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The landscape of circRNAs in gliomas temozolomide resistance: Insights into molecular pathways

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ABSTRACT

As the deadliest type of primary brain tumor, gliomas represent a significant worldwide health concern. Circular RNA (circRNA), a unique non-coding RNA molecule, seems to be one of the most alluring target molecules involved in the pathophysiology of many kinds of cancers. CircRNAs have been identified as prospective targets and biomarkers for the diagnosis and treatment of numerous disorders, particularly malignancies. Recent research has established a clinical link between temozolomide (TMZ) resistance and certain circRNA dysregulations in glioma tumors. CircRNAs may play a therapeutic role in controlling or overcoming TMZ resistance in gliomas and may provide guidance for a novel kind of individualized glioma therapy. To address the biological characteristics of circRNAs and their potential to induce resistance to TMZ, this review has highlighted and summarized the possible roles that circRNAs may play in molecular pathways of drug resistance, including the Ras/Raf/ERK PI3K/Akt signaling pathway and metabolic processes in gliomas.

1. Introduction

Gliomas are the most common primary malignant brain tumors globally. The World Health Organization (WHO) classifies low-grade gliomas (LGG) as tumors that are categorized as Grades I and II, as opposed to Grade III and IV high-grade gliomas, which include glioblastoma (GBM) [1]. Although LGGs have relatively favorable survival rate and fewer aggressive characteristics than their high-grade counterparts, their resilience and heterogeneity make treatment challenging [2]. Previous chemotherapeutic approaches for gliomas primarily targeted the blood-brain barrier (BBB), which was believed to impede anticancer drugs' access to tumor tissue and result in chemotherapy resistance [3]. According to tumor histology, immunohistochemistry, and molecular diagnostics, patients with GBM, need to take temozolomide (TMZ) regularly as the standard first-line chemotherapy drug after surgery in order to prolong patient survival and prevent glioma regrowth [4]. However, resistance to TMZ has emerged as a major challenge for the treatment of gliomas and usually results in poor prognosis and treatment failure [5]. Therefore, knowledge of the resistance mechanisms is necessary to reduce or eliminate the chemoresistance incidence. Several well-established mechanisms of treatment resistance in gliomas include alterations in drug transport and metabolism, suppression of apoptosis, activation of DNA repair enzymes, autophagic activity, the presence of glioma stem cells, mutations at drug target regions, and alterations in tumor microenvironment (TME) [6,7].

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Abbreviations

CircRNAs	Circular RNAs
EMT	Epithelial to mesenchymal transition
HCC	Hepatocellular carcinoma
NcRNAs	Non-coding RNAs
MiRNAs	MicroRNAs
TMZ	temozolomide;
CNS	central nervous system
OS	overall survival
BBB	blood-brain barrier
MGMT	methylguanine methyltransferase

Recent research findings have suggested that non-coding RNAs (ncRNAs) affect glioma TMZ resistance. NcRNAs can improve glioma chemoresistance by activating many signaling pathways such as Ras/Raf/ERK and PI3K/Akt axis [8]. It may be possible to reverse the chemoresistance linked to glioma by targeting the dysregulated expression of endogenous ncRNAs during the development of drug resistance with ncRNA antagonists or mimics [9–11]. NcRNAs are classified into two types: long ncRNAs (lncRNAs) and small ncRNAs.

Circular RNAs (circRNAs) are single-stranded molecules from the lncRNA family that lack the 5′-cap and 3′-polyA tail structures and have a covalently closed loop structure [12,13]. Remarkably, several of these ncRNAs have been proven to encode proteins in experiments [14]. CircRNAs are produced by non-sequential backsplicing of exons, introns, or a combination of both [15]. CircRNAs have been identified as tiny endogenous RNAs with a wide distribution, considerable variability, and a variety of regulatory activities [16]. Because they are widely distributed, almost one-eighth of the genes in the human transcriptome generate circRNAs, and their expression levels are more than ten times higher than those of the corresponding linear mRNAs [17,18]. Furthermore, circRNAs are more stable than linear RNAs due to their covalent closed-loop structure and lack of open terminal ends, which protects them from RNase R destruction [19–21]. CircRNAs are categorized into three groups according to their source: EciRNAs, EIciRNAs, and CiRNAs. Most circRNAs are created by exon skipping during pre-mRNA transcription, which results in an exon-rich lariat structure that is spliced internally to release introns and create exon-rich EciRNAs [193,194]. Although circRNAs with multiple exons can also create circRNAs, circRNAs are usually made from a single exon [22,23]. Because of their intrinsic circular nature, circRNAs are remarkably robust in extracellular plasma, like blood and saliva, as well as inside cells. It has also been demonstrated that exosomes transport circRNAs from the cell body into the extracellular fluid. Although the exact mechanism by which circRNAs regulate gene expression in distant tissues and cells from their manufacturing site is unknown, the existence of circulating circRNAs suggests that circRNAs associated with disease could be valuable diagnostic indicators [24]. In other words, circRNAs are a good candidate for a potential treatment to precisely regulate metabolism because of their remarkable stability, strong evolutionary conservation, and unique temporal and geographic expression [25]. They can also act as miRNA sponges to modify the miRNA-mRNA regulatory axis. It has been proposed that the stable characteristics of circRNA make them valuable as predictive biomarkers. Moreover, some investigations have demonstrated that circRNAs encode secret peptides, which will greatly advance our understanding of the principles of cellular physiology (Fig. 1) [26].

CircRNAs are widely distributed in neural tissues, suggesting a potential association with a variety of brain disorders, including gliomas [27]. Because they are present in serum and other body fluids, circRNAs have a strong prognostic and therapeutic importance in cancer [28]. Furthermore, mounting data demonstrating circRNA expression in gliomas emphasizes their function in the gliomas development and progression of [29]. In this review, we will address the potential functions of circRNAs in drug resistance molecular pathways, including the

