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Histone methylation machinery in gliomas: From enzymatic mechanisms to inhibitor development

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ABSTRACT

Glioma is the most common primary malignant tumor of the central nervous system (CNS). Advances in molecular pathology have established a robust causal link between histone modifications and glioma genesis. In addition to prior findings, recent empirical evidence has unequivocally substantiated the intricate and close relationship between histone modifications and temozolomide (TMZ) resistance, thereby advancing our understanding in this field. This article systematically reviews the roles of histone methylation modifications in glioma pathogenesis and their implications for the mechanisms of therapeutic drug action. Moreover, the latest research advancements concerning histone methylation - related enzymes and their inhibitors in the diagnosis and treatment of glioma were elaborately described, highlighting their significant implications for the field. It is highly anticipated that this review will serve as a catalyst, offering a novel and insightful direction for the ongoing research endeavors, diagnostic approaches, and therapeutic strategies pertaining to glioma.

1. Introduction

In light of current scientific understanding and empirical evidence, glioma is conventionally deemed to arise from neural stem cells bearing tumor initiating genetic modifications[1]. Among them, the most aggressive subtype is glioblastoma (GBM), which is predominantly characterized by wild-type isocitrate dehydrogenase (IDH) status[2]. Based on extensive scientific investigations, although it is recognized that multiple genetic, proteomic, cellular, and anatomical factors synergistically act to trigger recurrence and drive treatment resistance in glioma, the epigenetic landscape exhibits the greatest degree of diversity and heterogeneity compared to the other factors involved[3]. Currently, the predominant therapeutic approach for glioma involves a combination of surgical excision, radiotherapy (RT), and chemotherapy, wherein these modalities work in concert to combat the tumor[4]. Although progress has been made in the treatment of glioma with RT and chemotherapy, the clinical outcome of glioma remains poor because toxic side effects of these treatments and chemotherapy resistance in tumor cells[5]. In the current clinical landscape, the alkylating agent temozolomide (TMZ) holds a prominent position as one of the chemotherapy drugs most frequently utilized in treatment protocols[6]. However, nearly 50% of patients have the overexpression of O6-methylguanine-DNA methyltransferase (MGMT) in GBM[7]. MGMT functions as a DNA repair enzyme, specifically tasked with the elimination of the methyl group from O6-methylguanine (O6-MeG)[8]. Its physiological function is to prevent the replication of DNA into O6-methylthymine caused by mis-replication of O6-MeG during DNA replication[9]. When MGMT is lacking in cells, TMZ can specifically restrain the growth of tumor cells. This leads to DNA lesions and cell cycle stagnation, which in turn makes MGMT-deficient tumors responsive to inhibitors of ataxia telangiectasia and rad3-related protein[10]. However, recent studies have found that the use of TMZ, especially when lymphocyte-depleting agents or corticosteroids, brings the risk of herpes zoster[11]. Despite the fact that TMZ has the capacity to substantially elevate the survival rate among patients with GBM, its clinical therapeutic efficacy is constrained by the swift emergence of secondary drug resistance[12]. In the contemporary research landscape, numerous causes underlying TMZ resistance have been uncovered. Notably, the

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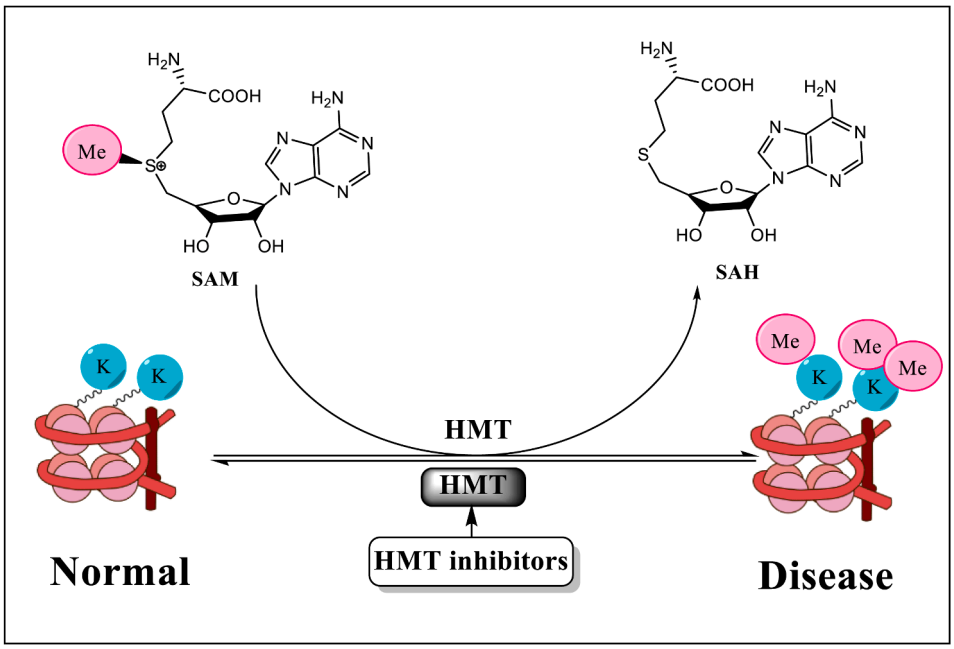

Fig. 1. The process of histone methylation catalyzed by HMT. Under the catalysis of HMT, SAM acts as a methyl donor, SAM is converted to SAH, and histone methylation occurs.

enhanced expression of MGMT emerges as one of the paramount factors leading to the emergence of TMZ resistance[8]. Furthermore, glioblastoma multiforme stem cells (GSCs) assume a pivotal role in mediating the resistance of GBM to TMZ. Research outcomes reveal that GSCs facilitate the resistance of GBM to TMZ by utilizing exosomes as vehicles to transmit ABCB4, a gene product whose transcription is mediated by ATF3[13]. Notably, this exosome-mediated resistance transmission is governed by histone methylation-dependent epigenetic plasticity in GSCs, where EZH2-mediated H3K27me3 and G9a-catalyzed H3K9me2 epigenetically upregulate ATF3 and ABCB4, respectively, driving tumor relapse. As a result, the quest for new treatment targets in glioma therapy and the formulation of novel medications to reverse TMZ resistance have taken center stage in contemporary research endeavors. Given its profound clinical implications, this line of research is crucial for mitigating the occurrence, relapse, and fatality rates of glioma.

Recent studies have found that the occurrence and development of glioma are closely related to epigenetic phenomena, including DNA methylation[14], chromatin remodeling[15] and histone modification [16], which have a significant impact on biological processes. Epigenetics represents a specialized sub-discipline within the broader field of genetics and simultaneously serves as a distinct and rapidly evolving area of biomedical research that centers on the exploration of gene function[17]. It involves heritable changes that occur without altering the DNA sequence, leading to phenotypic variations[18]. Abnormal epigenetic phenomena can cause abnormal gene expression, which in turn leads to the occurrence of glioma[19]. Regulating proteins and genes with epigenetic modifications has become a new target for the treatment of glioma[20]. Studies have shown that after TMZ is converted into a methylating cation, it can methylate histone H3 peptides and histone H3 proteins. This suggests that TMZ not only generates cytotoxic groups such as O6-MeG by methylating DNA, thereby causing single-strand and double-strand DNA breaks and killing tumor cells, but also exerts its effects by altering histone methylation[7]. This article serves as a critical synthesis that examines the pivotal role of histone methylation modifications in shaping the pathogenic processes of glioma and modulating drug action mechanisms. It provides a detailed overview of the ongoing preclinical drug research related to histone modifications, highlighting its significance in the field. Moreover, it extensively explores the current epigenetic research focused on overcoming TMZ resistance, which holds great promise for transforming the clinical treatment landscape of glioma. Beyond that, this work sheds light on the limitations of existing clinical treatments and, drawing on the analyzed phenomena, proposes forward looking research directions and potential improvements in disease prognosis prediction.

