Regulation of temozolomide resistance via lncRNAs: Clinical and biological properties of lncRNAs in gliomas (Review)

SUI LI[1], XIAOFANG XIE[2], FU PENG[1], JUNRONG DU[1] and CHENG PENG[2]

[1]Department of Pharmacology, Key Laboratory of Drug-Targeting and Drug Delivery System of The Education Ministry, Sichuan Engineering Laboratory for Plant-Sourced Drug and Sichuan Research Center for Drug Precision Industrial Technology, West China School of Pharmacy, Sichuan University, Chengdu, Sichuan 610041; [2]State Key Laboratory of Southwestern Chinese Medicine Resources, School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan 611137, P.R. China

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Abstract. Gliomas are a primary types of intracranial malignancies and are characterized by a poor prognosis due to aggressive recurrence profiles. Temozolomide (TMZ) is an auxiliary alkylating agent that is extensively used in conjunction with surgical resection and forms the mainstay of clinical treatment strategies for gliomas. However, the frequent occurrence of TMZ resistance in clinical practice limits its therapeutic efficacy. Accumulating evidence has demonstrated that long non-coding RNAs (lncRNAs) can play key and varied roles in glioma progression. lncRNAs have been reported to inhibit glioma progression by targeting various signaling pathways. In addition, the differential expression of lncRNAs has also been found to mediate the resistance of glioma to several chemotherapeutic agents, particularly to TMZ. The present review article therefore summarizes the findings of previous studies in an aim to report the significance and function of lncRNAs in regulating the chemoresistance of gliomas. The present review may provide further insight into the clinical treatment of gliomas.

Contents

Correspondence to: Dr Fu Peng or Professor Junrong Du, Department of Pharmacology, Key Laboratory of Drug-Targeting and Drug Delivery System of The Education Ministry, Sichuan Engineering Laboratory for Plant-Sourced Drug and Sichuan Research Center for Drug Precision Industrial Technology, West China School of Pharmacy, Sichuan University, 17 Renmin South Road, Chengdu, Sichuan 610041, P.R. China
E-mail: fujing126@yeah.net
E-mail: dujr_1@163.com

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1. Introduction

The World Health Organization (WHO) currently classifies gliomas into four grades, where a new classification was proposed in 2016 (1). These grades of interest are as follows: i) Diffuse low-grade gliomas (WHO I and II), which include diffuse astrocytoma and oligodendroglioma; ii) diffuse high-grade gliomas (WHO III), which include anaplastic astrocytoma with various mutated genes; and iii) glioblastoma (GBM; WHO IV), which is the most lethal variety of glioma (2). Glioblastoma multiforme (GBM) is a common type of brain malignancy that remains largely incurable. Despite the development of multi-modal therapeutic interventions, such as radiotherapy combined with temozolomide (TMZ) (3) and electrofield therapy combined with TMZ (4), the median survival rate of patients with GBM remains at ≤15 months (5).

TMZ is an orally administered alkylating antitumor drug that can cross the blood-brain barrier with a bioavailability reaching ~100%. It can be used to effectively treat newly diagnosed and relapsed GBM to prolong the survival rate of patients (6,7). Thus, TMZ is the main adjuvant therapeutic agent used in the treatment of glioma in clinical practice (8). However, the development of resistance to TMZ in glioma impairs its therapeutic efficacy, resulting in recurrence (9). A previous study evaluated the responses of 1,035 GBM tumors to therapies using multiple assaying technologies and discovered that gene mutations are largely responsible for resistance to treatment. The mechanisms of action of TMZ involve the alkylation of the O^6 site of guanine (O^6MeG), resulting in a base mismatch following subsequent DNA replication, causing DNA damage (10). TMZ resistance has become one of the largest obstacles in prolonging the survival of patients with glioma. Several mechanisms have been proposed to underlie the resistance to TMZ. The most common mode lies in the DNA repair system, including the O^6MeG DNA

methyltransferase (MGMT) pathway (11), DNA mismatch repair and base excision repair (12,13). In addition to the DNA repair system, GBM stemness and autophagy can play critical roles in mediating resistance to TMZ. Other factors, such as the EGFR, PTEN, p53 and PI3K/AKT/mTOR pathways, have all been reported to participate in the resistance process. Due to the high occurrence of TMZ resistance, the development of novel effective treatment methods for gliomas is of utmost urgency.

According to The Encyclopedia of DNA Elements statistics, RNAs account for 75% of the human genome, whilst the ratio of RNA to protein-coding genes is only ~3% (14). Influenced by the central genetic dogma, the untranslated region of genes was previously considered by prejudice to be 'junk' (15). However, at the end of the last century, the discovery of small regulatory non-coding RNAs (ncRNAs) has completely changed the understanding of the role of ncRNAs (16). Among these ncRNAs, there is a class of RNAs with base-pair lengths of ≥200 nucleotides, named long non-coding RNAs (lncRNAs). The function of lncRNAs in protein expression is similar to that of conventional RNAs. Both are transcribed from DNA by RNA polymerase II and are then modified, namely being 5'-capped, polyadenylated and/or spliced, before eventually becoming mature lncRNA (17,18). Compared with mRNAs, lncRNAs contain fewer but longer exons, where their expression levels in different tissues are typically lower (19,20). lncRNAs have been reported to perform a variety of molecular functions. They have been reported to regulate gene expression directly and indirectly by targeting specific proteins, including Polycomb group proteins and enhancer of zeste homolog 2 (EZH2). In addition, lncRNAs can also function as precursors of small RNAs and modulate RNA processing events. lncRNAs can also directly bind to proteins and modulate their function (21). It has been reported that lncRNAs and microRNAs (miRNAs/miRs) typically perform reciprocal functions. miRNAs can promote the degradation of lncRNAs, thereby diminishing the molecular functions of lncRNAs, whereas lncRNAs can also conversely target miRNAs directly to regulate their expression. lncRNAs can compete with miRNAs for binding to the same sites on mRNAs. Furthermore, lncRNAs can be spliced to generate miRNAs (22). Accumulating evidence has indicated that lncRNAs can function as regulatory molecules in cancer development. Han *et al* (23) previously reported key lncRNAs that can influence glioma pathogenesis using microarrays. However, the most recent network-based algorithms failed to adequately reflect the regulatory role in human tumors. Zhang *et al* (24) successfully developed a novel global network-based framework, termed 'LncRDNetFlow', to verify that lncRNAs play a key role in regulating cellular processes in different malignancies. Apart from the aforementioned reports, lncRNAs that are associated with cancer have been previously detected in the body fluids of patients with cancer, which suggests the potential of using lncRNAs as biomarkers and therapeutic targets for cancer applications (25). Of note, lncRNAs have been reported to participate in the development of resistance to chemotherapy in various human malignancies, such as head and neck squamous cell carcinoma, hepatocellular carcinoma, gastric cancer, pancreatic cancer, bladder cancer, including glioma (26-32).

In conclusion, lncRNAs are promising therapeutic targets for the treatment of human diseases, particularly glioma. Therefore, the present review article first summarizes research findings from the past 5 years regarding the signaling pathways underlying the resistance of glioma to TMZ, with a focus on oncogenic or tumor suppressive lncRNAs. Moreover, the association between lncRNAs and combination therapy with TMZ and immunosuppressive therapy for glioma is discussed, in an aim to provide further insight into the clinical treatment of glioma.

