioma stem cells, and the immunosuppressive tumor microenvironment while improving central nervous system drug delivery.

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Glioblastoma multiforme; brain cancer; signaling pathways; IDH-wildtype targeted therapy

1. Introduction

Glioblastoma multiforme (GBM) is the most aggressive primary malignant brain tumor in adults and remains associated with poor prognosis despite advances in multimodal therapy [1]. Current standard treatment consists of maximal safe surgical resection followed by radiotherapy and temozolomide-based chemotherapy; however, median survival remains approximately 15–18 months in most patients [2].

A major contributor to therapeutic failure is the extensive molecular and cellular heterogeneity of GBM. Common genetic alterations include EGFR amplification, PTEN loss, TP53 mutations, PDGFR dysregulation, and aberrant activation of signaling pathways such as PI3K/AKT/mTOR, Wnt, and TGF-β [3–6]. These pathways promote tumor proliferation, invasion, angiogenesis, immune evasion, and resistance to apoptosis, while compensatory pathway cross-talk limits the effectiveness of single-agent targeted therapies.

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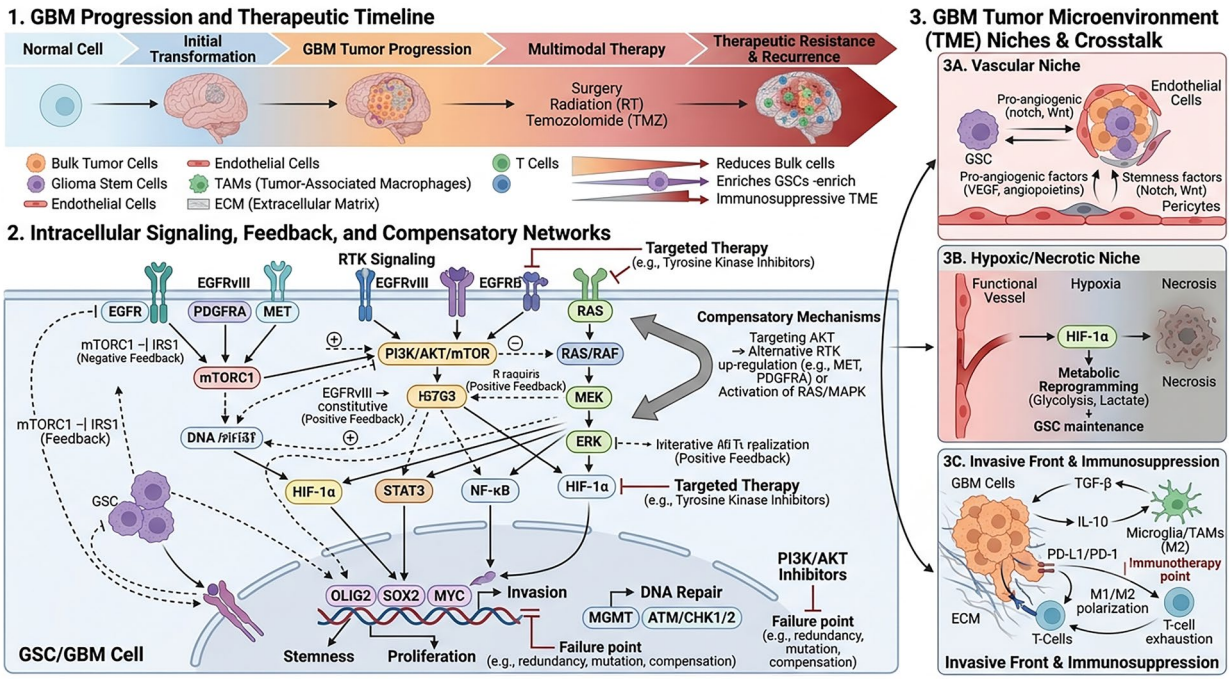

Figure 1. Overview of dysregulated signaling pathways contributing to glioblastoma progression and therapeutic resistance. Major signaling pathways, including EGFR, PI3K/AKT/mTOR, Wnt, and TGF-β, interact to promote tumor proliferation, invasion, glioma stem cell maintenance, immune evasion, therapeutic resistance, and disease progression in glioblastoma.

Abbreviations: GBM, glioblastoma; TME, tumor microenvironment; RT, radiotherapy; TMZ, temozolomide; GSC, glioma stem cell; TAM, tumor-associated macrophage; ECM, extracellular matrix; RTK, receptor tyrosine kinase; EGFR, epidermal growth factor receptor; EGFRvIII, epidermal growth factor receptor variant III; PDGFRA, platelet-derived growth factor receptor alpha; MET, mesenchymal-epithelial transition receptor; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; mTORC1, mechanistic target of rapamycin complex 1; IRS1, insulin receptor substrate 1; RAS, rat sarcoma; RAF, rapidly accelerated fibrosarcoma; MEK, mitogen-activated protein kinase kinase; ERK, extracellular signal-regulated kinase; HIF-1α, hypoxia-inducible factor-1 alpha; NF-κB, nuclear factor kappa B; STAT3, signal transducer and activator of transcription 3; MGMT, O6-methylguanine-DNA methyltransferase; ATM, ataxia telangiectasia mutated; CHK1/2, checkpoint kinase 1/2; VEGF, vascular endothelial growth factor; IL-10, interleukin-10; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1; TGF-β, transforming growth factor-β.

