Review

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The Potential Role of Histone Modifications in Glioblastoma Therapy: Review Article.

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The Potential Role of Histone Modifications in Glioblastoma Therapy: Review Article

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Abstract: Glioblastoma is considered the most aggressive primary brain tumor. Recurrence after treatment is a significant problem with a failed response to optimal therapies. The recurrence of GBM is linked to different cellular pathways and molecular pathways. Not only genetics are involved in gliomagenesis, but also epigenetics. Epigenetic mechanisms are highly involved in the pathogenesis of GBM. Histone modulation through acetylation, phosphorylation, ubiquitination, and methylation can regulate gene expression and may play a role in the pathogenesis of GBM. Preclinical and clinical studies currently target epigenetic enzymes in gliomas, including a new generation of histone deacetylase (HDAC) inhibitors. Herein, I tried to update current research in glioma epigenetic, focusing on the culprit of histone modifications and the use of HDAC target therapies as a possible treatment line for glioblastoma.

Keywords: glioma; histone; HDAC; therapy

1. Introduction

Glioblastoma is considered the most aggressive primary brain tumor. Recurrence after treatment is a significant problem, with a survival rate after one year ranging about 39.7% [1]. The recurrence of GBM is linked to different cellular pathways and molecular signaling. The genetic profile of glioma is complicated, as evidenced by multi-omics studies from the landscape of GBM in the Cancer Genome Atlas Research Network (TCGA), the Chinese Glioma Genome Atlas (CGGA), and other databases [2]. 1p and 19q co-deletions (oligodendroglioma-specific), IDH gene mutations, PTEN (Phosphatase and tensin homolog) gene mutations, TP53 mutations, TERT (Telomerase reverse transcriptase) gene promoter mutations, ATRX (Alpha thalassemia/mental retardation syndrome X-linked) gene mutations, and EGFR (Epithelial growth factor receptor) gene amplification are the most prominent genetic molecules involved in gliomagenesis [3]. Not only is genetic deregulation involved in gliomagenesis, but also epigenetics. Manipulation of genetics without affecting DNA itself is a crucial role of epigenetics [4]. Therefore, more knowledge in the field of epigenetics is required to understand the biology of GBM fully. Most clinical trials failed to promote prolonged survival of glioblastoma. The only trial with the best noticeable outcome was the European Organization for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada (NCIC) clinical trial in 2005 [5]. Since then, there were no other clinical trials with better survival chances.

Histone modulation through acetylation, phosphorylation, ubiquitination, and methylation can regulate gene expression. Histone can be modified through acetylation and deacetylation, affecting different physiological and pathological processes [6,7]. Histone acetyltransferase mediates acetylation, which is usually associated with gene activation. On the contrary, histone deacetylation is mainly associated with gene suppression **Figure 1** [7,8]. The detailed general characterization of how histone modifications affect gene expression, in general, is out of this review's scope. Abnormally activated HDACs have a role in the pathogenesis of glioma. Therefore, inhibitors of that enzyme can be a therapeutic option controlling apoptosis and cellular proliferation [9,10]. HDACs inhibitors are of particular importance in glioma targeted therapy as they can pass the blood-brain barrier at variable extents [11].

