Journal of Molecular Neuroscience (2019) 67:72–81
https://doi.org/10.1007/s12031-018-1211-2

Circular RNAs: Functions and Prospects in Glioma

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Received: 22 September 2018 / Accepted: 8 November 2018 / Published online: 20 November 2018

Abstract

Improving the survival rate of patients with glioma, a malignant tumor of the human brain has become increasingly important. In recent years, the function of circular RNAs (circRNAs) in different diseases and the pathophysiological mechanisms involved have been elucidated. In the pathophysiological mechanism, the primary function of circRNAs is to act as microRNA sponges. An increasing number of studies have found that circRNAs are differentially expressed in gliomas and regulate the occurrence, proliferation, and invasion of glioma and thus may be potential markers for the diagnosis of gliomas. Additionally, some circRNAs have been associated with glioma staging and may be useful in determining prognosis. Based on the stability and high conservation of circRNAs, we believe that circRNAs may have molecular targets that are useful for the treatment of glioma. In this review, we summarize the current research regarding the role of circRNAs in gliomas, discuss the potential value and role of circRNAs in gliomas, and provide new perspectives for future research.

Keywords Circular RNA · MicroRNA sponge · Biomarker · Targeted therapy

Introduction

Circular RNAs (circRNAs) are a special type of non-coding RNA consisting of a covalently closed-loop structure of endogenous RNA, in which there is no 5′ cap 3′ poly A tail (Qu et al. 2015). circRNAs were first discovered in the 1970s and considered to be the wrong shear product (Sanger et al. 1976). In 2012, when Salzman proposed that circRNAs are widely expressed in human cells, circRNA molecules began to receive attention (Salzman et al. 2012). With numerous studies focusing on circRNAs, many new features of these molecules have been revealed, including their stability, conservation, and specificity (Burd et al. 2010; Hansen et al. 2013; Zhang et al. 2013), and circRNAs have been shown to act as microRNA (miRNA) sponges, interact with RNA-binding proteins (RBPs), and regulate transcription (Memczak et al. 2013).

Glioma is the most common malignant intracranial tumor and poses a serious threat to human health (Torre et al. 2015). According to the histopathological features of the central nervous system tumors, outlined by the World Health Organization (WHO) and molecular parameters, gliomas can be classified as low (WHO grades I and II) or advanced (WHO grades III and IV) grade (Louis et al. 2016; Schwartzbaum et al. 2006). Although glioma patients can be treated with surgical resection combined with postoperative chemoradiotherapy, the median survival is only 12–18 months (Berges et al. 2012; Ferguson 2011; Li et al. 2015a; Stupp et al. 2005; Wang et al. 2016b). In recent years, researchers have begun to focus on the molecular mechanisms and biomarkers of gliomas and have developed molecular targeted therapies for glioma patients (Miller and Wen 2016; Wang and Jiang 2013) to inhibit disease progression.

Many studies have shown that circRNAs are involved in the regulation of malignant tumors, including gliomas (Huang et al. 2017). circRNAs play a vital role in many aspects of cancer, including the regulation of cell cycle, apoptosis, angiogenesis, invasion, and metastasis (Wang et al. 2017; Zhu et al. 2017). This review briefly describes circRNAs and discusses their role and potential value in the pathogenesis of glioma.

Biogenesis of circRNAs

The circRNAs identified to date are present mostly in the cytoplasm and are tissue-specific (Memczak et al. 2013;

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Salzman et al. 2013; Zhang et al. 2013). CircRNAs are classified into three categories: exon circRNAs (ecircRNAs), circular intron RNAs (ciRNAs), and exon intron circRNAs (EIciRNAs) (Fig. 1).

1. EcircRNAs bind competitively to miRNAs, thereby affecting the expression of downstream genes (Hansen et al. 2013). The biosynthesis of ecircRNAs is primarily achieved by lariat-driven, intron-pairing-driven, and RBP-driven cyclization (Chen and Yang 2015; Lasda and Parker 2014; Qu et al. 2015), although research has indicated that intron-pairing-driven cyclization is the most common method (Qu et al. 2015).