Comprehensive genomic profiling studies, including analyses from The Cancer Genome Atlas (TCGA), have demonstrated that GBM is driven by concurrent dysregulation of multiple interconnected signaling networks rather than isolated molecular abnormalities [3,7]. These interconnected mechanisms are summarized in Figure 1.

While several recent reviews have examined individual signaling pathways or specific therapeutic modalities in glioblastoma, comparatively fewer have integrated these pathways within the broader context of tumor heterogeneity, glioma stem cell biology, adaptive therapeutic resistance, and emerging biomarker-driven treatment strategies [8–10]. The aim of this review is therefore not to provide an exhaustive catalog of all molecular pathways implicated in glioblastoma, but to synthesize the current evidence for the key dysregulated signaling networks that have the strongest translational relevance and to examine how their interactions collectively contribute to disease progression and treatment failure. The pathways discussed in this review (EGFR, PI3K/AKT/mTOR, Wnt, and TGF-β) were prioritized because they are among the most extensively validated drivers of glioblastoma biology, exhibit substantial pathway crosstalk, regulate glioma stem cell maintenance and therapeutic resistance, and remain central targets of ongoing therapeutic development [8].

Recent advances in molecular neuropathology have also transformed the classification of diffuse gliomas. According to the WHO 2021 Classification of Central Nervous System Tumors, glioblastoma is now defined primarily as an IDH-wildtype diffuse astrocytic tumor with characteristic molecular features, while IDH-mutant tumors are classified separately as astrocytomas [11]. This molecular classification has important biological and therapeutic implications because these entities differ substantially in prognosis, genomic alterations, and treatment response. Accordingly, although this review refers to "GBM" for simplicity, the discussion primarily relates to IDH-wildtype glioblastoma unless otherwise specified.

1.1. Literature search strategy

This narrative review was developed through structured literature searches of PubMed, Scopus, and Google Scholar for articles published between January 2000 and December 2025. Search terms included combinations of "glioblastoma", "glioblastoma multiforme", "GBM", "signalling pathways", "therapeutic resistance", "EGFR", "EGFRvIII", "PI3K/AKT/mTOR", "Wnt", "TGF-β", "FGFR3–TACC3", "regorafenib", "glioma stem cells", and "immunotherapy".

Reference lists of relevant reviews, translational studies, and landmark clinical trials were also manually screened to identify additional studies. Priority was given to peer-reviewed original research articles, genomic profiling studies, clinical trials, translational investigations, and recent high-impact reviews with direct relevance to molecular signaling, tumor progression, treatment resistance, or emerging targeted therapies in GBM.

Studies were included if they were published in peer-reviewed journals, written in English, and directly addressed molecular signaling pathways, glioblastoma biology, therapeutic resistance, glioma stem cells, or emerging targeted therapeutic strategies. Original research articles, translational studies, genomic profiling studies, clinical trials, and high-quality review articles were considered. Articles with limited relevance to the review objectives, non-English publications, conference abstracts without full manuscripts, and studies lacking sufficient methodological detail were excluded. Study selection was performed through title and abstract screening followed by full-text assessment where appropriate.

253 articles were screened, of which 120 were selected for inclusion based on relevance, scientific impact, and recency. Due to the narrative nature of this review, formal systematic-review protocols and quantitative meta-analysis were not performed. Potential limitations therefore include selection bias and heterogeneity among included studies.

2. Genetic, epigenetic, and immune contributors to GBM progression

Progression of GBM is shaped by overlapping genetic, epigenetic, and immune mechanisms, which together help explain why therapies directed at single molecular targets have generally produced limited clinical benefit [12–14].

One of the most clinically significant epigenetic alterations in GBM is MGMT promoter methylation, which is present in approximately 50% of newly diagnosed tumors and is strongly associated with improved responsiveness to temozolomide chemotherapy [15]. Mechanistically, MGMT promoter methylation suppresses expression of the DNA repair enzyme O6-methylguanine-DNA methyltransferase (MGMT), thereby preventing efficient removal of temozolomide-induced O6-methylguanine DNA adducts. Persistence of these lesions during DNA replication results in repeated mismatch repair activation, accumulation of DNA damage, and ultimately tumor cell apoptosis, thereby increasing sensitivity to temozolomide [15]. Alterations in the p53 pathway are also central to GBM biology, contributing to impaired cell-cycle control, genomic instability, and resistance to apoptosis [3,7,16,17]. TCGA analyses suggest that approximately 85% of GBMs contain alterations affecting the p53 pathway, including TP53, CDKN2A, and MDM2 abnormalities [3,7].

Beyond genetic and epigenetic alterations, GBM is characterized by a highly immunosuppressive tumor microenvironment, containing tumor-associated microglia, monocyte-derived macrophages, and regulatory T cells that collectively support immune escape [18]. T-cell dysfunction and immune checkpoint expression, including CTLA-4 and PD-1, further contribute to immune evasion and may partly explain the limited success of immunotherapy in GBM [18].

