



Review Article

The Epigenetic–Metabolic Axis in Gliomas: Mechanisms and Implications



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Abstract

Gliomas remain a major challenge in brain cancer treatment. Although genetic mutations have been widely studied, recent research indicates that epigenetic changes, which alter gene activity without changing the DNA sequence, also contribute significantly to tumor growth and treatment resistance. This review seeks to elucidate the principal drivers and modulators of brain tumor development, emphasizing the complex interaction between tumor metabolism and epigenetic regulation. It highlights how metabolic intermediates influence chromatin structure and transcriptional events driving glioma progression. Metabolic intermediates, such as acetyl-CoA and S-adenosylmethionine, serve as essential epigenetic cofactors, directly impacting chromatin structure and gene expression. Additionally, metabolic disorders like diabetes not only frequently coexist with gliomas but also exacerbate tumor progression through mechanisms such as inflammation, oxidative stress, and epigenetic reprogramming. Tumors located near brain regions controlling heart function may also increase the risk of sudden death, particularly in diabetic patients. The review proposes a comprehensive framework to understand glioma development by linking metabolism, epigenetics, and overall health. This integrated perspective leads to novel personalized treatment approaches, targeting both the tumor and the patient's broader metabolic health, with the potential to improve survival rates and quality of life for glioma patients.

Introduction

According to the 2021 World Health Organization Classification of Central Nervous System (CNS) Tumors, brain tumors are mainly grouped into several primary categories.¹ These categories consist of gliomas, glioneuronal tumors (which can be either diffuse or circumscribed), ependymomas, and choroid plexus tumors. Another separate category includes embryonal tumors, such as medulloblastomas and atypical teratoid/rhabdoid tumors. Additional categories encompass pineal tumors, tumors of cranial and paraspinal nerves, meningiomas, mesenchymal tumors, melanocytic and hematolymphoid tumors, germ cell tumors, tumors in the sellar region, and metastatic tumors affecting the CNS. Gliomas are the most frequently diagnosed types of primary brain tumors. They vary in aggressiveness, ranging from slow-growing astrocytomas to the more aggressive glioblastoma multiforme (GBM), also known as glioblastoma, isocitrate dehydrogenase wild type. In

contrast, meningiomas, which arise from the protective covering of the brain, are typically benign; however, some may display malignant features.^{2,3} Medulloblastomas primarily occur in children and present considerable treatment challenges. The prognosis depends on the type, location, and molecular properties of the tumor.⁴

Despite advancements in neurosurgery, radiotherapy, and targeted therapies, managing high-grade gliomas, medulloblastomas, and atypical teratoid/rhabdoid tumors remains difficult.^{5,6} Numerous brain tumor survivors face significant neurological impairments, seizures, and cognitive obstacles, highlighting the need for innovative approaches to improve these outcomes and mitigate long-term effects.^{7,8} Nevertheless, researchers can only create new treatments by enhancing their comprehension of the molecular and epigenetic variations in brain tumors.^{9,10} This approach may uncover novel treatment targets and enhance the outlook for survivors. Scientists widely recognize that epigenetics, defined as heritable modifications in gene expression without changes to the DNA sequence, drives tumor initiation, progression, metastasis, and resistance to therapies.

The four primary epigenetic mechanisms that control gene expression and cellular activity include DNA methylation, modifications of histones, chromatin remodeling processes, and non-coding RNAs (ncRNAs).^{11–13} Irregularities in epigenetic regulation contribute to tumor formation and treatment resistance.¹⁴ For example, the methylation pattern of the O6-methylguanine-DNA methyltransferase (MGMT) promoter serves as a crucial predic-

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tive biomarker for the response of glioblastoma to alkylating chemotherapy.^{15,16} MGMT plays a vital role in repairing DNA damage caused by alkylating agents, such as temozolomide, by removing alkyl groups from the O6 position of guanine.¹⁷ Therefore, the status of MGMT methylation is a key aspect in evaluating treatment effectiveness, indicating the importance of epigenetic changes in cancer therapy. Similarly, changes in chromatin remodelers, such as those affecting the SWItch/Sucrose Non-Fermentable (SWI/SNF) complex, can alter chromatin accessibility, which may lead to more aggressive tumors.^{18,19} In addition to these modifications concerning DNA and histones, ncRNAs also impact the tumor microenvironment (TME), microRNAs (miRNAs) such as miR-21 and miR-10b promote tumor growth and invasion, while the tumor-suppressive long non-coding RNA (lncRNA) maternally expressed gene 3 is frequently silenced, contributing to uncontrolled tumor growth.^{20,21} Deciphering these intricate epigenetic networks opens new pathways for precision medicine, where targeted treatments aim to intervene with crucial epigenetic regulators. By integrating epigenetic insights into treatment protocols, scientists can refine therapeutic approaches, enhance patient outcomes, and ultimately address the persistent challenges in managing brain tumors.^{22,23}

Gliomas, meningiomas, and metastatic brain tumors are among the most common types of brain tumors. However, this review specifically focuses on gliomas, which will be the manuscript's primary subject. This review is structured around a cohesive framework that investigates how epigenetic dysregulation, metabolic alterations, and neurocardiovascular signaling are interrelated in influencing the biology and clinical outcomes of gliomas. The first aim is to gather the latest information on the epigenetic landscape of brain tumors, highlighting critical regulatory mechanisms, their interactions with tumor metabolism, and their importance for treatment responses and disease progression, especially concerning glioblastoma. The second aim is to identify the metabolic-epigenetic feedback loops that exist in gliomas, emphasizing that metabolic reprogramming is an acknowledged feature across all cancers and discussing evidence that systemic factors, such as diabetes, may worsen these pathways and promote glioma development. The final aim is to integrate emerging findings on how epigenetic changes associated with gliomas might be linked to dysfunction within the brain-heart axis, an increasingly important area in neurocardiology, and to examine how these interconnected mechanisms may contribute to the increased cardiovascular mortality observed in glioma patients. Essentially, this review presents a conceptual framework designed to direct future research towards targeted, mechanism-driven, personalized treatment approaches for gliomas. In this regard, the review discusses the key epigenetic pathways implicated in brain tumor development and their connections to metabolic reprogramming within these tumors. Furthermore, this framework relates to cardiovascular disease by underlining common factors such as oxidative stress, mitochondrial dysfunction, and inflammation. The review concludes with clinical and translational perspectives on biomarker development, therapeutic strategies, and future opportunities at the intersection of epigenetics, metabolism, oncology, and cardiovascular health.

Epigenetic mechanisms driving brain tumors

Epigenetic regulation plays a crucial role in the formation and progression of brain tumors, as it influences the key pathways vital for tumor growth and resistance to therapies. The primary epigenetic factors contributing to brain tumors can be divided into four essential mechanisms: DNA methylation, modifications of histones,

chromatin remodeling, and ncRNA. Each of these mechanisms will be discussed in detail in the corresponding sections of the article as it unfolds.

