

REVIEW ARTICLE

KDM6B: A critical epigenetic regulator in glioma pathogenesis and therapeutic targeting

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Abstract

Gliomas are among the most aggressive malignant brain tumors, and the clinical efficacy of current treatment modalities (e.g., surgical resection, radiotherapy, and chemotherapy) is far from satisfactory, resulting in dismal prognostic outcomes for patients. In recent years, aberrant histone modification has been identified as a crucial driver of glioma initiation and progression, opening up a novel and promising research direction for exploring the molecular mechanisms of gliomagenesis and developing targeted therapeutic strategies. Histone lysine demethylase 6B (KDM6B), also known as JmJc-containing protein D3 (JMJD3), exerts its biological function by catalyzing the demethylation of the repressive histone mark H3K27me2/3, thereby activating downstream gene transcription and participating in numerous physiological and pathological processes, such as neurogenesis, cell differentiation, and immune regulation. Abnormal expression or dysregulated enzymatic activity of KDM6B can disrupt multiple key signaling pathways associated with glioma development, leading to uncontrolled cell proliferation, enhanced invasion and infiltrative growth, and resistance to therapies. KDM6B represents a potential biomarker for the tumor grading and prognostic evaluation of glioma, with its clinical diagnostic value awaiting further large-scale clinical validation. Moreover, *in vitro* cell experiments and *in vivo* animal models have shown that targeted inhibition of KDM6B can effectively inhibit glioma progression. These advances have deepened our understanding of the epigenetic regulatory mechanisms underlying glioma development and hold great promise for improving the clinical therapeutic efficacy of glioma treatments.

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1. Introduction

Gliomas represent one of the most devastating and prevalent classes of central nervous system (CNS) malignancies, characterized by their highly aggressive growth pattern, extensive infiltrative behavior into surrounding normal brain tissue, and profound resistance to conventional standard-of-care therapies.¹ As the most common type of primary brain tumors in adults, gliomas account for approximately 30% of all CNS neoplasms and 80% of malignant brain tumors, imposing an enormous burden on global healthcare systems and severely compromising the patient's quality of life.¹ Epidemiological data have consistently revealed a clear gender predilection in glioma

incidence, with a higher prevalence in males than in females, and the peak incidence occurs in adults aged 45–70 years.² In contrast, pediatric glioma subtypes, such as diffuse intrinsic pontine glioma (DIPG), exhibit distinct clinical manifestations, molecular genetic characteristics, and prognostic profiles, and are associated with an even poorer clinical outcome due to their special anatomical location and limited treatment options.^{2,3} The prognosis of glioma patients varies dramatically depending on the pathological subtype and malignant grade defined by the World Health Organization (WHO): low-grade gliomas (WHO grades I–II) have a relatively favorable prognosis with a five-year overall survival (OS) rate of approximately 70%, while high-grade gliomas (grades III–IV) have an extremely poor prognosis with a five-year survival rate of less than 10%.³

Over the past three decades, the clinical management of gliomas has undergone incremental advances, but the core therapeutic modalities still rely on the combination of surgical resection, adjuvant radiotherapy, and temozolomide (TMZ)-based chemotherapy.³ Surgical resection aims to remove the maximum volume of tumor tissue while preserving the normal neurological function of patients, but it is often difficult to achieve complete resection due to the infiltrative growth of glioma cells, which is the main cause of postoperative recurrence. Radiotherapy can kill residual tumor cells after surgery and delay tumor progression, but it also causes irreversible damage to the surrounding normal brain tissue, leading to a series of neurotoxic side effects. TMZ, an oral alkylating agent, is the first-line chemotherapeutic drug for high-grade gliomas, but the development of acquired drug resistance in tumor cells severely limits its long-term clinical efficacy.⁴ For patients with glioblastoma (GBM), the most aggressive and malignant subtype of glioma, the median OS is still less than 15 months, and the 5-year survival rate is below 5%, which remains far below what is clinically needed.⁴ These clinical challenges have spurred intensive and in-depth research into the molecular drivers and regulatory mechanisms of gliomagenesis, with a growing focus on epigenetic dysregulation as a central and fundamental mechanism underlying tumor initiation, progression, therapy resistance, and recurrence.

2. Gliomas and epigenetics

Epigenetics refers to heritable changes in gene expression patterns that do not involve alterations to the primary DNA sequence, and it mainly includes DNA methylation, histone post-translational modifications (PTMs), non-coding RNAs (ncRNAs), and RNA methylation.^{5,6} Unlike genetic mutations, epigenetic modifications are

reversible and dynamic, which makes them ideal targets for the development of antitumor drugs. In recent years, a large number of studies have confirmed that epigenetic dysregulation is a defining hallmark of gliomas, and it can co-opt normal developmental and cellular regulatory programs to sustain uncontrolled proliferation, evade immune surveillance, promote invasion and metastasis, and induce therapy resistance.⁷

2.1. DNA methylation dysregulation in gliomas

DNA methylation is the most studied and well-characterized epigenetic modification, which mainly occurs at the C-5 position of cytosine in CpG dinucleotides and is catalyzed by DNA methyltransferases. In normal cells, DNA methylation plays an important role in gene imprinting, X-chromosome inactivation, and the maintenance of genome stability. In tumor cells, DNA methylation dysregulation mainly manifests as global hypomethylation and regional hypermethylation of tumor suppressor gene promoters. Global hypomethylation can lead to genomic instability and the activation of oncogenes, while promoter hypermethylation of tumor suppressor genes can cause their transcriptional silencing, thus promoting tumorigenesis and progression. In gliomas, DNA methylation dysregulation represents a hallmark epigenetic aberration, and the most typical example is the methylation status of the O⁶-methylguanine-DNA methyltransferase (*MGMT*) gene.⁸ *MGMT* is a DNA repair enzyme that can remove the methyl group from O⁶-methylguanine generated by alkylating chemotherapeutic drugs such as TMZ, thereby repairing DNA damage and mediating chemotherapy resistance. Hypomethylation within the gene body of *MGMT* is associated with elevated *MGMT* expression, which can significantly reduce the sensitivity of GBM patients to TMZ chemotherapy and lead to a poor prognosis.⁸ In contrast, hypermethylation of the *MGMT* promoter can inhibit its expression, and glioma patients with *MGMT* promoter hypermethylation have a better response to TMZ chemotherapy and a longer survival time.⁸ Therefore, the *MGMT* methylation status has become an important molecular biomarker for predicting the therapeutic response and prognosis of glioma patients receiving TMZ chemotherapy.