2. Prominent role of lncRNAs in glioma

In 2012, Zhang *et al* (33) first associated lncRNA expression with the grade of malignancy in human glioma. Furthermore, lncRNAs have been reported to be associated with the occurrence and progression of various malignancies such as colorectal cancer, gallbladder cancer, ovarian cancer in addition to modulating chemoresistance in glioma (34-38). The expression of a number of lncRNAs has been found to be upregulated in glioma and these lncRNAs have been proposed to function as oncogenes, whilst the expression levels of other lncRNAs have been found to be downregulated in glioma and those lncRNAs have been proposed to function as tumor suppressor genes. From an epigenetic perspective, lncRNAs play a key role in glioma. lncRNA maternally expressed 3 (MEG3) expression was previously reported to be decreased in glioma tissues due to its hypermethylation. Upstream, DNA methyltransferase 1 (DNMT1) was found to be the mediator of MEG3 promoter methylation, which suppressed the transcription of MEG3. In addition, DNMT1 promoted the proliferation and clonogenicity of glioma cells, whilst reducing apoptosis. The inhibition of DNMT1 was demonstrated to activate the p53 signaling pathway in glioma cells. Therefore, MEG3 hypermethylation by DNMT1 was concluded to decrease MEG3 expression, which may represent a molecular mechanism of glioma progression (39). In GBM cells with acquired TMZ resistance, a previous study found that 1,383 lncRNAs were significantly upregulated, whereas 1,309 lncRNAs were significantly downregulated compared with normal GBM cell lines using a human lncRNA microarray; this suggests that lncRNAs are closely associated with TMZ resistance (40). lncRNA long intergenic non-protein coding RNA (LINC)00473, the expression of which was found to be significantly increased in glioma, was found to be associated with a poor prognosis of patients with glioma by functioning as an oncogenic lncRNA (41). In addition, LINC00473 knockdown was revealed to inhibit glioma progression both *in vivo* and *in vitro*. The underlying mechanism was proposed to be the inhibition of miR-195-5p by LINC00473 by competing for binding to the same site on the corresponding mRNA. Downstream, Yes-associated protein 1 (YAP1) and TEA domain family member 1 (TEAD1) were found to be downstream targets of miR-195-5p, where both shared a negative correlation. Taken together, LINC00473 downregulation inhibited glioma growth by serving as a competing endogenous RNA (ceRNA) to block miR-195-5p function, thereby promoting YAP1 and TEAD1 expression (41). In another study, lncRNA small nucleolar RNA

host gene (SNHG)12 was found to be highly expressed in glioma, where functional analyses revealed that SNHG12 knockdown inhibited the proliferation and promoted the apoptosis of glioma cells (42). Downstream, SNHG12 was demonstrated to interact with Hu antigen R (HuR), an ubiquitous multi-faceted RNA-binding protein, to become stabilized (42). Furthermore, the lncRNA HOX antisense intergenic RNA (HOTAIR) was found to function as an oncogene that is highly expressed in glioma stem cells (GSCs). Functional assays revealed that downregulating HOTAIR expression suppressed GSC development by targeting the programmed cell death 4 protein (43). lncRNA H19 has also been reported to be highly expressed and negatively associated with miR-138 expression in glioma cell lines, according to reverse transcription-quantitative PCR (RT-qPCR) data (44). H19 knockdown was found to suppress angiogenesis in glioma, specifically by functioning as a ceRNA of miR-138 to inhibit its function, thereby promoting the expression of hypoxia-inducible transcription factors and VEGFs (44). In addition, H19 downregulation was also found to inhibit the angiogenesis of glioma by directly binding to miR-29a, which in turn inhibited vasohibin 2 expression, an angiogenic factor in glioma (45). A previous study demonstrated that the expression of the lncRNA colorectal neoplasia differentially expressed (CRNDE) was upregulated in glioma tissues and cells; subsequent functional analyses demonstrated that CRNDE promoted glioma cell proliferation in a mTOR signaling-dependent manner in glioma (46). Downstream, miR-384 expression was also revealed to be downregulated in glioma and inhibited by CRNDE, which increased the expression of piwi-like RNA-mediated gene silencing 4 protein (47). In addition, the lncRNA-MUF, which was induced by TGF-β, was reported to be another oncogene in GBM. The knockdown of lncRNA-MUF expression suppressed tumor growth and promoted apoptosis induced by TMZ by targeting miR-34a (48).

However, lncRNA taurine upregulated 1 (TUG1) was considered to be a suppressor of glioma cell proliferation by promoting apoptosis. The overexpression of TUG1 was found to increase the expression of caspases-3 and -9, whilst decreasing the expression of Bcl-1, suggesting that the suppressive effects of TUG1 were due to the inhibition of the pathways associated with cell apoptosis (49).

Gliomas have also been reported to regulate the expression of certain lncRNAs. Glioma cells retain the ability to secrete exosomes containing mRNAs, miRNAs, lncRNAs and angiogenic proteins into the surrounding microenvironment to regulate the function of target cells, by targeting downstream signaling pathways (50,51). Using electron microscopy and western blot analysis, exosomes secreted by glioma cells were previously found to transport lncRNA-activated by TGF-β (ATB) into astrocytes to activate them. Subsequently, lncRNA-ATB in glioma cell-derived exosomes were demonstrated to promote the proliferation of glioma cells by inhibiting miR-204-3p (52). Angiogenesis also plays a key role in glioma growth. It was reported that glioma-derived exosomes enriched in lncRNA-POU class 3 homeobox 3 promoted angiogenesis in glioma (53). Therefore, these aforementioned findings suggest that gliomas can export lncRNAs by secreting exosomes.

3. Oncogenic lncRNAs promote TMZ resistance in gliomas

Oncogenic lncRNAs (Table I) were previously found to be overexpressed or upregulated in gliomas, and this can promote TMZ resistance by targeting a multitude of signaling pathways.

c-Met pathway. c-Met is a receptor tyrosine kinase, the expression of which has been found to be upregulated in TMZ-resistant GBM (54). MGMT is an enzyme that removes the methyl group at O^6MeG, thereby affecting the activity of TMZ (11). Wu *et al* (55) reported that lncRNA-TMZ-associated lncRNA (TALC), a novel lncRNA associated with GBM recurrence, upregulated the expression of MGMT and promoted TMZ resistance by activating c-Met signaling.

TGF-β1/Smad signaling pathway. TGF-β1 is a cytokine that plays a crucial role in promoting tumor growth (56). Smad proteins are phosphorylated by TGF-β1 receptors, which relays the TGF-β1 signal into the nucleus (57,58). TGF-β has been reported to be a novel player in mediating resistance against both targeted and conventional therapeutic agents (59). The mechanism underlying this process appears to be associated with epithelial-mesenchymal transition (EMT) and the activity of cancer stem cells (60). However, the effects of TGF-β signaling on TMZ resistance in glioma remain to be a subject of further exploration.

The knockdown of K-homology splicing regulatory protein (KSRP) expression has been demonstrated to inhibit the expression of miR-198 (61). In addition, miR-198 may enhance sensitivity to TMZ by inhibiting the expression of MGMT, which is abrogated by TGF-β1 through the suppression of KSRP expression in GBM cells. TGF-β1 may also upregulate the expression of lncRNAs H19 and HOXD cluster antisense RNA 2 by activating Smad, which promotes GBM resistance to TMZ by activating MGMT and inhibiting miR-198. However, KSRP knockdown was shown to abolished the effects of TGF-β1 and lncRNA H19 on miR-198 and MGMT. In the clinic, TMZ tended to be more effective in patients with lower expression levels of TGF-β1 or lncRNA H19. Collectively, these observations suggest that TGF-β1 can confer resistance to TMZ by regulating the processing of lncRNAs and increasing the expression of MGMT (61).

