Role of non-coding RNAs in O^6-methylguanine-DNA methyltransferase-positive glioblastoma (Review)

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Abstract. Glioblastoma (GBM) is the most aggressive primary tumor of the central nervous system. The standard treatment consists of maximal surgical resection followed by concurrent radiotherapy and temozolomide (TMZ) chemoradiotherapy; however, the frequent emergence of TMZ resistance remains a major determinant of poor prognosis. The expression of O^6-methylguanine-DNA methyltransferase (MGMT) represents a central mechanism underlying resistance to TMZ chemotherapy. Although MGMT expression is primarily regulated by the methylation status of its promoter, it is also influenced by additional regulatory mechanisms. The present review therefore aims to systematically summarize the current understanding of how non-coding RNAs (ncRNAs), as key regulators, govern MGMT expression and contribute to this complex regulatory network. Specifically, it focuses on the roles of microRNAs (miRNAs/miRs), long ncRNAs (lncRNAs) and circular RNAs (circRNAs) in regulating MGMT expression. miRNAs regulate MGMT by directly binding to its mRNA or indirectly modulating upstream transcription factors. lncRNAs primarily act indirectly through competing endogenous RNA (ceRNA) networks, epigenetic remodeling or modulation of signaling pathways. circRNAs, often functioning as stable ceRNA molecules, provide an additional layer of complexity and stability in this regulatory network. Notably, interactions among different ncRNAs may be synergistic or antagonistic. Examples include the cooperative repression of MGMT by miR-181d and miR-409-3p, and the sequestration of miR-182-5p by lncRNA urothelial carcinoma-associated 1. Overall, the findings suggested that MGMT expression is governed by a dynamic, multi-layered regulatory system. Understanding this network has notable implications for elucidating GBM chemoresistance and identifying novel therapeutic strategies to reverse drug resistance.

Contents

1. Introduction

Glioblastoma (GBM) is the most aggressive and among the most common primary malignant brain tumors in adults (1). The incidence of GBM increases with age from 0.15 per 100,000 in children compared to 15.3 per 100,000 in aged of 75-84 years. Patients diagnosed with GBM typically die within a few months if left untreated (2,3). Despite extensive research over the past decades, GBM continues to exhibit one of the poorest prognoses among malignancies (4,5). The standard first-line treatment involves maximal surgical resection followed by concurrent radiotherapy and temozolomide (TMZ) chemotherapy. TMZ, the primary chemotherapeutic agent for GBM, exerts its effect by inducing DNA alkylation, predominantly at the N^7 and O^6 positions of guanine and the N^3 position of adenine or guanine. Among TMZ-induced DNA lesions, N^7-methylguanine accounts for 80-85%, N^3-methyladenine or -methylguanine constitutes 8-20%, and O^6-methylguanine (O^6-MeG) represents ~8%. The principal cytotoxic effect of TMZ therapy arises from DNA mismatches induced by O^6-MeG, leading to stalled DNA replication and the generation of DNA double-strand breaks (6). This severe DNA damage activates the ataxia-telangiectasia mutated (ATM)/checkpoint kinase 2 signaling pathway, resulting in p53-mediated G_2/M cell cycle arrest (7) and ultimately triggering tumor cell apoptosis and necrosis (8).

O^6-MeG-DNA methyltransferase (MGMT) is a DNA repair enzyme that counteracts alkylation-induced damage by transferring the methyl group from the O^6 position of guanine to a cysteine residue within its active site, thereby

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restoring the damaged guanine nucleotide (nt) (9). Elevated mRNA and protein expression levels of MGMT are strongly associated with tumor resistance to TMZ chemotherapy (10). MGMT gene expression is regulated by multiple epigenetic mechanisms, including promoter methylation and modulation by non-coding RNAs (ncRNAs). Promoter methylation is a principal mechanism in suppressing MGMT transcriptional activity (11,12), thereby reducing protein levels. Clinically, the MGMT+ status typically indicates an unmethylated promoter, active gene expression and high protein levels. By contrast, the MGMT- status corresponds to a methylated promoter, suppressed gene expression and minimal protein production. Patients with MGMT- status exhibit markedly prolonged overall survival following TMZ-based chemoradiotherapy (13). By contrast, a subset of patients with MGMT+ status exhibits poor responsiveness to TMZ (14,15). Since their tumors presumably retain functional MGMT protein, this treatment failure cannot be solely attributed to the canonical MGMT-mediated repair pathway, indicating that mechanisms beyond MGMT status contribute to TMZ resistance. Therefore, developing strategies to modulate MGMT expression is key to overcoming chemoresistance in GBM in the future.

ncRNAs have been recognized as pivotal regulators of cellular processes and oncogenesis. These functional RNA molecules, which do not encode proteins, primarily comprise microRNAs (miRNAs/miR), long ncRNAs (lncRNAs) and circular RNAs (circRNAs) (16-18). Among these molecules, miRNAs and lncRNAs serve as key regulators within the ncRNA transcriptome, modulating gene expression at transcriptional and post-transcriptional levels (19), and thus, exerting key influences on tumorigenesis, cancer progression and acquired drug resistance (20-23). In GBM, increasing attention has been directed toward their regulatory effects on MGMT expression (24-28). miRNAs can bind to MGMT mRNA, promote its degradation and induce MGMT silencing (29,30). By contrast, lncRNAs may function as competing endogenous RNAs (ceRNAs) by sequestering miRNAs, thereby reducing their regulatory impact on target mRNAs and influencing MGMT expression (31).

Advancements in next-generation high-throughput sequencing, gene silencing and gene editing technologies have provided notable evidence that, in addition to miRNAs and lncRNAs, circRNAs possess regulatory functions and are associated with various diseases, including malignancies such as GBM and lung cancer, as well as cardiovascular conditions like atherosclerosis (32-35). circRNAs can interact with protein complexes, RNA molecules and DNA to regulate a broad spectrum of physiological and pathological processes (36-38). Based on these developments, the present review systematically summarizes the molecular mechanisms through which distinct classes of ncRNAs regulate MGMT gene expression (Table I; Fig. 1). The primary aim of this synthesis is to elucidate the complex regulatory network governing MGMT expression, thereby identifying novel ncRNA-based therapeutic targets and strategies to overcome TMZ resistance in GBM.

2. miRNAs

miRNAs are small ncRNA molecules 19-22 nts in length that regulate gene expression either by sequence-specific inhibition of mRNA translation or by promoting mRNA degradation (29,39). As central regulators of cellular homeostasis, miRNAs govern key cellular processes, including proliferation, migration, cell cycle progression and apoptosis, thereby exerting a notable influence on overall cellular function (40,41). Dysregulated miRNA expression is closely associated with the pathogenesis of various clinical disorders, including cancer, neurodegenerative diseases and cardiovascular conditions (42-45). In GBM, aberrant miRNA expression serves as a key predictive biomarker for tumorigenesis and disease progression (46). These miRNAs act as oncogenes or tumor suppressors and directly modulate key pathways involved in tumor suppression (29). For instance, in GBM, dysregulated miRNAs such as miR-21, miR-10b and miR-7 have been shown to modulate tumor proliferation, invasion, and apoptosis by targeting key factors including PTEN, Rho and EGFR (29).

miRNAs in GBM. Extensive studies have established that dysregulated miRNA expression is closely associated with tumorigenesis and progression across various cancer types, including lung cancer, breast cancer, colorectal cancer and gastric cancer, and is closely associated with tumor initiation and progression (47-50). In GBM, aberrant miRNA expression constitutes a prominent molecular feature. Functionally, miRNAs act as oncogenes or tumor suppressors in GBM, modulating angiogenesis, regulating metabolic pathways and associated enzymatic activities, and influencing the differentiation of glioma stem cells (GSCs) (51). Previous studies have indicated that miRNAs regulate ~3% of glioma-related genes and 30% of protein-coding genes, with individual miRNAs capable of modulating the expression levels of up to 100 distinct mRNAs implicated in GBM (41), highlighting their pivotal role in GBM pathogenesis (51). Comprehensive analysis of miRNA expression patterns may facilitate the identification of numerous potential therapeutic agents, establishing miRNAs as notable candidates for GBM treatment.

miRNAs regulating MGMT expression. The methylation status of the MGMT promoter is a key determinant of therapeutic efficacy in GBM (52). Beyond promoter methylation, MGMT protein expression is also regulated through additional mechanisms, including post-transcriptional control. Among these, miRNA-mediated regulation via the mRNA 3'-untranslated region (3'-UTR) serves a key role (53). Kreth *et al* (53) identified two distinct MGMT transcript variants in GBM with differing 3'-UTR lengths (53). In normal brain tissue, only a shorter transcript of ~440 bp is expressed, containing a canonical poly(A) signal and a 105 nt 3'-UTR. By contrast, in GBM a longer transcript of ~850 bp is specifically expressed, which harbors an alternative poly(A) signal spanning 522 nt. In the study by Kreth *et al* (53), the analysis of patient samples revealed a notable negative association between MGMT expression and 3'-UTR length, with normal-length 3'-UTRs associated with reduced MGMT expression. This differential expression is closely associated with the sequence architecture of the 3'-UTR. Bioinformatics analyses indicated that the longer 3'-UTR contained a markedly higher density of potential miRNA-binding sites, rendering it more susceptible to miRNA-mediated post-transcriptional degradation. These

Table I. Mechanisms of non-coding RNAs in regulating MGMT expression.