2.2. Non-coding RNAs in glioma tumorigenesis

Non-coding RNAs are a class of RNA molecules that do not encode proteins but play important regulatory roles in gene expression, and they are classified into three major classes based on their length and structural characteristics: small ncRNAs (e.g., microRNAs), long non-coding RNAs (lncRNAs, >200 nucleotides in length), and circular RNAs (circRNAs). MicroRNAs are small single-stranded RNA

molecules with a length of 18–25 nucleotides, and they can bind to the 3' untranslated region of target mRNAs to inhibit their translation or induce their degradation, thereby regulating gene expression at the post-transcriptional level. LncRNAs are a class of long RNA molecules with complex secondary and tertiary structures, and they can regulate gene expression at the epigenetic, transcriptional, and post-transcriptional levels through a variety of mechanisms, such as chromatin remodeling, transcriptional activation or inhibition, and microRNA sponging. CircRNAs are a class of covalently closed circular RNA molecules formed by back-splicing of pre-mRNAs, and they can act as microRNA sponges and protein scaffolds. All these ncRNA subgroups serve as pivotal regulators of gene expression and exert indispensable roles in glioma tumorigenesis and progression, and they have great potential as diagnostic/prognostic biomarkers and therapeutic targets for gliomas.⁹

2.3. RNA methylation in gliomas

RNA methylation is an emerging and rapidly developing field of epigenetic research, which refers to the chemical modification of RNA molecules after transcription, and it modulates multiple aspects of RNA metabolism, including RNA stability, alternative splicing, translational efficiency, and nucleocytoplasmic shuttling. Among the known RNA methylation modifications, N⁶-methyladenosine (m⁶A) is the most prevalent and extensively characterized modification in eukaryotic mRNAs. In recent years, a large number of studies have confirmed that the dysregulation of the m⁶A modification machinery is tightly linked to the initiation and progression of gliomas.¹⁰

Beyond the epigenetic modifications outlined above, histone modifications also play a critical role in multiple processes underlying glioma tumorigenesis.¹¹

3. Histone methylation and expression regulation

Histone PTMs constitute a sophisticated and dynamic “histone code” that plays a crucial role in the regulation of chromatin structure and gene expression.^{12,13} These modifications occur on the flexible N-terminal tails of core histone proteins (H2A, H2B, H3, H4) that protrude from the nucleosome core, and they include a diverse set of covalent chemical modifications such as methylation, acetylation, phosphorylation, ubiquitination, and sumoylation.¹² The “histone code” is deciphered by specific regulatory proteins that recognize and bind to modified histone residues, thereby modulating chromatin accessibility—either promoting the formation of transcriptionally active euchromatin or repressive heterochromatin.^{13,14} Chromatin structure is closely linked

to gene expression: euchromatin is a loose chromatin structure that allows the binding of transcription factors and RNA polymerase II to DNA, thus promoting gene transcription; heterochromatin is a compact chromatin structure that inhibits the binding of transcription machinery to DNA, thus repressing gene transcription.^{13,14}

Among these histone PTMs, histone methylation is one of the most complex and functionally versatile modifications, characterized by its stability and ability to exert both activating and repressive effects on gene transcription.^{15,16} Histone methylation mainly occurs on the lysine and arginine residues of histone N-terminal tails, and the most studied lysine methylation sites include H3K4, H3K9, H3K27, H3K36, and H4K20. Lysine residues can be mono-methylated (me1), di-methylated (me2), or tri-methylated (me3), and the different degrees of methylation at the same residue can exert distinct biological functions. The functional outcome of histone methylation depends on the specific residue modified, the degree of methylation, and the histone subtype involved.^{15,16} Generally, histone methylation marks can be divided into activating marks and repressive marks: H3K4me3 at the promoter region of active genes and H3K36me3 at the transcribed gene bodies are typical activating marks that promote gene transcription; H3K9me3 in constitutive heterochromatin and H3K27me3 in facultative heterochromatin are typical repressive marks that inhibit gene transcription.^{17,18} For example, H3K27me3, a key repressive histone mark, is widely distributed in the genome and plays an important role in the regulation of cell differentiation, embryonic development, and tumorigenesis by silencing the expression of developmental regulatory genes and tumor suppressor genes.^{17,18}

Histone lysine methylation is a reversible process that is catalyzed by two classes of enzymes with opposite functions: lysine methyltransferases (KMTs) and lysine demethylases (KDMs).¹⁹ KMTs transfer methyl groups from S-adenosylmethionine to the lysine residues of histones, thereby mediating histone methylation and regulating gene expression. KDMs remove methyl groups from methylated histone lysine residues, thereby reversing histone methylation and modulating gene transcription. KDMs are classified into two main families based on their structural and catalytic characteristics: the flavin-dependent amine oxidases and the Fe²⁺- and α -ketoglutarate (α -KG)-dependent Jumonji C (JmjC) domain-containing demethylases.^{20,21} The JmjC domain-containing demethylases are the largest family of KDMs, and they can demethylate all three degrees of lysine methylation (me1, me2, me3).

Histone methylation is involved in a wide range of physiological processes, including embryonic development, cell differentiation, stem cell maintenance, and genome stability.^{22,23} The dysregulation of histone methylation, caused by the abnormal expression or activity of KMTs or KDMs, is closely implicated in the pathogenesis of various human diseases, such as cancer, neurological disorders, and cardiovascular diseases.^{24–26} In gliomas, dysregulation of H3K27 methylation is a prevalent epigenetic event that fuels glioma initiation and progression.^{27–29} H3K27 methylation is mainly catalyzed by the polycomb repressive complex 2 (PRC2), whose catalytic subunit is KMT6 (EZH2), and it is reversed by the JmjC domain-containing demethylases KDM6A (UTX) and KDM6B (JMJD3).^{27–29} Abnormalities in PRC2 (e.g., overexpression of EZH2) or dysfunctions in KDM6A and KDM6B can lead to the dysregulation of H3K27me3 levels in glioma cells, thereby disrupting the normal expression of downstream target genes and promoting glioma development.^{27–29} As a key H3K27me2/3 demethylase, KDM6B has attracted extensive attention due to its important role in the epigenetic regulation of glioma development, and the following sections will focus on the structural characteristics, biological functions, and specific role of KDM6B in gliomas.

