NcRNAs: Multi-angle participation in the regulation of glioma chemotherapy resistance (Review)

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Abstract. As the most common primary tumour of the central nervous system, gliomas have a high recurrence rate after surgical resection and are resistant to chemotherapy, particularly high-grade gliomas dominated by glioblastoma multiforme (GBM). The prognosis of GBM remains poor despite improvements in treatment modalities, posing a serious threat to human health. At present, although drugs such as temozolomide, cisplatin and bevacizumab, are effective in improving the overall survival of patients with GBM, most patients eventually develop drug resistance, leading to poor clinical prognosis. The development of multidrug resistance has therefore become a major obstacle to improving the effectiveness of chemotherapy for GBM. The ability to fully understand the underlying mechanisms of chemotherapy resistance and to develop novel therapeutic targets to overcome resistance is critical to improving the prognosis of patients with GBM. Of note, growing evidence indicates that a large number of abnormally expressed noncoding RNAs (ncRNAs) have a central role in glioma chemoresistance and may target various mechanisms to modulate chemosensitivity. In the present review, the roles and molecular mechanisms of ncRNAs in glioma drug resistance were systematically summarized, the potential of ncRNAs as drug resistance markers and novel therapeutic targets of glioma were discussed and prospects for glioma treatment were outlined. ncRNAs are a research direction for tumor drug resistance mechanisms and targeted therapies, which not only provides novel perspectives for reversing glioma drug resistance but may also promote the development of precision medicine for clinical diagnosis and treatment.

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Contents

1. Introduction

Gliomas are the most common malignancy of the central nervous system, accounting for 80% of all primary brain tumours. The recurrence and mortality rates of gliomas are high (1). Glioblastoma multiforme (GBM) is a grade 4 highly aggressive tumour. Although a variety of high-intensity treatment regimens (such as a combination of surgery and chemoradiotherapy) have been adopted, the median survival time for patients with GBM remains at only 12-15 months

and the 5-year survival rate is only 3-5% (1). A randomized phase III clinical study of temozolomide (TMZ) indicated that the median survival time for patients with GBM treated with a combination of TMZ and concurrent radiotherapy was 14.6 months and that the median survival time for patients treated with radiotherapy alone was 12 months (2). Although TMZ is currently the standard first-line chemotherapeutic drug for malignant gliomas, TMZ resistance has become a substantial obstacle to the chemotherapeutic treatment of gliomas and frequently leads to treatment failure and poor prognosis. Therefore, the regulatory processes leading to the development of drug resistance in gliomas have attracted extensive attention and become an emerging research hotspot. However, the specific molecular mechanisms by which noncoding (nc)RNAs act as key molecules to regulate the drug resistance of gliomas remain to be fully elucidated and remain a key scientific task that urgently requires to be resolved to improve the clinical treatment of gliomas.

In recent years, the development of next-generation sequencing technology and bioinformatics analysis has revealed information that was previously inaccessible. The human genome contains an estimated 20,000-25,000 protein-coding genes, accounting for <2% of the entire genome. The remaining 98% of the genome encodes functional RNA molecules that cannot be translated into proteins (3). Most of the ncRNAs involved in glioma drug resistance are microRNAs (miRNAs), long noncoding RNAs (lncRNAs) and circular RNAs (circRNAs), and they are being gradually uncovered. An increasing amount of evidence indicates that ncRNAs are not only biomarkers of tumour proliferation, invasion, apoptosis, autophagy and immune response, but also regulatory factors involved in glioma drug resistance. ncRNAs may act as oncogenes or tumour suppressor genes to mediate chemoresistance during the treatment of tumours (3,4). Therefore, ncRNAs have become key molecules in glioma drug resistance and the targeted regulation of ncRNAs may become a novel therapeutic strategy to reverse drug resistance in gliomas. In the present review, the relevant mechanisms of drug resistance in gliomas were discussed and the regulatory functions and mechanisms of ncRNAs in glioma drug resistance were systematically summarized. A series of hot issues and research trends of tumour drug resistance, ncRNA and vector modification are then briefly summarized, aiming to further analyze the potential significance of ncRNAs as novel therapeutic targets for the reversal of glioma drug resistance, and providing a new direction for basic research on tumor precision treatment.

2. Mechanisms of chemotherapy resistance in gliomas

In the past, chemotherapies for gliomas overemphasized the blood-brain barrier (BBB), which was thought to limit the access of anticancer drugs to tumour tissue, resulting in chemotherapy failure (1). In fact, scholars have demonstrated that the BBB in patients with malignant gliomas is frequently damaged to varying degrees. The tolerance of gliomas themselves to anticancer drugs is the most essential cause of chemotherapy failure (5). Therefore, revealing the mechanisms of resistance is of crucial importance for reducing or eliminating the phenomenon of chemoresistance. In the following chapter, several of the most recognized mechanisms of drug resistance in gliomas were summarized (Fig. 1).

Drug transport and metabolism. After reaching their therapeutic targets, numerous antitumour drugs are actively pumped out of tumour cells against the concentration gradient by transporter proteins, reducing the intracellular accumulation of drugs and causing drug resistance. This is a classic feature of pharmacokinetics. The 3 main proteins that cause drug resistance are P-glycoprotein (P-gp), multidrug resistance-associated protein (MRP) and breast cancer resistance protein (BCRP) (6). P-gp is an ATP-dependent drug efflux pump that binds to antitumour drugs and ATP simultaneously. It utilizes the energy from ATP to transport chemotherapeutic drugs out of glioma cells, resulting in drug resistance (7). In addition, P-gp is also expressed in vascular endothelial cells and participates in drug resistance caused by the blood-tumour barrier (BTB). MRP and P-gp have the same function. These proteins specifically recognize hydrophobic chemotherapy drugs. They bind to glutathione to form a glutathione S-conjugate pump and indirectly transport weakly basic chemotherapy drugs (7,8). In a study by Marinho *et al* (9), MRP1 and MRP3 were observed to be highly expressed in glioma cells and related to resistance to chemotherapy drugs, e.g. etoposide and vincristine. BCRP was initially isolated from multidrug-resistant breast cancer cells. BCRP is also highly expressed in glioma cells. It affects the efficacy of >20 anticancer drugs (including daunorubicin and mitoxantrone), resulting in drug resistance (10). In addition to the 3 types of transporters described above, major vault protein (MVP) and lung resistance-related protein (LRP) also induce drug resistance by interfering with drug transport (6). Studies have demonstrated that both MVP and LRP are highly expressed in drug-resistant glioma cells, particularly in tumour blood vessels.

Inhibition of apoptosis. When drug resistance occurs in tumours, the apoptotic/anti-apoptotic mechanism is in an unbalanced state. P53 is a classic tumour suppressor gene. Wild-type p53 directly induces the apoptosis of tumour cells. The mechanism by which glioma cells develop resistance in the process of TMZ chemotherapy frequently involves the deletion or mutation of wild-type p53 and the significantly increased expression of O6-methylguanine-DNA methyltransferase (MGMT). As a result, apoptosis cannot be induced in glioma cells (2,11). The B-cell lymphoma-2 (Bcl-2) gene is a well-known anti-apoptotic gene and causes drug resistance in tumour cells by inhibiting apoptosis. Therefore, Bcl-2 is also recognized as a novel drug resistance gene. In addition, the apoptosis system includes a key factor, the homeobox (HOX) gene. HOX is a transcription factor. This gene is likely to be highly expressed during chemotherapy and directly induces TMZ resistance through the PI3K/AKT signalling pathway. Furthermore, HOX increases the expression of MGMT through the nuclear factor κB (NF-κB) signalling pathway, which indirectly induces the development of drug resistance (12).

DNA damage repair. The destruction of the DNA structure of tumour cells to promote apoptosis is one of the most common mechanisms of action of drugs. Conversely, this strategy

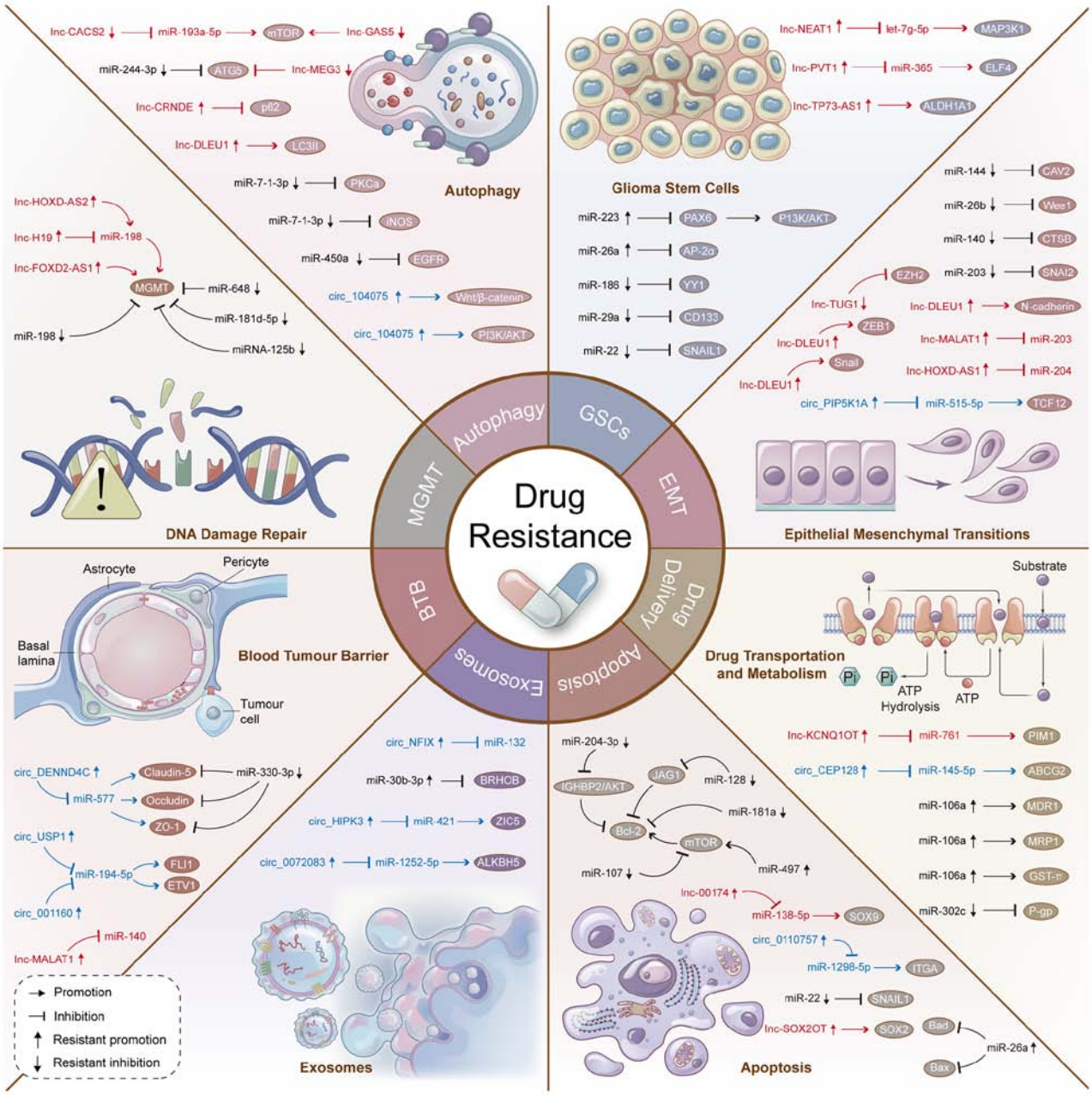

Figure 1. Novel ncRNAs and their downstream targets related to drug resistance mechanisms in glioma. Different ncRNAs (miRNAs, lncRNAs and circRNAs) and their downstream targets promote (or inhibit) chemotherapy resistance of glioma cells by regulating GSCs phenotype, EMT, drug transport, apoptosis, exosomes, blood tumour barrier, DNA repair and autophagy. EMT, epithelial-mesenchymal transition; GSC, glioma stem cell; lncRNA, long non-coding RNA; miR, microRNA; circRNA, circular RNA; MGMT, O6-methylguanine-DNA methyltransferase.

leads to the failure of chemotherapeutic drugs if glioma cells acquire an enhanced ability to repair damaged DNA during chemotherapy. MGMT is one of the predictive indicators of the prognosis and chemosensitivity of gliomas. The main function of MGMT is to repair intracellular DNA damage caused by alkylating agents. Therefore, MGMT induces resistance to antitumour drugs by preventing the formation of DNA crosslinking (13). Mismatch repair (MMR) is mainly involved in the repair of DNA replication errors. It prevents gene mutations and thus inhibits the occurrence, development and drug resistance of tumours. In addition, a complex regulatory network exists between MMR and MGMT. Studies have indicated that there is a negative correlation between them in glioma cells (11,14). Topoisomerase II (Top II) has also been an important focus of studies on chemoresistance in recent years. Top II maintains DNA stability and genome integrity in glioma cells by reducing drug efficacy (15). In addition, another study reported that the sensitivity of glioma cells to TMZ increases when the expression of poly(ADP-ribose) polymerase-1, base excision repair enzymes or high mobility group AT-hook 2 decreases (16).

Autophagy. Autophagy may exert opposite regulatory effects on tumours. It has either a promoting or an inhibitory effect and the final result depends on the type and state of the tumours. When tumour cells are stimulated by chemotherapeutic drugs, autophagy is activated as a stress response. Autophagy may provide sufficient energy for tumour cell metabolism through

degrading proteins, thereby promoting tumour development and reducing the efficacy of chemotherapeutic drugs. Studies have indicated that a number of signalling pathways are involved in TMZ-induced autophagy in glioma cells, including the PI3K/Akt/mammalian target of rapamycin (mTOR), hypoxia-inducible factor 1α (HIF-1α)/C-X-C chemokine receptor type 4 and Ras/Raf/MAPK kinase pathways (17). Therefore, inhibition of tumour drug resistance by regulating autophagy-related target genes may become a novel strategy for the treatment of drug resistance in gliomas.