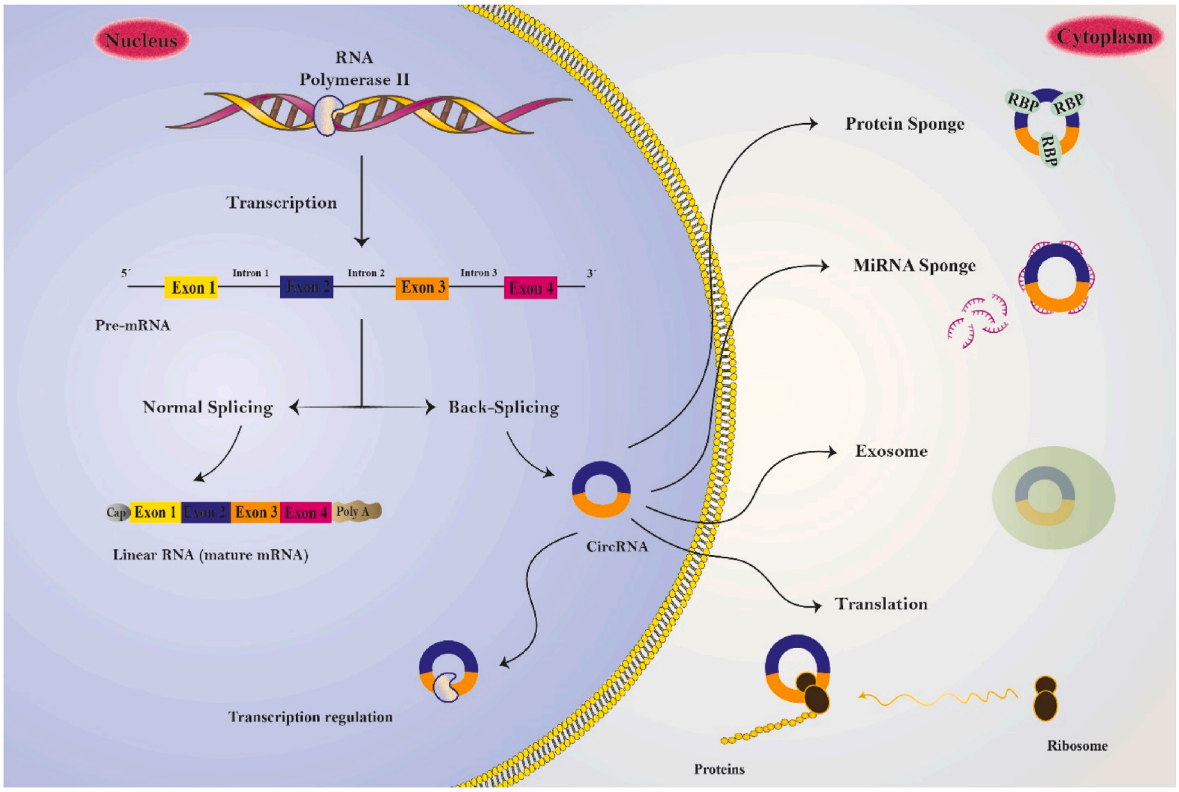

Fig. 1. A schematic illustration representing biogenesis and function of circRNAs.

Ras/Raf/ERK and PI3K/Akt signaling cascades and the metabolism of glioma cells.

2. Gliomas: a comprehensive overview

Gliomas are among the most prevalent and serious primary tumors that affect the CNS in adults [30]. The glioma nomenclature is determined by the glial cell of origin, which includes astrocytes, oligode ndrocytes, and ependymal cells, hence based on their morphologic shape, they are classified as astrocytomas, oligodendrogliomas, or ependymoma s, respectively [31]. According to the most recent WHO classification of CNS malignancies, adult diffuse gliomas are classified as follows: astrocytoma IDH-mutant (grade 2, 3, or 4), oligodendroglioma IDH-mutant and 1p/19q co-deleted (grade 2 or 3), and GBM IDH-wildtype (grade 4) [32,33]. IDH proteins catalyze the conversion of α-ketoglutarate into citrate and are engaged in the tricarboxylic acid cycle. The most prevalent IDH1 gene mutation is R132H, which results in a tridimensional alteration of the enzyme structure. The altered structure affects the enzyme activity that can change α-ketoglutarate into D2HG. The accumulation of this oncometabolite is toxic to the cell because it induces epigenetic modifications (histone modification and DNA methylation) that lead to aberrant gene expression [34]. In fact, D2HG acts as an inhibitor of several α-ketoglutarate-dependent dioxygenases, including histone demethylases and TET 5-methylcytosine hydroxylases, increasing global 5-methylcytosine levels and restricting histone methylation marks. Remarkably, gliomas with IDH mutations have a better prognosis because they react better to chemotherapy drugs like TMZ [35]. In addition to IDH mutations, the classification of gliomas is based on the 1p/19q loss of heterozygosity alteration. A feature of oligodendroglioma is the IDH mutation-related chromosomal 1p/19q codeletion, which enhances the prognosis and increases the spectrum of responsiveness to alkylating drug treatment [36,37].

Because no one therapy approach is suitable for GBM, a combination strategy will be required. Surgery will continue to be an important component of this multifaceted strategy until a free or least-invasive treatment is developed. Furthermore, multimodal immunotherapy is now being researched and appears to be effective. There are currently several planned clinical trials to investigate immune checkpoint inhibitors (ICIs). For instance, the addition of poly-ADP ribose polymerase (PARP) inhibitors, which produce synthetic death and overburden impaired DNA repair pathways, appears promising. Inhibiting PARP with medicines like olaparib can stimulate neoantigen formation, upregulate PD-L1, enhance type I interferon signaling, and modify TME to enhance tumor suppressive responses when combined with ICI [38]. Furthermore, suppressing PARP is likely to cause significant DNA damage, potentially sensitizing cancer cells to TMZ in GBM [39]. Hanna et al. found that olaparib combined with TMZ before surgery had a radio-sensitizing effect and was tolerable in individuals with recurrent GBM [40]. Nonetheless, the regulation of the immune response remains imprecise since overactivation might be detrimental to healthy tissues. ICI and vaccination together will be tested in one clinical experiment. Patients with GBM are increasingly receiving immunotherapy as part of a combination treatment regimen that also includes chemotherapy and radiation since the effects of every single therapy strategy may complement one another [41].

3. Temozolomide in chemotherapy: from history to molecular mechanisms

TMZ is a kind of anti-cancer drug which acts through alkylating DNA in cancerous cells [42]. It entered the market in 1999 for the first time and it was approved by the FDA for the treatment of GBM in 2005 [43]. This drug is taken orally and passes through the BBB well, and also has a bioavailability of about 100 %. TMZ is stable in acidic pH and is hydrolyzed in physiological pH (higher than 7) and finally turns into MTIC. Then, MTIC is also hydrolyzed and converted into methyl diazonium ions which can cause purine and pyrimidine bases to be methylated and ultimately cause DNA damage and induce apoptosis [44,45]. Because TMZ can disrupt DNA replication by alkylating the O6 site of guanine (O6MeG), more than 50 % of patients with GBM do not respond to this drug due to the mechanism of methylguanine methyltransferase (MGMT) [46,47]. This phenomenon actually repairs the damage caused by TMZ to DNA (By transferring guanine from methyl groups) and causes resistance. Other factors involved in TMZ resistance are including EGFR, PTEN, p53 and PI3K/AKT/mTOR pathways [48]. So far, several investigations have been done in relation to the drug resistance of TMZ. It has been observed that the interaction of PARP to O6-MGMT triggers PARylation in GBM cells treated with TMZ, which ultimately promotes the elimination of O6MeG additions from DNA via enhancing MGMT's interaction with chromatin [49,50]. Decreased expression of PIMREG increases TMZ sensitivity [51]. YTHDF2 can mediate TMZ resistance in GBM by inducing Akt and NF-κB cascades [52]. Silencing oncogenic factors is important for TMZ sensitivity. Downregulation of TRAP1 promotes ROS generation and make cancerous cells more sensitive to TMZ [53]. It has been demonstrated that upregulation of GNA13 expression decreases MGMT and p-RELA, increasing TMZ sensivity in glioma cells [54]. TMZ resistance in gliomas is caused by exosomal import of MIF, which also activates PI3K/Akt pathways [55]. Downregulation of ATF4 in GBM enhanced the ability of TMZ to induce cell death [56]. Many studies have shown that different mechanisms are involved in TMZ sensitivity or resistance. Various anticancer drugs have been used to increase the sensitivity of cancer cells to TMZ therapy py [57,58]. Oxyphyllanene B can cause TMZ sensitivity by overexpressing PACS2, which can interfere with and impair connection between the endoplasmic reticulum and mitochondria [50]. Celecoxib inhibits GBM proliferation and induces apoptosis and autophagy, then, it increases the sensitivity of TMZ [47,59]. Thus, there are various methods to overcome TMZ resistance [60,61]. In the growing research, several novel kinds of epigenetic variables have been identified, and all of them are critical to cancer patients' capacity for chemoresistance [195].

