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Review Article

The circular RNA and microRNA regulatory networks in glioma

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Abstract: Glioma is a common type of central nervous system tumor. Because the molecular mechanisms of the disease are not fully understood, the diagnosis of - and treatment for - glioma are still limited. At present, circular RNAs (circRNAs) have been shown to play a pivotal role in the initiation and progression of glioma. However, the complex regulatory mechanisms of circRNAs in glioma have not been well summarized. Emerging evidence has confirmed that circRNAs may function as a competing endogenous RNA (ceRNA) or a molecular sponge in regulating microRNAs (miRNAs). Hence, in the present review, the underlying roles and molecular mechanisms of the circRNA/miRNA pathway regulation network in glioma are described.

Keywords: circRNA, microRNA, glioma, targeted treatment, molecular network

Introduction

Glioma is a tumor originating from central nervous cells, accounting for 27% of central nervous system tumors [1]. It is characterized by high morbidity, high mortality, invasiveness, and poor prognosis. In recent years, the overall incidence rate of glioma has increased, ranking seventh among all malignant tumors [2, 3]. Although significant progress has been made in diagnosis and treatment, the median survival rate of patients is still very low, mainly because the molecular mechanisms of gliomagenesis are poorly understood [4].

Circular RNAs (circRNAs) are a special type of non-coding RNAs, which were first discovered in the Sendai virus [5]. circRNAs are classified into three types depending on the formation and composition of the sequences: exonic circRNAs (80% of the circRNAs currently found is exonic circRNA), intronic RNAs, and exonic-intronic circRNAs [6]. CircRNAs are mainly formed by self-splicing to remove introns, but the mechanisms are still not clear [7]. Initially, circRNAs were considered non-coding RNAs without any obvious biological functions in cells. However, with the application of second-generation RNA sequencing, it was found that circRNAs are a new type of RNAs that are different from linear RNAs, and the closed loop structure of circRNAs makes them not easy to degrade [5]. In human glioma, circRNAs have different expression patterns compared with adjacent normal tissues. For example, ciR-FBXW7 levels are decreased in glioma clinical samples compared with their paired tumor-adjacent tissues [8]. Circular tau tubulin kinase 2 (ciR-TTBK2) is up-regulated in glioma tissues and cell lines, but linear tau tubulin kinase 2 (TTBK2) is not differentially expressed in glioma tissues and cell lines [9]. These studies demonstrate that circRNAs may be suitable as targets for tumor diagnosis and treatment.

The current study shows that the regulatory functions of circRNA mainly include the following aspects: 1) Regulating gene transcription. CiR-ankrd52 associates with elongation RNA polymerase II (RNA Pol II) machinery and acts as a positive regulator of RNA Pol II transcription, which finally enhances the transcriptional activity of tumor-related genes [10]. 2) Regulating many physiological processes of cells by interacting with proteins. CiR-Foxo3 can form a complex with cell cycle-dependent kinase 2 (CDK2) and p21, thereby impeding cell cycle progression [11]. 3) Exonic circRNAs, mainly located in the cytoplasm, can be loaded into ribosomes and further translated into polypeptides. CiR-FBXW7 is highly expressed in the normal human brain. The spanning junction open

reading frame (ORF) in ciR-FBXW7 driven by internal ribosome entry site encodes a 21-kDa protein named F-box and a WD repeat domain containing 7 (FBXW7). The over-expression of FBXW7 in glioma U251 and U373 cells restrains cell proliferation and cycle progression but down-regulates FBXW7-induced malignant phenotypes *in vivo* and *in vitro* [8]. This discovery provides a new insight into the diversity of protein sources. 4) "miRNA sponge". MicroRNAs (miRNAs) can bind to target gene-specific sequences and participate in the development of various tumors including glioma. CircRNAs competitively bind specific miRNAs as "miRNA sponge" and inhibit the regulation of miRNAs on downstream target genes, which constitutes a complex molecular regulatory network [12]. The main mechanisms of the circRNA/miRNA pathway involved in glioma tumorigenesis are the activation of the abnormal proliferation signaling pathway, the regulation of cell invasion and metastasis mediated by epithelial mesenchymal transformation (EMT), the regulation of angiogenesis, and the inhibition of glioma cell apoptosis. Currently, the most studied "miRNA sponge" is cerebellar degeneration-related protein 1 antisense RNA (CDR1-AS), namely ciR-7. MiR-7 can directly down-regulate the oncogenes in numerous malignant tumor-associated signal pathways, such as the PI3K/AKT/mTOR [13], ERK [14], EGFR/STATE3 [15], and TGFβ/Smad [16] pathways. CDR1-AS contains more than 70 tandem miR-7 binding sites and can bind to more than 20,000 miR-7s in cells, which finally reverse the inhibitory effects of miR-7 on the target gene and promote tumor progression [17]. In addition, miRNA-671 is fully complementary to CDR1-AS and induces its degradation [18]. Briefly, circRNAs interact with miRNAs through a specific miRNA response element (MRE) and act as a tumor suppressor or as a proto-oncogene in tumorigenesis.