Glioma stem cells (GSCs). GSCs are present in glioma tissue. These cells have strong proliferation and differentiation abilities, and conventional radiotherapy and chemotherapy are virtually ineffective against them. Therefore, GSCs are considered to be the culprit of glioma recurrence. In addition, the powerful resistance mechanisms and long survival time of GSCs allow tumour drug resistance to increase with the intracellular accumulation of related mutations. Relevant mechanistic studies also indicate that glioma chemoresistance is closely related to the high expression of drug resistance genes in GSCs, including the multidrug resistance (MDR), MGMT and ATP-binding cassette (ABC) transporter genes (18).

Epithelial-mesenchymal transition (EMT). An increasing amount of evidence indicates that glioma cells may be converted to cells with stem-like properties through EMT. Furthermore, GSCs may overexpress EMT marker molecules and undergo the EMT process. These events eventually lead to the doubling of the number of GSCs, resulting in the aggravation of glioma biological behaviours such as invasion and drug resistance (19). EMT, GSCs and chemoresistance are regarded by certain scholars as key factors for malignant progression of gliom and are assumed to be the fundamental reason these tumours are difficult to cure. Therefore, targeted intervention or the reversal of EMT may serve as a novel research approach for the treatment of glioma chemoresistance.

Mutations at drug target sites. Abnormal expression caused by target gene mutations is one of the common mechanisms of chemoresistance in tumours. In gliomas, Top II is an important target of chemotherapeutic drugs. Its enzymatic activity mediates the unwinding of DNA double strands for replication. Certain studies have indicated that Top II in patients with recurrent gliomas is prone to mutation, which frequently leads to the loss of drug targeting and the development of drug resistance (15,20). In addition, a study by Santangelo *et al* (21) demonstrated that metallothionein is highly expressed in gliomas, another important cause of chemoresistance and poor prognosis.

Tumour microenvironment. The glioma microenvironment is composed of not only tumour cells, fibroblasts, immune cells and inflammatory cells, but also the surrounding intercellular matrix, microvessels and infiltrating biological molecules. Hypoxia caused by the high proliferation of tumour cells represents a common glioma microenvironment. Hypoxia stimulates the high expression of P-gp and MDR in glioma cells, thereby enhancing the vitality and drug resistance of tumour cells (22). Similarly, cytokines secreted by stromal cells, such as transforming growth factor (TGF) and vascular endothelial growth factor (VEGF), also inhibit the cytotoxicity of chemotherapeutic drugs (23).

3. miRNAs and glioma drug resistance

As the most extensively studied regulatory factors in ncRNA research, miRNAs have been indicated to target and bind to the 3'-untranslated region (3'-UTR) of mRNAs, resulting in the direct degradation of mRNAs or the blocking of translation. Studies have indicated that through such regulatory mechanisms, miRNAs directly or indirectly participate in tumour proliferation, metastasis, drug resistance and immunity. A number of abnormally expressed miRNAs have been detected in various drug-resistant glioma cells, indicating that miRNAs have a key role in glioma chemoresistance. The following is a summary of the research on the involvement of miRNAs in the resistance of gliomas to TMZ, cisplatin (DDP), nitrosourea and plant-derived anticancer drugs (Fig. 2).

miRNAs are involved in TMZ resistance. The main mechanisms underlying the cytotoxicity of TMZ are the destruction of the DNA structure in glioma cells, prevention of DNA repair and induction of apoptosis. As a second-generation alkylating agent, this drug has good bioavailability and central nervous system permeability. At present, TMZ-based chemotherapy regimens are widely used in the postoperative adjuvant treatment of high-grade gliomas and the salvage treatment of recurrent gliomas. Although the clinical application of TMZ has a 'milestone' significance, resistance to TMZ has become an important reason limiting the efficacy of chemotherapy. TZM resistance is a key scientific problem that requires to be urgently resolved in the clinical chemotherapy treatment of gliomas. To date, numerous studies have demonstrated a relationship between miRNAs and TMZ resistance in gliomas (Table I).

Oncogenic miRNAs promote the resistance of gliomas to TMZ. Studies have indicated that in the hypoxic microenvironment, the HIF1α/HIF2α-miR210-3p network forms a positive feedback loop with epidermal growth factor (EGF) and jointly promotes the malignant progression and TMZ resistance of GBM. Jana *et al* (24) further explored a novel strategy that used tachyplesin (Tpl) as a nanocarrier for anti-miR-210 in the treatment of GBM. The results indicated that this Tpl complex significantly inhibited the expression of miR-210 and induced the expression of tumour suppressor genes neuronal differentiation 2 and HIF3A in GBM cells in a targeted manner, thereby enhancing the TMZ sensitivity of GBM (24). miR-27a-3p is highly expressed in glioma tissues and various glioma cell lines. In addition, miR-27a-3p induces chemotherapy resistance of glioma cells to TMZ by degrading the downstream target neurofibromatosis type 1 (NF1). Of note, restoration of the expression of NF1 reverses this drug resistance effect (25). NEDD4 like E3 ubiquitin protein ligase (NEDD4L) has been demonstrated to be a direct target gene downstream of carcinogenic miR-513a-5p. The inhibitory effect of miR-513a-5p on NEDD4L is directly involved in the activation of the WNT/β-catenin signalling pathway by insulin-like growth factor 1 (IGF-1) and significantly reduces the cytotoxicity of TMZ to gliomas (26).

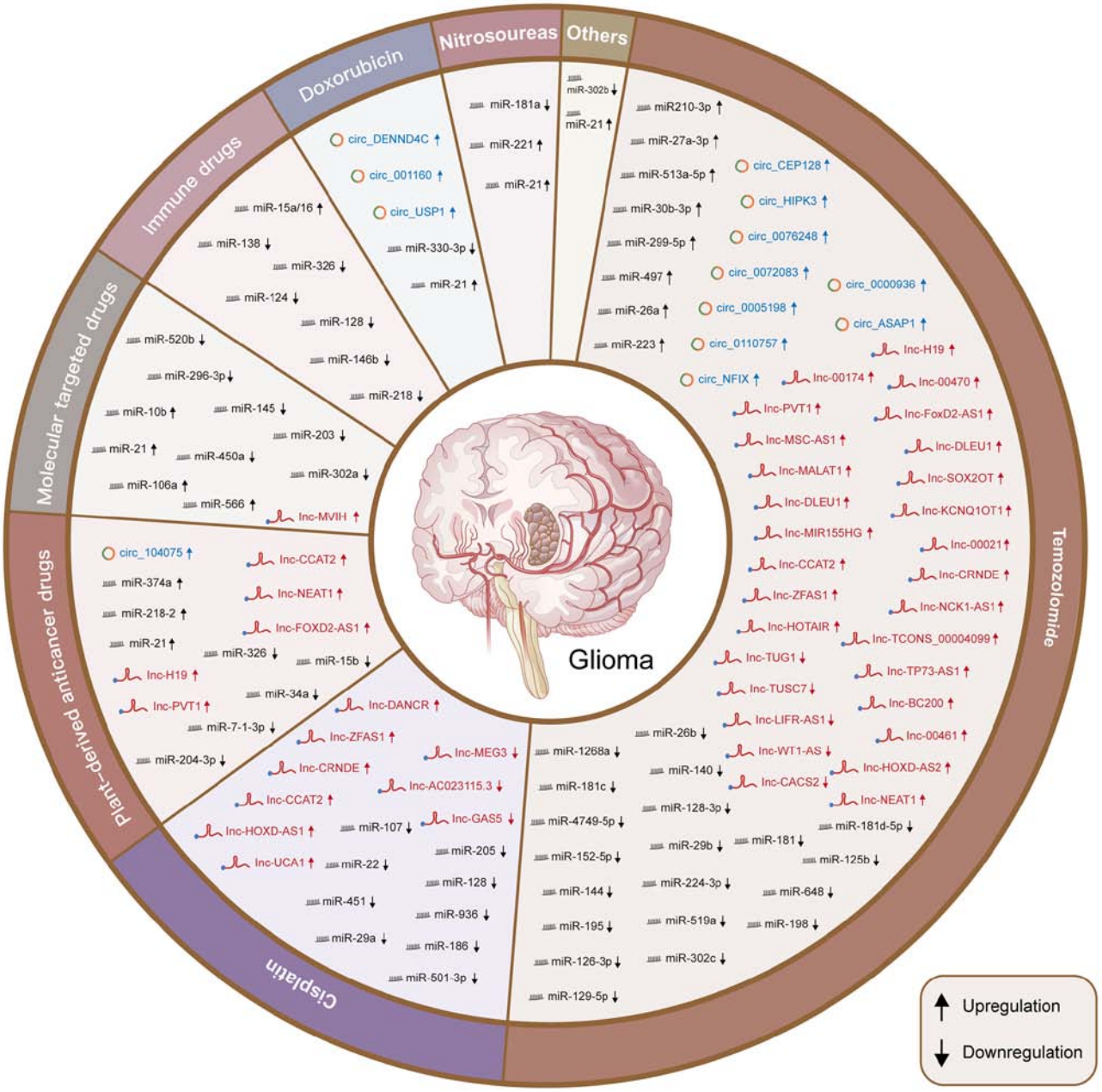

Figure 2. Novel ncRNAs related to antitumor drugs (including the proportion of genes involved in various drugs; temozolomide has a dominant role). Certain ncRNAs have differential expression and regulatory functions in the formation of drug resistance to various anti-tumor drugs (temozolomide, cisplatin, plant-derived anticancer drugs, molecular targeted drugs, immunotherapeutic drugs, doxorubicin and nitrosourea drugs), which may be used as a potential target for drug resistance treatment of glioma. NcRNA, noncoding RNA; lncRNA, long non-coding RNA; miR, microRNA; circRNA, circular RNA.

Studies have indicated that certain miRNAs regulate apoptosis-related signalling pathways and induce tumour cell escape from apoptosis, resulting in the resistance of gliomas to TMZ. For instance, HIF-1α-mediated miR-26a is a hypoxia-sensitive miRNA. The expression of miR-26a is significantly upregulated in GBM cells under hypoxic conditions. The upregulation of miR-26a directly induces the protective response of mitochondria and enhances TMZ resistance *in vivo* and *in vitro*. In addition, miR-26a inhibits the expression of Bcl-2-associated X protein (Bax) and Bcl-2-associated agonist of cell death, thereby reducing TMZ-induced apoptosis (27). Similarly, miR-299-5p, which is significantly expressed in glioma tissues and cell lines, regulates the MAPK/ERK signaling axis by targeting Golgi phosphoprotein 3, thereby inhibiting apoptosis and enhancing the chemoresistance of gliomas to TMZ (28). In addition, miR-497 upregulates the protein expression of mTOR and Bcl-2 through the IGF1 receptor/insulin receptor substrate 1 pathway, thereby inducing TMZ apoptosis resistance in glioma cells (29). GSCs have an important role in glioma chemotherapy through a variety of complex interlaced signalling networks. An increasing amount of evidence indicates that there is an association between miRNAs and GSC-driven drug resistance in gliomas. The expression of miR-30b-3p is significantly increased in hypoxic GSC-derived exosomes. miR-30b-3p may be transported in exosomes into recipient GBM cells, where it directly targets and binds to Ras homolog family member B to promote TMZ chemoresistance (30). In addition,

Table I. miRNAs involved in temozolomide resistance.

miRNA	Direction of differential expression	Genes and pathways	Mechanism	(Refs.)
miR-210-3p	↑	NeuroD2, HIF3A	-	(24)
miR-27a-3p	↑	NF1	-	(25)
miR-513a-3p	↑	NEDD4L, IGF-1	-	(26)
miR-26a	↑	Bad, Bax, AP-2α	Apoptosis, GSCs	(27,31)
miR-299-5p	↑	GOLPH3, MAPK/ERK	Apoptosis	(28)
miR-497	↑	IGFIR/IRS1, mTOR/Bcl-2	Apoptosis	(29)
miR-30b-3p	↑	RHOB	GSCs	(30)
miR-223	↑	PAX6/PI3K/AKT	GSCs	(32)
miR-181c	↓	RPN2, Tcf-4	-	(33)
miR-4749-5p	↓	RFC2	-	(34)
miR-152-5p	↓	FBXL7	-	(35)
miR-144	↓	FGF7, CAV2	-	(36)
miR-195	↓	CCNE1	Apoptosis	(37)
miR-126-3p	↓	SOX2/Wnt/β-catenin	Apoptosis	(38)
miR-181	↓	SELK	Apoptosis	(39)
miR-648, miRNA-125b	↓	MGMT	DNA damage repair	(40)
miR-181d-5p	↓	MGMT	DNA damage repair	(41)
miR-198	↓	MGMT	DNA damage repair	(42)
miR-26b	↓	Wee1	EMT	(43)
miR-140	↓	CTSB	EMT	(44)
miR-128-3p	↓	C-met, PDGFRα, Notch1, Slug	EMT	(45)
miR-29b	↓	-	Autophagy	(46)
miR-224-3p	↓	ATG5	Autophagy	(47)
miR-519a	↓	STAT3/Bcl-2/Beclin-1	Autophagy	(48)
miR-302c	↓	P-gp	Drug transport and metabolism	(49)
miR-1268a	↓	ABCC1	Drug transport and metabolism	(50)
miR-129-5p	↓	Wnt5a	Drug transport and metabolism	(51)

↑, upregulation; ↓, downregulation in temozolomide-resistant glioma; miR, microRNA; NeuroD2, neuronal differentiation 2; HIF3A, hypoxia-inducible factor 3 subunit α; NF1, neurofibromatosis type 1; NEDD4L, NEDD4 like E3 ubiquitin protein ligase; IGF-1, insulin-like growth factor 1; Bax, Bcl-2-associated X protein; Bad, Bcl2-associated agonist of cell death; GOLPH3, Golgi phosphoprotein 3; IGF1R, insulin-like growth factor 1 receptor; IRS1, insulin receptor substrate 1; mTOR, mammalian target of rapamycin; Bcl-2, B-cell lymphoma-2; RHOB, Ras homolog family member B; AP-2α, activating protein 2α; PAX6, Paired box 6; Tcf-4, transcription factor 4; RPN2, ribophorin II; RFC2, replication factor C subunit 2; FBXL7, F-box/LRR-repeat protein 7; FGF7, fibroblast growth factor 7; CAV2, Caveolin 2; CCNE1, Cyclin E1; SOX2, SRY-box 2; SELK, Selenoprotein K; MGMT, O6-methylguanine-DNA methyltransferase; CTSB, Cathepsin B; PDGFRα, platelet-derived growth factor receptor α; ATG5, autophagy-related gene 5; STAT3, signal transducer and activator of transcription 3; P-gp, P-glycoprotein; ABCC1, ATP-binding cassette subfamily C member 1; Wnt5a, wingless-related MMTV integration site 5A; GSCs, glioma stem cells; EMT, epithelial-mesenchymal transition.

high expression of exogenous miR-26a and miR-223 promotes the proliferative ability and sphere formation of GSCs, thereby inducing chemoresistance in glioma cells. Evidence indicates that miR-26a induces the proliferation of GSCs by targeting and binding to the 3'-UTR of activator protein 2α (AP-2α), thereby promoting the resistance of gliomas to TMZ (31). The expression of miR-223 is significantly increased in GBM cells. miR-223 directly binds to and negatively regulates paired box 6 and promotes the proliferation and differentiation of GSCs by regulating the PI3K/Akt signalling pathway, thereby reducing TMZ sensitivity and the growth inhibitory effect of TMZ (32).

