Molecular Therapy
Nucleic Acids
Review

miR-137: A Novel Therapeutic Target for Human Glioma

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MicroRNA (miR)-137 is highly expressed in the brain and plays a crucial role in the development and prognosis of glioma. In this review, we aim to summarize the latest findings regarding miR-137 in glioma cell apoptosis, proliferation, migration, invasion, angiogenesis, drug resistance, and cancer treatment. In addition, we focus on the identified miR-137 targets and pathways in the occurrence and development of glioma. Finally, future implications for the diagnostic and therapeutic potential of miR-137 in glioma were discussed.

Glioma is the most common malignant and invasive primary brain tumor.[1] It is characterized by high recurrence and mortality rates due to difficulty in complete resection by surgery and low sensitivity to chemoradiotherapy.[2] Although substantial improvements in the diagnosis and treatment of glioma have been made over the past several decades, the prognosis is still poor. The 5-year overall survival rate of patients is less than ten percent.[3] To date, the molecular mechanism involved in the development of glioma remains unclear. Therefore, it is necessary to develop new therapeutic strategies and improve the clinical outcome.

In recent decades, microRNAs (miRNAs) have started a revolution in molecular biology and are regarded as key players in tumors. miRNAs can block the expression of multiple target genes by sequence-specific binding to the 3′ untranslated region (3′UTR).[4,5] Emerging studies have shown that dysregulated miRNAs can rewire multiple critical cellular and biological processes that are deeply involved in glioma initiation and malignant progression.[4,6] In particular, microRNA-137 (miR-137), most abundantly expressed in the brain, may act as a central mediator to regulate the expression of over 1,000 predicted target genes.[7] Subtle changes in miR-137 may have profound impacts on the development of many kinds of tumors, including glioma.[6,8–10] This review provides a succinct but comprehensive summary of the literature on recent advances about the roles and mechanisms of miR-137 in glioma initiation and development, as well as its values in glioma diagnosis and treatment.

miR-137 Dysregulation Is Related to the Malignant Progression of Glioma

miR-137 is located on chromosome 1p21.3 within the nonprotein-coding RNA (ncRNA) gene AK094607.[11] As a brain-enriched miRNA, miR-137 is not only expressed in neurons but also present in glial cells. miR-137 regulation is driven by multiple mechanisms (Figure 1), including transcriptional, epigenetic, and long noncoding RNA (lncRNA) regulation. The main regulatory mechanism of miR-137 in glioma is transcriptional control. Of note, it is negatively regulated by repressor element-1 silencing transcription repressor (REST).[12,13] Given the potential involvement of REST in glioma pathology, REST-mediated miR-137 regulation could be an important molecular mechanism.[14] Moreover, there are 15 bp variable number tandem repeat (VNTR) elements near the 5′ end of the pre-miR-137 region.[15] In the human brain, the number of repeats at the VNTR locus ranges from 3 to 13, and the number of repeats is negatively associated with the expression level of miR-137.[16] However, whether altered VNTR in miR-137 affects glioma risk in patients remains unknown. Epigenetic transcriptional regulation constitutes another mechanism of miR-137 expression control. The genome region encoding miR-137 lies across a large density of CpG islands,[17] and its expression is inversely regulated by DNA methylation.[18,19] DNA hypermethylation of *miR-137* has been reported in different kinds of solid tumors,[20–22] including glioma,[6,23] with loss of *miR-137* expression and function. In mouse adult neuronal stem cells (NSCs), miR-137 is regulated by methyl-CpG-binding protein 2 (MeCP2)- and transcription factor (TCF) Sox2-mediated DNA methylation.[24] Sun et al.[25] demonstrated that nuclear receptor Tailless (TLX) recruits histone lysine-specific demethylase 1 (LSD1) to the miR-137 promoter and suppresses its transcription. In addition, LSD1 is also targeted by miR-137, creating a double-negative regulatory feedback loop.[26,27] More recently, lncRNAs negatively regulating the expression of miR-137 have also been identified. Several lncRNAs, such as lncRNA X-inactive-specific transcript (XIST),[28,29] lncRNA HOXA transcript antisense RNA, myeloid-specific 1 (HOTAIRM1),[30] and lncRNA noncatalytic kinase 1 antisense RNA 1 (NCK1-AS1),[31] are