First author/s, year	RNA	Mechanism in regulating MGMT	Effect on TMZ chemotherapy	(Refs.)
Kirstein *et al*, 2020; Kreth *et al*, 2013	miRNA	Direct targeting of the 3'-UTR of MGMT; regulating the expression of MGMT by modulating relevant pathways	Enhance the chemotherapeutic sensitivity to TMZ	(29,53)
Nadhan *et al*, 2024; Shahzad *et al*, 2021; Stackhouse *et al*, 2020	lncRNA	As a specific 'sponge' of miRNA, it weakens the regulatory effect of miRNA on mRNA; regulating the expression of MGMT through epigenetic mechanisms	Promote chemo-resistance to TMZ	(94,105,106)
Wu *et al*, 2024; Geng *et al*, 2022	circRNA	Functioning as a miRNA sponge, it modulates downstream MGMT expression via the constructed circRNA-miRNA-mRNA regulatory network	Promote chemo-resistance to TMZ	(153,154)

miRNA, microRNA; lncRNA, long non-coding RNA; circRNA, circular RNA; MGMT, O^6-methylguanine-DNA methyltransferase; TMZ, temozolomide; 3'-UTR, 3'-untranslated region.

findings provided a mechanistic perspective in understanding the heterogeneity of MGMT expression in GBM. The following section systematically reviews specific miRNAs that directly or indirectly target MGMT expression in GBM (Table II).

miR-142-3p. In GBM cell lines, Lee *et al* (54) demonstrated a marked inverse association between MGMT expression and miR-142-3p levels. Elevated MGMT expression was associated with low miR-142-3p levels, whereas low MGMT expression was associated with high miR-142-3p levels (54). Overexpression of miR-142-3p did not alter MGMT mRNA levels but markedly decreased protein expression, suggesting a direct regulatory interaction with the MGMT 3'-UTR. This mechanism was subsequently confirmed using a luciferase reporter assay (54). In chemotherapy sensitivity assays, cells overexpressing miR-142-3p exhibited markedly enhanced sensitivity to alkylating agents, including TMZ and carmustine (BCNU), with the most pronounced effect observed in the BCNU-treated group (54). These findings underscored the key role of miR-142-3p in regulating MGMT expression and enhancing chemosensitivity, positioning it as a potential biomarker and therapeutic target in GBM.

Additionally, a previous study has demonstrated that the pro-oncogenic cytokine interleukin-6 suppressed miR-142-3p expression, further supporting its role as a tumor suppressor (55). In summary, miR-142-3p enhances the sensitivity of GBM cells to alkylating chemotherapy by directly targeting the MGMT 3'-UTR and inhibiting its protein translation. This mechanism establishes a clear target for the development of personalized therapeutic strategies in GBM.

miR-181d. Zhang *et al* (56) established a miRNA-mediated regulatory mechanism for MGMT and demonstrated that miR-181d binds directly to the long 3'-UTR of MGMT, thereby suppressing its expression at the post-transcriptional level (53,56). *In vitro*, transfection of miR-181d mimics markedly reduced both MGMT mRNA and protein levels, and sensitized GBM cells to TMZ treatment (56). Clinical analyses revealed a notable association between elevated miR-181d expression and improved patient survival (56), indicating its potential as a favorable prognostic indicator. Furthermore, miR-181d expression is increased following TMZ monotherapy, radiotherapy or combination therapy, with the most pronounced elevation observed following combination treatment (57). These findings suggest that miR-181d may serve as a predictive biomarker in evaluating the efficacy of both chemotherapy and radiotherapy.

Subsequent studies have confirmed the direct regulatory effect of miR-181d on MGMT and elucidated its central role within a coordinated regulatory network. This regulatory role was established through systematic genome-wide microarray screening and analysis of clinical datasets. Notably, miR-181d can cooperate with other miRNAs, including miR-409-3p (58), miR-603 (59), miR-648 (60) and miR-661 (53), forming a synergistic regulatory network that modulates MGMT expression. Khalil *et al* (58) demonstrated a pronounced synergistic negative regulatory pattern between miR-181d and miR-409-3p in $MGMT^+$ GBM. Functional assays revealed that overexpression of either miRNA mimic in T98G cells reduced MGMT expression, whereas their combined application produced a marked synergistic enhancement. Furthermore, analysis of two major independent datasets, The Cancer Genome Atlas and the Chinese Glioma Genome Atlas, provided key insights: miR-181d was the only miRNA to exhibit a notable inverse association with MGMT mRNA levels; however, combination with miR-409-3p markedly improved the prediction of MGMT expression. These findings indicated that, in the complex *in vivo* environment, MGMT expression is governed by a precise regulatory network centered on miR-181d with cooperative contributions from additional miRNAs (58).

In summary, miR-181d functions as a tumor-suppressive miRNA and directly suppresses MGMT by targeting its mRNA, thereby reducing transcript and protein levels. Acting as a central hub within a cooperative regulatory network, miR-181d integrates signals from other miRNAs to precisely modulate MGMT expression. This coordinated regulation

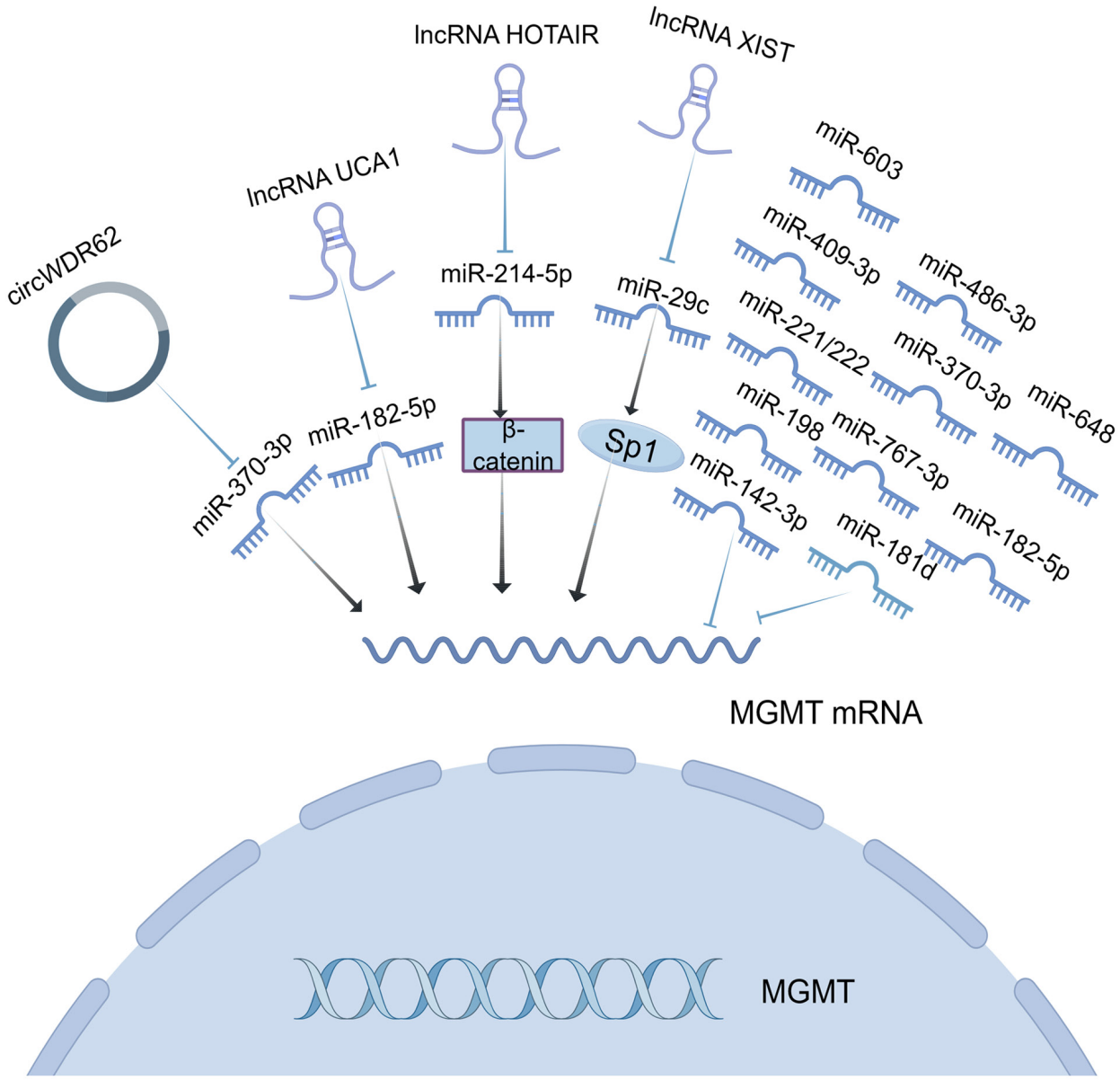

Figure 1. Core competing endogenous RNA network of miRNA, lncRNA and circRNA in regulating MGMT expression. Arrows denote promotion or positive regulation, while blunt-ended arrows represent inhibition or negative regulation. miRNA/miR, microRNA; lncRNA, long non-coding RNA; circRNA/circ, circular RNA; MGMT, O^6-methylguanine-DNAmethyltransferase; Sp1, specificity protein 1; HOTAIR, HOX transcript antisense RNA; UCA1, urothelial carcinoma-associated 1; WDR62, WD repeat domain 62.

enhances the chemosensitivity of GBM cells to TMZ. These findings enhance the understanding of the regulatory network governing MGMT, and establish miR-181d and its associated network as promising biomarkers with therapeutic potential in GBM.

miR-182-5p. Cheng *et al* (61) demonstrated that miR-182-5p was downregulated in high-grade GBM tissues and inversely associated with MGMT protein levels. Mechanistic investigation revealed that miR-182-5p directly binds to the 3'-UTR of MGMT mRNA, inhibiting MGMT protein expression via a post-transcriptional mechanism without altering mRNA levels. The specificity of this interaction was confirmed using a dual-luciferase reporter assay. Functional experiments indicated that transfection of miR-182-5p mimics markedly enhanced the chemosensitivity of GBM cells to TMZ, as evidenced by reduced cell viability and increased apoptosis. This effect was closely associated with MGMT protein downregulation and a concomitant increase in DNA damage markers, such as γ-H2A histone family member X and ATM (61). Beyond MGMT, miR-182-5p targets additional genes, such as neuropilin-1, and through this targeting, it further inhibits GBM-cell proliferation and migration (62).