By contrast, miRNAs may also act as tumour suppressors to reverse TMZ resistance in gliomas. In general, the expression of these miRNAs is downregulated in gliomas. The restoration of their expression is conducive to the enhancement of the sensitivity of tumour cells to chemotherapeutic drugs. For instance, overexpression of miR-181c inhibits the activity of β-catenin/transcription factor 4 (TCF-4) by targeting and binding to ribophorin II, thereby reducing the resistance of GBM cells to TMZ (33). Upregulation of miR-4749-5p causes the degradation of replication factor C subunit 2 (RFC2) and hinders RFC2 from performing DNA repair, thereby promoting TMZ-mediated cytotoxicity (34). In U251 glioma

cells, knockdown of miR-152-5p expression inhibited the chemoresistance of cells to TMZ through a targeted reduction in F-box/LRR-repeat protein 7 (35). In addition, *in vitro* molecular experiments have demonstrated that fibroblast growth factor 7 (FGF7) and caveolin 2 (CAV2) are target genes of miR-144. Knockdown of FGF7 induced apoptosis of U251 cells by activating the Akt/reactive oxygen species (ROS) pathway and knockdown of CAV2 inhibited the EMT of U251 cells. These events jointly increase the sensitivity of U251 cells to TMZ (36). In addition, certain tumour suppressor miRNAs enhance the sensitivity of glioma cells to TMZ by inducing apoptosis. The expression of miR-195 is significantly decreased in TMZ-resistant glioma cells and is negatively associated with the drug resistance index. miR-195 reverses the TMZ resistance of gliomas by targeting and binding to cyclin E1 and inducing apoptosis (37). Similarly, decreased expression of miR-126-3p has been detected in TMZ-resistant glioma tissues and cell lines. Furthermore miR-126-3p directly inhibits the expression of SRY-box 2 (SOX2) to induce Wnt/β-catenin inactivation, thereby promoting the apoptosis of glioma cells and enhancing the cytotoxicity of TMZ (38). In addition, the human miR-181 family has 8 members that have an important role in the occurrence and development of a variety of malignant tumours. Overexpression of miR-181 increases the Bax/Bcl-2 ratio and inhibits the proliferation of glioma cells by targeting and binding to the 3'-UTR of selenoprotein K, thereby enhancing the sensitivity of tumours to TMZ (39).

MGMT is a DNA repair enzyme that has been indicated to cause chemoresistance in tumours. The basic function of MGMT is to repair damaged guanine nucleotides by transferring the methyl group at the O6 site of guanine to a cysteine residue, thereby preventing gene mutation and cell death caused by alkylating agents. Through an examination of patients with MGMT methylation, Jesionek-Kupnicka *et al* (40) observed that the expression of MGMT was downregulated and negatively correlated with the expression of miR-648 and miR-125b. Another study reported that after delivering miRNA mimics into glioma cells, highly expressed miRNA-181d reverses the resistance of glioma cells to TMZ by targeting and binding to MGMT. Moreover, a genome-wide microarray analysis noted that miR-181d-5p only targets and binds to MGMT and that this specificity is of great value for the prediction of TMZ resistance (41). In addition, miR-198 also reduces the expression of MGMT in glioma cells, thereby enhancing the cytotoxicity of TMZ. However, the overexpression of TGF-β1 hinders the splicing and maturation of miR-198 by inhibiting KH-type splicing regulatory protein (KSRP) in human epidermal keratinocytes, thereby promoting MGMT demethylation and glioma drug resistance (42). EMT is a marker of malignant tumours. Its biological process has a vital role in the evaluation of malignant phenotypes and the clinical treatment of gliomas. miRNAs also regulate the EMT process, thereby reversing the resistance of gliomas to TMZ. For instance, miR-26b overexpression reverses the EMT of drug-resistant glioma cells by targeting and binding to WEE1 G2 checkpoint kinase, thereby increasing TMZ sensitivity in drug-resistant cells (43). Cathepsin B (CTSB) has been demonstrated to be a direct target of miR-140. miR-140 inhibits the EMT of tumour cells and enhances the cytotoxicity of TMZ by reducing the expression of CTSB (44). In another study, miR-128-3p expression was observed to be downregulated in glioma tissues and cell lines. Overexpression of miR-128-3p downregulated the expression of the EMT proteins C-Met, platelet-derived growth factor receptor α, Notch1 and Slug; as a result, the sensitivity of glioma cells to TMZ was enhanced (45).

Autophagy is a turnover process based on the lysosomal degradation of intracellular substances. Autophagy has been indicated to have an important role in numerous aspects of gliomas, particularly in drug-induced stress. miRNA-mediated autophagy has a key regulatory role in glioma drug resistance. Studies have indicated that overexpression of miR-29b enhances the sensitivity of U87MG and U251 cells to TMZ by inducing apoptosis and autophagy in these tumour cells. Consistent with the conclusions of *in vitro* experiments, the results of an *in vivo* nude mouse model of xenograft tumours confirmed that overexpression of miR-29b effectively inhibited tumour growth and enhanced the cytotoxicity of TMZ (46). Another study reported that under hypoxic conditions, HIF-1α affected the chemoresistance of tumour cells by negatively regulating the expression of miR-224-3p. Autophagy-related gene 5 (ATG5) is a direct target of miR-224-3p. High miR-224-3p expression reverses chemoresistance in LN229 cells and U251 cells by inhibiting ATG5-mediated hypoxic autophagy (47). In addition, high miR-519a expression increases the sensitivity of glioma cells to TMZ chemotherapy and such chemosensitization is achieved through miR-519a-mediated inhibition of the STAT3/Bcl-2/beclin-1 pathway and the regulation of autophagy and apoptosis (48). There is a large and complex interaction network between drug transport and TMZ resistance. Strategies to reverse the resistance of gliomas to TMZ through miRNA-mediated transporters have been widely studied. For instance, upregulation of miR-302c enhances the cytotoxicity of TMZ through the targeted inhibition of the transporter protein P-gp in drug-resistant glioma cells (49). Another similar study reported that the expression of ABC subfamily C member 1 (ABCC1) was upregulated in drug-resistant tumour cells. Overexpression of miR-1268a reversed this upregulation and inhibited the translation of ABCC1, thereby enhancing the chemosensitivity of drug-resistant cells to TMZ (50). Wnt5a is the key target of miR-129-5p. Overexpression of miR-129-5p blocks the activation of the protein kinase C (PKC)/ERK/NF-κB and c-Jun N-terminal kinase signalling pathways by inhibiting Wnt5a, thereby reversing the resistance of glioma cells to TMZ (51).

miRNAs are involved in DDP resistance. DDP is the most commonly used chemotherapeutic drug in the salvage treatment of recurrent gliomas. The main target of DDP is DNA. DDP covalently binds to the purine bases guanine and adenine to form intrastrand adducts, thus inhibiting DNA replication and transcription and causing DNA damage. Gliomas are highly sensitive to DDP. However, with the initiation of various repair mechanisms in tumour cells, drug resistance has seriously limited the clinical efficacy of DDP. Therefore, the development of strategies to reduce DDP resistance during treatment has become a focus of research. To date, a number of studies have explored miRNA-mediated DDP resistance in gliomas (Table II).

Table II. miRNAs involved in cisplatin resistance.

miRNA	Direction of differential expression	Genes and pathways	Mechanism	(Refs.)
miR-936	↓	-	-	(52)
miR-205	↓	E2F1	-	(53)
miR-451	↓	MMP-2	-	(54)
miR-186	↓	YY1	GSCs	(55)
miR-29a	↓	CD133	GSCs	(56)
miR-22	↓	SNAIL1	Apoptosis	(57)
miR-107	↓	mTOR	Apoptosis	(58)
miR-501-3p	↓	MYCN	Apoptosis	(59)
miR-128	↓	JAG1/Bcl-2	Apoptosis	(60)

↑, upregulation; ↓, downregulation in cisplatin-resistant glioma; miR, microRNA; E2F1, E2F transcription factor 1; MMP-2, matrix metallopeptidase 2; YY1, yin yang 1; mTOR, mammalian target of rapamycin; JAG51, Jagged canonical notch ligand 1; Bcl-2, B-cell lymphoma-2; GSCs, glioma stem cells.

A variety of miRNAs (such as miR-936, miR-205 and miR-451) are able to act as tumour suppressors to reverse DDP resistance in gliomas. According to a previous study, the expression of miR-936 was reduced in glioma tissues and cell lines and the restoration of miR-936 expression directly inhibited the chemoresistance of gliomas to DDP (52). Li *et al* (53) performed a similar study and their results indicated that DDP treatment decreases miR-205 expression in glioma cells and that the expression of miR-205 was lower in DDP-resistant cell lines than in DDP-sensitive cell lines. The overexpression of miR-205 in drug-resistant U87MG cells directly enhances apoptosis and cell cycle arrest and restores the sensitivity of tumour cells to DDP by targeting and binding to the 3'UTR of E2F1 (53). In addition, Alural *et al* (54) reported that erythropoietin enhanced the proliferation, invasion and DDP chemoresistance of glioma cells by downregulating the expression of miR-451. Restoration of the expression of miR-451 significantly reversed these effects. In this process, matrix metallopeptidase 2 (MMP-2) is the direct target of miR-451 (54). GSCs are a group of cells with self-renewal ability. New evidence indicates that GSC-related miRNAs are the key mediators of glioma chemoresistance. The expression of miR-186 is significantly reduced in glioma tissues. Yin Yang 1 (YY1) is a molecular marker of GSCs. The overexpression of miR-186 inhibits the development of the GSC phenotype by targeting and binding to YY1, thereby reversing the DDP resistance of gliomas (55). In addition, CD133-positive GSCs exhibit stronger resistance to DDP treatment. The overexpression of miR-29a improves CD133-mediated chemoresistance and increases the sensitivity of gliomas to DDP (56).

Certain tumour suppressor genes are able to reverse the DDP resistance of gliomas, mainly by regulating apoptosis. Exogenous miR-22 mimics induce cell cycle arrest in tumour cells by targeting and binding to SNAIL1, thereby enhancing the sensitivity of U87MG cells to DDP (57). Furthermore, the expression of miR-107 was observed to be decreased in glioma tissue and the expression of mTOR was significantly increased. Compared with those in parental U251 cells, the expression levels of miR-107 and mTOR exhibited similar trends in drug-resistant U251 strains. Overexpression of miR-107 *in vitro* promoted apoptosis of drug-resistant cells by inhibiting the expression of mTOR and survivin, thus significantly enhancing DDP-mediated cytotoxicity (58). Similarly, miR-501-3p targets and binds to the 3'-UTR of MYCN to promote DDP-induced apoptosis and proliferation arrest of glioma cells. Restoration of MYCN expression reversed the promoting effect of miR-501-3p (59). In addition, low miR-128 expression in glioma tissues and cell lines was able to reverse DDP resistance. The potential mechanism was determined to be as follows: Restoration of miR-128 expression increases the expression of Bax and decreases the expression of Bcl-2 by targeting and binding to the jagged canonical notch ligand 1 molecular locus, which promotes tumour cell apoptosis and S-phase arrest and eventually enhances DDP-mediated cytotoxicity (60).

miRNAs are involved in mono drug resistance to nitrosoureas. Nitrosourea drugs have gradually become second-line drugs in glioma chemotherapy due to the wide application of TMZ and the limitations of their efficacy and side effects. However, monochemotherapy with nitrosoureas (formustine, carmustine and nimustine) or combined chemotherapy with PVC (procarbazine + lomustine + vincristine) remains the best choice for the treatment of recurrent and TMZ-resistant gliomas (61). As alkylating agents with broad-spectrum antitumour activity, nitrosourea drugs may penetrate the BBB due to their nonionic properties and high lipid solubility. Nitrosourea drugs alkylate tumour cell DNA at multiple sites, inducing the formation of DNA crosslinking and the occurrence of single-strand or double-strand breaks, inhibiting DNA repair and ultimately altering the structure of DNA and proteins (61,62). Various miRNAs have been reported to be related to nitrosourea resistance in gliomas (Table III).

Several carcinogenic miRNAs have been indicated to promote the chemoresistance of glioma cells to nitrosoureas. For instance, the expression of miR-21 is significantly increased in drug-resistant glioma cells and the abnormal expression of miR-21 is the major cause of drug resistance in gliomas. In this process, miR-21 increases the resistance of gliomas to carmustine (BCNU) by reducing the expression of Spry2 (63).