Given the significance of comprehending TMZ resistance in human malignancies, particularly brain tumors, a thorough and current overview of recent developments in this area is necessary [62]. There are clear advantages when contrasting our study with prior published research that primarily addressed certain kinds of brain cancers, such as gliomas and GBM. Moreover, the significance of circRNAs in TMZ resistance in a range of malignancies, particularly brain tumors, is highlighted in this article.

4. Interplay between gliomas and circular RNAs

Compared to other organs, the CNS possesses a greater variety and abundance of circRNAs. Recent research has identified several ncRNAs associated with the development and propagation of gliomas. There is a growing interest in the characteristics and sequence of circRNA expression in gliomas within the field of non-coding RNA research [63,64]. CircRNAs have been found to influence glioma cell invasion and proliferation, and they may serve as ceRNAs in controlling tumor growth [65]. A recent study reports that several circRNAs regulate the glioma cells' apoptosis [66]. CircRNAs have the ability to act as miRNA sponges, which may impact glioma cell invasion and migration by controlling EMT—a process that is involved in early invasion and migration in various tumor types—through endogenous competitive processes [67,68]. Recent studies have revealed that some circRNAs may act as tumor promoters and have favorable effects on the development of gliomas. To maintain the carcinogenic potential of glioma stem cells, an oncogenic E-cadherin variant encoded by circRNA has to bind to the EGFR CR2 domain and activate EGFR independently of EGF [69]. Conversely, some circRNAs may also function as tumor suppressors in gliomas. It has been demonstrated that CDR1as expression in the brain was notably higher than in other normal organ tissues. On the other hand, glioma brain tissues have lower levels of CDR1as expression

than normal brain tissues. Particularly, it was shown that CDR1as inhibited carcinogenesis by disrupting the p53/MDM2 complex, which in turn reduced MDM2-mediated ubiquitination and allowed CDR1as to maintain p53 [70,71]. Jiang et al. report that circLRFN5 is down-regulated in GBM and linked to a bad prognosis for GBM patients [72]. CircLRFN5 overexpression inhibits GSC proliferation, neurosphere formation, stem cell identity, and tumorigenicity by inducing ferroptosis. Mechanistically, circLRFN5 binds to the PRRX2 protein and promotes its degradation via the ubiquitin-driven proteasomal pathway [72]. PRRX2 can transcriptionally upregulate GCH1, a ferroptosis suppressor, to produce the antioxidant tetrahydrobiopterin (BH4) in GSCs [72]. Selected circRNAs that involved in glioma progression are summarized in Table 1.

5. Relationship between circRNA and TMZ resistance in glioma tumors: molecular perspective

The rapid development of high-throughput sequencing methods has led to the discovery of abnormal expression of a large variety of ncRNAs, including circRNAs, lncRNAs, and miRNAs, in cancer tissues and cell lines [73–76]. These aberrantly generated ncRNAs are closely associated with drug resistance and the progression of cancer. It is well established that ncRNAs contribute to the establishment of cancer drug resistance through a variety of pathways, including the suppression of cell death pathways, encouragement of excessive drug efflux, autophagy facilitation, modification of CSC properties, and acceleration of the EMT [77,78]. Some of tumor suppressor circRNAs are associated with the TGF-β Pathway in gliomas [79]. It has been found that LRCC4 promoted the synthesis of circCD44 from the CD44 mRNA by blocking the interaction between CD44 pre-mRNA and SAM68 [80]. CircCD44 expression is downregulated in GBM tissues and cell lines. Furthermore, overexpression of circCD44 reduced GBM cell invasion, proliferation, and colony formation [79,81].

Accumulating evidences have demonstrated role of circRNAs in development of TMZ-resistant glioma [82]. Notably, circ_0000936 has been identified by Hua et al. as a contributor to TMZ resistance through its interaction with miR-1294 [83]. They successfully inhibited circ_0000936/miR-1294 axis by knocking down circ_0000936 expression leading to enhanced cancer cell response to TMZ. In their recent study, Hua et al. have revealed another novel circRNA/miRNA axis that promotes TMZ-resistance [84]. CircCEP128 is also an oncogenic circRNA that increases glioma cell proliferation and invasion. Elevated circCEP128 expression correlates with the development of TMZ resistance in glioma, acting through the miR-145-5p axis. Hua et al. were able to enhance glioma cell sensitivity to TMZ by targeting circCEP128 and suppressing circCEP128/miR-145-5p axis [84].

Furthermore, Circ-ASAP1 expression is incredibly high in recurrent GBM tissues and TMZ-resistant cell lines. Therefore, overexpression of Circ-ASAP1 resulted in increased proliferation of GBM cells and resistance to TMZ, which may be decreased by circ-ASAP1 knockdown [11,85]. Serum levels of exosomal circNFIX were found to be increased in TMZ-resistant patients, suggesting a poor prognosis. Additionally, circNFIX produced from TMZ-resistant cells spread TMZ resistance to sensitive glioma cells via regulating cell migration, invasion, and apoptosis subsequent to TMZ exposure. Further analysis revealed that the decrease of circNFIX enhanced TMZ sensitivity in resistant glioma cells by upregulating miR-132. Thus, circNFIX can increase TMZ resistance in gliomas by sponging miR-132 [75,86]. The next sections address the role of circRNAs in TMZ resistance in gliomas, with the goal of elucidating their actions as a target for mitigating TMZ-resistance as well as the underlying mechanisms (Fig. 2 and Table 2)

5.1. MAPK/mTOR signaling pathway and TMZ-resistance

CircRNAs contribute to cancer progression and drug resistance via regulating various signaling pathways such as MAPK/mTOR [87]. This pathway has essential role in cell response to extracellular stimuli and alteration, ultimately influencing the cancer cell's reaction to

Table 1
Some of circRNAs that are involved in glioma progression.