4. Structure and biological roles of KDM6B

4.1. Structural characteristics of KDM6B

KDM6B, also known as JmjC-containing protein D3 (JMJD3), is a conserved Fe²⁺- and α -KG-dependent histone demethylase that specifically catalyzes the demethylation of the repressive histone marks H3K27me2/3.^{30–32} The human *KDM6B* gene is located on chromosome 17p13.1, and it encodes a protein with a molecular weight of approximately 180 kDa.³³ Structural analysis has shown that KDM6B has a unique domain architecture that is essential for its enzymatic activity and biological function: it harbors two N-terminal nuclear localization signals that mediate the nuclear translocation of KDM6B, a C-terminal JmjC domain that serves as the catalytic core for its demethylase activity, and a zinc-finger domain that is responsible for DNA binding and determining the target gene specificity of KDM6B.³³ The JmjC domain is a highly conserved structural domain that contains the catalytic center for demethylation, and it requires multiple cofactors to exert its enzymatic activity, including oxygen, Fe²⁺, L-ascorbate, and α -KG.^{34,35}

The demethylation reaction catalyzed by KDM6B is an oxidative demethylation process: the JmjC domain uses molecular oxygen to oxidize the methyl group of H3K27me2/3 to form formaldehyde, and α -KG is

simultaneously oxidized to succinate and CO₂.^{34,35} By removing the repressive H3K27me3 mark from the promoter or enhancer regions of target genes, KDM6B can alter the chromatin structure, promote the binding of transcription factors and RNA polymerase II to DNA, and thus activate gene transcription.^{36,37} KDM6B can activate gene transcription through two main mechanisms: one is to promote the elongation of RNA polymerase II, thereby accelerating the process of gene transcription^{36,37}; the other is to disrupt the PRC2-mediated gene silencing complex, thereby inhibiting the repressive effect of PRC2 on gene expression.³⁸

4.2. Physiological functions of KDM6B

Histone lysine demethylase 6B plays essential and pleiotropic roles in a broad spectrum of biological processes, encompassing embryonic development, cellular plasticity, stem cell maintenance, and immune system modulation.^{39,40} During embryonic development, KDM6B is a key epigenetic regulator that governs the expression of *HOX* gene clusters, which are essential for the patterning of the posterior body axis in vertebrate species.^{30,41} *HOX* genes encode a family of homeodomain-containing transcription factors that regulate the spatial and temporal expression of downstream target genes during embryonic development, and their dysregulation is closely associated with embryonic developmental abnormalities. In addition to its role in embryonic development, KDM6B also mediates temperature-dependent sex determination in some reptilian species, such as turtles.⁴² In turtles, the incubation temperature of eggs determines the sex of offspring, and KDM6B is a key gene that mediates this process: high incubation temperature can induce the expression of KDM6B, which in turn activates the transcriptional expression of male-specific gene cascades by demethylating H3K27me3, thereby promoting the development of male embryos.⁴²

In the immune system, KDM6B plays a critical role in the regulation of inflammatory responses and immune cell differentiation.^{43,44} KDM6B can regulate lineage commitment and functional polarization of macrophages.⁴³ In addition, KDM6B serves as a master epigenetic regulator of early immunofibroblast differentiation, and its aberrant hyperactivation is closely associated with the onset and progression of chronic inflammatory disorders and autoimmune pathologies.⁴⁴ In the hematopoietic system, KDM6B supports the self-renewal and functional maintenance of hematopoietic stem cells through the precise modulation of lineage-specific gene expression signatures, and it is indispensable for hematopoietic stem cell self-renewal under conditions of inflammatory stimulation and proliferative stress.⁴⁵

4.3. Role of KDM6B in malignant tumorigenesis

Dysregulated expression or aberrant enzymatic activity of KDM6B has been implicated in the pathogenesis of multiple human disorders⁴⁶, with a particularly prominent role in malignant tumorigenesis and progression.^{46–49} KDM6B exerts an oncogenic role in most human malignancies, and its overexpression is closely associated with the malignant grade, invasion and metastasis, and poor prognosis of tumors.^{46–49} In Hodgkin's lymphoma, KDM6B expression is ectopically induced by Epstein–Barr virus infection, leading to its marked overexpression in tumor tissues.⁵⁰ The overexpression of KDM6B can activate the expression of oncogenes by demethylating H3K27me3, thereby promoting the proliferation and survival of lymphoma cells.⁵⁰ In prostate cancer, elevated KDM6B levels are closely correlated with high Gleason scores and inferior recurrence-free survival outcomes.⁵¹ Mechanistically, KDM6B promotes cancer cell proliferation by catalyzing the demethylation of the repressive histone mark H3K27me3 at the cyclin D1 gene promoter, thereby activating the expression of cyclin D1, a key regulator of the cell cycle.⁵¹ In renal cell carcinoma, KDM6B upregulation drives the epithelial–mesenchymal transition (EMT) program, a cellular reprogramming process that enhances the invasive and metastatic potential of cancer cells, thereby promoting tumor metastasis.^{52,53} In gastric cancer, *Helicobacter pylori* infection, a major risk factor for gastric cancer, triggers KDM6B upregulation, which in turn induces the expression of the chemokine receptor CXCR4 to facilitate cancer cell migration and metastasis.⁵⁴ In hepatocellular carcinoma, KDM6B sustains the aggressive malignant phenotype of cancer cells by promoting cell migration, invasion, and the acquisition of stem cell-like properties.⁵⁵ Cancer stem cells (CSCs) are a small subset of cancer cells with self-renewal capacity, and they are responsible for tumor initiation, progression, metastasis, and therapy resistance. KDM6B can promote the formation of CSCs in hepatocellular carcinoma by activating the expression of stem cell-related genes, thereby enhancing the malignant phenotype of tumor cells. In melanoma, KDM6B accelerates tumor progression and metastasis through the activation of the NF- κ B and BMP signaling cascades, which are key oncogenic signaling pathways involved in cell proliferation, invasion, and metastasis.⁵⁶ The above studies indicate that KDM6B is a key oncogene in multiple human malignancies, and targeting KDM6B has great potential as a novel antitumor therapeutic strategy. The following section will elaborate on the specific role and underlying molecular mechanisms of KDM6B in glioma initiation and progression.