Numerous additional signaling pathways also contribute to GBM progression but are beyond the primary scope of this review. Aberrant activation of Hippo/YAP signaling promotes tumor proliferation, invasion, stem-cell maintenance, and therapeutic resistance [19,20], while constitutive NF-κB signaling supports chronic inflammation, cell survival, and resistance to apoptosis. Alterations involving MET amplification and CDK4/6-mediated cell-cycle dysregulation have also emerged as clinically relevant drivers in molecular subsets of GBM and are being investigated as therapeutic targets. Collectively, these pathways interact extensively with the EGFR, PI3K/AKT/mTOR, Wnt, and TGF-β signaling networks, further illustrating the complexity and redundancy of GBM signaling biology and reinforcing the need for rational combination therapies [21].

Glioma stem cells (GSCs) are increasingly recognized as a fundamental driver of GBM initiation, progression, recurrence, and therapeutic resistance. These cells possess self-renewal capacity, multilineage differentiation potential, and enhanced resistance to radiotherapy and chemotherapy through efficient DNA repair, metabolic plasticity, and adaptive stress responses [22]. Importantly, several signaling pathways discussed throughout this review, including Wnt, PI3K/AKT/mTOR, TGF-β, and EGFR, contribute not only to tumor proliferation but also to the maintenance of the GSC phenotype [23]. Consequently, therapies capable of simultaneously targeting both differentiated tumor cells and GSC populations may be required to achieve durable clinical responses [24].

2.1. Glioma stem cell hierarchy, plasticity, and therapeutic resistance

Glioma stem cells are increasingly recognized as a dynamic tumor cell population that exists at the apex of the glioblastoma cellular hierarchy. These cells possess the capacity for long-term self-renewal and multilineage differentiation, giving rise to the heterogeneous tumor cell populations that comprise GBM. However, accumulating evidence indicates that this hierarchy is not rigid. Rather than following a strictly unidirectional developmental pathway, differentiated tumor cells can reacquire stem-like characteristics in response to environmental stress, highlighting the remarkable cellular plasticity of GBM [25].

This phenotypic plasticity is driven by multiple factors within the tumor microenvironment, including hypoxia, inflammation, metabolic stress, and therapeutic pressure. Following exposure to radiotherapy or temozolomide, surviving tumor cells may undergo dedifferentiation into stem-like states characterized by enhanced DNA repair capacity, metabolic adaptation, quiescence, and resistance to apoptosis. Consequently, therapy itself may inadvertently enrich the GSC population, contributing to treatment resistance and tumor recurrence [24].

Hypoxic regions within GBM further promote maintenance of the stem-like phenotype through activation of hypoxia-inducible factors (HIF-1α and HIF-2α). These signaling molecules enhance self-renewal, angiogenesis, metabolic reprogramming, and invasion while simultaneously reducing sensitivity to radiotherapy and chemotherapy. Perivascular and hypoxic niches therefore provide specialized microenvironments that support long-term GSC survival despite aggressive multimodal treatment [26,27].

Several developmental signaling pathways cooperate to maintain GSC function. Canonical Wnt/β-catenin signaling promotes self-renewal and proliferation, while Notch signaling maintains stem-cell identity and cellular quiescence. Hedgehog signaling contributes to tumor growth and survival, and TGF-β signaling enhances stemness, invasion, epithelial-to-mesenchymal-like transition, and immune evasion. Extensive crosstalk between these pathways generates substantial signaling redundancy, limiting the effectiveness of therapies directed against individual molecular targets [23,28].

The persistence of GSCs has important clinical implications. Although maximal safe surgical resection removes the bulk tumor mass, infiltrative GSCs frequently remain within surrounding brain tissue beyond the resection margin. Subsequent radiotherapy and temozolomide eliminate many proliferating tumor cells but often fail to eradicate these highly resistant stem-like populations. Surviving GSCs subsequently regenerate the heterogeneous tumor through continued self-renewal and differentiation, making recurrence almost inevitable. Consequently, durable therapeutic responses will likely require combination strategies capable of eliminating both differentiated tumor cells and GSC populations while simultaneously preventing therapy-induced cellular plasticity [23,28].

3. Current treatment strategies and therapeutic limitations in GBM

For patients with good performance status, current standard care typically involves maximal safe surgical resection followed by radiotherapy with concurrent and adjuvant temozolomide [2,29–31]. Tumor-treating fields may also be incorporated during maintenance therapy and have been associated with improved survival when added to temozolomide [32].

The landmark EORTC-NCIC trial and its long-term follow-up established radiotherapy plus temozolomide as the backbone of GBM treatment, demonstrating improved survival compared with radiotherapy alone [2,32,33]. For selected patients with MGMT-methylated GBM, lomustine-temozolomide combination therapy has also shown survival benefit compared with standard temozolomide-based therapy, although its role remains more selective than routine standard care [30,34,35].

Despite aggressive multimodal treatment, more than 90% of patients develop recurrent disease, with most recurrences occurring within 6–9 months of initial treatment. This recurrence is driven by diffuse tumor infiltration, molecular heterogeneity, and therapeutic resistance [36,37]. This reflects a major limitation of current management: even maximal safe resection and adjuvant therapy rarely eradicate infiltrative tumor cells beyond the radiographic margin. Although temozolomide and tumor-treating fields have improved outcomes, these gains remain modest, and GBM continues to be characterized by early recurrence and poor long-term survival [13,29,32]. In the recurrent setting, treatment options such as lomustine, bevacizumab, carmustine, PCV chemotherapy, and regorafenib may provide selected benefit, but durable disease control remains uncommon [30,38–40]

Tumor-treating fields require prolonged daily use, with clinical benefit appearing greatest among patients achieving high treatment adherence, typically exceeding 18 hours per day [29]. Despite demonstrated survival benefits in randomized clinical trials, widespread implementation remains controversial because of device cost, patient inconvenience, dermatological adverse effects, and ongoing debate regarding cost-effectiveness and patient selection [41,42]. Consequently, careful discussion with patients is required to balance potential survival gains against treatment burden [41].