CircRNA	miRNA/Signaling pathway	Expression	Related cellular process	Clinical significance	Ref
CEP128	MiR-145-5p	Upregulated	↑[a] Proliferation ↑ Invasion	Overcoming the drug resistance	[84]
CircNFIX	MiR-378e/RPN2 axis	Upregulated	Knockdown of this circRNA led to: Arrest of cell cycle Suppression of glycolysis, migration and invasion Induce of apoptosis	Treatment	[185]
Circ-CDC45	MiR-516b and miR-527	Upregulated	↑ Cell growth ↑ Proliferation ↑ Invasion	Prognosis and treatment	[186]
Hsa-circ-0014359	MiR-153/PI3K signaling	Upregulated	Promotes development of glioma via: ↑ Cell Viability ↑ Migration ↑ Invasion	Treatment	[187]
Circ-MAPK4 (has_circ_0047688)	MiR-125a-3p/MAPK	Upregulated	↑ Survival and ↓[b] apoptosis of glioma cells	Therapeutic target	[188]
CircGLIS3	Ezrin Phosphorylation	Upregulated	↑ Invasion ↑Angiogenesis	Diagnosis and therapy	[189]
CircNEIL3	HECTD4/IGF2BP3	Upregulated	↑ Tumorigenesis and carcinogenic progression	Prognostic biomarker and therapeutic target	[130]
CircPOSTN	MiR-361–5p/TPX2	Upregulated	↑ Cell Proliferation ↑ Aerobic Glycolysis ↓ Apoptosis	Diagnosis and treatment	[190]
CircBRAF	MiR-1290/FBXW7 Axis	Downregulated	↓ Cell Proliferation ↓ Metastasis ↓ Tumor Growth	Treatment target	[191]
CircHEATR5B	ZCRB1/circHEATR5B/HEATR5B-881aa/JMJD5/PKM2 pathway	Downregulated	↓ Glycolysis ↓ Proliferation	Targets for therapy	[192]

Abbreviations: CircRNA: circular RNA, MiR: microRNA, IGF2BP3; insulin-like growth factor 2 mRNA binding protein 3, TPX2; Xenopus kinesin-like protein 2, ZCRB1; zinc finger CCHC-type and RNA-binding motif 1, PKM2; pyruvate kinase M2, JMJD5; Jumonji C-domain-containing 5, IGF2BP3; insulin-like growth factor 2 mRNA binding protein 3, RPN2; Ribophorin-II.

[a] ↑ indicates the increased.

[b] ↓ indicates the decreased.

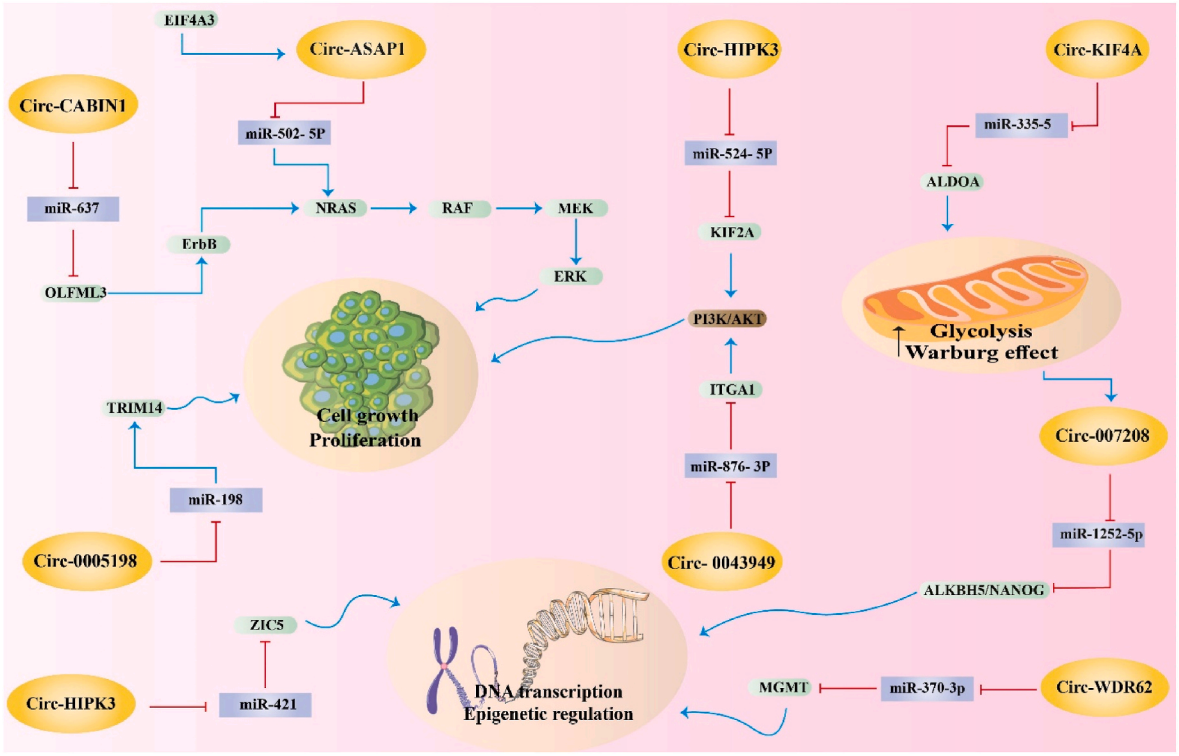

Fig. 2. An illustration of the interaction between circRNAs and TMZ-resistance in glioma progression. CircCABIN1, circHIPK3, circ-0005198 and circ-0043949 enhance TMZ-resistance via increasing cancer cell growth and proliferation through upregulating proliferative cellular pathways such as NRAS/RAF/MEK/ERK and PI3K/Akt. CircWDR62, circHIPK3 and circ-007208 regulate DNA transcription and replication leading to increased cell proliferation. Circ-007208 enhances DNA hyper methylation through ALKBH5/NANGO axis. Warburg effect and increased glycolysis promotes TMZ-resistance and participates in upregulation of circ-007208. CircKIF4A increases glycolysis via upregulating expression of ALDOA enzyme. CircASAP1 is a tumor suppressor and reduces TMZ-resistance via regulating NRAS/RAF/MEK/ERK pathway.

chemotherapeutic agents [88,89]. Tripartite motif (TRIM) is a group of protein that exert divers functions in cellular signaling, proliferation, apoptosis and differentiation [90]. TRIM14 is member of this family with carcinogenic effects, has been implicated in several cellular signaling pathways such as the Wnt pathway and PI3K pathway [91,92]. A recent research has revealed that TRIM14 promotes 5-FU resistance in gastric cancer through regulating MAPK/mTOR pathway, suggesting possible role of TRIM14 protein in drug resistance through regulating signaling pathways [93]. In glioma, TRIM14 is upregulated, particularly in TMZ-resistance cells [94]. Deng et al. revealed that upregulation of TRIM14 in glioma cells is related to circ_0005198/miR-198 axis [95]. High expression of cir_0005198 increases TRIM14 expression via inhibiting miR-198. Targeting circ_0005198/miR-198 axis through circ_0005198 knockdown or miR-198 mimic reduces TRIM14 expression and improves glioma sensitivity to TMZ [95]. Collectively, silencing circCEP128 and TRIM14 inhibits the progression of TMZ-resistant glioma cells through regulating MAPK/mTOR pathway [95].