Beyond conventional temozolomide (TMZ)-based chemo-radiotherapy, immunotherapy (IO) has emerged as a transformative strategy for glioma treatment, offering new hope for patients with recurrent disease[21,22]. However, its efficacy is severely limited by the immunosuppressive tumor microenvironment and epigenetic dysregulation, which together drive therapeutic resistance[23,24]. Recent studies have demonstrated that histone methylation acts as a critical bridge linking epigenetic abnormalities to both chemo-resistance and immunotherapy failure in gliomas[25,26]. From our perspective, targeting histone methylation machinery represents a promising dual strategy to overcome these barriers and enhance the efficacy of novel combination therapies.

1.1. Literature search strategy

We systematically searched PubMed and Web of Science up to May 2026. Inclusion criteria: original and review articles focusing on histone methylation, related enzymes and inhibitors in glioma. Exclusion criteria: non-English papers, letters, case reports, abstracts, and irrelevant studies.

2. Epigenetic regulation via histone methylation

2.1. Overview of histone methylation

Histone methylation represents a specific post-translational modification process characterized by the addition of methyl groups to the N-terminal lysine (Lys, K) or arginine (Arg, R) residues present on histone H3 and histone H4[27]. It assumes a pivotal function in the establishment and preservation of heterochromatin architecture, as well as in the processes of DNA repair, chromatin deactivation, and transcriptional regulation[28]. The process of histone methylation is predominantly executed through the catalytic activities of two key enzyme families: histone methyltransferases (HMTs) and histone demethylases (HDMs).

These enzymes work in a coordinated yet opposing manner to regulate the methylation status of histones[29]. Take lysine methylation for instance (refer to Fig. 1). During the activation phase, HMT acts as a catalyst to initiate a crucial biochemical reaction. Here, S-Adenosylmethionine (SAM) plays the pivotal role of a methyl donor. The methyl group, which is an integral part of the SAM molecule, is selectively and covalently attached to the specific histone substrate. Once this transfer is completed, SAM is metabolically converted into S-Adenosylhomocysteine (SAH). Simultaneously, the lysine amino acid residue on the histone experiences a methylation modification, altering its chemical properties and potentially influencing its function within the chromatin structure. Abnormal expression of methylation-related enzymes can cause gene mutations and amplification through direct or indirect methods, leading to the expression or inactivation of certain key proteins, and ultimately resulting in tumor occurrence[30]. Enzymes associated with histone methylation, along with their corresponding inhibitors, hold significant promise as emerging research foci in the quest for effective glioma treatment strategies. These molecular entities offer a novel avenue for exploring therapeutic interventions that could potentially disrupt the aberrant epigenetic processes underlying glioma pathogenesis[31].

2.2. HMT and its inhibitor

Within the realm of protein post-translational modification, histone methylation emerges as a pivotal regulatory factor that exerts a profound influence on chromatin remodeling processes and the intricate regulation of gene expression. It orchestrates a series of molecular events that ultimately shape the functional landscape of the genome[32]. Therefore, HMTs, which catalyze histone methylation, have become important participants in epigenetic modification[33]. HMTs can be categorized into four distinct subgroups, namely the SUV39 family, the RIZ family, and the SET1 family, based on their structural and functional characteristics. HMTs are capable of carrying out methylation reactions on the lysine and arginine amino acid residues of histone substrates. In light of their preference for different types of residues, they are subsequently divided into two well-defined subgroups, namely histone lysine methyltransferases (HKMTs) that operate on lysine and histone arginine methyltransferases (HRMTs) that focus on arginine[34]. Among them, arginine residues can be monomethylated or dimethylated[35], while lysine residues can undergo monomethylation[36], dimethylation and trimethylation[37]. Within the scope of this section, we aim to provide a comprehensive overview regarding the precise role that HMTs and their corresponding inhibitors play in the therapeutic landscape of glioma. We will delve into the molecular mechanisms, clinical implications, and potential future directions associated with this research area.

2.2.1. Enhancer of zeste homolog 2 (EZH2)

EZH2 is a particular type of histone methyltransferase, which is characterized by its ability to specifically target lysine amino acid residues for methylation. This protein holds a pivotal position as it is an integral and important member of the polycomb-group proteins (PCGs) family, contributing to the regulation of gene expression and cellular functions[38]. EZH2 catalyzes mono-, di-, and tri-methylation of lysine 27 on histone H3 (H3K27me1/2/3), thereby functioning as a critical epigenetic regulator of transcriptional repression through chromatin compaction, nucleosome positioning, and cooperative recruitment of downstream effector complexes[39]. Mutations or overexpression of EZH2 are associated with various types of cancers, such as breast cancer [40], prostate cancer and melanoma[41]. EZH2 expression is consistently upregulated in glioma tissues compared with normal brain tissue and is significantly associated with shorter overall survival, progression-free survival, and higher tumor grade in glioma patients [42]. Emerging evidence indicates that EZH2 promotes glioma progression by epigenetically silencing tumor suppressor genes and repressing the transcription of tumor-suppressive microRNAs[43].

Table 1
Epigenetic regulation in glioma pathogenesis: the role of histone methylation modulators and their inhibitors.

Class	Protein name	Effect	Representative inhibitors	References
HMTs	SUV39H1	Maintains cancer stem cell chromatin state and properties in GBM.	F5446 (marketed drug) Chaetocin (preclinical research stage)	[70,71]
	SUV39H2	Knockdown of SUV39H2 in glioma cells can inhibit stem cell proliferation and tumor growth, and enhance chemosensitivity.	OTS193320 (preclinical research stage OTS186935 (preclinical research stage)	[81]
	G9a	Contributes to immunosuppression through modulation of cellular activity the Fbxw7/Notch signaling pathway plays a regulatory role in glioma stem cells.	DCG066 (preclinical research stage MS1262 (preclinical research stage) UNC0638 (preclinical research stage) UNC0642 (preclinical research stage) MS8511 (preclinical research stage)	[124]
	EZH2	Facilitate the initiation and progression of glioma and enhance resistance to TMZ chemotherapy.	GSK343 (preclinical research stage GSK126 (phase I clinical trial) Tazemetostat (marketed drug) Valemetostat (marketed drug)	[125]
	SETD8	Targeted inhibition of GBM growth.	UNC0379 (preclinical research stage MS2749 (preclinical research stage) MS4534 (preclinical research stage)	[88]
HDMs	LSD1	Enhance the efficacy of TMZ in GBM.	Corin (preclinical research stage Iadademstat (clinical research stage) Bomedemstat (Phase III clinical trial)	[126]
	KDM4	Promotes the growth of glioma cells by activating the Akt-mTOR pathway through the expression of PDK1	QC6352 (preclinical research stage JIB-04 (preclinical research stage)	[110]
	KDM5A	Inhibition of glioma cell migration and invasion.	CPI-455 (preclinical research stage	[119]
	KDM5B	KDM5B suppresses antitumor immunity by epigenetically silencing retroelements.	CPI-455 (preclinical research stage AS-8351 (preclinical research stage) TK-129 (preclinical research stage)	[127]

Given that aberrantly activated EZH2 has the capacity to repress the physiological expression patterns of tumor suppressor genes, targeting and inhibiting EZH2 activity represents a promising strategy to impede tumor progression. In vivo experiments utilizing subcutaneous tumor models have demonstrated that down-regulating the expression level of the EZH2 protein can lead to a marked suppression of tumor growth. This inhibitory effect is accompanied by an enhancement of cellular apoptosis and a reduction in cell proliferation rates[44].