Table III. miRNAs involved in mono drug resistance to nitrosoureas.

miRNA	Direction of differential expression	Genes and pathways	Drug	(Refs.)
miR-21	↑	Spry2	Carmustine	(63)
miR-221	↑	PTEN	Carmustine	(64)
miR-181a	↓	Bcl-2/Caspase-9	Carmustine	(65)

↑, upregulation; ↓, downregulation in nitrosoureas drug-resistant glioma; miR, microRNA; Spry2, Sprouty2; PTEN, phosphatase and tensin homologue.

Table IV. miRNAs involved in the resistance to plant-derived anticancer drugs.

miRNA	Direction of differential expression	Genes and pathways	Drug	(Refs.)
miR-374a	↑	FOXO1	Etoposide	(68)
miR-218-2	↑	CDC27	β-lapachone	(69)
miR-21	↑	LRRFIP1	Teniposide	(70)
miR-326	↓	SHH/GLI1	Curcumin	(71)
miR-34a	↓	PD-L1	Paclitaxel	(72)
miR-204-3p	↓	IGFBP2/AKT/Bcl-2	Xanthohumol	(73)
miR-7-1-3p	↓	PKCa, iNOS	Luteolin, Silibinin	(74)
miR-15b	↓	MMP-9	Mangiferin	(75)

↑, upregulation; ↓, downregulation in plant-derived anticancer drug-resistant glioma; miR, microRNA; FOXO1, forkhead box protein O1; CDC27, cell division cycle 27; LRRFIP1, LRR binding FLII interacting protein 1; SHH, Sonic hedgehog; GLI1, GLI family zinc finger 1; PD-L1, programmed death-ligand 1; IGFBP2, insulin-like growth factor binding protein 2; PKCa, protein kinase C α; iNOS, inducible nitric oxide synthase; MMP-9, matrix metallopeptidase 9.

Similarly, miR-221 has been indicated to be highly expressed in glioma cells and BCNU-resistant cells. miR-221 targets and binds to the 3'-UTR of phosphatase and tensin homologue and promotes the proliferation and BCNU chemoresistance of tumour cells through the PI3K/AKT signalling pathway (64). miR-181a, which is expressed at a low level in U373 cells, binds to BCNU drug molecules, thus inhibiting cell migration and proliferation by downregulating MMP-2 and BTB domain and CNC homologue 1. In addition, miR-181a has been reported to increase BCNU-induced apoptosis and cell cycle arrest of U373 cells by regulating the expression of caspase-9, Bcl-2 and sirtuin 1 (SIRT1) (65).

miRNAs are involved in the resistance to plant-derived anticancer drugs. For thousands of years, Chinese herbal medicine has been used to provide remedies for various diseases. It has been widely applied in disease prevention and treatment. The antitumour effects of Chinese herbal medicine have always been a medical issue. With continuous developments in science and technology, the pharmacodynamic components of natural plants have gradually been revealed and researched. Since curcumin, paclitaxel and β-elemene have been proved to have significant antitumor effects, the anti-glioma effect of plant extracts has attracted significant attention from medical researchers (66). A large number of clinical studies have indicated that these natural extracts may not only have antitumour activities but also alleviate adverse reactions to chemoradiotherapy, improve the quality of life of patients and reduce the recurrence rate of tumours (67). In addition, an increasing number of *in vivo* and *in vitro* studies have explored the relationship between miRNAs and tumour sensitivity to Chinese herbal extracts (Table IV).

The expression of certain carcinogenic miRNAs directly affects the efficacy of chemotherapy. For instance, the expression of miR-374a is significantly increased in malignant gliomas. Knockdown of miR-374a directly increased the expression of forkhead box protein O1 (FOXO1) in glioma cells, enhancing the cytotoxicity of etoposide (68). miR-218 is a tumour suppressor gene. However, miR-218-2 is a cancer-promoting gene that is highly expressed in glioma tissues and cells and is positively associated with the growth, invasion, migration and β-lapachone resistance of glioma cells. In terms of the underlying mechanism, miR-218-2 promotes the chemoresistance of U87MG and U251 cells to β-lapachone by reducing the expression of the cell division cycle 27 (CDC27) gene (69). In addition, miR-21 acts as a modulator of teniposide chemoresistance. LRR binding friend leukaemia integration 1 transcription factor (FLI1) interacting protein 1 (LRRFIP1) has been identified as a direct target of miR-21, and miR-21 enhances the resistance of glioma cells to teniposide by targeting and binding to the 3'-UTR of LRRFIP1 (70).

Yin *et al* (71) reported that overexpression of miR-326 increased the chemosensitivity of malignant glioma cells to the anticancer drug curcumin. The results of *in vitro* experiments demonstrated that high miR-326 expression reduces the viability of tumour cells by inhibiting the sonic hedgehog/GLI

Table V. miRNAs involved in resistance to molecular targeted drugs.

miRNAs	Direction of differential expression	Genes and pathways	Drug	(Refs.)
miR-21, miR-10b	↑	-	Bevacizumab	(78)
miR-145	↓	P-gp, Bcrp	Sunitinib	(79)
miR-302a, miR-520b	↓	AKT1, PIK3CA, SOS1	Sunitinib	(80)
miR-106a	↑	MDR1, MRP1, GST-π	Gefitinib	(81)
miR-450a	↓	EGFR	Gefitinib	(82)
miR-566	↑	VHL	Nimotuzumab	(83)
miR-21	↑	VHL/β-catenin, PPARα/AP	Nimotuzumab	(84)
miR-203	↓	SNAI2	Imatinib	(85)
miR-296-3p	↓	EAG1	Imatinib	(86)

↑, upregulation; ↓, downregulation in glioma resistant to molecular targeted drugs; miR, microRNA; P-gp, P-glycoprotein; Bcrp, breast cancer resistance protein; PIK3CA, PI3K catalytic subunit α; SOS1, son of sevenless homologue 1; MDR1, multi-drug resistant 1; MRP1, multidrug resistance protein 1; GST-π, glutathione S-transferase pi; EGFR, epidermal growth factor receptor; VHL, von Hippel-Lindau; PPARα, peroxisome proliferator-activated receptor α; AP, activator protein; SNAI2, Snail family transcriptional repressor 2; EAG1, ether-à-go-go 1.

family zinc finger 1 signalling pathway, thereby enhancing the cytotoxicity of curcumin to U87MG and U251 cells (71). The expression of programmed death-ligand 1 (PD-L1) is significantly increased in paclitaxel-resistant U87MG cells. By directly acting on the 3'-UTR of PD-L1, miR-34a inhibits the progression and chemoresistance of tumour cells (72). Similarly, the expression of miR-204-3p is decreased in glioma cell lines. miR-204-3p targets and binds to the 3'-UTR of IGF binding protein 2 (IGFBP2) and enhances xanthohumol-induced tumour cell apoptosis by inhibiting the IGFBP2/AKT/Bcl-2 pathway (73). The application of rapamycin created a starvation state in glioma cells and induced autophagy. High miR-7-1-3p expression enhanced the antitumour activity of synergistic silibinin and luteolin treatment by inhibiting the expression of PKCα and inducible nitric oxide synthase in GBM cells. More importantly, miR-7-1-3p promoted apoptosis by inhibiting rapamycin-induced autophagy (74). In addition, mangiferin inhibited the expression of MMP-9 in U87MG cells by upregulating miR-15b, thereby promoting apoptosis. Conversely, the use of MMP-9 agonists and anti-miR-15b inhibitors significantly reduced the inhibitory effect of mangiferin on U87MG cells (75).

miRNAs are involved in resistance to molecular targeted drugs. Tumour-related molecular targeted therapy has become an important research field. In particular, molecular targeted therapy has achieved great success in the treatment of non-small cell lung cancer, malignant melanoma and chronic myeloid leukaemia (76), findings that have important guiding significance for the application of molecular targeted drugs in the treatment of malignant gliomas. Compared with traditional drugs, molecular targeted drugs are less toxic and only inhibit tumour cells. In terms of their mechanism of action, molecular targeted drugs accurately regulate specific receptors, key genes and regulatory molecules in tumour cells. Therefore, the application of molecular targeted drugs has become a novel treatment strategy for gliomas and is expected to improve the prognosis of patients with glioma. The mechanisms underlying the resistance of gliomas to molecular targeted drugs remain to be fully elucidated. However, certain miRNAs have been identified to directly participate in the regulation of the cytotoxicity of molecular targeted drugs (Table V).

Bevacizumab is a recombinant monoclonal immunoglobulin G (IgG) antibody. It specifically blocks the binding of VEGF-A to the VEGF receptor, thereby reducing angiogenesis and inhibiting tumour growth. In 2009, bevacizumab was approved by the Food and Drug Administration (FDA) of the US for the treatment of recurrent GBM (77). Siegal *et al* (78) performed a longitudinal study of the circulating miRNA levels in patients with glioma treated with bevacizumab. During treatment, the levels of miR-10b and miR-21 were negatively associated with changes in tumour diameter and bevacizumab had poor efficacy in the treatment of patients with high miR-10b and miR-21 expression (78). However, the specific underlying mechanisms of action remain elusive and require to be further investigated. Sunitinib is an anti-angiogenic tyrosine kinase inhibitor. Transfection with miR-145 mimics promoted the cytotoxic effects of sunitinib on GBM by directly acting on the 3'-UTR of P-gp and breast cancer resistance protein (Bcrp) (79). Similarly, miR-302a and miR-520b mimics directly targeted and bound to the 3'-UTR of AKT1, PI3K catalytic subunit alpha (PIK3CA) and son of sevenless homologue 1 (SOS1). These miRNAs inhibit the expression of receptor tyrosine kinase mediators (AKT1, PIK3CA and SOS1) in U87MG cells, thereby enhancing the sensitivity of tumour cells to sunitinib and increasing apoptosis. However, this regulatory effect of miR-302a and miR-520b has not been observed for TMZ (80).

Growth factor receptors are important regulatory proteins in the signalling networks of malignant gliomas. Resistance to novel drugs that target the epidermal growth factor receptor and platelet-derived growth factor receptor has been a focus of scientific exploration. miR-106a is an important molecule involved in drug resistance. miR-106a enhances the drug efflux ability and anti-apoptotic ability of drug-resistant U87MG cells by promoting the expression of Twist, AP-1 and Snail. Furthermore, miR-106a positively regulates the expression of glutathione S-transferase π to enhance the drug detoxification

Table VI. miRNAs involved in resistance to immunotherapeutic drugs.

miRNAs	Direction of differential expression	Genes and pathways	Drug	(Refs.)
miR-15a/16	↑	PD-1, Tim-3, LAG-3	PD-L1 inhibitor	(88)
miR-138	↓	CTLA-4, PD-1, FoxP3	CTLA-4 inhibitor, PD-1 inhibitor	(89)
miR-326	↓	SMO/Gli2	EGFRvIII-DC vaccine	(90)
miR-124, miR-128, miR-146b, miR-218	↓	E1A	OA-4MREs	(91)

↑, upregulation; ↓, downregulation in glioma resistant to immunotherapeutic drugs; miR, microRNA; PD-1, programmed cell death-1; Tim-3, T cell immunoglobulin and mucin-domain containing-3; LAG-3, lymphocyte-activation gene 3; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FoxP3, forkhead box protein P3; SMO, Smoothened; Gli2, GLI family zinc finger 2; E1A, adenovirus early regio; EGFRvIII-DC, epidermal growth factor receptor variant III-dendritic cell; OA-4MREs, oncolytic adenovirus to construct a recombinant oncolytic adenovirus.

ability of drug-resistant U87MG cells. Therefore, miR-106a increases the resistance of glioma cells to gefitinib synergistically through the abovementioned regulatory mechanisms (81). Compared with that in normal glial cells, the expression of miR-450a was observed to be significantly reduced in GBM. High miR-450a expression was indicated to regulate the PI3K/AKT/mTOR signalling pathway by inhibiting the translation of epidermal growth factor receptor (EGFR), thereby regulating apoptosis and autophagy and enhancing the sensitivity of glioma cells to gefitinib. In addition, the abovementioned responses induced by miR-450a were able to be reversed by the knockdown of WD repeat domain phosphoinositide-interacting protein 1 (WIPI1) (82). Inhibition of the highly expressed miR-566 in glioma cell lines negatively regulated von Hippel-Lindau (VHL), thereby increasing the sensitivity of tumour cells to nimotuzumab (83). In addition, miR-21 was indicated to regulate the EGFR/AKT signal conduction pathway through VHL/β-catenin and peroxisome proliferator-activated receptor α/AP and blocking this regulatory loop significantly inhibits the chemoresistance of glioma cells to nimotuzumab. More importantly, the combined therapeutic effect of nimotuzumab and a miR-21 inhibitor was superior to that of single drug treatment (84). In addition, increased Snail family transcriptional repressor 2 (SNAI2) expression was observed in imatinib-resistant GBM cells and silencing of SNAI2 directly inhibited the EMT process and drug resistance of tumour cells. Furthermore, miR-203 mimics increased the sensitivity of drug-resistant tumour cells to imatinib by targeting and binding to SNAI2 (85). As a tumour suppressor gene, miR-296-3p reduced the proliferative activity of GBM cells by inhibiting the proliferation regulator ether-à-go-go1, which was conducive to reducing the resistance of GBM cells to imatinib (86).

miRNAs are involved in resistance to immunotherapeutic drugs. Immune checkpoint inhibitors are monoclonal antibodies developed specifically for immune checkpoints. These inhibitors induce sustained antitumour immune responses by blocking the inhibitory effects of tumour cells on immune cells. The immune checkpoint inhibitors approved by the FDA include ipilimumab [cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor], nivolumab (PD-1 inhibitor) and avelumab (PD-L1 inhibitor) (87). The successful clinical application of these agents has brought new life to the immunotherapeutic treatment of malignant gliomas. According to research reports, certain miRNAs regulate immune checkpoints in glioma cells. For instance, compared with that in a wild-type nude mouse xenograft model, the growth of gliomas was significantly inhibited in miR-15a/16-deficient nude mice and the survival of the nude mice was significantly prolonged. More importantly, a large number of highly active and proliferative CD8+ T cells accumulated in the tumours of the miR-15a/16-deficient nude mice. This differential phenotype was induced by the miR-15a/16 deficiency-mediated low expression of PD-1, T cell immunoglobulin and mucin-domain containing-3 and lymphocyte-activation gene 3 (88). In addition, miR-138 targets and binds to CTLA-4, PD-1 and FOXP3 in CD4+ T and CD8+ T cells, resulting in the regression of glioma tissues in immunocompetent nude mice (89). Tumour vaccines have also been a hotspot of cancer research in recent years. The mechanism of action of tumour vaccines is to introduce tumour-related antigens into patients; this approach activates cellular and humoural immunity and induces inflammatory responses to enhance antitumour effects. Li *et al* (90) reported that miR-326 reduced the exocrine secretion of TGF-β1 in glioma cells through the smoothened (SMO)/Gli2 pathway, thereby improving the activity and killing ability of T cells and enhancing the cytotoxicity of the EGFR variant III-dendritic cell (EGFRvIII-DC) vaccine. More importantly, compared with the EGFRvIII-DC vaccine alone, combined administration of the EGFRvIII-DC vaccine and miR-326 achieved better therapeutic efficacy and exerted a stronger killing effect on U87MG cells (90) (Table VI).