5.2. *Ras/Raf/ERK signaling pathway and TMZ-resistance*

Intercellular communication is the main factor determining cancer response to chemotherapeutic drugs through regulation of several fundamental cellular processes [96,97]. The RAS/RAF/MEK/ERK (MAPK) signaling cascade plays a key role in intercellular communication and thereby participates several cellular processes including proliferation, differentiation, adhesion, migration, and apoptosis [98,99]. Dysregulation of this pathway, which involves RAS family protein activation, has been associated with aberrant proliferation and invasion in various cancers. RAS proteins are GTP-binding protein that are active in GDP-bound form and its activation is depended to GTP/GDP cycle regulators [100]. RAS activation results in MEK activation and cascade of phosphorylation/de-phosphorylation events, which results in cell proliferation and growth [101]. Zhang et al. showed that overactivation of RAS/RAF/MEK/ERK pathway is associated with development and progression of TMZ-resistance in glioma [102]. Investigating TMZ-resistant glioma cells demonstrated upregulation of NRAS, MEK1 and ERK1-2 proteins, controlled by CircASAP1/miR-502-5p [11]. CircASAP1 is abundantly expressed in TMZ-resistant glioma cells and promotes proliferation of these cells by suppressing miR-502-5p. Interestingly, miR-502-5p targets NRAS, and its downregulation by CircASAP1 increases NRAS expression, leading to overactivation of the RAS/RAF/MEK/ERK pathway [11].

5.3. *PI3K/Akt signaling pathway and TMZ-resistance*

The PI3K/Akt cascade is a major signaling pathway in the cell affecting several aspects of cell function and hemostasis [103]. Dysregulation of this pathway plays key role in pathogenesis of various diseases including cancer and chemoresistance [104,105]. Kinesin family are motor proteins facilitating intracellular transport through microtubule dynamics [106]. KIF2A, a member of the Kinesin-13 family, has been identified as a prognostic marker in multiple cancers. Upregulated KIF2A induces PI3K/AKT pathway activation, leading to increased cell proliferation, stemness, and chemoresistance [107]. CircHIPK3 is an oncogenic circRNA with significant role in development of TMZ-resistance in glioma [108]. Yin et al. demonstrated that circHIPK3 enhances TMZ resistance by participating in the overactivation of the PI3K/AKT signaling pathway [107]. KIF2A acts as a link between circHIPK3 and the PI3K/AKT pathway, as upregulation of circHIPK3 reduces miR-524-5p-mediated inhibition on KIF2A increasing its expression and leading to PI3K/AKT pathway activation. The circHIPK3/miR-524-5p axis is identified as one of PI3K/AKT pathway

Table 2
CircRNAs involved in glioma TMZ resistance.

CircRNA	miRNA	Signaling pathway	Function	Ref
Circ_0000936	MiR-1294	Not reported	Promotes TMZ-resistance	[83]
CircCEP128	MiR-145-5p	Not reported	Promotes TMZ-resistance	[84]
Circ -0005198	MiR-198	circ −0005198/ miR-198/ TRIM14 axis	Promotes TMZ-resistance via upregulating TRIM14 through miR-198 sponge	[95]
CircASAP1	MiR-502-5p	RAS/RAF/ MEK/ERK pathway	Promotes TMZ-resistance via miR-502-5p sponge leading to NRAS/MEK1/ERK 1–2 pathway activation	[11]
Circ_0043949	MiR-876-3p	miR-876-3p/ ITGA1 axis	↑[a] Circ_0043949 reduces inhibitory effect of miR-876-3p on ITGA1 leading to ITGA1 upregulation and TMZ-resistance	[112]
Circ _0110757	MiR-1298-5p	ITGA1/PI3k/ AKT/Bcl-2 signaling	Promotes TMZ-resistance via enhancing apoptosis through miR-1298-5p/ ITGA1/PI3k/AKT/Bcl-2 pathway	[111]
Circ HIPK3	MiR-524-5p	PI3K/AKT Pathway	CircHIPK3 promotes TMZ-resistance via miR-524-5p/KIF2A axis leading toPI3K/AKT Pathway activation	[107]
Circ _0072083	MiR-1252-5p	miR-1252-5p/ ALKBH5/ NANOG axis	Circ_0072083 enhances TMZ-resistance via regulating miR-1252-5p/ALKBH5/NANOG axis	[127]
Circ -HIPK3	MiR-421	miR-421/ZIC5 axis	↑ ZIC5 expression via miR-421 sponge	[108]
Circ WDR62	MiR-370-3p	miR-370-3p/ MGMT axis	↑ MGMT through miR-370-3p sponge enhancing TMZ-resistance	[141]
Circ CABIN1	MiR-637	ErbB signaling pathway	Promotes TMZ-resistant glioma via regulating OLFML3/miR-637 and activation of ErbB pathway	[142]
Circ _0042003	Not reported	Heparanase	↑ Expression of heparanase in TMZ-resistant cells	[155]
Circ KIF4A	MiR-335-5p	Glycolysis	↑ Glycolysis in TMZ-resistant glioma cells through regulating ALDOA	[121]

Abbreviations: CircRNA: circular RNA, MiR: microRNA, TRIM14; tripartite Motif 14, ALKBH5; Human AlkB homolog 5, MGMT; O-6-methylguanine-DNA methyltransferase.
[a] ↑ indicates the upregulation.

regulator and enhances TMZ-resistance by upregulating this pathway [107].

Integrin, a class of cellular proteins responsible for connecting cellular skeletal proteins to the extracellular matrix, play a crucial role in cell adhesion, and have been implicated in cancer initiation, development, progression, and chemoresistance, particularly in local invasion and metastasis [109]. In addition, integrins are also known to participate in regulating Z cellular signaling pathways. Integrin α1 (ITGA1) a member of integrin family with significant role in cancer progression, has been identified as a pre-malignant marker that promotes chemoresistance [110]. It has been found that ITGA1 is highly expressed in TMZ-resistant glioma cell lines [111]. Li et al. have revealed that ITGA1 overexpression in TMZ-resistant glioma is associated with upregulation of circ_0043949 and its sponge effect on miR-876-3p [112]. Knockdown of circ_0043949 enhanced the inhibitory effect of miR-876-3p on ITGA1 mRNA, suppressing ITGA1 expression and subsequently suppressing TMZ resistance [112]. ITGA1 has been repeatedly reported as regulator of PI3k/AKT signaling pathway. Li et al. showed that ITGA1 is upregulated in TMZ-resistant glioma cell lines and induces apoptosis via activating PI3k/AKT/Bcl2 signaling [111]. Researchers found a link between ITGA1 upregulation and the circ_0110757/miR-1298-5p axis, where circ_0110757 acts as a sponge for miR-1298-5p, reducing its inhibitory effect on ITGA1 and promoting PI3K/AKT/Bcl2 activation. Therefore, silencing circ_0110757 enhanced glioma cell sensitivity to TMZ, suppressing ITGA1/PI3K/AKT/Bcl-2 signaling and reducing both glioma progression and TMZ resistance [111].

