



Review

## Research progress on function and mechanism of long non-coding RNA in glioma

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### Article Info

### Abstract



#### Article history:

Received: January 17, 2024

Accepted: April 10, 2024

Published: May 31, 2024

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This review aimed to comprehensively summarize the role of long non-coding RNA (lncRNA) in gliomas, the most common malignant tumors in the central nervous system, and explore their potential clinical applications. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a systematic search using the PubMed database was conducted forty studies met the inclusion and exclusion criteria and were analyzed for type of intervention, the study's design, participants' demographics, and outcomes, including attrition. Gliomas, originating within the central nervous system, account for 40-45% of intracranial tumors. Despite advances in neurosurgical techniques, precise radiotherapy, and chemotherapy, the prognosis for glioma patients remains suboptimal. The review highlights the crucial regulatory role of lncRNA in gliomas. Differential expression of various lncRNAs, such as INHEG, SATB2-AS1, PSMB8-AS1, LINC01018, and SPRY4-IT1, has been observed in gliomas, suggesting their involvement in promoting or inhibiting tumorigenesis. Additionally, lncRNAs play roles in glioma characteristics such as proliferation, invasion, migration, angiogenesis, and the presence of glioma stem cells. The potential clinical applications of lncRNA in gliomas involve their association with tumor grading, diameter, metastasis, and family history. This review emphasizes the importance of understanding the molecular mechanisms involving lncRNA in gliomas. The identification of specific lncRNAs associated with gliomas provides potential molecular markers for diagnosis, differentiation, treatment, and prognosis evaluation. Further research is needed to uncover additional key lncRNAs and their underlying mechanisms, ultimately contributing to the improvement of glioma diagnosis and treatment.

**Keywords:** Glioma; Long non-coding RNA; Function; Mechanism

### 1. Introduction

Gliomas originate from tumors derived from neural ectodermal mesenchymal cells and are primary intracranial space-occupying lesions, accounting for approximately 40-45% of intracranial tumors. Clinical manifestations include headaches, nausea, and varying degrees of neurological impairment [1]. Currently, the specific mechanisms underlying the onset of gliomas remain unclear, potentially resulting from the interaction of genetic susceptibility factors and environmental carcinogenic factors [2]. Recently, the WHO classification has been modified to include molecular criteria, such as IDH mutations for diffuse astrocytoma and GBM, or the epigenetic mark H3K27M mutation for diffuse midline glioma, to provide more precise diagnosis and treatment. Glioma cells exhibit characteristics of unlimited proliferation and high invasiveness. Despite continuous advancements in neurosurgical techniques, precise radiotherapy, and chemotherapy drugs, the prognosis for patients with such tumors remains suboptimal [3]. Therefore, enhancing the etiological research of gliomas is crucial for developing novel molecular targeted drugs to improve prognosis.

An expanding research area in epigenetic regulation of tumorigenesis includes the field of non-coding RNAs. Among non-coding species, lncRNAs are being intensively investigated, and enticing progress has been made in recent years, revealing their roles in chromatin remodelling, transcription, posttranscriptional processing and intracellular trafficking [4,5]. lincRNAs consist of separate transcript units that are located between, but do not overlap with, protein-coding genes (PCGs) and represent the largest subclass of functionally characterized lncRNAs. Long non-coding RNA (lncRNA) refers to RNA molecules with a length between 200 and 100,000 nucleotides. Although they do not encode proteins, lncRNAs play a regulatory role in various cellular processes. Aberrant expression of lncRNAs is associated with several types of cancer, including glioma. Normal expression of lncRNAs is affected by functional mutations or epigenetic alterations, transforming them into cancer-associated transcripts present at every step of tumour development. Studies have revealed the significant regulatory role of lncRNA in gliomas, offering potential breakthroughs in the clinical diagnosis and treatment of gliomas [6,7]. At

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present, types, numbers and functions of lncRNA are not clear. More and more studies have shown that lncRNA is abnormally expressed in tumor cells, which can participate in the regulation of biological behaviors of tumor cells. This article reviews the function and mechanism of lncRNA in glioma. This review comprehensively covers these aspects: an overview of lncRNA, the involvement of lncRNA in the occurrence and development of gliomas, and the clinical applications of lncRNA in gliomas. It aims to provide a comprehensive summary of the functions and mechanisms of lncRNA in gliomas. We will also review the two sides of lncRNA epigenetic regulation in glioma, as both targets and drivers. Finally, arguments in favour of using lncRNAs as diagnostic tools and therapeutic targets in glioma will be presented.