In summary, miR-182-5p exhibits multifaceted tumor-suppressive functions in GBM. The findings highlighted

Table II. miRNAs involved in the regulation of MGMT in glioblastoma.

First author/s, year	miRNA	Expression	Regulation	Type	Molecular function	(Refs.)
Lee *et al*, 2018	miR-142-3p	Downregulated	Directly targets the 3'-UTR of MGMT	Tumor suppressor	MGMT protein Inhibits expression; enhances TMZ sensitivity	(54)
Zhang *et al*, 2012; Khalil *et al*, 2016	miR-181d	Downregulated	Directly targets the 3'-UTR of MGMT	Tumor suppressor	Reduces MGMT mRNA and protein expression; enhances TMZ sensitivity	(56,58)
Cheng *et al*, 2022	miR-182-5p	Downregulated	Directly targets the 3'-UTR of MGMT	Tumor suppressor	Inhibits MGMT protein expression; enhances TMZ sensitivity	(61)
Nie *et al*, 2017	miR-198	Downregulated	Directly targets the 3'-UTR of MGMT	Tumor suppressor	Inhibits MGMT protein expression; enhances TMZ sensitivity	(64)
Quinta-valle *et al*, 2013	miR-221/222	Upregulated	Directly targets the 3'-UTR of MGMT	Oncogenic	Reduces MGMT mRNA and protein expression; enhances TMZ sensitivity	(65)
Zhou *et al*, 2022	miR-214-5p	Downregulated	Targets β-catenin to indirectly regulate MGMT expression	Tumor suppressor	Inhibits MGMT protein expression; enhances TMZ sensitivity	(73)
Xiao *et al*, 2016	miR-29c	Downregulated	Targets Sp1 to indirectly regulate MGMT expression	Tumor suppressor	Inhibits MGMT protein expression; enhances TMZ sensitivity	(76)
Gao *et al*, 2016; Geng *et al*, 2022	miR-370-3p	Downregulated	Directly targets the 3'-UTR of MGMT	Tumor suppressor	Reduces MGMT mRNA and protein expression; enhances TMZ sensitivity	(81,154)
Khalil *et al*, 2016	miR-409-3p	Upregulated	Directly targets the 3'-UTR of MGMT	Oncogenic	Reduces MGMT mRNA and protein expression; enhances TMZ sensitivity	(58)
Wu *et al*, 2020	miR-486-3p	Downregulated	Directly targets the 3'-UTR of MGMT	Tumor suppressor	Inhibits MGMT protein expression; enhances TMZ sensitivity	(90)
Kush-waha *et al*, 2014	miR-603	Upregulated	Directly targets the 3'-UTR of MGMT	Tumor suppressor and oncogenic	Reduces MGMT mRNA and protein expression; enhances TMZ sensitivity	(59)
Kreth *et al*, 2013	miR-648	Upregulated	Directly targets the 3'-UTR of MGMT	Tumor suppressor	Inhibits MGMT protein expression; enhances TMZ sensitivity	(53)
Kreth *et al*, 2013	miR-767-3p	Upregulated	Directly targets the 3'-UTR of MGMT	Tumor suppressor	Degradation of MGMT mRNA; enhances TMZ sensitivity	(53)

miRNA/miR, microRNA; 3'-UTR, 3'-untranslated region; MGMT, O^6-methylguanine-DNA methyltransferase; TMZ, temozolomide; Sp1, specificity protein 1.

its potential as a therapeutic target, providing novel avenues for GBM treatment. Future research should investigate its translational potential and assess its efficacy in combination with existing therapies to potentially improve clinical outcomes and prognosis for patients with GBM in the future.

miR-198. Previous research has indicated that miR-198 is expressed at low levels in GBM tissue, and inversely associated with tumor malignancy and progression (63). Analysis of clinical samples further revealed that GBM tissues with high MGMT expression typically exhibit low miR-198 levels. Reduced miR-198 expression was strongly associated with poor patient prognosis. Overexpression of miR-198 markedly enhanced the chemosensitivity of GBM cells to TMZ both *in vitro* and *in vivo*, highlighting its pivotal role in regulating the chemotherapeutic response. Mechanistic experiments using a luciferase reporter assay confirmed that miR-198 directly binds to the 3'-UTR of MGMT mRNA, thereby inhibiting MGMT protein expression. Rescue experiments demonstrated that MGMT overexpression effectively reversed the TMZ-sensitizing effect mediated by miR-198, establishing a complete and functional 'miR-198/MGMT/TMZ sensitivity' regulatory axis (64).

In summary, miR-198 acts as a tumor-suppressive miRNA, enhancing TMZ chemosensitivity by directly targeting MGMT mRNA and inhibiting its translation. This finding elucidated a key molecular mechanism underlying GBM chemoresistance and provides a theoretical foundation for the development of precision therapeutic strategies targeting the miR-198/MGMT axis.

miR-221/222. In GBM and hepatocellular carcinoma (HCC) (65,66), miR-221/222 exerts a complex, dual-functional regulatory effect on MGMT. In GBM, Quintavalle *et al* (65) demonstrated that miR-221/222 directly targets the 3'-UTR of MGMT mRNA, suppressing its protein expression at the post-transcriptional level, a finding confirmed by luciferase reporter assays. Furthermore, investigations across multiple GBM and melanoma cell lines revealed that miR-221/222 overexpression markedly downregulated MGMT mRNA and protein levels. Functionally, miR-221/222 overexpression enhanced GBM cell sensitivity to TMZ and promoted apoptosis. However, the resulting impairment of MGMT-mediated DNA repair led to the accumulation of DNA damage markers, which may foster genomic instability and contribute to tumor progression (65).

This regulation is neither unidirectional nor devoid of potential adverse effects. In hepatocellular carcinoma, Chen *et al* (66) confirmed that miR-221-3p, the primary functional isoform of miR-221, directly targets MGMT. Inhibition of MGMT expression enhanced the proliferative, migratory, invasive and clonogenic capacities of HCC cells, while suppressing apoptosis. The study validated the binding site using bioinformatics prediction and dual-luciferase reporter assays, and demonstrated, via rescue experiments, that MGMT overexpression reversed the oncogenic effects of miR-221-3p. These findings established the pivotal role of the miR-221/MGMT axis in HCC pathogenesis (66).

Although miR-221/222 can enhance tumor sensitivity to alkylating agents such as TMZ by downregulating MGMT, it is highly expressed in various cancer types, including GBM, HCC, colorectal cancer and cervical cancer, and exhibits well-established oncogenic properties (65-68). For instance, miR-221/222 promotes malignant progression by targeting multiple tumor suppressors, including PTEN, p27 and tissue inhibitor of metalloproteinase 3 (69,70). This duality between enhancing chemosensitivity and driving tumor progression indicates a potential 'double-edged sword' effect of miR-221/222 in clinical applications. While its transient expression may improve the initial chemotherapy response rate, sustained high expression could ultimately result in poor prognosis by impairing DNA repair mechanisms and promoting tumor invasiveness.

In summary, miR-221/222 is a well-characterized oncomiR, frequently upregulated across various cancer types and strongly associated with poor patient prognosis. In GBM, miR-221/222 enhances tumor cell sensitivity to TMZ chemotherapy by directly targeting MGMT mRNA and suppressing its protein expression. While this finding provides a novel approach to overcoming TMZ resistance, it also underscores the dual role of miR-221/222. Future research should systematically elucidate the dynamic roles of miR-221/222 across distinct pathological stages and molecular contexts, and carefully assess its suitability as a therapeutic target, including delivery methods and potential risks in combination strategies.

miR-214-5p. miR-214-5p functions as a tumor-suppressive miRNA that exerts notable effects in multiple malignancies, including cervical and prostate cancers, by inhibiting key oncogenic phenotypes, including cell proliferation, migration and invasion (71,72). In GBM, a key regulatory mechanism involving miR-214-5p was revealed: Its overexpression markedly downregulates β-catenin and MGMT expression, whereas miR-214-5p inhibition produces the opposite effect. These findings underscore the pivotal regulatory role of miR-214-5p in GBM (73).

