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Opinion article

# Tumor Microenvironment Epigenetic Interactions in Glioblastoma

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## DESCRIPTION

The complex epigenetic interactions between glioblastoma cells and their microenvironment create therapeutic vulnerabilities and influence treatment response, offering new targets for intervention. Glioblastoma (GBM) is the most aggressive primary brain tumor, characterized by extensive intratumoral heterogeneity and resistance to conventional therapies. The Tumor Microenvironment (TME) plays a key role in GBM progression, with epigenetic modifications serving as key mediators of cell-cell communication and adaptive responses to therapeutic stress.

The hypoxic environment characteristic of GBM promotes extensive epigenetic reprogramming through Hypoxia-Inducible Factors (HIFs). HIF-1α activation leads to the recruitment of histone demethylases such as *JMJD2B* and *KDM3A*, which remove repressive marks from hypoxia-responsive genes. This creates a permissive chromatin environment for the expression of angiogenesis, metabolism, and invasion-related genes.

Tumor-Associated Macrophages (TAMs) represent a significant component of the GBM microenvironment and exhibit distinct epigenetic profiles compared to normal brain microglia. TAMs show increased DNA methylation at immune activation gene promoters, maintaining them in an immunosuppressive M2-like phenotype. The methylation of the CD40 promoter in TAMs prevents their activation and contributes to the immunosuppressive microenvironment. The interaction between GBM cells and astrocytes involves extensive epigenetic crosstalk. Reactive astrocytes in the tumor microenvironment release factors that promote histone modifications in GBM cells, including increased H3K27ac at enhancer regions of invasion-related genes. This epigenetic activation enhances the invasive capacity of GBM cells and contributes to treatment resistance.

The Blood-Brain Barrier (BBB) poses unique challenges for GBM treatment, and epigenetic modifications in endothelial cells influence BBB permeability. GBM-secreted factors induce DNA methylation changes in brain endothelial cells, leading to altered expression of tight junction proteins and increased vascular permeability. Understanding these epigenetic changes may help develop strategies to improve drug delivery to brain tumors.

Immune cell infiltration in GBM is limited, partly due to epigenetic silencing of immune-related genes. The promoter of *CXCL10*, a chemokine that attracts T cells, is frequently hypermethylated in GBM, reducing immune cell recruitment. Demethylating agents can restore *CXCL10* expression and improve immune cell infiltration, suggesting potential for combination immunotherapy approaches.

The IDH1 mutation, present in approximately 10% of GBMs, creates a unique epigenetic landscape through the production of the oncometabolite 2-Hydroxyglutarate (2-HG). 2-HG inhibits TET enzymes and α-ketoglutarate-dependent dioxygenases, leading to the CpG Island Methylator Phenotype (CIMP). This extensive hypermethylation affects thousands of genes and creates distinct therapeutic vulnerabilities. Extracellular Vesicles (EVs) released by GBM cells carry epigenetic information that can reprogram recipient cells in the microenvironment. GBM-derived EVs contain microRNAs that promote angiogenesis and suppress immune responses in target cells. The miR-21 carried by GBM EVs, for example, promotes M2 macrophage polarization and enhances tumor progression.

## CONCLUSION

The mechanical properties of the GBM microenvironment also influence epigenetic regulation. The stiff extracellular matrix characteristic of GBM activates mechanotransduction pathways that regulate chromatin organization and gene expression. YAP/TAZ signaling, activated by mechanical stress, promotes the expression of epigenetic modifiers that maintain stem cell characteristics. Therapeutic targeting of microenvironment-mediated epigenetic changes represents a promising approach for GBM treatment. Combination therapies that include epigenetic modulators, such as HDAC inhibitors or DNA methyltransferase inhibitors, along with standard-of-care treatments, have shown enhanced efficacy in preclinical models. The development of brain-penetrant epigenetic drugs is crucial for successful GBM treatment. Several epigenetic inhibitors with improved BBB penetration are being developed, including novel HDAC inhibitors and DNA methyltransferase inhibitors designed specifically for brain tumor treatment.

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