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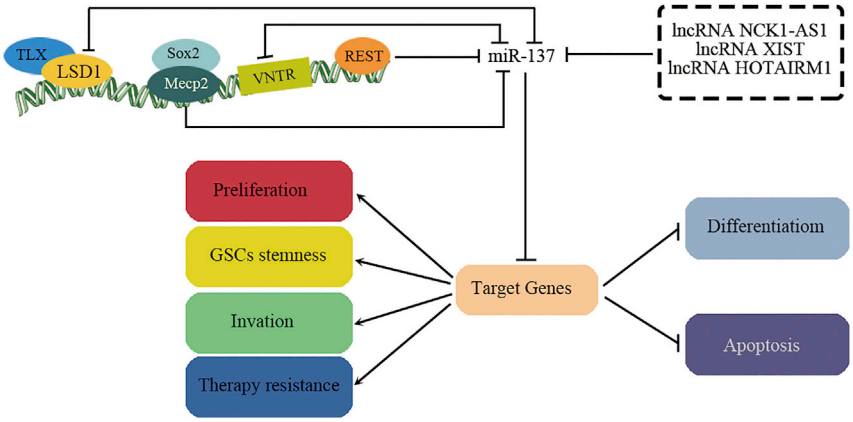

Figure 1. The miR-137 Regulators and Functions in Glioma Cells
→, upregulation or activation; ⊣, downregulation or inhibition.

reported to act as sponges or antagomirs that competitively regulate the expression and function of miR-137 in glioma cells. Together, these studies suggest that a complicated epigenetic modulation network is involved in miR-137 regulation, and imbalance of this regulatory circuit involving miR-137 and epigenetic changes may contribute to glioma pathology.

miR-137 expression is strictly regulated during brain development. More intriguingly, miR-137 dysregulation is associated with many brain disorders, suggesting that miR-137 is critical for brain functions.[11,32] Downregulation of miR-137 is associated with epithelial-mesenchymal transition (EMT) in a variety of tumors, such as breast cancer,[33–35] cervical cancer,[36] ovarian cancer,[37] non-small cell lung cancer,[38,39] and gastrointestinal stromal tumors.[40] However, EMT in glioma has not been reported to be associated with miR-137. Other related evidence shows that miR-137 expression is decreased in both glioma samples and cell lines compared to normal controls[17,41–45] and that miR-137 levels are inversely correlated with clinical stage and overall survival.[6,41] We speculate that miR-137 dysregulation may be related to glioma EMT, but further studies are needed.

miR-137 Is a Suppressor of Glioma

Gliomas are infiltrative tumors derived from glial cells and represent deadly and the most common type of primary malignant central nervous system tumor[1,2] Increasing evidence has indicated that miR-137 has great inhibitory effects on the proliferation, metastasis, and invasion of glioma cells.[6,17,41]

miR-137 Inhibits Glioma Cell Proliferation and Induces Glioma Stem Cell (GSC) Differentiation

Accelerated proliferation is a hallmark of cancer cells that contributes to the development of malignant tumors. This biological characteristic is thought to be even more important in glioma, as the uncontrolled growth of this brain cancer is key to its high lethality.

