Observational Study

Medicine

OPEN

Construction of a circRNA-miRNA-mRNA regulatory network in glioblastoma multiforme based on bioinformatics analysis

Dongpo Hu, MS[a,*], Kangjing Chen, MS[a]

Abstract

This study aimed to investigate the functional roles and molecular regulatory mechanisms of circular RNAs in the development of glioblastoma multiforme. Differentially expressed circular RNAs were identified by integrating RNA sequencing data and circular RNA microarray data from the Gene Expression Omnibus database. CircAtlas and CircInteractome databases were used to predict microRNAs (miRNAs) interacting with these circular RNAs. Survival analysis of the miRNAs was performed using data from the Chinese Glioma Genome Atlas. The miRTarBase database was used to predict miRNA target genes, followed by the construction of a circular RNA-miRNA-messenger RNA regulatory network specific to glioblastoma multiforme. Functional enrichment analysis was carried out using the DAVID website, and protein–protein interaction networks were created using the Search Tool for the Retrieval of Interacting Genes/Proteins website and Cytoscape. Hub genes were identified, and their expression and prognostic relevance in glioblastoma multiforme were further examined. Four differentially expressed circRNAs and 10 associated miRNAs related to glioblastoma multiforme prognosis were identified. Functional enrichment showed the miRNAs target genes were mainly involved in apoptosis, cell cycle regulation and enriched in cancer-related pathways like mitogen-activated protein kinase and PI3K-Akt. Through the circRNA-miRNA-messenger RNA regulatory network and survival analysis, 3 core genes (core hub genes: catenin beta 1, BCL2, nuclear factor kappa B subunit 1) were identified as significantly downregulated in glioblastoma multiforme and associated with patient survival. This study highlights the potential regulatory roles of circular RNAs in glioblastoma multiforme pathogenesis and their involvement in key molecular pathways. The findings offer a theoretical foundation for understanding glioblastoma multiforme development and may facilitate the identification of novel biomarkers for this aggressive cancer.

Abbreviations: CGGA = Chinese Glioma Genome Atlas, circRNAs = circular ribonucleic acids, CTNNB1 = core hub genes: catenin beta 1, DE-circRNAs = differentially expressed circribonucleic acids, GBM = glioblastoma multiforme, GO = gene ontology, JUN = Jun proto-oncogene, KEGG = Kyoto Encyclopedia of Genes and Genomes, NFKB1 = nuclear factor kappa B subunit 1, PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Keywords: circRNA, glioblastoma multiforme, miRNA, mRNA, network

1. Introduction

Glioblastoma Multiforme (GBM) is the most common and malignant type of primary brain tumor in adults, accounting for 48.6% of primary malignant brain tumors.[1] Its incidence rate remains high. The highly invasive and treatment-resistant nature of GBM poses a significant challenge in the field of neuro-oncology. Despite treatments such as surgical resection and chemoradiotherapy, the prognosis for most patients remains poor.[2] Therefore, it is imperative to conduct in-depth research on the pathogenesis of GBM, explore new treatment strategies, and identify more accurate molecular markers.

Circular ribonucleic acids (circRNAs) are a novel type of RNA molecules formed through a back-splicing process, where the downstream 5' splice donor is covalently linked to the upstream 3' splice acceptor.[3,4] Recent studies have demonstrated that the circular structure of circRNAs makes them highly stable and conserved,[5] circRNAs modulate disease pathogenesis through their interactions with microRNAs (miRNAs), RNA-binding proteins, and other regulatory factors, thereby emerging as promising candidate disease biomarkers.[4,6,7] Furthermore, circRNAs have been implicated in the regulation of numerous pathological conditions via the competitive endogenous RNA mechanism.[8,9] For instance, CDR1as can upregulate the expression of E2F3 by sequestering

This work was supported by Henan Province Science and Technology Plan Projects Funds (182102311237).

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available, and the analyses were conducted independently by the authors.

[a] School of Medical Technology, Shangqiu Medical College, Shangqiu, Henan, China.

** Correspondence: Dongpo Hu, School of Medical Technology, Shangqiu Medical College, No. 666, Yingbin Avenue, Shangqiu City, Henan 476100, China (e-mail: hudongpo123@126.com).*

How to cite this article: Hu D, Chen K. Construction of a circRNA-miRNA-mRNA regulatory network in glioblastoma multiforme based on bioinformatics analysis. Medicine 2025;104:19(e42392).

Received: 17 September 2024 / Received in final form: 25 February 2025 / Accepted: 18 April 2025

http://dx.doi.org/10.1097/MD.0000000000042392

miR-7-5p, thereby promoting cell growth and glucose metabolism in nasopharyngeal carcinoma cells.[10] In hepatocellular carcinoma, circACTN4 sequesters miR-424-5p, facilitating tumor growth and metastasis.[11] Accumulating evidence suggests that circRNAs exhibit elevated expression in the brain and neuronal tissues, and are intimately associated with gliomas.[12,13] However, the precise regulatory mechanisms underlying the involvement of circRNAs in glioma pathogenesis warrant further investigation.

In recent years, bioinformatics analysis has become an invaluable tool in cancer research, including the study of GBM. By leveraging large-scale genomic and transcriptomic data, bioinformatics approaches enable the identification of key molecular players and regulatory networks involved in disease progression. In this study, we obtained circRNA expression profiles from GBM patients and normal brain tissues from the Gene Expression Omnibus (GEO) database. We identified differentially expressed circribonucleic acids (DE-circRNAs) associated with GBM and constructed a competing endogenous RNA regulatory network in GBM. This work lays the foundation for elucidating the pathogenic mechanisms of GBM and provides a theoretical basis for the future development of biomarkers.

2. Methods

2.1. Data collection and differential expression analysis

The sequencing data and circRNA microarray data for GBM patients and healthy brain samples were both obtained from the GEO database (https://www.ncbi.nlm.nih.gov/gds). The dataset GSE165926 contains microarray data from 12 GBM patient brain tissues and 4 normal brain tissues, with the platform GPL21825. The GEO2R tool was used to perform differential analysis on GSE165926, and circRNAs with an adjusted P-value ≤ .05 and $|\log_2 FC| \geq 2$ were considered DE-circRNAs. GSE153692 is a high-throughput sequencing dataset comprising 3 GBM patient brain tissues and 3 normal brain tissues. The DESeq2 package[14] in R was used to perform differential analysis on GSE153692, and circRNAs with $P_{adj} \leq .05$ and $|\log_2 FC| \geq 2$ were considered DE-circRNAs. The intersection of the 2 datasets was taken to obtain the final list of DE-circRNAs. All datasets used in this study were obtained from publicly accessible open-access databases; therefore, no ethical approval or patient consent was required.