Cyanidin-3-O-glucoside (C3G), a natural flavonoid widely distributed in the plant kingdom, exhibits notable antitumor potential. Previous studies have indicated that C3G enhanced the chemosensitivity of GBM cells to TMZ and markedly upregulated miR-214-5p expression (73). Zhou *et al* (73) further demonstrated that C3G upregulated miR-214-5p, which directly binds to the 3'-UTR of catenin β-1, the gene encoding β-catenin, thereby suppressing β-catenin protein expression. As a key transcriptional co-activator in the Wnt signaling pathway, β-catenin directly initiates MGMT transcription. Therefore, miR-214-5p indirectly attenuates MGMT transcription by regulating β-catenin, thereby decreasing protein expression. Functional experiments further revealed that C3G and miR-214-5p enhanced TMZ-induced apoptosis in GBM cells, an effect reversed by a miR-214-5p inhibitor, indicating that the chemosensitizing action of C3G was highly dependent on miR-214-5p (73).

In summary, miR-214-5p functions as a tumor-suppressive miRNA in GBM, enhancing TMZ chemosensitivity by targeting the β-catenin/MGMT signaling axis. The natural small-molecule compound C3G, which activates this pathway, exhibits potential therapeutic value in reversing TMZ resistance in GBM, potentially providing a theoretical basis for the development of adjuvant anti-glioma agents.

miR-29c. miR-29 is frequently downregulated in most solid tumors, including breast cancer, lung cancer and glioblastoma, where it exerts notable tumor-suppressive activity

and is associated with a favorable patient prognosis (74-76). Functional heterogeneity exists within the miR-29 family. Specifically, miR-29c enhances TMZ chemosensitivity in GBM via dual mechanisms. miR-29c indirectly suppresses MGMT transcriptional activity by targeting the transcription factor specificity protein 1 (Sp1) (76,77) and restores the expression of multiple tumor suppressor genes via demethylation (78), collectively enhancing chemosensitivity. By contrast, miR-29b exhibits oncogenic properties in certain contexts and may promote tumorigenesis by repressing tumor suppressor genes, such as PTEN (79). This functional divergence underscores the complexity of miRNA regulatory networks, in which the net biological effect is determined by the relative influence and interactions among their targets within a particular cellular context. In GBM models of TMZ resistance, the tumor-suppressive function of miR-29c, mediated through the Sp1/MGMT axis, predominates over its potential oncogenic effects observed in other biological settings (79).

Mechanistically, Xiao *et al* (76) systematically delineated the regulatory pathway of miR-29c in GBM. This miRNA does not directly target MGMT mRNA; instead, it binds specifically to the 3'-UTR of the transcription factor Sp1, thereby inhibiting Sp1 protein translation. This suppression reduces Sp1-mediated transcriptional activation of the MGMT promoter, ultimately leading to decreased MGMT protein expression (76). Sp1, a ubiquitously expressed zinc-finger transcription factor present in virtually all mammalian cells and tissues (80), serves a key role in sustaining MGMT transcription. Therefore, the identification of the 'miR-29c/Sp1/MGMT' axis not only enhances the current understanding of chemoresistance mechanisms in GBM but also potentially provides a foundation for the development of novel therapeutic strategies.

In summary, miR-29c acts as a tumor-suppressive miRNA in GBM, enhancing TMZ sensitivity by indirectly regulating MGMT expression via Sp1 targeting. This mechanism provides a novel perspective on chemoresistance in GBM and establishes a strong theoretical basis for the development of miRNA-based adjuvant therapeutic strategies.

miR-370-3p. Gao *et al* (81) reported that miR-370-3p possesses potent tumor-suppressive properties in GBM. miR-370-3p is markedly downregulated in low-grade (WHO grade II) and high-grade (WHO grade IV) gliomas, as well as in GBM cell lines (82). Overexpression of miR-370-3p markedly suppresses tumor cell viability, reduces proliferation, and decreases the proportion of cells in the S and G_2/M phases of the cell cycle (81).

A negative association has been identified between MGMT and miR-370-3p expression (81). Mechanistically, miR-370-3p directly targets the 3'-UTR of MGMT mRNA, thereby downregulating its protein expression. *In vitro*, miR-370-3p upregulation markedly reduced MGMT mRNA and protein levels, enhancing GBM cell sensitivity to TMZ and increasing cell mortality. This direct regulatory relationship was confirmed using a luciferase reporter assay, in which mutation of the MGMT 3'-UTR binding site abolished the effect of miR-370-3p, indicating sequence-specific action. *In vivo*, combined administration of TMZ and miR-370-3p inhibited subcutaneous xenograft tumor growth, and analysis of the resected tumor tissues revealed notable downregulation of MGMT expression, further supporting the effectiveness of this regulatory pathway (83). Nadaradjane *et al* (83) proposed monitoring miR-370-3p levels during standard treatment, noting that a single measurement of its expression was not associated with overall survival. Notably, patients exhibiting sustained high miR-370-3p expression prior to disease recurrence exhibited prolonged survival (83).

In summary, miR-370-3p functions as a tumor-suppressive miRNA in GBM by downregulating MGMT expression at the mRNA and protein levels, thereby enhancing tumor sensitivity to TMZ chemotherapy. Although miR-370-3p is not a key determinant of overall patient survival, it represents a potential strategy in increasing TMZ sensitivity in patients with $MGMT^+$ GBM.

miR-409-3p. Khalil *et al* (58) reported that miR-409-3p expression was upregulated 4-5-fold in GBM samples compared with healthy brain tissues, and was negatively associated with MGMT expression. Specifically, miR-409-3p levels were elevated in samples with low MGMT expression but reduced in those with high MGMT expression. Experimental validation demonstrated that transfection of miR-409-3p mimics into MGMT-overexpressing GBM cells markedly downregulated MGMT mRNA and protein levels, enhancing cellular sensitivity to TMZ. These results indicated that miR-409-3p suppressed MGMT expression by promoting mRNA degradation and inhibiting translation (58). Notably, co-transfection of miR-409-3p mimics with the key regulator miR-181d produced a synergistic effect, suggesting that miR-409-3p functions as a co-regulatory factor alongside miR-181d, jointly modulating MGMT expression and influencing GBM response to alkylating agent chemotherapy (58).

In summary, miR-409-3p upregulation in human GBM samples suppresses MGMT transcription and protein expression. This property indicates the potential of miR-409-3p as a therapeutic strategy to enhance the responsiveness of patients with $MGMT^+$ GBM to alkylating chemotherapy agents; however, the upstream mechanisms driving miR-409-3p upregulation in GBM remain to be elucidated. Future studies should employ integrated approaches, including chromatin immunoprecipitation, protein-RNA interaction assays, and *in vitro* and *in vivo* rescue experiments, to comprehensively elucidate its underlying molecular mechanisms. These investigations could potentially establish a robust foundation for subsequent clinical development.

miR-486-3p. miR-486 is a key tumor-suppressive miRNA that is frequently downregulated in numerous malignant tumors (84,85). Dong *et al* (86) reported that upregulation of its family member miR-486-3p markedly enhanced the sensitivity of neuronal tumors to chemotherapeutic agents. Allicin (diallyl trisulfide), the principal bioactive constituent of garlic, is widely utilized as a dietary supplement and has garnered increasing research attention for its notable antitumor activity (87). Evidence indicated that allicin exerts antitumor effects by inducing tumor cell apoptosis and inhibiting proliferation, among other mechanisms (88). Allicin has exhibited promising therapeutic potential in multiple malignancies, including GBM (89).

In GBM cells, allicin treatment markedly increases miR-486-3p expression, as reported by Wu *et al* (90). Mechanistic analyses indicated that miR-486-3p directly binds to the 3'-UTR of MGMT mRNA, thereby inhibiting

its translation, and thus, reducing MGMT protein levels. Functionally, miR-486-3p overexpression markedly augmented TMZ-induced DNA damage and apoptosis and specifically reversed chemoresistance in TMZ-resistant cell lines. Notably, this effect was absent in MGMT- GBM cell lines. Furthermore, rescue assays confirmed that MGMT overexpression effectively reversed the TMZ-sensitizing activity mediated by miR-486-3p, thereby validating the proposed regulatory axis. *In vivo*, the combined administration of allicin and TMZ markedly prolonged the survival of treated mice, with a more notable effect observed in the miR-486-3p overexpression group (90).

In summary, allicin enhances GBM sensitivity to TMZ chemotherapy by upregulating miR-486-3p, which subsequently inhibits MGMT protein translation through targeted repression. This mechanism provides a molecular rationale for the combined therapeutic strategy of 'allicin + TMZ' and identifies miR-486-3p as a potential target in improving GBM treatment efficacy.

miR-603. Guo *et al* (91) reported that miR-603 expression was upregulated in GBM tissues. The study further demonstrated that miR-603 promoted malignant tumor progression by enhancing tumor cell proliferation and accelerating cell cycle progression. Mechanistic investigations revealed that miR-603 directly targets the tumor suppressor genes Wnt inhibitory factor 1 and catenin β-interacting protein 1, thereby activating the Wnt/β-catenin signaling pathway, which subsequently augments the proliferative and migratory capacities of tumor cells (91).

