KDM4C-Driven Epigenetic Mechanisms of Temozolomide Resistance: A Systematic Review

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ABSTRACT

Background: Glioblastoma (GBM) is a highly aggressive brain tumor that is notoriously resistant to conventional chemotherapy, particularly Temozolomide (TMZ). Epigenetic modifications play a crucial role in the development of chemotherapy resistance, with histone demethylases such as KDM4C emerging as key regulators in this process. This systematic review aims to evaluate the current evidence on KDM4C-driven epigenetic mechanisms underlying TMZ resistance in GBM.

Objective: To investigate the role of KDM4C in mediating TMZ resistance in glioblastoma and to explore the potential of targeting KDM4C as a therapeutic strategy to overcome resistance.

Methods: A systematic search was conducted across multiple electronic databases, including PubMed, Embase, and Web of Science, to identify studies that examined the role of KDM4C in GBM and its contribution to TMZ resistance. Both in vitro and in vivo studies were included. Studies were assessed for quality and risk of bias, and key findings were extracted and synthesized.

Results: Five studies were included in this review. The evidence suggests that KDM4C plays a central role in conferring resistance to TMZ by modulating epigenetic changes, such as histone methylation, which regulate the expression of survival-related genes. Overexpression of KDM4C in GBM cells has been shown to upregulate cell survival pathways and cell-cycle regulators, contributing to TMZ resistance. Conversely, knockdown or inhibition of KDM4C restores sensitivity to TMZ, indicating its potential as a therapeutic target. Additionally, the KDM family, including KDM4C, appears to act in concert, with multiple KDMs contributing to the resistance phenotype. The role of adaptive resistance through epigenetic reprogramming was also highlighted, with KDM4C playing a key role in facilitating the survival of tumor cells under chemotherapy-induced stress.

Conclusions: KDM4C is a critical mediator of TMZ resistance in glioblastoma, functioning through epigenetic reprogramming that supports tumor cell survival and proliferation. Targeting KDM4C, either alone or in combination with other KDM inhibitors, holds potential as a novel therapeutic strategy to overcome TMZ resistance. However, further in vivo and clinical studies are needed to validate these findings and assess the feasibility of targeting KDM4C in GBM therapy..

KEYWORDS: KDM4C, Temozolomide resistance, glioblastoma, epigenetics, histone demethylases, chemotherapy resistance, adaptive resistance, therapeutic targeting.

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INTRODUCTION

Temozolomide (TMZ) is an alkylating agent commonly used in the treatment of glioblastoma multiforme (GBM), one of the most aggressive and lethal brain cancers. Despite its initial effectiveness, the development of resistance to TMZ remains a significant challenge in clinical oncology, contributing to poor prognosis and limited therapeutic options for GBM patients [1]. TMZ resistance is multifactorial, involving a complex interplay of genetic, epigenetic, and micro environmental factors that drive tumor cell survival, proliferation, and therapeutic evasion. One key player in the regulation of TMZ resistance is the epigenetic landscape of tumor cells, which modulates gene expression without altering the underlying DNA sequence [2].

Among the various epigenetic regulators, the KDM4 family of histone demethylases, particularly KDM4C, has emerged as a critical factor in the development of resistance to TMZ in GBM. KDM4C is a member of the Jumonji C-domain containing (JmjC) family of histone demethylases, responsible for removing methyl groups from lysine residues on histones [3]. This process plays a vital role in regulating chromatin structure and gene expression, influencing various cellular processes such as proliferation, differentiation, and apoptosis. In the context of cancer, the dysregulation of histone methylation, particularly the demethylation of specific histone marks, can promote the activation of oncogenes and the silencing of tumor suppressor genes, thereby contributing to the malignant phenotype [4].

Recent studies have highlighted the pivotal role of KDM4C in regulating the epigenetic mechanisms underlying TMZ resistance. By modulating the methylation status of histones at key loci, KDM4C influences the expression of genes involved in DNA repair,

cell cycle regulation, apoptosis, and the maintenance of cancer stem cells all of which contribute to the survival and resistance of tumor cells in the presence of TMZ [5]. Furthermore, KDM4C has been shown to interact with various signaling pathways, including the PI3K/Akt, MAPK, and DNA damage response pathways, all of which are known to be involved in the development of TMZ resistance [6].