miR-137 regulates cell proliferation, mainly by affecting the cell cycle and promoting stem-cell differentiation. Transfection of miR-137 into glioma cell lines and tumor-derived neural stem cells leads to cell-cycle exit, whereas silencing miR-137 leads to the opposite outcome. It has been proven that miR-137 triggers cell-cycle arrest in the G1 phase by suppressing the phosphorylation of cyclin-dependent kinase 6 (CDK6) and retinoblastoma-associated protein-1 phosphorylation and the expression of nuclear casein kinase and CDK substrate 1 (NUCKS1) protein. Overexpression of miR-137 inhibits proliferation, migration, and survival and arrests the cell cycle in G1 phase inglioma cells, whereas repression of miR-137 exerts the opposite effects.[46,47] In contrast, lncRNA XIST promotes glioma cell growth by acting as an endogenous sponge by competing with miR-137, thereby upregulating the level of the miR-137 target gene Rac1 (the small GTP-binding protein Ras-related C3 botulinum toxin substrate 1).[29] *In vitro*, miR-137 levels increase gradually during the differentiation of NSCs. Ectopic expression of miR-137 in human induced pluripotent stem cell (iPSC)-derived NSCs reduces proliferation and accelerates neuronal differentiation and migration.[48] Moreover, miR-137 induces the differentiation of adult NSCs, oligodendroglioma-derived stem cells, and GSCs.[17] Recently, miR-137 was also reported to enhance neuronal differentiation by inducing mitochondrial biogenesis, fusion, fission, and oxidative phosphorylation (OXPHOS).[48] miR-137 accelerates mitochondrial biosynthesis by upregulating the expression of TCF A of mitochondria (TFAM) and nuclear factor erythroid 2-related factor 2 (NRF2). In addition, miR-137 regulates mitochondrial dynamics by inducing mitochondrial fusion and fission events, resulting in increased mitochondrial content and activation of OXPHOS and oxygen consumption.[48]

miR-137 Induces Glioma Cell Apoptosis

Almost all cancer types feature suppression of apoptosis. In glioma, it has been extensively shown that the antiapoptotic capability of tumor cells is associated with disease progression and resistance to therapies. A study showed that miR-137 is involved in inducing apoptosis in noncancerous diseases.[49] miR-137 induces caspase-3 activity in hippocampal neural stem cells by targeting BCL2L13 (a B cell chronic lymphocytic leukemia/lymphoma 2 [BCL-2] family member).[49] In this way, miR-137 also enhances the apoptotic process in glioblastoma (GBM) cells by directly targeting Bcl-2.[50] In addition, glutamine transporter solute carrier 1 family member 5 (SLC1A5) plays an important role in regulating cell metabolism by mediating glutamine uptake.[51] Since glutamine is considered to be a conditionally essential amino acid in rapidly proliferating cancer cells, SLC1A5 has favorable effects on tumor development.[52] Accordingly, it was also reported that direct inhibition of SLC1A5 by miR-137 enhances glioma cell oxidative stress and triggers lipid peroxidation, which eventually

induces tumor cell death.[51] Thus, miR-137 could be a very promising target for the treatment of glioma.

miR-137 Inhibits Glioma Cell Invasion

The high lethality of glioma is closely correlated with its ability to infiltrate the surrounding tissue, which leads to rapid postsurgery recurrence owing to incomplete resection. Molecular mechanisms underlying glioma cell invasion and migration usually involve factors that induce degradation of the extracellular matrix (ECM) or cell motility. Recent studies have proven that miR-137 contributes to the above processes. *In vitro*, miR-137 exerts inhibitory effects on glioma cell migration and invasion, reducing matrix metalloproteinase 2 (MMP2) and matrix metalloproteinase 9 (MMP9) levels and reducing ECM degradation, whereas inhibition of miR-137 expression enhances glioma cell invasiveness.[53] miR-137 is expressed at low levels in glioma tissues, particularly in high-grade glioma, which might contribute to the acquisition of invasive potential. Emerging evidence has shown that miR-137 directly targets C-X-C motif ligand 12 (CXCL12), epidermal growth factor receptor (EGFR) and cyclooxygenase-2 (COX-2), which are highly expressed in high-grade tumors and correlate with glioma cell growth and metastasis and poor prognosis.[41,54,55] Moreover, it has been demonstrated that lncRNA HOTAIRM1 promotes glioblastoma cell proliferation and invasion by upregulating transcriptional factor specificity protein 1 (SP1) expression by sponging miR-137.[30] Recently, it was reported that stanniocalcin-1 (STC1), a secreted glycoprotein hormone, may act as a novel metastasis/metastatic dissemination-promoting factor regulated by miR-137 in glioblastoma.[56,57] STC1 is closely related to the degree of glioma malignancy. The mRNA and protein levels of STC1 in high-grade glioma tissues are much higher than those in low-grade glioma tissues. The overall survival of patients with high STC1 was significantly lower than that of patients with low STC1.[56] miR-137 has a predicted binding site in STC1 mRNA, and the miR-137 analog is involved in downregulating STC1 mRNA expression in glioblastoma cells.[57] Therefore, the inhibitory effect of miR-137 on glioma invasion and metastasis may be partly implemented by suppressing STC1.