## 2. Materials and Methods

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a systematic search using the PubMed database was conducted. Forty studies met the inclusion and exclusion criteria and were analyzed for type of intervention, the study's design, participants' demographics, and outcomes, including attrition.

## 3. Results

### 3.1. Overview of lncRNA

Initially, long non-coding RNAs (lncRNAs) were considered genomic transcription "noise" without biological functionality. However, it was later discovered that lncRNAs participate in various biological processes, including X-chromosome silencing, genomic imprinting, transcriptional activation, and interference, closely linking them to the onset and progression of various diseases [8]. lncRNAs are primarily located in the nuclear chromatin, exhibiting mRNA-like structures but lacking open reading frames, rendering them incapable of encoding proteins [9]. Most lncRNAs possess a conserved secondary structure. This conservation and specificity suggest that, in the process of inheritance, they not only serve as auxiliary intermediaries but also play diverse regulatory roles: 1) Transcriptional interference: Initiating transcription in the upstream promoter region of coding genes, disrupting the expression of adjacent protein-coding genes; 2) Inhibition of RNA polymerase II: Suppressing RNA polymerase II or mediating chromatin remodeling and histone modification processes, influencing gene expression; 3) Binding to transcripts: Interfering with mRNA splicing, forming different splicing forms, or generating endogenous small interfering RNAs (siRNAs) to regulate gene expression; 4) Binding to specific proteins: Regulating the activity of corresponding proteins. 5) Structural component: Forming nucleic acid-protein complexes with proteins; 6) Precursor for small RNA: Serving as a precursor substance for small RNA [10,11]; 7) A crucial step in lncRNA research is identifying those associated with specific diseases. Common methods include traditional genetic approaches, gene chips, and high-throughput RNA sequencing [12]. Currently, while the functions of a few lncRNAs are relatively clear, the majority remain an extensive unknown field, holding significant research value and meaning.

### 3.2. lncRNA Involvement in the Occurrence and Development of Gliomas

Numerous studies indicate differential expression of lncRNAs in gliomas: Liu et al. [13] demonstrated elevated expression of lncRNA INHEG in glioblastomas, while Gu et al. [14], analyzing tumor genomic data sets, found downregulation of lncRNA SATB2-AS1 in both low-grade gliomas and glioblastomas. This suggests that lncRNAs play a role in either promoting or inhibiting cancer in gliomas.

## 4. Discussion

The development of malignant tumors involves the accumulation of genetic changes and the process of clonal selection. Tumor cells possess biological characteristics such as unlimited proliferation, invasiveness, metastasis, and angiogenesis. lncRNA PSMB8-AS1 competitively binds with miR-382-3p, enhancing the expression of BCAT1, thereby promoting the in vitro proliferation and migration of glioma cells, inhibiting apoptosis, and stimulating the in vitro growth of transplanted tumors [15]. lncRNA LINC01018 acts as a sponge for miR-942-5p, selectively inhibiting KNG1, and enhancing the proliferation, invasion, and migration abilities of glioma cells [16]. The growth and metastatic capabilities of tumors depend on neovascularization, providing sufficient oxygen, nutrients, and waste removal to maintain metabolism and survival. Gliomas, being the most vascularized malignant tumors [17], exhibit overexpression of lncRNA SPRY4-IT1, which, by sequestering miR-101-3p, upregulates EZH2, inducing VEGFA and promoting glioma cell proliferation and angiogenesis [18].

