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Review

Circular RNAs in glioma progression: Fundamental mechanisms and therapeutic potential: A review

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Highlights

- Circular RNAs are dysregulated in glioma and function as emerging regulators of glioma progression via multiple mechanisms.
- Circular RNAs regulate glioma cell fate through DNA damage repair, cell death, angiogenesis, and metabolic reprogramming.
- Circular RNAs shape the glioma tumor microenvironment through non-coding RNA networks and feedback loops.
- Targeting circular RNA networks offers novel opportunities for glioma diagnosis, prognosis, and therapeutic development.

Abstract

Gliomas are the most common primary malignant brain tumors, characterized by aggressive invasion, limited therapeutic options, and poor prognosis. Despite advances in surgery, radiotherapy, and chemotherapy, the median survival of glioma patients remains disappointingly low. Therefore, identifying glioma-associated therapeutic targets and biomarkers is of significant

clinical importance. Circular RNAs (circRNAs) are a class of naturally occurring long non-coding RNAs (lncRNAs), notable for their stability and evolutionary conservation. Increasing evidence indicates that circRNA expression is dysregulated in gliomas compared to adjacent non-tumor tissues and contributes to the regulation of glioma-related biological processes. Furthermore, numerous circRNAs function as oncogenes or tumor suppressors, mediating glioma initiation, progression, and resistance to temozolomide (TMZ). Mechanistically, circRNAs regulate glioma biology through diverse pathways, including acting as miRNA sponges, binding RNA-binding proteins (RBPs), modulating transcription, and even encoding functional peptides. These features highlight the potential of circRNAs as diagnostic and prognostic biomarkers, as well as therapeutic targets for glioma. This review summarizes the dysregulation and functions of circRNAs in glioma and explores key mechanisms through which they mediate tumor progression, including DNA damage repair, programmed cell death (PCD), angiogenesis, and metabolic reprogramming. Our aim is to provide a comprehensive perspective on the multifaceted roles of circRNAs in glioma and to highlight their potential for translational application in targeted therapy.

Introduction

Gliomas are the most commonly diagnosed malignant primary brain tumors in adults. These tumors exhibit significant heterogeneity and are associated with poor prognosis [1]. The current standard of treatment, known as the Stupp regimen, consists of maximal safe surgical resection followed by radiotherapy and adjuvant temozolomide (TMZ) [2]. However, the overall survival (OS) of patients with high-grade gliomas, especially glioblastoma (GBM), remains limited to approximately 12–15 months [2,3]. Sensitivity to TMZ is closely associated with the methylation status of the O^6-methylguanine-DNA methyltransferase (MGMT) promoter. Patients with unmethylated MGMT promoters typically exhibit TMZ resistance and have worse prognoses [4]. Although the EF-14 trial demonstrated that adding tumor-treating fields (TTFields) to the Stupp regimen prolonged OS to 20.9 months in GBM patients [5], the high cost remains a major barrier to widespread implementation. Immune checkpoint inhibitors targeting epidermal growth factor receptor (EGFR) variant III (e.g., pembrolizumab, nivolumab), as well as peptide vaccines such as rindopepimut, have not shown significant efficacy in phase II or III clinical trials [[6], [7], [8]]. Similarly, targeted therapies including bevacizumab, anlotinib, and regorafenib have exhibited limited clinical efficacy [[9], [10], [11]]. Oncolytic virotherapy aimed at activating anti-tumor immune responses are still in the early stages of clinical investigation for glioma treatment [12,13]. Overall, progress in glioma treatment remains limited, underscoring the urgent need for more effective therapeutic strategies to improve patient outcomes. Emerging strategies, such as targeting circular RNAs (circRNAs), are gaining attention as our understanding of glioma molecular mechanisms deepens.

CircRNAs are a class of naturally occurring long non-coding RNAs (lncRNAs) that are broadly expressed in eukaryotic cells. The single-stranded circRNA was first identified in a virus-like pathogen by Sanger et al. in 1976 [14]. Owing to their covalently closed-loop structure, circRNAs are highly resistant to degradation by exonucleases and ribonucleases, resulting in greater

stability compared to linear RNAs [15]. Historically, due to the absence of 5′ caps and 3′ tails, circRNAs were considered non-functional byproducts of aberrant splicing events [16]. However, advances in sequencing technologies have revealed that circRNAs play critical roles in human biology, including acting as microRNA (miRNA) sponges [17], binding to RNA-binding proteins (RBPs) [18], regulating gene transcription and alternative splicing [19], and even participating in protein translation [20]. Moreover, dysregulated circRNAs are extensively implicated in tumor-associated processes, such as cell proliferation, migration, invasion, epithelial–mesenchymal transition (EMT), and drug resistance [21,22]. Notably, circRNAs exhibit differential expression between glioma and adjacent non-tumor tissues and participate in the regulation of glioma-associated biological processes. Therefore, circRNAs hold great potential as biomarkers and therapeutic targets for glioma diagnosis and treatment.