miR-137 Blocks Glioma Angiogenesis

Angiogenesis is another important process involved in the malignant progression of glioma. Increasing investigations have shown that miR-137 is linked to glioma angiogenesis by modulating a variety of angiogenic targets. For example, lncRNA XIST was observed to regulate angiogenesis positively *in vivo* by directly modulating the expression of miR-137 in glioma, which targets tight junction protein gene zonula occludens-2 (ZO-2) and forkhead box C1 (FOXC1), and FOXC1 is able to induce chemokine (C-X-C motif) receptor 7b (CXCR7) expression and activate angiogenesis.[28] In addition, the aberrant high expression of FOXC1 in glioma-associated endothelial cells (GECs) leads to a decreased permeability of the blood tumor barrier (BTB) by increasing the expression of tight junction proteins (ZO-1, claudin-5, and occludin).[28] In addition, miR-137 was recently shown to regulate the proliferation and angiogenesis of glioblastoma cell lines *in vivo* by directly targeting polycomb group protein enhancer of zeste 2 (EZH2).[58] Therefore, miR-137 and the related molecules of the angiogenic pathway could be a potential therapeutic target in the treatment of glioma.

miR-137 Suppresses GSC Development and Stemness Maintenance

The GSC hypothesis proposes that tumors harbor a small subpopulation of cells characterized by self-renewal capability, high migration rates, and unlimited growth capacity to drive gliomagenesis; this population of cells is also responsible for tumor aggressiveness, recurrence, and therapy resistance. The roles of miR-137 in regulating GSCs have received much attention in recent years. For example, the origin of gliomas is largely unknown, but they are supposed to originate from GSCs, which might consist of transformed NSCs. Silber et al.[17] demonstrated that miR-137 was much lower in GSCs than in NSCs, whereas overexpression of miR-137 induced neuronal differentiation in both cell types. In particular, ectopic expression of miR-137 significantly suppresses the self-renewal of GSCs by decreasing OCT4, SOX2, NANOG, and sonic hedgehog (SHH) levels.[6] Furthermore, miR-137 inhibits glioblastoma stemness through various targets, such as glioma pathogenesis-related protein 1 (GLIPR1) and Musashi-1 (Msi1), which are related to testes-specific vespid and pathogenesis protein 1 (RTVP-1) and STC1.[6,57,59] For example, miR-137 reduces the transcriptional expression of RTVP-1, while RTVP-1 facilitates the self-renewal of GSCs by enhancing CXXR4.[6] miR-137 is involved in regulating the expression of STC1, whereas the latter enhances the stem-like characteristics of glioblastomacells by activating the NOTCH1-SOX2 signaling pathway.[57,59] Msi1 is a stem-cell protein involved in self-renewal that has the opposite expression pattern and function to miR-137, and these proteins inhibit each other. Msi1 and miR-137 are regulators of molecular conversion between self-renewal and differentiation, and they share 141 target genes related to differentiation, development, and morphogenesis. In gliomas, miR-137 has an anticancer effect, whereas Msi1 is a proto-oncogene. The balance between Msi1 and miR-137 is a key determinant of cell fate, and the disruption of this balance may lead to glioma development.[60]

Given their critical roles in glioma initiation, propagation, and maintenance, GSCs offer an attractive therapeutic target. miR-137 is essential for the canonical differentiation of GSCs and neural progenitor cells. Abrogation of its expression could lead to GSC formation and gliomagenesis. Upregulation of miR-137 in GSCs could be a therapeutic method for GSC differentiation, thereby eliminating their stem-cell properties. Thus, the understanding of the roles of miR-137 in GSCs may offer an innovative clinical strategy for the early diagnosis and treatment of glioma.