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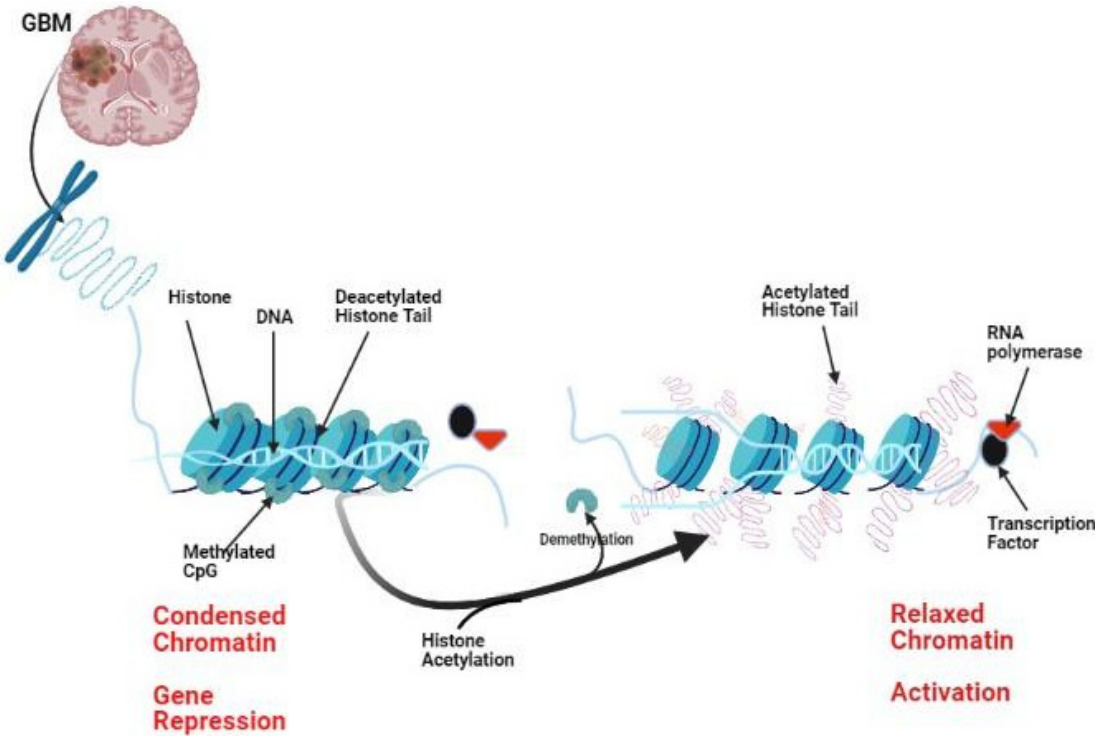

Figure 1. Histone undergoes certain post-translational modifications that control gene expression. Histone acetylation promotes relaxation of the DNA, while deacetylation makes histones more compact with resulting gene repression. Methylation of CpG islands is associated with more condensed heterochromatin, while demethylation favors euchromatin and exposure of DNA to the action of RNA-polymerases and transcription factors.

2. Histone Modifications in Glioma:

2.1. Histone Deacetylation in Glioma:

Abnormal HDAC activity was identified in some cancers, but the complete mechanisms involved have not been fully elucidated [12]. Some HDACs are upregulated in certain tumors and downregulated in others [13]. HDACs have multiple types and functions, which make them a prominent target for molecular therapy. Before we can discuss the effective targeted therapy models, we should focus the light on categories of HDACs and the suggested roles they have in GBM. Studies investigating the role of HDACs in the literature are few. The types of HDACs are classified based on similarities to those found in yeast, and they vary in the cellular location and structure [12]. Classical HDACs include the following: Class I (HDAC 1-3, 8), II (HDAC 4-7, 9-10), and IV (HDAC 11), which are Zn^{2+} dependent, while class III is Zn^{2+} independent [14]. It is reported that classes II and IV are expressed at high levels in a low-grade astrocytoma [13].

HDAC1 and HDAC2 have been reported to be highly expressed in GBM cell lines, and HDAC2 knocking down increased the response to temozolomide therapy [15]. A higher expression of HDAC3 is associated with a dismal prognosis and was noticed in specific aggressive phenotypes of glioma cell lines [16]. In a specific study by Wang and his colleagues, HDAC6 was upregulated in GBM cell lines, and the response to TMZ treatment was enhanced following knocking down that enzyme [17]. Class III HDACs comprise a group of proteins named the sirtuin (SIRT) family [18]. Aberrant expression of class III HDACs was noticed in GBM cell lines, and Feng et al. noticed that SIRT1 and SIRT6 were downregulated in these cells [19] while other studies reported upregulation [20]. HDAC class IV has only one type, which is HDAC 11 [21]. It was reported that the expression of HDAC11 decreases in the more aggressive GBM tumors and has a dismal prognosis [13].

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2.2. Histone acetylation in Glioma:

Histone acetylation leads to an increased gene activity by allowing more DNA exposure for transcription complexes [22]. Acetylation is accomplished using histone acetyltransferases HATs. HATs have some role in cellular signaling, DNA damage repair, and cell cycle regulation [23,24]. HATs include the following, GNAT superfamily, MYST family, p300/CBP, nuclear receptor coactivators (SRC-1, ACTR, TIF2), TAFII250, and TFIIIC [25]. The one that was extensively studied in GBM is the p300/CBP and termed KAT2B, EP300 [26]. P300 acts as a tumor suppressor in GBM and an inhibitor for acetyltransferase P300 is highly expressed in GBM and makes the prognosis worse [26]. A group of researchers found that PI3K/Akt signaling activation, a highly involved pathway in gliomagenesis and PIK3CA expression, was recruited by H3K23 acetylation enhanced by a specific HAT called KAT6A, which belongs to the MYST family [27]. Some studies have investigated the role of HATs in GBM, as illustrated in **Table 1**.