EZH2 not only can act as a transcriptional repressor to mediate transcriptional silencing, but also can bind to STAT3 and methylate it, thereby enhancing the activity of STAT3 by increasing its tyrosine phosphorylation[45]. For glioma, the STAT3 signaling pathway is the key regulator driving mesenchymal transition. Particularly in the mesenchymal subtype of GBM, downstream genes of STAT3 are markedly overexpressed[46]. Alterations in EZH2 may interfere with the epigenetics of the genome and simultaneously generate other genetic changes, such as TP53 mutations and CDKN2A deletions[47]. In recurrent GBM following RT, EZH2 demonstrates a notable elevation in its expression profile. Furthermore, there exists an inverse relationship between the expression magnitude of EZH2 and the prognostic outlook of the patients. The MELK /FOXM1 /EZH2 signaling axis promotes the development of RT resistance in glioma stem cell-like cells. When it comes to the compound GSK343, it serves as a specific inhibitor for EZH2. In the cellular context, once GSK343 exerts its inhibitory effect on EZH2, it brings about a decline in the level of H3K27me3, which is a histone modification closely related to gene regulation. Additionally, GSK343 has the ability to initiate the degradation pathway of 53BP1, a protein involved in DNA damage response. By interfering with these two important cellular processes, GSK343 effectively curtails the excessive proliferation of neuroblastoma, a highly aggressive type of cancer[48]. Although GSK343 is not yet an approved drug on the market, it is well-known for its ability to regulate the processes of apoptosis and autophagy in cells[49]. As of May 2026, GSK343 is still in the preclinical research stage and has not yet entered any human clinical trials (Phase I and beyond). Other representative EZH2 inhibitors are GSK126[50], Tazemetostat[51] and Valemetostat[52] (Table 1). The results of its phase I clinical trial were not satisfactory because inhibiting EZH2 activity with GSK126 would lead to an increase in the number of myeloid-derived suppressor cells (MDSCs), while the number of $CD4^+$ and IFN-γ^+ $CD8^+$ T cells involved in anti-tumor immunity would decrease [53]. Tazemetostat is a methyltransferase inhibitor and antineoplastic drug that has been marketed in clinical practice. It is mainly used for the treatment of lymphoma[54]. Valemetostat, a clinically available agent, is a potent, novel dual inhibitor of EZH2 and EZH1 commonly used in the treatment of lymphoma[55]. While EZH2 primarily generates H3K27me3 repressive marks, G9a mediates H3K9me2. Emerging evidence suggests that these two systems can cooperate or compensate for each other in glioma, synergistically silencing tumor suppressor genes through distinct but cross-talking histone methylation pathways[56].

EZH2-mediated H3K27me3 silencing also shapes an immunosuppressive microenvironment in glioma. EZH2 represses the transcription of chemokines (e.g., CXCL9/10/11) and MHC-I genes, impairing $CD8^+$ T cell infiltration and antigen presentation[57]. Meanwhile, EZH2 upregulates PD-L1 and promotes the recruitment of myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs). Inhibitors of EZH2 (e.g., tazemetostat) can reverse these effects, restore immunogenicity, and synergize with immune checkpoint inhibitors (ICIs) such as anti-PD-1/PD-L1 in preclinical glioma models[58].

EZH2-mediated H3K27me3 plays a critical role in conferring TMZ resistance in glioma[59]. Elevated EZH2 expression epigenetically silences DNA repair-related tumor suppressors (e.g., PTEN, p53), enhancing DNA damage repair capacity and reducing TMZ-induced cytotoxicity[60]. Moreover, EZH2 upregulates MGMT expression indirectly via epigenetic modulation of its promoter region, which directly counteracts the DNA alkylation effect of TMZ[61]. In addition, EZH2 maintains GSC stemness and promotes an immunosuppressive microenvironment, both of which contribute to TMZ insensitivity. Inhibition of EZH2 (e.g., by tazemetostat or GSK343) reduces H3K27me3 levels, downregulates MGMT, impairs DNA repair, and sensitizes glioma cells to TMZ.

2.2.2. G9a

The protein G9a, also commonly referred to by its other name EHMT2, plays a crucial role in the cellular machinery as a histone methyltransferase. It belongs to a well-defined group of proteins known as the SET family, which is characterized by a specific conserved domain involved in histone modification processes. It mainly catalyzes the dimethylation modification of histone H3 lysine 9 (H3K9me2) and is closely related to epigenetic regulation[62]. The level at which G9a is expressed shows a significant relationship with the glioma classification criteria established by the World Health Organization (WHO). This association provides a strong indication that G9a could potentially contribute to the development and advancement of gliomas. In situations where there is a deficiency of G9a, the DNA damage that occurs is repaired via a unique process. This process involves interfering with the normal formation of aggregates composed of replication protein A (RPA) and Rad51. By disrupting these aggregates, cancer cells become more vulnerable to double strand breaks (DSBs), which are severe forms of DNA damage. It is important to note that the ability of G9a to perform this function is highly dependent on the presence of Casein kinase 2 (CK2). CK2 acts by adding a phosphate group to G9a at the serine 211 position. This phosphorylation event is a crucial step that allows G9a to be recruited to chromatin, where it can carry out its functions related to cell proliferation and survival[63]. Compound DCG066, a G9a inhibitor previously screened out by our laboratory, was found in our recent research to inhibit the proliferation of glioma cells and accelerate their apoptosis[64]. It is still in the preclinical research stage. UNC0638 and its optimized version UNC0642 can inhibit the growth and reproduction of various cancer cells by suppressing G9a[65]. MS1262 is a novel brain-penetrating G9a inhibitor that targets AD-related protein pathology and reverses abnormal protein expression in AD models by regulating translation and phosphorylation mechanisms, demonstrating potential neuroprotective activity[66]. These findings also suggest that G9a inhibitors can be potential drugs for the treatment of glioma. MS8511 is a selective covalent irreversible inhibitor of G9a. Compared with the non-covalent G9a inhibitor UNC0642, MS8511 demonstrates stronger efficacy in enzymatic and cellular experiments[67]. In 2024, researchers discovered the first-in-class leading G9a proteinase-targeting chimeric (PROTAC) degrader - MS8709. MS8709 can induce G9a degradation in a concentration, time and ubiquitin-proteasome system (UPS) dependent manner[68]. As of May 2026, no G9a inhibitors have been approved for marketing by authoritative drug regulatory agencies such as the FDA and NMPA worldwide. All the above-mentioned G9a inhibitors are still in the preclinical stage.

G9a-catalyzed H3K9me2 is closely linked to TMZ resistance in glioma. High G9a expression promotes efficient DNA DSB repair by recruiting repair proteins (e.g., RPA, Rad51) to damaged chromatin, thereby mitigating TMZ-induced DNA damage. G9a also maintains GSC properties and enhances autophagic flux, which further protects glioma cells from TMZ-mediated cell death[69]. Pharmacological inhibition of G9a (e.g., DCG066, UNC0642) disrupts DNA repair, suppresses autophagy, and impairs GSC self-renewal, ultimately restoring TMZ sensitivity in resistant glioma cells.

