Neuroscience
Volume 420, 1 November 2026, Pages 102-119

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Targeting glioblastoma epigenetics: mechanisms, microenvironmental interplay, and therapeutic potential

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Highlights

- Glioblastoma is an aggressive, invasive malignancy with near-inevitable recurrence, posing a major clinical challenge.
- Complex epigenomic pathways drive glioblastoma progression and cellular heterogeneity.
- Epigenetic modifications are promising therapeutic targets that could be manipulated to improve outcomes.
- This review discusses the epigenetic landscape of the glioblastoma microenvironment and its therapeutic targeting potential.

Abstract

Glioblastoma (GBM) is an intricate intracranial tumor that has catastrophic outlook. It originates from glial cells having an average life expectancy of one and a half years. Despite intensive multimodal therapy, the tumor's innate treatment resistance and high recurrence rate lead to nearly inevitable recurrence. Recent advancements have shifted the focus toward the interplay between genetic drivers and the tumor microenvironment landscape. WHO classification defined GBM as an IDH-wildtype tumor, distinguishing it from IDH-mutant. Present review explores the complex epigenetic mechanisms such as DNA methylation, histone modification and RNA editing that drive GBM progression, shape the tumor microenvironment and facilitate immune evasion. The review further discusses severe translational barriers, including blood brain barrier penetrance, tumor heterogeneity, and the immunosuppressive effects of steroids. Finally, we highlight the therapeutic potential of targeting these epigenetic vulnerabilities through inhibitors of histone deacetylase and DNA methyltransferase, either alone or combined with modern immunotherapies to overcome treatment resistance and improve patient outcomes.

Graphical abstract

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Introduction

Glioblastoma (GBM) is a complicated intracranial tumor that originates from glial cells characterized by fulminant tumor expansion, extensive infiltration into healthy parenchyma and remarkable heterogeneity contributing to tumor's resistance to conventional therapies (Dvorsky et al., 2021). Despite the integrated therapy, the average life expectancy for adults with glioma is between 14 and 30months, while for children with glioma, it is between 10 and 30months (Mackay et al., 2017, Komaei et al., 2018). Globally, 3.1 individuals out of every 100,000 are diagnosed with GBM annually, making it responsible for nearly half of all brain tumor cases. However, clinical evidence analysis a handful of established risk factor such as genetic predisposition, exposure to ionizing radiation, and certain hereditary syndrome (Spoto et al., 2025).

Based on the 2021 WHO classification of the central nervous system tumors, GBM is defined as an isocitrate dehydrogenase (IDH)-wildtype tumor, whereas tumors harboring mutations in the IDH1 or IDH2 gene are classified separately as astrocytoma, IDH-mutant. The first line treatment remains maximal safe surgical resection, succeeded by irradiation treatment and anti-neoplastic therapy. However, because of its infiltrative property, complete removal of glioma is nearly impractical. Residual glioma progression inevitably occurs and TMZ is highly liable to drug resistance (Hu et al., 2023a). The effectiveness of TMZ is further compromised by severe inter- and intra-tumor heterogeneity as well as local immunosuppression which physically and biologically restricts drug delivery. Additionally, TMZ-based treatments frequently produce hematologic toxicities (Gerber et al., 2007, Wu et al., 2021). Nonetheless, irradiation therapy must be tuned meticulously, since it can spawn critical or permanent damage to the CNS. These treatment primarily manage symptoms rather than offering a cure, so it is important to look into the biological processes that cause GBM to get worse (Bleeker and O'Rourke, 2022, Liu et al., 2022). These biological mechanisms encompass signaling networks, metabolic irregularities, genetic and epigenetic alterations. For an extended period, it was believed that gene mutations were the sole contributors to the development of cancer. Nonetheless, as our comprehension of cancer biology has progressed, data indicates that abnormal epigenetic modifications are essential for nearly every phase of tumor development and dissemination (Yang and Vousden, 2011). Tumorigenesis can result from modifications in gene expression, often due to the malfunction of epigenetic modifications, like chromatin remodeling and co-translational changes of DNA and histones (DeCarvo et al., 2003). This review examines the genetic and epigenetic mechanisms governing the GBM tumor microenvironment (TME) and its prospective therapeutic targets.

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Section snippets

Epigenetic microenvironment of glioblastoma

Glioma microenvironment is uniquely characterized by its interaction with blood brain barrier (BBB). The surrounding BBB maintains the cerebral homeostasis by excluding the neurotoxins, peripheral leucocytes as well as therapeutic molecules, while facilitating the influx of essential nutrients (Kim et al., 2021). Through secretion of vascular permeability factors and maturation, tumor facilitates the breakdown tight junction (TJ) proteins and basal lamina components (Dasenaun and Prat, 2015) ....

