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The role and clinical relevance of long non-coding RNAs in glioma

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ABSTRACT

Glioma represents a complex and heterogeneous disease, posing significant challenges to both clinicians and researchers. Despite notable advancements in glioma treatment, the overall survival rate for most glioma patients remains dishearteningly low. Hence, there is an urgent necessity to discover novel biomarkers and therapeutic targets specifically tailored for glioma. In recent years, long non-coding RNAs (lncRNAs) have emerged as pivotal regulators of gene expression and have garnered attention for their involvement in the development and progression of various cancers, including glioma. The dysregulation of lncRNAs plays a critical role in glioma pathogenesis and influences clinical outcomes. Consequently, there is growing interest in exploring the potential of lncRNAs as diagnostic and prognostic biomarkers, as well as therapeutic targets. By understanding the functions and dysregulation of lncRNAs in glioma, researchers aim to unlock new avenues for the development of innovative treatment strategies catered to glioma patients. The identification and thorough characterization of lncRNAs hold the promise of novel therapeutic approaches that could potentially improve patient outcomes and enhance the management of glioma, ultimately striving for better prospects and enhanced quality of life for those affected by this challenging disease. The primary objective of this paper is to comprehensively review the current state of knowledge regarding lncRNA biology and their intricate roles in glioma. It also delves into the potential of lncRNAs as valuable diagnostic and prognostic indicators and explores their feasibility as promising targets for therapeutic interventions.

1. Introduction

Glioma, the most prevalent and aggressive malignant tumor within the central nervous system (CNS), poses a significant challenge due to its high recurrence rate and mortality [1]. Globally, the number of cancer diagnoses has been on the rise, with approximately 11 million cases reported annually and an estimated increase to 16 million by 2020 [2,3]. Correspondingly, the incidence of glioma is also increasing, with around 200,000 new cases reported each year. In 2016, the World Health Organization (WHO) introduced a novel molecular diagnosis concept for CNS tumors, leading to the reclassification of various tumors, including diffuse glioma, medulloblastoma, and other embryonal tumors, such as IDH-wildtype glioblastoma. Moreover, the classification now includes diffuse midline glioma - H3 K27 M mutant, RELA fusion-positive ependymomas, WNT-activated and SHH-activated medulloblastoma, and C19MC amplified multilayered chrysanthemum embryonal tumor [4–6]. Despite advancements in multimodal treatment approaches encompassing surgical resection, radio- and chemotherapy (Fig. 1), the overall survival rate for glioma patients remains disappointingly low, especially for glioblastoma, where the median survival time is only about 14 months [7].

Like other tumors, glioma is considered a genetic disease, with the involvement of two main categories of genes: proto-oncogenes and anti-oncogenes. Among the identified oncogenes are epidermal growth factor receptor (EGFR), basic fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF) [8–15]. Additionally, tumor suppressor genes such as p53, phosphatase and tensin homolog (PTEN), retinoblastoma protein (Rb), and E2F1 have been found to play crucial roles in

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glioma development [16–21]. Uncovering novel biomarkers and therapeutic targets is crucial for gaining a better understanding of glioma and developing more effective treatments. Recent research has revealed that only a small fraction (2%) of genes in the human genome encode proteins, while most of the genome consists of non-coding genes [22]. Non-coding RNAs (ncRNAs) are categorized based on their nucleotide length into short ncRNAs and long non-coding RNAs (lncRNAs). While ncRNAs do not directly code for proteins, they exert significant regulatory functions in both transcription and translation processes. Short ncRNAs, such as microRNAs (miRNAs) and transfer RNAs (tRNAs), are typically around 200 nucleotides long. In contrast, lncRNAs, which exceed 200 nucleotides in length, play vital roles in glioma pathogenesis through epigenetic regulation, transcriptional modulation, and post-transcriptional modifications, thereby holding a unique and essential role in glioma's molecular biology [23].

The objective of this review is to explore the molecular biological mechanisms through which lncRNAs contribute to the initiation and progression of glioma. Additionally, the review aims to assess and anticipate the clinical implications of lncRNAs in glioma research.

2. Biological overview of lncRNAs

The complexity of the human gene transcriptome has revolutionized our understanding of RNA's potential, highlighting the significant role of many lncRNAs in transcription [24,25]. Presently, the Coding Project (GENCODE V26) has identified approximately 16,000 human lncRNA genes, generating over 28,000 distinct transcripts. Moreover, protein-coding genes can produce non-coding transcriptional variants, further adding to the diversity of non-coding transcripts in cells. lncRNAs are characterized by their nonprotein-coding nature, with lengths ranging from nearly 200 nucleotides to over 100 kilobases [26]. Based on their genomic locations and backgrounds, lncRNAs can be classified into five categories: sense (transcribed from the sense strand of a protein-coding gene), antisense (transcribed from the opposite mRNA), introns (transcribed from introns of protein-coding genes), intergenic (transcribed from intergenic regions), and two-way (bidirectional transcription at or near the start of sense and antisense transcription) [27].