With the continuous development of bioengineering technology, researchers have used gene editing technology to transform viruses with strong replication ability into oncolytic viruses. Various oncolytic adenoviruses promote the apoptosis of glioma cells, with low toxicity in normal cells. These viruses display high specificity and selectivity. To improve the cytotoxicity and specificity of oncolytic adenoviruses, Yao *et al* (91) combined the miRNA response elements (MRE) of 4 glioma inhibitory miRNAs (miR-124, miR-128, miR-146b and miR-218) with an oncolytic adenovirus to construct a recombinant oncolytic adenovirus (OA-4MREs). *In vivo* and

Table VII. miRNAs involved in resistance to other drugs.

miRNA	Direction of differential expression	Genes and pathways	Drug	(Refs.)
miR-330-3p	↓	ZO-1, Occludin, Claudin-5	Doxorubicin	(92)
miR-21	↑	E-cadherin, RECK, VHL, P21	Doxorubicin, Tamoxifen, 5-fluorouracil	(93-96)
miR-302b	↓	-	All-trans retinoic acid	(97)

↑, upregulation; ↓, downregulation in glioma resistant to other drugs; miR, microRNA; ZO-1, zonula occludens-1; RECK, reversion-inducing cysteine-rich protein with kazal motifs; VHL, von Hippel-Lindau; P21, cyclin-dependent kinase inhibitor 1A.

in vitro experiments demonstrated that the MREs regulated the replication ability of the virus by targeting and binding to adenovirus early region 1A (E1A). Compared with the proliferative adenovirus, OA-4MREs had a stronger cytotoxic effect on glioma cells. Of note, it was also observed that OA-4MREs had no significant cytotoxicity in normal tissues and cells and only produced a limited number of viral offspring (91). Therefore, OA-4MREs exhibited high safety, allowing further testing in clinical practice.

miRNAs are involved in resistance to other drugs. Doxorubicin (Dox) has a wide range of toxic effects on Top II. It is a highly effective broad-spectrum anticancer drug. The mechanism of action involves the intercalation of Dox into the DNA of tumour cells, thereby inhibiting nucleic acid replication. An increasing amount of evidence indicates that miRNAs are related to Dox resistance in gliomas. miR-330-3p inhibitors reduce the proliferative, migratory and invasive capabilities of glioma cells. The combined application of a miR-330-3p inhibitor and a low dose of human endothelial monocyte activating peptide II increased the permeability of the BTB by reducing the expression of zonula occludens-1 (ZO-1), occludin and claudin-5, thereby enhancing the chemotherapeutic efficacy of Dox on gliomas (92). As one of the first miRNAs detected, miR-21 has been demonstrated to be highly expressed in gliomas and to be involved in the regulation of tumour drug resistance. For instance, therapies combining Dox and miR-21 inhibitors induced apoptosis of T98G cells resistant to Dox chemotherapy, thereby increasing the sensitivity of T98G cells to Dox (93). Similarly, in another study, the highly synergistic effect of Dox and miR-21 inhibitors was indicated to block the EMT of U87MG and LN299 cells by enhancing the expression of the tumour suppressor genes E-cadherin, reversion-inducing cysteine-rich protein with kazal motifs, VHL and P21, thereby reversing Dox resistance in tumour cells (94). In addition to the above-mentioned drugs, knockdown of miR-21 reduced the resistance of glioma cells to tamoxifen and 5-fluorouracil (5-FU) (95,96). By contrast, knockdown of miR-302b significantly increased the resistance of glioma cells to all-trans retinoic acid (97) (Table VII).

4. LncRNAs and glioma drug resistance

LncRNAs are ncRNAs with a length of >200 nucleotides. A number of studies have indicated that lncRNAs are composed of promoter regions, exons, antisense sequences, enhancer sequences, 3'- and 5'-UTRs, introns, and intergenic and intragenic regions of the genome. LncRNAs have key roles in physiological activities, including epigenetic regulation, cell cycle regulation and cell differentiation regulation through multiple pathways and mechanisms (98). These RNAs have become a focus of genetic research. More importantly, lncRNAs have been indicated to serve as biomarkers for the diagnosis, treatment, prognostication, drug response prediction and other pathological processes of gliomas by interacting with miRNAs to form a competing endogenous RNA (ceRNA) network, participating in histone modification and directly binding to target genes (98). In this chapter, the roles of related lncRNAs in the development of chemotherapy resistance in gliomas are discussed and a sufficient theoretical basis for the comprehensive understanding of the mechanisms of tumour drug responses are provided.

LncRNAs are involved in TMZ resistance. A number of carcinogenic lncRNAs have been indicated to induce TMZ resistance in gliomas. For instance, knockdown of lncRNA zinc finger antisense 1 (ZFAS1), lncRNA LINC00021 and lncRNA NCK1-AS1 not only inhibited tumour proliferation, migration and invasion, but also reversed the TMZ resistance of gliomas (99-101). LncRNA TCONS_00004099 is a newly discovered ncRNA. It inhibits TMZ-induced apoptosis by regulating the downstream target protein tyrosine phosphatase receptor type F (PTPRF) (102). LncRNA HOX antisense intergenic RNA (HOTAIR) is an oncogene. It was recently discovered that knocking out lncRNA HOTAIR significantly reduced TMZ resistance in gliomas by targeting calcium binding and coiled-coil domain 1 and zinc finger CCCH-type containing 10 (103). As a ceRNA, lncRNA HOTAIR may act as an miRNA sponge. It promotes the malignant development and TMZ resistance of gliomas by adsorbing miR-125/HK2 (104). *In vitro*, lncRNA BC200 promotes TMZ resistance in tumours; this process is induced by antagonizing miR-218-5p (105). High lncRNA miR155HG expression is negatively associated with the quality of life of patients with gliomas. Knockdown of miR-155HG inhibits the Wnt/β-catenin pathway by effectively downregulating the expression of polypyrimidine tract-binding protein 1 in tumour cells, thereby reducing the resistance of gliomas to TMZ (106). In addition, another ceRNA molecule, lncRNA colon cancer associated transcript 2 (CCAT2), has been indicated to regulate the expression of checkpoint kinase 1 (Chk1) through the sponge adsorption of miR-424, thereby promoting TMZ resistance in gliomas (107) (Table VIII).

Table VIII. LncRNAs involved in temozolomide resistance.

LncRNAs	Direction of differential expression	Genes and pathways	Mechanism	(Refs.)
ZFAS1	↑	-	-	(99)
LINC00021	↑	-	-	(100)
NCK1-AS1	↑	-	-	(101)
TCONS_00004099	↑	PTPRF	-	(102)
HOTAIR	↑	CALCOCO1, ZC3H10, miR-125/HK2	-	(103,104)
BC200	↑	miR-218-5p	-	(105)
MIR155HG	↑	PTBP1/Wnt/β-catenin	-	(106)
CCAT2	↑	miR-424/Chk1	-	(107)
MSC-AS1	↑	miR-373-3p/CPEB4	Apoptosis	(108)
SOX2OT	↑	SOX2	Apoptosis	(109)
LINC00461	↑	miR-216a/AQP4	Apoptosis	(110)
00174	↑	miR-138-5p/SOX9	Apoptosis	(111)
FOXD2-AS1	↑	MGMT	DNA damage repair	(112)
H19	↑	miR-198/MGMT	DNA damage repair, EMT	(113,116)
HOXD-AS2	↑	miR-198/MGMT	DNA damage repair	(113)
TP73-AS1	↑	ALDH1A1	GSCs	(114)
NEAT1	↑	let-7g-5p/MAP3K1	GSCs	(115)
PVT1	↑	miR-365/ELF4	GSCs	(116)
DLEU1	↑	ZEB1, N-cadherin, Snail, P62, ATG7	EMT, Autophagy	(117)
MALAT1	↑	miR-203/miR-140	EMT	(118)
CRNDE	↑	P62	Autophagy	(119)
LINC00470	↑	miR-134/MYC/ABCC1	Drug transport and metabolism	(120)
KCNQ1OT	↑	miR-761/PIM1	Drug transport and metabolism	(121)
LIFR-AS1	↓	miR-4262/NF-κB	-	(122)
WT1-AS	↓	miR-494-3p/p-AKT	-	(123)
CACS2	↓	miR-193a-5p/mTOR	Autophagy	(124)
TUG1	↓	EZH2	EMT, GSCs	(125)
TUSC7	↓	MDR1, miR-10a	Apoptosis	(126)

↑, upregulation; ↓, downregulation in glioma resistant to temozolomide; lncRNA, long non-coding RNA; miRNA, microRNA; PTPRF, protein tyrosine phosphatase receptor type F; CALCOCO1, coiled-coil domain 1; ZC3H10, zinc finger CCCH-type containing 10; HK2, hexokinase 2; PTBP1, polypyrimidine tract-binding protein 1; Chk1, checkpoint kinase 1; CPEB4, cytoplasmic polyadenylation element binding protein 4; SOX2, SRY-box 2.

Certain lncRNAs may also act as regulators of apoptosis and MGMT to mediate chemotherapy resistance in gliomas. For instance, knockdown of lncRNA MSC-AS1 regulated the miR-373-3p/cytoplasmic polyadenylation element binding protein 4 axis in glioma cells through the PI3K/Akt signalling pathway, significantly enhancing the induction of apoptosis during TMZ treatment and reducing the half-maximal inhibitory concentration (IC_{50}) of TMZ (108). LncRNA SOX2 overlapping transcript (SOX2OT) is not only a biomarker for predicting the high recurrence risk and poor prognosis of gliomas, but also an important regulator of chemoresistance to TMZ. In addition, *in vivo* and *in vitro* studies have indicated that lncRNA SOX2OT directly regulates the SOX2-bound AlkB homolog 5 (ALKBH5) protein. As a result, SOX2 is demethylated, further inhibiting apoptosis and enhancing the resistance of tumour cells to TMZ chemotherapy (109). miR-216a acts as a tumour suppressor. Silencing of lncRNA LINC00461 regulates cellular aquaporin-4 by upregulating the expression of miR-216a, ultimately leading to apoptosis and the antagonization of TMZ resistance in gliomas (110). In addition, lncRNA 00174, as a ceRNA molecule, acts as a 'molecular sponge' in the process of drug treatment; it directly adsorbs miR-138-5p to upregulate SOX9 protein expression and promote the development of TMZ resistance in gliomas (111). High MGMT expression reduced TMZ-mediated cytotoxicity. Furthermore, MGMT induces its own methylation during the process of guanine demethylation and immediately becomes inactivated. Therefore, it is called a 'suicide enzyme'. LncRNA FOXD2-AS1 is overexpressed in recurrent gliomas and its high expression

is significantly associated with poor prognosis of patients. Silencing lncRNA FOXD2-AS1 not only reduced the proliferative and metastatic abilities of glioma cells but also induced hypermethylation of the MGMT promoter region and enhanced the sensitivity of glioma cells to TMZ (112). In addition, lncRNA H19 and lncRNA HOXD-AS2 regulated functional mechanisms different from the abovementioned ceRNA mechanism. As an RNA-binding protein, KSRP binds to follistatin-like 1 and promotes the formation of mature miR-198. TGF-β1 upregulates the expression of H19 and HOXD-AS2 through SMAD signalling and prevents the maturation of miR-198, ultimately decreasing the expression of miR-198 and increasing the expression of MGMT, significantly enhancing the resistance of gliomas to TMZ chemotherapy (113).