In this review, we summarize the roles of circRNAs in glioma progression, with a particular focus on the tumor microenvironment (TME) and the functional characteristics of circRNAs. We also explore the underlying molecular mechanisms to offer new insights into developing more effective glioma treatments.

Section snippets

TME for gliomas

TME encompasses the internal and external conditions that support tumor cell initiation, growth, and metastasis. Compared to other solid tumors, the glioma TME is uniquely specialized, largely due to the presence of distinct tissue-resident cells. Once thought to be passive bystanders in gliomagenesis, these cells are now known to engage in bidirectional communication with glioma cells, thereby facilitating tumor development and progression [23,24]. Moreover, the blood-brain barrier (BBB)—a …

Biogenesis-based circRNA classification

CircRNAs are classified based on their biogenesis into four types: exonic circRNAs (ecircRNAs), exon-intronic circRNAs (EIcircRNAs), circular intronic RNAs (ciRNAs), and tRNA intronic circular RNAs (tricRNAs). EcircRNAs are the most abundant subtype and are primarily localized in the cytoplasm [37]. CircRNA biogenesis differs from canonical RNA splicing, as the flanking introns are typically longer. EcircRNAs are generally produced via back-splicing, in which the 5′ splice donor site downstream …

DNA damage repair and glioma progression

Postoperative radiotherapy and TMZ chemotherapy are standard treatments used to target residual glioma cells. At the molecular level, extensive DNA damage results in single-strand breaks (SSBs) or more cytotoxic double-strand breaks (DSBs), leading to cell cycle arrest and ultimately cell death. Mutations or defects in DNA repair pathways promote tumorigenesis by increasing genomic instability. In contrast, established tumors may rely on intact and active repair mechanisms to resist …

PCD in the glioma microenvironment

PCD is a fundamental mechanism that eliminates abnormal cells and maintains tissue homeostasis. In gliomas, the major forms of PCD—apoptosis, pyroptosis, ferroptosis, and autophagy—have been extensively studied. These pathways play critical roles in shaping the immunosuppressive TME and influencing therapeutic responses [94]. Cellular stress activates B-cell lymphoma 2 (Bcl-2) family proteins Bax and Bak, increasing mitochondrial membrane permeability [95]. As a result, cytochrome *c* is released …

CircRNA regulation of angiogenesis mediates glioma progression

Angiogenesis, the process of forming new blood vessels, is a hallmark of cancer and a crucial mechanism driving tumor progression [121]. In malignant tumors, genetic mutations alone are often insufficient to drive progression. Tumor cells must also induce angiogenesis to meet their growing demands for oxygen and nutrients [122]. Oxygen and nutrients can diffuse only 100–200 μm from the nearest capillary into surrounding tissue [123]. Beyond this distance, tumor cells cannot survive unless new …

Glioma progression and the Warburg effect

Energy metabolism reprogramming is a hallmark of tumorigenesis driven by genomic instability [135], with abnormal glucose metabolism as a key feature. Under aerobic conditions, normal somatic cells generate ATP via oxidative phosphorylation (OXPHOS), switching to glycolysis and lactate production only in hypoxic environments. However, Warburg observed that cancer tissues in both rats and humans consumed more glucose and secreted more lactate than normal tissues even in the presence of oxygen, a …

Conclusions and future prospects

Gliomas are among the most aggressive tumors of the central nervous system and represent a significant threat to patient health. Historically, the OS of glioma patients, particularly those with GBM, has been extremely poor. Despite therapeutic advances, including the introduction of TTFields, the median OS has only modestly improved from 16.0 to 20.9 months. Nevertheless, this improvement remains limited, with a 5-year survival rate of just 13% [5]. As a result, glioma-related research has …

Abbreviations

AGO2
: argonaute 2 …

Akt
: protein kinase B …

ALDOA
: Aldolase A …

ALKBH5
: AlkB homolog 5 …

ARID1A
: AT-rich interaction domain 1A …

AS
: alternative splicing …

ATGL
: adipose triglyceride lipase …

BBB
: blood–brain barrier …

Bcl-2
: B-cell lymphoma 2 …

Bcl-9
: B-cell lymphoma 9 …

BDNF
: brain-derived neurotrophic factor …

BHB
: bulge–helix–bulge …

BRCA2
: breast cancer type 2 susceptibility protein …

BRIP1
: BRCA1-interacting protein 1 …

ceRNA
: competing endogenous RNA …

CHEK1
: checkpoint kinase 1 …

ciRNA
: circular intronic RNA …

circRNA
: CIRCULAR RNA …

CRISPR/Cas
: regularly interspaced short …

…

CRediT authorship contribution statement

Hongbin Wang: Writing – review & editing, Writing – original draft. **Chenbin Bian:** Writing – review & editing, Writing – original draft. **Yidan Zhang:** Data curation. **Li Zhang:** Data curation. **Feng Wang:** Visualization, Validation, Supervision, Conceptualization. …

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Declaration of competing interest

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