   1.1 Lariat-driven circularization is characterized by exon skipping due to the partial folding of the RNA during the transcription of pre-mRNA, which closes the original non-adjacent exon. Thus, the spanned area forms a lasso, and the intron in the lasso is eliminated to form an ecircRNA (Chen and Yang 2015).

   1.2 Intron-pairing-driven cyclization differs from lariat-driven in that intron pairing drives the formation of circRNAs by a reverse shear mechanism, while the two flanking introns pass through the ALU complementary component. This method is also involved in the regulation of circRNA production (Chen and Yang 2015; Zhang et al. 2014).

   1.3 Other mechanisms, such as RBP-driven circularization, rely on the intron quaking (QKI)–binding sequence, bound by the RBP QKI, to promote the formation of circRNAs (Conn Simon et al. 2015). The RNA-editing enzyme ADAR inhibits circRNA formation by disrupting the reverse complementary pairing structure of the flanking introns (Ivanov et al. 2015).

2. ciRNAs are located mainly in the nuclei of eukaryotes and are characterized by a 7-nucleotide GU-rich motif near the 5′ splice site and 11 nucleotides near the C-containing motif. When the exon at the 3′ end is excised, the 2′-OH group of the exposed intron attacks the 5′ splice site to form a noose (Petkovic and Muller 2015). This RNA molecule is resistant to the effects of debranching enzymes (Zhang et al. 2013).
3. EIciRNAs are considered an intermediate product in the production of ecircRNAs, and studies have claimed that EIciRNAs are a result of the stable retention of introns between exons (Jeck et al. 2012; Li et al. 2015b). Unlike ecircRNAs, ciRNAs and EIciRNAs may regulate the interaction of RNA polymerase II and U1 small nuclear ribonucleoproteins (Eidem et al. 2016).

CircRNAs in Biological Processes and Diseases

With the development of RNA and chromatin immunoprecipitation sequencing, as well as other technologies, recent evidence has linked circRNAs to diseases of the cardiovascular system, nervous system, and blood (Li et al. 2018d; Wang et al. 2018b; Yi et al. 2018; Zhou et al. 2018b), especially cancers, including lung cancer, hepatocellular carcinoma, breast cancer, and colorectal cancer (Chen et al. 2018a;