5. KDM6B and glioma development

From a molecular perspective, gliomas discussed in this review can be broadly considered as mutation-defined glioma subtypes (e.g., H3K27-altered and IDH1/2-mutant gliomas) and sporadic gliomas without a unifying defining mutation discussed here.⁵⁷

5.1. KDM6B in mutation-defined glioma subtypes

Mutation-defined glioma subtypes are characterized by specific driver mutations that are causally linked to tumor initiation and progression, among which H3K27M alterations and isocitrate dehydrogenase 1/2 (IDH1/2) mutations are particularly well studied.^{58,59} These mutations can induce profound epigenetic dysregulation in glioma cells, thereby promoting tumorigenesis and progression, and they are closely associated with the clinical characteristics and prognosis of glioma patients.^{58,59}

H3K27M mutations are a lysine-to-methionine substitution at residue 27 of histone H3 (including H3.1, H3.2, and H3.3). They are predominantly detected in pediatric high-grade gliomas, including DIPG and diffuse midline glioma (DMG).^{60,61} Pediatric high-grade gliomas with H3K27M mutations are associated with a highly aggressive tumor phenotype, rapid disease progression, and extremely poor clinical prognosis. Functionally, H3K27M mutations can elicit a unique and profound epigenetic landscape in glioma cells, which is characterized by global depletion of the repressive histone mark H3K27me3.⁶² The H3K27M mutant histone can bind to the PRC2 complex with high affinity and inhibit its enzymatic activity, thereby reducing the global level of H3K27me3 and leading to the activation of a large number of developmental regulatory genes and oncogenes. This global depletion of H3K27me3 theoretically antagonizes the H3K27 demethylase activity of KDM6B, because the substrate of KDM6B (H3K27me2/3) is significantly reduced in H3K27M-mutant glioma cells.⁶²

Isocitrate dehydrogenase 1/2 mutations are the most common genetic mutations in adult low-grade gliomas and secondary GBM, and they are detected in approximately 70–80% of low-grade gliomas.⁵⁹ Unlike H3K27M mutations, IDH1/2-mutant gliomas generally exhibit a more favorable prognosis relative to their wild-type counterparts, with patients displaying prolonged OS and improved therapeutic responsiveness.⁶³ The IDH1 and IDH2 genes encode isocitrate dehydrogenases that catalyze the conversion of isocitrate to α -KG in the tricarboxylic acid cycle. A hallmark of mutated IDH1/2 enzymes is their neomorphic catalytic activity: they lose their normal catalytic function and instead catalyze the conversion of

α -KG to 2-hydroxyglutarate (2HG), an oncometabolite that accumulates to high levels in IDH1/2-mutant glioma cells. 2HG acts as a competitive inhibitor of multiple α -KG-dependent dioxygenases, including KDM6B and other JmjC domain-containing demethylases, as well as DNA demethylases.⁶⁴ The inhibition of KDM6B activity by 2HG leads to the accumulation of H3K27me3 in glioma cells, thereby silencing the expression of differentiation-related genes and blocking the terminal differentiation of lineage-specific progenitor cells. Glioma specimens harboring IDH1/2 mutations consistently exhibit elevated global histone methylation levels, which is a key epigenetic feature of these gliomas.⁶⁵ Although IDH1/2 mutations inhibit KDM6B activity, the dysregulation of the KDM6B-H3K27me3 axis still plays an important role in the development of IDH1/2-mutant gliomas, and targeting this axis has potential therapeutic value for these gliomas.

5.2. KDM6B in sporadic gliomas

Sporadic gliomas account for the vast majority of gliomas, and they are mainly caused by the accumulation of somatic mutations and epigenetic dysregulation, without obvious genetic predisposition. High-grade sporadic gliomas, especially GBM, are the most aggressive subtype of gliomas, and they are associated with an extremely poor prognosis⁴. In sporadic gliomas, particularly high-grade subtypes such as GBM, KDM6B expression is markedly upregulated relative to normal brain tissues, and this finding has been widely confirmed by multiple independent studies.⁶⁶ Transcriptomic analyses from public databases (e.g., GEPIA, The Human Protein Atlas) have shown that the mRNA expression level of KDM6B is significantly higher in glioma tissues than in normal brain tissues, and immunohistochemical assays have further confirmed the overexpression of KDM6B protein in glioma tissues.⁶⁶ Importantly, KDM6B expression levels are tightly correlated with the malignant grade of sporadic gliomas, with higher expression detected in high-grade tumors (WHO grades III–IV) compared to low-grade lesions (WHO grades I–II). The expression level of KDM6B is also closely associated with the clinical prognosis of sporadic glioma patients: patients with high KDM6B expression have a shorter overall survival time and a poorer prognosis compared to patients with low KDM6B expression. These clinical findings indicate that KDM6B is a potential diagnostic and prognostic biomarker for sporadic gliomas, and its overexpression is a key epigenetic event that promotes the malignant progression of sporadic gliomas (Table 1).