A literature search revealed various lncRNAs affecting TMZ resistance in glioma, as well as their functions and targets (62-82). This list of lncRNAs is presented in Table I.

Wnt/β-catenin signaling pathway. Using transcriptome sequencing, a previous study found that the Wnt/β-catenin pathway was significantly activated in TMZ-treated glioma cells in a PI3K/Akt pathway-dependent manner. Mechanistically, Akt activation promoted β-catenin translocation into the nucleus, resulting in the transcriptional activation of Wnt/β-catenin signaling to suppress apoptosis whilst promoting TMZ resistance (83). Sex-determining region Y-box9 pro-tein (SOX9) has been found to be overexpressed in GBM, where it can stimulate GBM growth by activating Wnt/β-catenin signaling (84). In another study, Li *et al* (71) explored the effects of LINC00174 on glioma cells. They found that LINC00174 expression was increased in glioma tissues, and that LINC00174 knockdown significantly inhibited the

Table I. The function and target of oncogenic lncRNAs affecting TMZ resistance in glioma.

lncRNA	Cell lines	Targets/ regulators	Signaling pathways	Functional impact	(Refs.)
LINC01410	GBM/TMZ-resistant GBM cells	miR-370-3p	PTEN/AKT TMZ resistance	Promotes glioma growth and	(62)
MIR155HG	-	-	PD-1/PD-L1 axis	Indicates a poorer overall survival in GBM	(63,64)
FoxD2-AS1	-	MGMT miR-98-5p	PI3K/PTEN/Akt	Impairs glioma cell sensitivity to TMZ, induces MGMT promoter hypermethylation, and inhibits invasion, proliferation, migration and the TMZ resistance of drug-resistant glioma cells	(67)
BCYRN1/ BC200	-	miR-218-5p	p53 site	Promotes the proliferation, migration, invasion and TMZ resistance	(68)
lnc-TALC	-	miR-20b-3p	p38/MAPK c-Met pathway	Influences the sensitivity of glioma to TMZ	(55,70)
LINC00174	-	miR-138-5p	Wnt/β-catenin	Inhibits glioma cell proliferation in TMZ-resistant glioma cells	(71)
CCAT2	SHG44/U251	miR-424	P53 site	Promotes the proliferation, invasion and migration of glioma cells	(69)
H19	U87MG/U251	MDR, MRP, and ABCG2 genes	Wnt/β-Catenin NF-κB	Enhances the resistance of TMZ-resistant cells	(72-74)
LINC00021	-	E2F1	p21/Notch	Improves TMZ resistance and apoptosis in TMZ-resistant cells	(75)

lncRNAs, long non-coding RNAs; TMZ, temozolomide; GBM, glioblastoma multiforme; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; FoxD2-AS1, forkhead box D2-antisense RNA1; BCYRN1, brain cytoplasmic RNA1; TALC, TMZ-associated lncRNA; CCAT, colon cancer-associated transcript; MDR, multi-drug resistance gene; MRP, multidrug resistance-associated protein; ABCG2, ATP binding cassette subfamily G member 2.

proliferation of TMZ-resistant glioma cells. Mechanistically, the knockdown of LINC00174 expression suppressed the growth of TMZ-resistant glioma by sponging miR-138-5p, which negatively targets SOX9. Therefore, LINC00174 was proposed to activate Wnt/β-catenin signaling by targeting the miR-138-5p/SOX9 axis. Furthermore, *in vivo* experiments also revealed consistent findings (71).

It has been previously demonstrated that the expression level of lncRNA H19 is significantly increased in patients with glioma resistant to TMZ (73). An *in vitro* TMZ drug-resistant cell model was established and the model was verified using RT-qPCR. Silencing H19 expression enhanced the sensitivity of TMZ-resistant cells to TMZ by downregulating the expression of a number of genes, including multidrug resistance mutation, multidrug resistance-associated protein and ATP binding cassette subfamily G member 2. Therefore, H19 was proposed to be a novel therapeutic target for TMZ-resistant gliomas (73). In addition, other studies have previously investigated the specific mechanisms involved in lncRNA H19-mediated regulation. H19 knockdown was found to inhibit EMT by promoting the expression of the epithelial marker, E-cadherin, whilst inhibiting that of the mesenchymal markers, vimentin and zinc finger E-box binding homeobox (ZEB)1. Furthermore, H19 downregulation was found to decrease the expression of β-catenin and its downstream targets, c-Myc and surviving, in TMZ-treated glioma cells. However, H19 reversed the resistance of glioma cells to TMZ by repressing EMT and targeting Wnt/β-Catenin pathway (72). A recent study also reported that lncRNA PSMG3-AS1 was significantly upregulated in GBM. PSMG3-AS1 was observed to promote TMZ resistance in glioma cells by binding to c-Myc in the nucleus (74).

The silencing of lncRNA miR-155 host gene (MIR155HG) expression was previously reported to promote glioma sensitivity to TMZ through the Wnt/β catenin pathway by

inhibiting poly-pyrimidine tract-binding protein 1 expression (64). Furthermore, the knockdown of LINC00511 expression enhanced the sensitivity of U87-R glioma cells to TMZ by targeting miR-126-5p and activating Wnt/β-catenin signaling (82). It has also been previously reported that EGFR signaling plays a key role in GBM (85), by regulating lncRNA nuclear enriched abundant transcript 1 (NEAT1) expression and in turn promoting glioma cell growth by targeting the Wnt/β-catenin pathway. Taken together, these results suggest that NEAT1 is a potential therapeutic target in GBM (86).

p21/Notch pathway. TMZ has been shown to induce GBM cell senescence and autophagy, which promote GBM cell survival without affecting proliferation (87). TMZ-induced senescence has been found to be dependent on p21 activity. GSCs are a main cause of TMZ resistance. MMP14 is an enzyme that is localized to the cell membrane (88). It was previously reported that TMZ treatment increased MMP14 expression in GSCs, which activated Notch signaling (89). In another study, the expression of lncRNA LINC00021 was revealed to be markedly upregulated in TMZ-resistant GBM cells, and the silencing LINC00021 expression promoted TMZ sensitivity, whilst suppressing the apoptosis of TMZ-resistant cells (75). Additionally, the expression of p21 was found to be downregulated by LINC00021 by targeting EZH2. Western blot analysis revealed that LINC00021 knockdown inhibited Notch expression. Therefore, LINC00021 was concluded to promote the malignant features of GSCs and the chemoresistant phenotype through the p21/Notch axis (75).

