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Glioblastoma

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Abstract

Glioblastoma (GBM) is the most common and aggressive malignant brain tumor in adults, with a five-year survival rate of approximately 7%. Despite maximal surgical resection followed by radiotherapy and alkylating chemotherapy, most patients experience recurrence, reflecting the tumor's marked biological heterogeneity and resistance to treatment. This review examines how cellular plasticity within cancer stem-like populations, epigenetic regulation, and microenvironmental signaling contribute to therapeutic failure in GBM, and how emerging AI-based imaging approaches may complement existing strategies.

Single-cell and functional studies support a state-based model of glioblastoma stem cells (GSCs), in which stem-like properties are dynamically acquired and lost in response to microenvironmental cues and therapeutic pressure. Hypoxic and perivascular niches stabilize these states, while epigenetic programs involving regulators such as EZH2, BMI1, and histone deacetylases shape transcriptional responses that promote stress tolerance and persistence. Developmental pathways, including Notch, further modulate these programs in a context-dependent manner. Together, these mechanisms help explain how GBM evades eradication and re-establishes disease after treatment.

Clinically, recent advances such as Tumor Treating Fields have produced modest survival gains, and molecular biomarkers enable limited stratification. Radiomic and machine learning approaches extend personalization by extracting quantitative features from routine magnetic resonance imaging (MRI), but remain constrained by cohort size, imaging variability, and interpretability.

Integrating insights from stem cell biology, epigenetic regulation, and AI-assisted diagnostics reframes GBM as a dynamic, state-driven disease. Progress is therefore likely to depend on strategies that address plasticity and heterogeneity while combining biological and computational approaches to guide more adaptive and individualized care.

Keywords: glioblastoma; cancer stem cell; epigenetic regulation; tumor microenvironment; cellular plasticity

Introduction and Definition

Glioblastoma (GBM) is the most common and aggressive malignant brain tumor in adults, representing nearly half of all cases. With a five-year survival rate of just 7%, it has one of the poorest prognoses among adult cancers. Incidence rates peak between 75 and 84 years, and while advancements in GBM therapy continue, survival rates remain stagnant [1].

According to the World Health Organization (WHO) classification, GBM is defined by specific histological and molecular criteria, with isocitrate dehydrogenase (IDH)-wildtype glioblastomas typically classified as CNS WHO grade 4 tumors. IDH refers to the isocitrate dehydrogenase enzymes encoded by IDH1 and IDH2. Mutations in these genes define a major molecular class of adult-type diffuse gliomas that is distinct from IDH-wildtype gliomas and reflects a different underlying molecular pathogenesis. IDH-wildtype refers to a lack of mutation in the IDH1 and IDH2 genes. Three genetic parameters diagnose GBM grade 4 even in cases where the tumor's histology would suggest a lower grade. These parameters include: presence of a telomerase reverse transcriptase (TERT) promoter mutation, increased copies of the epidermal growth factor receptor (EGFR) gene, and the gain and loss of chromosome 7 and 10 respectively (+7/−10) [2].

A major contributor to the poor prognosis of Glioblastoma includes the high degree of cellular diversity within the tumor, often referred to as "intratumoral heterogeneity" [3]. Glioblastoma tends to migrate quickly into brain tissue, making it hard to remove during resection. The migratory nature of the tumor also carries a high rate of recurrence that diverges from the original tumor, limiting the predictive value of initial biopsies.

There is currently an ongoing search for better treatment methods to combat GBM's aggressive nature and recurrence. Gaining a deeper understanding of the

molecular processes, mechanisms of resistance, and pathogenesis of GBM can allow us to build upon current predictive strategies and therapies. Emerging technologies like radiomic analysis are now being explored to address these challenges and improve patient outcomes.

This entry will explore and synthesize recent information regarding the current understanding of glioblastoma with the assistance of AI chatbots, particularly using Deepseek for concise and clear communication.