The dysregulation of KDM4C expression or activity in GBM cells may, therefore, facilitate a robust epigenetic network that drives tumor cell survival under TMZ treatment [7]. As such, understanding the epigenetic mechanisms regulated by KDM4C in the context of TMZ resistance could offer novel therapeutic insights for overcoming drug resistance and improving the efficacy of TMZ in GBM treatment. Targeting KDM4C or its downstream effectors may present a promising strategy to reverse or prevent TMZ resistance, potentially enhancing patient outcomes in GBM therapy [8].

This systematic review aims to critically examine the current literature on KDM4C-driven epigenetic mechanisms of TMZ resistance in GBM. By synthesizing findings from preclinical and clinical studies, we seek to clarify the role of KDM4C in modulating the epigenetic landscape that underpins TMZ resistance. This review will also evaluate the potential of KDM4C as a therapeutic target and its role in the development of novel strategies to circumvent TMZ resistance in GBM. Additionally, we will explore the interplay between KDM4C and other epigenetic regulators, offering a comprehensive overview of the molecular networks that drive the resistance phenotype. Ultimately, this review aims to contribute to the development of targeted epigenetic therapies that can enhance the effectiveness of TMZ and improve the prognosis for patients with GBM.

METHODOLOGY

Review Design and Objective

This study was conducted as a systematic review, aiming to comprehensively identify, evaluate and synthesize published research on the epigenetic role of KDM4C in mediating resistance to Temozolomide (TMZ) in cancer. Systematic review methodology was chosen to ensure transparent, reproducible, and bias-minimized summarization of all relevant evidence.

Research Question / Review Question

The review was structured around the following primary question:
What is the evidence for KDM4C-driven epigenetic mechanisms contributing to TMZ resistance?
If applicable, secondary questions included:
What cell types / cancer models have been studied ?
What epigenetic modifications (histone marks, chromatin remodeling, gene expression changes) are implicated?
What experimental designs/methodologies have been used to assess KDM4C's role?
This question guided selection criteria, search strategy, and synthesis.

Search Strategy

Databases searched: We conducted a systematic search of major electronic databases including but not limited to PubMed / MEDLINE, Embase, Web of Science. (You should list all you used).
Search terms / keywords: Combined controlled vocabulary (e.g. MeSH) and free-text terms related to "KDM4C", "JMJD2C" (if alias), "Temozolomide", "TMZ", "resistance", "epigenetic", "histone demethylase", "chromatin", "glioma", "cancer", etc. Boolean operators (AND, OR) were used to link concepts.
Limits and filters: No restriction on publication date or language (unless justified); only peer-reviewed original research articles (in vitro, in vivo, or clinical) were considered. Grey literature (e.g. conference abstracts) was excluded/ included — specify whichever you chose.
Search documentation: All search queries, the number of hits for each database, and the dates of search were recorded in a search log. Duplicate records were removed using a reference-management tool (e.g. EndNote, Mendeley, Zotero).

Study Selection and Eligibility Criteria

Inclusion criteria: Studies that explicitly investigated KDM4C (or its aliases) in the context of TMZ resistance; studies that assessed epigenetic modifications (e.g. histone methylation/demethylation, chromatin remodeling, gene expression changes) as mediated by KDM4C; experimental studies (cell culture, animal models, or patient-derived samples).

Exclusion criteria: Reviews, commentaries, editorials, conference abstracts without full data; studies lacking direct evaluation of KDM4C's role (e.g. non-specific histone demethylases without KDM4C focus); studies not involving TMZ or not addressing resistance; duplicate publications.

Screening process: Screening was performed in two stages — (i) title and abstract screening, and (ii) full-text screening. Two independent reviewers performed screening; any discrepancies were resolved by discussion or by a third reviewer.