EMT signaling pathway. EMT has been observed to not only promote cell migration, but also chemoresistance in tumor cells. Wen *et al* (90) reported that the expression of EMT markers was upregulated in oxaliplatin-resistant human gastric cancer cell lines. In addition, EMT has been found to be associated with the resistance of pancreatic cancer to treatment (91). In another study, Peng *et al* (92) discussed that EMT can be regulated through miRNAs and summarized a list of drug candidates that may suppress EMT in cancer. EMT was also identified to be part of the mechanism underlying cancer resistance to EGFR tyrosine kinase inhibitors in both mouse models and in clinical non-small cell lung cancer (NSCLC) specimens (92). However, the effects of EMT on TMZ resistance in glioma cells remain unclear and require further investigation. Previously, a novel lncRNA TCONA_00004099 was identified through the analysis of sequencing data, the expression levels of which were high in glioma tissues and cell lines (79). In both *in vitro* and *in vivo* models, TCONA_00004099 knockdown was found to inhibit glioma progression and promote TMZ-induced U87 and U251 cell apoptosis. This mechanism of resistance associated with TCONA_00004099 in glioma was then examined using miRNA mimics. TCONA_00004099 was demonstrated to sponge the miRNA TCONA_00004099 and its target protein tyrosine phosphatase, receptor type F, which is involved in EGF signaling (79). Therefore, these findings reveal potentially novel therapeutic targets for TMZ-resistant glioma. lncRNA EGFR-AS1 was previously observed to promote the proliferation, migration and invasion, whilst inhibiting the apoptosis of glioma cells by regulating miR-133b/ribosomal receptor for activated C-kinase 1 (RACK1) (80). However, the effects of lnc-EGFR-AS1 on the sensitivity of GBM cells to TMZ requires further investigation both *in vivo* and *in vitro* (80). lncRNA HOTTIP expression was reported to be significantly elevated in SF268 glioma cells, particularly resistant to TMZ (93). Moreover, the expression of miR-10b and the mesenchymal markers, ZEB1/ZEB2, was increased, while the expression of E-cadherin was decreased in SF268, indicating that EMT plays a crucial role in TMZ resistance. Moreover, EMT was reversed in HOTTIP overexpressing cell lines by silencing miR-10b. Thus, HOTTIP regulated TMZ resistance in glioma cells via the EMT signaling pathway by targeting miR-10b (93).

FGFR3, platelet-derived growth factor receptor (PDGFR) and EGFR have all been found to be among the upregulated receptor tyrosine kinases involved in GBM tumorigenesis (94,95), which are also associated with the EMT process. The expression profile of FGFR3 was consistent with that of EGFR, whereby FGFR inhibition enhanced NSCLC sensitivity to EGFR inhibitors (96). Furthermore, PDGFR was found to promote the EMT process in glioma by promoting ZEB1 expression, an inducer of EMT (97). Cui *et al* (76) previously reported that lncRNA colon cancer-associated transcript 1 (CCAT1) expression was increased in glioma tissues, whilst that of miR-181b was downregulated. CCAT1 silencing was observed to significantly suppress the malignant biological behavior of glioma cells, which was reversed with miR-181b inhibitors. In addition, CCAT1 was found to function as a ceRNA with miR-181b to promote the expression of FGFR3 and PDGFR. Collectively, CCAT1 downregulation suppressed glioma growth by targeting miR-181b, resulting in the downregulation of the endogenous targets, FGFR3 and PDGFR (76). However, the effects of CCAT1 on the resistance of gliomas to TMZ and EMT require further *in vivo* and *in vitro* investigations.

p38/MAPK pathway. The function of p38 MAPK signaling is to relay extracellular stimuli through the cell (98). The activation of the p38 MAPK pathway has been reported to promote glioma invasiveness (99). Nuclear transcription factor erythroid 2p45 (NF-E2)-related factor 2 (Nrf2) has also been shown to promote the resistance of glioma cells to the combined treatment of TMZ and radiotherapy (100). In addition, another previous study found that TMZ increased Nrf2 expression by activating the p38 MAPK signaling pathway, leading to the development of TMZ resistance (101).

The role of lnc-TALC in promoting the resistance of GBM to TMZ has been observed. Furthermore, lnc-TALC can be incorporated into exosomes and exported to tumor-associated macrophages to promote M2 polarization. M2 macrophage polarization has been shown to be associated with the secretion of complement components C5/C5a, which occurs after the binding of lnc-TALC to enolase 1 to promote the phosphorylation of p38 MAPK. Furthermore, C5/C5a can promote the resistance to chemotherapy of GBM. Taken together, lnc-TALC can potentially regulate the microenvironment of GBM to improve GBM resistance to TMZ chemotherapy through the p38 MAPK pathway (70).

PTEN/PI3K/Akt pathway. PTEN is a protein phosphatase that targets the lipid phosphatidylinositol-3,4,5-triphosphate (PIP3), which is the product of PI3K. PTEN mutation and PI3K activation promote the accumulation of PIP3, resulting in the activation of AKT (102). PI3K/AKT signaling activation is associated with the expression of MGMT, the main factor of TMZ resistance. Supporting this, the pan-PI3K inhibitor, PX-866, has been found to block TMZ-induced autophagy, whilst promoting GBM cell death (103). In addition, the activation of PTEN/PI3K/AKT signaling has been reported to be an essential step in the development of TMZ resistance in GBM cells in a MGMT-dependent manner (104-106).

In glioma tissues and cells resistant to TMZ, the expression of the lncRNA musculin antisense RNA1 (MSC-AS1) has been demonstrated to be increased. MSC-AS1 knockdown has been shown to induce cell apoptosis and promote TMZ sensitivity by targeting the PI3K/AKT pathway (65). Cytoplasmic polyadenylation element binding protein (CPEB4) is an RNA-binding protein that participates in autophagy. The increased expression of CPEB4 has been found to be associated with migration, tumor growth, angiogenesis, metastasis and invasion (66). Additionally, the suppression of lncRNA-forkhead box D2-antisense RNA1 (FoxD2-AS1) expression has been found to inhibit the invasion, proliferation, migration and of TMZ-resistant glioma cells by promoting miR-98-5p expression, which inhibits CPEB4 expression (67). These data suggest that FoxD2-AS1 can inhibit glioma chemoresistance to TMZ by modulating the miR-98-5p/CPEB4 axis (58). Furthermore, the expression of CPEB4, as a target of miR-373-3p, was also found to be regulated by MSC-AS1. Specifically, MSC-AS1 knockdown inhibited the malignant behavior of glioma cells and increased their sensitivity to TMZ by sponging miR-373-3p, which activated the PI3K/Akt pathway both *in vitro* or *in vivo* (65). Similarly, the expression of the non-catalytic region of tyrosine kinase adaptor protein 1-antisense RNA1 was reported to be increased in glioma tissues and cells resistant to TMZ, which facilitated the resistance to TMZ by activating the miR-137/tripartite motif containing 24 pathways (81). In addition, in a previous study, the expression of the lncRNA LINC01410 was found to be upregulated in GBM and in GBM cells resistant to TMZ. LINC01410 silencing promoted the sensitivity of TMZ-resistant cells whilst also upregulating the expression of PTEN but reducing the phosphorylation of AKT. Inhibition of miR-370-3p reversed the effects of LINC01410 silencing on the malignant biological behavior of GBM cells. Based on these findings, LINC01410 was concluded to promote glioma growth and TMZ resistance by sponging miR-370-3p to inhibit the PTEN/AKT pathway (62).

p53 signaling. p53 is a key transcription factor that can regulate the transcription of target genes in response to DNA damage. p53 suppresses the gene expression of O^6-alkylguanine DNA alkyltransferase. In addition, Y-box binding protein 1 and mouse double minute 2 homolog were found to be overexpressed in glioma cells and were previously found to be associated with TMZ resistance by directly targeting p53 (107,108). Therefore, p53 may be associated with the resistance of glioma cells to TMZ.