Table 1. Studies Involving HATs in Glioma.

HAT involved	Mechanism involved	Reference
KAT6A/MYST3	Glioma cell-induced proliferation through H3K23ac/TRIM24-PI3K/AKT pathway	27
KAT8	Manipulation of the H4K16 acetylation level in microglia, using the intrinsic H4K16 acetyltransferase activities, adjusted the microglia's tumor-supporting function.	92
KAT3B	An inhibitor for KAT3B acetyltransferase is highly expressed in GBM and correlates with a dismal prognosis.	26

2.3. Histone Methylation in Glioma:

Lysine and arginine are methylated on histones, mostly H3 and H4, by the two enzymes lysine methyltransferase (KMTs) and arginine methyltransferase (PRMTs), which include different subtypes **Table 2** [28]. Various studies reported the clinical significance of aberrations related to methyltransferases and their association with different cancers [29–31]. A study reported that the KMT G9a is abnormally expressed in some brain tumors [32]. Moreover, a high expression rate of KMT G9a is noted to be associated with more aggressive behavior in glioma [33]. Researchers investigated the role of certain KMTs as SUV39H1 and SETDB1 in gliomagenesis, and they observed the upregulated expression in malignant glioma cell lines. Moreover, knocking down SUV39H1 and SETDB1 induced a high rate of apoptosis and a diminished migratory capacity of cells [34]. The arginine methyltransferase 2 (PRMT 2) was highly expressed in GBM and linked to an unfavorable prognosis [35]. The proposed mechanistic role of PRMT2 is thought to be through H3R8 methylation, whose function is associated with promoter enhancement and active gene expression suggesting its potential oncogenic activity [35]. We tried to list the different studies that involved KMTs and PRMTs in GBM. **Table 3.**

Table 2. Lysine and arginine methyltransferases subtypes.

Methyltransferases		
KAMTs	**PRMTs**	
	Type 1	**Type 2**
SET1	PRMT1	PRMT5
SET2	PRMT2	PRMT7
SMYD	PRMT3	PRMT9
SUV4-20	PRMT6	
SET7/9	PRMT8	
SUV39	PRMT4	

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Table 3. Studies Involving Methyltransferases in Glioma.

HATs	Cell line used	Effect	Reference
KMT1A	Glioma cell lines (GOS-3, 1321N1, T98G, U87MG)	Positive correlation with aggressive tumors	**34**
KMT2A	Cell lines isolated from primary human GBM	Glioma stem cells were blunted following silencing of KMT2A	**93**
KMT3A	Patient-derived tumor cells	Expressed in High-grade pediatric glioma	**94**
KMT4	Xenograft models	Inhibition of KMT4 reduced stem cell expression of stemness markers	**95**
KMT6	Patient-derived GBM cultures	Reduced expression levels of KMT6 are associated with low expression of oncogenes as c-myc.	**97**
PRMT1	T98G, U87MG, and A172 cell lines and mouse xenografts	Highly expressed in glioma cell lines	**96**
PRMT2	U87 and T98G cell lines	Expressed in high-grade gliomas and associated with poor prognosis.	**35**
PRMT5	U373MG and LN229 cell lines	The expression is high in the high-grade glioma	**98**

2.4. Histone Demethylation in Glioma:

There is an increasing interest in the enzyme N-methyl-lysine demethylase (KDM1, also known as LSD1, AOF2, or BHC110) as a possible target for therapy in cancer [36]. Methylation and demethylation of histone's arginine side chains are of equal scientific importance as acetylation, phosphorylation, and ubiquitination. Demethylation of histone contributes to cellular development, so dysregulation of that biochemical process may result in disorganized cellular development and tumorigenesis [37]. Work is promoted to further study histone demethylases because of the evident success of demethylase inhibitors in the field of cancer [38]. Several histone demethylases are overexpressed in GBM and are suspected of having a role in TMZ resistance [39]. Sareddy et al. reported that KDM1A is expressed too much in glioma cell lines, and using pargyline to inhibit it reduced cellular proliferation [40]. Targeting KDM2A by micro RNA-3666 halted the migration of glioma cells [41]. Moreover, knocking down KDM2B blunted the numbers of glioma stem cells in primary GBM cultures suggesting that KDM2B is fundamental for GBM cell initiation and survival. [42]. A significant increase in acidic vesicular organs and autophagy-related proteins was noticed following inhibition of KDM4A using siRNA, suggesting a therapeutic role [43]. Synthetic pharmacological inhibitors against KDM4B are effective in TMZ- resistant glioma cells, suggesting a role of KDM4B in resistance to therapy [44].