While many identified lncRNAs are found in both the nucleus and cytoplasm [28], they were previously regarded as transcriptional noise for several decades [29]. However, recent research has demonstrated that lncRNAs are actively involved in various biological processes and may play pivotal roles in the development of diverse diseases, including cancer [30,31]. In glioma cells, lncRNAs primarily regulate gene expression through three mechanisms: epigenetic regulation, transcriptional regulation, and interaction regulation with miRNAs.

2.1. Epigenetic regulation

Upon the discovery of lncRNAs capability to regulate gene expression, researchers recognized their significant role in epigenetic gene regulation, which holds particular importance in the pathogenesis of glioma. Epigenetic mechanisms, including DNA methylation, have been identified as essential factors in glioma development. Numerous studies have highlighted the involvement of lncRNAs in the epigenetic regulation of genes that contribute to glioma pathogenesis. For instance, alterations in the expression of lncRNA- POU Class 3 Homeobox 3 (POU3F3) have been found to modulate the methylation status of POU3F3 gene [32]. Notably, homeobox transcript antisense intergenic RNA (HOTAIR) is a well-known lncRNA epigenetic gene regulator. It indirectly silences homeobox D Cluster (HOXD) genes by facilitating the recruitment of the polycomb repressive complex 2 (PRC2) to the HOXD gene cluster, thereby promoting complex trimethylation of chromatin, leading to the repression of HOXD gene expression [33–35]. LncRNA X-inactive specific transcript (XIST) has been shown to play a role in chromatin regulation by modifying DNA/RNA and histone status [36].

2.2. Regulation of transcription level

LncRNAs have demonstrated their capability to regulate gene transcription activity and modify RNA functions by interacting with transcription factors. One example is the lncRNA tumor suppressor in lung cancer-1 antisense-1 (TSLC1-AS1), which is transcribed from the antisense strand of the tumor suppressor gene TSLC1. This lncRNA functions to silence the expression of TSLC1 by targeting its mRNA. Moreover, lncRNA TSLC1-AS1 has shown a positive correlation with other tumor suppressors, including B-Raf proto-oncogene, serine/threonine kinase (BRAF), while BRAF has displayed a negative correlation with neurofibromatosis type 1 (NF1), Von Hippel-Lindau (VHL), and phosphoinositide-3-kinase regulatory subunit 1 (PIK3R1) [37].

Apart from interacting with transcription factors, lncRNAs may contribute to gliomas through their involvement in various other RNA regulatory processes, such as gene splicing, RNA editing, and even protein translation. For instance, the lncRNA highly upregulated in liver cancer (HULC) has been found to suppress the molecular eukaryotic initiation factor 4E (eIF4E), thereby regulating other proteins that inhibit angiogenesis [38].

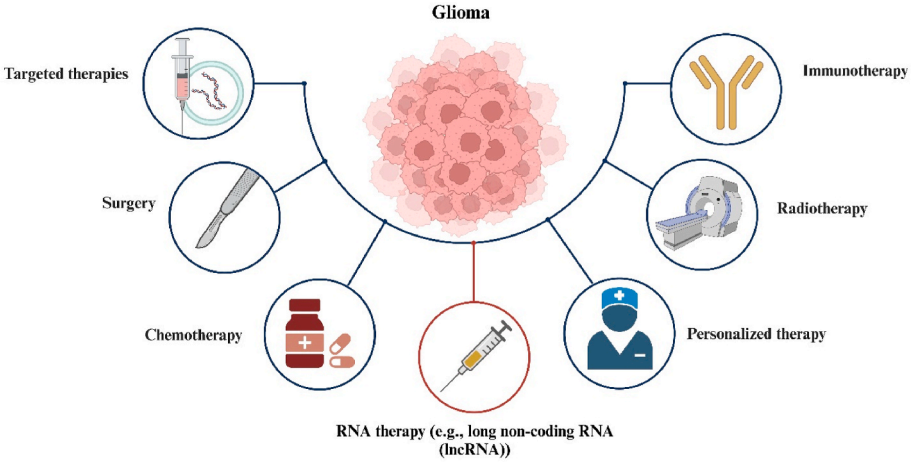

Fig. 1. Basic strategies in the treatment of gliomas. One of these is RNA interference (RNAi) between tumor targets and genes, where long non-coding RNAs (lncRNAs) show the potential.