GSCs are an important factor in glioma heterogeneity and are closely related to tumour recurrence and treatment resistance. An increasing number of lncRNAs have been indicated to regulate tumour drug resistance through stemness-maintaining transcription factors and stem cell-related regulatory pathways. LncRNA TP73-AS1 is an oncogene that is overexpressed in GBM tissues, particularly in GSC tissues. It promotes the TMZ resistance of GSCs through the targeted regulation of the metabolic gene ALDH1A1 (114). LncRNA nuclear-enriched abundant transcript 1 (NEAT1) has been confirmed to have a cancer-promoting effect. In addition, it acts as a ceRNA and interferes with the binding of the tumour suppressor gene let-7g-5p and MAPK kinase kinase 1, thus promoting the malignant development of GSCs during TMZ treatment (115). The lncRNA plasmacytoma variant translocation 1 (PVT1) promotes the proliferation, migration and invasion of glioma cells by activating SOX2. In addition, lncRNA PVT1 positively regulates the expression of E74-like ETS transcription factor 4 (ELF4) in GCSs through the sponge adsorption of miR-365. High ELF4 expression further induces asymmetric cell division of GCSs, thereby enhancing TMZ resistance (116). EMT is closely related to glioma invasion, migration and chemotherapy resistance, and lncRNAs may act as key factors that regulate these biological behaviours. LncRNA H19 has a central role in inducing TMZ chemoresistance in gliomas. *In vitro*, the induction of EMT, the activation of oncogenic signalling pathways and the alteration of the tumour microenvironment are all important mechanisms by which H19 participates in chemotherapy resistance (117). In addition, silencing lncRNA deleted in lymphocytic leukaemia 1 (DLEU1) inhibits the TMZ-induced EMT process by regulating the expression of marker proteins (i.e., zinc finger E-box-binding homeobox 1, N-cadherin and Snail) in glioma cells, thereby increasing the sensitivity of tumour cells to TMZ (118). Similarly, a study by Baspinar *et al* (119) indicated that lncRNA metastasis associated lung adenocarcinoma transcript 1 (MALAT1) reduces the expression of miR-203, thereby inducing EMT by enhancing the synthesis of thymidylate synthase and ultimately promoting the resistance of glioma cells to TMZ. Furthermore, knocking out MALAT1 enhanced the permeability of the BTB by upregulating the expression of miR-140, which markedly improved the targeting effect and biological efficacy of TMZ in the treatment of tumours and provides novel gene therapy strategies for gliomas (119).

Autophagy is a highly conserved process. Numerous molecular complexes and oncoproteins have key roles in various stages of autophagy. Therefore, it is not surprising that lncRNAs directly participate in the regulation of autophagy by regulating the activity and expression of the abovementioned molecules. The lncRNA colorectal neoplasia differentially expressed (CRNDE) is highly expressed in TMZ-resistant patients and knocking down lncRNA CRNDE significantly enhanced the TMZ chemosensitivity of glioma cells. In terms of the underlying mechanisms, silencing CRNDE directly reduces the expression of light chain (LC)3II/I, beclin1 and autophagy-related 5 (ATG5), thereby inhibiting autophagy related to PI3K/AKT/mTOR pathway activation and ABCG2 expression (120). In the study by Lv *et al* (118), lncRNA deleted in lymphocytic leukemia 1 (DLEU1) was confirmed to have a crucial role in GBM progression and TMZ resistance. Knocking down DLEU1 inhibited autophagy by negatively regulating the expression of P62 and ATG7 in GBM cells and increased the sensitivity of tumour cells to TMZ by inducing apoptosis. The reduction in the accumulation of chemotherapeutic drugs is one of the main mechanisms of drug resistance. For instance, lncRNA LINC00470 directly targets the miR-134/MYC pathway to enhance the resistance of glioma cells to TMZ. During TMZ treatment, the miR-134/MYC pathway upregulates the expression of ABCC1 in glioma cells and there is a positive correlation between MYC and ABCC1 expression (121). The interaction between lncRNA KCNQ1 opposite strand/antisense transcript 1 (KCNQ1OT1) and miR-761 also has an important role in the development, progression and chemoresistance of GBM. KCNQ1OT1 upregulates PIM1 expression through the sponge adsorption of miR-761. Overexpression of PIM1 directly induces the activation of multidrug resistance mutation 1 (MDR1), c-MYC and survivin, thereby enhancing TMZ resistance (122).

A variety of tumour suppressor lncRNAs reverse TMZ resistance in gliomas. For instance, in glioma tissues and cell lines, low expression of lncRNA leukaemia inhibitory factor receptor-AS1 enhances the sensitivity of tumour cells to TMZ by targeting the miR-4262/NF-κB axis (123). In U87MG cells overexpressing lncRNA Wilms tumour 1 AS, the IC_{50} of the chemotherapeutic agent TMZ is significantly reduced. The underlying mechanism involves the inhibition of phosphorylating AKT activation through the sponge adsorption of miR-494-3p, reversing chemotherapy resistance in GBM (124). Jiang *et al* (125) reported that lncRNA cancer susceptibility 2 (CACS2) may be used as a biomarker for the diagnosis and treatment of gliomas. Furthermore, lncRNA CACS2 acts as a ceRNA molecule to reverse the resistance of tumour cells to TMZ, primarily through the miR-193a-5p/mTOR signalling pathway-mediated inhibition of autophagy. The results of *in vivo* and *in vitro* experiments indicated that lncRNA taurine upregulated gene 1 inhibits the EMT process and GSC phenotype of gliomas by downregulating the expression of enhancer of zeste homologue 2 (EZH2), thereby reducing TMZ resistance (126). In addition, lncRNAs have been indicated to affect the apoptosis of TMZ-resistant glioma cells. For instance, lncRNA tumour suppressor candidate 7 (TUSC7) is a tumour suppressor gene that reduces the TMZ resistance of glioma cells by inhibiting the expression of MDR1. Furthermore, lncRNA TUSC7 induces apoptosis through targeted silencing

Table IX. LncRNAs involved in cisplatin resistance.

LncRNA	Direction of differential expression	Genes and pathways	Mechanism	(Refs.)
DANCR	↑	AXL	-	(127)
CCAT2	↑	miR-424/Chk1	-	(107)
ZFAS1	↑	miR-432-5p	-	(128)
HOXD-AS1	↑	miR-204	EMT, GSCs	(129)
UCA1	↑	Wnt/β-catenin	Apoptosis	(130)
CRNDE	↑	miR-29c-3p	Apoptosis	(131)
GAS5	↓	mTOR	Autophagy	(132)
MEG3	↓	ATG5	Autophagy	(133)
AC023115.3	↓	miR-26a/GSK3β	Autophagy	(134)

↑, upregulation; ↓, downregulation in glioma resistant to cisplatin; lncRNA, long non-coding RNA; miRNA, microRNA; AXL, axial length; Chk1, checkpoint kinase 1; mTOR, mammalian target of rapamycin; ATG5, autophagy-related gene 5; GSK3β, glycogen synthase kinase 3β; GSCs, glioma stem cells; EMT, epithelial mesenchymal transition.

of miR-10a expression, thereby increasing the sensitivity of drug-resistant cells to TMZ (127).

LncRNAs are involved in DDP resistance. Evidence indicates that certain carcinogenic or tumour suppressor lncRNAs mediate the resistance of gliomas to DDP chemotherapy. For instance, the lncRNA differentiation antagonizing non-protein coding RNA, which is highly expressed in drug-resistant glioma cell lines, activates the PI3K/AKT/NF-κB signalling pathway by inducing the expression of AXL in drug-resistant tumour cells, thereby promoting resistance to DDP. Similar results were obtained in an *in vivo* experiment (128). LncRNA CCAT2-mediated promotion of tumour cell chemoresistance is the major cause of the poor overall survival and progression-free survival of patients with GBM. In terms of the mechanism, CCAT2 acts as a sponge for miR-424. It enhances the chemotherapy resistance of GBM cells to DDP by inhibiting the molecular degradation of Chk1 by miR-424 (107). Similarly, the role of lncRNA ZFAS1/miR-432-5p in glioma chemoresistance has also been confirmed (129). LncRNA HOXD cluster AS1 (HOXD-AS1) is an oncogene. High HOXD-AS1 expression has been observed in DDP-resistant glioma clinical specimens and cell lines. LncRNA HOXD-AS1 jointly promotes the resistance of tumour cells to DDP by competitively binding to miR-204. Furthermore, knocking down HOXD-AS1 inhibits the GSC phenotype and the EMT process, thereby enhancing DDP sensitivity and reducing tumour cell proliferation, migration and invasion (130). In addition, certain lncRNAs affect the DDP resistance of glioma cells by regulating apoptosis-related pathways. For instance, lncRNA urothelial carcinoma associated 1, which is highly expressed in drug-resistant glioma cell lines, reduces DDP-induced apoptosis and cell cycle arrest by activating Wnt/β-catenin signalling, thereby promoting the chemoresistance of tumour cells to DDP (131). Similarly, the lncRNA CRNDE has been reported to inhibit DDP-induced apoptosis by competitively binding to miR-29c-3p in glioma cells (132) (Table IX).

In addition to the oncogenic lncRNAs related to DDP resistance, there are several tumour suppressor lncRNAs that enhance the sensitivity of tumour cells to DDP. All of these tumour suppressor lncRNAs are closely related to autophagy in glioma cells. The expression of mTOR is downregulated in drug-resistant glioma cell lines, promoting DDP-induced autophagy. The downregulation of mTOR ultimately mediates an increase in the expression of autophagy-related protein LC3II and a decrease in the expression of autophagy substrate p62 in tumour cells, thereby enhancing chemotherapy resistance to DDP. Of note, overexpression of lncRNA growth arrest specific 5 activates mTOR signalling and restores the sensitivity of glioma cells to DDP (133). LncRNA maternally expressed 3 enhances the chemical sensitivity of U87MG cells to DDP by inhibiting the expression of ATG5. In terms of the mechanism, ATG5 is a key molecule in the formation of autophagic vacuoles. Silencing ATG5 significantly inhibits autophagy in tumour cells and ultimately increases the cytotoxic effect of DDP in U87MG cells (134). LncRNA AC023115.3 is another lncRNA that sensitizes glioma cells to DDP *in vivo* and *in vitro*. It inhibits tumour cell autophagy and promotes DDP-induced apoptosis through the miR-26a/glycogen synthase kinase 3β signalling pathway (135).

LncRNAs are involved in resistance to other drugs. In addition to mediating the resistance of gliomas to TMZ and DDP, certain lncRNAs are also involved in the resistance of gliomas to other chemotherapeutic drugs, such as natural anticancer drugs and molecular targeted drugs. Both lncRNA CCAT2 and Chk1 are highly expressed in teniposide-resistant glioma cells. The potential mechanism of drug resistance is the sponge adsorption of miR-424 by CCAT2, which enhances the chemoresistance of glioma cells to teniposide through the upregulation of Chk1 expression (107). A recent study showed that the overexpression of lncRNA H19 plays an important role in the development of curcumin resistance. Knocking down lncRNA H19 reverses curcumin resistance by regulating vitamin D receptor (VDR), and VDR is a direct target of miR-143 in gliomas (136). Lv *et al* (137) performed a similar study, according to which high lncRNA FOXD2-AS1 expression increased the me3 modification ability of H3K27 by mediating the activation of EZH2 in glioma cells, thereby

Table X. LncRNAs involved in resistance to other drugs.

LncRNA	Direction of differential expression	Genes and pathways	Drug	(Refs.)
CCAT2	↑	miR-424	Teniposide	(107)
H19	↑	miR-143/VDR	Curcumin	(135)
FOXD2-AS1	↑	EZH2	Curcumin	(136)
NEAT1	↑	miR-194-5p	Isoliquiritigenin	(137)
PVT1	↑	-	Paclitaxel	(138)
MVIH	↑	miR-137	Cediranib	(139)

↑, upregulation; ↓, downregulation in glioma resistant to other drugs; lncRNA, long non-coding RNA; miRNA, microRNA; VDR, vitamin D receptor; EZH2, enhancer of zeste homolog 2.

promoting the chemoresistance of tumour cells to curcumin. Curcumin is a natural antitumour drug. Of note, combined therapy with curcumin and TMZ significantly enhanced the cytotoxicity of the drugs (137). Silencing lncRNA NEAT1 promoted the sensitivity of U87MG cells to isoliquiritigenin by inhibiting tumour angiogenesis. Knocking down NEAT1 significantly enhanced the inhibitory effect of miR-194-5p on the AKT-fibroblast growth factor 2/TGF-β/VEGF signalling pathway, thereby reversing the resistance of glioma cells to isoliquiritigenin (138). Compared with that in parental SHG-44 cells, lncRNA PVT1 is highly expressed in drug-resistant SHG-44 cells. Overexpression of PVT1 promotes paclitaxel resistance; the primary mechanism is the enhancement of paclitaxel sensitivity through the regulation of apoptosis (139). In addition, lncRNA microvascular invasion in hepatocellular carcinoma (MVIH) was reported to be involved in the resistance of glioma cells to cediranib. It enhanced the resistance of gliomas to cediranib through the sponge inhibition of miR-137. By contrast, knocking down MVIH significantly reduced glycolysis and cell proliferation and sensitized glioma cells to cediranib (140) (Table X).

5. CircRNAs and drug resistance of gliomas

In recent years, circRNAs have received widespread attention as a new type of ncRNA. Unlike traditional linear RNAs, the 3' and 5' ends of circRNAs are covalently connected. Therefore, circRNAs form covalently closed loop structures that resist cleavage by ribonucleases and display stronger stability, conservation and tissue/cell specificity (141). Due to these characteristics, circRNAs, as molecular targets for the malignant progression of gliomas, have demonstrated great potential in the regulation of tumourigenesis, tumour proliferation, tumour invasion and prognosis. For instance, circPIP5K1A has been indicated to be upregulated in gliomas. It induces the expression of TCF12 in glioma cells by competitively binding to miR-515-5p, thereby promoting tumour proliferation, invasion and EMT (142). Similarly, circCDC45 promotes the expression of colony stimulating factor 1 through the sponge adsorption of miR-485-5p. It has a key role in the entire malignant progression of GBM and has become a potential marker for the diagnosis and treatment of gliomas (143). In addition, with the development of chemoresistance and the need for chemotherapy, an increasing amount of evidence indicates that circRNAs also have important roles in the drug resistance mechanisms of gliomas.