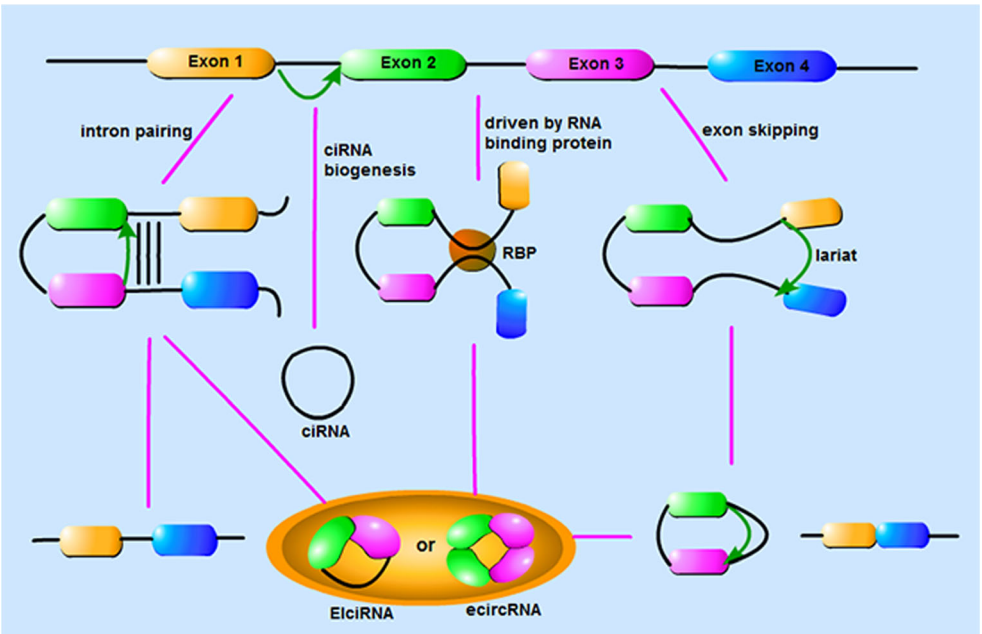

Fig. 1 The biogenesis of circular RNAs (circRNAs). circRNAs are regulated by three different mechanisms: intron-pairing-driven cyclization, RNA-binding protein (RBP)-driven cyclization, and lariat-driven cyclization. *circRNA* circular RNA, *ecircRNA* exon circRNA, *ciRNA* circular intron RNA, *EIciRNA* exon intron circRNA

Cheng et al. 2018; Huang et al. 2017). Studies have shown that circRNAs regulate tumor development by acting as oncogenes or tumor suppressors. circRNAs also function as diagnostic and prognostic indicators (Han et al. 2017; Zhao and Shen 2017). Studies have suggested several functions of circRNAs, as follows (1) circRNAs act as miRNA sponges to regulate miRNA target genes (Hansen et al. 2013) (e.g., ciRS-7, which has more than 70 selectively conserved miRNA target sites). In gastric cancer, circPVT1 acts as a sponge for miR-125, thereby regulating cell proliferation (Chen et al. 2017). (2) circRNAs regulate gene expression. Studies have shown that EIciRNAs interact with U1 small nuclear ribonucleoproteins to enhance parental gene expression (Li et al. 2015b; Wang 2015) (e.g., circEIF3J and circPAIP2 promote transcription of EIF3J and PAIP2 (Li et al. 2015b; Zlotorynski 2015)). (3) circRNAs interact with RBPs, affecting biological processes (Abdelmohsen et al. 2017; Wurth and Gebauer 2015) (e.g., circFoxo3 regulates heart aging by binding to and blocking the aging-associated proteins ID1 and E2F1 and the stress-related proteins HIF1a and FAK (Du et al. 2017)). (4) Finally, circRNAs are involved in RNA and protein transfer and storage (Hentze and Preiss 2013; Petkovic and Muller 2015) (Fig. 2).

CircRNAs and Glioma

In recent years, studies have shown that a large number of circRNAs are abnormally expressed in gliomas compared with brain tissues adjacent to tumors. Therefore, circRNAs may play an important role in the development of glioma. We discuss the role of these differentially expressed circRNAs in gliomas below (Table 1 and Fig. 3).

CircRNAs Interact with miRNAs and Regulate Glioma Progression

A reported (Chen and Duan 2018) that hsa_circ_0000177 was upregulated in glioma tissues, and luciferase reporter assays confirmed that hsa_circ_0000177 acts as a sponge targeting miR-638. It was found that FZD7 is a target of miR-638 and is upregulated by hsa_circ_0000177. FZD7 activates the Wnt signaling pathway, which contributes to the development of malignant gliomas (Bai et al. 2017; Wu et al. 2017). Further studies revealed that knockdown of hsa_circ_0000177 led to the inhibition of Wnt signaling, whereas miR-638 inhibition or FZD7 recovery promoted Wnt signaling in glioma cells, indicating that hsa_circ_0000177 promotes Wnt signaling by the up-regulation of the expression of FZD7, which promotes adhesion in stromal tumors. Another study (Li et al. 2018a) showed that cir-ITCH positively regulates the expression of the tumor suppressor gene ITCH (Wan et al. 2016; Zhu et al. 2017). cir-ITCH promoted the expression of ITCH by acting as a sponge targeting miR-214 and inhibiting Wnt/β-catenin signaling, thereby inhibiting tumor cell proliferation. However, cir-ITCH expression is downregulated in glioma tissues (Li et al. 2018a). Both of these circRNAs regulate the proliferation of tumor cells via the Wnt pathway.