In tumor cells, a subpopulation with stem cell characteristics, known as tumor stem cells, exhibits biological features such as self-renewal, multi-lineage differentiation potential, and resistance to conventional treatments [19]. Glioma stem cells induce tumor angiogenesis, promote tumor invasion and spread, display high tolerance to radiotherapy and chemotherapy, and rapidly re-establish tumors under the pressure of conventional treatments, leading to rapid glioma recurrence [20]. Increasing research focuses on crucial molecular regulatory pathways associated with these biological features to obtain efficient and reliable therapeutic targets. For instance, lncRNA GSCAR, highly expressed in gliomas, shortens the overall survival time of patients. Knocking down GSCAR expression reduces SOX2 expression, inhibiting the self-renewal ability of glioma stem cells but promoting cell response to the therapeutic drug temozolomide [21]. Wang et al. [22], using the TANRIC database and PCR detection, found upregulated expression of lncRNA RP11-279C4.1 in glioma tissues and cell lines. As an oncogenic gene, RP11-279C4.1 promotes the malignant phenotype of gliomas, including cell proliferation, migration, invasion, and self-renewal ability, by regulating the miR-1273g-3p/CBX3 axis.

Furthermore, lncRNAs participate in gliomas by regulating the blood-brain tumor barrier, sensitivity to radiotherapy and chemotherapy, and tumor metabolism. For example, lncRNA MIAT acts as a sponge for miR-140-3p, regulating the expression of its target gene ZAK. This increases the permeability of the blood-brain tumor barrier, promoting the penetration of the anti-tumor drug actino-

mycin, and inducing apoptosis in glioma cells [23]. Cao et al. [24], through a comprehensive genome-wide transcriptional survey, identified 51 lncRNAs with abnormal expression in glioma samples, of which 27 were drug-resistant lncRNAs, maintaining abnormal expression even after radiotherapy and chemotherapy. Knocking down SNHG1 and UBL7-AS1 among them promoted the proliferation of glioblastoma cells. Dong et al. [25], using RNA immunoprecipitation technology, identified a novel lncRNA, MDH2, as a tumor factor that directly binds to MDH2 and PSMA1, acting as a molecular scaffold. This promotes the ubiquitination of MDH2 and its binding to proteasomes, accelerating the degradation of MDH2, and leading to changes in mitochondrial membrane potential and the NAD<sup>+</sup>/NADH ratio, thereby hindering glycolysis in glioma cells.

#### 4.1. Potential Clinical Applications of lncRNA in Gliomas

Currently, neuroimaging techniques are the primary diagnostic methods for intracranial lesions. However, distinguishing intracranial lesions with similar radiological features is challenging, and assessing postoperative progression of gliomas is difficult [26]. Tumor cells are on a micrometer scale, while MRI imaging resolution is on a millimeter scale, leading to potential delays in diagnosis. Histological examination remains the "gold standard" for diagnosing gliomas, requiring the acquisition of tumor tissue through surgery or biopsy and subsequent pathological testing to determine the specific pathological type of glioma [27]. At present, molecular characteristics have become a research hotspot in the diagnosis and treatment of gliomas [28,29]. Molecular pathological diagnosis further divides gliomas based on the molecular genetic level, which is crucial for accurately assessing the biological characteristics and clinical prognosis of gliomas. lncRNA-ANRIL and SOX9 show abnormal expression in gliomas, closely correlating with tumor grading, tumor diameter, distant metastasis, and a family history of gliomas [30]. Yang et al. [31] constructed a risk model based on lncRNA genes associated with pseudouridine from tumor genomic maps and the Chinese glioma genomic map. They found that a model composed of four lncRNAs—DNAJC27-AS1, GDNF-AS1, ZBTB20-AS4, and DNMBP-AS1—effectively predicted the prognosis of glioma patients. Moreover, the risk score generated by this model was closely related to the sensitivity of patients to radiotherapy and chemotherapy.

Širvinskas et al. [32], through RNA sequencing of postoperative tumor samples and normal brain tissues from 26 glioma patients, found significantly upregulated expression of the antisense lncRNA CHROMR in glioma tissues, with higher expression correlating to lower patient survival rates. Zhao et al. [33], using the GSE4290 dataset obtained from the Gene Expression Omnibus, selected differentially expressed genes and lncRNAs. After minimum absolute shrinkage and selection operator analysis, they identified nine optimal features, including lncRNAs GABPB1-AS1, HAR1A, LINC00599, SNAI3-AS1, SNHG1, and mRNAs FABP6, MBOAT7, SLC25A1, UST, closely related to energy metabolism, aiding in predicting the prognosis of low-grade gliomas.