Based on this, this review aims to summarize the advances of the circRNA/miRNA pathway and its potential application in glioma diagnosis and treatment.

CircRNA/miRNA pathway

CiR-NT5E/miR-422a axis

CiR-NT5E is regulated by adenosine deaminase RNA specific B2 (ADARB2) binding to sites flanking circRNA-forming introns, and it is stable in the cytoplasms of glioma cells [19]. Additionally, numerous studies also indicate that miR-422a acts as a tumor suppressor in glioma. miR-422a can restrain glioma proliferation and invasion by targeting insulin like growth factor 1 (IGF1) [20] and PI3KCA [21].

Through a microarray analysis of 3 paired glioma clinical tissues with low miR-422a expression, Wang *et al.* [22] identified that ciR-NT5E was significantly enhanced in glioma clinical samples when miR-422a was down-regulated. Furthermore, by constructing the ciR-NT5E expression vector containing a luciferase gene and transfecting it into glioma U87 cells, researchers found that ciR-NT5E might function as a sponge for miR-422a. Mechanically, ciR-NT5E affects the survival, apoptosis, and migration of glioma cells by up-regulating phosphatidylinositol 3-kinase (PI3K) sex determining region Y-box 4 (SOX4), p-Akt, CDK4, and p-Smad2 protein levels, which are also mediated by miR-442a inhibition [22]. Hence, silencing the ciR-NT5E/miR-422a pathway may represent a promising therapeutic strategy for glioma treatment.

CircRNAs/miR-124 axis

MiR-124 is a more in-depth study of non-coding RNA that is highly conserved *in vivo* and expressed from nematodes to humans. The three coding genes of human miR-124 are located at 8p23.1, 8q12.3, and 20q13.33, respectively [23]. The methylation of the CpG island in the promoter can cause an abnormal expression of miR-124, thus inducing a malignant phenotype of the cells [24]. MiR-124 can inhibit the malignancy of glioma by inhibiting the syndecan binding protein (SBP) [25], neuropilin-1 (NRP-1) [26], and cyclin D2 [27]. Qiao *et al*. reported that miR-124 suppresses glioblastoma growth and enhances temozolomide (TMZ)-based chemotherapy by down-regulating aurora kinase A (AURKA) [28]. Mucij *et al.* also found that miR-124 counteracts the pro-survival stress responses of glioma patients [29].

CiR-MMP9 derived from matrix metalloproteinase-9 (MMP-9) is a differentially expressed circRNA in glioma. CiR-MMP9 is up-regulated in glioma and act as an oncogene to promote the proliferation, migration, and invasion of glioma cells. Acting as competitive endogenous RNAs (ceRNAs), ciR-MMP9 competes for the shared

MRE (5'-CAAACG-3') of miR-124, which leads to the up-regulation of CDK4 and AURKA by inhibiting miR-124 [30]. Therefore, the ciR-MMP9/miR-124 axis may become a potential therapeutic drug target for glioma treatment.