4. Molecular signaling pathways and emerging therapeutic targets in GBM

EGFR signaling is one of the most extensively studied oncogenic drivers in GBM and contributes to tumor proliferation, migration, invasion, and survival [43,44]. Following activation, EGFR engages downstream signaling cascades, particularly the PI3K/AKT/mTOR pathway, thereby promoting tumor growth, survival, and treatment resistance [43,44]. EGFR amplification and overexpression occur in approximately 35–45% of GBMs and are associated with aggressive tumor behavior [43,45]. Among EGFR-amplified tumors, the EGFRvIII variant, caused by deletion of exons 2–7, is one of the most clinically relevant alterations and results in constitutive receptor activation [43,45].

Despite strong biological rationale, EGFR-targeted therapies have demonstrated limited clinical efficacy in GBM, including studies involving tyrosine kinase inhibitors and monoclonal antibodies [43]. This limited clinical benefit is likely explained by intratumoral heterogeneity, variable EGFR expression across tumor regions, compensatory downstream signaling, and challenges with adequate CNS drug delivery [43,46]. A summary of the key dysregulated pathways are provided in Table 1.

Concurrent PTEN loss further complicates EGFR-targeted therapy by constitutively activating the PI3K/AKT/mTOR pathway downstream of EGFR, allowing tumor cells to maintain survival signaling even when EGFR is inhibited [47]. Consequently, both monoclonal antibodies that block extracellular receptor activation and tyrosine kinase inhibitors targeting intracellular kinase activity may demonstrate reduced efficacy in PTEN-deficient or EGFRvIII-positive tumors. In addition, feedback activation of alternative receptor tyrosine kinases and MAPK signaling can restore downstream pathway activity following EGFR inhibition, further limiting durable clinical responses [48]. These findings support the development of biomarker-guided combination therapies targeting multiple interconnected signaling pathways.

Table 1. Key dysregulated signaling pathways and therapeutic implications in glioblastoma.

Pathway	Key alteration	Biological effect	Therapeutic approaches	Clinical development stage	Major limitation	Predictive biomarkers
EGFR	EGFR amplification / EGFRvIII	Proliferation, invasion	TKIs, monoclonal antibodies	Mostly Phase I–III; no approved targeted therapy	Resistance, heterogeneity	EGFR amplification, EGFRvIII expression
PI3K/AKT/mTOR	PTEN loss, PIK3CA mutation	Survival, metabolism	PI3K/mTOR inhibitors	Early clinical trials	Toxicity, redundancy	PTEN loss, PIK3CA mutation
Wnt	β-catenin activation	Stemness, invasion	Experimental Wnt inhibitors	Preclinical/early phase 1	Limited clinical data	Nuclear β-catenin expression
TGF-β	TGF-β overexpression	Immune suppression	TGF-β inhibitors	Early clinical trials	Systemic toxicity	TGF-β expression, SMAD activation

Summary of the principal signaling pathways involved in glioblastoma, including their major molecular alterations, biological effects, therapeutic approaches, clinical development stage, major limitations, and predictive biomarkers.
Abbreviations: EGFR, epidermal growth factor receptor; EGFRvIII, epidermal growth factor receptor variant III; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; PTEN, phosphatase and tensin homolog; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TKI, tyrosine kinase inhibitor; TGF-β, transforming growth factor-β; SMAD, suppressor of mothers against decapentaplegic; Wnt, Wingless/Integrated signaling pathway.

Clinically, EGFRvIII has been associated with aggressive tumor biology, although its independent prognostic value remains inconsistent across studies, partly due to intratumoral heterogeneity and variable expression over time [49]. Its tumor-specific expression has supported development of EGFRvIII-directed vaccines, antibodies, CAR-T cells, and other targeted approaches; however, clinical benefit has remained limited because of antigen loss, heterogeneous expression, compensatory pathway activation, and challenges achieving effective CNS drug delivery [50].

Collectively, these findings suggest that EGFR inhibition alone is unlikely to provide durable disease control because of intratumoral heterogeneity, adaptive signaling compensation, and coexistence of parallel oncogenic pathways. Furthermore, EGFR amplification alone has not consistently predicted therapeutic response across clinical trials. This may reflect substantial spatial and temporal heterogeneity in EGFR expression, with resistant tumor subclones persisting despite treatment. These findings highlight the limitations of relying on single molecular biomarkers and support the need for comprehensive molecular profiling when selecting patients for targeted therapy [51].

Regorafenib is an oral multi-kinase inhibitor that targets angiogenic, stromal, and oncogenic kinases, including VEGFR, PDGFR, FGFR, KIT, RET, RAF-1, and BRAF [52]. By targeting these pathways, regorafenib may inhibit tumor cell proliferation, angiogenesis, and microenvironment-mediated resistance [53–55]. Regorafenib may also exert immunomodulatory effects, potentially reducing tumor-associated immunosuppression and enhancing anti-tumor immune activity [56,57]. Preclinical GBM models have demonstrated anti-tumor activity with regorafenib, supporting its investigation in recurrent disease [53,58]. Its anti-angiogenic activity appears particularly important, as VEGFR inhibition may reduce tumor vascularization and nutrient supply within GBM xenograft models [53,58].