Body

Cellular Pathogenesis

One hypothesis that attempts to explain the progression and propagation of GBM is the cancer stem cell hypothesis. Early transcriptional classification of glioblastoma relied on bulk DNA and RNA profiling, which revealed mixed transcriptional signals within tumors, but it could not resolve the underlying cellular heterogeneity. Advances in single-cell transcriptomic profiling have since revealed structured cellular states within tumors, including a continuum of stemness associated with cancer stem-like behavior [4]. These insights reframed the cancer stem cell concept by clarifying how stem-like properties are distributed across tumor cell populations. Rather than being confined to a fixed subpopulation, stem-like transcriptional programs appear to be variably expressed across tumor cells and influenced by cellular context [4, 5].

Cancer stem cells (CSCs), as well as glioblastoma stem cells (GSCs), are defined by their capacity for self-renewal and tumor propagation [5, 6]. Rather than behaving as a uniform population, GBM tumors exhibit marked cellular heterogeneity, with stem-like properties enriched in a subset of cells at any given time, while remaining dynamically regulated through cellular plasticity [5–7]. Genomic analyses support a state-based model of CSC identity, with multiple putative CSC-associated transcriptional programs rather than a single conserved stem-like signature [5]. This plasticity can complicate therapeutic targeting because CSC identity is not always cleanly separable from non-stem-like tumor cells. As a result, therapies aimed at eliminating CSCs may find it difficult to selectively target all tumor-propagating cells.

Cellular plasticity in glioblastoma enables tumor cells to reversibly transition between stem-like and non-stem-like states under the influence of microenvironmental cues and therapeutic pressure, including chemotherapy and radiation [5]. In temozolomide-treated glioblastoma models, a quiescent CSC population persists during treatment, becomes relatively enriched, and can later re-enter the cell cycle after therapy, contributing to tumor regrowth [6]. Moreover, experimental studies demonstrate that differentiated neural lineage cells can reacquire stem-like molecular and phenotypic features under defined oncogenic and environmental conditions, establishing the feasibility of dedifferentiation programs in glioma [8]. Together, these findings support a model in which GBM recurrence may arise from both the persistence of stem-like states during therapy and the potential reacquisition of stem-like properties under permissive conditions. In the example of temozolomide-treated mouse and patient-derived xenograft models, quiescent stem-like populations persist during therapy and can subsequently exit quiescence, re-enter the cell cycle, and contribute to tumor regrowth, consistent with a role in post-treatment recurrence.

Extending the CSC framework into its spatial context, features of the tumor microenvironment (TME) play a central role in stabilizing stem-like states in GBM. For instance, hypoxia, a component of a hypoxic or necrotic microenvironment, is characterised by insufficient perfusion, elevated hypoxia inducible factor (HIF) signaling and pro-angiogenic programs that support stem-like maintenance [7]. Hypoxia stabilizes hypoxia-inducible factors (HIFs), which activate transcriptional programs in GSCs that enhance their self-renewal, promote angiogenesis (the formation of new blood vessels), and increase invasive potential. While hypoxia is most pronounced in peri-necrotic regions, it also intersects with vascular organization to shape multiple stem-supportive niches within GBM [7]. In perivascular niches, direct interactions between GSCs and endothelial cells, along with extracellular matrix components and secreted factors such as osteopontin, provide signals that maintain stem-like states and suppress differentiation. Together, peri-necrotic and perivascular niches constitute spatially defined microenvironments that converge to provide oxygen gradients, vascular-derived cues, and paracrine signaling to promote GSC maintenance and therapeutic resistance [3, 7].