CircRNAs are involved in TMZ resistance. A number of studies have demonstrated that carcinogenic circRNAs are involved in TMZ chemoresistance of gliomas. For instance, the expression of circRNA_ankyrin repeat and Pleckstrin homology domain 1 (circ_ASAP1) is significantly upregulated in recurrent GBM tissues and TMZ-resistant cell lines. The sponge function of circ_ASAP1 directly inhibits the targeted binding of miR-502-5p to the 3'-UTR of neuroblastoma ras viral oncogene homologue (NRAS), thereby increasing the expression of NRAS and promoting the resistance of GBM cells to TMZ (144). Circ_0000936 promotes the TMZ resistance and proliferation of glioma cells by competitively binding to miR-1294. By contrast, restoration of miR-1294 eliminates the promoting effect of circ_0000936 on TMZ resistance in drug-resistant cells (145). Another carcinogenic circRNA, circ_0076248, induces the expression of p53 and SIRT1 in tumour cells through the sponge adsorption of miR-181a. It has been demonstrated to reduce the sensitivity of gliomas to TMZ (146). Exosomes derived from TMZ-resistant glioma cells mediate the transfer of chemoresistance to TMZ-sensitive glioma cells via circ_0042003 (147). Therefore, exosomal circRNAs have an undeniable role in TMZ resistance. These circRNAs directly participate in the development of chemoresistance by targeting multiple mechanisms. Exosomal circRNA_homeodomain interacting protein kinase 3 (circ_HIPK3) promotes TMZ resistance in glioma cells by inhibiting apoptosis. Specifically, circ_HIPK3 regulates the miR-421/Zic family member 5 signalling pathway, resulting in drug resistance (148). In a clinical study from Ding *et al* (149), the expression of exosomal circ_0072083 was increased in the body fluids of TMZ-resistant patients, which was negatively associated with the overall survival of the patients. Furthermore, circ_0072083 promotes AlkB homolog 5 (ALKBH5)-mediated demethylation by targeting miR-1252-5p, thereby upregulating Nanog homeobox (NANOG) expression and conferring TMZ chemoresistance in glioma cells *in vitro* and xenograft tumour tissues *in vivo* (149). CircRNA_nuclear factor I/X (circ_NFIX) is not only a member of the exosomal circRNA family but also an inducer of TMZ resistance in GBM cells. A study by the same authors indicated that exosome-mediated circ_NFIX

Table XI. CircRNAs involved in temozolomide resistance.

CircRNA	Direction of differential expression	Genes and pathways	Mechanisms	(Refs.)
ASAP1	↑	miR-502-5p/NRAS	-	(143)
0000936	↑	miR-1294	-	(144)
0076248	↑	miR-181a, p53, SIRT1	-	(145)
HIPK3	↑	miR-421/ZIC5, miR-524-5p/KIF2A	Exosome, apoptosis	(147,151)
0072083	↑	miR-1252-5p/ALKBH5	Exosome	(148)
NFIX	↑	miR-132	Exosome	(149)
0110757	↑	miR-1298-5p/ITGA	Apoptosis	(150)
0005198	↑	miR-198/TRIM14	Apoptosis	(152)
CEP128	↑	miR-145-5p/ABCG2	Drug transport and metabolism	(153)

↑, upregulation; ↓, downregulation in glioma resistant to temozolomide; circRNA, circular RNA; miRNA, microRNA; NRAS, neuroblastoma ras viral oncogene homologue; SIRT1, Sirtuin 1 ZIC5, Zic family member 5; KIF2A, kinesin family member 2A; ALKBH5, AlkB homolog 5; ITGA, integrin α8; TRIM14, tripartite motif-containing 14; ABCG2, ATP-binding cassette superfamily G member 2.

significantly reduced the expression of miR-132 in recipient cells through the sponge adsorption of miR-132, ultimately leading to the acquisition of drug resistance in TMZ-sensitive glioma cells (150). In summary, emerging research has revealed key exosomal circRNAs and the related pathways that regulate chemoresistance in glioma cells, findings that may improve the clinical benefits of TMZ treatment for patients with glioma (Table XI).

Evidence indicates that several circRNAs induce TMZ resistance by regulating apoptosis-related genes. Circ_0110757, formed by the reverse splicing of exons of myeloid-cell leukaemia 1, has been indicated to be upregulated in TMZ-resistant glioma cell lines. The underlying drug resistance mechanism is that circ_0110757 acts as a molecular sponge for miRNA and inhibits TMZ-induced apoptosis through the miR-1298-5p/ITGA signalling pathway (151). Similarly, circ_HIPK3 stimulates the upregulation of kinesin family member 2A (KIF2A) expression in glioma cells by interacting with miR-524-5p, thereby inhibiting TMZ sensitivity and apoptosis. Of note, KIF2A not only acts as a downstream target of miR-524-5p but also activates the PI3K/AKT signalling pathway in the entire drug resistance mechanism induced by circ_HIPK3 (152). Circ_0005198 is a ceRNA highly expressed in glioma tissues, serum samples and TMZ-resistant cells. It competitively binds to miR-198 to regulate the expression of tripartite motif-containing 14. Knocking down circ_0005198 expression directly limits the biological behaviours of drug-resistant gliomas and significantly increases tumour sensitivity to TMZ (153). In addition, circRNAs target ABC transporters, generating drug resistance through the promotion of drug excretion. A study by Hua *et al* (154) demonstrated that silencing circRNA_centrosomal protein 128 (circ_CEP128) increases the concentration of TMZ in glioma cells by reducing the expression of ATP-binding cassette superfamily G member 2 (ABCG2), thereby enhancing cytotoxicity. In summary, circRNAs activate proteins and pathways in glioma cells. They are expected to become key targets for the treatment of TMZ resistance.

CircRNAs are involved in resistance to other drugs. During the treatment of gliomas, the presence of the BTB seriously hinders the effective delivery of antitumour drugs to the central nervous system. The following studies use the BTB as the breakthrough point to explore the key role of multiple carcinogenic circRNAs in the formation of Dox resistance in-depth. Gao *et al* (155) reported that circRNA_ubiquitin specific protease 1 (circ_USP1) is highly expressed in glioma-derived microvascular endothelial cells (GDMECs) *in vitro*. It acts as a sponge of miRNAs and binds to miR-194-5p. Therefore, knocking down circ_USP1 directly reduces the expression of tight junction-related proteins (claudin-5, occludin and ZO-1) in GDMECs by mediating the miR-194-5p/FLI1 axis, thereby destroying the integrity of the BTB, increasing the permeability of Dox and eventually promoting the Dox-induced apoptosis of glioma cells (155). Another study indicated that the RNA-binding protein K homology (KH) domain-containing, RNA-binding, signal transduction-associated protein 3 (KHDRBS3) is upregulated in GDMECs. KHDRBS3 binds to circRNA_DENN/MADD domain containing 4C (circ_DENND4C) to form a ribonucleoprotein complex, increasing its stability. Similarly, circ_DENND4C acts as a molecular sponge of miR-577, which also affects the permeability of the BTB. Knocking down circ_DENND4C significantly enhanced the degradation of downstream target genes (claudin-1, occludin and ZO-1) by miR-577, promoted the penetration of Dox across the BTB and ultimately led to the apoptosis of glioma cells (156). CircRNA_001160 is considered an important regulator of GDMEC growth. It enhances Dox resistance. The underlying mechanism is as follows: CircRNA_001160 upregulates the expression of ETS variant

Table XII. CircRNAs involved in resistance to other drugs.

CircRNA	Direction of differential expression	Genes and pathways	Drug	(Refs.)
USP1	↑	miR-194-5p/FLI1	Doxorubicin	(154)
DENND4C	↑	miR-577/Claudin-5,Occludin, ZO-1	Doxorubicin	(155)
001160	↑	miR-195-5p/ETV1	Doxorubicin	(156)
104075	↑	Wnt/β-catenin, PI3K/AKT	Matrine	(157)

↑, upregulation; ↓, downregulation in glioma resistant to other drugs; circRNA, circular RNA; miRNA, microRNA; FLI1, Friend leukemia integration 1 transcription factor; ZO-1, Zonula occludens-1; ETV1, ETS variant transcription factor 1.

transcription factor 1 (ETV1) through the sponge adsorption of miR-195-5p; overexpressed ETV1 binds to the promoters of tight junction-related proteins, thereby increasing the expression of tight junction-related proteins and ultimately blocks the delivery of Dox to glioma cells and inhibits Dox-induced apoptosis (157). In addition, the role of circRNA_104075 in the chemotherapy resistance of gliomas has been confirmed. Regarding the mechanism, circRNA_104075 induces glioma cell autophagy by activating the Wnt/β-catenin and the PI3K/AKT signalling pathways, thereby reducing the cytotoxicity of matrine (158). In summary, the regulatory mechanism of circRNAs may provide novel strategies for treating glioma chemoresistance (Table XII).

6. Future perspectives

Tumour drug resistance is a multifactorial and complex biological process. To completely eliminate tumour chemoresistance, it is necessary to reveal its molecular mechanism from an aetiological perspective to develop new antitumour drugs. To this end, the present study proposes the research prospects of tumour drug resistance, ncRNA and drug delivery systems, aimed to reveal the molecular mechanism of tumour drug resistance from an epigenetic perspective and clarified the role of ncRNA and nanocarriers in the treatment of tumours via multiple channels, targets and levels to confer a novel basis and strategy for the clinical management of tumour chemoresistance.

Ferroptosis, a newly defined type of programmed cell death, is closely related to oxidative stress and the disruption of redox homeostasis is also crucial for the chemoresistance of tumour cells (159). Wu *et al* (160) indicated that nanodrugs with silica particles used as carriers are able to dissolve and release Fe_3O_4 particles and glutaminase inhibitors under acidic conditions, thus consuming glutathione in tumour cells and reversing the drug resistance of tumour cells to oxaliplatin by inducing ROS-dependent ferroptosis. Wang *et al* (161) indicated that ovarian tumour domain-containing ubiquitin aldehyde-binding protein 1 (OTUB1) and solute carrier family 7 member 11 (SLC7A11) directly bind to circ_BGN as RNA binding proteins, and circ_BGN significantly enhances OTUB1-mediated SLC7A11 deubiquitination, thereby suppressing ferroptosis. Erastin, a ferroptosis inducer, is able to reverse the above molecular mechanisms and restore the sensitivity of drug-resistant breast cancer cells to trastuzumab. The combination of everolimus and erastin is able to synergistically reduce the viability of renal cell carcinoma cells and induce ferroptosis, thereby reversing the drug resistance of tumour cells to everolimus by inhibiting the activation of the mTOR/4E-binding protein 1 (4EBP1) signalling pathway (162). Furthermore, the development of novel drugs based on active ingredients from Traditional Chinese Medicine is also of great value to solve tumour chemoresistance. Statistics indicate that >75% of 200 approved drugs for the treatment of malignant tumours contain active ingredients from Traditional Chinese Medicine (163). It is well accepted that an increase in MGMT is able to enhance the chemoresistance of glioblastoma and tubeimoside-I, a natural extract of *Bolbostemma paniculatum*, induces glioblastoma cell apoptosis by reducing MGMT expression and sensitizes TMZ-resistant glioblastoma cells to chemotherapy (164). Similarly, cinobufotalin has been identified as an active antitumour ingredient that attenuates resistance to cisplatin by inducing enkurin expression to suppress non-muscle myosin heavy chain IIA-mediated c-Myc deubiquitination in lung adenocarcinoma (165).

ncRNAs are able to regulate a variety of biological processes, representing a class of promising biomarkers for tumour diagnosis and prognosis. The traditional view is that ncRNA is a functional RNA molecule that does not encode any protein. However, with the significant advancements of translatomics and mass spectrometry in recent years, researchers determined that certain ncRNAs have a coding function and are able to translate into functionally independent micropeptides in tumour cells (166). For instance, lncRNA-encoded peptide-AP attenuates the pentose phosphate pathway by interacting with transaldolase 1, causing ROS accumulation in colorectal cancer cells and inducing apoptosis, which eventually sensitizes colorectal cancer cells to oxaliplatin (167). Aberrant activation of the Hedgehog (Hh) pathway is able to drive the occurrence and development of multiple tumour types. Wu *et al* (168) confirmed that circ_SMO is able to encode a novel protein, SMO-193a.a., which is critical for Hh signal transduction and drives malignant progression of glioblastoma. CircMAPK14-175aa, a novel tumour suppressor protein encoded by circRNA_mitogen-activated protein kinase 14 (circ_MAPK14), inhibits colorectal cancer progression and metastasis by reducing the nuclear translocation of MAPK14 via competitively binding to MAPK kinase 6 to facilitate ubiquitin-mediated degradation of FOXC1 (169). N^6-methyladenosine (m^6A) methylation is the most prevalent post-transcriptional RNA modification in the transcriptome. Previous studies have unveiled the critical importance of the

interaction between m^{6}A methylation and ncRNA in tumour proliferation, metastasis, drug resistance and immunity (170). Pan *et al* (171) revealed that methyltransferase-like 3 (METTL3)-dependent m^{6}A methylation promotes the processing and maturation of miR-181b-5p by DiGeorge syndrome critical region 8, thus reducing the expression of neurocalcin δ and inhibiting the 5-FU sensitivity of colorectal cancer cells. In addition, high expression of METTL3 has been indicated to promote m^{6}A modification and enhance lncRNA ABHD11-AS1 transcript stability and expression, resulting in a poor prognosis of patients with non-small cell lung cancer (172). In addition, dysregulation of ncRNAs affects m^{6}A modification. Xie *et al* (173) identified circRNA_ protein tyrosine phosphatase receptor type A (circ_PTPRA) as a tumour suppressor that abolishes the promoting effect of IGF-2 mRNA-binding protein 1 (IGF2BP1) on breast cancer cell proliferation, migration and invasion. Mechanistically, circ_PTPRA interacts with the KH domains of IGF2BP1 and blocks the recognition of IGF2BP1 by m^{6}A-modified RNAs, resulting in the downregulation of fatty acid amide hydrolase and MYC mRNA stability.