5.4. *CircRNAs promoting TMZ-resistance via regulating cancer cell metabolism*

Metabolism of cancer cell is significantly different from normal cells, due to high rate of proliferation and turnover in cancer tissue [113,114]. Warburg effect or increased rate of aerobic glycolysis is one of the profound metabolism alteration in cancer cells and is associated with development of chemoresistance [115,116]. Glycolysis provides ample ATP and energy for cancer cells to grow and proliferate in hypoxic microenvironment. Metabolic alteration in cancer cell attributes to mitochondria dysregulation and changes in enzymes expression [117]. Aldolase A (ALDO A), a key glycolysis enzyme, is abundantly expressed in tumor cells [118]. Elevated expression of ALDOA participates in carcinogenesis and can be a predictor of poor prognosis in cancers [119]. Increased level of glycolysis in glioma cell line enhances TMZ-resistance, as cancer cell are being provided with energy and high amount of glycolysis intermediates which promote its growth even in exposure to TMZ [120]. CircKIF4A has been shown to increase glycolysis rate in TMZ-resistance cell lines [121]. High expression of circKIF4A leads to upregulation of ALDO A and subsequently glycolysis. ALDO A mRNA is direct target of miR-335-5p and downregulation of miR-335-5p increases ALDO A expression and function. CircKIF4A as miR-335-5p sponge, mitigates its inhibitory effect in TMZ-resistance glioma cells. Cancer cells enhance the level of glycolysis by upregulating circKIF4A, so targeting and knocking down this circRNA improve TMZ-treatment outcomes [121].

5.5. *Exosomal circRNAs: novel targets for reducing TMZ-resistance*

Exosomes, a common type of Extracellular vesicle (EVs), are nanostructures released by cells and play an essential role in intracellular interactions by carrying cellular components [122,123]. CircRNAs are widely distributed and persistently expressed in exosomes [124], and certain investigations have demonstrated their ability to be encapsulated and perform functions within exosomes. Exosomal circRNAs are abundantly expressed in TME and regulate tumors malignant behavior via transferring proteins and ncRNAs through their oncogenic or oncostatic effects [125]. Role of exosomal circRNAs in development of TMZ-resistance glioma have been demonstrated in several studies [126]. Exosomal circ_0072083 are abundantly expressed in TMZ-resistant glioma microenvironment and promotes TMZ resistance through a complex mechanism involving m6A demethylation [127]. It has also been demonstrated that KHDRBS3 and hnRNPA2B1 packages short RNA molecules into exosomes, such as circ_0088300, circNEIL3 and circCCAR1, respectively [128–131]. It is yet unclear how particular circRNAs are packaged into exosomes selectively, and more research is needed to understand this process. According to research, exosomal circRNAs usually act as protein sponges or decoys and miRNA sponges or stabilizers [132–134]. They may function as translational patterns or control the gene expression [135]. A growing body of research indicates that specific exosomal circRNAs exhibit aberrant expression in cancerous

cells and tissues. These circRNAs may influence tumor growth via pathways including immune escape, angiogenesis advancement, metabolic reprogramming, treatment resistance, growth, and invasion.

NANOG is a transcriptional factor highly expressed in cancer stem cells and enhances cancer progression via regulating cell stemness and self-renewal through different pathways [136,137]. Elevated expression of NANOG in TMZ-resistant glioma cells indicates its role in drug resistance. Circ_0072083 induces NANOG mRNA demethylation and stability via activating ALKBH5, which leads to upregulation of NANOG in glioma cell lines. The effects of circ_0072083 are mediated by downstream miRNA sponge activity. In glioma, circ_0072083 enhances TMZ-resistance by regulating ALKBH5/NANOG axis via miR-1252-5p sponge [127]. The Warburg Effect is characterized as metabolism alteration in cancer cells favoring anaerobic glucose metabolism rather than aerobically [138,139]. This effects contributes to development of chemoresistance in several cancers. Interestingly Ding et al. found that exosomal circ_0072083 release was promoted by Warburg effect, making it a valuable diagnostic and prognostic factor for glioma and TMZ-resistance [127]. However, studies have demonstrated that expression of carcinogenic circRNA will further increase in chemoresistant cells leading to increased cell malignant behavior. Exosomal circ-HIPK3, an oncogenic circRNA, is upregulated in glioma and has higher expression in TMZ-resistant cells, suggesting its role in chemoresistance. Han et al. has shown that circ-HIPK3 knockdown promotes glioma cell response to TMZ through miR-421 sponging, leading to upregulation of ZIC5 [108]. Zinc finger protein of the cerebellum 5 (ZIC5) is direct target of miR-421 and have been widely reported as tumor-promoting factor [140]. This study demonstrated that Exosomal circ-HIPK3 induces TMZ-resistant in distant cells by increasing expression of an oncogenic protein through miR-421/ZIC5 axis in glioma [108]. CircWDR62 is an oncogenic circRNA highly expressed in glioma tissue and promotes cell proliferation, migration and invasion. Geng et al. revealed that circWDR62-containing exosomes are abundant in TMZ-resistance glioma microenvironment and higher expression of exosomal circWDR62 is associated with poor prognosis and lower survival rate [141]. The downstream target of exosomal circWDR62 is miR-370-3p, acting as a sponge to suppress its expression. The function of circWDR62/miR-370-3p axis leads to upregulation of MGMT protein, which is a prognostic biomarker in GBM [141]. Previous studies have shown that hyper-methylation of MGMT reduces its function and improves treatment outcome in glioma. Geng et al. demonstrated that suppressing MGMT function by reducing exosomal circWDR62 expression enhances TMZ response and improves treatment outcomes, suggesting that targeting exosomal circWDR62 is effective in reducing TMZ resistance in glioma [141].

A recent study by Liu et al. demonstrated that exosomal circCABIN1 changes glioma cell response to TMZ by overactivating ErbB signaling pathway [142]. ErbB pathway participates in cell proliferation, differentiation and apoptosis, and its downstream members are highly expressed in various cancers [143–145]. Functions of ErbB pathway is closely connected with other signaling pathways such as PI3K and MAPK pathway, and all together enhance cancer cell stemness in tumor tissue [146,147]. Olfactomedin-like 3 (OLFML3) is one of ErbB members with upregulated expression in TMZ-resistant glioma cells. Liu et al. showed that circCABIN1 upregulation promotes OLFML3 overexpression via inhibiting miR-637, leading to ErbB pathway overactivation [142]. CircCABIN1 is highly expressed in glioma cell lines and associated to poor prognosis and higher rate of glioma recurrence. The upregulation of circCABIN1 is due to overexpression of EIF4A3 protein which promotes linear CABIN1 RNA cyclization and leads to circCABIN1 formation [142]. Liu et al. created an exosomal form of circCABIN1 inhibitor RNA (siRNA) and labeled it with angiopep-2 (ANG) to improve BBB transmission. Administration of this Ang-multi-siRNA-exo with TMZ to mice with GBM significantly improved treatment outcome and response to TMZ therapy comparing to TMZ alone, highlighting circCABIN1 as an important target for reducing TMZ resistance [142].