The Underlying Molecular Mechanisms by which miR-137 Inhibits Gliomagenesis

miR-137 acts as a gene-network hub by blocking the expression of multiple target genes. miR-137 has over 1,300 predicted target genes,[46] and a number of downstream target genes of miR-137 have been experimentally verified in glial cells (summarized in Table 1

Table 1. mRNA Targets of miR-137 in Glioma Development and Function

Targets	Major Functions	References
LSD1	promoting NSC or GSC proliferation and inhibiting differentiation	25
EZH2	promoting proliferation and angiogenesis of glioma cells	58
RTVP-1	promoting GSCs' self-renewal and inhibiting their differentiation	6
TCF4	binding to β-catenin and triggering Wnt/β-catenin signaling	61
CDK6	cell-cycle regulator	17
COX2	promoting glioma cell proliferation and invasion	41
EGFR	increasing cell growth and decreasing cell apoptosis	55
FOXK1	promoting proliferation and cell-cycle transition and inhibiting apoptosis	62
PDGFRα	increasing cell growth and reducing cell apoptosis	60
ZO-2	angiogenesis and blood tumor barrier permeability	28
CSE1L	inhibiting glioma cell proliferation, invasion	63
Msi1	promoting self-renewal, proliferation, tumorigenesis	60
RasGRF1	promoting glioma cell proliferation and inhibiting apoptosis	23
Rac1	promoting glioma cell proliferation and inhibiting apoptosis	50
CENPE	promoting pediatric high-grade glioma cell proliferation	45
PTP4A3	promoting GBM cell proliferation, migration, and invasion	64
SP1	promoting cell proliferation and invasion	30
FOXC1	angiogenesis and blood tumor barrier permeability	28
TRIM24	drug resistance	31
CAR	drug resistance	65
STC1	promoting metastasis and cell proliferation	57
CXCL12	promoting cell proliferation and invasion	54
NUCKS1	promoting cell proliferation and drug resistance	66
BCL2	inhibiting apoptosis	50
SLC1A5	regulating cell growth, survival, and proliferation	51

GBM, glioblastoma.

and Figure 2). These target genes, to a certain extent, illustrate the molecular mechanism underlying the inhibition of gliomagenesis by miR-137. In particular, miR-137 is located at a node of several essential cellular signaling networks of glioblastoma cell aggressiveness. Moreover, miR-137 could potentially alter basic cell biological processes by regulating chromatin-state reprogramming and inhibiting tumorigenesis.