2.2. Prediction of miRNA binding sites on circRNAs

The Circular RNA Interactome database[15] and the circAtlas 3.0 database[16] was used to Predicted the miRNA Binding Sites on DE-circRNAs, The intersection of the results from both databases was used for subsequent analysis.

2.3. Survival analysis

The miRNA expression profiles and clinical data of GBM patients' brain tissues were downloaded from the Chinese Glioma Genome Atlas (CGGA).[17] Based on the miRNA expression levels, patients were divided into high and low expression groups. Survival analysis was performed using the survival package (https://github.com/therneau/survival) in R. miRNAs with $P \leq .05$ were considered to significantly affect the survival of GBM patients and were used for subsequent analysis.

2.4. Target gene prediction

For each miRNA, we predicted all its downstream target genes using the experimentally validated miRNA-target interaction database miRTarBase.[18]

2.5. Construction of the circRNA-miRNA-mRNA network

From the Search Tool for the Retrieval of Interacting Genes/Proteins database,[19] we obtained protein–protein interaction information for all the target proteins. By integrating the regulatory relationships among DE-circRNAs, miRNAs, and miRNA target genes, we constructed a circRNA-miRNA-messenger RNA (mRNA) regulatory network. The network was visualized using Cytoscape 3.10.1 software (https://cytoscape.org/).

2.6. Enrichment analyses

The target genes were subjected to Gene Ontology (GO) functional enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis using the DAVID database.[20] GO terms or KEGG pathways with a false discovery rate value <0.05 were considered significantly enriched.

2.7. Identification of hub genes and expression analysis

In Cytoscape software, we utilized the CytoHubba plugin and employed the Maximal Clique Centrality algorithm to identify hub genes.[21] The top 5 ranked genes were selected as the core hub genes.

In the UCSC Xena database,[22] we selected TCGA-GBM and GTEx brain tissue samples, and analyzed the expression levels of the core hub genes. Student t test was used to assess the differential expression of the core hub genes between GBM and normal brain tissues.

3. Results

3.1. Identification of DE-circRNAs

Differential expression analysis of the GSE165926 dataset was performed using GEO2R, with the threshold of adjusted P-value ≤ .05 and $|\log_2 FC| \geq 2$, yielding 642 upregulated and 962 downregulated DE-circRNAs (Fig. 1A). For the GSE153692 dataset, differential expression analysis was conducted using DESeq2, with the criteria of $P_{adj} \leq .05$ and $|\log_2 FC| \geq 2$, resulting in 5 upregulated and 14 downregulated DE-circRNAs (Fig. 1B). By taking the intersection of the up- and downregulated circRNAs from the 2 datasets, 2 upregulated circRNAs, "hsa_circ_0001730" and "hsa_circ_0019223," and 3 downregulated circRNAs, "hsa_circ_0005054," "hsa_circ_0005114," and "hsa_circ_0006916," were identified (Table 1). These 5 circRNAs will be the subjects of further investigation.

3.2. Prediction of miRNA binding sites for DE-circRNAs

To explore the functions of these DE-circRNAs, circAtlas and circInteractome were utilized to predict the miRNA binding sites of the 5 DE-circRNAs. The results showed that "hsa_circ_0001730," "hsa_circ_0019223," "hsa_circ_0005054," "hsa_circ_0005114," and "hsa_circ_0006916" had 47, 31,70, 64, and 65 miRNA binding sites, respectively, in the circAtlas database, and 12, 54,16, 294, and 20 miRNA binding sites, respectively (Fig. 2A–E), in the circInteractome database. By taking the intersection of the results from circAtlas and circInteractome, we obtained 2, 4, 1, 5, and 3 miRNA bindings for each circRNA, respectively (Table 2).

3.3. Survival analysis of circRNA-associated miRNAs in GBM

To further refine the selection, we performed survival analysis on the 14 miRNAs by integrating the miRNA expression and clinical data from the CGGA database, survival analysis was

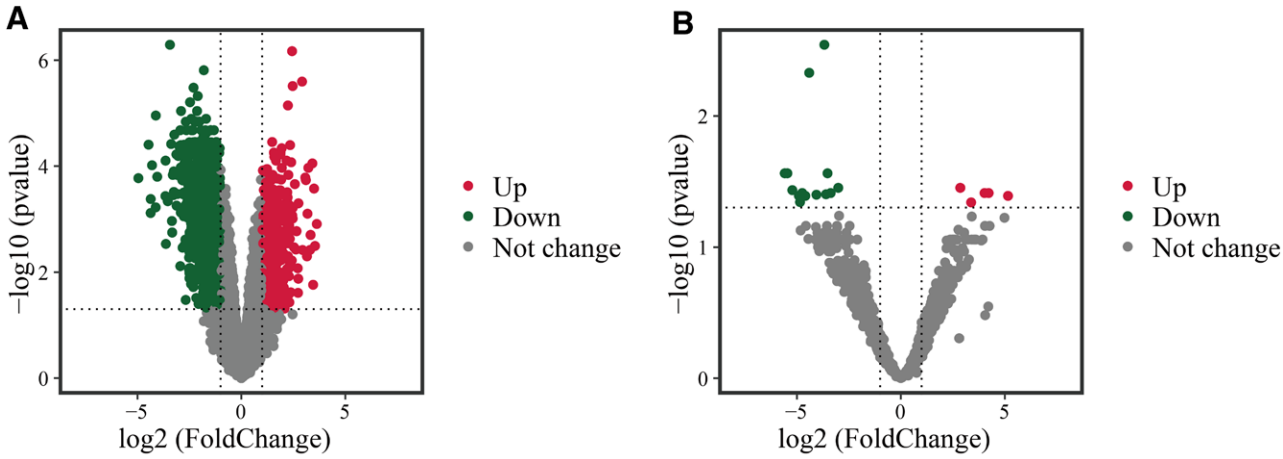

Figure 1. Volcano plots of DE-circRNAs. (A) GSE165926 dataset. (B) GSE153692 dataset. DE-circRNAs = differentially expressed circ ribonucleic acids.