However, genome-wide screening and clinical data analysis conducted by Kushwaha *et al* (59) revealed a more complex, dual regulatory role for miR-603 in GBM. In addition to its oncogenic functions, miR-603 mediates post-transcriptional repression of MGMT by binding specifically to the 3'-UTR of its mRNA (59). *In vitro* experiments confirmed that miR-603 overexpression markedly decreased MGMT mRNA and protein levels and enhanced GBM cell sensitivity to TMZ chemotherapy. This effect was further validated in animal models (59). Notably, the study demonstrated a notable synergistic interaction between miR-603 and miR-181d in suppressing MGMT expression, wherein their combined application produced a markedly stronger inhibitory effect compared with that of either miRNA alone (59).

Based on these findings, miR-603 represents a therapeutic target with a dual regulatory mechanism. miR-603 enhances chemosensitivity by suppressing MGMT, while promoting malignant tumor progression through the Wnt/β-catenin signaling pathway. Abate *et al* (92) developed an innovative self-assembling nanoparticle (SANP)-based co-delivery system capable of simultaneously loading miR-603 and miR-221 to achieve efficient MGMT suppression. This delivery system markedly improved miRNA transport across the blood-brain barrier. In an orthotopic GBM model, it effectively reversed TMZ resistance, providing a novel nano-therapeutic strategy to overcome chemoresistance in GBM (92).

In summary, the SANP platform exhibits therapeutic potential for brain diseases by enabling efficient miRNA delivery. Notably, the present review underscores the role of miRNAs in overcoming chemoresistance in cancer therapy, highlighting the prospect of developing more effective combination antitumor therapies.

miR-648 and miR-767-3p. Kreth *et al* (53) identified a key regulatory mechanism for MGMT in GBM beyond promoter methylation: Post-transcriptional regulation mediated by miRNA targeting of an elongated 3'-UTR. The study emphasized the key roles of miR-648 and miR-767-3p in this regulation. Although both miRNAs target the long 3'-UTR isoform of MGMT, their mechanisms of action differ markedly.

Both miR-767-3p and miR-648 are upregulated in GBM tissue. Co-transfection of these miRNAs enhanced GBM chemosensitivity to TMZ (53). Mechanistic investigation revealed that miR-767-3p binds to the long 3'-UTR isoform of MGMT mRNA, inducing its degradation and thereby suppressing MGMT expression at the post-transcriptional level. By contrast, miR-648 predominantly inhibits MGMT protein expression at the translational stage without markedly reducing mRNA levels (53). However, Kushwaha *et al* (59) reported that the effect of miR-648 transfection on MGMT expression was inconsistent, reflecting its highly context-dependent nature, which may arise from variable ratios of long and short MGMT 3'-UTR isoforms across different cellular models. The specific isoform ratio directly influences the accessibility of the target site for miR-648 (59).

In summary, miR-767-3p suppresses MGMT expression via mRNA degradation, whereas miR-648 primarily exerts its effect through translational inhibition. Both miRNAs are upregulated in GBM and their co-transfection markedly enhances GBM sensitivity to TMZ. This synergistic mechanism establishes a novel molecular foundation and therapeutic approach in reversing TMZ resistance. Nonetheless, its clinical translational potential requires validation in larger sample cohorts and *in vivo* models.

3. lncRNAs

lncRNAs are a class of ncRNA molecules >200 nts in length. Initially regarded as transcriptional 'noise' lacking notable biological function (93), lncRNAs are now established as key regulatory factors, a recognition driven by advances in transcriptomics. In cancer biology, lncRNAs orchestrate core cellular processes in tumor cells through complex regulatory networks, including proliferation, apoptosis and metabolic reprogramming, as well as key pathological processes such as epithelial-mesenchymal transition, migration, invasion, metastasis, maintenance of cancer stem cell properties and chemoresistance (94). These diverse functions position lncRNAs as integral components of cancer gene regulatory networks, establishing them as key nodes that determine malignant phenotypes (95). lncRNAs are dysregulated across various tumor types, including breast, prostate, lung and colorectal cancers and glioblastoma. Their aberrant expression can exert either oncogenic or tumor-suppressive roles, driving tumor progression through remodeling of the cancer epigenome (94). Several studies have indicated that dysregulated lncRNAs serve a key regulatory role in the initiation and progression of GBM (96-99). Therefore, lncRNAs hold promise both as biomarkers for GBM diagnosis and prognosis and as novel therapeutic targets.

lncRNAs in GBM. Dysregulated lncRNA expression is closely associated with the initiation, progression and therapeutic resistance of GBM (100). Mechanistically, lncRNAs influence malignant behaviors in GBM through multiple strategies, including epigenetic modifications, ceRNA network regulation, signaling pathway intervention and tumor microenvironment remodeling. Functionally, lncRNAs serve a dual role in GBM, acting both as oncogenic promoters and tumor suppressors (101). Accordingly, lncRNAs exert essential regulatory effects on key pathological processes, including tumor proliferation, invasion, maintenance of stemness, metabolic reprogramming and immune evasion (102,103). These findings highlight the potential of lncRNAs as novel biomarkers for early diagnosis, prognostic evaluation and monitoring of therapeutic response in GBM. Furthermore, their roles in GBM tumorigenesis, progression and metastasis are influenced not only by altered expression levels but also by specific genomic localization (104). lncRNAs participate in complex regulatory networks of GBM by modulating the expression levels of proximal or distal coding genes through cis- or trans-regulatory mechanisms (104).

This mechanistic insight enhances the current understanding of the functional complexity of lncRNAs in GBM pathogenesis and establishes a theoretical basis for the development of novel therapeutic strategies targeting these molecules. In summary, lncRNAs serve a key role in GBM pathogenesis and progression.

lncRNAs regulating MGMT expression. In GBM, lncRNAs regulate MGMT expression through multiple molecular mechanisms, thereby influencing tumor sensitivity to TMZ chemotherapy. The principal mechanism involves lncRNAs functioning as ceRNAs, molecular sponges that sequester specific miRNAs, thereby relieving miRNA-mediated inhibition of MGMT and indirectly upregulating its expression. Alternatively, certain lncRNAs modulate MGMT expression by epigenetically regulating its promoter. These lncRNAs recruit chromatin-modifying complexes to the MGMT locus, altering histone modification patterns or DNA methylation, thereby promoting chromatin remodeling and directly regulating MGMT transcription (94,105). Furthermore, lncRNAs can indirectly modulate MGMT by regulating upstream signaling pathways, such as the c-Met/AKT and NF-κB signaling pathways. By interfering with these signaling networks, which serve as key regulatory hubs for MGMT expression, lncRNAs exert precise control over MGMT expression (106).

Collectively, these mechanisms demonstrate that lncRNAs influence MGMT expression through multi-layered regulatory networks, thereby contributing to chemoresistance in GBM. Targeting these relevant lncRNAs may provide a novel strategy to reverse TMZ resistance. The following section systematically reviews lncRNAs currently identified as regulators of MGMT expression (Table III).

lncRNA urothelial carcinoma-associated 1 (UCA1). lncRNA UCA1 is a primate-specific lncRNA transcribed in human trophoblasts, where it promotes the proliferation of trophoblast stem cells. The ectopic expression of lncRNA UCA1 impairs trophoblast syncytialization and is associated with activation of the interferon signaling pathway (107). As a well-established oncogene, UCA1 regulates key biological processes in various tumors, including cell proliferation, metastasis and apoptosis (108-110). In high-grade GBM tissues and cells, MGMT and lncRNA UCA1 are upregulated. Knockdown of lncRNA UCA1 or upregulation of miR-182-5p enhances GBM sensitivity to TMZ, characterized by reduced cell viability, increased apoptosis, decreased MGMT protein levels and accumulation of DNA damage markers. Notably, inhibition of miR-182-5p reverses the sensitizing effect of lncRNA UCA1 knockdown, restores MGMT expression and diminishes TMZ efficacy (61). Mechanistic studies have indicated that miR-182-5p directly targets both lncRNA UCA1 and the 3'-UTR of MGMT mRNA, thereby negatively regulating MGMT expression (61). Furthermore, miR-182-5p regulates C-X-C motif chemokine ligand 14 secretion, glycolysis and tumor invasion within glioma-associated stromal cells (111), and contributes to GBM proliferation and migration (112). Collectively, these findings establish the central role of the lncRNA UCA1/miR-182-5p/MGMT regulatory axis in mediating chemoresistance in GBM.

In summary, miR-182-5p expression is negatively associated with lncRNA UCA1 and MGMT levels, whereas lncRNA UCA1 and MGMT exhibit a notable positive association at the tissue level. Mechanistic studies have indicated that lncRNA UCA1 sequesters miR-182-5p, thereby alleviating its post-transcriptional suppression of MGMT (61). This process results in upregulation of MGMT protein, enhanced DNA repair capacity and promotion of TMZ resistance (61). These findings underscore the complex regulatory role of lncRNAs in tumor drug resistance and establish a theoretical foundation for the development of combination therapies targeting lncRNA UCA1 or miR-182-5p.

lncRNA HOX transcript antisense RNA (HOTAIR). HOTAIR is a well-characterized oncogenic lncRNA. lncRNA HOTAIR is minimally expressed in normal brain tissues but is upregulated in human GBM tissues and TMZ-resistant GBM cells (113). Exosome-derived lncRNA HOTAIR from serum has been reported to promote TMZ resistance in GBM cells, whereas knockdown of lncRNA HOTAIR enhances TMZ sensitivity both *in vivo* and *in vitro* (114). Clinical data further indicate that elevated lncRNA HOTAIR expression is associated with poor response to TMZ therapy in patients with GBM (115). Functional experiments demonstrated that modulating lncRNA HOTAIR expression directly impacted TMZ sensitivity in GBM cells: Knockdown enhanced cytotoxicity, while overexpression induced a chemoresistant phenotype. lncRNA HOTAIR is among the most notably upregulated lncRNAs in GBM cell lines compared with parental human GSCs, underscoring its key role in GBM malignancy and potential clinical relevance (116).