DNA methylation: Balancing gene silencing and activation in brain tumors

DNA methylation serves as a crucial epigenetic modification that plays a significant role in the formation of brain tumors.^{24,25} DNA methyltransferases (DNMTs) add methyl groups to cytosine within cytosine-phosphate-guanine dinucleotides, affecting the epigenetic landscape of brain tumors. The methylation patterns in brain tumors frequently alter, resulting in either gene silencing or inappropriate gene activation, which aids in tumor proliferation and resistance to therapy.^{24–26} Numerous brain tumors, including gliomas and GBM, exhibit hypermethylation of tumor suppressor genes (TSGs) alongside global hypomethylation, contributing to genomic instability.^{27,28} Four primary DNMTs regulate these epigenetic alterations, each possessing unique but interconnected roles. The primary maintenance methyltransferase, DNMT1, preserves DNA methylation patterns during cell division, ensuring that epigenetic modifications are inherited and stable in daughter cells, which can silence crucial regulatory genes.^{29,30} DNMT3A introduces new methylation signatures throughout development; however, its dysregulation in brain tumors leads to abnormal patterns that promote cancer progression.^{31,32} DNMT3B further enhances tumor growth by silencing apoptotic pathways and tumor-suppressor mechanisms.^{33,34} While DNMT3L does not have enzymatic activity, it regulates DNMT3A and DNMT3B, influencing the epigenetics of brain tumors.^{35,36} The collective activities of these DNMTs result in a complex array of methylation changes that facilitate tumor growth, immune evasion, and resistance to treatment, suggesting that they could be viable targets for epigenetic-based therapies aimed at brain tumors.^{37,38} The following section provides a detailed analysis of their roles concerning brain tumors.

DNMT dysregulation: The hidden driver of brain tumor aggression and resistance

The silencing of TSGs through the dysregulation of DNMTs in brain tumors is one of the most extensively documented effects. In gliomas, DNMT1 and DNMT3B influence phosphatase and tensin homolog deleted on chromosome 10 via promoter methylation, which enhances cell survival and proliferation by inhibiting the phosphoinositide 3-kinase/protein kinase B signaling pathway.^{39,40} Likewise, the methylation of retinoblastoma transcriptional corepressor 1 and cyclin-dependent kinase inhibitor 2A/B by DNMT3B disrupts cell cycle regulatory checkpoints in high-grade gliomas and medulloblastomas, facilitating tumor growth.^{41–43} Extensive studies reveal a prevalent occurrence of promoter hypermethylation in GBM, particularly in genes involved in DNA repair, apoptosis, and tumor suppression, indicating the importance of DNMTs in tumor progression.^{44,45} Conversely, hypomethylation promotes tumor aggressiveness by enhancing the expression of oncogenes and increasing genomic instability. Research indicates that hypomethylation by DNMT1 of long interspersed nuclear element-1 and Alu elements in GBM leads to chromosomal rearrangements and amplifications that support tumor evolution.^{46,47} Genome-wide profiling of methylation indicates that hypomethylation correlates with higher tumor grades and poorer prognoses, highlighting the role of DNMT regulation in tumor biology.⁴⁸ While alterations in DNMTs are uncommon in primary glioblastomas, mutations in DNMT3A are frequently observed in pediatric gliomas and medulloblastomas, often in conjunction with histone H3 lysine (H3K) 27

to methionine mutation.^{49,50} This disruption of typical epigenetic mechanisms fosters a stem-like phenotype in tumors.⁵¹ The simultaneous loss of H3K27 trimethylation alongside DNMT3A dysfunction propels the development of the most aggressive diffuse midline gliomas.^{52,53} Single-cell analyses affirm that these epigenetic modifications contribute to tumor resilience and recurrence by preserving undifferentiated glioma stem-like cells.^{54,55}

The epigenetic shield of therapy-resistant glioma stem cells

GBM contains a subset of glioma stem-like cells, which are crucial in contributing to resistance against therapy and tumor recurrence. DNMT enzymes are essential for preserving the self-renewal capabilities of these cells.^{56,57} There is an increased expression of DNMT3B in glioma stem-like cells, which methylates important differentiation genes, thereby sustaining their stem-like characteristics.^{58,59} Research models indicate that blocking DNMT1 and DNMT3B promotes glioma cell differentiation, decreases tumor growth, and increases their response to conventional treatments, showing significant therapeutic potential.^{60,61} DNMTs also have various intrinsic and extrinsic effects on tumors, as they are not simply drivers of tumor-intrinsic changes but also actively shape the TME, especially by subverting immune surveillance, creating an immunosuppressive niche, and reducing tumor immunogenicity. Targeting DNMTs can thus have dual benefits, including the restoration of tumor suppressor activity and the reactivation of anti-tumor immunity.^{62,63}

DNMTs: The epigenetic architects of immune evasion and glioma survival

Aberrant methylation driven by DNMT1 and DNMT3B in GBM aids tumors in evading immune detection by silencing genes responsible for antigen presentation and enhancing PD-L1 levels, a crucial immune checkpoint protein.^{64,65} Additionally, these DNMTs recruit myeloid-derived suppressor cells, creating an immunosuppressive environment that obstructs anti-tumor immune responses.^{63,66,67} Recent research emphasizes the role of DNMT-driven methylation patterns in gliomas and their influence on immune cell infiltration, highlighting the significance of epigenetic regulation in tumor-immune interactions.^{68,69} In summary, DNMT1, DNMT3A, and DNMT3B facilitate the advancement of brain tumors by silencing TSGs, preserving genomic stability, supporting glioma stem cells, and influencing immune responses. Ongoing research will continue to illuminate the intriguing epigenetic mechanisms governed by DNMTs, thereby paving the way for more effective and targeted treatments for aggressive brain tumors.

Histone modifications: The hidden drivers of brain tumor progression

Post-translational modifications of histones serve as crucial regulators of gene expression, greatly impacting cellular activities and playing an integral role in the development of brain tumors.^{70,71} Histones are protein structures that wrap around DNA and can undergo various chemical alterations, including acetylation, methylation (mono-, di-, and tri-methylation), phosphorylation, ubiquitination, sumoylation, lactylation, serotonylation, and crotonylation.^{72,73} These post-translational modifications of histones lead to changes in the structure of histones, modifying chromatin organization and influencing the accessibility of DNA for transcription. The enzymes that alter histones during the formation of brain tumors create conditions that either encourage or inhibit the expression of genes involved in cell growth, differentiation, and survival.^{74,75} Together, these modifications comprise a complex “histone

code” that is recognized by chromatin remodeling complexes and transcription factors, which is vital in regulating gene expression during tumor development.^{76,77} When histone modifications are disrupted, they can interfere with normal cellular processes, activate oncogenes, or silence TSGs, contributing to the excessive cell growth observed in brain tumors. At certain locations in the genome, these modifications influence gene regulation in ways that lead to essential cancer characteristics, such as bypassing growth control, resisting apoptosis, maintaining growth signals, and modifying metabolism.^{78,79} Gaining insights into these modifications is vital for brain tumor research, as it may reveal new mechanisms underlying tumor progression and help identify possible treatment approaches targeting these alterations.

Modifications in histones are crucial for the regulation of genes and the structure of chromatin, affecting functions such as the cell cycle and DNA repair. In brain cancers like GBM and gliomas, irregular histone modifications can promote tumor growth and enhance malignancy.^{80,81} The process of histone acetylation, which is influenced by acetyltransferases and histone deacetylases (HDACs), is essential for gene expression. Elevated activity of HDACs in gliomas is linked to poorer outcomes, whereas HDAC inhibitors, such as vorinostat and panobinostat, have shown potential in preclinical investigations by facilitating cell differentiation and inhibiting tumor growth.⁸²⁻⁸⁴ Methylation of histones, especially at H3K27 and H3K9, is another critical factor in the advancement of gliomas.^{85,86} Mutations in isocitrate dehydrogenase 1 and 2 lead to increased levels of 2-hydroxyglutarate, which inhibits HDACs, alters chromatin structure, and promotes tumor progression.^{87,88} The phosphorylation of histones, including histone H3 serine 10 and H2A histone family member X, also plays a role in glioma development.⁸⁹ A rise in histone H3 serine 10 phosphorylation in GBM is associated with more aggressive tumor behavior and poorer prognosis, while higher levels of γ -H2A histone family member X, an indicator of DNA damage, reflect a compromised DNA damage response that aids tumor cells in surviving treatments.^{90,91} Ubiquitination of histones, for instance, monoubiquitination of histone H2A at lysine 119 and monoubiquitination of histone H2B at lysine 120, is significant in chromatin dynamics and transcription regulation.^{92,93} Mutations in Polycomb repressive complex 1, which is responsible for the ubiquitination of histone H2A at lysine 119, are essential for TSG silencing in gliomas, playing a part in the oncogenic process.^{94,95} Likewise, the ubiquitination of histone H2B lysine 120 is implicated in the process of transcription elongation, further propelling GBM progression.^{96,97}