Table 1

DE-circRNAs in GBM.

circRNA	circBase ID	Host gene	Log_2FC/P_{adj}	
			GSE165926	GSE153692
chr7:100410368|100410830	hsa_circ_0001730	EPHB4	1.92/0.00018	4.02/0.039
chr10:95790439|95792009	hsa_circ_0019223	PLCE1	1.14/0.0041	5.15/0.041
chr15:33149215|33194241	hsa_circ_0005054	FMN1	−4.37/0.00077	−4.85/0.045
chr8:105080739|105161076	hsa_circ_0005114	RIMS2	−3.63/0.0029	−4.41/0.0047
chr5:78734832|78752841	hsa_circ_0006916	HOMER1	−2.042/0.0012	−3.68/0.0029

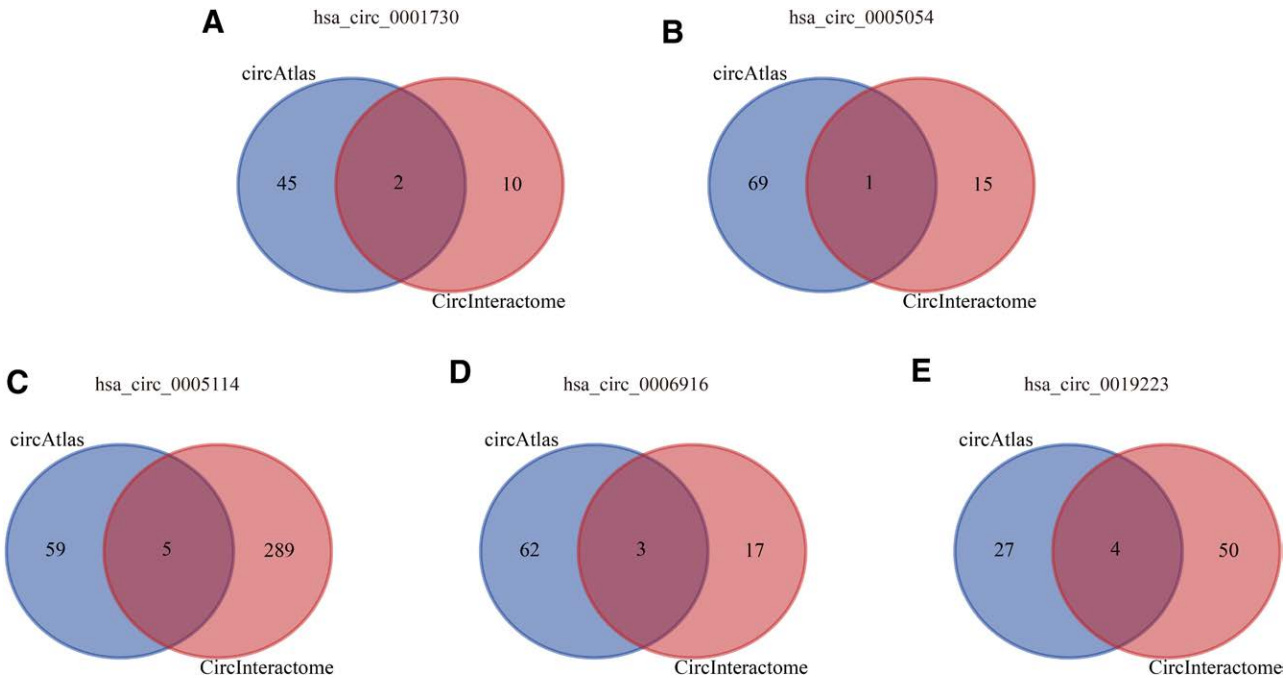

Figure 2. Prediction of circRNA-miRNA interactions based on the circAtlas and circInteractome databases. (A) circRNA-miRNA interactions of hsa_circ_0001730. (B) circRNA-miRNA interactions of hsa_circ_0005114. (C) circRNA-miRNA interactions of hsa_circ_0005114. (D) circRNA-miRNA interactions of hsa_circ_0006916. (E) circRNA-miRNA interactions of hsa_circ_0019223. circRNAs = circular ribonucleic acids, miRNA = microRNA.

conducted using the survival package in R. The results showed that "hsa-miR-139-5p," "hsa-miR-346," "hsa-miR-571," "hsa-miR-885-3p," "hsa-miR-885-5p," "hsa-miR-1182," "hsa-miR-1183," "hsa-miR-1225-5p," "hsa-miR-1231," and "hsa-miR-1283" exhibited significant impacts on survival in GBM patients. Notably, high expression of these miRNAs was associated with significantly prolonged survival in GBM patients. It is worth mentioning that hsa_circ_0005054 binds

Table 2

circRNA-miRNA binding prediction.

circRNA	miRNA
hsa_circ_0001730	hsa-miR-1182 hsa-miR-1289
hsa_circ_0019223	hsa-miR-1208 hsa-miR-1283 hsa-miR-885-5p hsa-miR-885-3p
hsa_circ_0005054	hsa-miR-502-5p
hsa_circ_0005114	hsa-miR-1183 hsa-miR-1231 hsa-miR-1289 hsa-miR-139-5p hsa-miR-346
hsa_circ_0006916	hsa-miR-1225-5p hsa-miR-571 hsa-miR-578

miRNA = microRNA.