2.3. Interaction regulation with miRNAs

Certain lncRNAs possess the ability to interact with miRNAs, effectively sequestering them and preventing their interaction with target mRNAs. For instance, lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1) plays a role in promoting glioma development by regulating miR-449b-5p [39]. This interaction is in line with the competing endogenous RNA (ceRNA) hypothesis, wherein lncRNAs can influence the expression of target genes that are under the control of miRNAs. In both glioma and normal tissues, specific lncRNAs can interact with miRNAs, acting as ceRNAs to modulate the availability of miRNAs for binding to their target mRNAs. For example, knockdown of lncRNA X-inactive specific transcript (XIST) has been shown to suppress cancer stem cells in human glioblastoma by upregulating miR-152 [36]. Another study found that overexpression of the lncRNA glioma tumor suppressor gene cancer susceptibility candidate 2 (CASC2) led to a significant reduction in miR-21 expression, and mutual inhibition between CASC2 and miR-21 was mediated by Argonaute-2 (Ago2) [40,41].

3. Molecular biological role of lncRNAs in glioma

LncRNAs play the role of tumor suppressor genes and oncogenes in the occurrence and development of tumors, thereby affecting tumor phenotype, clinicopathological manifestations and prognosis [42]. Understanding the main biological roles of lncRNAs in glioma is of great significance for fully understanding the occurrence, development, and clinical treatment of glioma (Fig. 2).

LncRNAs play a crucial role in increasing the incidence, migration, and invasion of malignant glioma. For instance, the proto-oncogene H19 is upregulated, promoting the invasion of glioma cells through the induction of miR-675 expression [43]. Additionally, POU3F3, a highly conserved functional translation regulator, is significantly elevated during glioma development [32]. Two target genes of POU3F3, namely lncRNA ASLNC22381 and ASLNC20819, mediate downstream signaling cascades and insulin-like growth factor 1 (IGF-1) activity, influencing cell proliferation and viability by binding to the IGF-1 receptor correlator. This molecular mechanism is believed to play a critical role in glioma occurrence and development [44].

As already mentioned above, some lncRNAs can interact with miRNAs, hindering miRNAs from binding to their target mRNAs in gliomagenesis. For example, Cao et al. demonstrated that overexpression of lncRNA gastric cancer high expressed transcript 1 (GHET1) led to increased survival, migration, and invasion of glioma U251 cells [45]. The overexpression of lncRNA GHET1 resulted in the upregulation of cell cycle genes (cyclin D1, cyclin-dependent kinase 4 (CDK4), cyclin-dependent kinase 6 (CDK6)) and pre-metastatic genes (matrix metallopeptidase 9 (MMP9) and vimentin). Additionally, lncRNA GHET1 overexpression activated janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) and p53/survivin signaling pathways by downregulating miR-216a, thereby promoting glioma progression. The lncRNA plasmacytoma variant translocation 1 (PVT1) functions as an oncogene and is highly expressed in various tumors, including human gliomas, gastric cancer (GC), and non-small cell lung cancer (NSCLC). When lncRNA PVT1 is downregulated, it negatively regulates miR-424, leading to the inhibition of activity, migration, and invasive capabilities of human glioma cells [46]. On the other hand,