Furthermore, histone sumoylation on histone H4 is generally associated with transcriptional repression through the recruitment of corepressor complexes. Rather than directly compacting chromatin,⁹⁸ its regulatory effects mainly involve modulating chromatin-associated proteins. In contrast, chromatin decondensation and gene activation are primarily linked to H4K16 acetylation,⁹⁹ and dysregulation of these marks may contribute to tumor progression. A newer modification, lactylation, occurs when lactate is incorporated into histones, connecting it to the metabolic adaptation of tumor cells.^{100,101} In GBM, elevated lactate levels resulting from aerobic glycolysis facilitate histone lactylation, aiding the expression of genes that promote growth and survival in low-oxygen environments.^{102,103} Another novel modification, serotonylation, entails the addition of serotonin to histones, impacting gene regulation and chromatin configuration.¹⁰⁴ In brain tumors, serotonylation might influence mechanisms such as neurotransmitter signaling and interactions within the TME, although its function

in gliomas is still being explored.^{105,106} Finally, crotonylation, linked to butyric acid metabolism, is characterized by the addition of a crotonyl group to histones, facilitating gene activation and the relaxation of chromatin.¹⁰⁷ Increased crotonylation at H3K18 in GBM promotes the expression of oncogenic genes, driving tumor progression and immune evasion.^{108,109} The combination of these histone modifications is essential for chromatin remodeling and gene expression, positioning them at the heart of brain tumor biology. As studies progress, these modifications could uncover new therapeutic targets, paving the way for epigenetic treatments designed to reverse abnormal chromatin alterations and more effectively fight brain tumors.

The role of chromatin remodeling complexes in brain tumors

Brain cancers result from intricate genetic and epigenetic alterations that contribute to their development, proliferation, and resistance to treatment. Among the various epigenetic regulators, chromatin remodelers are crucial, as they manage chromatin accessibility and gene expression.¹¹⁰ These complexes rearrange nucleosomes, affecting transcription, DNA repair, and replication processes.¹¹¹ When they become dysregulated, they can trigger oncogenic pathways or silence TSGs, altering normal gene regulation. Families such as SWI/SNF, Imitation SWItch (ISWI), chromodomain helicase DNA-binding protein (CHD), and inositol requiring 80 (INO80) have surfaced as significant contributors to brain tumor biology, functioning as either facilitators or inhibitors of malignancy.^{112,113} The ISWI chromatin remodeling family, which includes SWI/SNF-related, matrix-associated actin-dependent regulator of chromatin, subfamily A (SMARCA), member 1, also known as SNF2L, and SMARCA5, also known as SNF2H, is involved in regulating nucleosome positioning and gene suppression.^{114,115} Dysregulation of these components in GBM and medulloblastoma disrupts DNA repair mechanisms and the cell cycle, fostering tumor growth.^{116,117} Elevated levels of SMARCA5 further enhance GBM cell growth and contribute to resistance against radiation therapy, underscoring its significance in therapeutic resistance.^{118,119} Focusing on SMARCA5 can enhance the sensitivity of tumors to radiation, indicating its potential as a target for therapy. In medulloblastoma, dysfunction of ISWI modifies chromatin structure, allowing cells to remain undifferentiated and fueling tumor development, highlighting the significance of chromatin remodeling in supporting cellular identity.^{120,121} CHD4, part of the CHD family, suppresses gene expression by compacting chromatin within the nucleosome remodeling and deacetylase complex.^{122,123} In gliomas, increased levels of CHD4 contribute to malignancy by silencing differentiation genes and promoting self-renewal of GBM stem cells.^{124,125} Research using clustered regularly interspaced short palindromic repeats-associated protein 9 has pinpointed CHD4 as a weakness in GBM stem-like cells, where its inhibition slows tumor growth and induces differentiation.¹²⁶ This indicates that CHD4 is crucial not only for sustaining tumors but also for driving GBM plasticity, making it a promising target for therapy. The INO80 complex plays a critical role in genomic stability by repairing DNA damage, controlling replication stress, and regulating transcription.¹²⁷ Although INO80 is known to support oncogenic programs in several cancers, direct evidence that its function is co-opted in glioblastoma to induce genomic instability and promote tumor growth or therapy resistance remains limited and warrants further investigation.^{128,129} Evidence suggests that knocking down INO80 disrupts DNA repair, diminishing the survival of glioblastoma cells.^{130,131}

Furthermore, blocking INO80 increases the effectiveness of temozolomide treatment, indicating it might serve as a valuable target for enhancing GBM therapy.^{132,133} The connection between chromatin remodeling complexes and brain tumor formation makes them significant biomarkers and potential therapeutic targets. Expanding our knowledge of how various remodeling families interact could provide new insights into tumor development, differentiation, and response to treatment. Targeting these chromatin-related mechanisms may lead to advancements in precision oncology, where targeted modulators can help overcome therapy resistance and enhance patient outcomes.

ncRNAs: Epigenetic architects of brain tumor progression

ncRNAs, which encompass miRNAs, lncRNAs, and circular RNAs (circRNAs), play vital roles in regulating gene expression within the molecular pathology of brain tumors, especially GBM.^{134,135} miRNAs, which are small single-stranded RNAs approximately 22 nucleotides in length, control gene expression after transcription by binding to particular messenger RNAs, resulting in either translational repression or degradation.¹³⁶⁻¹³⁸ The alteration of miRNA expression is associated with various diseases, including brain cancer. For example, in GBM, miR-21 is elevated and targets TSGs like phosphatase and tensin homolog deleted on chromosome 10 and programmed cell death 4, thereby promoting processes such as cell proliferation, invasion, and resistance to apoptosis.^{139,140} Pre-clinical models indicate that inhibiting miR-21 can improve the efficacy of chemotherapy agents like taxol in GBM cell lines, while *in vivo* studies have shown that reducing miR-21 expression stifles tumor growth and boosts apoptosis, making miR-21 a promising candidate for therapeutic approaches aimed at enhancing tumor sensitivity to standard treatments.^{141,142}

The well-established tumor suppressor miR-34a is usually found at lower levels in high-grade gliomas, which induces tumor progression by enhancing the Notch signaling pathway that sustains glioma stemness and contributes to therapy resistance.^{143,144} Importantly, the MRX34 Phase I trial, which was examining a miR-34a mimic in patients with advanced solid tumors, including GBM, was discontinued due to severe immune-related adverse events, resulting in patient fatalities.¹⁴⁵ Nonetheless, preclinical studies have shown that using nanoparticles to deliver miR-34a can help overcome resistance to the chemotherapeutic agent temozolomide in GBM, underscoring its potential as a therapeutic option despite issues related to immune toxicity and delivery techniques.¹⁴⁶ Ongoing human clinical trials are assessing miR-34a mimics in combination with various treatment regimens, incorporating stricter safety protocols to mitigate earlier concerns.