miR-137 Targets Multiple Chromatin-Modifying Proteins in Glioma

Gliomagenesis is a multistep process involving both genetic and epigenetic mechanisms. Histone modifications and chromatin structure alterations play important roles in chromatin-based gene regulation. An increasing number of studies have demonstrated that histone-modifying enzymes and chromatin modifiers affect genome stability in gliomas.[67,68] Accumulated evidence has shown that miR-137 acts as an epigenetic regulator that contributes to chromatin-state changes in glioma. First, miR-137 affects histone methylation levels by directly inhibiting LSD1 and EZH2.[24,58,69] LSD1 specifically catalyzes the removal of methyl groups from histone H3 at lysine 4 to activate transcription, whereas EZH2 is a histone methyltransferase that mediates gene silencing by catalyzing histone methylation.[70] Notably, as one of the master epigenetic proteins, LSD1 plays an important role in GSC stemness.[71,72] miR-137 also inhibits proliferation and angiogenesis of glioblastoma cells by directly regulating the level of EZH2.[58] Second, tripartite motif-containing 24 (TRIM24) is a member of the transcription intermediary factor family and has been reported to bind with H3K23ac to regulate the development of a variety of tumors.[31] Recently, it was reported that miR-137 directly targets TRIM24 to suppress glioma development and improve chemosensitivity by activating the phosphatidylinositol 3-kinase (PI3K)-Akt signaling pathway.[73,74] Third, miR-137 regulates chromosome assembly and chromosome positioning at the metaphase plate by targeting chromosome segregation 1-like (CSE1L) and centromere-associated protein-E (*CENP-E*), respectively. CSE1L is critical in maintaining genomic stability and is involved in apoptosis, cell survival, nucleocytoplasmic transport, microvesicle formation, and cancer metastasis.[63] CENP-E is essential in mitosis and exhibits periodic accumulation and loss with cell-cycle stages.[75] Additionally, there is now a substantial body of evidence validating that the loss of CENP-E function causes cell-cycle arrest in mitosis.[45] Fourth, nuclear casein kinase and NUCKS1, a chromatin-associated nuclear DNA-binding protein, have been documented to play pivotal roles in cell-cycle progression and proliferation.[18,76] NUCKS1 affects tumor development by influencing the cellular response to DNA damage, homologous recombination, and DNA repair.[76] The increased expression of NUCKS1 has been documented in several kinds of cancers.[77,78] Recently, Giunti et al.[66] demonstrated that the tumor-suppressive effects of miR-137 are mediated by the negative regulation of NUCKS1 protein expression in human pediatric glioblastoma tissues.

miR-137 Modulates Multiple Signaling Pathways in Glioma Cells

Emerging studies demonstrate that miR-137 acts as a gene network hub modulating key nodes of various essential tumor signaling pathways. First, miR-137 regulates glioma cell proliferation through the Akt/mammalian target of rapamycin (mTOR) signaling pathway. miR-137 inhibits the expression of protein tyrosine phosphatase 4A3 (PTP4A3), which regulates the activity of the Akt/mTOR signaling pathway by inducing Akt and mTOR dephosphorylation.[64] Second, researchers also demonstrated that miR-137 blocks cell growth by inhibiting the Wnt/β-catenin pathway and negatively regulates FOXK1 expression in glioma cells.[62] Wnt signaling is one of the key cascades in the regulation of human tumor growth and development, especially cell proliferation. Studies have confirmed that the Wnt/β-catenin signaling pathway regulates the growth of

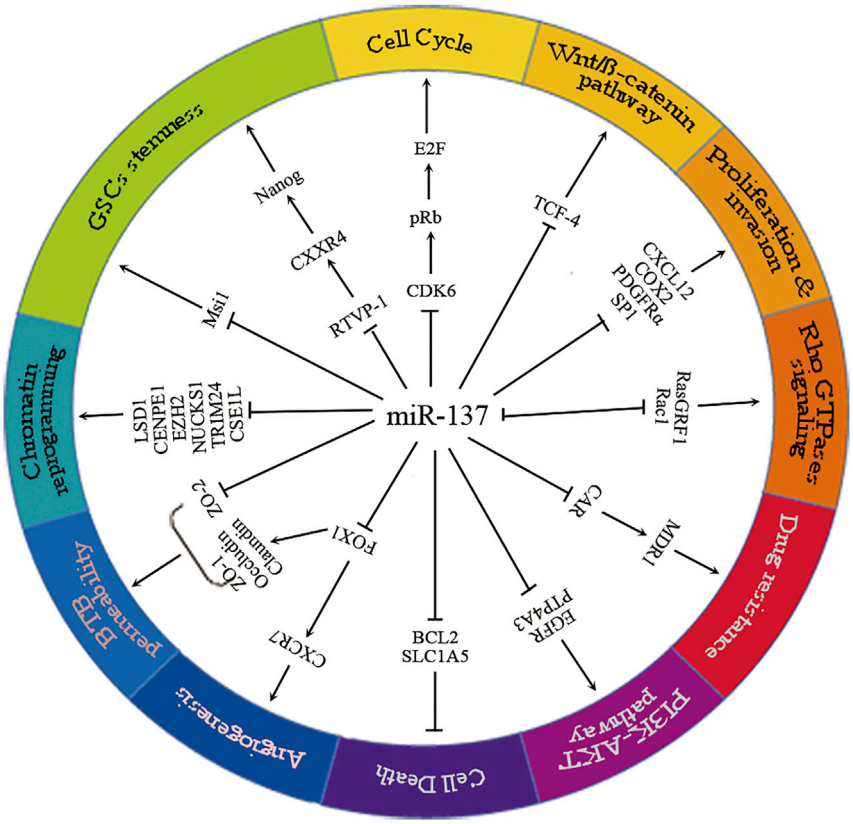

Figure 2. The Functions of miR-137 in Glioma Cell Development and the Underlying Molecular Mechanisms