While the cancer stem cell hypothesis shows promising evidence into the pathogenesis of GBM, some limitations should be addressed. First, defining CSCs by markers or transcriptional stemness alone can be ambiguous, and functional validation remains central to distinguishing stem-like tumor propagating states from other tumor cell states; accordingly, GSCs should not be conflated with the tumor cell of origin, as stem-like properties can emerge independently of the initial cell type [3, 5]. Second, tumor heterogeneity remains difficult to model in vitro and xenograft systems rely on artificial culture conditions and can incompletely capture the vascular, immune, and hypoxic microenvironments that regulate stem-like behavior [3, 5]. Third, CSC biomarkers such as CD133 are not universally expressed across GBM tumors, limiting their reliability as universal identifiers; consequently, marker-based enrichment strategies typically require specimen-specific validation rather than assuming a conserved CSC marker across tumors [3, 5].

Epigenetic Mechanisms of Resistance

Epigenetic dysregulation is an important contributor to glioblastoma heterogeneity. Epigenetic mechanisms regulate gene expression without altering the DNA

sequence and include DNA methylation, histone modifications, and chromatin remodeling [9]. In GBM, distinct epigenetic programs are associated with stem-like tumor cells in a state- and microenvironment-dependent manner. These programs are not uniformly fixed across tumors but vary with local conditions, aligning with transcriptional states that support proliferation or stress adaptation. Proneural and mesenchymal glioma stem-like cells rely on different epigenetic regulators, with EZH2-associated programs enriched in proneural, perivascular states and BMI1-associated programs linked to mesenchymal and hypoxic conditions, where they support stem-like phenotypes under environmental stress [10, 11]. This organization of epigenetic programs contributes to functional heterogeneity within GBM tumors and has implications for therapeutic response.

Developmental signaling pathways, including Notch, play important roles in shaping transcriptional programs in glioblastoma. Notch signaling functions as a cell–cell communication pathway that regulates cell fate decisions, differentiation state, and proliferative capacity through receptor-specific and context-dependent transcriptional effects, rather than acting as a simple on–off driver of tumor growth. Differential expression of individual Notch receptors has been linked to glioma grade and cellular identity, with elevated Notch4 expression observed in grade 4 glioblastoma and associated with less differentiated, stem-like tumor phenotypes [12]. Other studies demonstrate context-dependent interactions between Notch signaling and EGFR expression, as well as variable associations with apoptotic signaling, underscoring the heterogeneity of Notch pathway activity across molecular GBM subtypes [13]. In parallel, epigenetic regulators such as histone deacetylases are frequently dysregulated in GBM and contribute to altered chromatin states and transcriptional programs that support tumor maintenance and cellular plasticity [11].

Histone deacetylases (HDACs) are key components of the epigenetic machinery that shape transcriptional programs in glioblastoma. By regulating histone acetylation, HDACs influence chromatin accessibility and gene expression, contributing to the maintenance of oncogenic transcriptional states. Dysregulation of HDAC activity has been implicated in glioma-associated epigenetic alterations, making these enzymes targets of therapeutic interest [11, 14]. HDAC inhibitors are actively being investigated in GBM, including in combination with radiation and alkylating chemotherapy, as reflected in early-phase clinical trials [11]. In addition, preclinical studies in non-GBM tumor models indicate that HDAC inhibition can modulate antitumor immune responses, providing a rationale for exploring epigenetic-immunotherapy combinations, although their efficacy in GBM remains under investigation [15, 16]. Together, these epigenetic programs provide a mechanistic basis for the failure of conventional cytotoxic therapies to achieve durable disease control in GBM and motivate the development of treatment strategies that either disrupt adaptive transcriptional states or incorporate them into patient stratification and therapeutic design.

Current and Advancing Treatment Methods

Standard care for newly diagnosed glioblastoma in patients younger than 70 remains maximal safe resection followed by radiotherapy with concomitant and adjuvant temozolomide, with carmustine (BCNU) wafers used in selected cases. Despite this aggressive multimodal approach, most patients experience tumor recurrence [17]. The addition of Tumor Treating Fields (TTFields) to maintenance temozolomide represents one of the few recent advances to demonstrate a survival benefit. In the EF-14 trial, TTFields extended median overall survival from 16.0 to 20.9 months, a 4.9-month increase, and raised the actuarial 5-year survival estimate from 5% to 13%. TTFields deliver low intensity, alternating electric fields that disrupt mitosis in dividing tumor cells, producing antimitotic and pro-apoptotic effects [18]. Even with this advance, long-term outcomes remain poor, emphasizing the need for more individualized strategies.