The levels of lncRNA brain cytoplasmic RNA1 (BCYRN1) were previously found to be increased in the blood and tumor tissues from patients with GBM. Furthermore, the expression of BCYRN1 differed significantly from that of isocitrate dehydrogenase 1 (IDH1) and the p53 status and was markedly higher compared with both p53 and Ki-67 expression. The silencing of BCYRN1 expression was previously reported to inhibit the proliferation, migration, invasion and reverse resistance to TMZ in GB cells by sponging miR-218-5p (68).

Compared with normal tissues, higher expression levels of lncRNA CCAT2 were previously found in glioma tissues and cells and were found to negatively correlate with those of miR-424 (69). In addition, different glioma cell lines exhibited varying degrees of resistance to chemotherapeutic agents. Specifically, SHG44 was the most resistant cell line whereas U251 cells were more sensitive to agents, such as TMZ. However, regardless of the cell line tested, the knockdown of CCAT2 expression or the overexpression of miR-424 markedly inhibited the proliferation, invasion and migration of glioma cells (69). Furthermore, checkpoint kinase 1 (CHK1), which is activated by DNA damage, was reported to be a target of miR-424. The overexpression of CHK1 reversed the effects of miR-424 overexpression in both p53 wild-type and p53 mutant glioma cells (109). Taken together, these findings suggest that lncRNA CCAT2 expression is upregulated in glioma tissues and cells, which in turn promotes tumor growth and resistance to TMZ possibly through the miR-424/CHK1 axis (69).

PIM1/survivin pathway. PIM1 is a serine/threonine kinase that plays a key role in promoting cell proliferation and conferring chemoresistance in various malignancies, such as prostate cancer, HER2-positive breast cancer, high-risk neuroblastoma, triple negative breast cancer and so on (110-113). The expression of survivin can be decreased by the MGMT inhibitor (114). In addition, TMZ-induced senescence results in tumor cell cycle arrest, promoting TMZ resistance. Song *et al* (115) previously indicated that the knockdown of survivin promoted glioma cell sensitivity to TMZ treatment by inducing the apoptosis of senescent cells. Furthermore, survivin nuclear trapping has been found to facilitate GBM response to TMZ (116).

The lncRNA potassium voltage-gated channel subfamily Q member 1 opposite strand/antisense transcript one gene (KCNQ1OT1) was previously reported to promote the proliferation and colony formation of glioma cells by negatively regulating miRNA-761 expression. It was also found to impair the effects of TMZ on the promotion of the apoptosis of glioma cells *in vitro*. Furthermore, the overexpression of KCNQ1OT1 was found to increase survivin expression by promoting PIM1 expression in glioma cells. *In vivo*, the experimental results were consistent with their *in vitro* counterparts. Taken together, it was found that lncRNA KCNQ1OT1 played a significant role in glioma sensitivity to TMZ by sponging miR-761 to activate PIM-1/survivin signaling, which may be exploited as a potential prognostic target (78).

Programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) signaling pathway. Over the past decade, immune checkpoint inhibitors have become a topic of extensive research for tumor treatment. Among these, PD-1/PD-L1 have been found to exert promising therapeutic

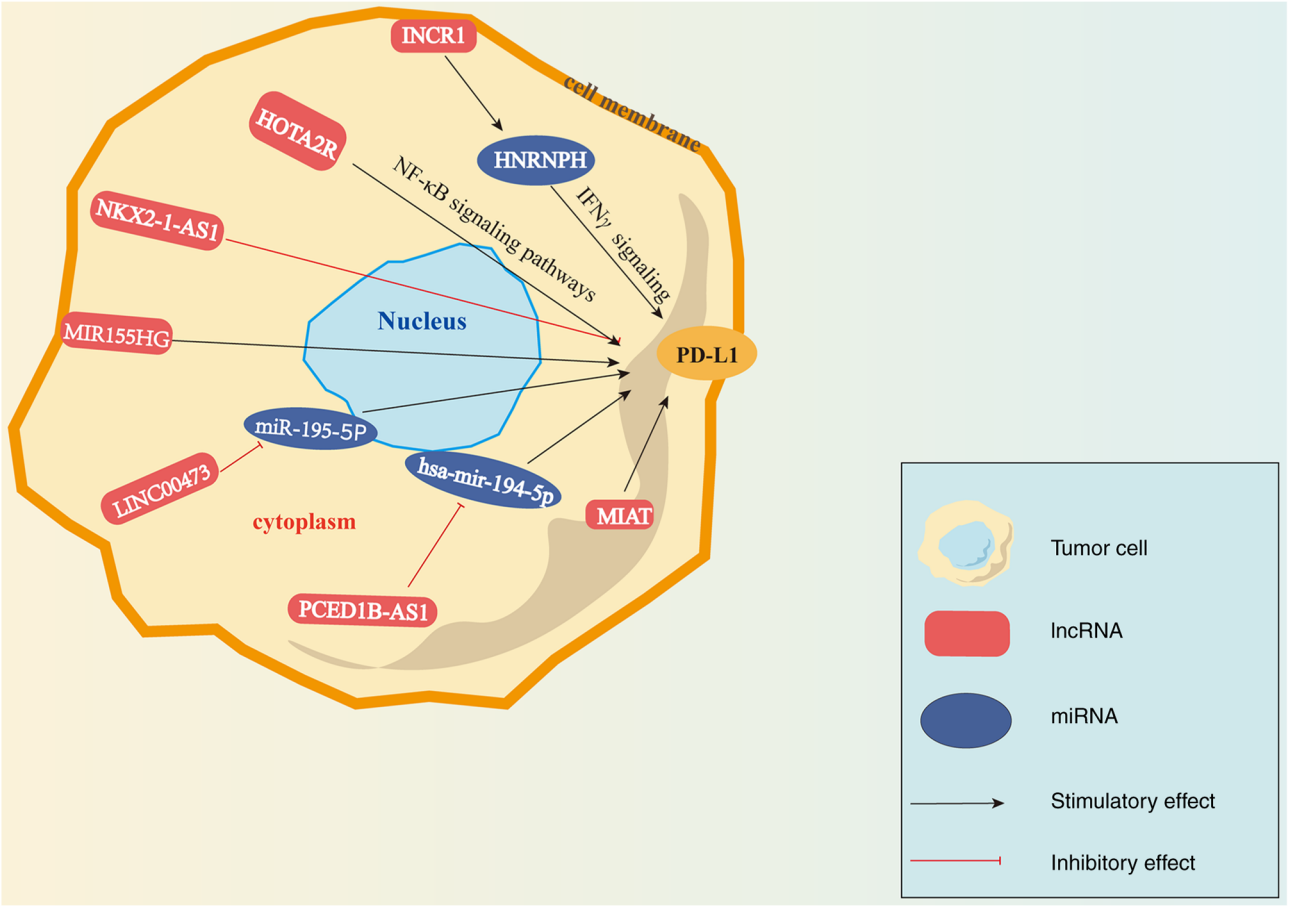

Figure 1. lncRNAs regulate the PD-1/PD-L1 axis in tumor cells. lncRNAs, long non-coding RNAs; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

effects against various malignancies. PD-L1 has also been shown to be strongly expressed in a wide range of tumor cells, including breast cancer, oral squamous cell carcinoma and nasopharyngeal carcinoma (117-119). The PD-1/PD-L1 signaling pathway plays a constructive role in tumor immunosuppression by inducing T-cell death and activating tumor immune escape (120).