It has been documented that immune cells that infiltrate the tumor immunological microenvironment contribute to tumor invasion and dissemination [148,149,196]. When circNEIL3 is stored into exosomes and transferred to tumor-associated macrophages (TAMs) within gliomas, hnRNPA2B1 confers TAMs immunosuppressive characteristics by maintaining IGF2BP3, which in turn accelerates the growth of gliomas [130]. Furthermore, exosomal circBTG2 from macrophages overexpressing RBP-J inhibits the miR-25-3p/PTEN pathway to prevent the growth of gliomas [150]. This reveals a novel mechanism by which immune cell-derived exosomal cargos affect circRNA and downstream genes in tumor cells, and it offers a potential treatment target for gliomas.

Given the crucial role of exosomes in the TME, several factors regulate their release and composition. Heparanase, an endoglycosidase that cleaves heparin sulfate, is abundantly expressed in TME [151,152]. Tumor-promoting effects of heparanase is associated with its role in remodeling extracellular matrix as elevated expression of heparanase in tumor tissue increases cancer cell invasion and metastasis [151,153]. Some evidence suggested that heparanase participates in intercellular signaling by regulating exosome secretion and composition [154]. Si et al. revealed that heparanase-mediated exosomal regulation participates in development of TMZ-resistance in glioma [155]. Heparanase was upregulated in both TMZ-sensitive and TMZ-resistant glioma cells, however its expression was significantly higher in TMZ-resistant cells, indicating role of heparanase in TMZ-resistance [155]. Si et al. also demonstrated that exosomal circ_0042003 promotes TMZ-resistance of glioma cells and heparanase enhances TMZ-resistance by positively increasing expression of exosomal circ_0042003 in glioma microenvironment [155]. These findings demonstrate significant role of exosomal circRNAs in TMZ-resistance and importance of targeting them for treatment.

6. Circular RNAs: promising biomarkers and therapeutic targets

It is well acknowledged that most cancer types are treatable with an early diagnosis. Histopathology, magnetic resonance imaging, and computerized tomographic scanning are often used diagnostic tools and indicators for malignancy [156,157]. However, some of these methods are costly and intrusive. Therefore, low-cost, less intrusive methods are therefore required. Because circRNAs exhibit a high degree of tissue- and disease-specificity and are significantly dysregulated in a range of cancer types, they represent a huge potential for cancer detection (Fig. 3) [158,159]. CircRNAs may be useful in the assessment of cancer susceptibility risk [160]. Nonetheless, the majority of circRNA detections performed currently are achieved in tissues and cell lines. There are limitations with liquid biopsy, a less intrusive technique, in the clinical setting. It is challenging to precisely identify and detect circRNA due to its low quantity. Consequently, in order to increase the accuracy of circRNA detection, researchers must enhance the detection techniques. Among the therapeutic approaches that target circRNas include the CRISPER/Cas system, antisense oligonucleotides, short interfering RNAs, and inhibiting molecular interactions [158]. CircRNA is anticipated to be used in conjunction with conventional techniques in the near future to provide highly sensitive early treatment assessment.

Overexpression of circRNAs lead to glioma growth, cell cycle, invasion, and metastasis by affecting target mRNAs or complementary miRNAs closely associated with cancer-related signaling pathways, such as Wnt/β-catenin, Notch, and PI3K/AKT/mTOR [161–163]. According to research, the prognosis of gliomas is correlated with multiple circRNA categories. The first category includes circRNAs that have the ability to encode proteins, like circ-FBXW7, circ-AKT3, and circ-SHPRH [164]. These circRNAs are associated with a poor prognosis and are underexpressed in gliomas. They are able to encode tumor suppressor proteins. The second category consists of exosomal circRNAs. CircRNAs are widely dispersed and persistent in exosomes, where they are involved in drug resistance and the delivery of specific therapeutic compounds

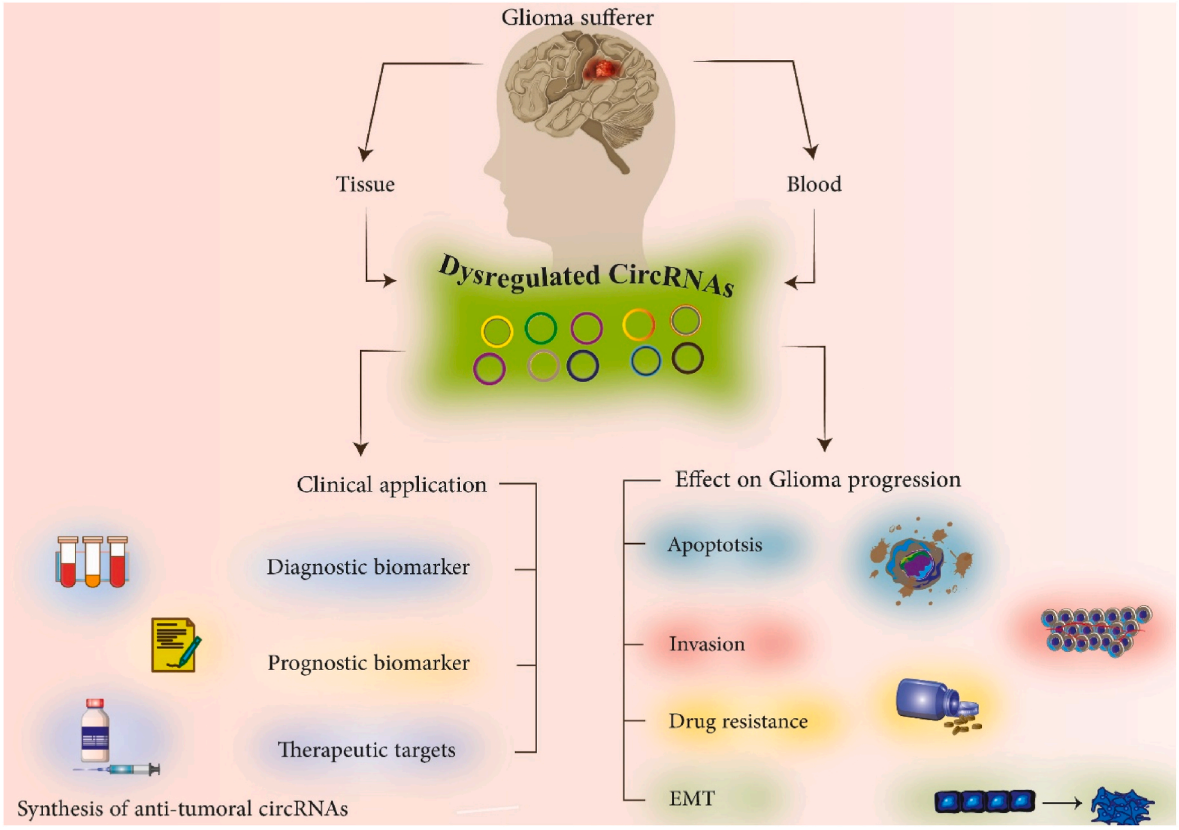

Fig. 3. CircRNAs play an important role in molecular pathways involved in glioma development, influencing apoptosis, invasion, drug resistance, EMT and progression. Their clinical importance lies in serving as potential biomarkers for diagnosis, prognosis, and targeted therapeutic interventions in glioma patients.