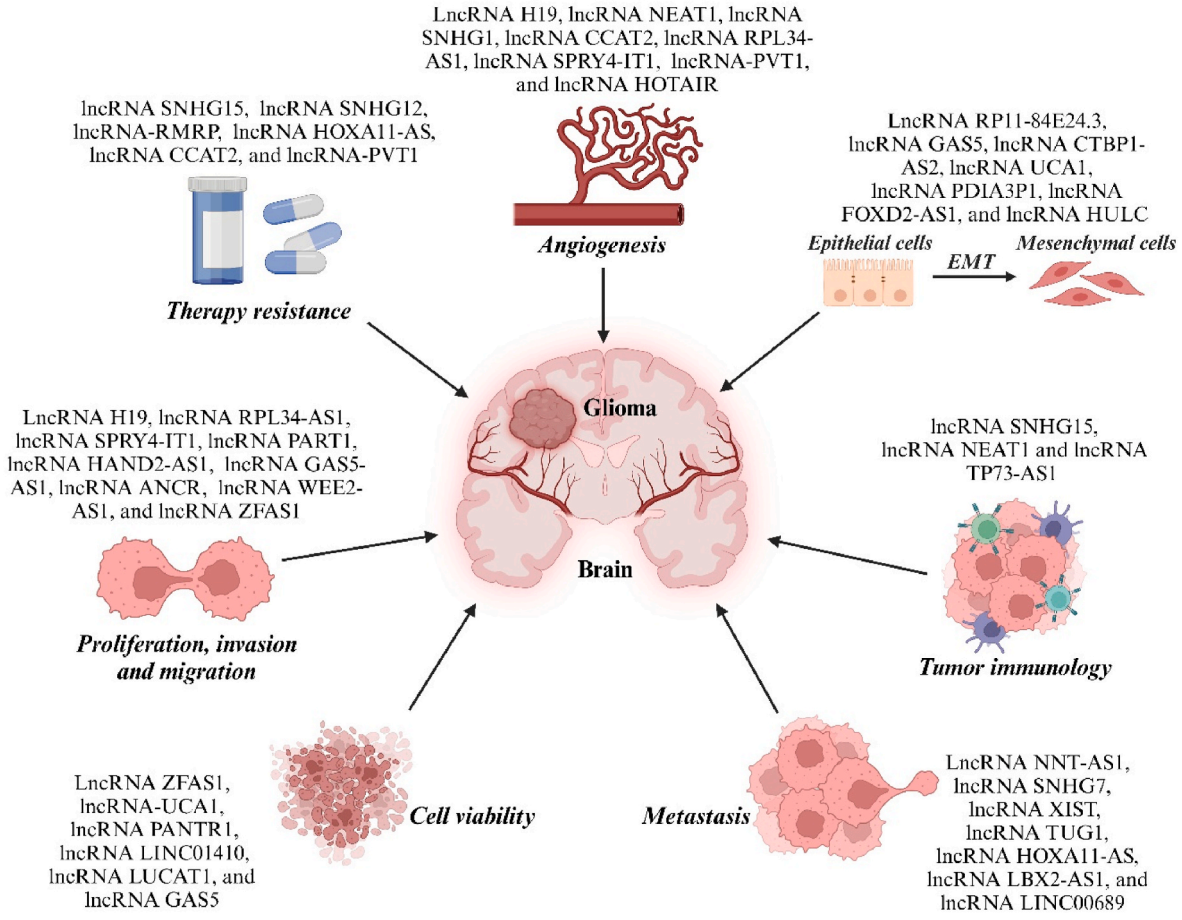

Fig. 2. An example of the most studied long non-coding RNAs (lncRNAs) and the processes of glioma tumorigenesis in which they are involved. The figure shows the role of lncRNAs in glioma by promoting epithelial-mesenchymal transition (EMT), proliferation, metastasis, chemo- and radiotherapy resistance, invasion, immune microenvironment, tumor cell viability, and angiogenesis.

increased expression of lncRNA tumor protein P73 antisense RNA 1 (TP73-AS1) is associated with poor patient survival. Downregulation of TP73-AS1 suppresses cell proliferation and invasion, and its interaction with miR-142 plays a crucial role in various diseases, including cancer, with downstream effects on RAS-related C3 botulinum toxin substrate 1 (Rac1) levels, leading to activation of multiple cellular pathways [47–50]. Furthermore, lncRNA ECONEXIN is upregulated in glioma tissues, promoting cell proliferation, and influencing the expression of the topoisomerase 2α (TOP2A) gene through interactions with miR-411–5p [51]. In contrast, certain lncRNAs have been found to slow down or inhibit the malignant progression of glioblastoma. The downregulation of lncRNA maternally expressed gene 3 (MEG3) is associated with the progression of glioblastoma, but its overexpression inhibits the growth and proliferation of glioblastoma cells and promotes cell apoptosis [52,53]. Similarly, overexpression of lncRNA CASC2 can inhibit the proliferation, migration, and invasion of glioblastoma cells and induce tumor cell apoptosis. The relationship between CASC2 and miR-21 is of particular interest, with miR-21 negatively regulating CASC2 [40]. On the other hand, the exact pathway by which lncRNA MDC1-AS induces cell proliferation through mediator of DNA damage checkpoint 1 (MDC1) remains unclear [54]. TSLC1-AS1, the antisense regulatory factor of the tumor suppressor gene TSLC1, also plays a role in inhibiting cell growth, although the exact mechanism is not fully understood [37]. Lastly, ADAMTS9-AS2, which is downregulated in glioblastoma and correlates with glioma grading, has been shown to inhibit cell migration and invasion upon overexpression [55,56]. Numerous studies are currently underway to develop a potential therapeutic approach based on interactions between lncRNAs and miRNAs, which reveal the vital role of this interaction in proliferation, angiogenesis, invasion, metastasis, cell survival and resistance to therapy in glioma (Table 1) [57–66].

Table 1
Some last studies about long non-coding RNAs (lncRNAs)-microRNAs (miRNAs) interactions in glioma.