Mechanistic studies have demonstrated that lncRNA HOTAIR functions as a ceRNA by sequestering miR-214-3p, thereby relieving its post-transcriptional inhibition of β-catenin and activating the Wnt/β-catenin signaling pathway (115). This pathway is markedly enriched in patients with high lncRNA HOTAIR expression and is closely associated with poor prognosis and TMZ resistance in GBM. Upon activation, β-catenin translocates into the nucleus and acts as a transcriptional co-activator, directly binding to the lymphoid enhancer factor/T cell factor sites within the MGMT promoter to promote MGMT

Table III. lncRNAs involved in the regulation of MGMT in glioblastoma.

First author/s, year	lncRNA	Expression	Regulation	Type	Molecular function	(Refs.)
Cheng *et al*, 2022	UCA1	Upregulated	Targeting miR-182-5p can indirectly regulate MGMT expression	Oncogenic	Regulates MGMT expression; enhances TMZ resistance	(61)
Lan *et al*, 2024	HOTAIR	Upregulated	Activates the miR-214/β-catenin/MGMT pathway	Oncogenic	Regulates MGMT expression; enhances TMZ resistance	(115)
Du *et al*, 2017	XIST	Upregulated	Activates the miR-29c/Sp1/MGMT pathway	Oncogenic	Regulates MGMT expression; enhances TMZ resistance	(118)
Wu *et al*, 2019	TALC	Upregulated	Competitively binds to miR-20b-3p and activates the c-Met/STAT3/p300 signaling axis, promotes acetylation in the MGMT promoter region	Oncogenic	Regulates MGMT expression; enhances TMZ resistance	(122)
Xin *et al*, 2023	PRADX	Upregulated	PRADX and EZH2 binding promotes methylation in the MGMT promoter region	Oncogenic	Regulates MGMT expression; enhances TMZ resistance	(125)

miR, microRNA; MGMT, O^6-methylguanine-DNAmethyltransferase; TMZ, temozolomide; Sp1, specificity protein 1; PRADX, PRC2 and DDX5-associated lncRNA; EZH2, enhancer of zeste homolog 2; TALC, TMZ-associated lncRNA in glioblastoma recurrence; XIST, X-inactive specific transcript; HOTAIR, HOX transcript antisense RNA; UCA1, urothelial carcinoma-associated 1; lncRNA, long non-coding RNA.

transcription (115). This β-catenin-mediated transcriptional activation results in elevated MGMT protein levels and confers resistance to TMZ. Experimental validation confirmed this regulatory axis: Knockdown of lncRNA HOTAIR decreased β-catenin and MGMT levels, whereas treatment with the β-catenin agonist SKL2001 reversed the TMZ-sensitizing effect of lncRNA HOTAIR silencing (115,117). Furthermore, lncRNA HOTAIR expression is notably negatively associated with MGMT promoter methylation, with patients exhibiting promoter methylation typically displaying lower lncRNA HOTAIR levels (115). These findings suggest that lncRNA HOTAIR may participate in the MGMT regulatory network by modulating the epigenetic landscape, although the precise underlying mechanism remains to be elucidated (115).

In summary, upregulation of lncRNA HOTAIR constitutes a notable risk factor for TMZ resistance in GBM. The regulation of the miR-214/β-catenin/MGMT pathway via ceRNA activity by lncRNA HOTAIR represents a central mechanism mediating this chemoresistance. However, the regulation of MGMT by lncRNA HOTAIR extends beyond a single pathway. Key areas for further investigation include its crosstalk with epigenetic regulatory networks, context-dependent functions across distinct GBM molecular subtypes and its translational potential as a therapeutic target.

lncRNA X-inactive specific transcript (XIST). The lncRNA XIST is upregulated in multiple malignancies, including GBM (118), ovarian cancer (119) and non-small cell lung cancer (120), where it functions as an oncogene. In GBM, elevated lncRNA XIST expression is closely associated with larger tumor volume, advanced World Health Organization grade and reduced overall survival, underscoring its potential as a biomarker of poor prognosis (121). Functional experiments have indicated that lncRNA XIST knockdown effectively inhibits GBM cell migration, invasion and proliferation, while promoting apoptosis. Furthermore, lncRNA XIST silencing enhances the chemosensitivity of GBM cells to TMZ (121). These findings highlight the pivotal role of lncRNA XIST in regulating malignant progression and mediating drug resistance in GBM (121).

At the mechanism level, lncRNA XIST directly binds and sequesters miR-29c, reducing its biological activity and alleviating its inhibitory effect on downstream target genes. In TMZ-resistant GBM models, the antitumor and chemosensitizing effects of lncRNA XIST knockdown were partially reversed by a miR-29c inhibitor, confirming the central role of the XIST/miR-29c axis in regulating chemoresistance (118). Further experiments demonstrated that this regulatory axis enhanced DNA damage repair capacity and promoted TMZ resistance by modulating the expression levels of the transcription factor SP1 and MGMT. Specifically, SP1, a transcriptional regulator of the mismatch repair key protein MutS homolog 6 (MSH6), is negatively regulated by miR-29c, whereas MGMT directly reverses O^6-MeG lesions induced by TMZ. Knockdown of XIST markedly reduced the protein levels of

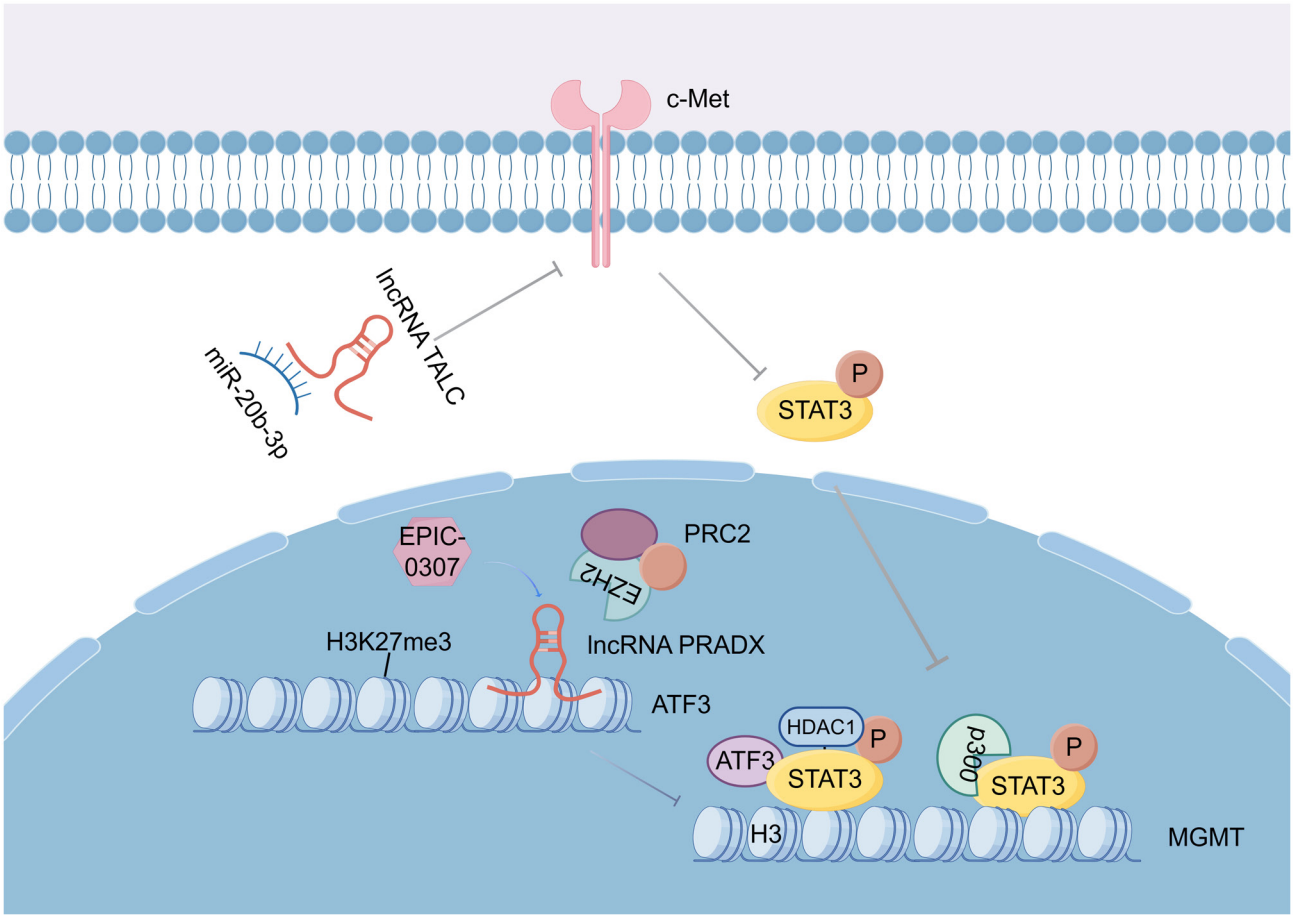

Figure 2. Schematic diagram illustrating the mechanisms by which lncRNAs TALC and PRADX regulate MGMT expression. Arrows denote promotion or positive regulation, while blunt-ended arrows represent inhibition or negative regulation. lncRNA, long non-coding RNA; MGMT, O^6-methylguanine-DNA methyltransferase; PRADX, PRC2 and DDX5-associated lncRNA; TALC, temozolomide-associated lncRNA in glioblastoma recurrence; ATF3, activating transcription factor 3; P, phosphorylation; H3K27me3, trimethylation of histone H3 lysine 27; HDACI, histone deacetylase inhibitor; miR, microRNA.