[124]. Other circRNAs that are linked to a poor prognosis in gliomas include circEPHB4, circCPA4, circ-MAPK4, circ-POSTN, circNFIX, circSCAF11, circ-U2AF1, and circLGMN [165]. Improved tumor size, WHO grade, and histopathological grade were also linked to circ-MAPK4 and circ-POSTN and circPIP5K1A ectopic expression, respectively [166]. In addition, the Warburg effect-induced release of exosomal circ_0072083 enhances TMZ resistance in gliomas by upregulating NANGO expression through multiple mechanisms [127]. Therefore, circ_0072083 have been identified as effective therapeutic targets for cancers due to their abundant expression in the TME and their transferability.

Anti-tumor therapy will undoubtedly enter a new age thanks to circRNA. Genetically modified bacteria are superior to any surgical tool because they can be introduced and remain there until the tumor is totally removed, selectively eradicating glioblastoma while protecting healthy brain tissue. Recently, modified circRNA vectors have been used to identify a novel way to express protein [167]. The findings demonstrated that delivered exogenous circRNA into cells by cationic lipid transfection could effectively produce certain proteins, suggesting that circRNA is a promising agents with potential applications in the field of protein production. On the other hand, circRNA transfer in vivo presents more challenge. Meganck et al. used the recombinant adeno-associated virus (AAV) vector to create tissue-specific circRNA expression vectors [168]. These innovative vectors were also shown to be capable of efficiently expressing and translating proteins in mice. As a result, certain biological vectors packed with circRNA may be used in clinical settings. Additional research is required to find more stable and targeted vectors that are appropriate for circRNA delivery both in vivo and in vitro.

The application of synthetic or foreign circRNAs will be restricted due to research indicating that they may be immunogenic [169,170]. It's interesting to note that m6A alteration has the ability to abolish circRNA immunity and designate self circRNAs [169]. Nevertheless, there is little data to support circRNA's immunogenicity. More research is needed to determine whether circRNAs stimulate the immune system and how to reduce their immunogenicity. Studies recently showed that in comparison to conventional RNA editing techniques, circular ADAR-recruiting RNAs (circ-arRNAs) or circular ADAR-recruiting guide RNAs (cadRNAs) allow for more stable, persistent, accurate, and efficient adenosineto-inosine RNA editing [171,172]. Additionally, circ-arRNA effectively fixed a TP53 gene mutation in cell culture [171]. These findings highlight the widespread use of circRNAs in RNA editing techniques. According to another promising study, a circRNA vaccination was shown to protect mice and rhesus macaques against SARS-CoV-2 by enhancing robust immune responses and greater and longer-lasting antigen synthesis [173]. These investigations have opened up new possibilities for the use of circRNA in medicine. Meanwhile, the main challenge to the therapeutic utility of circRNA molecules is the effective delivery of these molecules to their intended target. Additionally, given that circRNAs in EVs may serve as tumor antigens to initiate an immune response against the tumor through circRNA interaction with miRNA and protein, circRNA may play a role in immunity and be a target for immunotherapy. We compiled circRNAs that can be utilized to support diagnosis and treatment of gliomas and other disorders when combined with other conventional indicators. CircRNAs are expected to be used in clinical settings to use as diagnostic and prognostic biomarkers, and therapeutic targets.

7. Conclusion

GBM is one of the biggest risks to human health today; it is thought to have arisen from brain progenitors [174]. Unfortunately, despite the use of common therapeutic methods like operation, radiation, and alkylating agent chemotherapy, like TMZ, the median survival rate of patients with gliomas still declines significantly [175,176]. Moreover, a

substantial obstacle to the treatment effectiveness of GBM is the development of drug resistance in over half of glioma patients receiving TMZ [177]. To lessen or completely eradicate medication resistance, it is imperative to understand the molecular mechanisms behind resistance. Numerous research conducted in the last few years have demonstrated the critical roles of circRNAs in tumor development, progression, and drug resistance (Fig. 3) [178,179]. This article provided an overview of recent research on the relationship between circRNAs and TMZ resistance in gliomas. It has been shown that circRNAs control GBM cell growth, invasion, and migration. In addition, circRNAs regulate glioma resistance to TMZ via sponging miRNAs and other signaling pathways. Numerous recently discovered circRNAs and signaling pathways may be targets for cutting-edge treatments meant to extend the lives of cancer patients [180,181]. The remarkable ability of circRNA to bind proteins and miRNAs, along with its unique cellular stability, make it a potentially valuable therapeutic vector [182,183]. Cancer may be prevented by exogenously introducing circRNA, which has many binding sites for miRNAs and/or oncogenic proteins, to restore the normal regulatory network [184]. On the other hand, TMZ can reversely control lncRNA expression levels to increase TMZ therapy efficacy. It has been demonstrated that heparanase-mediated exosomal hsa_circ_0042003 delivers from TMZ-resistant glioma cells to drug-sensitive cells, hence contributing to glioma's resistance to TMZ [155]. The TMZ-resistant GBM treatments may target circASAP1 since upregulation of the protein increases GBM cell expansion and TMZ resistance through the circASAP1/miR-502-5p/NRAS regulatory complex [11].

It was discovered that numerous circRNAs act as miRNA sponges, controlling the circRNA-miRNAs-mRNA axis or contributing to drug resistance processes via triggering cancer-promoting signaling cascades. The majority of research on circRNAs and drug resistance is restricted to in vivo and in vitro tests. However, the mechanisms are still unclear, and with the new resistance mechanisms to be determined, the importance of circRNAs in the field will increase. The majority of circRNAs revealed in gliomas have only been linked to a few well-known medications, indicating that more circRNAs need to be found and linked to drug resistance in gliomas. When considering all of the possible circRNAs, it remains difficult to determine which one should be the primary target for cancer treatment. Thus, patient monitoring for an extended period of time and investigation into the connection between circRNAs and medication resistance are necessary in this context. The regulatory complex consisting of target mRNAs, miRNAs, and circRNAs may be linked to the systematic and extensive treatment resistance of malignancies. Further investigation is necessary to clarify the specific molecular pathways linking circRNAs to treatment resistance in malignancies and to examine circRNAs' potential application in clinical settings.

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