Tumor immune microenvironment (TIME)

The TIME is a complicated, constantly shifting ecosystem encircling tumor, consisting of immunocytes, mesenchymal stem cells and extracellular messengers acting as a double-edge sword, either stimulating or inhibiting tumor progression (Kacarska et al., 2025). GBM actively shapes the hostile environment, by manipulating the TIME that severely suppresses antitumor response leading to immune evasion. Depending on their function the immunocytes are bifurcated into two classes, pro-tumor or ....

TME metabolic reprogramming

GBM is fundamentally characterized by the Warburg effect, where tumor cells preserve energy through aerobic glycolysis even in oxygen replete conditions (Bélanger et al., 2011, Kucharzewska et al., 2015, Bruce et al., 2017). Under hypoxic environment, the deactivation of prolyl hydroxylase domain proteins allows HIF-1α to stabilize and imported into the nucleus. There, it interacts with hypoxia-responsive elements, directly upregulating glucose transporters and lactate dehydrogenase A to ....

DNA methylation dynamics

DNA methylation conducted by DNA methyl-transferase (DNMT) to the cytosine within cytosine phosphate-guanine dinucleotides has a significant impact on formation of brain tumor. Aberrant DNA methylation is a paradoxical pattern characterize by global hypomethylation occurring simultaneously with hypermethylation of CpG islands. Mutation in IDH1 or IDH2 genes leads to the production in α-ketoglutarate (α-KG) level and subsequently produces D-2-hydroxyglutarate (2-HG) leading towards inhibition of ....

BBB/BBTB

The fundamental obstacle in the management of GBM is the restriction of drug delivery imposed by the BBB/BBTB. The BBB is damaged in GBM leading to the formation of leaky BBTB due to downregulation of tight junction proteins like claudin-1 and VEGF. The enhanced permeability and retention are primarily confined to the necrotic core and the tumor mass. Research indicates that the pore size of BBTB in intracranial models ranges from 7–100nm, severely restricting the passive diffusion of large ....

Optimal sequencing and radiotherapy modalities

Determining the appropriate order of surgery, radiotherapy (RT), and chemotherapy is a complex clinical challenge in neuro-oncology. Stupp and colleagues established a standard treatment sequence for newly diagnosed GBM patients aged between 18–70. The optimal regimen involves administering focal RT along with daily TMZ, followed by an additional six months of TMZ therapy. This combination reduced the relative risk of mortality by 37%, achieving a 2-year survival rate of 26.5% compared to ....

Immune-cold microenvironment and steroid exposure

Despite the monumental success of immune-checkpoint inhibitors (ICIs) such as anti-PD-1 (nivolumab, pembrolizumab) and anti-CTLA-4 (ipilimumab) in melanoma and non-small lung cancer, these agents have failed to demonstrate an overall survival benefit in phase III GBM trials, including "immune-cold" phenotype of the GBM microenvironment, which operates on multiple interconnected immunosuppressive axes (Schoenhoft et al., n.d.). First, antigen-poorly unevenly limits immune recognition. GBM tumor ....

Pseudo-progression and necrosis

Accurate non-invasive imaging is crucial to assess the therapeutic efficacy of treatment. For years, the standard approach was based on Macdonald criteria, which evaluated tumor progression was based on 2D measurements of post-gadolinium T1 weighted MRIs. A 25% or greater increase in the cross-sectional area was interpreted as progression of treatment failure (Wen et al., 2010). The underlying problem with this approach is that contrast enhancement primarily highlights the compromised BBB, where gadolinium is ....

Biomarker-guided patient selection

The traditional framework for oncology clinical trials is inefficient for an aggressive disease like GBM. Developing a single compound through pipeline often requires a decade, only to fail in phase III due to reliance on unvalidated surrogate endpoints or inadequate control arms in early phase (Alexander et al., 2017). The New Approaches in Brain Tumor Therapy (NABTT) recommends implementing this by running single-cohort phase II studies combining RT and TMZ with novel agents, attempting to ....

Immunotherapy

Tumor initiation and progression are deeply intertwined with the host's immune system (Schreiber et al., 2011). In the early stages, immune cells actively seek and destroy malignancies. However, if the tumor is not entirely eliminated, a state of equilibrium takes place where highly unstable tumor cells are forced into dormancy by adaptive immune components, specifically T lymphocytes, IFN-γ, and IL-12 (Aqbi et al., 2018, Jahanban-Esfahlan et al., 2019). Eventually, these cells undergo ....

CRediT authorship contribution statement

Swapnil Raut: Writing – original draft, Conceptualization. **Lokesh Kumar Bhatt:** Writing – review & editing, Conceptualization. ....

Funding

None. ....

Data availability

No datasets were generated or analyzed during this study. ....

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. ....

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