2.2.3. SUV39H1

HMT SUV39H1 belongs to the SUV39 family and can catalyzes the trimethylation modification of histone H3 lysine 9 (H3K9me3), recruit transcriptional repressors, and lead to transcriptional silencing of the modified genes[70]. A body of research has revealed that SUV39H1, functioning as H3K9 methyltransferases, is intricately linked to the progression of glioma. Elevated expression levels of SUV39H1 have been observed in both glioma cells and corresponding tumor tissues. Based on

these findings, the present study posits that SUV39H1 holds promise as a novel biomarker for the development of targeted tumor therapies in the future[71].

The activation of transforming growth factor-β (TGFβ) signaling pathway can reduce the expression of MXI1 through Runt-related transcription factor 1 (RUNX1)/SUV39H1-mediated H3K9me3 modification and regulate the expression of target genes such as BCL3 and MGP, thereby promoting the malignant progression of glioma[72]. SUV39H1 can recruit H3K9 to the miR-200c promoter by interacting with Methyl CpG-binding protein 2 (MeCP2), increase the accumulation of H3K9 in the miR-200c promoter, and cause Epithelial-to-mesenchymal transition (EMT) in glioma cells[73]. SUV39H1 inhibitors include Chaetocin[74] and F5446[75]. Chaetocin is a widely used natural metabolite that can reduce H3K9 methylation in cells[76]. A large number of studies have shown that chaetocin has extensive anti-tumor activity both in vitro and in vivo[77]. As of May 2026, it has remained in the preclinical research stage and has never entered human clinical trials. F5446 has not yet been approved for commercial distribution as a drug and is predominantly employed within the realm of scientific research endeavors. Research findings have indicated that F5446, an inhibitor targeting Suv39h1, exerts a significant inhibitory effect on the phenotypic transformation observed in mice[78].

SUV39H1-mediated H3K9me3 contributes to TMZ resistance via epigenetic regulation of key resistance genes. SUV39H1 interacts with MeCP2 to repress miR-200c, which triggers EMT and enhances TMZ tolerance[79]. Additionally, SUV39H1 maintains the chromatin state of cancer stem cells, promoting their survival under TMZ treatment[80]. Inhibition of SUV39H1 by chaetocin or F5446 reduces H3K9me3 levels, restores miR-200c expression, suppresses EMT and stemness, and significantly increases TMZ-induced cell death in glioma.

2.2.4. SUV39H2

In the context of epigenetic regulation, SUV39H2 serves as a specialized methyltransferase that specifically targets histone H3K9. Through extensive research, it has been discovered that this protein shows a significantly elevated expression pattern in glioma tissues when compared to normal brain tissues. Further analysis has revealed that the activity of SUV39H2 is not merely a passive marker but is actively involved in the biological processes of glioma. Specifically, there is a direct and positive relationship between the enzymatic activity of SUV39H2 and the advancement of glioma, as well as the overall survival duration of patients suffering from this aggressive brain tumor[81]. During mitosis, SUV39H2 moves to the centromere and functions as an HMT to methylate the H3K9 site. The H3K9me3 state leads to the silencing of E2F-responsive genes that regulate the cell cycle and cell differentiation[82]. Knockdown of SUV39H2 in glioma cells inhibits stem cell properties and cell proliferation, promotes chemosensitivity, while SUV39H2 itself promotes hedgehog signaling via down-regulation of HHIP expression[81]. OTS193320 is a potent and selective small-molecule inhibitor targeting SUV39H2, which was developed by OncoTherapy Science. As of May 2026, this compound is still at the global preclinical research stage and has not yet entered any phase of human clinical trials[83]. Later, on the basis of OTS193320, OTS186935 was designed and synthesized. It has the potential to be used in preclinical research due to its good in vivo efficacy and low toxicity[84]. Notably, combinatorial regimens of epigenetic inhibitors with novel therapeutic systems may further reverse TMZ resistance. For instance, epigenetic regulation combined with engineered exosome delivery, NIR-II phototherapy, or immune activation has been proven to enhance blood–brain barrier penetration, boost intratumoral drug accumulation, and reactivate the immunosuppressive microenvironment[85]. Such synergistic strategies provide a promising direction to conquer multidrug resistance in glioma.

SUV39H2 drives TMZ resistance in glioma primarily through activation of the hedgehog signaling pathway. SUV39H2 downregulates HHIP via H3K9me3 modification, leading to hyperactivation of hedgehog signaling, which enhances GSC proliferation, stemness, and drug resistance. Knockdown or pharmacological inhibition of SUV39H2 (e.g., OTS193320) restores HHIP expression, inhibits hedgehog signaling, impairs GSC function, and markedly sensitizes glioma cells to TMZ.

2.2.5. SETD8

SETD8 is a lysine monomethyltransferase HMT from the SET gene family, has the unique capacity to methylate the 20th lysine residue of H4 histone, generating H4K20me1. This histone modification is not just a simple chemical change; it has a significant impact on gene regulation, being involved in both gene silencing and transcriptional activation. Given its crucial role in gene expression, it is not surprising that H4K20me1 is closely related to the emergence and progression of multiple tumors, highlighting its importance in cancer research and potential for therapeutic intervention[86]. Studies have reported that SETD8 is highly expressed in glioma tissues and cell lines and is regulated by miR-382, and is also involved in the carcinogenesis and progression of glioma, which also reveals a new therapeutic target for glioma cancer [87]. UNC0379, the first substrate-competitive inhibitor of SETD8, was reported to exhibit higher selectivity for SETD8 compared to other methyltransferases. The latest research indicates that the small molecule SETD8 inhibitor UNC0379 can inhibit the proliferation of GBM cells by inducing DNA damage and activating cell cycle checkpoints[88]. As of May 2026, the compound is still at the preclinical stage globally with no progression into human clinical trials. Constrained by low in vivo bioavailability and unfavorable pharmacokinetic profiles, it serves merely as a canonical chemical probe for basic research and has not been further developed for clinical use[89]. Second-generation inhibitors such as MS2749 and MS4534 maintain high selectivity while their cellular activity is 3 to 10 times higher than that of UNC0379. Currently, they are in the stage of in vitro validation and pharmacokinetic optimization. Of note, the H4K20me1 mark deposited by SETD8 is not static. It can be further demethylated by KDM4 family members (JMJD2A, etc.), creating a dynamic balance that regulates DNA damage repair. This antagonistic relationship between SETD8 and KDM4 on H4K20 methylation fine-tunes the recruitment of DNA repair proteins such as 53BP1 in glioma cells[90].

SETD8-mediated H4K20me1 is a critical regulator of TMZ resistance by modulating DNA damage repair. SETD8 promotes the recruitment of 53BP1 to DNA DSBs, enhancing non-homologous end joining (NHEJ) repair and reducing TMZ-induced DNA damage accumulation. High SETD8 expression also correlates with increased MGMT activity and GSC maintenance. Inhibition of SETD8 by UNC0379 blocks H4K20me1, impairs 53BP1 recruitment, suppresses DNA repair, and synergistically enhances TMZ cytotoxicity in glioma.

2.2.6. Others

The H3K4 methyltransferase MLL4 also known as KMT2D, can positively regulate H3K4me3, thereby directly activating tumor suppressor genes. However, MLL4 can also down-regulate tumor suppressor genes by reducing broad H3K4me3 and super-enhancers, inducing the occurrence of medulloblastoma[91]. Recently, it has been found that MLL4 mediates differentiation and tumor suppression through ferroptosis[92].