Clinical interest in regorafenib increased following the REGOMA trial, which demonstrated improved overall survival compared with lomustine in patients with recurrent GBM [40]. However, interpretation of REGOMA remains cautious because subsequent real-world and mechanistic studies suggest that treatment benefit may vary across molecular subgroups, highlighting the need for predictive biomarkers [40,59].

Patient-reported outcome data from REGOMA also suggest that regorafenib does not substantially worsen quality of life compared with lomustine, supporting its tolerability in selected recurrent GBM patients [60]. This balance between survival benefit and tolerability is clinically important in recurrent GBM, where treatment goals often include both disease control and preservation of neurological function [60].

Despite its clinical activity, regorafenib is associated with a well-recognized toxicity profile that requires careful patient selection and monitoring [61,62]. The most frequently reported adverse events include hand-foot skin reaction, hypertension, fatigue, diarrhea, mucositis, and hepatotoxicity, with dose reductions or temporary treatment interruption commonly required in clinical practice [62]. Although these toxicities are generally manageable with supportive care and dose modification, they may affect treatment adherence and quality of life. Consequently, the decision to use regorafenib should balance its survival benefit against the risk of treatment-related toxicity, particularly in patients with recurrent glioblastoma who often have limited functional reserve [61].

The clinical activity of regorafenib in recurrent glioblastoma is also influenced by its central nervous system pharmacokinetic properties [63]. Although regorafenib is capable of reaching intracranial tumors, CNS exposure is limited by high plasma protein binding and active efflux transporters such as P-glycoprotein and breast cancer resistance protein at the blood–brain barrier. Furthermore, blood–brain barrier disruption is highly heterogeneous within glioblastoma, resulting in variable drug distribution between contrast-enhancing tumor regions and infiltrative tumor margins. These pharmacokinetic limitations may contribute to inter-patient variability in treatment response and support ongoing investigation of combination strategies and drug-delivery approaches that improve intratumoural drug penetration [63].

Emerging biomarker analyses suggest that molecular profiling may help identify GBM patients more likely to benefit from regorafenib, although these findings remain preliminary and require further validation [64,65]. Additional preclinical evidence suggests that regorafenib may exert anti-tumor effects through induction of autophagic arrest and disruption of GBM cellular metabolism [66].

4.1. Receptor tyrosine kinases and FGFR3–TACC3 fusions

Among receptor tyrosine kinase alterations in GBM, the FGFR3–TACC3 fusion has emerged as a rare but potentially actionable molecular subtype, occurring in approximately 3–5% of IDH-wildtype diffuse gliomas [67–69].

FGFR3–TACC3 fusion proteins promote oncogenic signaling through persistent activation of proliferative and survival pathways involved in tumor progression [70,71]. These downstream pathways include RAS/MAPK, PI3K/AKT, and STAT3, which collectively support cell growth, survival, and therapy resistance [71]. In normal physiology, FGFR signaling is tightly regulated to support controlled cellular proliferation, differentiation, and survival [71]. However, oncogenic FGFR alterations such as FGFR3–TACC3 fusions disrupt this regulatory balance, resulting in sustained proliferative signaling and therapeutic resistance [71–73].

The close chromosomal proximity of FGFR3 and TACC3 on chromosome 4p16 is thought to facilitate fusion formation in gliomas [70]. Collectively, these findings support continued investigation of FGFR-targeted therapies and molecularly stratified treatment approaches in this small but potentially targetable subgroup of GBM patients.

4.2. Natural killer cell immunotherapy in GBM

Natural killer (NK) cell-based immunotherapy has emerged as a promising experimental treatment strategy in GBM due to its ability to target tumor cells independently of antigen presentation mechanisms. Unlike many conventional therapies, NK cells may selectively eliminate tumor cells while limiting damage to surrounding normal tissue. GSCs appear particularly susceptible to NK-cell-mediated cytotoxicity because of reduced MHC class I expression and increased expression of activating ligands [74]. Experimental studies have demonstrated greater NK-cell cytotoxicity against CD133+/Nestin + glioma stem-like cells compared with more differentiated tumor populations [75]. These findings suggest that NK-cell-based therapies may help target resistant GSC populations, although clinical translation remains limited by challenges including immune suppression within the GBM microenvironment and poor immune-cell trafficking into the tumor [75].

Emerging chimeric antigen receptor natural killer (CAR-NK) cell therapies represent a promising next-generation extension of conventional NK-cell immunotherapy. CAR-NK cells combine the innate cytotoxicity of NK cells with antigen-specific tumor recognition and may offer several advantages over CAR-T cells, including lower risk of cytokine release syndrome, reduced neurotoxicity, and the potential for allogeneic "off-the-shelf" manufacture [76]. Although CAR-NK therapy remains in the early stages of clinical development for glioblastoma, it represents an important direction for future immunotherapeutic strategies [77].