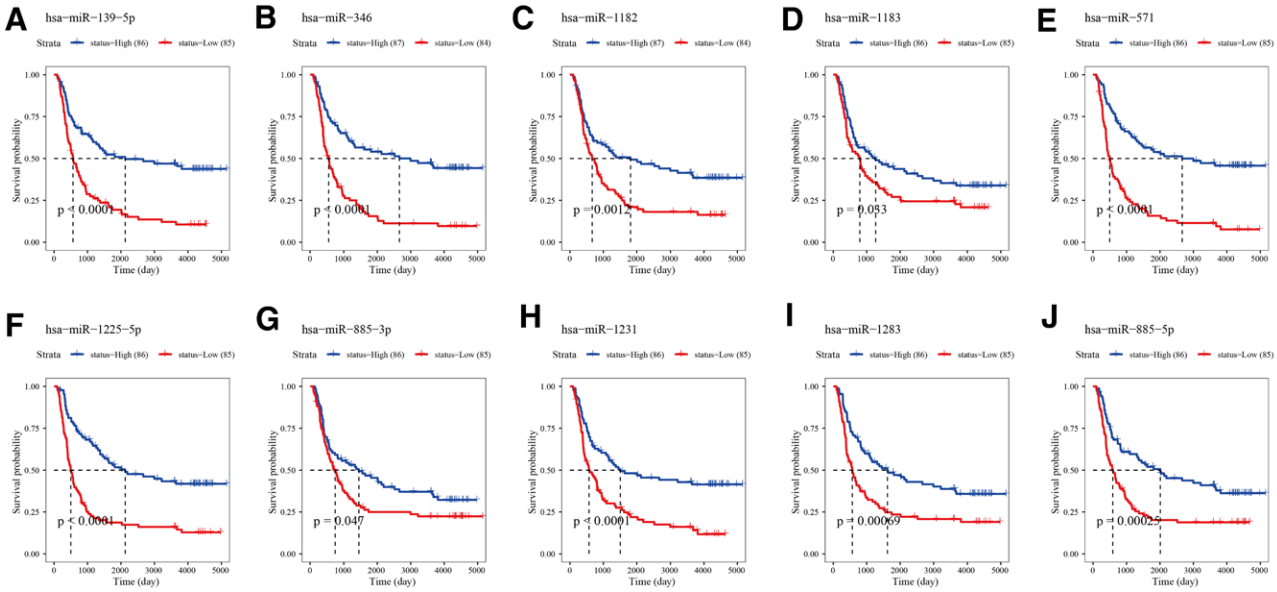

Figure 3. Survival analysis of miRNAs. (A) hsa-miR-139-5p. (B) hsa-miR-346. (C) hsa-miR-1182. (D) hsa-miR-1183. (E) hsa-miR-571. (F) hsa-miR-1225-5p. (G) hsa-miR-885-3p. (H) hsa-miR-1231. (I) hsa-miR-1283. (J) hsa-miR-885-5p. miRNA = microRNA.

to only one miRNA, hsa-miR-502-5p, which did not show a significant effect on survival in GBM (Fig. 3A–J). Therefore, hsa_circ_0005054 was excluded from subsequent analyses.

3.4. Functional analysis of miRNA target genes

The experimentally validated miRNA target gene database miRTarBase was utilized to predict the target genes of the aforementioned 10 miRNAs. The results showed that these 10 miRNAs bound to a large number of target genes. Among them, hsa-miR-139-5p bound to the highest number of target genes (105), while hsa-miR-1225-5p bound to the lowest number (36). We integrated all target genes, a total number of 711 target genes were obtained. The DAVID database was employed to perform KEGG pathway and GO functional enrichment analyses. The results indicated significant enrichment in biological processes such as transcription processes, phosphorylation of serine residues, cell apoptosis, cell division regulation, and cytokine response. The cellular components were mainly enriched in the cytoplasm, transcription complexes, and telomeres. The molecular functions were primarily enriched in protein binding, transcription activator activity, protein binding, and substrate recognition for ubiquitin-mediated proteolysis (Fig. 4). The KEGG pathway analysis revealed enrichment in the mitogen-activated protein kinase (MAPK) signaling pathway, PI3K-Akt signaling pathway, PD-L1 expression and PD-1 checkpoint pathway in cancer (Fig. 5A). To further understand the molecular mechanisms underlying GBM pathogenesis, we also performed KEGG pathway enrichment analysis on differentially expressed genes between GBM and normal brain tissues. As shown in Figure 5B, this analysis revealed significant enrichment in multiple neurological and signaling pathways. The most significantly enriched pathways included calcium signaling pathway, pathways of neurodegeneration in multiple diseases, cAMP signaling pathway, and neuroactive ligand-receptor interaction. Other notably enriched pathways included MAPK signaling, PI3K-Akt signaling, GABAergic synapse, and dopaminergic synapse pathways. Interestingly, there was overlap with pathways identified in our circRNA-miRNA-mRNA network analysis, particularly the MAPK and PI3K-Akt signaling pathways, suggesting these may be key mechanisms in GBM development. These findings suggest that the circRNA-miRNA-mRNA regulatory network may influence GBM progression and patient outcomes by modulating fundamental cellular processes and oncogenic signaling cascades.

3.5. Construction and analysis of the circRNA-miRNA-mRNA regulatory network

To further elucidate the functional interactions and key players, we queried the protein–protein interactions among the 711 target genes in Search Tool for the Retrieval of Interacting Genes/Proteins database. By integrating the regulatory relationships among all circRNAs, miRNAs, and mRNAs, we constructed a circRNA-miRNA-mRNA regulatory network using Cytoscape software (Fig. 6). Employing the cytoHubba plugin in Cytoscape, we analyzed the circRNA-miRNA-mRNA regulatory network and identified the top 5 ranked core hub genes: catenin beta 1 (CTNNB1), BCL2 apoptosis regulator (BCL2), nuclear