LncRNAs	Expression of lncRNAs	miRNAs	Targets	Function	Ref.
HOXA11-AS	Up	let-7b-5p	Tpl2-MEK1/2-ERK1/2 axis	Sensitizes glioblastoma cells to ROS, drastically impairing tumor growth and prolonging survival of mouses	[57]
MIR210HG	Down	miR-377–3p	LMX1A	Suppresses glioma cell proliferation	[58]
PDCD4-AS1	Down	miR-30b-3p	METTL7B	Inhibits glioma cell proliferation, invasion, migration, and induces cell cycle arrest	[59]
GSCAR	Down	miR-6760–5p	SRSF1	Promotes tumor cell responses to TMZ	[60]
SPRY4-IT1	Down	miR-101–3p	EZH2 and VEGFA	Achieves cell proliferation and angiogenesis	[61]
LINC01018	Up	miR-942–5p	KNG1	Suppresses the migration, invasion, and proliferation of glioma cells	[62]
LINC01018	Up	miR-182–5p	ADRA2C, RAB6B, RAB27B, RAPGEF5, STEAP2, TAGLN3, and UNC13C	Inhibits cell proliferation and metastasis	[63]
TUSC7	Up	miR-10a-5p	BDNF/ERK axis	Suppresses glioma cell proliferation and migration	[64]
LINC01426	Down	miR-661	Mdm2	Inhibits proliferation and induces apoptosis	[65]
DANCR	Up	miR-33b	DLX6/ATG7 axis	Promotes intracellular autophagy and proliferation and reduce apoptosis	[66]

Abbreviations: MIR210HG, MIR210 Host Gene; PDCD4-AS1, PDCD4 Antisense RNA 1; GSCAR, Glioma stem cell associated lncRNA; SPRY4-IT1, Sprouty RTK signaling antagonist 4-intronic transcript 1; LINC01018, Long Intergenic Non-Protein Coding RNA 1018; TUSC7, Tumor Suppressor Candidate 7; LINC01426, Long Intergenic Non-Protein Coding RNA 1426; DANCR, Differentiation Antagonizing Non-Protein Coding RNA; TMZ, Temozolomide; Tpl2, Tumor progression locus 2; MEK1/2, Mitogen-activated protein kinase kinase 1/2; ERK1/2, Extracellular signal-regulated kinase 1/2; LMX1A, LIM Homeobox Transcription Factor 1 Alpha; METTL7B, Methyltransferase-like 7B; SRSF1, Serine/arginine-rich splicing factor 1; EZH2, Enhancer Of Zeste 2 Polycomb Repressive Complex 2 Subunit; VEGFA, Vascular endothelial growth factor A; KNG1, Kininogen 1; ADRA2C, Adrenoceptor Alpha 2C; RAB6B, Ras-related protein Rab-6B; RAB27B, Ras-related protein Rab-27B; RAPGEF5, Rap guanine nucleotide exchange factor 5; STEAP2, Six-transmembrane epithelial antigen of the prostate-2; TAGLN3, Transgelin 3; UNC13C, unc-13 homolog C; BDNF, Brain-derived neurotrophic factor; ERK, Extracellular signal-regulated

4. Study the clinical significance of lncRNAs in glioma

4.1. LncRNAs serve as targets for the diagnosis and treatment of gliomas

Numerous lncRNAs have been found to influence the expression of specific genes through knockout or overexpression, offering potential as molecular targets for future clinical drug therapy against gliomas. For instance, studies on Chinese glioblastoma patients revealed that overexpression of HOTAIR is negatively correlated with patient prognosis. In animal models, inhibiting HOTAIR was shown to suppress the invasion and metastasis of glioblastoma polymorphic cells [67]. Knocking out HOTAIR in glioma cells hindered their biological development, and miR-326 is believed to play a role in regulating this process [35]. Another potential therapeutic target is the tumor suppressor gene TSLC1, which influences glioma occurrence and development by modulating methylation. Inhibiting or knocking out TSLC1 can accelerate glioma cell proliferation and metastasis, whereas upregulating TSLC1 has the opposite effect, making it a promising clinical molecular target [68].

Moreover, research on lncRNAs in tissue and biofluids samples has identified 80 lncRNAs with different expression levels in tumor tissue samples compared to normal samples. Among them, lncRNA MIR210 Host Gene (miR210HG) showed potential as a diagnostic biomarker for gliomas. Its stable expression was detected in all serum samples from glioma patients, with higher levels in high-risk groups (WHO III or IV). As a glioma biomarker, miR210HG exhibited a sensitivity of 86.21% and a specificity of 72.41% [69]. Table 2 and Table 3 provides a summary of potential diagnostic and prognostic markers of lncRNAs in gliomas [67, 70–76].

4.2. LncRNAs and chemoresistance in glioma

Chemotherapy is a widely used and effective approach for treating glioblastoma, but its effectiveness is hindered by multidrug resistance

kinases; Mdm2, Mouse double minute 2 homolog; DLX6, Distal-Less Homeobox 6; ATG7, Autophagy Related 7.

Table 2
Long non-coding RNAs (lncRNAs) that hold diagnostic significance in gliomas (tumor tissue and biofluids).