HMT NSD1 is a type of proteinase containing a SET catalytic domain, which uses nucleosomes as substrates to complete the dimethylation modification of H3K36[93]. Studies have shown that the restoration of NSD1 expression can reduce colony formation density and inhibit cell growth[94]. Screening a large number of different types of tumors indicates that hypermethylation of the NSD1 CpG island is a common event in neuroblastoma and glioma. Most importantly, high methylation of NSD1 is a predictive indicator of poor prognosis in high-risk neuroblastoma. The present findings underscore the critical significance of NSD1 epigenetic inactivation in both neuroblastoma and glioma. This inactivation process can result in the disturbance of histone methylation

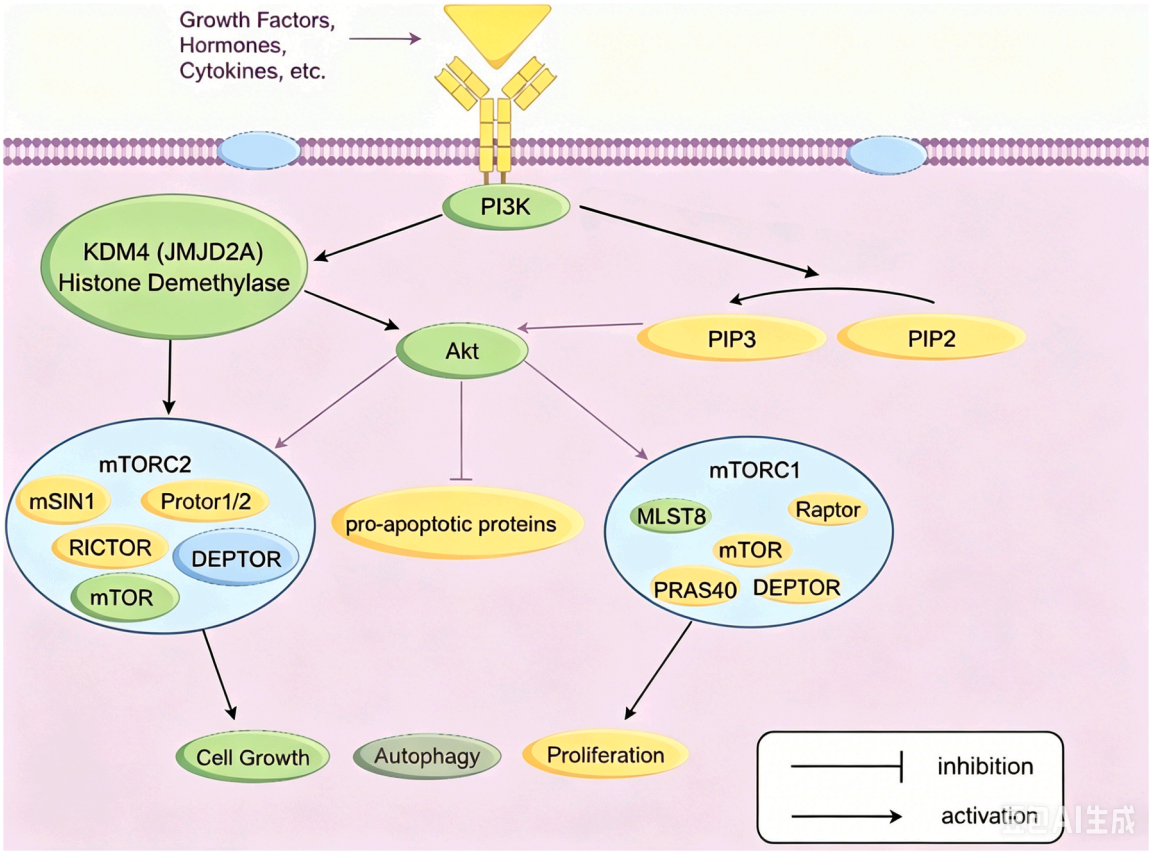

Fig. 2. KDM4 (JMJD2A)-mediated activation of the PI3K/Akt/mTOR signaling pathway. The histone demethylase KDM4 (JMJD2A) directly activates the PI3K/Akt/mTOR cascade, promoting cell proliferation, growth, and survival by regulating downstream mTORC1/mTORC2 complexes.

patterns and holds potential translational value, serving as a prognostic indicator for these malignancies.

Furthermore, the Polycomb Repressive Complex 2 (PRC2) serves as a crucial epigenetic regulator implicated in the process of DSB repair. This complex is composed of several key components, namely embryonic ectoderm development (EED), the SUZ12 subunit (which has an inhibitory function within the complex), the EZH1 subunit (acting as an activator), and EZH2. The catalytic domains of EZH1 and EZH2 are usually in an autoinhibited state, but their interaction with SUZ12 can terminate this autoinhibition and promote the activity of HMT[95]. During the progression of recurrent tumors following RT, there is a notable upregulation in the expression of NIMA - related kinase 2 (NEK2). This increased NEK2 expression plays a crucial role in maintaining the stability of EZH2 and shielding the EZH2 protein from proteasome mediated degradation. Meanwhile, the expression level of NEK2 is significantly increased in glioma samples, suggesting that NEK2 may be a potential target for GBM treatment[96].

2.3. HDM and its inhibitors

DNA methylation is an epigenetic modification process where methyl groups are appended to specific loci of genomic DNA (such as CpG islands) under the action of DNA methyltransferases (DNMTs)[97]. In normal conditions, methylation can modulate the spatio-temporal expression of genes. For example, when the promoter region of a tumor - suppressor gene experiences hypermethylation, it can impede gene transcription, causing the gene to lose its function of inhibiting abnormal cell proliferation. The central function of demethylases, conversely, is to reverse the abnormal hypermethylation state by removing methyl groups from DNA molecules. This action re-activates silenced key genes and maintains the epigenetic equilibrium of the genome[98]. The Histone lysine demethylases (HKDMs) discovered so far are mainly divided into Lysine specific demethylase (LSD) and Jumonji C domain-containing (JMJD). (Table 1)

2.3.1. LSD1

LSD1(KDM1) is the first discovered HDM responsible for the demethylation of H3K4me1/2 and H3K9me1/2[99,100]. Numerous studies have revealed that LSD1 serves as a critical factor in driving the advancement of solid tumors, encompassing neuroblastoma, breast cancer, lung cancer, prostate cancer, ovarian malignancy, and colorectal cancer[101]. LSD1 and ubiquitin-specific protease 7 (USP7) are pivotal players in facilitating the proliferation and invasive capacity of GBM cells. A growing body of research has unveiled that, in comparison to normal tissues, GBM exhibits significantly elevated expression levels of both USP7 and LSD1. Moreover, these heightened expression patterns are intricately linked to the progression of the tumor. During progression, both increase simultaneously and are predictive factors for a poor prognosis. Inhibiting the activity of USP7 and LSD1 can suppress the p53 signaling pathway, thereby inhibiting tumor cell proliferation and invasion. Inhibiting LSD1 has selective cytotoxicity and promotes immune gene signaling, increasing NK cell killing, providing therapeutic opportunities for GBM[102].