→, upregulation or activation; ⊣, downregulation or inhibition.

glioma.[79] FOXK1 activates the Wnt/β-catenin signaling pathway and promotes glioma cell proliferation and cell-cycle transformation and inhibits apoptosis.[62] miR-137 directly binds to the 3′ UTR of FOXK1 and suppresses its expression, therefore inhibiting its effect on glioma cell proliferation and apoptosis.[62] In addition, TCF4 controls critical steps of glioma development by interacting with β-catenin[80] and was reported to be regulated by miR-137.[11] Therefore, miR-137 may restrain Wnt/β-catenin signaling by disrupting TCF4 binding to β-catenin in glioma cells. Third, Rho GTPase signaling is another well-known pathway closely related to glioma development.[81] Rac1 is one of the most characteristic Rho GTPases in the regulation of cell migration and plays a key role in regulating cytoskeleton reorganization as well as the cell cycle and apoptosis of tumor cells.[18,50] In gliomas, increased Rac1 facilitates the growth and invasion behavior of glioma cells by regulating cyclin D1, MMP2, Bcl-2, and BCL-2-associated X protein (Bax).[82,83] miR-137 suppresses the Rac1 gene by binding directly to the 3′ -UTR, thereby inhibiting the development of gliomas.[50] On the other hand, guanine nucleotide exchange factors (GEFs) control the activation and inactivation of Rho GTPase, whereas Ras protein-specific guanine nucleotide-releasing factor 1 (RasGRF1) is one of the GEFs that regulates cell proliferation and apoptosis.[84,85] miR-137 also directly inhibits RasGRF1 expression by binding to the 3′ -UTR, therefore leading to cell proliferation suppression and inducing apoptosis in astrocytoma.[23]

miR-137 May Be a Biomarker of Glioma

Tumor biomarkers provide important information for diagnosis, therapy response, and prognosis. The role of miR-137 in glioma development and the extensive alterations in miR-137 expression make it an important candidate biomarker.[42] miR-137 signatures have been identified in both glioma tissue and the blood of glioma patients. Li et al.[86] recently demonstrated that serum miR-137 is downregulated in glioma patients compared to healthy controls. In addition, low serum miR-137 levels are strongly associated with high glioma clinical grades and poorer survival in glioblastoma patients, highlighting the potential of miR-137 as a useful, noninvasive diagnostic marker for glioma.

Thus far, O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation has been the only confirmed clinical molecular predictive factor in glioma.[87] miR-137 transcription is regulated by the promoter hypomethylated CpG island.[88] A recent study indicated that the promoter methylation status of miR-137 may be another possible biomarker, although replication of this finding is needed.[6] Thus, miR-137 may be used as a valuable indicator for pathological diagnosis and prognosis evaluation of malignant glioma.

miR-137 Boosts the Chemosensitivity of Glioma Cells

Chemotherapy is the most attractive cancer therapy method. Multidrug resistance (MDR) remains the leading cause of glioma treatment failure. Recently, an increasing amount of evidence has shown that miR-137 exerts important effects on chemotherapy resistance in a variety of tumors.[89–91] For example, Zhu et al.[92] demonstrated that miR-137 is involved in MDR in breast cancer by the regulation of MDR1 (P-glycoprotein) by targeting Y-box binding protein-1 (YB-1), indicating that miR-137 might be a valuable target for preventing and reversing MDR in cancer cells. In GSCs, EGFR activity is elevated and is required to maintain chemotherapy resistance, and EGFR is a direct target of miR-137.[93] Interestingly, miR-137 expression is upregulated in glioma cells after treatment with temozolomide (TMZ) and correlated with reduced resistance to TMZ.[94] Most importantly, it was reported that miR-137 negatively regulates constitutive androstane receptor (CAR), and CAR upregulates MDR1 and reduces intracellular drug accumulation and cellular sensitivity to doxorubicin.[65] Remarkably, Chen et al.[31] demonstrated that lncRNA NCK1-AS1 could increase the drug resistance of glioma cells to TMZ by