Personalization is currently anchored in molecular biomarkers. A systematic review and meta-analysis show that MGMT promoter methylation and IDH1 mutation are significantly associated with improved overall survival in GBM. MGMT methylation is a positive prognostic marker, particularly in patients treated with alkylating agents such as temozolomide, while IDH1 mutation confers an independent survival advantage [19]. These markers illustrate the value of molecular stratification, but they capture only a fraction of GBM's biological heterogeneity.

Radiomics and machine learning aim to extend personalization by extracting high-dimensional quantitative features from routine MRI. Deep learning and radiomic models can achieve high diagnostic accuracy and outperform conventional radiologic assessment in tasks such as distinguishing GBM from metastases. However, these methods are not yet clinic-ready. Limitations include relatively small, single-institution cohorts, sensitivity of features to scanner and acquisition variability, and limited biological interpretability [20]. In the treatment-response setting, Patel et al. highlight that post-therapy MRI changes often reflect a mixture of tumor progression and treatment effects, complicating ground-truth assignment. Their work underscores that current radiomic models, while promising, remain constrained by segmentation burden, heterogeneous imaging pipelines, and single-center data [21].

Future work therefore focuses on broader validation across institutions [21], reducing sensitivity to scanner and acquisition differences, and combining imaging with clinical and molecular data to improve model reliability [20]. Rather than replacing histopathology, radiomics and machine learning are best viewed as decision-support tools

that refine risk stratification and move GBM care toward genuinely personalized treatment.

Conclusion

Glioblastoma is characterized by pronounced biological diversity, invasive growth, and a high likelihood of recurrence after treatment. The evidence reviewed in this paper supports a model in which stem-like tumor-propagating states are not confined to a single, stable subpopulation, but instead exist along a continuum shaped by cellular context, microenvironmental cues, and therapeutic pressure. These states are stabilized within spatially defined niches influenced by hypoxia, vascular signaling, and paracrine interactions, while epigenetic regulation and developmental pathways such as Notch contribute to state-specific transcriptional programs. As a result, cellular identity in GBM is dynamic rather than fixed, complicating attempts to target "cancer stem cells" as a discrete entity.

Clinically, management remains centered on maximal resection followed by radiotherapy and temozolomide, with most patients developing recurrent disease. The addition of Tumor Treating Fields has produced a modest survival benefit, but long-term outcomes remain limited. Molecular biomarkers such as MGMT promoter methylation and IDH1 mutation provide valuable prognostic and predictive information, yet they capture only part of the biological variability observed within and between tumors. Radiomic and machine learning approaches extend this effort by extracting quantitative information from routine imaging, but their current utility is constrained by cohort size, variability in imaging protocols, and challenges in biological interpretation and response assessment.

Taken together, the literature portrays GBM as a disease shaped by interacting layers of heterogeneity across cellular state, microenvironment, epigenetic regulation, and clinical phenotype. Progress is therefore likely to depend on approaches that integrate these dimensions rather than treating them in isolation.

List of Abbreviations

CSC: cancer stem cell
GBM: glioblastoma
GSC: glioblastoma stem cell
HDAC: histone deacetylase
HIF: hypoxia-inducible factor
IDH: isocitrate dehydrogenase
TME: tumor microenvironment
TTFields: tumor treating fields
WHO: World Health Organization

Conflicts of Interest

The author declares that they have no conflicts of interest.

Authors' Contributions

JAY: made substantial contributions to the literature search, the generation of prompts, drafting and editing the manuscript, and submitting the final version of the manuscript for publication.

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