CiR-ITCH spans several exons of itchy E3 ubiquitin protein ligase (ITCH), and has inhibitory effects on colorectal cancer [31], hepatocellular carcinoma (HCC) [32], and esophageal squamous cell carcinoma (ESCC) [33] through specific MREs that can bind to the 3' untranslated region (3'-UTR) of ITCH, which degrades the phosphorylated form of disheveled (Dvl) through the proteasome pathway and further restrains the activation of the Wnt/β-catenin signal. In glioma, Feng *et al.* [34] found that a decreased ciR-ITCH level is closely associated with the poor prognosis of glioma patients, and it also plays a tumor-suppressive role in glioma U87 and U251 cells. By analyzing the miRanda and TargetScan databases, the researchers found that five miRNAs (miR-124, miR-7, miR-17, miR-126, and miR-128) contain complementary sequences to both the ciR-ITCH and 3'-UTR regions of ITCH. However, RNA precipitation (RIP) shows a specific enrichment of ciR-ITCH and miR-214, but the other miRNAs show no enrichment in glioma cells, suggesting that ciR-ITCH specifically sponges miR-214, which promotes linear ITCH expression and inhibits glioma progression [34]. These results indicate that the CircRNA/miR-124 axis has a very complex regulatory mechanism, and different circRNAs can sponge the same RNA to regulate the expression of downstream genes via specific MREs in glioma, which remains to be further studied.

The CiR-NFIX/miR-34a-5p axis

The notch signal is an evolutionarily highly conserved pathway, mainly composed of Notch1-4, diskless (DSL), and suppressor of hairless (SuH). The notch signal can promote nerve growth and differentiation and is also closely related to gliomagenesis [35, 36]. Saito *et al*. [37] supposed that targeting Notch leads to the inhibition of glioma. Sun *et al.* [38] reported that blocking the laminin-411-Notch axis inhibited glioma through tumor microenvironment crosstalk. MiR-34a-5p targets the 3'-UTR of Notch and suppresses glioma progression. In addition, Di *et al.* found that MiR-34a-5p induced the multi-chemoresistance of osteosarcoma through the notch pathway [39]. A recent finding showed that ciR-NFIX was upregulated in glioma cells and acts as a sponge of miR-34a-5p. The downregulation of ciR-NFIX inhibits the notch1 level and the downstream proteins Hes1, Jagged1, and the hes related family bHLH transcription factor with YRPW motif 2 (HEY2) in the notch pathway, which inhibits cell migration and proliferation and induces cell apoptosis in glioma [40, 41]. Briefly, these findings reveal a possible mechanism of the oncogene ciR-NFIX in glioma progression by regulating the CiR-NFIX/miR-34a-5p/Notch pathway.

The CiR-HIPK3/miR-654 axis

Currently, surgical resection is still the preferred treatment for glioma. However, the 5-year survival rate is only 5% [42]. CiR-HIPK3 has been reported to regulate the initiation and progression of multiple cancers, such as lung cancer [43], prostate cancer [44], bladder cancer [45], and liver cancer [46]. CiR-HIPK3 also promotes the proliferation and invasion of glioma cells by targeting Sate3 after binding to miR-124-3p, so it is involved in glioma progression [47]. Jin *et al.* [48] reported that miR-654 was identified as a target of ciR-HIPK3, but the oncogene insulin like growth factor 2 mRNA binding protein 3 (IGF2BP3) is targeted by miR-654, resulting in the proliferation and invasion of glioma U87 and U251 cells. Notably, a survival rate analysis of 48 glioma clinical samples using a Kaplan-Meier curve demonstrated that the over-expression of ciR-HIPK3 predicts a poor prognosis (The overall survival rate in the 48th month is less than 20%) in glioma patients, suggesting that ciR-HIPK3 might serve as a prognostic marker for glioma [48].

CiR-ATP8B4/miR-766-5p axis

Radiotherapy is a typical and aggressive treatment for glioma, but the inherent and acquired resistance of glioma cells seriously affects the effects of radiotherapy [49]. Circ-RNAs in extracellular vesicles (EVs) are closely related to the radioresistance of tumor cells [50]. In a study by Zhao *et al*. [51], glioma U251 cells were serially treated with 5 Gy of radiation using a ^{60}Co source to establish radioresistant glioma U215 cells (RR-U215). Then, EVs were isolated from the RR-U125 cell culture media, and an RT-qPCR analysis indicated that ciR-