In addition to miRNAs, lncRNAs and circRNAs play crucial roles in glioma progression. The lncRNA HOX transcript antisense intergenic RNA (HOTAIR) promotes the development of glioma by engaging with the Polycomb repressive complex 2, resulting in the epigenetic silencing of TSGs.¹⁴⁷⁻¹⁴⁹ Elevated levels of HOTAIR help sustain characteristics associated with glioblastoma stem cells and contribute to resistance against chemotherapy and radiation; hence, HOTAIR is a promising target for therapeutic approaches designed to counteract these effects.^{150,151} A phase I trial is currently examining a strategy that targets HOTAIR using small-molecule inhibitors to interrupt its function, and initial findings indicate encouraging responses in glioma patients who have undergone prior treatments.¹⁵¹ Likewise, circFBXW7 serves as a molecular sponge, meaning it interacts with and inhibits glioma-related miRNAs such as miR-223, impacting crucial signaling pathways tied to the stemness and growth of glioma cells.^{152,153}

Table 1. Summary of key epigenetic mechanisms, dysregulated components, and pro-tumorigenic effects in glioma

Epigenetic mechanism	Primary dysregulated component	Pro-tumorigenic effects
DNA methylation	DNMT1, DNMT3A, DNMT3B	Silencing of tumor suppressor genes (TSGs) such as PTEN, RB1, and CDKN2A/B; genomic instability through hypomethylation (e.g., LINE-1, Alu elements); and enhanced cell survival, proliferation, and resistance to therapy ^{164,165}
DNMT dysregulation	DNMT1, DNMT3A, DNMT3B	Inhibition of apoptosis (e.g., silencing of apoptotic genes), promotion of cancer progression (e.g., silencing of TSGs like PTEN and RB1), and increased genomic instability (e.g., LINE-1 and Alu hypomethylation) ¹⁶⁴⁻¹⁶⁶
Histone modifications	HDACs, HATs, H3K27, H3K9, H2AK119ub, H2BK120ub, H4K16, lactylation, crotonylation	Activation of oncogenes (e.g., through acetylation and phosphorylation), silencing of tumor suppressor genes (e.g., through methylation and ubiquitination), chromatin remodeling that promotes tumor growth and survival, and immune evasion mediated through lactylation and crotonylation ^{167,168}
Chromatin remodeling	SWI/SNF (SMARCA1, SMARCA5), ISWI, CHD4, INO80	Disruption of DNA repair mechanisms (e.g., INO80, SWI/SNF, ISWI), altered cell cycle regulation (e.g., SMARCA5, ISWI), enhanced tumor growth and therapeutic resistance (e.g., SMARCA5), and increased tumor stemness and plasticity (e.g., CHD4, SMARCA5) ^{169,170}
Non-coding RNAs (ncRNAs)	miR-21, miR-34a, HOTAIR, circFBXW	Promotion of tumor proliferation and invasion (e.g., miR-21, HOTAIR), maintenance of glioma stem cell characteristics (e.g., miR-34a, HOTAIR), and resistance to chemotherapy and radiation (e.g., miR-21, miR-34a) ¹⁷¹
Immune evasion	DNMT1, DNMT3B, PD-L1, MDSCs	Silencing of antigen presentation genes (e.g., through DNMT1, DNMT3B), increased PD-L1 expression (e.g., through DNMT-driven methylation), recruitment of MDSCs, and suppression of anti-tumor immune responses, fostering immune evasion ^{172,173}

Alu, Alu repeat elements; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; CHD4, chromodomain helicase DNA-binding protein 4; circFBXW7, circular FBXW7 RNA; DNMT, DNA methyltransferase 1; DNMT3A, DNA methyltransferase 3A; DNMT3B, DNA methyltransferase 3B; H2AK119ub, monoubiquitination of histone H2A lysine 119; H2BK120ub, monoubiquitination of histone H2B lysine 120; H3K27, histone H3 lysine 27; H3K9, histone H3 lysine 9; H4K16, histone H4 lysine 16; HATs, histone acetyltransferases; HDACs, histone deacetylases; HOTAIR, HOX transcript antisense intergenic RNA; INO80, inositol requiring 80 complex; ISWI, Imitation SWItch; LINE-1, long interspersed nuclear element-1; MDSCs, myeloid-derived suppressor cells; ncRNAs, non-coding RNAs; PD-L1, programmed death-ligand 1; PTEN, phosphatase and tensin homolog; RB1, retinoblastoma transcriptional corepressor 1; SMARCA1, SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 1; SMARCA5, SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 5; SWI/SNF, Switch/Sucrose Non-Fermentable Complex; TSGs, tumor suppressor genes.

By modulating these oncogenic miRNAs, circFBXW7 presents a novel strategy for mitigating glioma progression. Levels of circulating circFBXW7 have been recognized as potential biomarkers for monitoring glioma progression and treatment effectiveness, with early studies suggesting that these circRNAs could be utilized alongside imaging methods to track changes in tumors.^{154,155}

Despite the challenges faced by miRNA-based treatments like MRX34 due to immune toxicity and delivery issues, ongoing studies underscore the importance of ncRNAs in the biology of GBM. Recent human studies indicate that integrating miRNA therapies with immune checkpoint inhibitors may enhance treatment outcomes. For instance, current clinical trials are exploring the effects of combining anti-PD-1 or anti-PD-L1 therapies with miRNA treatment, which shows potential in overcoming resistance mechanisms in GBM.^{156,157} As the role of ncRNAs becomes clearer, precision medicine strategies appear more promising, providing targeted therapies and non-invasive biomarkers for early detection and monitoring.¹⁵⁸ The integration of ncRNA-targeted treatments with standard therapies holds considerable potential for improving the management and prognosis of GBM in the future.

Moreover, ncRNAs are found in extracellular vesicles, including exosomes, which circulate in blood and cerebrospinal fluid (CSF).^{159,160} This indicates that circulating miRNAs may act as promising non-invasive biomarkers. Specific miRNA profiles identified in serum and CSF samples from glioma patients have been associated with tumor grade, severity, and response to treatment.^{161,162} A recent study identified a particular miRNA profile in CSF that could predict patient prognoses and treatment responses in GBM.¹⁶³ These results highlight the potential of liquid biopsy methods for GBM, providing a more convenient and less invasive

option for monitoring tumor progression and treatment outcomes.

In summary, miRNAs, lncRNAs, and circRNAs are crucial in the molecular pathology of GBM. Their roles in gene regulation, tumor development, and responses to therapy make them promising candidates for both diagnostic and therapeutic applications. Table 1 presents a summary of the key epigenetic mechanisms, their dysregulated components, and the associated pro-tumorigenic effects observed in glioma.¹⁶⁴⁻¹⁷³ Ongoing research, which includes more human studies and clinical trials, is essential for improving delivery methods and fine-tuning these strategies to enhance treatment outcomes in GBM. While this compilation of ncRNAs is not exhaustive, as it goes beyond the scope of this overview article, it establishes a strong basis for future research into the roles of ncRNAs in GBM and other brain tumors. A deeper comprehension of ncRNAs, their mechanisms of action, interactions within various molecular pathways, and potential as therapeutic targets is paving the way for novel tailored treatment approaches. Expanding the catalog of vital ncRNAs implicated in glioma progression and evaluating their potential clinical relevance may help bridge the current gap between preclinical discoveries and therapeutic implementation.