LncRNAs	Expression	ROC curve	Sensitivity, %	Specificity, %	Ref.
DLX6-AS1	Up	0.736	–	–	[70]
ELF3-AS1	Up	0.8073	67.23	85.22	[71]
ASB16-AS1	Up	0.96923	–	–	[72]
NEF	Down	0.7908	–	–	[73]
ANRIL	Up	0.860	81.62	90.83	[74]
HOTAIR	Up	0.913	86.1	87.5	[75]
GSCAR	Up	0.971	–	–	[76]

Note: - , not represented; ROC curve, Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic value of lncRNAs for glioma.

(MDR) [89]. Temozolomide (TMZ) is the primary chemotherapeutic drug utilized for glioblastoma treatment due to its alkylating properties [90]. Li et al. discovered that increasing the expression of metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) in U251/TMZ and U87/TMZ cell lines enhanced the sensitivity to TMZ and resulted in reduced expression of zinc finger E-box binding homeobox 1 (ZEB1) protein [91]. The upregulation of MALAT1 was inversely associated with the expression of MDR-related proteins, cell viability, and the epithelial-mesenchymal transition (EMT) status. In in vivo experiments, overexpression of MALAT1 led to enhanced tumor resistance to TMZ.

Additionally, KIAA0495/pipeline defect assessment manual (PDAM) is commonly overexpressed in oligodendroglial tumors, and animal studies have shown that this gene induces resistance to cisplatin, suggesting its significant role in the molecular development of oligodendroglial tumors. Therefore, a molecular targeting therapy could be designed based on this mechanism to target specific points [86].

4.3. The role of lncRNAs in glioma radiotherapy

Radiation therapy is a commonly used treatment for gliomas, and its effectiveness is influenced by the sensitivity of the tumor to radiation. LncRNAs, crucial regulators of various biological processes, play significant roles in glioma development and pathogenesis. Aryankalayil et al. identified several radiation-induced lncRNAs involved in DNA damage response and immune response [92]. These include lncRNAs such as PVT1, taurine upregulated gene 1 (Tug1), tumor protein p53 pathway corepressor 1 (Trp53cor1), damage-induced (DINO), and MEG3, which are affected by radiation and are associated with the tumor suppressor p53. Gm14005 (Morrbid) and Theiler's murine encephalitis virus possible gene1 (TMEVPG1) are also regulated by radiation at different time points and doses, showing potential as blood radiation biomarkers.

Moreover, the oncogene hyaluronan-mediated motility receptor (HMMR) is highly expressed in glioblastoma and promotes tumor growth. Li et al. discovered that the HMMR antisense lncRNA, HMMR-AS1, is highly expressed in glioblastoma cell lines and stabilizes HMMR expression [93]. Deletion of HMMR-AS1 leads to reduced HMMR expression, inhibiting cell migration, invasion, and mesenchymal phenotype, both in vitro and in vivo. Furthermore, HMMR-AS1 expression reduces the radiation sensitivity of glioblastoma cells by reducing the expression of DNA repair proteins like ATM, RAD51, and polycomb group complex 1 (PRC1). Targeting HMMR-AS1 may be a potential strategy for glioblastoma treatment. LncRNAs have a dual role in glioma radiotherapy, and studying the mechanisms of radiotherapy resistance can enhance our understanding of relevant molecular pathways in tumor cells and provide effective countermeasures to improve the clinical efficacy of glioma radiotherapy.

4.4. Correlation between lncRNAs and the prognosis of glioma patients

MALAT1 expression is elevated in glioma patients compared to healthy adults, and it positively correlates with glioma grading, tumor size, and overall survival. Hence, it can serve as a molecular marker to predict the prognosis and survival of glioma patients [87]. Other potential molecular markers for prognosis include HOTAIR, HOXA11-AS, and NEAT1. HOTAIR is linked to glioma's pathological grading, molecular typing, and prognosis [33]. HOXA11-AS, a cell cycle-regulating lncRNA transcribed from the 5′ end of HOXA, can also be used as a molecular marker for glioma progression [88]. NEAT1's expression is significantly upregulated in high-grade gliomas and is associated with patient survival after chemotherapy [94]. Furthermore, lncRNA AB073614 is found to be overexpressed in high-grade gliomas compared to low-grade gliomas and normal brain tissue. Its expression is correlated with overall survival and may serve as a potential negative prognostic biomarker for glioma [95]. Conversely, RP11-838n2.4 downregulation is positively associated with TMZ resistance and poor prognosis [96]. In another study by Zhi et al., 59 differentially expressed lncRNAs were identified when comparing tumor tissue samples (WHO grades II-IV) with normal brain samples [97]. Among these, ENST00000545440 and NR_002809 were linked to the high clinical

Table 3
Long non-coding RNAs (lncRNAs) that hold prognostic significance in gliomas (tumor tissue and biofluids).