5.3. The roles of KDM6B in glioma progression

Histone lysine demethylase 6B exerts a pivotal oncogenic role in glioma progression by regulating multiple cellular processes, including cell proliferation, migration and invasion, apoptosis, cellular senescence, TMZ resistance, and the tumor immune microenvironment (Figure 1).⁶⁷ *In vitro* and *in vivo* studies have consistently confirmed that targeting KDM6B can effectively inhibit these malignant cellular processes and suppress glioma progression, which further supports the potential of KDM6B as a therapeutic target for gliomas.^{66,68,71}

Histone lysine demethylase 6B contributes to glioma progression through the following mechanisms:

- (i) Promotion of cell proliferation and invasion: Cell proliferation and invasion are the two most important malignant characteristics of glioma cells, and they are the main causes of tumor growth and postoperative recurrence. *In vitro* functional assays using glioma cell lines (e.g., U87, U251) have demonstrated that KDM6B knockdown by small-interfering RNA or short hairpin RNA potently inhibits cell proliferation, migration, and invasive capacity⁶⁸, whereas KDM6B overexpression exerts the opposite pro-tumorigenic effects. This oncogenic function is tightly linked to the ability of KDM6B to transcriptionally regulate the expression of a variety of invasion-related genes and key transcription factors.
- (ii) Suppression of apoptosis: Apoptosis is a programmed cell death process that plays an important role in the maintenance of normal cellular homeostasis and the elimination of abnormal cells. The evasion of apoptosis is a hallmark of malignant tumors, and glioma cells exhibit a strong resistance to apoptotic stimuli, which is one of the main reasons for their poor response to antitumor therapies. Pharmacological inhibition of KDM6B by small-molecule inhibitors (e.g., GSK-J4) not only elicits robust apoptotic responses in H3K27M-mutant glioma cells but also effectively induces programmed cell death in established glioma cell lines (e.g., U87, U251).⁶⁶ The induction of apoptosis by KDM6B inhibition is mainly mediated by the upregulation of pro-apoptotic genes and the downregulation of anti-apoptotic genes. This observation underscores the critical role of KDM6B in mediating apoptotic resistance—a hallmark of glioma malignancy—and further supports its potential as a therapeutic target for both mutation-defined (e.g., H3K27M-mutant) and sporadic glioma subtypes.

Table 1. Characteristics of KDM6B across selected glioma types

Type	Genetic drivers	KDM6B expression/ activity	Molecular mechanisms	Clinical features
Mutation-defined gliomas	H3K27M mutant	Equivalent to high activity	Mutations reduce the level of H3K27me2/3	Poor prognosis
	IDH1/2 mutant	low activity	Competitive inhibition of enzymatic activity	Good prognosis
Sporadic gliomas	Unidentified	High expression/activity	Participates in multiple glioma progression pathways	High grade and poor prognosis

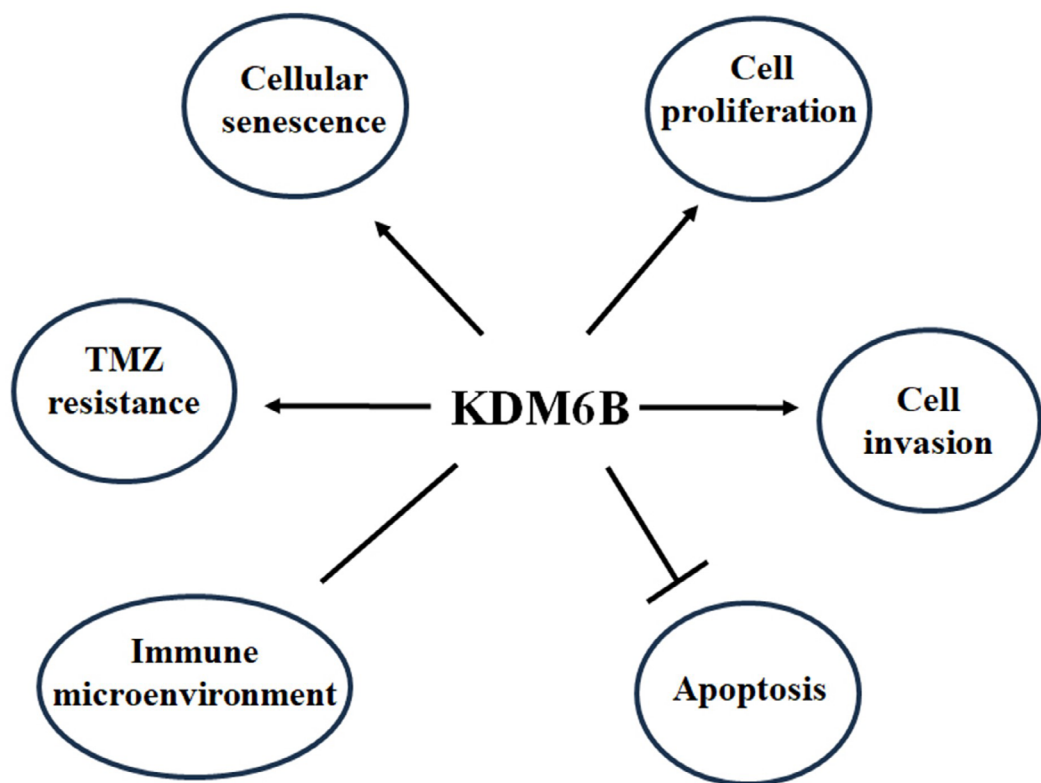


Figure 1. The role of KDM6B in glioma progression. Image created by the authors. Abbreviation: TMZ: Temozolomide.

(iii) Regulation of cellular senescence: Cellular senescence is a state of irreversible cell cycle arrest that is triggered by various stress signals, such as DNA damage, oncogene activation, and oxidative stress. Cellular senescence is an important antitumor mechanism that can inhibit the proliferation of abnormal cells and prevent tumorigenesis. However, emerging evidence implicates KDM6B in the regulation of cellular senescence in gliomas. Its enzymatic activity

can modulate tumor progression and therapeutic responses by shaping the senescence-associated secretory phenotype (SASP) and remodeling the tumor microenvironment.^{69,70} The SASP is a complex set of cytokines, chemokines, and growth factors secreted by senescent cells, which can exert both antitumor and pro-tumor effects depending on the cellular context. Our previous work has established that KDM6B is critically involved in vitamin D₃-induced senescence

in glioma cells.⁷¹ The biologically active form of vitamin D₃, 1,25-dihydroxyvitamin D₃, can upregulate the expression of KDM6B in glioma cells, which in turn promotes the transcription of senescence-related genes via H3K27me3 demethylation, thereby inducing glioma cell senescence.⁷¹ These findings indicate that KDM6B plays a dual role in the regulation of cellular senescence in gliomas, and targeting KDM6B can modulate the senescence process of glioma cells to inhibit tumor progression.