Corin, an inhibitor that can act on both LSD1 and histone deacetylases, plays a crucial role in modulating the activity of promoters and enhancers. By simultaneously inhibiting the deacetylation process of H3K27ac and the demethylation process of H3K4me1, it brings about substantial changes in chromatin. As a result, it triggers multiple phenotypic responses in diffuse intrinsic pontine glioma (DIPG) cells, such as cell death, cell cycle arrest, and cell differentiation. Additionally, these changes at the cellular level lead to transcriptional alterations that are associated with the survival time of individuals with DIPG[103]. As

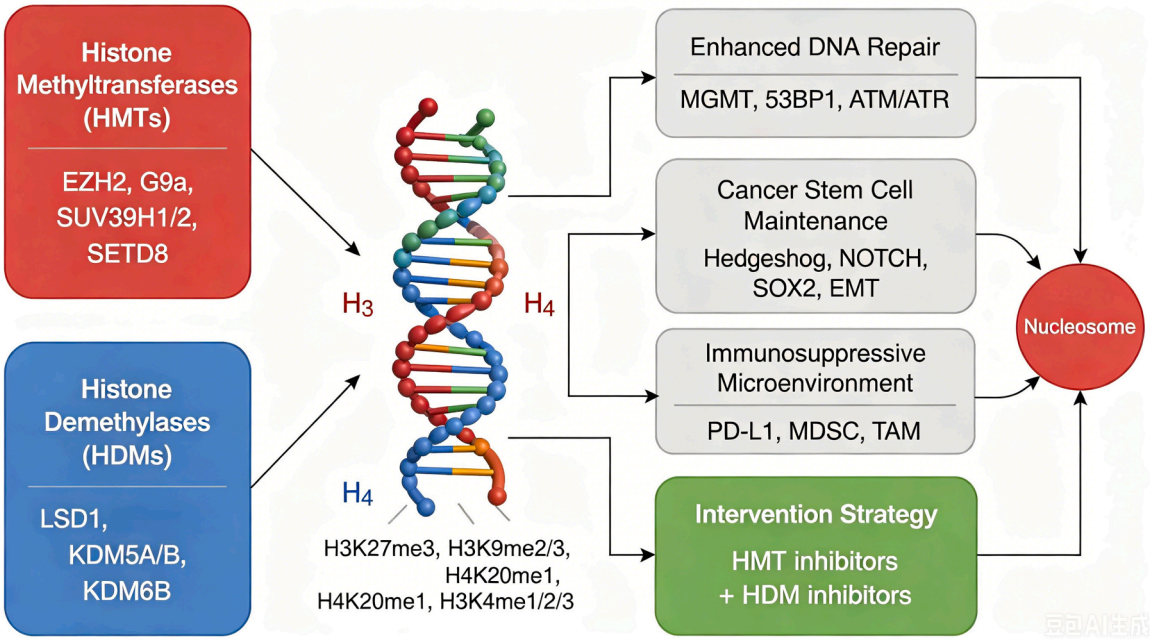

Fig. 3. Unified model: histone methylation machinery drives temozolomide resistance in glioma. This Fig. illustrates how dysregulated histone methylation drives TMZ resistance via three core axes: enhanced DNA repair, cancer stem cell maintenance, and immunosuppressive microenvironment remodeling.

of May 2026, this compound is still in preclinical development globally with no initiation of human clinical trials. Its further development is hampered by poor in vivo pharmacokinetic properties and low oral bioavailability, limiting its application solely to basic research as a chemical probe. Meanwhile, superior selective LSD1 monoinhibitors including Iadademstat and bomedemstat have progressed to clinical development. Iadademstat, a drug that has entered clinical studies, has a significant effect in the treatment of acute myeloid leukemia[104]. Bomedemstat (formerly known as IMG-7289, MK-3543) is an orally bioavailable, irreversible small-molecule inhibitor targeting LSD1 (KDM1A). As of May 2026, it has advanced to Phase III clinical development globally, representing one of the most clinically mature LSD1 inhibitors. It is mainly being developed for myeloproliferative neoplasms, including essential thrombocythemia, polycythemia vera and myelofibrosis, and is also under clinical investigation for acute myeloid leukemia[105]. Although LSD1 and JMJD family demethylases employ distinct catalytic mechanisms, they often co-occupy the promoters of key tumor suppressor genes in glioma. There, they coordinate to remove different methylation marks—LSD1 demethylates H3K4me1/2 while JMJDs target H3K9me3 and H3K27me3—thereby achieving precise epigenetic regulation of gene expression[106].

LSD1 inhibition exerts dual anti-glioma and immunomodulatory effects[107]. LSD1 represses endogenous retroviral elements (EREs) and double-stranded RNA (dsRNA) accumulation; LSD1 inhibitors induce ERE/dsRNA-mediated viral mimicry, activating the RIG-I/MAVS/IFN pathway and increasing type I interferon production[108]. This triggers dendritic cell maturation and enhances NK and $CD8^+$ T cell-mediated cytotoxicity. Combinations of LSD1 inhibitors (e.g., bomedemstat) with ICIs have shown synergistic anti-tumor efficacy in glioma preclinical studies[109].

LSD1-mediated demethylation of H3K4me1/2 and H3K9me1/2 is essential for TMZ resistance in glioma. LSD1 upregulates MGMT and DNA repair genes by removing repressive histone marks, accelerating repair of TMZ-induced DNA lesions. LSD1 also maintains GSC stemness and suppresses anti-tumor immunity, creating a protective microenvironment against TMZ. Inhibition of LSD1 reverses these effects, downregulates MGMT, impairs DNA repair, enhances anti-tumor immunity, and sensitizes glioma to TMZ.

2.3.2. *JMJD*

Experimental findings clearly demonstrate a significant contrast in the expression profiles of JMJD2A and specific histone modifications between glioma and normal brain tissues. JMJD2A shows a substantially higher expression in glioma tissues when compared to normal brain counterparts. Conversely, the histone modifications H3K9me3 and H3K36me3 are present at relatively low levels in glioma tissues. In vitro studies reveal that when the expression of JMJD2A is knocked down, the growth rate and colony forming ability of three commonly used glioma cell lines, U251, T98G, and U87MG, are markedly reduced. Furthermore, in vivo xenograft experiments provide solid evidence that targeting JMJD2A can effectively curb the growth of T98G glioma cells within a living organism. The histone demethylase JMJD2A plays a critical role in activating the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway in glioma[110,111]. As shown in Fig. 2, KDM4 upregulates PDK1 expression, which triggers the activation of the PI3K/Akt/mTOR cascade [112]. This pathway is a highly conserved intracellular signaling pathway, and its activation promotes glioma cell proliferation, survival, and metabolic reprogramming, linking histone demethylation to oncogenic kinase signaling[113]. (Fig. 2)

JMJD3, also known as KDM6B, promotes the EMT and migration of glioma cells through the C-X-C motif chemokine ligand 12 (CXCL12)/C-X-C motif chemokine receptor 4 (CXCR4) axis[114]. Recently, some scholars found that, KDM6B can catalyze the demethylation of H3K27me3 in the promoter region of SNAI1, providing new insights into the mechanism by which KDM6B promotes glioma metastasis[115]. They also discovered that KDM6B can promote the transcription of INK4A by eliminating the repressive mark H3K27me3 trimethylation near its promoter, and this new regulatory mechanism is involved in the inhibitory effect of vitamin D3 on glioma, which is beneficial for the prevention and adjuvant treatment of glioma[116]. KDM4 promotes the growth of glioma cells by activating the Akt-mTOR pathway through the expression of PDK1[110]. At present, the main KDM4-related inhibitors are QC6352[117] and JIB-04[118] (Table 1). As of May 2026, neither QC6352 nor JIB-04, the two KDM4 inhibitors, have entered clinical trials and are still in the preclinical research stage, mainly used as research tool compounds. HDM KDM5A suppresses the migration and invasion of glioma cells through the downregulation of ZEB1[119].