Despite encouraging preclinical findings, broader immunotherapeutic approaches in GBM, including immune checkpoint inhibitors and CAR-T-cell therapies, have thus far produced limited survival benefit in large clinical studies. Representative clinical trials support these findings. In the phase III CheckMate 143 trial, nivolumab failed to improve overall survival compared with bevacizumab in patients with recurrent glioblastoma. Similarly, early clinical studies of CAR-T-cell therapies have demonstrated encouraging safety and occasional durable responses in selected patients but have not yet translated into consistent survival benefit across broader patient populations [78,79]. Factors contributing to these disappointing outcomes include profound immune suppression within the tumor microenvironment, antigen heterogeneity, corticosteroid use, and restricted immune-cell trafficking across the blood–brain barrier. Continued optimization of combinational immunotherapeutic strategies and improved biomarker selection may therefore be necessary to improve clinical efficacy.

4.3. Emerging therapeutic strategies beyond conventional targeted therapy

Several additional therapeutic strategies have recently emerged with the aim of overcoming the limitations associated with conventional pathway-directed therapies. Among these, antibody-drug conjugates (ADCs) offer the potential to selectively deliver highly potent cytotoxic agents to tumor cells expressing specific surface antigens while limiting systemic toxicity. Although early clinical studies targeting receptors such as EGFR have demonstrated acceptable safety profiles, therapeutic efficacy has remained modest owing to heterogeneous antigen expression, antigen loss during treatment, limited tumor penetration, and the blood–brain barrier [80].

Oncolytic viruses have also generated considerable interest because they combine direct tumor cell lysis with activation of anti-tumor immune responses. Viral replication within tumor cells promotes release of tumor-associated antigens and inflammatory mediators, potentially converting the highly immunosuppressive glioblastoma microenvironment into one that is more immunologically active. However, clinical translation has thus far been limited by inefficient viral delivery, antiviral immune responses, restricted intratumoural spread, and the profound immune suppression characteristic of GBM [81].

Collectively, these emerging approaches highlight an important shift away from targeting single molecular pathways in isolation. Instead, future therapeutic strategies will likely integrate targeted therapies with immunotherapy, viral therapy, or other multimodal approaches to simultaneously address tumor heterogeneity, adaptive resistance, and immune evasion [80].

Additional experimental strategies are also undergoing early clinical evaluation. Personalized neoantigen vaccines aim to stimulate patient-specific anti-tumor immune responses by targeting tumor-specific mutations identified through genomic sequencing [82]. Bispecific antibodies seek to enhance immune-cell activation by simultaneously engaging tumor antigens and cytotoxic immune cells, although tumor heterogeneity remains a significant challenge. Engineered CAR-NK cells may provide advantages over CAR-T therapies through reduced toxicity, lower risk of cytokine release syndrome, and the potential for allogeneic "off-the-shelf" treatment [83].

Finally, targeted protein degradation technologies, including proteolysis-targeting chimeras (PROTACs), represent an emerging strategy capable of degrading previously difficult-to-target oncogenic proteins rather than simply inhibiting their activity. Although these approaches remain largely investigational, they illustrate the rapidly expanding therapeutic landscape beyond conventional pathway inhibition [84].

4.4. WNT signaling in GBM progression and invasion

The Wnt signaling pathway contributes to multiple hallmarks of GBM progression, including glioma stem cell maintenance, invasion, therapeutic resistance, and mesenchymal transition [85–88].

In glioma stem cells, Wnt/β-catenin activation promotes proliferation, self-renewal, and resistance to therapy, reinforcing its role in aggressive and recurrent GBM [88,89].

Wnt5a, a noncanonical Wnt ligand, has been linked to increased tumor cell motility and invasion across several cancers [85–87]. In GBM, Wnt5a may promote glioma migration and infiltration partly through upregulation of matrix metalloproteinases, which degrade the extracellular matrix and support local invasion [90–92]. In glioma stem cells, Wnt5a overexpression may induce a mesenchymal-like, highly migratory phenotype, further supporting its role in GBM invasion and treatment resistance [88,91,92].

4.5. PI3K/AKT/mTOR signaling and therapeutic resistance

The PI3K/AKT/mTOR pathway is a major regulator of cellular growth, metabolism, survival, and stress responses, and is among the most frequently dysregulated signaling networks in GBM [47,93]. Aberrant activation of this pathway promotes tumor proliferation, survival, invasion, metabolic adaptation, and resistance to apoptosis, thereby contributing substantially to GBM progression [47].

Activation of receptor tyrosine kinases such as EGFR and PDGFR stimulates PI3K signaling, resulting in downstream AKT and mTOR activation that enhances tumor cell growth and survival [93]. AKT promotes GBM cell survival through suppression of apoptosis and activation of pro-survival signaling pathways [94–96]. mTOR regulates protein synthesis, metabolism, and tumor growth downstream of AKT, and dysregulation of this axis contributes to therapeutic resistance in GBM [47,93].

PIK3CA mutations and PTEN loss are among the most common mechanisms underlying PI3K/AKT/mTOR activation in GBM and are associated with enhanced tumor survival, motility, and invasive capacity [97]. In PTEN-deficient GBM, dependence on specific PI3K isoforms such as p110β may further contribute to pathway complexity and therapeutic resistance [98].

Despite strong biological rationale, clinical translation of PI3K/AKT/mTOR inhibition has remained limited by pathway redundancy, compensatory signaling, toxicity, and inadequate CNS drug penetration [58,99,100].