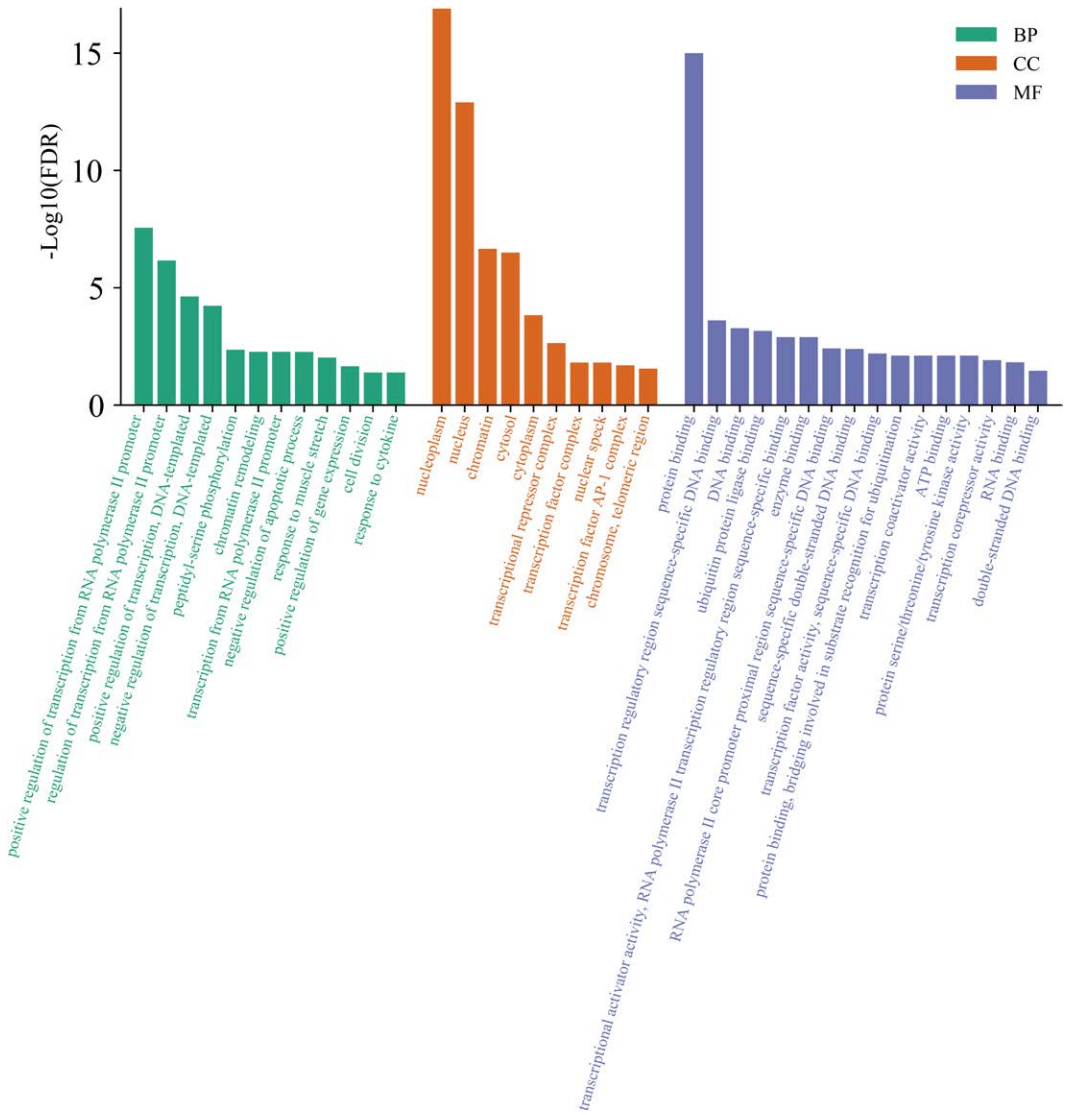

Figure 4. Gene ontology enrichment analysis.

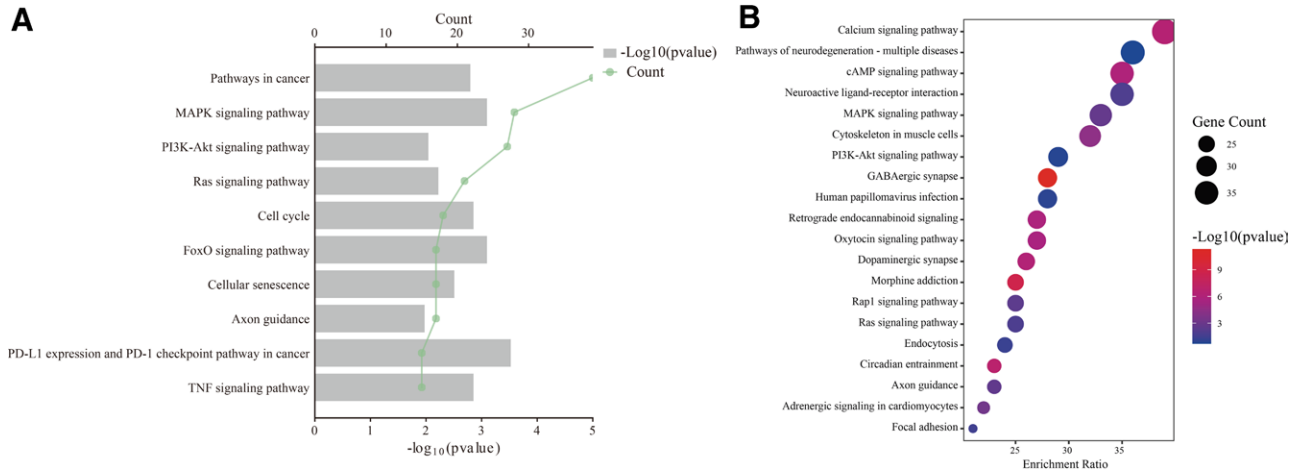

Figure 5. KEGG pathway enrichment analysis. (A) Bar chart showing KEGG enrichment pathways of miRNA target genes. (B) Bubble plot showing enrichment pathways of differentially expressed genes between GBM and normal brain tissues. GBM = glioblastoma multiforme, KEGG = Kyoto Encyclopedia of Genes and Genomes, miRNA = microRNA.