Additionally, the overexpression of KDM5B promotes the proliferation, migration, invasion and sphere formation of glioma cells, and accelerates tumor growth in nude mice. CPI-455 is a pyrimidine derivative of KDM5A and KDM5B inhibitor, and CPI-455 is known to reduce the stem-like properties of cancer cells by inhibiting KDM5B[120]. As of May 2026, CPI-455 remains in the preclinical research stage and has not entered any human clinical trials. TK-129 is an oral potent KDM5B inhibitor with low toxicity and cardioprotection by inhibiting KDM5B and blocking KDM5B-related Wnt pathway[121]. As of May 2026, the KDM5B inhibitor TK-129 is still at the preclinical stage globally with no human clinical trials initiated, serving solely as a research tool compound and lead compound for basic pharmacological studies. And AS-8351 is a small molecule inhibitor of KDM5B that suppresses KDM5B activity by competitively binding to the Fe(II) cofactor, thereby displacing α-ketoglutarate[122]. As of May 2026, AS-8351 is entirely in the preclinical research stage and has not progressed to any human clinical trials. The enzymes and inhibitors related to histone methylation are summarized in Table 1. The entirety of these research findings collectively underscores the significant potential that drugs associated with histone methylation hold for clinical applications, suggesting promising avenues for the development of novel therapeutic strategies in relevant medical fields.

JMJD family demethylases promote TMZ resistance through multiple pathways. KDM4 (JMJD2A) activates the PI3K/Akt/mTOR pathway via PDK1 upregulation, enhancing cell survival and TMZ tolerance. KDM5A/B maintain GSC stemness and silence retroelements, suppressing anti-tumor immunity and DNA damage response[123]. KDM6B (JMJD3) promotes EMT and migration via CXCL12/CXCR4 axis, increasing TMZ resistance. Inhibition of KDM4 (JIB-04), KDM5 (CPI-455), or KDM6B (GSKJ4) impairs these pathways, suppresses stemness and EMT, restores immunity, and reverses TMZ resistance in glioma.

2.4. Histone methylation inhibitors reverse TMZ-resistant glioma

Collectively, the dysregulation of histone methylation machinery, including HMTs and HDMs such as LSD1 and JMJD2A, leads to a cascade of epigenetic events that converge on multiple TMZ resistance mechanisms. Mechanistically, TMZ exerts cytotoxicity by inducing O^6-methylguanine, which activates MGMT, MMR, and BER pathways, with MGMT being the key mediator of TMZ resistance[128]. We propose a unified schematic model to integrate these interconnected pathways (Fig. 3. Drug resistance is the main cause of GBM tumor recurrence and subsequent patient death[129]. RT elicits DNA DSBs, triggering a cascade of epigenetic remodeling characterized by elevated histone methylation. This specific methylation signature orchestrates the recruitment of DNA repair machinery, facilitates chromatin relaxation, and thereby enhances repair efficiency. While TMZ remains the cornerstone of glioma chemotherapy, its clinical efficacy is frequently compromised by acquired resistance. Collectively, aberrant histone methylation acts as a unifying upstream driver that converges on three core resistance axes: enhanced DNA repair, sustained GSC stemness, and immunosuppressive microenvironment remodeling, forming an integrated epigenetic–resistance regulatory network. Consequently, identifying novel pharmacological agents capable of reversing this resistance and restoring TMZ sensitivity has become a pivotal focus in neuro-oncology research. Recently, it has been found that maoecrystaline induces ferroptosis in GSCs via REST/LRSAM1-mediated ubiquitination of SLC40A1 to overcome TMZ resistance[130].

After being converted into a methylated cation, TMZ can methylate histone H3 peptides and histone H3 proteins. This phenomenon indicates that TMZ not only generates cytotoxic groups such as O6-MeG through DNA methylation, leading to single-strand and double-strand DNA breaks and killing tumor cells, but also exerts its effects by altering protein methylation. Mechanistically, histone methylation enzymes (HMTs/HDMs) and their marks directly control the transcription of key resistance genes, linking epigenetic dysregulation to TMZ insensitivity. For instance, relevant studies have shown that H4K20 methyltransferase SETD8 inhibitor (UNC0379) and H3K9 methyltransferase G9a inhibitor (BIX-01294) are effective radiosensitizers for glioma cells. These repressive marks promote chromatin condensation, facilitating recruitment of DDR proteins (53BP1, RPA, Rad51) and indirectly upregulating MGMT[131]. UNC0379 blocks H4K20 methylation and reduces the recruitment of 53BP1 protein to DSBs, although the deletion of 53BP1 only leads to limited changes in radiosensitivity. Furthermore, treatment with BIX-01294, either as a monotherapy or in conjunction with TMZ, led to a marked accumulation of microtubule-associated protein 1 light chain 3 II (LC3-II) in LN18 glioma cells. This observation indicates that autophagic activation not only facilitates the anti-tumor efficacy of TMZ but also implies that pharmacological inhibition of G9a can potentiate the radiosensitivity of glioma cells[132]. Additionally, studies have shown that the combination of anti-tumor drugs and histone methylation-related drugs can also promote anti-tumor effects. For example, reduced H3K27me2/3 levels increased sensitivity to bleomycin treatment, indicating that a new therapeutic strategy can be applied to the treatment of gliomas with abnormally high expression of H3K27me2/3[133]. GSKJ4 inhibits the growth of GBM cells, activates the apoptotic pathway in both wild-type and TMZ-resistant cells, and has a good effect on pediatric DIPG. On the other hand, TMZ blocks the G2 phase of the cell cycle, and JIB04 (an inhibitor of KDM5A) inhibits the G1 phase. These two molecules may work synergistically because JIB04 prevents cells from entering the G2 phase and hinders the accumulation of cells treated with TMZ in G2. The most effective way to act on both wild-type and TMZ-resistant cells is the combined application of JIB04 and GSKJ4[134]. Moreover, HDM KDM5A is known to be a key factor in GBM resistance to TMZ. Endogenous or exogenous overexpression of H3K4me3 demethylase KDM5A is associated with transient and reversible resistance to TMZ. Inactivation of KDM5A with shRNA can restore the sensitivity of resistant cells to TMZ[135]. The multi-specific KDM inhibitor JIB04 (mainly for KDM5A) and the specific KDM5 inhibitor CPI-455 inhibit proliferation and restore sensitivity to TMZ[134]. Additionally, SUV39H2 controls the chemosensitivity of glioma cells by regulating the hedgehog signal, so the knockout of SUV39H2 is beneficial to the sensitivity of glioma cells to TMZ[81]. Inhibitors induce chromatin relaxation, impairing DDR protein recruitment, blocking DNA repair, downregulating MGMT, and promoting apoptosis. Moreover, the combination of epigenetic regulation with microenvironment-responsive phototherapy may provide a novel strategy to overcome temozolomide resistance. Such synergistic systems can enhance blood–brain barrier penetration, improve intratumoral accumulation, reactivate the immune microenvironment, and thereby comprehensively enhance glioma treatment outcomes[136]. In summary, these findings support a unified model: histone methylation aberrations drive TMZ resistance by dysregulating DNA repair, GSC maintenance, and immune suppression, while epigenetic inhibitors reverse these programs and restore chemosensitivity. The integration of artificial intelligence with epigenetic therapy and nanomedicine may further optimize drug screening, prognostic prediction, and personalized therapeutic regimens, thereby improving the efficacy of temozolomide-based glioma treatment[21].

Beyond chemosensitization, histone methylation targeting has emerged as a promising strategy to overcome immunotherapy resistance in glioma. Dysregulated histone methylation (e.g., EZH2, G9a, SUV39H2) drives immune exclusion and immune checkpoint molecule upregulation[137]. In contrast, inhibitors of EZH2, LSD1, or KDM5B can remodel the immune microenvironment, increase tumor immunogenicity, and sensitize gliomas to ICIs. Epigenetic–immunotherapy combinations represent a high-potential emerging direction for overcoming both TMZ resistance and immune tolerance in glioma[138].