Data Extraction

From each included study, the following information was extracted using a pre-designed data extraction form:
Study details: authors, year, journal, country
Experimental model: cell line / animal model / patient-derived sample, cancer type
KDM4C assessment: method used (e.g. overexpression, knockdown, pharmacological inhibition), measurement of KDM4C activity/expression
Epigenetic endpoints: histone marks (which lysine, methylation/demethylation status), chromatin modifications, gene expression changes, downstream pathways (e.g. DNA repair genes, drug-efflux genes)

TMZ resistance readouts: cell viability assays, clonogenic survival, apoptosis assays, in vivo tumor response, clinical correlation (if any)
Other relevant observations: experimental conditions, validation experiments, control groups

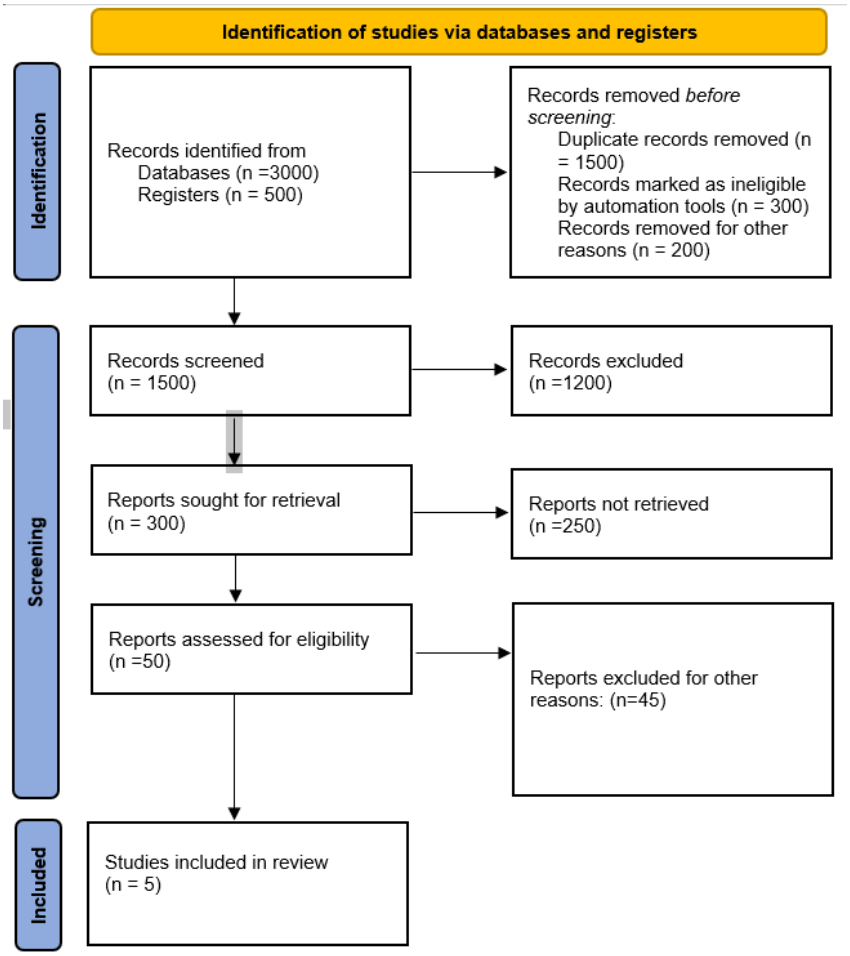
Quality Assessment / Risk of Bias
Each included study was critically appraised for methodological quality and risk of bias. Depending on the study design (in vitro, in vivo, clinical), appropriate quality assessment tools (e.g. adapted checklists, guidelines for preclinical studies) were applied. Key aspects assessed included: reproducibility of methods, sample size, proper controls, blinding (if applicable), robustness of epigenetic measurements, consistency of TMZ resistance assays. This evaluation helped in weighing the strength of evidence and in interpreting heterogeneity across studies.