Furthermore, several studies have demonstrated that a number of lncRNAs are associated with PD-1/PD-L1 in different types of cancer (Fig. 1). A previous study demonstrated that human antisense lncRNA-NK-2 homeobox 1 antisense RNA1 (NKX2-1-AS1) negatively regulated the expression of endogenous CD274/PD-L1, and that NKX2-1-AS1 knockdown was able to upregulate the expression of genes that are involved in cell adhesion and checkpoints (121). In addition, PD-1/PD-L1 was found to exert promoting effects on diffuse large-B-cell lymphoma (DLBCL), and lncRNA SNHG14 expression negatively correlated with miR-152-3p, the expression of which was decreased in DLBCL tissues and cell lines. Furthermore, SNHG14/miR-152-3p inhibited apoptosis and promoted cell proliferation in cytotoxic T-lymphocytes (CTLs) in DLBCL by sponging the PD-1/PD-L1 checkpoint (122). Similarly, SNHG15 lncRNA, which is highly expressed in gastric cancer cells, was reported to increase the expression of PD-L1 (123). Zhou *et al* (124) found that in pancreatic cancer tissues and cell lines, the expression of LINC00473 was increased, whilst that of miR-195-5p was decreased, and the expression of PD-L1 was increased. Mechanistically, LINC00473 upregulated PD-L1 expression by targeting miR-195-5p. Furthermore, $CD8^+$ T-cells could be activated either by the silencing of LINC00473 expression or increasing miR-195-5p expression, which inhibited PC progression (124). In addition to these aforementioned pre-clinical findings, a database analyses have also revealed the potential of lncRNAs in regulating PD-1/PD-L1 signaling. According to The Cancer Genome Atlas-liver hepatocellular carcinoma (HCC) dataset, PC-esterase domain-containing 1B-antisense RNA1 promoted PD-L1 and PD-L2 expression by inhibiting hsa-miR-194-5p expression, resulting in immunosuppression in HCC (125). Similarly, the association between lncRNA-myocardial infarction associated transcript (MIAT) and immunomodulatory regulation in HCC was also investigated. The results revealed that the expression of MIAT in HCC was positively associated with that of PD-1/PD-L1. Furthermore, MIAT reduced the sensitivity of HCC to sorafenib, an anticancer drug, mediating immune escape (126).

Previous studies have demonstrated that various lncRNAs can regulate the PD-1/PD-L1 axis in gliomas. The lncRNA interferon (IFN)-stimulated non-coding RNA 1 (INCR1) can be transcribed from the PD-L1 locus following stimulation by tumor IFNs and can promote checkpoint blockade resistance in GBM. INCR1 knockdown was found to inhibit PD-L1

expression and enhance GBM cell sensitivity to cytotoxic T-cell-mediated cell death (127). Mechanistically, INCR1 was found to promote the expression of PD-L1 genes by binding to heterogeneous nuclear ribonucleoprotein H1 (HNRNPH1), a nuclear ribonucleoprotein, to negatively regulate the transcription of PD-L1. In summary, INCR1 lncRNA can regulate PD-L1 expression and responses to immune checkpoint therapy by targeting HNRNPH1 after IFNγ signaling (127). Similarly, the lncRNA HOTAIR was also found to be highly expressed in glioma cells (77). Bioinformatics analysis revealed that HOTAIR activated the expression of proteins in the NF-κB signaling pathway. Furthermore, the downregulation of HOTAIR expression was found to inhibit PD-L1 expression *in vivo*, suggesting that HOTAIR can improve the sensitivity of glioma cells to immune checkpoint inhibitor therapy. In summary, HOTAIR positively regulated PD-L1 expression by targeting the NF-κB signaling pathway in gliomas (77). According to the existing public bioinformatics database, higher levels of the lncRNA MIR155HG have been shown to be associated with a poorer overall survival of patients with GBM. In addition, the levels of MIR155HG expression have been demonstrated to be significantly consistent with those of PD-L1, suggesting that MIR155HG can be used predict the efficacy of immune checkpoint inhibitor therapy (63). Taken together, lncRNAs may represent a therapeutic target that can regulate the effects of PD-1/PD-L1 treatment in various types of cancer, particularly gliomas. However, T-cells in GBM are very unresponsive to immunotherapy, and PD-1 checkpoint blockade cannot be overcome through intracellular regulation. Further research on combination therapy is still in progress (128). Due to chemo-immunotherapy resistance, Miyazaki *et al* (129) used a TMZ-treated glioma model to examine the effects of anti-PD-L1 antibody on the tumor microenvironment. They also established TMZ-resistant TS (TMZRTS) cells to examine the effects of anti-PD-L1 antibody on glioma growth. The results of their study revealed that anti-PD-L1 antibody significantly suppressed tumor growth and markedly decreased CD163-positive M□ infiltration into tumors. However, the safety and effectiveness of clinical therapy need to be further studied (129). Nivolumab is a type of PD-1 inhibitor. Recent research has reported that a patient with GBM received nivolumab treatment for almost 2 years following standard radiotherapy and TMZ therapy. Magnetic resonance imaging revealed a continuous shrinking of the tumor (130), suggesting that the combined application with PD-1 inhibitor may be effective for the treatment of gliomas. Clinically, TMZ is used as an adjuvant therapy for patients with glioma, while the prognosis is poor. Thus, exploring the role of PD-1/PD-L1 combined with TMZ is of therapeutic significance. Notably, it was demonstrated that stereotactic radiation, which to date is a conventional treatment for glioma, combined with anti-PD-1 blockade enhanced the long-term survival rate of tumor-bearing mice (131), which provided further evidence of the potential of combining TMZ with PD-1 inhibitors. In a previous clinical study, 47 patients were divided into two subgroups (132). One subgroup of 27 patients, which was named as ADCTA, was treated with concomitant chemo-radiotherapy (CCRT). Moreover, the patients also received post-surgical adjuvant immunotherapy with an autologous dendritic cell/tumor antigen vaccine. The other subgroup was only treated with CCRT and TMZ without immunotherapy as the control group. The results of that study demonstrated that the ADCTA group exhibited a markedly low TIL $PD\text{-}1^{+}/CD8^{+}$ ratio within the GBM tumor compared with the control group, which prolonged the overall survival rate of the patients. On the whole, that study suggested that adjuvant immune therapy for the immune system combined with conventional therapies, such as TMZ has great potential for the treatment of GBM (132). In conclusion, the com-bination of immune checkpoint inhibitors and anti-tumor chemical drugs, such as TMZ, has a promising therapeutic effect on glioma, which further provides new insight into the treatment of gliomas in clinical practice.

4. Tumor suppressive lncRNAs influence the sensitivity of gliomas to TMZ

The expression of a number of tumor suppressor lncRNAs (Table II) has been found to be downregulated in gliomas compared with normal brain tissues (38). The re-expression of these tumor suppressor lncRNAs can enhance the therapeutic effects of TMZ by regulating the mTOR, PTEN/AKT and p53/NF-κB signaling pathways.

mTOR signaling pathway. mTOR is a serine/threonine kinase that can regulate cell proliferation (133). Tomar *et al* (83) previously observed that mTOR signaling was activated following TMZ treatment. A novel inhibitor (Rapalink-1) targeting the mTOR pathway was previously identified to function synergistically with TMZ to reduce cell proliferation (134). Autophagy is a process that has been previously associated with TMZ resistance. Zou *et al* (135) reported that the upregulation of autophagy was mediated by transient receptor potential cation channel subfamily C member 5 in glioma cells, which promoted TMZ resistance through the mTOR signaling pathway. Based on this finding, it can be hypothesized that the mTOR pathway is associated with autophagy, thereby affecting TMZ resistance.