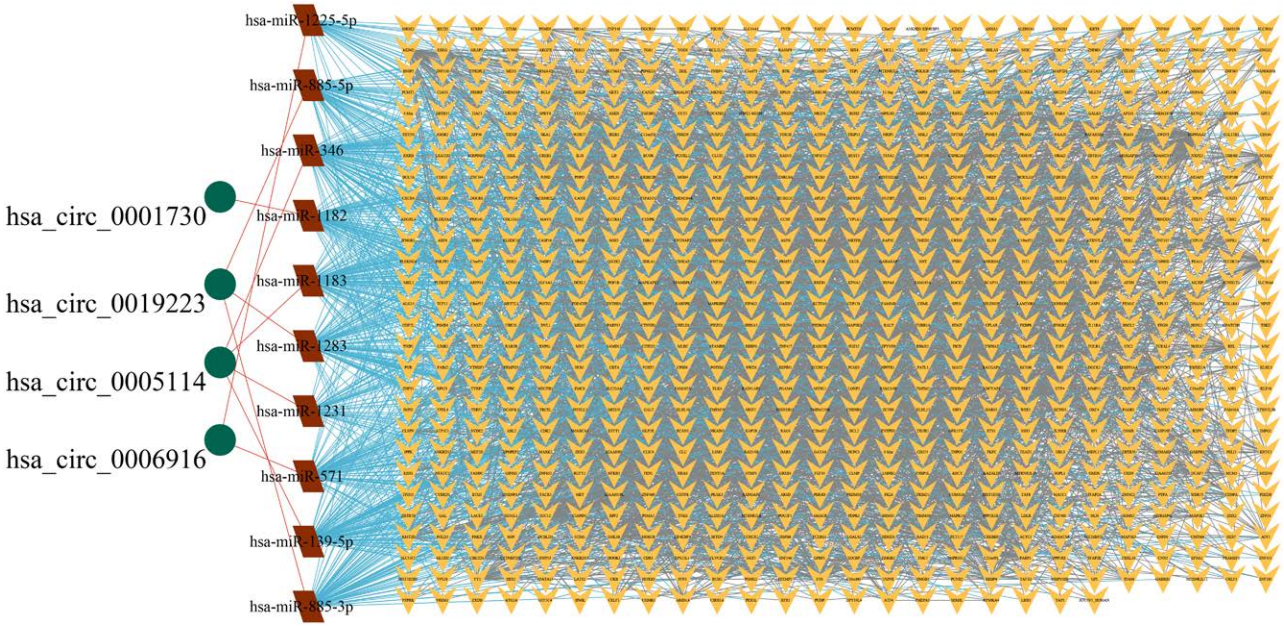

Figure 6. Network of circRNA-miRNA-mRNA interactions in GBM. The green circles represent circRNAs, the brown squares represent miRNAs, and the yellow triangles represent mRNAs. circRNAs = circular ribonucleic acids, GBM = glioblastoma multiforme, miRNA = microRNA, mRNA = messenger RNA.

factor kappa B subunit 1 (NFKB1), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), and Jun proto-oncogene (JUN). These genes play crucial roles in cancer development. For instance, CTNNB1 is an important member of the Wnt signaling pathway, mediating cell adhesion, and its upregulation is associated with poor patient outcomes in various cancers.[23] BCL2 is a key regulator of cell apoptosis and plays a significant role in cancer development and progression.[24] NFKB1 is a transcription factor involved in inflammation and cancer.[25] PIK3CA is a critical component of the PI3K/Akt pathway, which regulates cell growth and survival.[26] JUN is a proto-oncogene that regulates cell proliferation and apoptosis.[27]

3.6. Downregulation of hub genes in GBM associates with prognosis

To examine the clinical relevance of the hub genes in GBM, we analyzed their expression patterns and prognostic significance. Using the UCSC Xena database, we compared the expression levels of these genes between GBM patient brain tissues and normal brain tissues. Surprisingly, all 5 hub genes showed significantly overexpressed expression in GBM tissues (Fig. 7A). Using the Human Protein Atlas database and immunohistochemistry (IHC) techniques, we further assessed the local expression pattern of the 5 hub genes in GBM and normal brain tissue samples.[28] The immunohistochemistry results confirmed significantly elevated protein expression of these hub genes in GBM tissues compared to normal brain tissues (Fig. 7E), providing further validation of their upregulation at the protein level in GBM pathology. We then integrated gene expression data with clinical information from the CGGA database to assess the impact of these genes on patient outcomes. Kaplan–Meier survival analysis revealed that lower expression of CTNNB1 (Fig. 7B), NFKB1 (Fig. 7C), and JUN (Fig. 7D) was significantly correlated with favorable prognosis in GBM patients. The results indicate that the hub genes we identified play important roles in GBM.

4. Discussion

GBM is a highly invasive primary brain tumor, and its treatment and prognosis remain a significant clinical challenge. As a novel class of RNA molecules, circRNAs have emerged as important players in the development and progression of many diseases, including GBM. Existing studies indicate that circRNAs play crucial roles in GBM pathogenesis. For example, circSMARCA5 can regulate splicing factors such as SRSF1, SRSF3, and PTB to inhibit tumor cell migration.[29] In contrast, circNT5E binds to miR-422a, promoting the occurrence of GBM.[30] Therefore, further investigating the regulatory relationships of circRNAs in GBM can aid in understanding their functions in cancer and provide a basis for improved diagnosis and treatment of GBM.

In this study, we systematically analyzed the circRNA expression profiles in 2 GBM datasets, GSE165926 and GSE153692, using bioinformatics methods. We identified 4 DE-circRNAs across different datasets: hsa_circ_0001730, hsa_circ_0019223, hsa_circ_0005114, and hsa_circ_0006916, suggesting their potential regulatory roles in GBM. Previous studies have shown that hsa_circ_0001730, hsa_circ_0019223, and hsa_circ_0006916 can exert regulatory functions by binding to miRNAs in hepatocellular carcinoma, but their roles in gliomas remain unclear.[31–33] Notably, previous studies found that hsa_circ_0005114 is downregulated in gliomas and is a potential therapeutic target.[34] Therefore, we further predicted the miRNAs bound by these 4 DE-circRNAs. Among the 14 candidate miRNAs, hsa-miR-139-5p, hsa-miR-346,hsa-miR-571, hsa-miR-885-3p, hsa-miR-885-5p, hsa-miR-1182, hsa-miR-1183, hsa-miR-1225-5p, hsa-miR-1231 and hsa-miR-1283 were found to be associated with significantly longer survival in GBM patients when highly expressed, indicating their potential regulatory roles in GBM. Next, we predicted the target genes of these miRNAs using the experimentally validated miRNA-target interaction database miRTarBase, followed by GO and KEGG functional enrichment analyses. The results showed significant enrichment of target genes in functions related to transcription, protein phosphorylation, cell apoptosis, cell division regulation, and cytokine response. Additionally, these genes are involved in important cancer-related signaling pathways, such as the MAPK signaling pathway, the PI3K-Akt signaling pathway, PD-L1 expression, and the PD-1 checkpoint pathway in cancer. Dysregulation of these functions and pathways is closely associated with cancer development and progression.