modulating the miR-137/transcription intermediary factor 1a (TRIM24) axis.

These results provide new theoretical support for miR-137 in glioma treatment and prognosis. We assume that miR-137 facilitates the re-sensitization of drug-resistant glioma cells and contributes to better prognosis and survival in glioma patients.

Exosomes May Be an Effective Vehicle Enabling the Use of miR-137 in the Diagnosis and Treatment of Glioma

Exosomes are 40–100 nm diameter lipid bilayer vesicles secreted by most mammalian cells. The composition of exosomes varies slightly depending on the cell type from which they are derived. Glioma cell-derived exosomes are rich in the oncogenic proteins EGFR variant III,[95] angiogenic factors,[96] and noncoding RNAs,[96–99] which may facilitate the transmission of carcinogens between cancer cells, thus forming a positive-feedback loop or facilitating communication between cancer cells and adjacent stromal cells.

Characteristic carcinogens carried by cancer cell-derived exosomes can be used as biomarkers for disease diagnosis. Exosomes from cancer cells have been identified as important transporters of carcinogenic miRNAs.[96,100] For example, exosomal miR-21 was one of the first miRNAs recommended for use in the diagnosis of patients with glioblastoma multiforme.[101] miR-137-containing exosomes were found in the serum of healthy people and patients with dementia or Parkinson's disease.[102,103] However, there have been no reports related to miR-137-containing exosomes in glioma patients.

In addition to functioning in diagnosis, exosomes have unique therapeutic advantages that can be applied to glioma therapy: small exosomes can penetrate the blood-brain barrier,[104] facilitate immune escape,[105] increase molecule half-life,[106,107] and enable the ability to target specific types of cancer cells. [108] Exosomes not only protect therapeutic agents, including small-molecule inhibitors, therapeutic small interfering RNAs (siRNAs), and even peptides, but also improve their bioavailability and overall efficacy.[109–112] Based on our understanding of miR-137, exosomal miR-137 may play a good therapeutic role in glioma. Further studies of exosomal miR-137 will very possibly facilitate the diagnosis and treatment of glioma.

Summary and Prospect

In this review, we highlighted the function and mechanisms of miR-137 in glioma cell proliferation, apoptosis, invasion, and angiogenesis and in glioma treatment to provide evidence for further investigations. miR-137 may be implicated in the core pathophysiologic mechanisms underlying glioma pathogenesis, and targeting miR-137 offers great therapeutic potential for improving the outcome of glioma patients.

Emerging evidence strongly suggests that targeting miR-137 is of great value in glioma therapy, but so far, research on inhibiting glioma by regulating miR-137 has remained in the experimental stage at the cell level. One of the greatest challenges regarding the efficacy of miRNA-based glioma therapies is the absence of effective delivery methods to the brain. Currently, the development and optimization of novel delivery methods, such as exosomes, adeno-associated viruses, and nanoparticles, will pave the way for the clinical application of miR-137 as a weapon against glioma. We hope that our review will attract the attention of the scientific research community and clinical practitioners and encourage them to carry out treatments targeting miR-137 as soon as possible.

AUTHOR CONTRIBUTIONS

Y.W. wrote the manuscript. R.C. contributed to critical revision/review of the manuscript. X.Z., R.G., and J.Y. edited the manuscript. Y.L. and G.M. were responsible for the conception and final approval of the manuscript. All authors approved the manuscript.

CONFLICTS OF INTEREST

The authors declare no competing interests.

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