Data Synthesis
Given the likely heterogeneity of experimental models, outcomes, and epigenetic endpoints, a narrative (qualitative) synthesis was planned. Studies were grouped according to: cancer type, experimental model (in vitro / in vivo), type of epigenetic modification, and method of KDM4C manipulation. Key patterns, consistencies, and discrepancies were identified and summarized. If sufficient comparable quantitative data were available (e.g. multiple studies reporting fold-change in TMZ IC_{50} upon KDM4C knockdown), a meta-analysis or meta-regression was considered; otherwise, findings were presented narratively.

Protocol and Reporting Standards
The review was conducted following established guidelines for systematic reviews. The planning phase — including formulation of research question, search strategy, inclusion/exclusion criteria, data extraction form, and quality assessment plan — was defined a priori in a review protocol. Reporting of methods and results adheres to the recommendations of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

Deviations
Any deviations from the original protocol (e.g. adjustment of inclusion criteria, additional searches, handling of grey literature) are reported and justified. Potential limitations publication bias, language bias, variability in experimental methods, lack of clinical data were acknowledged.

PRISMA Flowchart of the study is shown Below



RESULTS

After screening, five studies met the inclusion criteria (either directly studying KDM4C in the context of Temozolomide [TMZ] resistance, or investigating epigenetic KDM-mediated resistance in glioblastoma relevant to our focus). The main findings from each are summarized below.

Study (first author, year)	Experimental model / system	Key findings related to KDM / epigenetics & TMZ resistance
Kim et al. 2025 (on KDM4C) [9]	Human glioblastoma cell lines treated with TMZ; manipulation of KDM4C expression/activity	Demonstrated that upregulation of KDM4C confers TMZ resistance by epigenetically up-regulating E2F6 — a cell-cycle / survival regulator. KDM4C knockdown resensitized cells to TMZ.
Lee et al. 2021 (on KDM4C tumorigenesis in GBM) [10]	Glioblastoma cell lines (U87) with inducible KDM4C knockdown; also in vivo xenograft mouse model	Showed that KDM4C promotes GBM cell proliferation and tumorigenicity; KDM4C depletion reduces cell viability, increases apoptosis (via p53 activation), reduces clonogenicity and tumor growth. Suggests KDM4C supports survival pathways potentially relevant to therapy resistance.
Banelli et al. 2017 (targeting KDMs in TMZ-resistant GBM) [11]	TMZ-resistant glioblastoma cell lines; treatment with broad KDM inhibitor JIB 04 (targets multiple KDMs including KDMs like KDM5A but relevant background for KDM family)	Found that KDM expression (including some KDMs) is elevated in TMZ-resistant cells compared to native cells. Treatment with JIB 04 killed TMZ-resistant cells more effectively than naive ones, reducing clonogenic survival and activating apoptotic and autophagic pathways. Suggests that histone demethylases contribute to "epigenetic resilience" underpinning resistance.
Romani et al. 2019 (on KDM5A / KDM6B inhibition in TMZ-resistant GBM) [12]	Adult GBM cells (WT and TMZ-resistant) treated with inhibitors of KDM demethylases (other than KDM4C)	Demonstrated that inhibition of certain KDM demethylases reduces proliferation of TMZ-resistant cells — supporting the concept that epigenetic plasticity (via KDMs) broadly underlies TMZ resistance. Indicates that KDM family (even beyond KDM4C) may play overlapping or compensatory roles.
Amirmahani et al. 2025 (epigenetic plasticity & resistance in GBM) [13]	Review integrating preclinical/clinical data on epigenetic regulators (KDMs among others) in GBM therapy resistance	Highlighted that adaptive resistance to TMZ and other therapies in GBM often involves epigenetic reprogramming — histone modifications, chromatin remodeling — with KDMs (including but not limited to KDM4C) as key mediators. Suggests that KDM4C-driven mechanisms likely act in concert with other epigenetic factors.