With the wide application of nanomedicine in tumour treatment, researchers have developed various drug delivery systems to increase the *in vivo* delivery of therapeutic drugs or nucleic acids. Of note, these delivery carriers have unique molecular structures and application advantages, which may enhance therapeutic effects by improving the retention time of the contents *in vivo* and the bioavailability, but they still lack selectivity and affinity. To address the above shortcomings, the surface of carrier materials may be modified and the high affinity between ligands and receptors and the differential expression of receptors or antigens between tumour cells and normal cells may be utilized to achieve more accurate targeted therapies. At present, proteins and peptides are commonly used for active modification of carrier materials. For instance, lactoferrin (Lf), a multifunctional glycoprotein, is only expressed in brain capillaries. Qi *et al* (174) indicated that a targeted delivery system modified by Lf is able to markedly improve the ability of docetaxel liposomes to cross the BBB and enhance brain targeting effects, demonstrating its potential as a promising chemotherapeutic drug delivery system for glioblastoma. Angiopep-2 (Ang) is able to specifically bind to receptor-related protein 1 (LRP-1), which is highly expressed on the glioma cell membrane. Nanoparticles with addition of the Ang polypeptide possess obvious brain targeting characteristics and do not destroy the integrity of the BBB. However, the targeting effect of Ang polypeptide modification is ineffective in normal glial cells with LRP-1 deficiency (175). Mahmoudi *et al* (176) attempted to use arginine-glycine-aspartate (RGD) peptide-modified liposomes as delivery carriers of curcumin for the targeted treatment of glioma. They indicated that, compared with free curcumin, RGD-modified curcumin liposomes significantly improved the tissue targeting, water solubility and biocompatibility of drugs (176). Borneol, a crystal extracted from the resin and volatile oil of *Dipterocarpus aromatica* Gaertn. f., was able to change the brain neurotransmitter level by inhibiting P-gp expression and then improve the physiological BBB permeability. Conjugation of the drug delivery system surface with borneol not only reduce the cytotoxicity of the drug delivery system itself but also effectively improved the penetration of 5-FU into the brain (177). Furthermore, menthol extracted from the leaves and stems of peppermint has also been demonstrated to enhance the ability of drugs to cross various physiological barriers, such as the BBB, gastrointestinal mucosa barrier and skin. Menthol-modified casein nanoparticles are able to significantly increase the distribution of drugs in the brain and their targeting efficiency for glioma cells is even higher than that of transferrin-modified nanoparticles (178).

7. Discussion

At present, the most common strategy for the chemotherapeutic treatment of gliomas is to induce apoptosis by destroying the DNA structure. The mechanisms of drug resistance tend to be diverse, including drug excretion, DNA repair, apoptosis, EMT and the GSC phenotype. In recent years, RNA-sequencing (RNA-Seq) technology has developed rapidly and become an indispensable tool for analysing differential genes at the transcriptome level. Due to its high-throughput, high-accuracy and high-sensitivity characteristics, RNA-Seq technology has further uncovered the link between ncRNAs and the epigenetics of a variety of cancers and opened the door for ncRNA research to move towards clinical practice.

Numerous studies have demonstrated that ncRNAs are related to chemotherapy response. In the complex regulatory network, ncRNAs participate in glioma chemoresistance by activating multiple signalling pathways. As the first ncRNA to be studied, miRNAs bind to the 3'-UTR of target genes and exert their regulatory activity by inhibiting the translation of downstream proteins. The studies related to the involvement of lncRNAs and circRNAs in chemoresistance mainly focus on their role as sponge molecules of miRNAs, regulating drug resistance through the ceRNA mechanism. By contrast, only a small number of studies focused on functional mechanisms related to RNA-binding proteins. Furthermore, 2 mechanisms (namely, regulation of transcription and regulation of translation) have not been reported in relation to drug resistance. Relevant studies indicate that numerous protein targets are not able to interact with drug molecules due to the lack of a suitable protein structure or transcription factors and thus are 'not ready for medicine' (179). Encouragingly, compared with protein-coding genes widely used as targets for glioma treatment, ncRNAs have inherent application potential. The molecular fragments of ncRNAs account for nearly 98% of the entire human genome, providing a sufficient target selection scope for glioma chemotherapy (3). In addition, although almost all traditional drugs used for glioma chemotherapy face the challenge of drug resistance, there is currently no report on ncRNA drug resistance. Furthermore, a series of chemical modifications may be added to ncRNA drugs so that the circulation half-life of ncRNA drugs will be longer than that of small-molecule or antibody drugs.

In summary, ncRNAs have a key regulatory role in glioma chemoresistance. Targeted correction of the dysregulated expression of endogenous ncRNAs during the development of drug resistance using ncRNA antagonists or mimics may be an effective treatment strategy for the reversal of glioma chemoresistance. Researchers have developed a variety of miRNA-based therapeutic tools, such as anti-miRs,

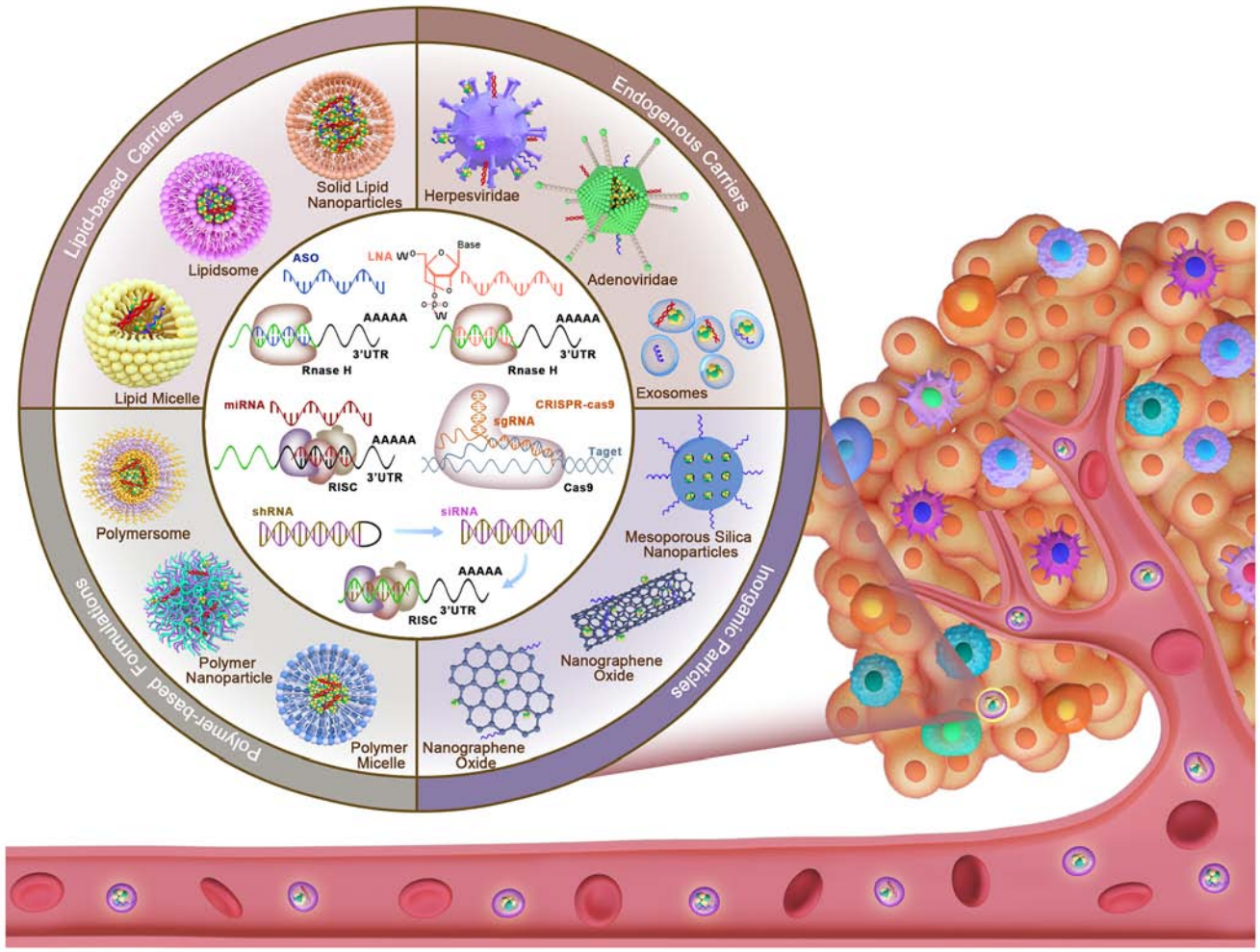

Figure 3. Novel nanoparticles loaded with targeting nucleic acid sequences for the treatment of glioma drug resistance. Various new nano-delivery systems (endogenous carriers, inorganic particles, polymer-based formulas and lipid-based carriers) may be loaded with a variety of nucleic acid treatment tools [ASO, LNA, miRNA, siRNA, shRNA and CRISPR-cas9] that may be delivered into glioma cells to correct the unbalanced expression of endogenous noncoding RNAs during the formation of drug resistance by releasing inclusions to cause a reversal of chemoresistance in gliomas. Due to their accuracy, they have markedly improved the delivery efficiency of glioma nucleic acid therapy. siRNA, small interfering RNA; ASO, antisense oligonucleotide; LNA, locked nucleic acid; miRNA, microRNA; shRNA, short hairpin RNA; sgRNA, single guide RNA; CRISPR, clustered regularly interspaced short palindromic repeats; cas9, CRISPR-associated system 9.

antagomiRs, sponge inhibitors, mimics, agomiRs and pre-miRs. MRX34 is a miR-34a mimic encapsulated by liposomal nanoparticles. As the first mono nucleic acid drug to enter clinical trials, MRX34 has achieved satisfactory clinical results in the treatment of renal cell carcinoma, acral melanoma and hepatocellular carcinoma. However, the trial was stopped as patients developed serious adverse reactions (180). Cobomarsen is an anti-miR-155 based on locked nucleic acid modification. It regulates cell proliferation and differentiation by targeting carcinogenic miR-155 in patients. In phase II clinical trials that enrolled patients with lymphoma and leukaemia, patients had good tolerance to systemically administered and intratumourally administered cobomarsen (181). In terms of GBM treatment, Regulus Therapeutics Inc. announced a novel anti-miR-10b-based drug candidate, RGLS5579, in 2019; however, it is still in the preclinical stage (182). In addition, the expression of carcinogenic lncRNAs and circRNAs may be inhibited by specific small interfering RNAs (siRNAs) or short hairpin RNAs, and the overexpression of tumour suppressor lncRNAs and circRNAs in tumour cells may be achieved by delivery with specific vectors. However, as lncRNAs and circRNAs are emerging research targets, the related mechanisms require to be further explored. Therefore, lncRNA- and circRNA-based treatments are still in the early stages.

Although ncRNA therapy has broad prospects, it is still a great challenge to select key target ncRNAs from a large number of candidates and choose the appropriate delivery system. ncRNAs are able to simultaneously target multiple functional genes in a regulatory network. However, while the ncRNAs exert powerful regulatory functions, off-target effects cannot be avoided. Target ncRNAs may exert effects on genes other than target genes, resulting in nonspecific regulation and unexpected effects. Therefore, target ncRNAs must be selected based on strict standards, with the comprehensive consideration of the overall response of ncRNA drugs *in vivo*. Limited delivery efficiency is also an important factor hindering ncRNA therapy. To date, a variety of efficient novel delivery systems have been developed, e.g. virus-based delivery systems, cationic lipid delivery systems, polymer delivery systems and antibodies (183). These delivery systems

not only enhance the delivery efficiency of ncRNAs but also improve their biological stability and pharmacokinetic distribution. However, while maintaining a high delivery efficiency of therapeutic ncRNAs, it is necessary to consider the potential damage to human organs caused by the carrier itself. Viral vectors and cationic nanoparticles not only have certain toxicity but also induce immunogenic responses. Furthermore, excessive cationic components readily cause decomposition of the carrier particles at the glomerular basement membrane, resulting in renal clearance of ncRNAs (175). Although scientific researchers have made great efforts to design a variety of promising noncationic nucleic acid carriers (octameric ribonucleoprotein, exosomes, spherical nucleic acids and siRNA conjugates) to load ncRNAs (183,184), viral vectors and cationic nanoparticles are still the most commonly used delivery methods in ncRNA therapy. In other words, the toxicity and immunogenicity of nucleic acid carrier systems cannot be overcome at present. Therefore, developing an efficient and nontoxic carrier system is key to the success of glioma ncRNA therapy. In addition, with the development of clinical techniques such as liquid biopsy and secretion examination in recent years, the use of ncRNAs as an early screening index of drug sensitivity has become another potential research direction. More interestingly, the combined administration of ncRNAs and chemotherapeutic drugs for the sensitization of gliomas also appears to be promising and is worthy of further translational research and clinical trials. In conclusion, there is still a long way to go before the comprehensive application of ncRNA therapy in clinical practice. However, the development of ncRNA-based therapies may be an effective supplement to traditional therapy and may overcome the chemoresistance of tumour cells and thereby improve the prognosis of patients with glioma (Fig. 3).

8. Conclusion

In conclusion, chemotherapy is an important component of comprehensive glioma treatment, but chemoresistance markedly limits the prognosis of patients with glioma. The present review focuses on the functions and mechanisms of miRNAs, lncRNAs and circRNAs in glioma chemoresistance and ultimately illustrates that ncRNA-mediated precision therapy may be an ideal therapeutic strategy to overcome chemoresistance in gliomas. Although these ncRNAs have great potential for monitoring and reversing anticancer drug resistance, there are numerous ncRNAs that are closely associated with drug resistance that remain elusive and require to be identified and further explored.

In addition, more scientific research and clinical trials are urgently required to develop ncRNA-based therapies to improve the prognosis of patients with glioma. Thus, ncRNAs will have an even more important role in future glioma research and treatment.

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Availability of data and materials

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Authors' contributions

ZMZ and YYC were the major contributors to the writing and revision of the manuscript. XCG and YHZ performed the literature search, XCW and QYY participated in discussions. TTW, CL and YX revised this article critically for important intellectual content. JCD, KBZ and ZWS gave approval for the final version of the manuscript. All authors have read and approved the final 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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