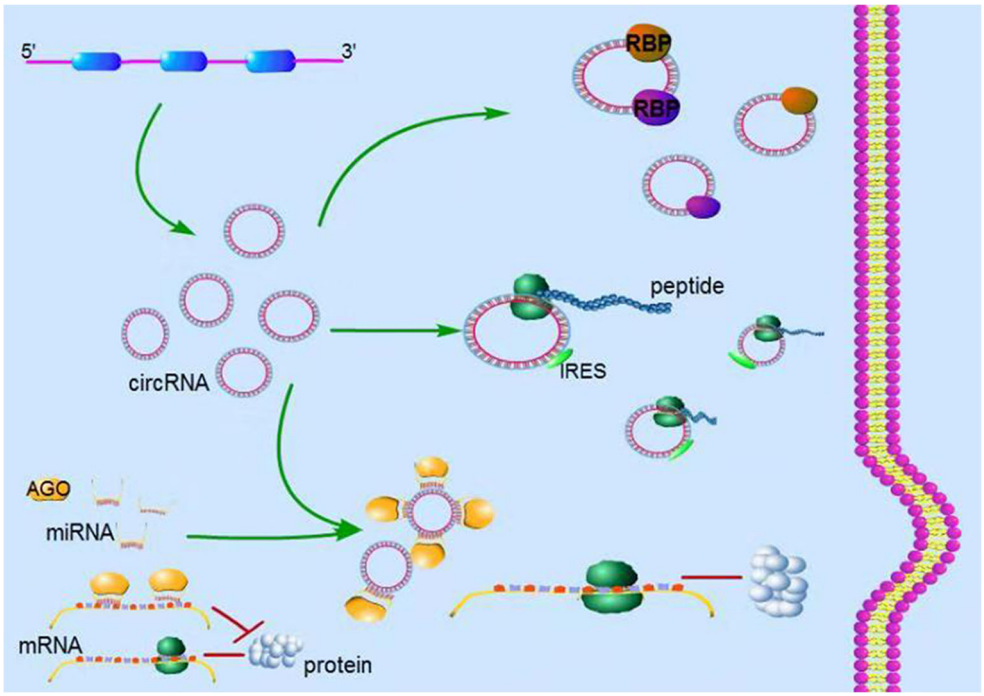

Fig. 2 Function of circRNAs. Most circRNAs act as microRNA (miRNA) sponges or sequesters. circRNAs may also encode peptides with an internal ribosome entry site (IRES). circRNAs possessing RBP motifs may function as sponges or decoys for proteins. *IRES* internal ribosome entry site, *RBP* RNA-binding protein, *circRNA* circular RNA, *miRNA* microRNA

Table 1 Upregulated or downregulated circRNAs are functions and mechanisms in glioma