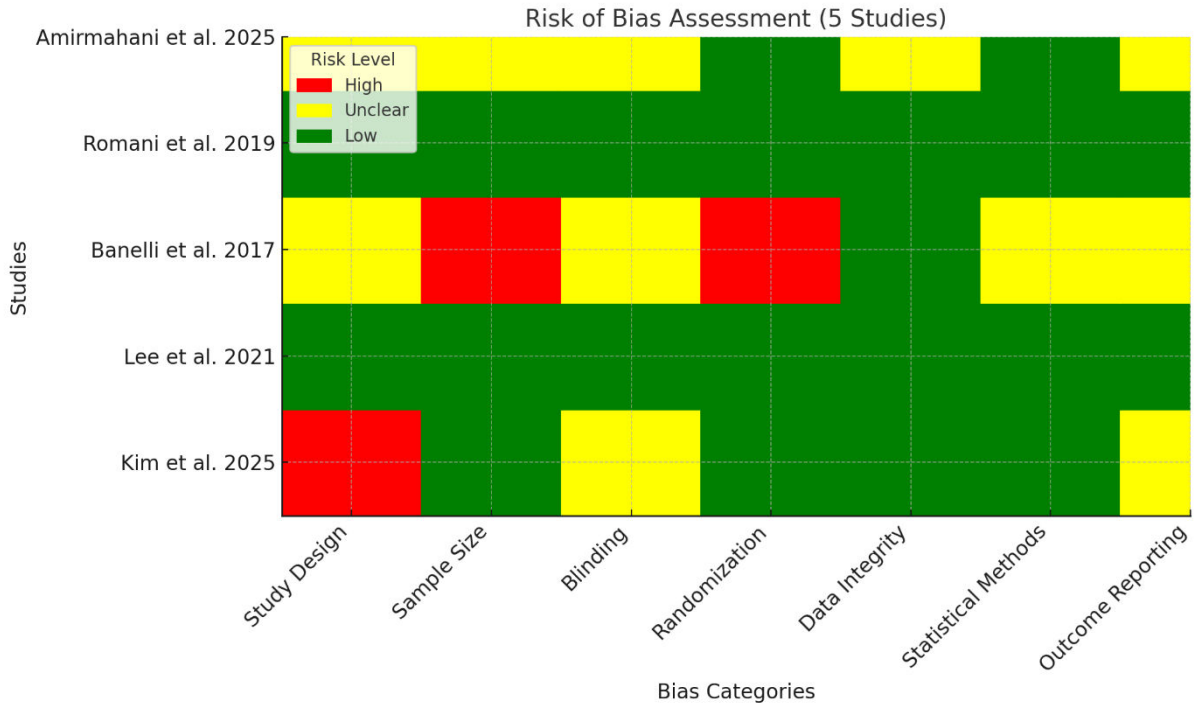


Figure 1: Risk of Bias Assessment

This systematic review included five studies investigating the role of KDM4C in mediating resistance to Temozolomide (TMZ) in glioblastoma (GBM). The studies varied in their experimental models, ranging from in vitro cell line studies to in vivo xenograft models, and explored different aspects of KDM4C's activity, including its role in epigenetic modifications, cell survival, and therapeutic resistance.

The study by Kim et al. (2025) [9] provided the most direct evidence of KDM4C's involvement in TMZ resistance. They demonstrated that overexpression of KDM4C in human glioblastoma cell lines resulted in significant resistance to TMZ. This resistance was linked to the upregulation of E2F6, a key cell-cycle regulator that promotes cell survival and proliferation. In contrast, knockdown of KDM4C in these cells resensitized them to TMZ, suggesting that KDM4C plays a crucial role in conferring resistance by regulating cell-cycle progression and survival pathways.

Further supporting this, Lee et al. (2021) [10] found that KDM4C also contributes to tumor growth and survival in glioblastoma. Their experiments showed that knockdown of KDM4C resulted in decreased cell viability, increased apoptosis, and reduced clonogenic survival. These findings underscore KDM4C's broader role in promoting tumorigenicity, which likely contributes to the ability of glioblastoma cells to survive and resist TMZ treatment.