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2.5. Histone Ubiquitination in Glioma:

Histone ubiquitination frequently happens in two regions of histone, H2A at lysine 119 (H2AK119ub1) and H2B at lysine 120 (H2BK120ub1) [45]. Abnormal histone ubiquitination could alter tumor suppressors and oncogenes [46]. Frequent studies reported many deregulated ubiquitination enzymes in different cancer types marking ubiquitination an exciting item to study cancer [47]. Certain deubiquitinating enzymes regulate that process and include 2A-DUB, USP21, USP16, and BRCA1, and their deregulation could have a role in carcinogenesis [46]. Different research studied abnormal ubiquitin expression patterns in GBM **Table 4.** Ubiquitin-specific proteases as USP1,3,4,10,13 are expressed at a higher rate in GBM cells than in normal brains and are linked to poor survival [47–49].

Table 4. Studies Involving Ubiquitin Specific Enzymes in Glioma.

Ubiquitin specific enzymes	Preclinical study	Reference
USP1	USP1 is overexpressed in glioma stem cells. Inhibition of USP1 increased radiosensitivity of GBM cells	99
USP3	USP3 is highly expressed in GBM and correlates with poor prognosis.	100
USP4	USP4 is highly expressed in GBM cells	49
USP 10	USP 10 is overexpressed and linked to poor survival in GBM patients	101
USP 13	USP13 is highly expressed in GBM and is required by glioma stem cells to maintain its stemness features.	47
USP 15	USP15 attenuates the WNT pathway mediated by stabilization of HECTD1, supporting a tumor-suppressing role of USP15 in GBM cells.	48
USP28	USP 28 is overexpressed in GBM cell lines and is associated with a high grade of glioma.	102

2.6. Histone Sumoylation and Glioma:

Sumoylation is a type of post-translational modification attaching ubiquitin-related modifier (SUMO) groups to histones [50]. Sumoylation is reported to be involved in different cellular processes as apoptosis and signal transduction [51]. Four isoforms of SUMO have been identified and include SUMO1,2,3,4 [52]. E1 enzyme (SAE1 and SAE2/UBA2) and E2 enzyme are involved in SUMO modification [53]. SUMO-1 and SUMO-2/3 proteins were found to be expressed in both low and high-grade gliomas [54]. A study observed that SAE1 enhances glioma cells' growth via the Akt signaling pathway, which is a major pathway involved in gliomagenesis [55].

2.7. Histone Phosphorylation and Glioma:

Histone phosphorylation is one of the post-translational modifications that may play a role in cell division, apoptosis, and gene expression. However, little is known about the prognostic implication of histone phosphorylation in human cancer. Histone phosphorylation importantly occurs when DNA damage repair ensues as the phosphorylated histone H2A functions to localize the sites of DNA repair [56]. Phosphorylation of specific proteins was also linked to regulation of proliferative genes such as serine 10 and 28 of H3 and serine 32 of H2B phosphorylation which has been involved in EGF responsive gene regulation [57]. Specific phosphorylated histones' proteins are reported to be associated with certain proto-oncogenes as c-fos, c-jun, and c-myc [58]. Research investigating phosphorylated histones' roles in GBM is limited in the literature. The phosphorylation level of H3T3, T6, S10, S28, Y41, and T45 was analyzed in 42 GBM samples. That analysis depicted a high level of pH3T6, pH3S10, or pH3Y41 linked to poor survival [59]. Moreover, pharmacological inhibition of the

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phosphorylation process using enzastaurin increased GBM cells' sensitivity to irradiation/TMZ treatment [59].