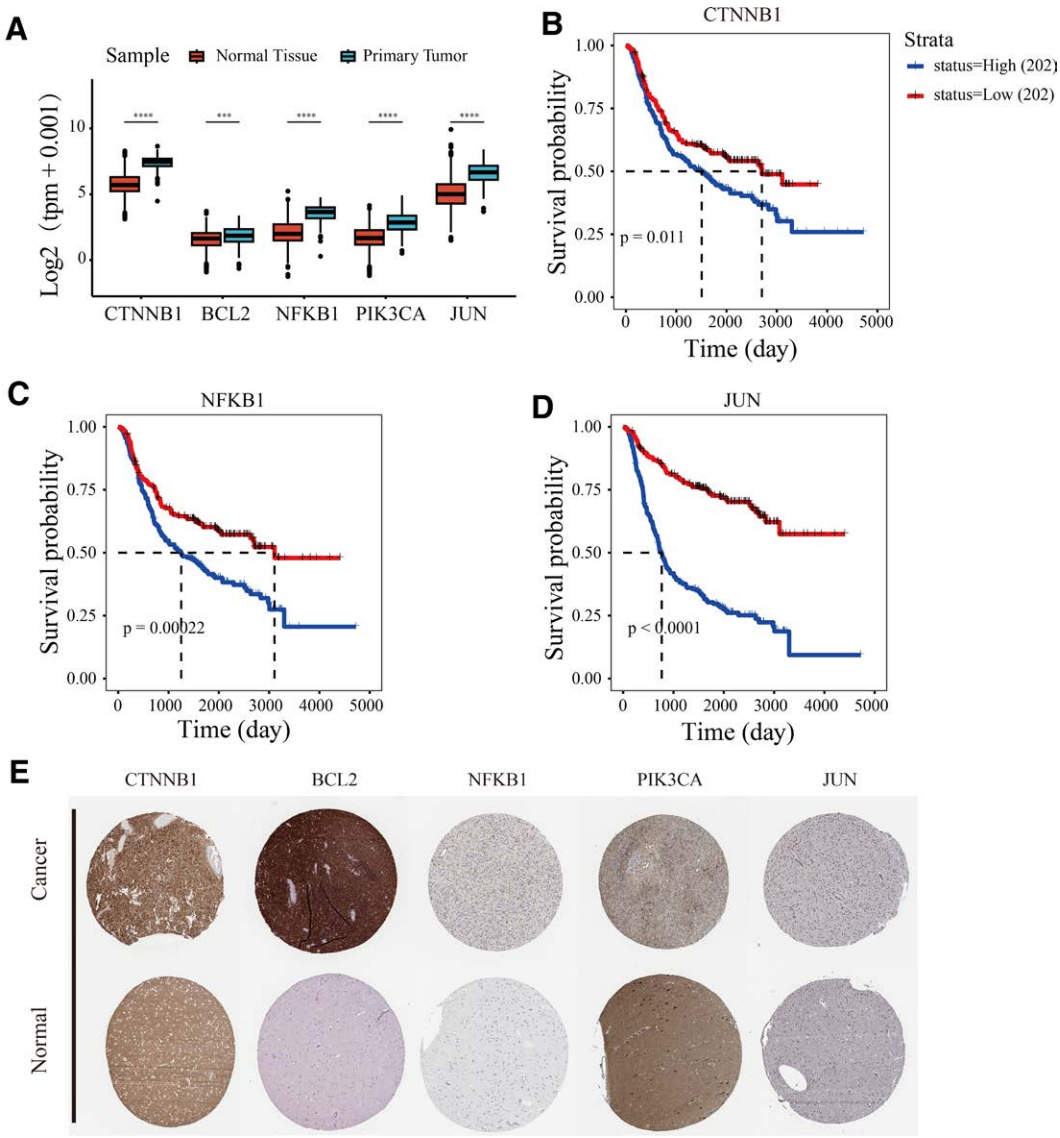

Figure 7. Expression and survival analysis of hub genes. (A) Expression of hub genes. (B) Survival curve of CTNNB1. (C) Survival curve of NFKB1. (D) Survival curve of JUN. (E) Representative IHC micrographs of 5 hub genes in GBM and normal tissue from the HPA database.[28] CTNNB1 = core hub genes: catenin beta 1, HPA = Human Protein Atlas, GBM = glioblastoma multiforme, JUN = Jun proto-oncogene, NFKB1 = nuclear factor kappa B subunit 1.

Finally, we constructed a circRNA-miRNA-mRNA regulatory network and analyzed the network to identify the top 5 ranked hub genes: CTNNB1, BCL2, NFKB1, PIK3CA, and JUN. These genes play crucial roles in cancer development. Expression analysis revealed that all hub genes were significantly upregulated in gliomas. Furthermore, survival analysis ($P < .05$) demonstrated that higher expression levels of CTNNB1, BCL2, NFKB1, and PIK3CA were associated with longer survival times in GBM patients, indicating their potential prognostic value.

In summary, through comprehensive bioinformatics analyses, this study identified 4 DE-circRNAs in GBM and constructed a circRNA-miRNA-mRNA regulatory network. Functional enrichment analyses suggested the involvement of these circRNAs in critical cancer-related pathways. Additionally, 5 hub genes with pivotal roles in cancer development and progression were identified. These findings provide valuable insights into the regulatory mechanisms of circRNAs in GBM, laying a foundation for potential biomarkers and therapeutic targets. However, this preliminary study has several limitations. It relies on publicly available datasets, which may introduce variability due to differences in sample handling and methodologies. Moreover, the circRNA-miRNA-mRNA network is based on predictive databases, and future work will involve experimental validation to confirm these interactions and further substantiate our findings.

Author contributions

Funding acquisition: Dongpo Hu.
Methodology: Dongpo Hu.
Resources: Kangjing Chen.
Software: Kangjing Chen.
Visualization: Dongpo Hu.
Writing – original draft: Dongpo Hu, Kangjing Chen.
Writing – review & editing: Dongpo Hu.

References

[1] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209–49.
[2] Thakkar JP, Dolecek TA, Horbinski C, et al. Epidemiologic and molecular prognostic review of glioblastoma. Cancer Epidemiol Biomarkers Prev. 2014;23:1985–96.