Metabolic-epigenetic feedback loops in gliomas: A central framework

The central narrative of this section is the increasing awareness that glioma development is influenced not just by genetic mutations but also by intricate metabolic and epigenetic feedback loops. These relationships create a dynamic interaction where metabolic

Table 2. Key metabolite–epigenetic interactions in glioma

Metabo- lite	Source/Pathway	Epigenetic target(s)	Mechanism of interaction	Functional consequences of glioma
α-KG	TCA cycle; IDH-wild-type metabolism	TETs, Jumonji demethylases	Cofactor for DNA/histone demethylation	Encourages the expression of tumor-suppressor genes, improves differentiation, diminishes stem-like characteristics, and curtails proliferation and aggressiveness ¹⁸¹
2-HG	Mutant IDH1/2	TETs, Jumonji demethylases	Inhibits α-KG– dependent dioxygenases	Inhibits differentiation of cells, boosts glioma stemness, promotes tumor advancement, heightens resistance to therapy, and facilitates evasion of the immune system ¹⁸²
Acetyl- CoA	Glucose/fatty acid metabolism	HATs	Substrate for histone acetylation	Triggers oncogenes (such as MYC), promotes growth, ensures survival during metabolic stress, and facilitates metabolic reprogramming ¹⁸³
SAM	One-carbon/ methionine cycle	DNMTs, HMTs	Methyl donor for DNA/histone methylation	Inhibits tumor-suppressor genes (such as PTEN, CDKN2A/B), enhances cell growth, maintains stem cell-like properties, and increases resistance to chemotherapy ¹⁸⁴
NAD ⁺	Glycolysis, OXPHOS	Sirtuin	Cofactor for deacetylation	Sustains glioma stem-like cells, enhances survival amid metabolic and oxidative stress, aids energy balance through oxidative phosphorylation, and plays a role in resistance to therapy ¹⁸⁵
FAD	Fatty acid oxidation	LSD1	Cofactor for demethylation	Inhibits tumor differentiation, maintains stem cell characteristics, promotes malignancy, and accelerates tumor growth ¹⁸⁶
Lactate	Aerobic glycolysis	Histone lactylation	Donor for his- tone lactylation	Encourages growth, blood vessel formation, survival under low oxygen conditions, and evasion of the immune system within the glioma microenvironment ¹⁸⁷
SCFAs	Microbiota fermentation	HDACs	HDAC inhibition	Promotes differentiation, inhibits proliferation, and may enhance the sensitivity of glioma cells to treatment ¹⁸⁸
BHB	Ketogenesis	HDACs; histone β-hydroxybutyrylation	HDAC inhibition	Improves the survival of glioma in conditions of nutrient deprivation, promotes stem cell characteristics, and enables metabolic adaptability ¹⁸⁹
Succinate and & Fumarate	TCA dysfunction, IDH mutations	TETs, Jumonji demethylases	Inhibits α-KG– dependent dioxygenases	Encourages glioma characteristics, advances tumor development, contributes to therapy resistance, and hinders differentiation ^{190,191}

2-HG, 2-hydroxyglutarate; Acetyl-CoA, acetyl coenzyme A; BHB, β-hydroxybutyrate; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; DNMTs, DNA methyltransferases; FAD, flavin adenine dinucleotide; HDACs, histone deacetylases; HMTs, histone methyltransferases; IDH, isocitrate dehydrogenase; LSD1, lysine-specific demethylase 1; NAD⁺, Nicotinamide adenine dinucleotide (oxidized form); OXPHOS, oxidative phosphorylation; PTEN, phosphatase and tensin homolog; SAM, S-adenosylmethionine; SCFAs, short-chain fatty acids; TCA, tricarboxylic acid; TETs, ten-eleven translocation enzymes; α-KG, α-ketoglutarate.

reprogramming and epigenetic changes reinforce each other, enhancing tumor growth and resistance to therapies. This section examines how gliomas exploit metabolic and epigenetic processes to bolster their survival, increase aggressiveness, and evade treatment by integrating these mechanisms. The combined effects of metabolic and epigenetic modifications offer a comprehensive framework for understanding glioma biology and exploring new potential therapeutic strategies.

As previously stated, the evolution of conceptual frameworks in cancer biology, which now includes epigenetic dysregulation alongside genetic mutations, has enhanced our comprehension of tumor development. This combined perspective is particularly relevant to gliomas. Although mutations in genes responsible for histone proteins, DNA- and histone-modifying enzymes, and chromatin remodelers can initiate tumor formation, abnormal gene expression can arise independently of these mutations, highlighting the significance of non-genetic elements in advancing glioma development and progression.

Simultaneously, metabolic reprogramming has been identified as a hallmark of cancer.^{174,175} This reprogramming may arise from

mutations in key metabolic enzymes or from environmental and dietary influences. Importantly, cancer metabolism and epigenetics are closely intertwined: metabolites such as acetyl-CoA, S-adenosylmethionine, α-ketoglutarate, and nicotinamide adenine dinucleotide serve as essential cofactors for chromatin-modifying enzymes, thereby directly linking nutrient availability and metabolic flux to the regulation of gene expression.^{176,177} This metabolic-epigenetic crosstalk creates self-sustaining loops that reinforce oncogenic transcriptional programs and promote gliomagenesis.^{178–180} The relationships between metabolites and epigenetic changes, as described in Table 2, are crucial in governing tumor development and resistance to therapy in gliomas.^{181–191} These mechanisms not only affect gene expression but also influence the TME, facilitating glioma advancement. Gaining a more profound insight into this interaction between metabolites and epigenetics provides important perspectives on potential treatment approaches aimed at altering both metabolic and epigenetic pathways to enhance treatment outcomes.

The complexity of this interaction is further heightened within the context of systemic metabolic disorders such as diabetes mel-

litis. Hyperglycemia, insulin resistance (IR), and chronic inflammation characteristic of diabetes foster a tumor-supportive micro-environment by enhancing aerobic glycolysis, facilitating anabolic growth, and disturbing redox balance—processes that collectively contribute to the epigenetic reprogramming of glioma cells.^{192–194} Diabetes thus not only drives glioma development at the molecular level but also influences disease prognosis by altering inter-organ communication networks.^{195–197}

Emerging evidence additionally highlights the critical role of the brain-heart axis in glioma progression and clinical outcomes.^{198,199} Gliomas located near autonomic regulatory centers can disrupt cardiovascular homeostasis, increasing the risk of arrhythmias, cardiac dysfunction, and sudden death.^{200,201} This neuro-cardiac dysregulation is particularly aggravated in diabetic individuals, who are already predisposed to cardiovascular complications.^{202,203} Consequently, the interplay among glioma progression, metabolic disorders, and brain-heart signaling forms a multifaceted framework for understanding glioma-related clinical outcomes.

Hence, in this subsection, we examine the interplay between metabolic and epigenetic dysregulations in glioma, explore how diabetes exacerbates glioma development, and underscore the brain-heart axis as a compelling paradigm influencing mortality. These interconnected systems highlight the urgent need for integrative approaches in glioma research and treatment. One significant comorbidity that accelerates glioma progression is diabetes. Below, we present an evidence-based analysis of how diabetes acts as a catalyst for glioma development by altering the supply of metabolites and signaling within the TME, thereby exacerbating glioma progression through modulation of key metabolic, immune, vascular, and epigenetic pathways.

Diabetes as a Catalyst for glioma progression: An evidence-based analysis

Diabetes is characterized by high blood glucose levels caused by insufficient insulin production, impaired insulin action, IR, or a combination of these factors.²⁰⁴ This condition contributes to glioma progression through complex biological pathways involving metabolic, immune, epigenetic, and vascular changes.^{205,206} Persistent hyperglycemia supplies excess glucose that fuels glioma cells, which predominantly rely on aerobic glycolysis, commonly known as the Warburg effect, for energy. Prolonged high blood glucose enhances glucose uptake by tumor cells, coinciding with increased expression of glucose transporters and glycolytic enzymes, thereby promoting faster cell growth and improved survival.^{207,208}

Additionally, elevated insulin levels resulting from IR and increased insulin-like growth factor 1 activate the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin pathway, a key driver of tumor growth in GBM, further supporting tumor expansion and resistance to cell death.^{209,210} In diabetic conditions, the immune environment also undergoes significant changes: glial cells release pro-inflammatory cytokines such as interleukin (IL)-6, which promote angiogenesis and tumor invasion while suppressing effective anti-tumor immune responses.^{211,212} Moreover, high blood glucose impairs the immune system's ability to recognize and eliminate tumor cells, allowing gliomas to thrive.²¹³