2.8. Targeting Histone-Modifying Enzymes in Glioma

Despite the significant advances in molecular research focusing on GBM, the hallmark treatment proven to be the best is the classical radical surgical resection plus TMZ and radiotherapy [60]. Total excision of GBM is almost impossible due to microscopic infiltration of cells beyond radiological tumor borders, making complementary treatments a valuable tool in therapeutic strategies. What complicates treatment is the diffuse heterogeneity of the GBM microenvironment that makes GBM a notorious tumor for therapy failure. Glioma stem cells also reduce the efficacy of targeted therapies as they have an inherent capacity of self-renewal, initiating and recurring new tumor cells pool [61]. Preclinical trials testing different targeted therapies related to histone enzymes have been reported, but some only have well-established outcomes and are promoted for clinical trials **Table 5**. Most GBM research uses different glioma cell lines such as U87 and U251 as models for experimental trials. To some extent, GBM cell lines are different from human primary tissue samples, especially in the case of studying signaling and genetic profiling, and that eventually leads to some discrepancy in the results of experimental animals, preclinical, and clinical trials [62].

Table 5. Certain Clinical Trials Involving HDACi in Glioma.

HDAC inhibitor	Combination therapy	Tumor type	Result	Sponsor	Reference
Vorinostat	Temozolomide + Isotretinoin, bortezomib	Recurrent GBM	Still active		
	Bevacizumab	Recurrent GBM	No change in overall survival or progression-free survival compared to bevacizumab therapy.	Duke University Durham	74
	Temozolomide + Bevacizumab	Recurrent GBM	Progression-free survival for six months was not affected.	Duke University Durham	75
	Bevacizumab + Irinotecan, Temsirolimus	Diffuse intrinsic pontine glioma	Active		
	Radiotherapy	High –grade glioma and anaplastic astrocytoma	Active	National Cancer Institute	
Valproic acid	VPA, temozolomide, and radiotherapy	Newly diagnosed GBM in adults	Active	National Cancer Institute	
Romidepsin		Recurrent GBM	Completed and showed that romidepsin is ineffective in the treatment of recurrent GBM.		85

		Pediatric intrinsic pontine glioma	Active	
Panobinostat	Bevacizumab	Recurrent GBM	Adding this agent to bevacizumab did not improve the outcome compared to bevacizumab alone.	103
	Convection-enhanced delivery (CED)	Diffuse pontine glioma		

3. HDAC inhibitors (HDACi)

HDACi have been investigated as a therapy for many cancers, and candidates of this family have shown promising results in certain tumors as vorinostat for primary cutaneous T-cell lymphoma [63]. Most of the HDACi used in preclinical and clinical trials are specific for each enzyme class and are usually used as a combination therapy with other targeted therapies. HDACi work through different mechanisms as an anti-cancer therapy. HDACi can untwist chromatin's condensation, allowing TMZ and other chemotherapeutics to gain more access to DNA [64]. They may initiate autophagy through the production of complex immunomodulatory cytokines [65]. HDACi is reported to reduce the effect of VEGF, which plays a master role in hypoxia-induced angiogenesis in GBM [66]. Apoptosis can be achieved through different mechanisms using HDACi [67]. A famous HDACi called vorinostat was reported to induce DNA damage and double-strand breaks [68]. Another possible mechanism of the anticancer effect of HDACi in the production of reactive oxygen species, which help destroy tumor cells [69]. We will focus on the most prominent candidates of HDACi that were used in clinical trials.

3.1. Vorinostat:

This agent was used in stage I and II clinical trials to treat different cancers with an acceptable range of side effects [70,71]. Vorinostat was used in a phase II trial of North Central Cancer Treatment Group (NCCTG) in patients with recurrent GBM [72]. In this study, the patients receiving vorinostat showed progression-free survival at six months of about 15.2 % and median overall survival of 5.7 months [72]. Combination therapy of vorinostat, bevacizumab) anti-VEGF (erlotinib, a tyrosine kinase receptor inhibitor, bortezomib, a proteasome inhibitor, and isotretinoin with or without TMZ was tested. This combination aims at blocking all possible routes for resistance to therapy [73–75]. In a study conducted by the Adult Brain Tumor Consortium (ABTC), vorinostat combined with TMZ was used in patients with malignant gliomas who had previously received radiotherapy [76]. Results from this trial encouraged the ABTC and NCCTG to start a phase II trial of vorinostat with radiotherapy and TMZ in newly diagnosed GBM patients. Vorinostat combination with bevacizumab plus irinotecan was published as a phase I clinical trial [77]. HDAC inhibitors' ability to enhance the antitumor activity of both bevacizumab and topoisomerase I inhibitors was also supported by the preclinical data published in different studies [78–80]. In patients with recurrent GBM, a proteasome inhibitor bortezomib was added to vorinostat as a part of phase II clinical trial conducted by NCCTG. The median time of progression was about 1.4 months (range 0.5–5.6 months), and the median overall survival was about 2.4 months [80].