[3] Jeck WR, Sharpless NE. Detecting and characterizing circular RNAs. Nat Biotechnol. 2014;32:453–61.
[4] Verduci L, Tarcitano E, Strano S, Yarden Y, Blandino G. CircRNAs: role in human diseases and potential use as biomarkers. Cell Death Dis. 2021;12:468.
[5] Pritchard CC, Grady WM. Colorectal cancer molecular biology moves into clinical practice. Gut. 2011;60:116–29.
[6] Hansen TB, Jensen TI, Clausen BH, et al. Natural RNA circles function as efficient microRNA sponges. Nature. 2013;495:384–8.
[7] Zhou WY, Cai ZR, Liu J, Wang DS, Ju HQ, Xu RH. Circular RNA: metabolism, functions and interactions with proteins. Mol Cancer. 2020;19:172.
[8] Min X, Liu DL, Xiong XD. Circular RNAs as competing endogenous RNAs in cardiovascular and cerebrovascular diseases: molecular mechanisms and clinical implications. Front Cardiovasc Med. 2021;8:682357.
[9] Rong D, Sun H, Li Z, et al. An emerging function of circRNA-miRNAs-mRNA axis in human diseases. Oncotarget. 2017;8:73271–81.
[10] Zhong Q, Huang J, Wei J, Wu R. Circular RNA CDR1as sponges miR-7-5p to enhance E2F3 stability and promote the growth of nasopharyngeal carcinoma. Cancer Cell Int. 2019;19:252.
[11] Chen Q, Wang H, Li Z, et al. Circular RNA ACTN4 promotes intrahepatic cholangiocarcinoma progression by recruiting YBX1 to initiate FZD7 transcription. J Hepatol. 2022;76:135–47.
[12] Hanan M, Soreq H, Kadener S. CircRNAs in the brain. RNA Biol. 2017;14:1028–34.
[13] Tang C, He X, Jia L, Zhang X. Circular RNAs in glioma: molecular functions and pathological implications. Noncoding RNA Res. 2024;9:105–15.
[14] Love MI, Huber W, Anders S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. Genome Biol. 2014;15:550.
[15] Dudekula DB, Panda AC, Grammatikakis I, De S, Abdelmohsen K, Gorospe M. CircInteractome: A web tool for exploring circular RNAs and their interacting proteins and microRNAs. RNA Biol. 2016;13:34–42.
[16] Wu W, Zhao F, Zhang J. circAtlas 3.0: a gateway to 3 million curated vertebrate circular RNAs based on a standardized nomenclature scheme. Nucleic Acids Res. 2024;52:D52–60.
[17] Zhao Z, Zhang KN, Wang Q, et al. Chinese Glioma Genome Atlas (CGGA): a comprehensive resource with functional genomic data from Chinese glioma patients. Genomics Proteomics Bioinformatics. 2021;19:1–12.
[18] Huang HY, Lin YC, Cui S, et al. miRTarBase update 2022: an informative resource for experimentally validated miRNA-target interactions. Nucleic Acids Res. 2022;50:D222–30.
[19] Szklarczyk D, Kirsch R, Koutrouli M, et al. The STRING database in 2023: protein-protein association networks and functional enrichment analyses for any sequenced genome of interest. Nucleic Acids Res. 2023;51:D638–46.
[20] Sherman BT, Hao M, Qiu J, et al. DAVID: A web server for functional enrichment analysis and functional annotation of gene lists (2021 update). Nucleic Acids Res. 2022;50:W216–21.
[21] Chin CH, Chen SH, Wu HH, Ho CW, Ko MT, Lin CY. cytoHubba: identifying hub objects and sub-networks from complex interactome. BMC Syst Biol. 2014;8(Suppl 4):S11.
[22] Goldman MJ, Craft B, Hastie M, et al. Visualizing and interpreting cancer genomics data via the Xena platform. Nat Biotechnol. 2020;38:675–8.
[23] AmeliMojarad M, AmeliMojarad M, Cui X, shariati P. Pan-cancer analysis of CTNNB1 with potential as a therapeutic target for human tumorigenesis. Inf Med Unlocked. 2023;42:101331.
[24] Qian S, Wei Z, Yang W, Huang J, Yang Y, Wang J. The role of BCL-2 family proteins in regulating apoptosis and cancer therapy. Front Oncol. 2022;12:985363.
[25] Zhang T, Ma C, Zhang Z, Zhang H, Hu H. NF-kappaB signaling in inflammation and cancer. MedComm (2020). 2021;2:618–53.
[26] Peng Y, Wang Y, Zhou C, Mei W, Zeng C. PI3K/Akt/mTOR pathway and its role in cancer therapeutics: are we making headway? Front Oncol. 2022;12:819128.
[27] Wisdom R, Johnson RS, Moore C. c-Jun regulates cell cycle progression and apoptosis by distinct mechanisms. EMBO J. 1999;18:188–97.
[28] Uhlen M, Fagerberg L, Hallstrom BM, et al. Proteomics. Tissue-based map of the human proteome. Science. 2015;347:1260419.
[29] Barbagallo D, Caponnetto A, Cirnigliaro M, et al. CircSMARCA5 inhibits migration of glioblastoma multiforme cells by regulating a molecular axis involving splicing factors SRSF1/SRSF3/PTB. Int J Mol Sci . 2018;19:480.
[30] Wang R, Zhang S, Chen X, et al. CircNT5E acts as a sponge of miR-422a to promote glioblastoma tumorigenesis. Cancer Res. 2018;78:4812–25.
[31] Zhou XY, Yang H, Bai YQ, Li XL, Han SY, Zhou BX. hsa_circ_0006916 promotes hepatocellular carcinoma progression by activating the miR-337-3p/STAT3 axis. Cell Mol Biol Lett. 2020;25:47.
[32] Tan Y, Du B, Zhan Y, et al. Antitumor effects of circ-EPHB4 in hepatocellular carcinoma via inhibition of HIF-1alpha. Mol Carcinog. 2019;58:875–86.
[33] Liang ZX, Liu HS, Xiong L, et al. A novel NF-kappaB regulator encoded by circPLCE1 inhibits colorectal carcinoma progression by promoting RPS3 ubiquitin-dependent degradation. Mol Cancer. 2021;20:103.
[34] Wei B, Wang L, Zhao J. Circular RNA hsa_circ_0005114-miR-142-3p/miR-590-5p-adenomatous polyposis coli protein axis as a potential target for treatment of glioma. Oncol Lett. 2021;21:58.