At the epigenetic level, hyperglycemia fosters the formation of advanced glycation end-products (AGEs) that modify histone proteins non-enzymatically, disrupting chromatin structure and gene

regulation.^{214,215} These modifications can activate oncogenes or silence TSGs. Furthermore, AGEs interact with their receptor, the receptor for advanced glycation endproducts, triggering inflammatory pathways that further promote tumor growth.^{216,217} Diabetic hyperglycemia also elevates vascular endothelial growth factor, which damages the blood–brain barrier (BBB), increasing its permeability.^{218,219} This compromised barrier allows immune cells to infiltrate brain tissue and supplies nutrients to support tumor expansion.^{220,221} In addition, oxidative stress and inflammation caused by diabetes exacerbate BBB disruption, thereby facilitating glioma progression.^{222,223}

In addition to localized changes within the TME, the brain-heart axis has emerged as a crucial systemic pathway linking diabetes to glioma progression and poorer clinical outcomes.²²⁴ This axis encompasses autonomic nervous system (ANS) regulation, through which the brain modulates heart rate, rhythm, and contractility in response to emotional, cognitive, and physiological stimuli, as well as neuroendocrine signaling via the hypothalamic-pituitary-adrenal (HPA) axis, both vital for maintaining cardiovascular stability.^{225–227} In diabetes, these systems are frequently disrupted. Diabetic autonomic neuropathy, characterized by excessive sympathetic activity and diminished parasympathetic tone, impairs cerebral blood flow regulation and fosters hypoxic conditions within the glioma microenvironment.^{228,229} This hypoxia stabilizes hypoxia-inducible factor-1 α , which promotes angiogenesis and tumor progression while simultaneously damaging the BBB, facilitating tumor invasion and immune cell infiltration.^{230,231}

Furthermore, chronic neuroinflammatory responses elevate pro-inflammatory cytokines such as tumor necrosis factor- α and IL-6, activating tumor-supportive glial cells like microglia and astrocytes, which further fuel glioma growth.²³² Impaired cardiac autonomic function in diabetes, reflected by reduced heart rate variability (HRV), signifies brain-heart axis disruption and is associated with worse outcomes in glioma patients.^{233–235} A decline in HRV indicates reduced parasympathetic anti-inflammatory activity, which normally restrains tumor-promoting inflammation. Additionally, neurohormones secreted by the heart, including brain natriuretic peptide (BNP) and adrenomedullin, influence tumor growth, vascular remodeling, and resistance to anti-angiogenic therapies.^{236,237} In diabetes, dysregulated levels of these hormones can exacerbate vascular abnormalities and increase glioma invasiveness.^{238,239}

At the molecular level, metabolic stress and impaired brain-heart communication act synergistically to influence glioma epigenetics.^{240,241} Elevated glucose levels and oxidative stress lead to aberrant DNA methylation and histone modifications that silence TSGs.^{242,243} Moreover, abnormal neurohormonal signaling alters miRNA profiles and epigenetic regulators, promoting tumor cell survival and proliferation.^{244,245} Recognizing the brain-heart axis as a key systemic mediator of diabetes-induced glioma progression opens promising therapeutic avenues. Strategies such as vagus nerve stimulation, cardiovascular function enhancement, and targeting neuroinflammation may help improve cerebral perfusion, preserve BBB integrity, and enhance treatment efficacy in diabetic glioma patients.^{246–248}

Overall, diabetes-driven metabolic and neurocardiovascular dysregulation creates a biologically permissive environment that supports aggressive glioma behavior and worsens prognosis. Addressing this intricate network of metabolic, epigenetic, and brain-heart interactions offers novel opportunities to slow glioma progression in diabetic individuals. [Figure 1](#) illustrates an overview of the metabolic-epigenetic feedback loops in gliomas, depicting

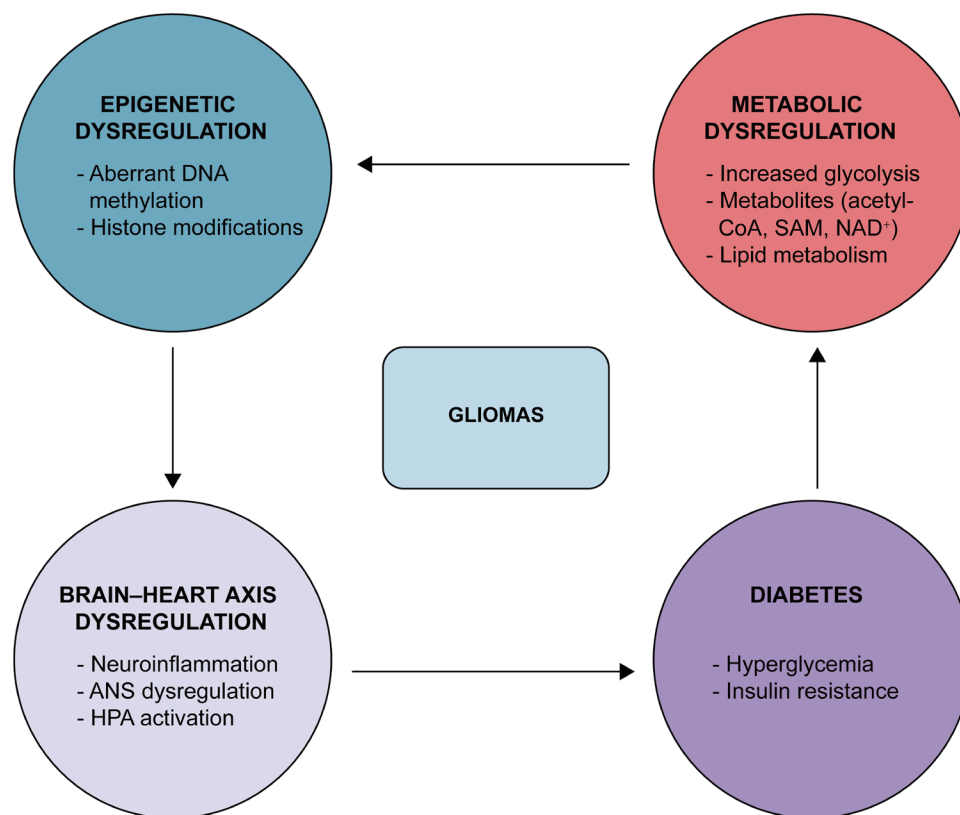


Fig. 1. Metabolic-epigenetic feedback loop. This illustration depicts how disruption within the brain-heart connection impacts diabetes as part of a larger metabolic and epigenetic feedback mechanism. The autonomic signaling imbalance, marked by increased sympathetic activity, reduced vagal tone, and the stimulation of the hypothalamic-pituitary-adrenal (HPA) axis, elevates stress hormone levels and systemic inflammation, which subsequently reduce insulin sensitivity, hinder insulin release from the pancreas, and cause fluctuations in blood glucose levels. Additionally, imbalanced metabolites such as nicotinamide adenine dinucleotide (NAD⁺), acetyl-CoA, and S-adenosylmethionine (SAM) alter the functions of epigenetic enzymes and metabolic signaling, further compromising metabolic control. The bidirectional arrow illustrates the cyclical nature of this connection: dysfunction in the brain-heart axis leads to metabolic chaos and diabetes, while diabetes, which is defined by persistent high blood sugar, oxidative stress, inflammation, and alterations in metabolite levels, further disrupts autonomic regulation and cardiovascular control, creating a self-perpetuating cycle that exacerbates metabolic and epigenetic dysregulation. ANS, autonomic nervous system.

how tumor-driven metabolic reprogramming and systemic imbalances exacerbate epigenetic dysregulation. This self-reinforcing cycle contributes to tumor progression and related comorbidities through disruptions in the brain-heart axis.