In vitro, the expression of the lncRNA cancer susceptibility candidate 2 (CASC2) was found to be decreased in glioma tissues and cell lines, the upregulation of which was associated with a longer survival time (136). Clinically, TMZ treatment significantly inhibited glioma proliferation, whilst the upregulation of CACS2 expression resulted in the opposite effect. Furthermore, a downstream target of CASC2 was determined to be miR-193a-5p, with which negatively correlated (136). In TMZ-resistant glioma cells, CASC2 upregulation impaired autophagy, which was reduced by TMZ by inhibiting miR-193a-5p expression, thereby activating the mTOR pathway. These data suggest that upregulating the expression of CASC2 may be a potential therapeutic target for patients with TMZ-resistant glioma. However, further clinical trials are required to examine the feasibility of this target (136).

lncRNA growth arrest specific 5 (GAS5) has been reported to play a constructive role in various tumor types, such as gastric cancer and NSCLC. It has been observed to inhibit the proliferation, migration and invasion of human glioma cells by targeting miR-18a-5p or miR-196a-5p (137,138). In addition, GAS5 can reverse glioma cell resistance to cisplatin by preventing excessive autophagy through activation of mTOR

Table II. Functions and targets of tumor suppressive lncRNAs affecting TMZ resistance in glioma.

lncRNA	Cell lines	Targets/ regulators	Signaling pathways	Functional impact	(Refs.)
CASC2	-	miR-181a/ miR-193a-5p	PTEN/p-AKT mTOR	Impairs TMZ resistance and proliferation of glioma.	(131,137)
GAS5	U251 U87	miR-18a-5p/ miR-196a-5p	mTOR	Suppresses the proliferation, migration, and invasion of humanglioma cells; attenuates gliomacell resistance	(132,135)
ZNF281	U251s	-	NF-κB1	Suppresses the self-renewal capacity and invasion of glioma stem-like cells	(139)
PR-LncRNA	-	SOX	p53	Inhibits the malignant behavior of glioma cells	(139)
LIFR-AS1	-	miR-4262	NF-κB	Inhibits glioma cell growth and enhance glioma cell sensitivity to TMZ	(140)

lncRNAs, long non-coding RNAs; TMZ, temozolomide; CASC2, cancer susceptibility candidate 2; GAS5, growth arrest specific 5; ZNF281, zinc finger protein 281; LIFR-AS1, leukemia inhibitory factor receptor-antisense RNA1.

signaling (139). Similarly, in another previous study (140), which investigated the U251 and U87 cell lines, the expression of GAS5 was found to be decreased, and the upregulation of GAS5 was able to inhibit tumor growth by sponging glutathione-S-transferase M3, the overexpression of which has been associated with chemoresistance. However, the effects of GAS5 on the resistance of glioma cells to TMZ require further examination *in vitro* and *in vivo* (140).

PTEN/p-AKT pathway. lncRNAs can also regulate resistance to TMZ by targeting the PTEN, p53 and PI3K/AKT/mTOR pathways (141). In a previous study, the overexpression of lncRNA CACS2 was found to reverse the resistance of glioma cells to TMZ by suppressing miR-181a expression (142). In addition, CASC2 promoted PTEN protein expression and inhibited AKT phosphorylation by targeting miR-181a in a reversible manner by miR-181a overexpression. Therefore, CASC2 may be a clinically relevant lncRNA that can mediate TMZ resistance by regulating miR-181a expression (142).

p53/NF-κB pathway. NF-κB is a transcription factor and plays a key role in cell survival, inflammation and immune responses. In particular, NF-κB has been found to be associated with cellular senescence in response to chemotherapy. Accordingly, senescence induced by chemotherapy and mediated by NF-κB is a key characteristic of superior therapeutic outcomes (143). Therefore, NF-κB will likely affect TMZ resistance by modulating cellular senescence.

The p53-regulated tumor suppressor signature of lncRNAs (PR-lncRNAs) was first identified in colorectal cancer (144). In glioma, the expression of PR-lncRNAs was found to be negatively associated with its grade (145). A previous functional study reported that PR-lncRNA knockdown aggravated glioma malignancy by inhibiting SOX activity. This suggests that the downregulation of PR-lncRNAs can abrogate the beneficial effects of PR-lncRNAs on cell proliferation, migration, invasion and resistance to TMZ *in vitro* (145). Similarly, the expression of leukemia inhibitory factor receptor-antisense RNA1 (LIFR-AS1) has also been found to be decreased, whereas that of miR-4262 was found to be increased in glioma tissues and cell lines. The overexpression of LIFR-AS1 inhibited glioma cell proliferation and enhanced glioma cell sensitivity to TMZ by inactivating the miR-4262/NF-κB pathway (146). lncRNA-zinc finger protein 281 (ZNF281) was previously reported to be expressed at lower levels in glioma stem-like cells (U251s) compared with those in normal brain tissues. Furthermore, lncRNA-ZNF281 was able to suppress the self-renewal capacity and invasion of glioma stem cells by activating the NF-κB signaling pathway *in vitro* and *in vivo* (147).

The various mechanisms of lncRNAs in the regulation of TMZ resistance in glioma are illustrated in Fig. 2.

5. Conclusions and future perspectives

GBM, which is considered to originate from neural stem cells or progenitors, remains to be one of the greatest threats to human health to date. Regrettably, even with the traditional treatment methods of gliomas, including surgery, radiation therapy and alkylating agent chemotherapy, such as TMZ, the overall survival of patients with gliomas has not improved satisfactorily (148). Additionally, >50% patients with glioma treated with TMZ develop resistance to this drug, which has become a major obstacle in the clinical treatment efficacy of glioma (9). Apart from DNA repair systems, the mechanism underlying chemotherapy resistance also included translesion synthesis (TLS). When DNA lesions occur due to chemotherapy and/or radiation, such as following treatment with