CircRNA	Expression change	Function	Possible mechanism	Correlated with the pathological grades	Authors
hsa_circ_0000177	Up	Proliferation (+) Invasion (+)	Promotes the malignant behaviors through FZD7-induced activation of Wnt pathway by sponging miR-638	Maybe	Chen and Duan (2018)
circRNA ITCH	Down	Proliferation (−) Migration (−) Invasion (−) Apoptosis (+)	cir-ITCH plays an anti-oncogenic role through sponging miR-214 and regulating ITCH-Wnt/β-catenin pathway	Maybe	Li et al. (2018a)
circNT5E	Up	Proliferation (+) Migration (+) Invasion (+) Apoptosis (−)	circNT5E acts as a sponge of microRNA-422a	Maybe	Wang et al. (2018c)
circNFIX	Up	Proliferation (+) Migration (+) Apoptosis (−)	circNFIX has on glioma progression through the upregulation of NOTCH1 via the Notch signaling pathway by sponging miR-34a-5p		Xu et al. (2018)
hsa_circ_0007534	Up	Proliferation (+) Migration (+)	Promoting ZIC5 expression by repressing miR-761	Maybe	Li et al. (2018b)
hsa_circ_0046701	Up	Proliferation (+) Invasion (+)	hsa_circ_0046701 functions as a sponge for miR-142-3p and regulates the expression of ITGB8	Maybe	Li et al. (2018c)
hsa_circ_0012129	Up	Proliferation (+) Migration (+) Invasion (+)	hsa_circ_0012129 as a sponge of miR-661	Maybe	Xie 2018
hsa_circ_0008344	Up	Proliferation (+) Migration (+) Invasion (+) Apoptosis (−)	Hsa_circ_0008344 knockdown suppressed the proliferation migration and invasion of glioblastoma cells, but promoted tumor cell apoptosis		Zhou et al. (2018a)
circ-CFH	Up	Proliferation (+)	Sponging miR-149 and regulating the AKT1 signaling pathway	Maybe	Bian et al. (2018)
circHIPK3	Up	Proliferation (+) Invasion (+)	circHIPK3 contributes to glioma progression through sponging miR-654 from IGF2BP3		Jin et al. (2018)
circ-TTBK2	Up	Proliferation (+) Migration (+) Invasion (+) Apoptosis (−)	circ-TTBK2 promotes glioma malignancy by regulating miR-217/HNF1β/ Derlin-1 pathway	Maybe	Zheng et al. (2017)
CDR1-AS	Down	Unknown	May be degraded by miR-671-5p		Barbagallo et al. (2016)
circ-FBXW7	Down	Upregulation of FBXW7-185aa inhibited proliferation and cell cycle acceleration	circ-FBXW7 encodes FBXW7-185aa protein		Yang et al. (2018)
circ-SHPRH	Down	proliferation(−)	circ-SHPRH translating the novel functional protein SHPRH-146aa, with potential implications as a tumor suppressor		Begum et al. (2018); Zhang et al. (2018)
circSMARCA5	Down	Migration(−)	circSMARCA5 is predicted to function as modulator of several RBPs;splicing of SRSF3 is regulated by CircSMARCA5	Maybe	Barbagallo et al. (2018)
cZNF292 circRNA	Up	Proliferation (+) Tube formation (+)	Silencing cZNF292 suppresses tube formation by inhibiting glioma cell proliferation and cell cycle progression.		Yang et al. (2016)
circ-SHKBP1	Up	GEC migration (+) Angiogenesis (+)	circ-SHKBP1 Regulates the Angiogenesis of U87 Glioma-Exposed Endothelial Cells through miR-544a/FOXP1 and miR-379/FOXP2 Pathways		He et al. (2018)
hsa_circ_0001649	Down	Proliferation (−) Apoptosis (+)	Enhanced hsa_circ_0001649 inhibits tumor growth and proliferation,facilitates glioma cell apoptosis via Bcl-2/caspase-3 pathway	Maybe	Wang et al. (2018d)