- (iv) Regulation of TMZ resistance: TMZ is the first-line chemotherapeutic agent for gliomas, but the development of acquired resistance in glioma cells severely compromises its clinical efficacy and leads to tumor recurrence. The mechanisms of TMZ resistance in gliomas are complex and include the upregulation of DNA repair enzymes (e.g., MGMT), the activation of anti-apoptotic signaling pathways, and the epigenetic dysregulation of gene expression. Recent studies have identified KDM6B as a key mediator of TMZ resistance in GBM cells.⁷² Pharmacological inhibition of KDM6B can effectively suppress the proliferation of both naive and TMZ-resistant GBM cells.⁷³ Furthermore, combinatorial treatment with KDM6B inhibitors and KDM5A inhibitors (e.g., JIB 04) exerts a robust synergistic antitumor effect against TMZ-resistant cells, highlighting a promising therapeutic strategy to overcome chemoresistance.⁷⁴
- (v) Modulation of the tumor immune microenvironment: The tumor immune microenvironment (TIME) is a complex cellular and molecular ecosystem that surrounds tumor cells, and it includes immune cells (e.g., T cells, macrophages, microglia), stromal cells, and a variety of cytokines and chemokines. The TIME plays a crucial role in the regulation of tumor initiation, progression, and therapy response, and the immunosuppressive TIME in gliomas is one of the main reasons for the poor response to immunotherapy. Accumulating evidence indicates that KDM6B plays a critical role in regulating the immune landscape of gliomas.⁷⁵ Myeloid cells, including tumor-associated macrophages and microglia, are the most abundant immune cells in the glioma TIME, and they exhibit an immunosuppressive phenotype that promotes glioma progression and immune evasion. Myeloid-specific KDM6B inhibition has been shown to reprogram the immunosuppressive phenotype of myeloid cells into a pro-inflammatory phenotype, thereby enhancing the antitumor immune response and sensitizing GBM to programmed cell death protein 1 (PD-1) blockade immunotherapy.⁷⁶ This finding suggests that KDM6B may suppress antitumor immunity by modulating

myeloid cell function, and it provides a novel rationale for combining epigenetic therapy (targeting KDM6B) with immunotherapy (e.g., PD-1 inhibitors) in the management of gliomas.⁷⁶

5.4. Underlying molecular mechanisms of KDM6B in gliomas

The oncogenic functions of KDM6B in gliomas are primarily mediated by its intrinsic histone demethylase activity, which selectively erases the repressive H3K27me3 mark from the promoters or enhancers of target genes, thereby facilitating their transcriptional activation. To date, several key target genes and signaling pathways regulated by KDM6B have been elucidated (Figure 2), including oligodendrocyte transcription factor 2 (*OLIG2*), snail family transcriptional repressor 1 (*SNAIL1*), cyclin-dependent kinase inhibitors (CDKIs), and platelet-derived growth factor receptor alpha (*PDGFRA*). Notably, these target genes play important roles in the malignant progression of gliomas.

The major molecular mechanisms by which KDM6B promotes glioma progression include the following:

- (i) Regulation of *OLIG2* expression: *OLIG2* is a master regulator of glioma development and progression, and it is highly expressed in almost all glioma subtypes. *OLIG2* plays a critical role in the maintenance of the malignant phenotype of glioma cells by regulating cell proliferation, invasion, and the maintenance of glioma stem cells. Mechanistically, KDM6B binds directly to the *OLIG2* promoter region and catalyzes the demethylation of H3K27me3, leading to transcriptional upregulation of *OLIG2*.^{77,78} A significant positive correlation between KDM6B and *OLIG2* mRNA expression levels has been observed in glioma tissues, and genetic or pharmacological inhibition of KDM6B significantly attenuates *OLIG2* expression. These findings underscore the critical role of the KDM6B–*OLIG2* axis in driving glioma progression in glioma cells.⁷⁸ Targeting this axis has great potential as a novel therapeutic strategy for gliomas.
- (ii) Activation of an *SNAIL1*-associated EMT-like program: The EMT is a cellular reprogramming process that converts epithelial cells into mesenchymal cells with enhanced migratory and invasive capacity, and it plays a crucial role in tumor invasion and metastasis. *SNAIL1* is a core transcription factor governing the EMT process, and it can repress the expression of epithelial markers (e.g., E-cadherin) and activate the expression of mesenchymal markers (e.g., N-cadherin, vimentin), thereby promoting the EMT process. KDM6B promotes glioma cell migration

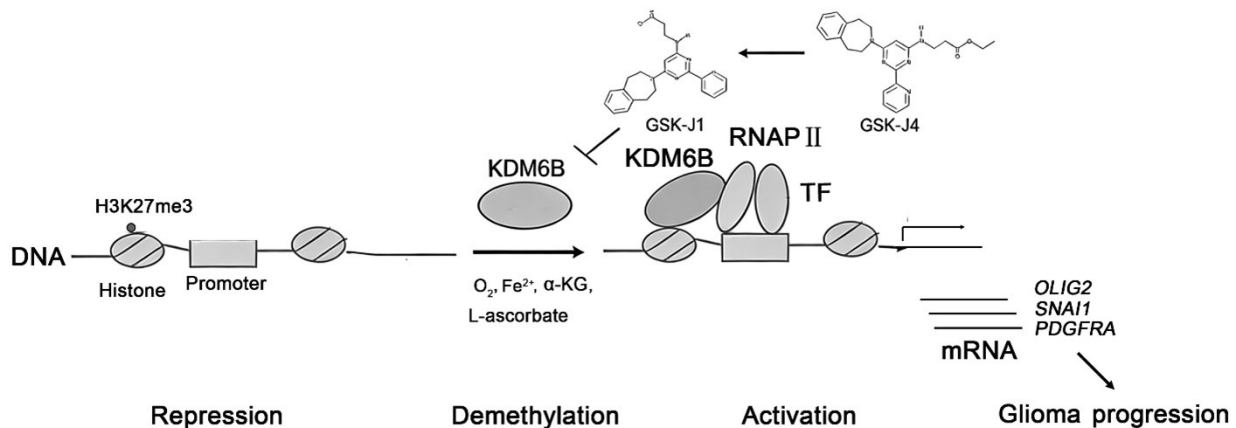


Figure 2. The molecular mechanisms of KDM6B involvement in glioma progression. Image created by the authors.
Abbreviations: α -KG: α -ketoglutarate; RNAPII: RNA polymeraseII; TF: Transcription factor.