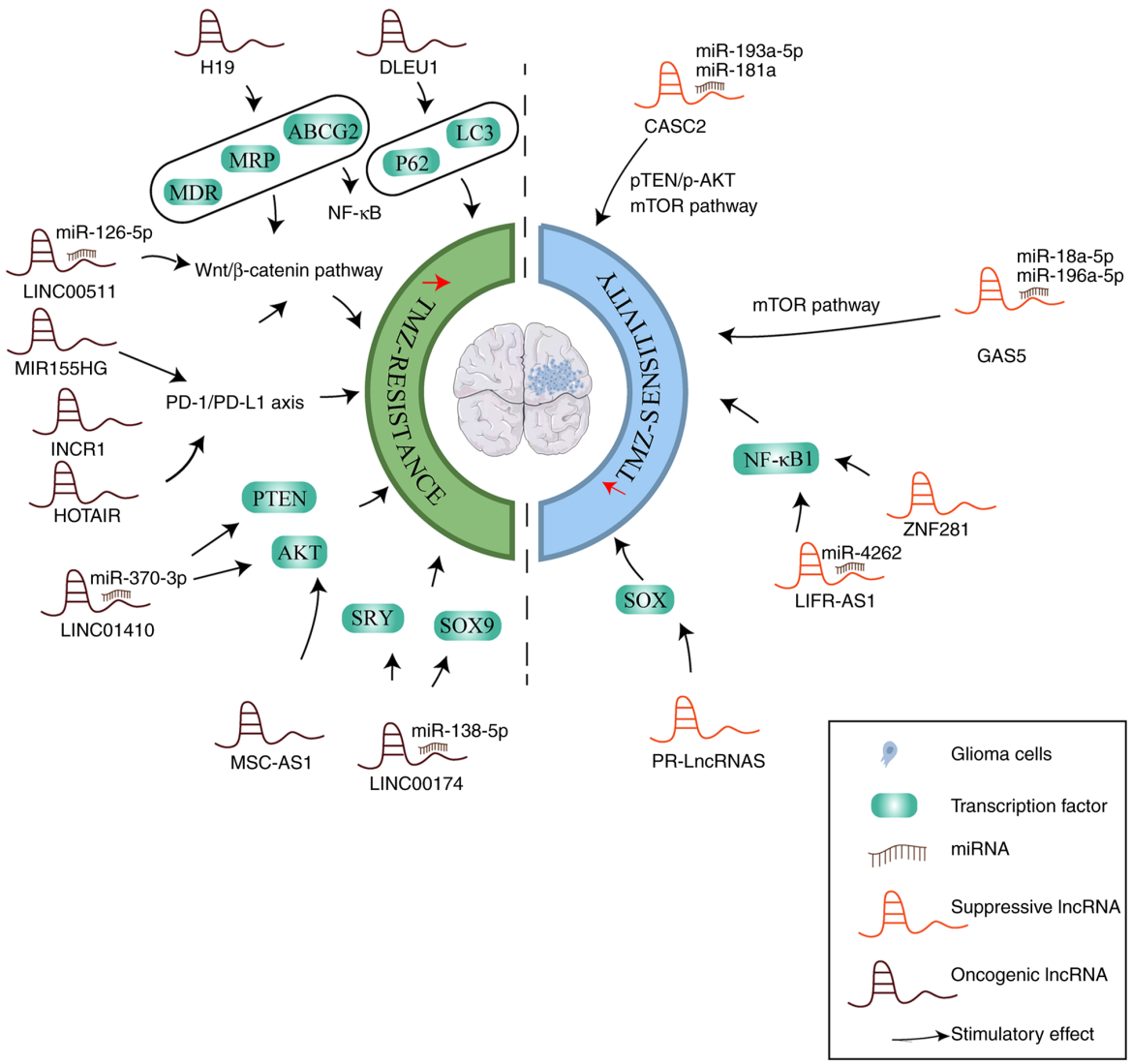

Figure 2. Mechanisms of lncRNAs in the regulation of TMZ resistance in glioma. lncRNAs, long non-coding RNAs; TMZ, temozolomide; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; INCR1, IFN-stimulated non-coding RNA 1; MSC-AS1, musculin antisense RNA1; CASC2, cancer susceptibility candidate 2; GAS5, growth arrest specific 5; ZNF281, zinc finger protein 281; LIFR-AS1, leukemia inhibitory factor receptor-antisense RNA1; MDR, multi-drug resistance gene; MRP, multidrug resistance-associated protein; ABCG2, ATP Binding Cassette Subfamily G Member 2; DLEU1, deleted in lymphocytic leukemia 1.

cisplatin and TMZ, TLS can bypass these types of lesions at the cost of increasing the risk of mutations (149), which in turn increases the risk of developing chemotherapeutic resistance. The TLS process involves several key regulators, including RAD18 (150), DNA polymerases (POL)κ, POLι, POLη or REV1 (which introduce a nucleotide opposite the lesion) and TLS DNA polymerase, such as POLζ (comprising of the Rev3L/Rev7/Pold2d/Pold3 complex) (149,151). Peng *et al* (152) previously reported that the overexpression of POLκ increased the TMZ resistance of GBM cells which were previously TMZ-sensitive. The higher expression of POLκ significantly promoted TMZ sensitivity *in vitro* and in orthotopic xenograft mouse models. Furthermore, other TLS polymerases, such as Rev1 and Rev7, have been proposed as targets for developing agents for reversing chemoresistance (151,153). RAD18 was previously found to be overexpressed in GBM cell lines, where it promoted resistance to radiotherapy by inhibiting the expression of p53 (154).

lncRNAs have been demonstrated to regulate the survival, proliferation, apoptosis and invasion of GBM cells (155). Furthermore, lncRNAs play a key role in regulating the resistance of gliomas to TMZ by sponging miRNAs and various signaling pathways. However, TMZ can conversely regulate the levels of lncRNA ex-pression to enhance the effectiveness of TMZ treatment. Recently, lncRNA ATXN8OS was found to be mainly located in the cytoplasm and to be downregulated in glioma cell lines (156). Functional experiments proved that ATXN8OS enhanced TMZ sensitivity of glioma *in vivo* and *in vitro*. Mechanistically, ATXN8OS stabilized glutaminase 2 mRNA to promote the ferroptosis of glioma cell lines, which may become a new target of TMZ resistance (154). High mobility group box 1 protein (HMGB1), which is a highly conserved protein, has been reported to be expressed in a variety of cell types and can be secreted into the tumor microenvironment to function as a tumor-derived signal. HMGB1 expression has been found to be upregulated in GBM and to

influence GBM growth. GSCs play a crucial role in patients with TMZ-resistant glioma, and HMGB1 expression has been found to be upregulated in GSCs (157). HMGB1 can then alter the expression profile of mRNAs, lncRNAs and miRNAs in GSCs. Since TMZ-induced HMGB1 expression can promote the formation of GSCs, this process is inhibited when the secretion of HMGB1 is decreased. In terms of the mechanism, TMZ-induced upregulation of HMGB1 has been found to promote the formation of GSCs through the Toll-like receptor 2/NEAT1/Wnt pathway. Taken together, TMZ-induced HMGB1 may serve as a potential therapeutic target for the treatment of patients with TMZ-resistant GBM (157). In addition, a number of traditional Chinese medicine ingredients have also been reported to affect TMZ resistance by regulating the expression of lncRNAs. Isoliquiritigenin has been found to inhibit the expression of metabolic enzymes of arachidonic acid (AA), such as cyclooxygenase-2 (COX-2), microsomal prostaglandin E synthase-1 (mPGES-1) and cytochrome P450 (CYP) 4A11, all of which serve significant roles in glioma angiogenesis. Furthermore, isoliquiritigenin can enhance the therapeutic effects of TMZ in a rat C6 glioma model. In terms of the mechanism, isoliquiritigenin can reprogram COX-2-, mPGES-1- and CYP4A-mediated AA metabolism in glioma by suppressing angiogenic Akt/fibroblast growth factor 2/TGFβ/VEGF signaling, which was achieved by sponging miR-194-5p and lncRNA NEAT1 (158). To conclude, lncRNAs may serve as potential therapeutic and prognostic targets to improve the sensitivity of glioma to TMZ. However, enormous research efforts remain necessary to transform this basic concept into a feasible clinical strategy.

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Authors' contributions

The present review article was conceptualized by all the authors (SL, XX, FP, JD and CP). SL was involved in the study design and in the preparation of the original draft. FP, XX and JD edited the manuscript. FP, JD and CP were involved in funding-related administration. SL and FP were involved in manuscript revision. All authors have read and agreed to the published version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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