Taken together, diabetes-induced metabolic, inflammatory, and neurocardiovascular alterations create a systemic environment that accelerates glioma progression and exacerbates its physiological consequences. The convergence of metabolic stress, epigenetic instability, and impaired brain-heart communication significantly heightens the susceptibility of diabetic glioma patients to cardiovascular complications. This intricate interplay of metabolic and epigenetic dysregulation provides a foundation for the brain-heart axis, a pivotal systemic pathway that links these disruptions to poorer clinical outcomes. As we transition to a discussion of the brain-heart axis, it becomes evident that this axis influences glioma progression and contributes to the elevated cardiovascular morbidity and mortality observed in these patients. A more profound understanding of brain-heart interactions, within the context of glioma and epigenetics, will elucidate how the neurocardiovascular connection further promotes tumor growth and complicates treatment outcomes in this patient population, which the following section intends to address.

Glioma, epigenetics, and the brain-heart axis: A triad in cardiovascular mortality

Over the past few decades, growing interest in the bidirectional communication between the brain and the heart has fueled the emergence of neurocardiology—a field dedicated to understanding the neural mechanisms that govern cardiovascular function and dysfunction.²⁴⁹ At the core of this neurocardiac interface are brain regions such as the anterior cingulate cortex, amygdala, insular cortex, hypothalamus, parabrachial nucleus, periaqueductal gray, and medullary centers.^{250,251} These areas regulate cardiac activity via the ANS, engaging both its sympathetic and parasympathetic branches to integrate cardiovascular control with emotional and cognitive processes.^{252,253}

A pivotal element in this communication is the HPA axis, which coordinates the body's response to stress. Upon activation, the HPA axis triggers the release of glucocorticoids—such as cortisol—that can influence cardiovascular function both directly, by altering vascular reactivity and myocardial performance, and indirectly, by disrupting autonomic balance. Chronic HPA axis activation, as seen in prolonged psychological stress or neurological disease, is associated with ANS dysregulation, systemic inflammation, and elevated cardiovascular risk.²⁵⁴ In essence, chronic

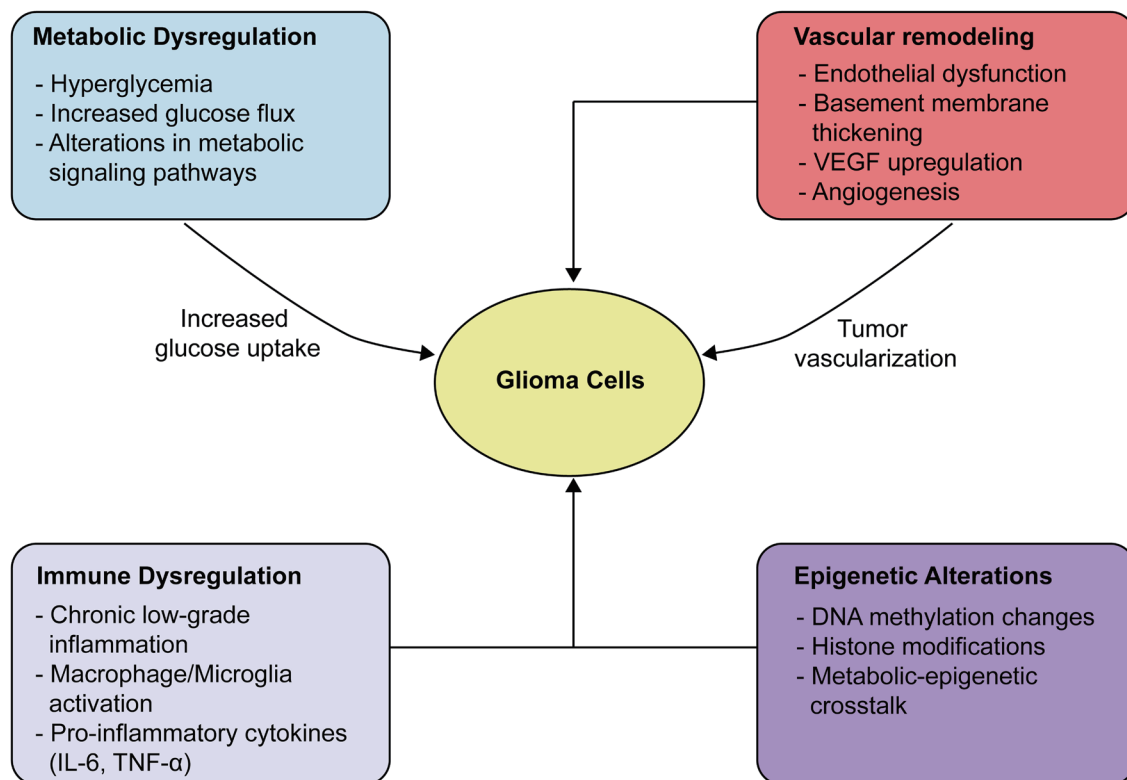


Fig. 2. Mechanistic interplay between diabetes and glioma progression. The diagram depicts the pathways by which diabetes facilitates the advancement of glioma, organized around a central figure composed of themed modules. In the middle are glioma cells, encircled by four primary diabetes-related disturbances: metabolic imbalance, vascular changes, immune system disruption, and epigenetic alterations. Within the metabolic module, elevated blood sugar levels and increased glucose metabolism enhance glioma's uptake of glucose and support its metabolic needs. In the vascular module, problems with the endothelium, heightened expression of vascular endothelial growth factor (VEGF), and increased angiogenesis provide a pro-angiogenic environment that supports tumor growth. In the immune module, persistent low-level inflammation, activation of microglia, and pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) produce inflammatory signals that create a supportive environment for tumors. In the epigenetics module, diabetes-related changes in DNA methylation, histone modifications, and the interplay between metabolic and epigenetic factors come together to influence gene regulation within glioma cells. The arrows illustrate the suggested mechanistic connections from each module to the central glioma cells, emphasizing how the metabolic, vascular, immune, and epigenetic disturbances induced by diabetes interact through interconnected and mutually reinforcing mechanisms to enhance glioma progression.

activation of the HPA axis has been consistently linked to autonomic dysregulation, systemic inflammation, and an increased risk of cardiovascular events. This body of evidence supports the notion that prolonged HPA axis activation contributes significantly to cardiovascular morbidity and mortality across diverse populations.

On the other hand, pro-inflammatory cytokines such as IL-1 β , IL-6, and tumor necrosis factor- α further impair autonomic regulation, damage endothelial function, promote arrhythmias, and contribute to cardiac injury. These cytokines also activate the HPA axis in a feedback loop, creating a self-perpetuating cycle of stress and heightened cardiac vulnerability.^{255,256} A compelling example of this interconnectedness is found in GBM, the most aggressive form of primary brain tumor. Cardiovascular complications, once thought to stem primarily from local tumor effects, are increasingly recognized as manifestations of widespread CNS influence, driven by neuroinflammation, disrupted stress responses, and treatment-induced autonomic imbalance.^{257–259}

In summary, the brain–heart connection represents a complex, dynamic network, emerging as a compelling paradigm governed by neuroendocrine signaling, inflammatory pathways, and stress regulation. As research continues to illuminate these intricate interactions, neurocardiology is evolving into a vital interdisciplinary

field, offering profound insights into the pathophysiology and management of multifaceted disorders. As shown in [Figure 2](#), diabetes-linked hyperglycemia disrupts the BBB, promotes inflammation and epigenetic changes, and fuels glioma growth through increased glucose uptake and vascular endothelial growth factor-driven angiogenesis, while also impairing autonomic regulation via the brain–heart axis.