3.2. Valproic acid

The European Organization for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada (NCIC) trials found exciting results regarding using the antiepileptic valproic acid with a distinguished effect on outcome [81]. Valproic acid (VPA) is considered a class I selective HDAC inhibitor [82]. Valproic acid is known for its antiepileptic properties, but it also has an HDAC inhibiting activity. A better survival with TMZ and radiotherapy was observed in patients receiving VPA as the only antiepileptic drug [82]. The mechanism behind the effect of VPA in prolongation of survival in GBM patients is still not fully explained. Some researchers suggested that VPA increases the bioavailability of TMZ by diminishing its clearance [83]. A phase II trial study was conducted to investigate the effect of VPA in GBM patients who are on chemo and radiotherapy [84]. This study showed a progression-free survival of about 10.5 months. In another study conducted by Deepthi Valiyaveettil et al., VPA with combined chemo and radiotherapy in GBM patients, the PFS was about ten months, and overall survival was about 16 months [84].

3.3. Romidepsin (FK228)

This agent was studied in a trial conducted by the North American Brain Tumor Consortium in patients with recurrent glioma who are on enzyme-inducing antiepileptic drugs (EIAEDs) and evaluate the antitumor efficacy of romidepsin in patients with recurrent glioblastoma who were not receiving EIAED. The resulting median PFS was only six weeks [85]. Mice treated with both romidepsin and TMZ drugs significantly reduced tumor weights and volumes compared to each drug alone [104]. Our results suggested that FK228 augmented temozolomide sensitivity in human glioma cells partially by blocking PI3K/AKT/mTOR signal pathways [104]. A study by Nguyen et al. reported the combined inhibition of TRAP1 by gamitrinib and romidepsin or panobinostat caused synergistic growth reduction of established and patient-derived xenograft (PDX) glioblastoma cells [105].

3.4. Panobinostat

FDA approved this HDACi in the treatment of multiple myeloma. It is still under investigation in an active clinical trial in children with diffuse intrinsic pontine glioma with marizomib, a proteasome inhibitor. (Source: https://clinicaltrials.gov).

3.5. Limitations of HDACi in clinical practice:

Some side effects were reported using HDACi which include neutropenia and thrombocytopenia [86]. Cardiotoxicity was noticed, which is potentially hazardous [87]. Resistance to therapy was observed in several studies, and the mechanisms of resistance are variable. One proposed mechanism is the activation of anti-apoptotic transcription factor NF-κB and other anti apoptotic proteins [88]. A slackened BBB permeability was noticed with most of HDACi [89]. The potential benefits that HDACi might offer in CNS disorders encouraged researchers to explore the brain uptake of HDAC inhibitors as potential templates for developing HDAC inhibitors fully penetrating the BBB. Brain uptake of trichostatin A (TSA)-like hydroxamates and (KB631) in the baboon brain was negligible [90,91]. On the contrary, five patients post-treatment with vorinostat exhibited an increase in histone acetylation in their post-surgical specimens, proving that vorinostat reached a sufficient concentration in the tumor [72].

4. Conclusion and future perspectives:

There is a compelling need for new studies exploring epigenetics in GBM. Therapies to prolong survival in GBM are still limited, although new molecular therapies have emerged. Some virulent features characterizing glioblastoma can be targeted using different histone deacetylase inhibitors. Recent clinical trials have demonstrated potentially effective models of therapies targeting epigenetics but failed to achieve maximum intratumoral concentration levels. Research should be directed at managing how to achieve a high CNS level of those therapies. Discovering more about the epigenetics

of glioma may establish new GBM classifications that will be epigenetically based and help with the proper selection of the targeted therapy.

Abbreviations

ABTC	The Adult Brain Tumor Consortium
EIAEDs	Enzyme-inducing antiepileptic drugs
EORTC	European Organization for Research and Treatment of Cancer
GBM	Glioblastoma
DNA	Deoxynucleic acid
EGF	Epidermal Growth Factor
HDAC	Histone Deacetylase
HDACi	Histone Deacetylase Inhibitors
HATs	Histone Acetyltransferases
NCIC	National Cancer Institute of Canada
USP	Ubiquitin Specific Protease
TMZ	Temozolomide

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