The limited clinical success of PI3K/AKT/mTOR-targeted therapies highlights a broader challenge in GBM treatment: inhibition of a single signaling pathway often results in compensatory activation of alternative survival mechanisms. This adaptive plasticity may partly explain why promising preclinical findings have not consistently translated into meaningful clinical benefit. Combination therapies integrating PI3K pathway inhibition with immunotherapy, radiotherapy, or other targeted approaches may therefore be required to overcome resistance mechanisms more effectively [101].

Although mTOR inhibition suppresses protein synthesis and anabolic metabolism, GBM cells frequently exhibit adaptive metabolic plasticity that enables continued survival. Tumor cells can compensate by increasing glycolysis, glutamine metabolism, fatty acid oxidation, oxidative phosphorylation, and autophagy, thereby maintaining ATP production and biosynthetic capacity despite mTOR blockade [102–104]. This metabolic reprogramming,

together with compensatory activation of parallel signaling pathways, contributes to resistance against mTOR-targeted therapies and supports the rationale for combination treatment strategies targeting both signaling and tumor metabolism [102–104].

4.6. TGF-β signaling, immune evasion, and invasion

TGF-β signaling plays a major role in GBM progression through regulation of proliferation, invasion, immune suppression, apoptosis, and tumor cell plasticity [105,106]. Canonical TGF-β signaling occurs through phosphorylation and activation of SMAD transcription factors downstream of TGF-β receptors [105,107]. TGF-β also activates non-canonical pathways including Ras/Raf/MEK/ERK and PI3K/AKT signaling, promoting invasion and therapeutic resistance [107,108].

In GBM, dysregulated TGF-β signaling promotes tumor progression by enhancing invasion, angiogenesis, stem-like behavior, and resistance to cytotoxic therapy [107]. Elevated TGF-β activity has also been associated with more aggressive disease and poorer clinical outcomes in GBM patients [109]. GBM cells secrete TGF-β2 to suppress anti-tumor immune responses and facilitate immune evasion within the tumor microenvironment [110]. Upregulation of TGF-β isoforms further contributes to immune suppression, tumor invasion, angiogenesis, and resistance to radiotherapy and chemotherapy [111].

Given its broad influence across multiple tumor-promoting processes, TGF-β signaling remains an attractive therapeutic target, although effective clinical inhibition has proven challenging due to pathway complexity and systemic toxicity.

5. Why targeted therapies repeatedly fail in GBM

Despite major advances in the molecular understanding of glioblastoma, targeted therapies have rarely produced durable clinical benefit. This reflects the highly adaptive and heterogeneous nature of GBM, where multiple resistance mechanisms can sustain tumor growth even when a dominant pathway is inhibited.

A key barrier is intratumoral heterogeneity. Different tumor regions may contain distinct genetic alterations, signaling dependencies, and cellular phenotypes, allowing resistant subclones to survive targeted treatment. For example, EGFR amplification or EGFRvIII expression may be restricted to specific tumor populations, limiting the effectiveness of therapies directed at these alterations alone. This heterogeneity also promotes tumor evolution during treatment, as resistant clones are selected under therapeutic pressure.

Compensatory pathway activation further reduces the effectiveness of targeted agents. Inhibition of EGFR, PI3K/AKT/mTOR, or related signaling networks may trigger activation of alternative survival pathways, restoring proliferative signaling despite treatment. Cross-talk between EGFR, PI3K/AKT/mTOR, Wnt, MAPK, and TGF-β pathways creates signaling redundancy that undermines single-agent therapies.

Another major translational barrier is the blood-brain barrier and blood-tumor barrier. Although contrast-enhancing tumor regions show partial vascular disruption, infiltrative tumor cells often extend into brain regions where the barrier remains relatively intact. Endothelial tight junctions, pericytes, astrocytic end-feet, abnormal tumor vasculature, high interstitial pressure, and active efflux transporters such as P-glycoprotein and breast cancer resistance protein can restrict therapeutic drug accumulation within GBM tissue. Consequently, many agents with strong preclinical activity fail to achieve sufficient and spatially uniform concentrations in the CNS. Modern delivery strategies, including nanoparticle-based carriers, convection-enhanced delivery, focused ultrasound-mediated barrier disruption, implantable or intratumoural delivery systems, and engineered cellular therapies, are therefore increasingly being investigated to improve drug penetration into infiltrative tumor compartments.

Overall, the repeated failure of targeted therapies in GBM is unlikely to reflect a lack of relevant molecular targets. Rather, it reflects the difficulty of suppressing a dynamic tumor system characterized by heterogeneity, pathway redundancy, adaptive resistance, glioma stem cell persistence, and limited drug delivery across the blood–brain barrier. Future approaches will therefore need biomarker-guided combination therapies that target multiple resistance mechanisms simultaneously.

6. Future directions: toward biomarker-driven combination therapy

Future research should increasingly focus on overcoming the biological barriers that have repeatedly limited successful translation of targeted therapies into meaningful clinical benefit. Rather than relying on inhibition of

individual signaling pathways, future treatment strategies will likely require biomarker-driven combination therapies capable of simultaneously targeting multiple oncogenic pathways, glioma stem cells, and the immunosuppressive tumor microenvironment. Advances in next-generation sequencing, single-cell and spatial transcriptomics, CRISPR-based functional screening, molecular profiling, and AI-based radiomic/multimodal prognostic modeling are expected to improve patient stratification and enable more personalized therapeutic approaches [112,113].