and invasion, at least in part, by transcriptionally upregulating *SNAI1* expression.^{68,79} By demethylating H3K27me3 at the *SNAI1* promoter, KDM6B activates *SNAI1* transcription, thereby triggering the EMT process and augmenting the invasive and metastatic capacity of glioma cells. The KDM6B–*SNAI1*–EMT axis is a key regulatory pathway for glioma invasion and metastasis, and targeting this axis can effectively inhibit the invasive and metastatic potential of glioma cells.

- (iii) Regulation of *CDKI* expression: CDKs are a class of proteins that inhibit the activity of cyclin-dependent kinases, thereby regulating cell cycle progression and cellular senescence. The main CDKs include *CDKN1A* (p21), *CDKN2A* (p16), and *CDKN2B* (p15), and their downregulation is a common event in gliomas, leading to uncontrolled cell cycle progression and proliferation. KDM6B has been shown to modulate glioma cell senescence by regulating the expression of CDKs. Our prior study demonstrated that 1,25-dihydroxyvitamin D₃ induces glioma cell senescence by upregulating KDM6B, which in turn promotes the transcription of *CDKN1A* and *CDKN2A* via H3K27me3 demethylation.⁷¹ Recent investigations have further expanded this regulatory network, revealing that KDM6B modulates the expression of multiple cell-cycle and senescence-related regulators (e.g., *CDKN1A* and *TP53*) involved in TMZ-induced glioma cell senescence.^{80–83}
- (iv) Upregulation of *PDGFRA*: *PDGFRA* is a receptor tyrosine kinase that plays an important role in cell proliferation, migration, and survival, and its overexpression and activation are common events in gliomas. *PDGFRA* is a key oncogene in gliomas, and

it is closely associated with the malignant grade and poor prognosis of glioma patients. Our recent work has identified a novel mechanism by which KDM6B promotes glioma cell proliferation: the transcriptional upregulation of *PDGFRA*.⁸⁴ Mechanistically, KDM6B not only reduces H3K27me3 enrichment at the *PDGFRA* promoter but also induces chromatin loop formation, which facilitates physical interactions between distal enhancers and the *PDGFRA* promoter, ultimately enhancing its transcriptional activity.⁸⁴ Chromatin loop formation is a key epigenetic mechanism that regulates gene expression by bringing distal regulatory elements (e.g., enhancers) into close proximity with gene promoters. The KDM6B–*PDGFRA* axis is a novel oncogenic signaling pathway in gliomas, and targeting this axis can effectively inhibit glioma cell proliferation.

6. Therapeutic implications of targeting KDM6B in gliomas

Given the well-established oncogenic role of KDM6B in glioma initiation and progression, targeted inhibition of this histone demethylase has emerged as a promising therapeutic strategy for glioma intervention.^{85,86} In recent years, a panel of small-molecule inhibitors against KDM6B has been developed, and preclinical investigations have validated their robust antitumor efficacy across multiple experimental models, including glioma cell lines, patient-derived xenografts, and animal models.⁸⁷ These small-molecule inhibitors mainly target the JmjC domain of KDM6B, the catalytic core for its demethylase activity, and they inhibit the enzymatic activity of KDM6B by competing with cofactors (e.g., α -KG) or binding to the active site of the JmjC domain. Among these agents, GSK-J4—a dual

inhibitor targeting both KDM6A and KDM6B—has been the most extensively characterized and studied to date for the treatment of gliomas.⁸⁸

GSK-J4 is a prodrug that is rapidly hydrolyzed in cells to GSK-J1, the active form of the inhibitor, which is otherwise cell impermeable. Mounting *in vitro* and *in vivo* preclinical evidence demonstrates that GSK-J4 exerts its antitumor effects by abrogating the demethylase activity of KDM6B, which in turn restores the repressive H3K27me3 modification at the promoters of KDM6B-driven oncogenes (e.g., *OLIG2*, *SNAIL*, *PDGFRA*) and consequently suppresses malignant tumor cell proliferation, invasion, and survival.⁸⁹ Notably, GSK-J4 possesses the unique ability to cross the blood–brain barrier (BBB)—a critical pharmacokinetic advantage that is essential for the treatment of CNS tumors such as gliomas.⁹⁰ The BBB is a highly selective semipermeable membrane that separates the blood from the brain parenchyma, and it prevents most small-molecule drugs from entering the brain, which is a major challenge for the development of glioma therapeutics. The ability of GSK-J4 to cross the BBB makes it a promising candidate for the clinical treatment of gliomas.

In the context of H3K27M-mutant gliomas (e.g., DIPG), GSK-J4 has been shown to enhance the sensitivity of tumor cells to conventional chemotherapy and radiotherapy, thereby potentiating the overall antitumor response.^{91,92} Dordaviprone (ONC201)—a recently United States Food and Drug Administration-approved therapeutic agent for H3K27M-mutant DMG—exerts its therapeutic effects by restoring global H3K27me3 levels and inducing tumor cell apoptosis.⁹³ Intriguingly, KDM6B inhibition by GSK-J4 may synergize with dordaviprone by further normalizing the dysregulated H3K27me3 epigenetic landscape in H3K27M-mutant glioma cells, thus implicating KDM6B as a viable therapeutic target for the clinical management of H3K27M-mutant DMG.⁹³ Preclinical studies have shown that the combination of GSK-J4 and dordaviprone exerts a stronger antitumor effect than single-agent treatment in H3K27M-mutant glioma models, which provides a novel combinatorial therapeutic strategy for these intractable gliomas.⁹³