MSH6, SP1 and MGMT, an effect reversed by miR-29c inhibition. These findings indicated that the lncRNA XIST/miR-29c axis coordinately regulates SP1 and MGMT expression in TMZ-resistant GBM cells (118).

In summary, upregulation of lncRNA XIST constitutes a notable risk factor for TMZ resistance in GBM, primarily by regulating the miR-29c/Sp1/MGMT signaling pathway, thereby modulating cellular chemosensitivity.

lncRNA TMZ-associated lncRNA in GBM recurrence (TALC). A previously uncharacterized lncRNA in GBM, designated lncRNA TALC, is highly expressed in TMZ-resistant tissues. lncRNA TALC is located at the AL358975 locus, spans two exons and comprises 418 nts. Mechanistically, lncRNA TALC expression is regulated by the phosphorylated-AKT/FOXO3 signaling axis. Specifically, phosphorylated-AKT inhibits FOXO3 nuclear translocation, relieving the FOXO3-mediated repression effect of the lncRNA TALC promoter and promoting its transcription (122). Highly expressed lncRNA TALC competitively binds to miR-20b-3p, alleviating its post-transcriptional inhibition of c-Met mRNA and activating the c-Met/STAT3 signaling axis, which enhances TMZ resistance in GBM (122). Subsequent investigation demonstrated that lncRNA TALC activated the c-Met/STAT3/p300 pathway, facilitating the formation of a STAT3-histone acetyltransferase p300 complex that localizes at the MGMT promoter region. This process increases histone acetylation levels at histone H3 lysine (H3K) 9, H3K27 and H3K36 sites, remodels chromatin accessibility, and augments MGMT transcription (122). Functional experiments revealed that miR-20b-3p inhibition increased MGMT expression, whereas its overexpression suppressed it. These findings confirmed the central role of the lncRNA TALC/miR-20b-3p/c-Met axis in the epigenetic regulation of MGMT (Fig. 2) (122).

In summary, within GBM, the AKT signaling pathway upregulates lncRNA TALC expression. Functioning as a ceRNA, lncRNA TALC sequesters miR-20b-3p, thereby activating downstream c-Met signaling. This cascade ultimately remodels histone acetylation at the MGMT promoter, resulting in increased MGMT expression and the induction of TMZ resistance. Therefore, targeting lncRNA TALC offers a promising strategy to overcome TMZ resistance and provides a novel strategic avenue to enhance therapeutic outcomes in patients with GBM.

PRC2 and DDX5-associated lncRNA (PRADX). Li *et al* (123) identified an lncRNA designated PRADX (transcript ID, ENST00000449248.1). This lncRNA is upregulated in GBM and colon adenocarcinoma (COAD) and is predominantly localized within the nucleus (103). A subsequent study demonstrated that lncRNA PRADX is upregulated in

mesenchymal GBM, where it promotes tumor invasion and metastasis by modulating the tumor microenvironment (124).

Mechanistic investigations have revealed that lncRNA PRADX interacts with enhancer of zeste homolog 2 (EZH2), the catalytic subunit of the polycomb repressive complex 2 (PRC2). This interaction facilitates the recruitment of PRC2 to specific gene promoter regions, where it catalyzes trimethylation of H3K27 (H3K27me3) deposition. Therefore, it induces the epigenetic silencing of multiple tumor suppressor genes, including p21 and p53 upregulated modulator of apoptosis. Furthermore, the PRADX-EZH2 interaction indirectly influences MGMT expression through a sophisticated multi-layered regulatory network. PRADX suppresses activating transcription factor 3 (ATF3) transcription by maintaining H3K27me3 at its promoter. ATF3, functioning as a pivotal transcription factor, forms a complex with phosphorylated-STAT3 and histone deacetylase 1 (HDAC1). This complex is recruited to the MGMT promoter, where it represses MGMT transcription by reducing H3K27 acetylation levels. Although this indirect regulatory mechanism introduces complexity to the therapeutic targeting, it provides valuable insights for developing combination treatment strategies. The small-molecule inhibitor EPIC-0307 disrupts the PRADX-EZH2 interaction, thereby relieving the transcriptional repression of ATF3 (125). Through the ATF3/pSTAT3/HDAC1 axis, EPIC-0307 downregulates MGMT expression (Fig. 2) and markedly enhances the cytotoxic efficacy of TMZ (125).

In summary, PRADX is an oncogenic lncRNA that is highly expressed in GBM and COAD. PRADX regulates MGMT expression by directly binding to EZH2 and mediating epigenetic silencing. The small-molecule compound EPIC-0307 targets the PRADX-EZH2 interaction and exhibits synergistic antitumor activity when combined with TMZ. This regimen markedly enhances therapeutic efficacy against GBM and offers a potential approach to reversing TMZ resistance.

4. circRNAs

circRNAs constitute a class of single-stranded ncRNAs composed of 100-1,000s of nts. circRNAs form through back-splicing of precursor mRNA or linear RNA, producing a covalently closed circular structure with joined 3'- and 5'-ends. This conformation confers resistance to ribonuclease R degradation (126,127), thereby enhancing the stability of circRNAs compared with their linear mRNA counterparts. Studies have demonstrated that circRNAs can arise from diverse genomic region and can be generated through multiple circularization patterns. These characteristics confer notable heterogeneity in circRNA sequence composition and length, which contributes to their broad functional diversity (127-129). circRNAs participate in key biological processes in numerous human cancer types, such as cervical cancer, colorectal cancer, pancreatic cancer and glioblastoma (130-135). Their functions include acting as miRNA sponges, interacting with proteins, regulating gene splicing or transcription, translating into proteins or peptides, and contributing to epigenetic regulation (128). Notably, circRNA expression is dysregulated in neurological disorders, cardiovascular diseases and multiple cancer types, including breast cancer, colorectal cancer, hepatocellular carcinoma and glioblastoma (128,135-139). In oncogenesis, specific circRNAs possess oncogenic or tumor-suppressive roles (140,141). These properties underscore their potential as diagnostic biomarkers and therapeutic targets (142,143).

circRNAs in GBM. circRNAs are abundantly expressed in brain tissue and perform key biological functions. circRNAs serve a key role in cancer development and progression (139). Previous studies have demonstrated that circRNAs contribute to the pathological processes of GBM (144,145). Numerous circRNAs are dysregulated in GBM tissues and this dysregulation is closely associated with tumorigenic mechanisms. These circRNAs regulate proliferation, invasion, migration and cell cycle progression of GBM cells, underscoring their potential in diagnosis, prognostic evaluation and therapeutic strategies for GBM (146). circRNAs are either upregulated or downregulated in GBM cells and tissues, functioning through diverse molecular mechanisms. In therapeutic contexts, circRNAs have emerged as a promising class of targets. Oncogenic circRNAs can be precisely silenced using gene knockdown technologies. By contrast, tumor-suppressive circRNAs can be restored or enhanced through vector-based delivery or synthetic biology, thereby modulating key tumor-associated signaling pathways (145,147). Furthermore, exosome-based circRNA delivery systems offer a novel method to modulate the tumor microenvironment and reverse treatment resistance (147). Collectively, these strategies are advancing GBM diagnosis and therapy toward greater precision, dynamic monitoring and individualized treatment.

circRNAs regulating MGMT expression. Previous research has indicated that circRNAs regulate gene expression at transcriptional and post-transcriptional levels. Their primary mechanisms include functioning as miRNA sponges to sequester miRNA activity (148), acting as RNA-binding protein (RBP) sponges or protein scaffolds to participate in diverse biological processes (149,150), and directly regulating translation to mediate polypeptide synthesis (151,152). As central components of the ceRNA mechanism, circRNAs modulate downstream target gene expression by establishing a circRNA/miRNA/mRNA regulatory axis, which contributes to malignant tumor progression (153). Notably, in GBM, specific circRNAs act as molecular sponges by competitively binding to miRNAs that target MGMT. This interaction relieves post-transcriptional inhibition of MGMT mRNA, leading to increased MGMT protein expression and subsequent TMZ resistance (154). The following section details circRNAs that regulate MGMT expression in GBM (154).