Importantly, these technologies provide complementary information that may directly address several of the major barriers responsible for previous therapeutic failures. Single-cell and spatial transcriptomic analyses can identify resistant tumor subclones, characterize glioma stem cell niches, and reveal spatial interactions between tumor cells and the immune microenvironment that are not detectable using bulk sequencing [114,115]. CRISPR-based functional screening can prioritize genes essential for tumor survival and identify synthetic lethal interactions that may represent novel therapeutic vulnerabilities [116]. Among currently available biomarkers, MGMT promoter methylation remains the most clinically established predictor of temozolomide response, while EGFR amplification/EGFRvIII, FGFR3–TACC3 fusions, and emerging regorafenib-associated molecular signatures represent promising candidates for molecularly guided patient selection [7,117]. Of the emerging therapeutic strategies discussed in this review, regorafenib for recurrent disease, molecularly selected FGFR-targeted therapies, advanced CNS drug-delivery technologies, and next-generation cellular immunotherapies currently appear closest to broader clinical translation because each has demonstrated encouraging early clinical evidence while addressing recognized mechanisms of therapeutic resistance [62,118].

Improved drug delivery will also be essential. Nanoparticle-based drug carriers, convection-enhanced delivery, focused ultrasound-mediated blood–brain barrier disruption, engineered immune-cell therapies, and intratumoural delivery systems may enhance drug penetration into infiltrative tumor regions. Combining these technologies with emerging approaches such as antibody-drug conjugates, oncolytic viruses, CAR-T cells, and immune checkpoint blockade may ultimately produce greater therapeutic benefit than any individual modality alone [118,119].

Recent advances have also produced increasingly sophisticated targeted drug-delivery platforms. Stimuli-responsive nanocarriers capable of releasing therapeutic agents in response to tumor-specific conditions such as acidic pH, hypoxia, or elevated reactive oxygen species may improve selective intratumoural drug release while limiting systemic toxicity [120]. Dual-catalytic nanosponges are being investigated to remodel the glioblastoma microenvironment by simultaneously enhancing oxidative stress and disrupting tumor metabolism, thereby improving therapeutic efficacy. In addition, receptor-specific peptide conjugates targeting glioma stem cell-associated markers, including CD133, integrin α6 (ITGA6), or transferrin receptor-mediated pathways, may enhance selective tumor uptake and local drug bioavailability while reducing off-target exposure. Although these technologies remain largely preclinical, they represent promising strategies for overcoming blood-brain barrier limitations and improving delivery of pathway-directed therapies [121–123].

7. Limitations

This review has several limitations. As a narrative review, article selection was not performed using formal systematic-review methodology and may therefore be subject to selection bias. Additionally, the rapidly evolving nature of molecular neuro-oncology means that emerging therapeutic strategies and biomarker discoveries may continue to alter the current understanding of GBM biology and treatment. Some therapeutic approaches discussed remain supported primarily by preclinical or early-phase clinical evidence and therefore require further validation in larger prospective studies.

8. Conclusion

IDH-wildtype glioblastoma remains one of the most therapeutically challenging primary brain malignancies owing to extensive molecular heterogeneity, infiltrative growth, and the persistence of glioma stem cells, which collectively promote treatment resistance and tumor recurrence. Dysregulation of signaling pathways including EGFR, PI3K/AKT/mTOR, Wnt, and TGF-β contributes not only to tumor proliferation and invasion, but also to adaptive resistance, immune evasion, and glioma stem cell maintenance. Although these pathways provide biologically compelling therapeutic targets, clinical translation has been hindered by pathway

redundancy, compensatory signaling, intratumoral heterogeneity, and limited drug delivery across the blood–brain barrier. Future progress in GBM treatment will likely depend on integrated molecular profiling, biomarker-driven patient stratification, and rational combination therapies capable of simultaneously targeting multiple tumor-promoting mechanisms.

9. Future perspective

Over the next 5–10 years, GBM management is likely to shift toward increasingly personalized, biomarker-driven treatment strategies guided by comprehensive molecular profiling, single-cell and spatial transcriptomics, and artificial intelligence-assisted clinical decision support. Rather than relying on single-agent targeted therapies, future treatment paradigms will likely employ rational combination approaches that simultaneously target multiple dysregulated signaling pathways, GSCs, and the immunosuppressive tumor microenvironment. Advances in central nervous system drug-delivery technologies, including nanoparticle-based systems, focused ultrasound-mediated blood–brain barrier disruption, and engineered cellular therapies, may further improve therapeutic efficacy. Continued integration of genomic, transcriptomic, radiomic, and clinical data is expected to enhance patient stratification, accelerate precision medicine approaches, and support the development of more effective therapies capable of improving long-term outcomes for patients with GBM.

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Author contributions

CRediT: **William Li**: Conceptualization, Formal analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing; **Jia Ming Chen**: Supervision, Writing – review & editing; **Yi Chao Ma**: Supervision, Writing – review & editing.

Author contributions (CRediT)

William Li and Jia Ming Chen undertook conceptualization, investigation, revisions, and writing.

Yi Chao Ma contributed to supervision, critical review and editing of the manuscript, and project oversight.

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