Significance of the review

This analysis offers a novel, cohesive model for the complex relationship between diabetes and glioma development, an area that has otherwise been insufficiently examined in existing research. Unlike earlier studies that examined metabolic, epigenetic, immune, and neurovascular mechanisms separately, we integrate these components to show how metabolic disruptions linked to diabetes can significantly influence glioma behavior. A primary contribution of this research is to elucidate how hyperglycemia-induced metabolic dysregulation leads to epigenetic alterations, specifically via non-enzymatic histone modifications mediated by AGE and the receptor for advanced glycation endproducts–NF-

κB signaling pathway, offering new perspectives on how systemic metabolism disruption affects the molecular factors of tumors. Another development is the recognition of the brain–heart axis as an essential factor influencing glioma aggressiveness in patients with diabetes, illustrating how diabetic autonomic neuropathy and neurohormonal irregularities, such as varying levels of BNP and adrenomedullin, promote compromise of the BBB and increased tumor invasiveness. This review expands the conceptual framework of glioma research by demonstrating these integrated systems and establishes a basis for future translational pathways, including nanoparticle-enabled epigenetic therapies, focused metabolic interventions, digital neurosurveillance, and multi-omics-based biomarker identification. With the convergence of neurocardiology, epigenetics, and oncology, a more integrated, personalized, and systems-based strategy for glioma treatment is becoming not just essential but also increasingly achievable.

Limitations

This review underscores the intricate connection between diabetes and the progression of glioma; however, it is important to acknowledge several limitations. Most conclusions are based on animal models, and the integration of metabolic, epigenetic, and neurovascular mechanisms remains largely theoretical due to the lack of robust clinical data. Genetic mutations, environmental factors, and prior treatments further complicate this relationship, and challenges persist in delivering nanoparticle therapies across the BBB. While GLP-1 receptor agonists show potential therapeutic promise, their effects on glioma, particularly in diabetic patients, remain uncertain. Imaging and liquid biopsy technologies offer promising advancements for early detection and diagnostic guidance, but their development is still in progress, and the impact of comorbid conditions, such as diabetes, remains poorly understood. Additionally, epigenetic therapies aimed at reversing metabolic alterations could introduce adverse effects, adding complexity to the issue. Ultimately, further clinical research and translatable evidence are essential to refine these strategies and develop effective therapeutic interventions for patients with metabolic comorbidities.

Future directions

To advance research and treatment for GBM, a thorough approach is required that addresses not only the complex nature of the tumor but also overarching issues, such as related metabolic disorders. The key to effectively managing GBM lies in personalized medicine, which integrates nanotechnology, imaging, liquid biopsy, omics technologies, and digital health to improve detection, monitoring, and treatment results, especially for patients with comorbidities like diabetes that can exacerbate disease progression. One promising approach is the implementation of nanoparticle-enhanced epigenetic therapies. While the BBB typically limits the delivery of medications to the brain, its partial compromise in GBM creates a unique chance to take advantage of this heightened permeability. Nanoparticles can be tailored to deliver epigenetic agents, such as DNA methylation inhibitors, HDAC inhibitors, or RNA therapies, directly to cancer cells. These nanoparticles can be modified with ligands targeting receptors unique to tumors or transport mechanisms that traverse the BBB, and they can be engineered to respond to the TME for precise drug release. Future studies should focus on creating delivery systems that are safe, efficient, and precise, reducing systemic toxicity while enhancing

therapeutic outcomes, particularly for those with metabolic disorders like diabetes, which can influence drug metabolism and immune responses.

Tackling metabolic comorbidities such as diabetes must be a key component of glioma therapy. The notable impact of elevated blood glucose and IR on glioma progression underscores the importance of incorporating metabolic management into therapeutic approaches. Upcoming clinical trials should classify patients based on their metabolic characteristics and explore the application of glucose-lowering drugs, insulin-sensitizing compounds, and personalized nutrition strategies. Significantly, glucagon-like peptide-1 receptor agonists, already established in metabolic disease intervention and increasingly recognized for their potential neuroprotective effects in cognitive decline, may also warrant investigation in this context.^{260,261} These approaches might improve general metabolic health and could influence tumor behavior via epigenetic alterations and immune system mechanisms.

Moreover, enhancing the early identification and real-time observation of tumors using advanced neuroimaging techniques is another crucial area of emphasis. Cutting-edge imaging methods, such as diffusion tensor imaging, perfusion magnetic resonance imaging, magnetic resonance spectroscopy, and positron emission tomography using molecular probes, can detect subtle alterations in tumor metabolism, blood flow, and microenvironmental factors before they become clinically apparent.^{262,263} Integrating these imaging techniques with blood-derived biomarkers such as exosomal circRNAs can significantly enhance early diagnostic accuracy and facilitate more precise monitoring of treatment responses.^{264,265} This approach is particularly crucial for diabetic individuals, since their altered blood flow patterns and inflammatory responses might complicate or accelerate disease progression. Moreover, liquid biopsy is emerging as an important, less invasive approach for monitoring glioma. While analyzing CSF is informative, it is limited by the invasive nature of lumbar puncture.^{266,267} Future research should focus on improving blood-based biomarkers, such as circulating tumor DNA, miRNAs, circRNAs, and protein panels, for accurate detection of gliomas at a molecular level. These biomarkers offer reliable and readily available methods to track tumor activity, assess treatment efficacy, and detect early signs of recurrence or metastasis. Liquid biopsy, when integrated with imaging and clinical data, can play a vital role in tailoring personalized treatment approaches, especially for patients with metabolic imbalances.

Ultimately, digital neuro-surveillance offers an innovative approach for managing neurological events linked to glioma. Seizures and strokes commonly occur and can be life-threatening for patients with glioma. Through the use of wearable and implantable devices that provide continuous electroencephalographic monitoring, measure blood flow, and perform physiological assessments, immediate detection of impending neurological crises can be attained.²⁶⁸ Machine learning techniques can analyze complex physiological data to predict seizures or ischemic events before clinical symptoms appear, enabling prompt interventions.²⁶⁹ For patients with glioma, especially those with diabetes or impaired vascular control, customized digital monitoring systems may greatly improve safety, reduce emergency hospital visits, and enhance overall quality of life.²⁷⁰

Together, these interdisciplinary advancements highlight the significance of integrating nanotechnology, metabolic control, state-of-the-art diagnostics, and digital health into a cohesive strategy for glioblastoma treatment. The combination of these techniques provides promise for improving clinical outcomes while

also reshaping the field of neuro-oncology in relation to personalized and precision medicine.

Conclusions

Gliomas serve as robust models for investigating the complex interplay between genetic, epigenetic, and metabolic networks in cancer biology. Conventional treatments primarily focus on inducing cytotoxicity by targeting cellular machinery; however, increasing evidence suggests that durable cancer control requires strategies that also address the underlying epigenetic and metabolic reprogramming that drive therapeutic resistance. Metabolic–epigenetic feedback loops are thought to play a central role in glioma progression and intersect with systemic conditions such as diabetes and cardiovascular dysfunction, further underscoring the clinical relevance of these networks. For instance, the brain–heart axis illustrates how gliomas may exert effects beyond the CNS, reinforcing the need for a holistic approach to patient care. Looking ahead, integrating insights from metabolism, immunity, vascular biology, and epigenetic regulation will be critical for designing personalized interventions that target multiple vulnerabilities, thereby improving outcomes and quality of life. Ultimately, disrupting interconnected metabolic, immune, epigenetic, and vascular networks represents a key step toward achieving durable or even transformative therapeutic responses in glioma and associated comorbidities.

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Conflict of interest

The authors have nothing to declare.

Author contributions

Conceptualization, formal analysis, original draft preparation, project supervision, project administration, funding acquisition (SKC), and writing—review and editing (SKC, DC). Both authors have approved the final version and publication of the manuscript.

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