circWDR62. The WD repeat domain 62 (WDR62) gene comprises 32 exons and encodes a protein consisting of 1,523 amino acid residues that localizes to the minus ends of mitotic spindle microtubules. During neurogenesis, WDR62 is highly expressed in the forebrain, particularly in the ventricular and subventricular zones, where it serves a key role in neuronal proliferation and migration (155). The host gene WDR62 is markedly upregulated in various tumor tissues, such as bladder cancer, breast cancer and renal cancer, and is closely associated with poor prognosis (156,157). Studies have demonstrated that circWDR62 expression is elevated in TMZ-resistant GBM tissues and their derived exosomes, with

high expression being positively associated with poor prognosis in patients with GBM (154). Knockdown of circWDR62 effectively suppressed TMZ resistance and malignant progression in GBM. At the molecular level, circWDR62 was predominantly localized in the cytoplasm and functioned as a ceRNA by sequestering miR-370-3p, thereby alleviating the inhibitory effect of this miRNA on downstream target genes. Dual-luciferase reporter assays confirmed direct binding between circWDR62 and miR-370-3p, as well as between miR-370-3p and the 3'-UTR of MGMT mRNA. Furthermore, rescue experiments demonstrated that MGMT overexpression reversed the TMZ sensitization and suppression of malignant phenotypes induced by circWDR62 silencing, functionally validating the circWDR62/miR-370-3p/MGMT regulatory axis (29,154). Notably, circWDR62 can be packaged into exosomes and transferred from TMZ-resistant to sensitive cells, inducing similar resistance and malignant progression in recipient cells. This mechanism facilitates the 'horizontal transmission' of chemoresistance within the tumor microenvironment, revealing a novel biological role for exosomal circRNA in the dissemination of chemoresistance in GBM (154).

However, this study had certain limitations (154). Although the ceRNA mechanism was experimentally validated, whether circWDR62 regulates MGMT expression via RBPs or other epigenetic mechanisms, such as transcriptional regulation, remains to be elucidated. Furthermore, the potential roles of circWDR62 in remodeling the tumor immune microenvironment and metabolic reprogramming warrant further research.

In summary, exosome-encapsulated circWDR62 functions as a miR-370-3p sponge to regulate MGMT, thereby promoting TMZ resistance and the malignant progression of GBM *in vitro* and *in vivo*. These findings provided novel insights into the mechanisms underlying TMZ resistance in GBM and suggest potential avenues for developing therapeutic strategies against TMZ-resistant GBM.

5. Conclusion

Despite advances in surgical techniques and radiochemotherapy, GBM survival rates have not improved, with chemoresistance remaining the primary cause of treatment failure (5). Elucidating the mechanisms of TMZ resistance in GBM and developing strategies to overcome it are key to improve therapeutic regimens and enhance glioma prognosis. Increasing evidence indicates that ncRNAs serve a key role in tumor chemoresistance (101,129,158,159). The present review systematically examined how miRNAs, lncRNAs and circRNAs modulate GBM sensitivity to TMZ through direct or indirect regulation of MGMT expression. Multiple miRNAs, including miR-142-3p, miR-181d and miR-182-5p, directly target the 3'-UTR of the MGMT mRNA, promoting its degradation or inhibiting translation, thereby reducing MGMT protein levels and enhancing TMZ efficacy. Furthermore, certain miRNAs, such as miR-29c, indirectly regulate MGMT expression by targeting transcription factors, including Sp1. The expression levels of these miRNAs are closely associated with GBM prognosis, indicating their potential as biomarkers or therapeutic targets. Notably, synergistic interactions between miRNAs, such as the combination of miR-181d and miR-409-3p, can more effectively suppress MGMT expression, offering novel insights for combination therapy strategies.

lncRNAs regulate MGMT expression either by competitively binding to miRNAs via the ceRNA mechanism or by recruiting epigenetic modification complexes, such as PRC2. For instance, lncRNA UCA1 alleviates MGMT inhibition by sequestering miR-182-5p, whereas HOTAIR promotes TMZ resistance by activating the miR-214-3p/β-catenin/MGMT pathway. Aberrant expression levels of these lncRNAs are closely associated with malignant progression and chemoresistance in GBM, indicating that targeting of lncRNAs may represent a promising strategy in overcoming drug resistance in the future.

circRNAs function as miRNA sponges, regulating downstream gene expression through ceRNA networks. For example, circWDR62 upregulates MGMT expression by sequestering miR-370-3p, thereby promoting TMZ resistance. Their high stability and tissue-specific expression render circRNAs promising targets for GBM diagnosis and therapeutic intervention.

Although existing studies have preliminarily elucidated the key role of ncRNAs in MGMT regulation and highlighted their translational potential, the field faces notable challenges. The high complexity of ncRNA regulatory networks, and their context-dependent functions and limitations, such as *in vivo* delivery efficiency, remain major obstacles to clinical translation. Therefore, future research should further define the precise roles of ncRNAs within specific cell populations and spatial contexts, and develop efficient, targeted delivery strategies. This dual focus is key to translating mechanistic insights into clinical practice.

6. Challenges and future perspectives

The present review systematically examines the mechanisms by which ncRNAs regulate MGMT expression to influence TMZ resistance in GBM, providing a theoretical foundation in targeting ncRNAs to overcome chemoresistance. Nevertheless, translating these findings into clinical practice remains challenging. To advance this field and enable clinical translation, future research should employ spatial and single-cell multi-omics technologies to resolve heterogeneity of ncRNA regulation. Analyses based on bulk tissue samples capture averaged signals from diverse cell populations and tumor regions, thereby obscuring the inherent complexity of ncRNA regulatory networks. GBM exhibits pronounced intratumoral heterogeneity, encompassing distinct tumor cell subpopulations and varied components of the tumor microenvironment (160-162). This heterogeneity contributes to the apparent functional discrepancies observed for the same ncRNA across different studies or within distinct regions of a single tumor. Integrating spatial transcriptomics with single-cell RNA sequencing holds considerable potential in mapping ncRNA expression at single-cell resolution. This approach enables the identification of specific ncRNA expression patterns across cellular subpopulations and allows precise assignment of their functions to particular cell types. Simultaneously, it provides insights into the spatial distribution of ncRNA expression within tumor regions, such as the core and invasive front, facilitating investigation of key questions,

such as whether molecules such as exosomal circWDR62 undergo directional 'horizontal transmission'. Furthermore, integration of multi-omics data supports the construction of cell type-specific ceRNA networks, enhancing the precise elucidation of regulatory mechanisms by which ncRNAs modulate key genes, such as MGMT.

Future research should address the challenges associated with the technical and clinical translation of ncRNAs as liquid biopsy biomarkers. Although ncRNAs derived from blood or cerebrospinal fluid, particularly exosomal circRNAs, demonstrate potential due to their stability (139,146,147), the absence of standardized protocols in sample processing and detection remains a major obstacle. Variability in experimental procedures across studies limits reproducibility and comparability of results. Furthermore, improving the specificity of detection methods to distinguish tumor-derived signals from background noise and enhancing sensitivity to identify early-stage or minimal residual disease are primary objectives for future technological advancements. Simultaneously, the development of advanced bioinformatics pipelines is key to accurately identify and functionally annotate low-abundance ncRNAs amid large-scale sequencing data.

Future research should also address the barriers to clinical translation of ncRNA-targeted therapies. ncRNA-based therapeutics, including miRNA mimics and inhibitors, face challenges such as low delivery efficiency, off-target effects and potential drug resistance. The blood-brain barrier and blood-tumor barrier constitute major physical obstacles to drug delivery, necessitating the development of smart carriers that can specifically target GBM cells and efficiently penetrate these barriers. Since a single miRNA can regulate hundreds of targets, artificial intervention may induce unforeseen off-target effects and toxicity. These off-target effects and potential toxicities can be mitigated through tumor-specific promoters, chemically modified antisense oligonucleotides to enhance specificity or intraoperative local administration to reduce systemic toxicity. Furthermore, tumor cells may develop resistance to ncRNA therapies through mechanisms such as target mutation or pathway activation (105,163,164). Therefore, clinical trial designs should consider combination therapies and dynamic resistance monitoring. Emerging technologies, including long-read sequencing, interactomics (such as cross-linking and immunoprecipitation sequencing) and clustered regularly interspaced short palindromic repeat-based high-throughput functional screening, are expanding the current understanding of ncRNA regulatory dimensions (127). These approaches extend beyond the classical ceRNA mechanism, elucidating transcriptional regulatory roles and enabling the identification of novel key regulatory nodes.

Therefore, these advancements are anticipated to converge in the realization of ncRNA-guided personalized precision medicine. By integrating patient-derived multi-omics profiles with dynamic liquid biopsy monitoring, a digital predictive model can be developed to assess the risk of both intrinsic and acquired TMZ resistance in a patient, identify optimal ncRNA targets or combination strategies and guide dynamic adjustment of treatment regimens, thereby progressing toward truly individualized precision medicine. In summary, ncRNAs serve a key role in regulating MGMT and mediating TMZ resistance in GBM. Research in this domain is transitioning from a discovery phase to a key stage of mechanistic elucidation and clinical translation. The full potential of ncRNAs to improve the prognosis of patients with GBM can be realized only by utilizing insights from emerging technologies and fostering multidisciplinary collaboration to address technical and biological challenges in biomarker development and targeted therapy.

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Authors' contributions

YG reviewed the literature and wrote the first draft. JG produced the figures. WX collected part of the data. YL supervised and revised the manuscript. YG, JG, WX and YL were involved in writing the paper. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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