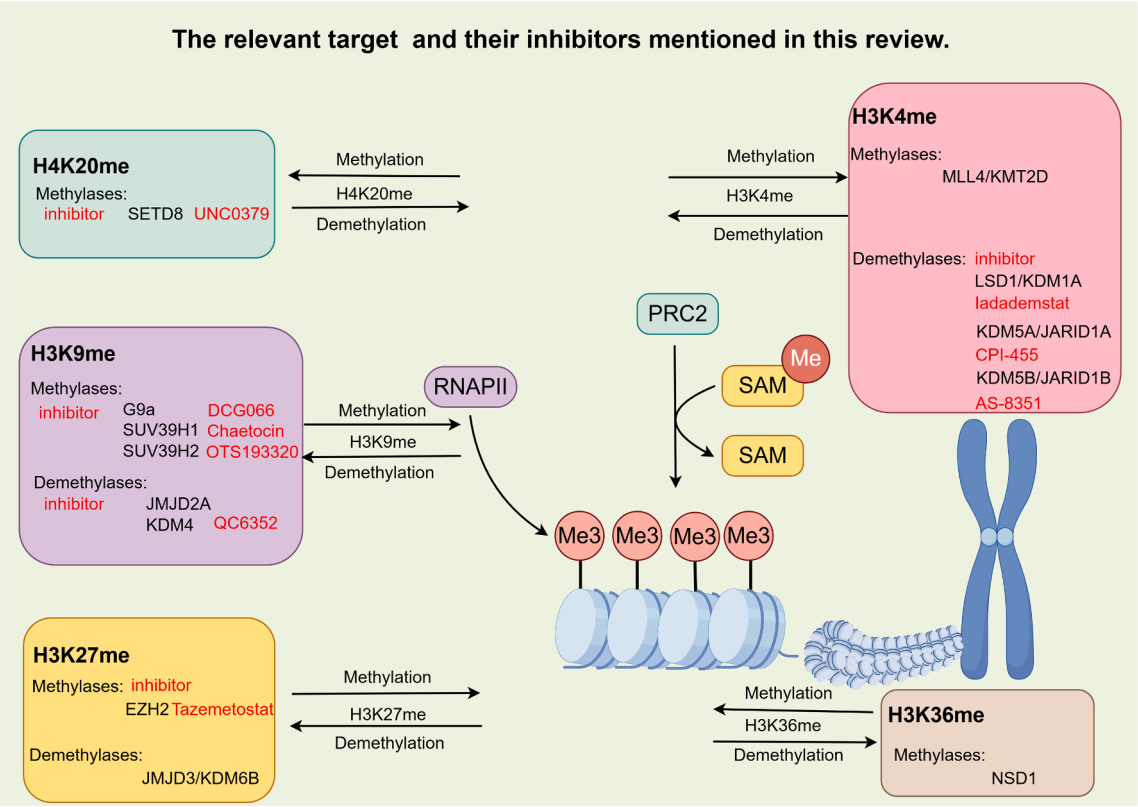

Fig. 4. Relevant target and their inhibitors mentioned in this review. It depicts key histone methylation modifications, the enzymes involved in adding or removing methyl groups, and selected inhibitors targeting specific demethylases for potential medical applications.

2.5. Crosstalk of Histone Methylation Marks in Glioma

Histone methylation marks act synergistically or antagonistically rather than in isolation, forming a coordinated epigenetic network in glioma. A key interaction occurs between H3K27me3 and H3K9me2/3 [59]. EZH2-mediated H3K27me3 and G9a/SUV39H-dependent H3K9me2/3 frequently co-occupy promoters of tumor suppressors (e.g., PTEN, p53) and exert synergistic repression: H3K27me3 triggers chromatin condensation, while H3K9me2/3 reinforces silencing via HP1 recruitment[71]. This dual repression drives glioma progression and stemness.

Compensatory effects exist between the two pathways: EZH2 inhibition often upregulates G9a and elevates H3K9me2/3, and vice versa, limiting single-agent efficacy. Antagonistic crosstalk is also observed at oncogenic loci, where H3K27me3 may displace H3K9me3 to derepress genes such as MYC.

Furthermore, SETD8-catalyzed H4K20me1 crosstalks with H3K9/H3K27 methylation in DNA damage repair. In TMZ-resistant glioma, increased H3K27me3 and H3K9me3 enhance SETD8 activity, promoting 53BP1 recruitment and DNA repair[71]. Overall, these interconnected marks drive glioma pathogenesis and TMZ resistance, highlighting the need for combinatorial epigenetic therapies.

3. Conclusion

As a prevalent primary intracranial malignancy, glioma is distinguished by a dismal prognosis, marked by frequent recurrence, rapid progression, and significant therapeutic challenges. Current clinical management relies predominantly on maximal surgical resection followed by adjuvant radiotherapy and chemotherapy. However, this approach is severely limited for certain subtypes, such as DIPG, which remain surgically inaccessible due to their critical anatomical locations. Furthermore, the efficacy of radiotherapy and chemotherapeutic agents is often compromised by systemic toxicity and the inevitable development of drug resistance. While emerging evidence suggests that inhibitors targeting histone methylation can resensitize gliomas to TMZ, the precise molecular mechanisms underlying this reversal effect remain incompletely understood. Consequently, there is an urgent imperative to investigate novel therapeutic modalities and to delineate the intricate circuitry of drug resistance in glioma.

At present, the mutual regulation mechanism of signaling pathways related to the occurrence and development of glioma remains unclear, which is crucial for determining therapeutic targets and the related drug development process. In recent years, studies have shown that histone methylation modification is closely related to the proliferation, metastasis, invasion and prognosis of glioma. Therefore, regulating histone methylation modification enzymes plays an important role. The continuous development of drugs related to histone modification enzymes and the combined treatment of RT and chemotherapy have achieved encouraging progress.

To translate these findings into clinical practice, we propose two actionable directions: first, rational combination regimens of epigenetic inhibitors with TMZ, such as EZH2 inhibitor (tazemetostat) + TMZ, G9a inhibitor (UNC0642) + TMZ, LSD1 inhibitor (bomedemstat) + TMZ, or dual inhibition of EZH2 and G9a, which together suppress DNA repair, deplete glioma stem cells, and remodel the immunosuppressive microenvironment to reverse TMZ resistance. Second, key histone methylation marks—including H3K27me3, H3K9me2/3, and H4K20me1—can serve as predictive biomarkers for precision diagnostics: elevated H3K27me3 or H3K9me2 may indicate poor prognosis and TMZ resistance, while their reduction after epigenetic therapy can serve as a pharmacodynamic readout to guide personalized treatment decisions.

Although this review focuses on abnormal histone methylation modification, other epigenetic changes are also closely related to the

pathogenesis of glioma. There is no doubt that a comprehensive and in-depth understanding of the epigenetics of glioma will make a significant contribution to their effective treatment and improvement of patient prognosis (Fig. 4).

Ethics approval and consent to participate

Not applicable.

Data availability

No data were used for the research described in the article.

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CRediT authorship contribution statement

Xiaoran Wang: Writing – review & editing, Writing – original draft, Supervision. **Wenqi Liu:** Writing – review & editing, Writing – original draft, Project administration, Funding acquisition. **Jie Sun:** Methodology, Conceptualization. **Xiuhong Wei:** Writing – original draft, Supervision. **Zengyong Wang:** Supervision, Project administration. **Lanlan Zang:** Supervision, Project administration, Funding acquisition.

Declaration of competing interest

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

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