LncRNAs	Ensembl ID	Chromosome	Length (bp)	Tumor	Effect on Prognosis	Ref.
HOTAIR	ENSG00000228630	12	12.649	glioblastoma	negative	[67]
MCM3AP-AS	ENSG00000215424	21	30.174	glioblastoma	positive	[77]
PART1	ENSG00000152931	5	59.945	glioblastoma	positive	[78]
MIAT	ENSG00000225783	22	30.051	glioblastoma	positive	[78]
GAS5	ENSG00000234741	1	4983	glioblastoma	positive	[78]
RP11–838N2.4	ENSG00000266835	18	12.729	glioblastoma	positive	[79]
NR_002809	ENSG00000212694	12	8640	astrocytoma	negative	[80]
XLOC_010967	–	–	–	astrocytoma	positive	[80]
BC002811	–	–	–	astrocytoma	positive	[80]
TPT1-AS1	ENSG00000170919	13	52.069	glioma	positive	[81]
TUSC7	ENSG00000243197	3	14.347	glioma	positive	[82]
AGAP2-AS1	ENSG00000255737	12	2117	glioma	negative	[83]
LINC01198	ENSG00000231817	13	31.372	glioma	negative	[83]
SPRY4-IT1	ENSG00000281881	5	703	glioma	negative	[84]
ZEB1-AS1	ENSG00000237036	10	114.170	glioma	negative	[85]
KIAA0495	ENSG00000227372	1	11.773	glioblastoma	negative	[73,86]
MALAT1	ENSG00000251562	11	8755	glioma	negative	[76,87]
HOXA11-AS	ENSG00000240990	7	4776	glioma	negative	[77,88]

Note: - , not represented.

stage of astrocytoma. High NR_002809 expression and low BC002811 and XLOC-010967 expression were significantly associated with poor prognosis and survival in glioma patients. These lncRNA biomarkers offer accurate predictions of survival rates in low-grade glioma patients without the need for normal brain tissue, which can be difficult to obtain. Larger cohort studies with comprehensive clinical information will be conducted in the future to validate the role of lncRNA signals.

4.5. Correlation between lncRNAs and glioma angiogenesis

One of the primary characteristics of malignant tumors is the continuous generation of blood vessels, known as angiogenesis [98]. Glioblastoma, being the most vascular tumor among solid tumors, exhibits a prominent feature of ongoing vessel generation, which drives its progression. While hypoxia is a common factor promoting angiogenesis, emerging evidence suggests that non-hypoxic mechanisms can also stimulate vessel formation [99–101]. The key regulator of vessel generation under low-oxygen conditions is the vascular endothelial growth factor (VEGF), whose expression is significantly reduced in response to hypoxia. In glioblastoma cells, hypoxic conditions lead to high-level expression of hypoxia-inducible factor (HIF-1) and VEGF, which play critical roles in various processes, including anaerobic glycolysis, metabolism, vessel generation, metastasis, and epithelial-mesenchymal transition (EMT) pathways [102].

Interestingly, under normal oxygen conditions, glioma cells induce vessel generation by activating the phosphoinositide 3-kinases (PI3Ks)/Akt/mammalian target of rapamycin (mTOR) signaling pathway. A serine/arginine-rich protein kinase 1 (SRPK1), abundant in serine/arginine residues, promotes vessel generation in glioma cells under normal oxygen levels by regulating Akt phosphorylation and VEGF splicing [103]. Additionally, lncRNA POU3F3 has been found to be transported via extracellular vesicles to endothelial cells, where it triggers the formation of new blood vessels [32]. Studies have shown that high expression of lncRNA POU3F3 induces vessel generation by promoting the expression of basic fibroblast growth factor (bFGF), vascular endothelial growth factor-A (VEGF-A), and basic fibroblast growth factor receptor (bFGFR). Similarly, lncRNA highly up-regulated in liver cancer (HULC) regulates the expression of the ESM-1 gene, leading to increased expression of endothelial cell-specific molecule 1 (ESM-1), a molecular marker of vessel generation that is activated by the VEGF/-PI3K pathway [38].

4.6. LncRNAs and regulation of blood-tumor barrier in glioma

The efficacy of glioma treatment is affected by the presence of the blood-tumor barrier (BTB), which involves the tight regulation of tight junction proteins such as claudin and occludin, as well as multiprotein complexes containing zonula occludens (ZO) proteins acting as cytoplasmic scaffolds [104,105]. Inhibition of lncRNA MALAT1 expression has been found to increase BTB permeability and decrease the levels of tight junction proteins. Additionally, MALAT1 is targeted by miR-140, which further regulates BTB permeability and the expression of tight junction proteins. The expression levels of MALAT1 and miR-140 are inversely correlated. Furthermore, miR-140 targets the nuclear transcription factor Y subunit alpha (NFYA) gene, acting as a transcription factor to regulate the expression of ZO-1, occludin, and claudin-5 [106].