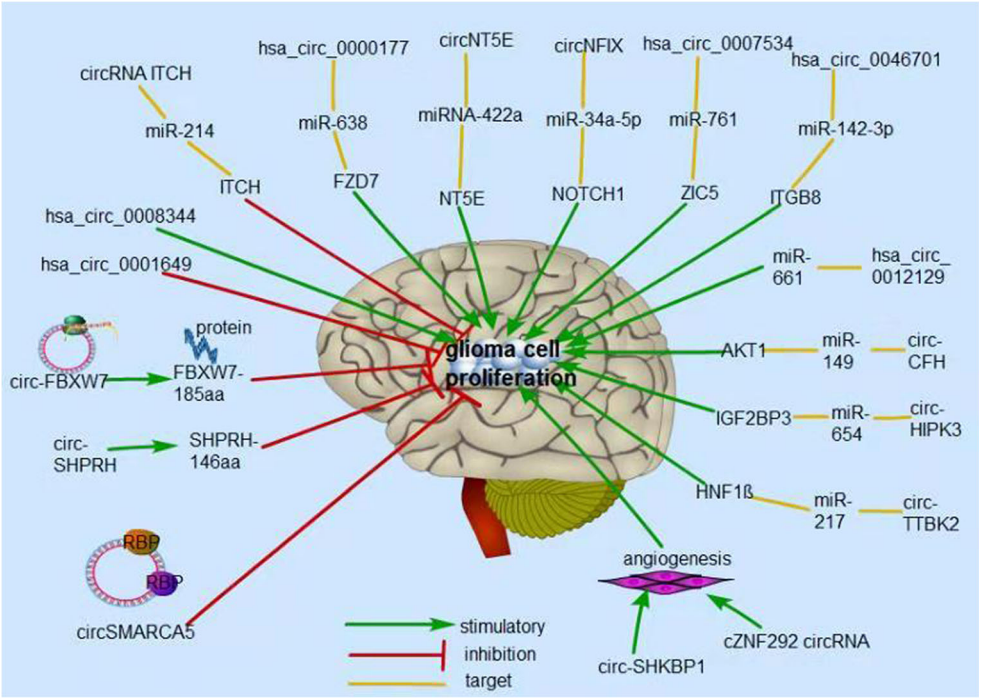

Fig. 3 circRNAs are involved in the regulation of glioma cell proliferation. *circRNA* circular RNA, *miRNA* microRNA

Wang et al. reported (Wang et al. 2018c) that circNT5E is overexpressed in glioma cells. As a sponge targeting miR-422a, knockdown of circNT5E significantly inhibited the growth, proliferation, invasion, and migration of U251 cells and promoted apoptosis in in vivo experiments. It was also shown that circNT5E promoted glioma growth. At the same time, ADAR2 was found to be involved in the biogenesis of circNT5E. ADAR1 knockdown increased the circNT5E level, and ADARB2 rescued ADAR1-induced circNT5E downregulation. Xu et al. Found circNFIX (Xu et al. 2018), an miR-34a-5p sponge, was found to inhibit the downstream proteins HEY2, Jagged1, and Hes1 expression in the notch signaling pathway in glioma by transfecting glioma cells with a small interfering RNA targeting circNFIX (si-circNFIX) or miR-34a-5p mimics. They injected U87 cells transfected with si-circNFIX into the right limb of mice and found that the tumor size and volume were reduced compared with the control group. Tumor cells were extracted from the mice, and the expression of circNFIX, miR-34a-5p, and NOTCH1 was verified by qRT-PCR and western blotting. These results indicated that si-circNFIX inhibited glioma tumor growth by suppressed NOTCH1 expression in vivo.

Many studies have shown that circRNAs act as miRNA sponges during the progression of glioma. For example, hsa_circ_0007534 promoted the proliferation and migration of glioma cells by upregulating the expression of ZIC5 by acting as a sponge targeting miR-761 (Li et al. 2018b); hsa_circ_0046701 regulated the expression of ITGB8 by targeting miR-142-3p (Li et al. 2018c); hsa_circ_0012129 regulated the proliferation of glioma cells by acting as a sponge targeting miR-661 (Xie 2018); loss of hsa_circ_0008344 inhibited the migration and invasion of glioblastoma cells, possibly by binding to miR433-3p/miR450b-3p (Zhou et al. 2018a); circ-CFH acted as a sponge targeting miR-149 and regulated the AKT1 signaling pathway (Bian et al. 2018); and circHIPK3, which has been detected in many tumors (Chen et al. 2018b; Zeng et al. 2018), targeted miR-654 to regulate the oncogene IGF2BP3 (Jin et al. 2018; Zhou et al. 2017). All of these circRNAs are upregulated in glioma tissues.

A report found (Zheng et al. 2017) that circ-TTBK2 was negatively correlated with miR-217, in that circ-TTBK2 was upregulated and miR-217 downregulated in glioma cells. HNF1β is a target of miR-217 and acts as an oncogene in various tumors (Yuan et al. 2014). The researchers demonstrated that miR-217 functionally targeted circ-TTBK2 and reversed circ-TTBK2-mediated glioma cell progression.

Another study found (Barbagallo et al. 2016) that CDR1-AS is downregulated in gliomas compared with normal brain tissue and is negatively correlated with miR-671-5p expression. Experimental data have suggested that downregulation of CDR1-AS results from miR-671-5p-mediated degradation of CDR1-AS, and CDR1-AS is the only circRNA known to be degraded by an miRNA (miR-671-5p) (Hansen et al. 2011). In summary, circRNAs and miRNAs interact to participate in cancer formation and development and play important roles in tumor cell proliferation, migration, invasion, and apoptosis.