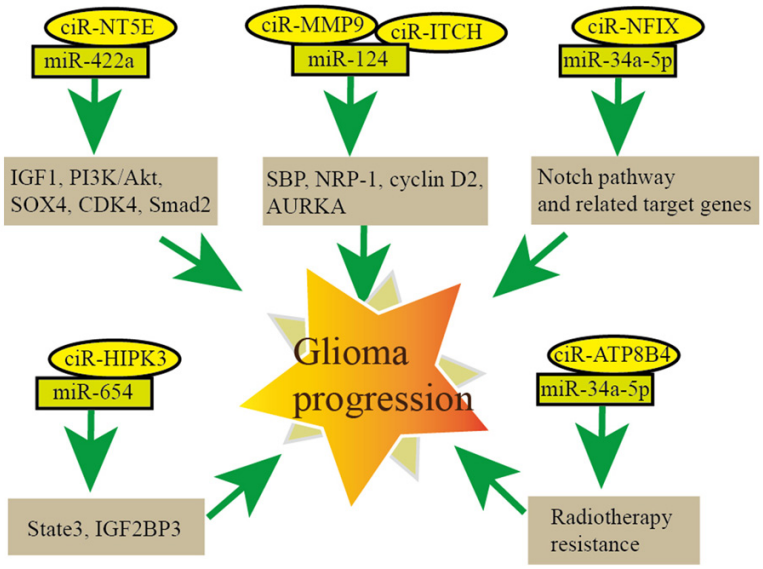

Figure 1. The circular RNA and microRNA regulatory networks in glioma.

ATP8B4 expression was significantly up-regulated in EVs compared with those from non-EVs. Moreover, the results from miRanda and RNAhybrid showed that ciR-ATP8B4 might regulate miR-766-5p function as an miRNA sponge. Hence, researchers concluded that the ciR-ATP8B4/miR-766-5p axis in RR-EVs might be involved in glioma radioresistance [51].

Conclusion

Nowadays, the incidence of glioma is increasing yearly [52, 53]. Therefore, it is particularly essential to find novel markers for the early diagnosis and effective therapeutic targets for glioma. CircRNAs have been known since the 20th century, but they were considered to be a splicing error that has only rarely been considered. Recent studies have confirmed that circRNAs are widely expressed in organisms and have specific biological functions such as promoting alternative splicing, transcriptional regulation, encoding proteins, antiviral immune responses, and miRNA sponges, making our understanding of eukaryotic transcriptomes more profound [5, 6].

As with other non-coding RNAs, circRNAs also play a pivotal role in the development of glioma, but the 3' and 5' ends of circRNAs are not exposed. Therefore, it is not sensitive to exonuclease, which makes circRNA more stable in cells [54]. As mentioned above, there is a significant difference in the expression of circRNAs between glioma samples and paired normal tissues. Additionally, Song *et al.* [55] reported that 3001 circRNAs have been detected in human cells, of which 476 circRNAs are differentially expressed in brain tissue and glioma. Zhang *et al.* [56] reported that SHPRH, produced by circ-SHPRH, was significantly reduced in 81% of glioma samples. Patients with a higher level of SHPRH experienced an extended survival period as opposed to those who have a lower expression. Therefore, circRNAs may be used as markers for the early diagnosis of glioma. However, circRNAs have not been used clinically, and a reliable diagnostic or prognostic marker standard needs further exploration.

Tumorigenesis is a multi-stage and multi-step complex process. It is well known that circRNAs function mainly as miRNA sponges to regulate target gene expression, which constitutes the circRNA/miRNA regulatory network in gliomagenesis [57, 58]. The circRNA/miRNA axes are relatively more studied in HCC, gastric cancer, and lung cancer, but less so in other malignant tumors, including glioma [57]. Aside from the circRNA/miRNA axis mentioned above, the ciR-0007534/miR-761/ZIC5 axis [59], the ciR-0005198/miR-1294 axis [60], and the hypoxia-associated ciR-DENND2A/miR-625-5p axis [61] also participates in glioma phenotypic transformation, proliferation, migration, invasion, and chemotherapy resistance, which makes these signals act as potential therapeutic targets for glioma (**Figure 1**).

At the same time, we should also pay attention to the shortcomings. The formation mechanism of the circRNA/miRNA axis and their roles in glioma still have not been deeply studied. Researchers should draw on the research ideas of the lncRNA/miRNA axis to establish a systematic circRNA database and construct a circRNA/miRNA network, which will be beneficial for further revealing the pathogenesis of glioma. Additionally, importantly, a uniform naming standard is also urgently needed in circRNA data management. Overall, we believe

that more and more circRNA/miRNA networks will be discovered as research progresses further. The conservatism, stability, and tissue specificity of circRNAs will make them become promising markers and targets for glioma diagnosis, therapy, and prognosis.

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Disclosure of conflict of interest

None.

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