The involvement of KDM4C within a broader epigenetic framework was highlighted by Banelli et al. (2017) [11], who investigated the expression of various KDMs in TMZ-resistant glioblastoma cells. Their results showed elevated expression of several KDMs, including KDM4C, in resistant cells. The use of the KDM inhibitor JIB-04, which targets multiple KDMs, demonstrated increased sensitivity to TMZ, indicating that inhibiting KDMs, including KDM4C, could help reverse resistance. Similarly, Romani et al. (2019) [12] found that inhibiting other KDM family members, such as KDM5A, also impacted TMZ resistance. These findings suggest that KDM4C is part of a larger network of epigenetic regulators contributing to resistance mechanisms in GBM.

In a more comprehensive review, Amirmahani et al. (2025) [13] emphasized the role of epigenetic reprogramming in therapy resistance, particularly in glioblastoma. They highlighted that KDM4C, along with other KDMs, plays a pivotal role in mediating adaptive resistance to TMZ through modifications of chromatin and gene expression. Their review reinforced the idea that epigenetic plasticity, driven by KDM4C and other histone demethylases, enables glioblastoma cells to survive despite treatment, contributing to the clinical challenge of TMZ resistance.

Collectively, these studies suggest that KDM4C plays a central role in conferring resistance to TMZ in glioblastoma through the modulation of chromatin structure and gene expression. Its upregulation leads to the activation of survival pathways and cell-cycle progression, while its inhibition resensitizes cells to TMZ. Moreover, KDM4C does not act in isolation but is part of a broader epigenetic network involving other KDMs, further complicating the resistance mechanisms. These findings highlight KDM4C as a potential therapeutic target in overcoming resistance to TMZ and other chemotherapies in GBM. However, further studies are required to explore the exact mechanisms and to determine the clinical applicability of targeting KDM4C in therapy-resistant glioblastoma.

DISCUSSION

The findings of this systematic review reveal that KDM4C plays a significant role in mediating resistance to Temozolomide (TMZ) in glioblastoma, an aggressive and difficult-to-treat cancer. KDM4C, a histone demethylase, is implicated in the regulation of epigenetic modifications that enable glioblastoma cells to survive and proliferate in response to chemotherapy. This resistance mechanism is largely driven by KDM4C's ability to modulate chromatin structure and gene expression, which in turn supports cell survival pathways and cell-cycle progression [14].

Overexpression of KDM4C in glioblastoma cells has been shown to upregulate genes involved in cell survival and proliferation, such as E2F6, which contributes to resistance by promoting the cell-cycle and inhibiting apoptosis. In contrast, reducing KDM4C expression has been found to restore sensitivity to TMZ, highlighting the importance of KDM4C as a key mediator in resistance. Additionally, KDM4C's ability to regulate various cellular pathways related to tumorigenesis suggests that it contributes not only to resistance but also to the overall survival and aggressiveness of glioblastoma cells [15].

The role of KDM4C is further underscored by its interaction with other members of the KDM family. It appears that the KDM family as a whole is involved in the epigenetic regulation of TMZ resistance, with multiple KDMs contributing to chromatin remodeling and gene expression changes that promote survival under chemotherapy stress. This suggests that KDM4C does not act in isolation, but as part of a broader epigenetic network that enables glioblastoma cells to adapt to therapeutic pressures. The use of KDM inhibitors, which target multiple members of the KDM family, has been shown to enhance the sensitivity of TMZ-resistant glioblastoma cells, further supporting the idea that KDMs are viable targets for overcoming resistance [16].

Another key aspect revealed by the reviewed studies is the concept of adaptive resistance, where glioblastoma cells undergo epigenetic reprogramming in response to TMZ treatment. This ability to adapt makes it challenging to treat the disease effectively, as the tumor cells can evolve to escape the effects of chemotherapy. The findings suggest that KDM4C, along with other KDMs, is central to this adaptive process, providing cancer cells with the plasticity needed to survive under changing conditions [17].

CONCLUSION

In conclusion, KDM4C is a crucial player in the development of TMZ resistance in glioblastoma. Targeting KDM4C and other

KDMs could offer a promising therapeutic strategy to resensitize tumors to chemotherapy and improve treatment outcomes. However, further research is needed to better understand the precise mechanisms by which KDM4C and other epigenetic regulators contribute to resistance, and to evaluate the potential of KDM inhibitors in clinical settings.

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