For sporadic gliomas, preclinical studies have also demonstrated robust antitumor efficacy of KDM6B inhibitors, either as monotherapies or in combinatorial regimens with standard-of-care chemotherapy (e.g., TMZ), immune checkpoint blockade therapy (e.g., PD-1 inhibitors), or other epigenetic modulators (e.g., KDM5A inhibitors).^{73,74,76} As a monotherapy, GSK-J4 can effectively inhibit the proliferation of sporadic glioma cells and induce their apoptosis *in vitro*.⁶⁶ In combinatorial regimens, the

combination of KDM6B inhibitors and TMZ can reverse TMZ resistance and enhance the chemotherapeutic efficacy of TMZ in sporadic GBM models.⁷³ The combination of KDM6B inhibitors and PD-1 inhibitors can reprogram the immunosuppressive tumor immune microenvironment and enhance the antitumor immune response, thereby exerting a synergistic antitumor effect in sporadic GBM models.⁷⁶ The combination of KDM6B inhibitors and KDM5A inhibitors can exert a robust synergistic antitumor effect against TMZ-resistant sporadic GBM cells.⁷⁴ These encouraging preclinical findings warrant further rigorous clinical evaluation to validate their therapeutic utility in human glioma patients. To date, most clinical trials of KDM6B inhibitors remain in early phases (I/II), with a primary focus on evaluating safety, tolerability, and preliminary efficacy in heavily pretreated patients with CNS tumors. Combination regimens incorporating chemotherapy, radiotherapy, or immunotherapy are prioritized in trial design, owing to the limited efficacy of KDM6B inhibitor monotherapy observed in preclinical models. No large-scale Phase III clinical trials of KDM6B inhibitors have been reported to date.

Nevertheless, several critical challenges must be addressed to facilitate the successful clinical translation of KDM6B-targeted therapies for gliomas. First, the development of next-generation selective KDM6B inhibitors with optimized specificity, pharmacokinetic profiles, and BBB permeability is urgently needed.⁸⁵ Most currently available KDM6B inhibitors (e.g., GSK-J4) are dual inhibitors of KDM6A and KDM6B, and they may cause off-target toxicity due to the inhibition of KDM6A, which has important tumor suppressor functions in some tissues. Therefore, the development of highly selective KDM6B inhibitors that only target KDM6B without affecting KDM6A is essential to improve the therapeutic index and reduce side effects.⁸⁵ Second, the identification of reliable predictive biomarkers to enable precise patient stratification and personalized treatment planning is critical. Third, the optimization of drug delivery systems to enhance the accumulation of KDM6B inhibitors in glioma tissues is also an important challenge.

7. Challenges and future perspectives

Despite the considerable potential of KDM6B as a diagnostic/prognostic biomarker and therapeutic target in gliomas, several critical challenges must be addressed to facilitate its successful clinical translation and application in clinical practice. First, in the realm of diagnosis and prognosis assessment, the standardization of KDM6B detection methodologies and the establishment of unified expression cutoff values tailored to distinct glioma subtypes remain urgently needed. Currently, KDM6B

detection methods include immunohistochemistry, quantitative real-time polymerase chain reaction (PCR), RNA sequencing, and single-cell sequencing, and different studies use different detection methods and reference thresholds, leading to inconsistent results and hindering the reliable clinical utility of KDM6B as a diagnostic or prognostic biomarker. For example, PCR typically uses cycle threshold, immunohistochemistry uses staining scores, and sequencing uses transcripts per million. As a result, expression levels can usually be compared only within the same experimental system. The establishment of standardized detection protocols and unified expression cutoff values for different glioma subtypes is essential to realize the clinical application of KDM6B as a biomarker. In addition, the combination of KDM6B with other clinical and molecular biomarkers (e.g., MGMT methylation status, IDH1/2 mutation status) can improve the accuracy of glioma diagnosis and prognostic evaluation, and this is a promising research direction for the future. Second, in therapeutic development, the creation of highly selective KDM6B inhibitors with favorable safety profiles and optimal pharmacokinetic properties is a pivotal prerequisite for clinical advancement. Thus, next-generation inhibitors with enhanced subtype specificity and reduced adverse effects are essential to improve the therapeutic index. Third, the identification of robust predictive biomarkers for KDM6B-targeted therapies is critical for precise patient stratification, ensuring that individuals most likely to benefit from such interventions are accurately selected while avoiding unnecessary treatment-related harms. Finally, the molecular mechanisms underlying KDM6B function in diverse glioma subtypes remain incompletely elucidated. Further dissecting these subtype-specific regulatory networks will provide a more comprehensive theoretical foundation for personalized therapeutic strategies.

In the future, the advancement of multi-omics technologies (e.g., genomics, epigenomics, transcriptomics, proteomics) will enable a deeper understanding of the complex regulatory circuitry orchestrated by KDM6B in gliomas, including its interactions with other epigenetic modifiers, signaling pathways, and the tumor microenvironment. Concurrently, large-scale prospective clinical trials are needed to validate the clinical value of KDM6B as a diagnostic/prognostic biomarker and to evaluate the efficacy and safety of KDM6B-targeted monotherapies or combinatorial regimens in diverse patient cohorts. It is anticipated that continuous research—integrating basic science discoveries with clinical translational efforts—will elevate KDM6B to a key role in the personalized management of glioma patients, ultimately improving the clinical outcomes of this

devastating and currently incurable disease.

8. Conclusion

In conclusion, this review highlights the pivotal role of KDM6B in glioma pathogenesis as an important epigenetic regulator and its emerging potential as a therapeutic target. In gliomas, KDM6B has been reported to promote tumor-associated phenotypes by modulating the expression of genes involved in cell proliferation, invasion, infiltration, and therapy resistance through epigenetic regulation of H3K27 methylation. Preclinical studies have shown that targeting KDM6B can inhibit glioma growth and enhance treatment sensitivity, underscoring its potential for therapeutic development. Although significant challenges remain in translating these findings into clinical practice, ongoing research into the precise mechanisms of KDM6B action and the development of selective inhibitors may contribute to improved treatment strategies and support the development of more effective, personalized epigenetic therapies for glioma patients.

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Conflict of interest

The authors declare they have no competing interests.

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