CircRNAs-Encoding Proteins and RBP-Binding circRNAs Are Involved in the Progression of Glioma

In addition to acting as miRNA sponges, circRNAs can also encode proteins involved in disease progression. Yang found (Yang et al. 2018) that the expression of circ-FBXW7 was lower in gliomas compared with normal brain tissue. Circ-FBXW7 is formed by exons 3 and 4 of the FBXW7 gene, and there is a potential open reading frame in circ-FBXW7 that encodes a protein of 185 amino acids. Conservation analysis indicates that this open reading frame can be translated. An internal ribosomal entrance site (IRES) is required for 50-cap-independent translation (Mokrejs 2006). The dual luciferase vector system indicated that the IRES of circ-FBXW7 induces independent translation of 50 caps. To confirm that circ-FBXW7 can be translated in human cells, FLAG-tagged plasmids were transfected into 293 T cells, and the translation products were assessed, indicating that the FLAG tag antibody is only in circ-FBXW7-FLAG and FBXW7-FLAG. A protein of approximately 22 kDa was detected in the transfected cells, indicating that the circ-FBXW7-FLAG vector was translated (FBXW7-185aa). The researchers then established circ-FBXW7 and FBXW7-FLAG overexpression constructs, which were expressed in U251 and U373 cells and resulted in G1 phase arrest. When circ-FBXW7 was knocked down, decreased expression of FBXW7-185aa and increased cell cycle and cell viability rates were observed. These results indicate that FBXW7-185aa, but not circ-FBXW7, induces cell cycle arrest and inhibits proliferation of glioma cells. Additionally, FBXW7-185aa competitively interacted with USP28 and released FBXW7a to degrade c-Myc, a key regulator of tumorigenesis (Yada et al. 2004). In gliomas, circ-SHPRH also encodes protein (Begum et al. 2018). In previous studies, circ-SHPRH was shown to be a biomarker of hepatocellular carcinoma (Qin et al. 2016). Begum indicated that circ-SHPRH encodes the novel protein SHPRH-146aa. Using liquid chromatography–mass spectrometry, direct production of SHPRH-146aa from circ-SHPRH was demonstrated. SHPRH is an important tumor suppressor (Unk et al. 2006), and SHPRH-146aa protects SHPRH from degradation (Zhang et al. 2018), thereby regulating tumor progression.

A study (Barbagallo et al. 2018) identified a circRNA, circSMARCA5, that binds to RBPs and exhibits decreased expression in gliomas; overexpression of circSMARCA5 was shown to inhibit tumor cell migration. CircSMARCA5 is predicted to be rich in binding sites for several RBPs. In U87MG cells overexpressing circSMARCA5, the expression of serine and arginine-rich splicing factor 3 (SRSF3) RNA isoforms was increased, which contains exon 4. This exon is usually skipped in a manner dependent on SRSF1, a known positive regulator of oncoproteins involved in cell migration (Ghigna et al. 2005). SRSF3 interacts with two other splicing factors, polypyrimidine bundle–binding proteins 1 and 2, which positively regulate glioma cell migration.

CircRNAs Are Involved in the Formation of Blood Vessels in Gliomas and Promote the Development of Gliomas

Glioma is a typical vascular-dependent solid cancer, and thus anti-angiogenic therapies can be effective in treating glioblastoma (Gatson et al. 2012; Jain et al. 2007). Studies have shown that circRNAs are involved in the formation of glioma blood vessels and promote the progression of glioma.

The report (Yang et al. 2016) found that silencing of the circRNA (cZNF292) inhibited glioma cell proliferation, and that the key factors regulating tumor tube formation (Wang et al. 2016a) were the levels of vascular endothelial growth factor A (VEGF-A), epidermal growth factor, and active-transforming growth factor-β1. Expression of VEGF receptor-1/2 (VEGFR-1/2) and EGF receptor and phosphorylation of VEGFR-1/2 were reduced in cZNF292 downregulated U87MG and U251 cell lines. In cZNF292-silenced U87MG cells, the cell cycle was arrested at the S/G2/M phase, and the cell cycle has been closely linked to tube formation (Du et al. 2016; Liu et al. 2016). It was also found that the expression of Wnt/β-catenin-signaling pathway members (β-catenin, APC, Axin, STAT3, and STAT5 (Kim et al. 2016; Shehade et al. 2015)), which regulate cell cycle progression, was altered accordingly, indicating that cZNF292 is downregulated by the Wnt/β-catenin pathway. Thus, this signaling pathway regulates the cell cycle to inhibit tumor tube formation.