Another lncRNA, NEAT1, exhibits low expression levels associated with upregulated miR-181–5p, which, in turn, regulates BTB permeability and the expression of ZO-1, occludin, and claudin-5 through SRY-Box transcription factor 5 (SOX5) [107]. Downregulation of lncRNA TUG1 expression leads to increased BTB permeability and decreased expression of BTB-related proteins ZO-1, occludin, and claudin-5. LncRNA TUG1 competes with miR-144 for the expression of tight junction proteins and inhibits the expression of heat shock transcription factor 2 (HSF2), which acts as a transcription factor for tight junction proteins. This relationship has been confirmed in animal models [108]. Similarly, the downregulation of lncRNAs HOTAIR and XIST, along with the upregulation of miR-148b-3p and miR-137, results in increased BTB permeability and decreased expression of ZO-1/2 and Occludin tight junction proteins [109]. The differential expression of lncRNA MEG3 affects BTB permeability through the P-element induced wimpy testis (PIWI)-like protein 1 (PIWI1)/MEG3/miR-330/runt-related transcription factor 3 (RUNX3) axis, influencing the molecular occurrence and development of glioma cells [110]. These findings suggest that lncRNAs hold potential as gene targets for regulating the BTB and should be further explored clinically to provide new approaches for glioma treatment.

5. Conclusion

As research into lncRNAs and their roles in glioma continues to progress, the potential for transformative therapeutic strategies becomes increasingly evident. Harnessing the power of lncRNAs opens up exciting possibilities for targeted therapies that can specifically address the underlying molecular alterations driving glioma development and progression. By leveraging the knowledge gained from high-throughput genomics and transcriptomics research, scientists can identify novel lncRNA candidates with significant functional implications in glioma biology. The advent of advanced technologies, such as RNA interference, provides a powerful tool for exploring the precise functions of lncRNAs in gliomas. This revolutionary approach allows for the selective silencing or modulation of specific lncRNAs, shedding light on their impact on tumorigenesis and potentially paving the way for the development of innovative treatments tailored to individual patients.

Moreover, the integration of lncRNAs into diagnostic and prognostic models holds great promise for precision medicine in glioma patients. By identifying lncRNA signatures associated with distinct glioma subtypes or clinical outcomes, clinicians can make informed decisions regarding treatment approaches, leading to improved patient management and personalized therapeutic strategies. However, it is crucial to acknowledge that the journey towards harnessing the full potential of lncRNAs in glioma therapy is still in its early stages. More extensive research is needed to unravel the complexities of lncRNA biology in the context of glioma pathogenesis fully. Collaborative efforts across various disciplines, including computational biology, functional genomics, and bioinformatics, will be essential to decipher the intricate interactions between lncRNAs and other molecular players in gliomas. In addition to targeted therapy, lncRNAs hold the potential to revolutionize liquid biopsy approaches for glioma detection and monitoring. The stability of lncRNAs in bodily fluids, such as blood and cerebrospinal fluid, presents a valuable opportunity for non-invasive molecular diagnostics, enabling early detection and real-time monitoring of disease progression or treatment response.

Overall, the exploration of lncRNAs in gliomas represents a promising frontier in cancer research, with the potential to transform how we understand, diagnose, and treat these devastating brain tumors. As the field continues to advance, it is hoped that lncRNAs will take center stage as game-changing therapeutic targets, ushering in a new era of precision medicine for glioma patients. The convergence of cutting-edge technologies and collaborative efforts will undoubtedly drive us closer to a future where gliomas can be effectively managed and conquered, offering hope for a brighter outlook for patients and their loved ones.

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CRediT authorship contribution statement

Ilgiz Gareev: made substantial contributions to conception and design, been involved in drafting the manuscript or revising it critically

for important intellectual content, has given final approval for the version published. **Manuel de Jesus Encarnacion Ramirez:** made substantial contributions to acquisition of data. **Renat Nurmukhametov:** made substantial contributions to acquisition of data. **Denis Ivliev:** Wang made substantial contributions to analysis and interpretation of data. **Alina Shumadalova:** Wang made substantial contributions to analysis and interpretation of data. **Tatiana Ilyasova:** Wang made substantial contributions to analysis and interpretation of data. **Aferin Beilerli:** Wang made substantial contributions to analysis and interpretation of data. **Chunlei Wang:** made substantial contributions to analysis and interpretation of data, All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of competing interest

The authors declare that no conflicts of interest exist.

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