The spread rate of cancer cells in gliomas is much faster than in other malignant tumors, making early treatment

crucial. Comprehensive therapies are commonly used, involving surgical removal to quickly eliminate tumors, and release compressed nerves, and postoperative treatments such as radiotherapy, chemotherapy, and immunotherapy to control residual cancer cells. Some studies have explored new approaches to glioma treatment based on lncRNAs: Temozolomide is a commonly used alkylating chemotherapy drug for treating glioblastoma multiforme. However, some patients develop resistance. By comparing the expression levels of non-coding RNAs in temozolomide-resistant/sensitive glioma samples, lncRNAs ARFRP1 and RUSC2 were found to regulate five target genes in the AMPK, AKT, mTOR, and TGF- $\beta$  signaling pathways. This activation or inhibition of autophagy leads to temozolomide resistance [34]. In gliomas receiving anti-PD-1/PD-L1 immunotherapy, single-cell RNA sequencing analysis of lncRNA expression profiles revealed the widespread upregulation of lncRNA NEAT1 in patients with longer survival, indicating a close correlation between NEAT1 and the benefits of glioma immunotherapy [35]. Given the crucial role of tumor-infiltrating lymphocytes in effective immunotherapy, a study analyzed sequencing data from purified immune cells, low-grade glioma cell lines, and tissues to identify 16 highly effective lncRNAs related to tumor-infiltrating immune cells. These lncRNAs were closely associated with immune features, including microsatellite instability, tumor mutation burden, and interferon-gamma, allowing for more accurate clinical monitoring and selection of potential beneficiaries of immunotherapy [36].

Currently, research on using lncRNAs as therapeutic targets for glioma treatment is still in the theoretical exploration stage. The safe and effective intervention of lncRNA expression in the human body requires further research. At the cellular level, common techniques such as RNA interference, antisense oligonucleotides, or small molecule inhibitors are used to alter lncRNA expression. While antisense oligonucleotides or small molecule inhibitors have been used for non-lncRNA targets, relevant pharmacokinetics and efficacy have preclinical data support [37,38]. Whether they are applicable to lncRNAs needs verification in comprehensive clinical trials. Additionally, as lncRNA research deepens, lncRNA carriers are continually being discovered. Exosomes can release bioactive cargo into the tumor microenvironment or transfer their contents (including lncRNAs) as a form of cell-to-cell communication. Li et al. [39] found that lncRNA TALC can be incorporated into exosomes and transferred to tumor-associated macrophages, promoting M2 polarization of microglial cells, reshaping the glioblastoma microenvironment, reducing tumor sensitivity to temozolomide chemotherapy. This suggests that the interaction mediated by TALC between glioblastoma cells and microglial cells can weaken chemotherapy efficacy, and intervention with TALC during treatment may overcome temozolomide resistance. Another study found that lncRNA PTENP1 can be packaged into exosomes derived from human umbilical cord mesenchymal stem cells and transferred to human glioma U87 cells. Through competitive binding with miR-10a-5p, it stabilizes PTEN, exerting anti-tumor capabilities [40].

#### 5. Conclusion

Gliomas, as the most common malignant tumors in the central nervous system, present a pressing clinical chal-



lenge for improving efficacy and enhancing patient prognosis. With the advancement of molecular technologies, the biological functions of lncRNAs in gliomas have garnered widespread attention. LncRNAs not only influence the onset and malignant progression of gliomas through various mechanisms but also hold promise as novel molecular markers for the diagnosis, differentiation, treatment, and prognostic assessment of gliomas. Future efforts should focus on uncovering more critical lncRNAs and their underlying mechanisms of action, aiming to elevate the diagnostic and therapeutic standards for gliomas.

### Conflict of Interests

The author has no conflicts with any step of the article preparation.

### Consent for publications

The author read and approved the final manuscript for publication.

### Ethics approval and consent to participate

No human or animals were used in the present research.

### Informed Consent

The authors declare not used any patients in this research.

### Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Authors' contributions

FT and XZ designed the study and performed the experiments, FT collected the data, XZ analyzed the data, FT and XZ prepared the manuscript. All authors read and approved the final manuscript.

### Funding

None.

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