He reported (He et al. 2018) that circ-SHKBP1 was significantly upregulated in glioma-exposed endothelial cells (GECs), and knockdown of circ-SHKBP1 inhibited GEC angiogenesis and AGGF1 expression. That study found that circ-SHKBP1 is a functional target of miR-544a/miR-379, whereas FOXP1 and FOXP2 are targets of miR-544a and miR-379, respectively. Previous studies have shown that FOXP1 can promote cancer progression and regulate vascular function (Gomez et al. 2014; Potente et al. 2005). Furthermore, miR-544a/miR-379 inhibits circ-SHKBP1-mediated GEC angiogenesis, and FOXP1/FOXP2 promotes GEC angiogenesis by upregulating AGGF1 transcription. Thus, circ-SHKBP1 knockdown or miR-544a/miR-379 overexpression inhibits glioma angiogenesis in vivo.

CircRNAs Are Associated with the Pathological Grade and Prognosis of Glioma

circRNAs play an important role in gliomas, affecting the proliferation, invasion, migration, and apoptosis of glioma cells by interacting with miRNAs and proteins encoded by circRNAs and regulating angiogenesis. Some circRNAs have also been shown to be associated with the pathological grade of gliomas, including hsa_circ_0007534, hsa_circ_0001649, hsa_circ_0000177, and circRNA ITCH (Chen and Duan 2018; Li et al. 2018a, b; Wang et al. 2018d), which are

different from grades I and II in grades III and IV gliomas. Hsa_circ_0001649 can also function as an independent prognostic marker for glioma patients after surgery: lower levels suggest a poor prognosis (Wang et al. 2018d).

Conclusions and Perspectives

circRNAs are abundantly expressed in the human brain and participate in the physiological processes of the brain development (Chen and Schuman 2016; Filippenkov et al. 2017; van Rossum et al. 2016); glioma is a malignant tumor in the human brain that poses a serious threat to human health. It has become increasingly evident that circRNAs are involved in glioma cell proliferation, migration, invasion, and cell cycle progression and are important in the diagnosis, prognosis, and treatment of glioma. circRNAs can be used as biomarkers of glioma (Wang et al. 2018a) and thus have diagnostic significance. Circ-FBXW7 and circ-SHPRH can also be used as prognostic markers, to help assess the prognosis of patients. circRNAs have fewer off-target and side effects compared to siRNAs (Han et al. 2018); thus, circRNAs, such as hsa_circ_0001649, cZNF292 circRNA, hsa_circ_0046701, circNT5E, and circ-TTBK2, are more advantageous targets of molecular therapies. circSMARCA, which binds the RBP SRSF1, is a potential target of glioma molecular therapy and promising drug inhibitor for glioblastoma. Circ-SHKBP1 is also of potential value in antiangiogenic therapy. The use of random RNA-sequencing technology (Song et al. 2016; Yuan et al. 2018) has identified many important tumor RNAs. It is worth noting that in glioma progression, most of the circRNAs identified an act as miRNA sponges, suggesting that other potential mechanisms require further exploration. Based on the global cancer burden (Bray et al. 2018), further studies will be necessary to reveal the molecular mechanisms underlying the role of circRNAs in the pathogenesis of glioma and to improve our understanding of the regulatory network involved. Finally, further elucidation of the relationship between circRNAs and the pathogenesis of glioma will accelerate the clinical application of circRNAs in the diagnosis and treatment of this disease.

Funding information This work was supported by the National Natural Science Foundation of China (NSFC): 81860225. And Jiangxi Provincial Postgraduate Innovation Fund Project (No. YC2017-S102).

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