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REVIEW

LncRNA as potential biomarker and therapeutic target in glioma

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Abstract

Glioma is the most frequent type of malignant tumor in the central nervous system, accounting for about 80% of primary malignant brain tumors, usually with a poor prognosis. A number of studies have been conducted on the molecular abnormalities in glioma to further understand its pathogenesis, and it has been found that lncRNAs (long non-coding RNA) play a key role in angiogenesis, tumor growth, infiltration and metastasis of glioma. Since specific lncRNAs have an aberrant expression in brain tissue, cerebrospinal fluid as well as peripheral circulation of glioma patients, they are considered to be potential biomarkers. This review focuses on the biological characteristics of lncRNA and its value as a biomarker for glioma diagnosis and prognosis. Moreover, in view of the role of lncRNAs in glioma proliferation and chemoradiotherapy resistance, we discussed the feasibility for lncRNAs as therapeutic targets. Finally, the persisting deficiencies and future prospects of using lncRNAs as clinical biomarkers and therapeutic targets were concluded.

Keywords Long noncoding RNA · Glioma · Biomarker · Therapeutic target

Introduction

Glioma is the most common and aggressive primary tumor of central nervous system, accounting for about 80% of primary malignant brain tumors [1]. In the 2016 World Health Organization (WHO) classification, gliomas are categorized into diffuse astrocytoma, oligodendroglioma and glioblastoma based on histological characteristics [2]. Glioblastoma is the most frequent and malignant subtype, with a median survival of only 14.1 months [3]. Innovatively, molecular features are incorporated into the diagnostic criteria of glioma according to the classification, including isocitrate dehydrogenase (IDH) mutation and 1p/19q codeletion. Therefore, a better understanding of the genetic and molecular pathogenesis of glioma could contribute to more effective therapies. In recent years, emerging fields like genomics, transcriptomics and proteomics have brought an explosion of information about glioma. Accordingly, the research on glioma biomarkers is developing rapidly [4], and long non-coding RNA (lncRNA) have been paid more and more attention.

LncRNAs are a class of non-coding RNAs with longer than 200 nucleotides, involved in transcriptional, post-transcriptional and epigenetic levels of gene regulation [5, 6]. The way in which lncRNAs interacts with other biomolecules and modulates gene expression may be roughly fall into five categories (Fig. 1). (1) Signals. Under different stimulation, lncRNAs are specifically transcribed and participate in signal transduction. Some lncRNAs have regulatory function in the signaling pathways after being transcribed, while others simply act as by-products in the regulatory pathways [7]. (2) Molecular decoys. This kind of lncRNAs directly bind to DNA-binding proteins or other transcription factors, thus blocking the action of this signaling pathway and regulating downstream gene transcription[8]. In particular, lncRNAs may act as effective natural microRNA sponges that regulate gene expression by competitively

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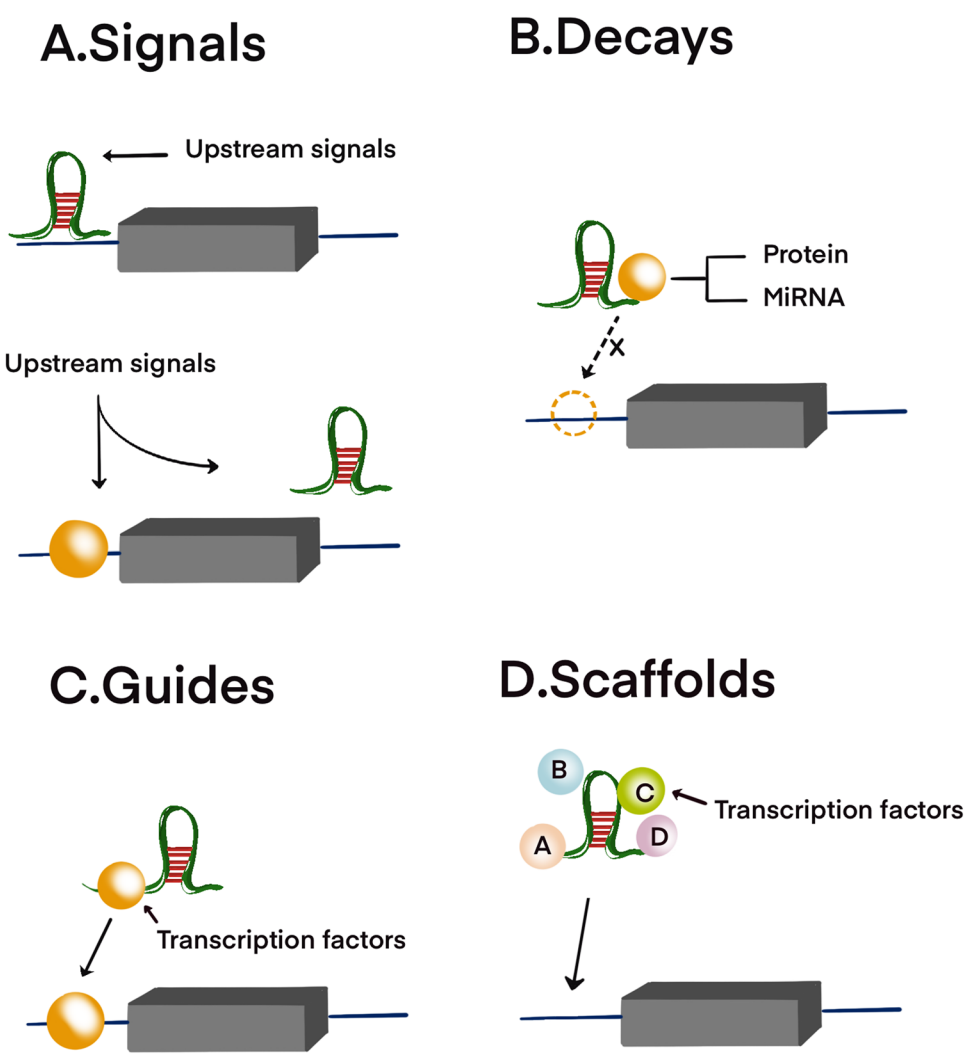

Fig. 1 Four action modes of lncRNA mechanism. Four action modes of lncRNA mechanism. **A** Signals. LncRNAs are specifically transcribed under the stimulation of upstream signals and participate in signaling pathway as signal transduction molecules. **B** Decays. LncRNAs directly bind to transcription factors or miRNAs, thereby blocking the action and signaling pathway of the molecules and regulating downstream gene transcription. **C** Guides. LncRNAs are combined with proteins and chromatin-modifying complexes, which are then localized to specific DNA sequences. **D** Scaffolds. Multiple related transcription factors bind to the same lncRNA and jointly regulate gene transcription or inhibition

binding microRNAs which known as competitive endogenous RNAs (ceRNAs) [9]. (3) Molecular guides. LncRNAs bind to those proteins and chromatin-modifying complexes, which usually identified as transcription factors, and then recruit them to specific sequences in the chromatin [10]. (4) Scaffolds. Multiple related transcription factors bind to single lncRNA molecule to initiate cross talk and integration between different signaling pathways. LncRNA scaffolds can co-regulate gene transcription temporally and spatially, which are conducive to the body and cells to produce feedback to external signals quickly [11].

Recent evidence indicates that aberrant lncRNA expression plays an important role in glioma pathogenesis [12], such as biogenesis, proliferation, angiogenesis and treatment resistance. When compared with mRNAs. the expression level of lncRNAs is higher in brain tissues than in other tissues [13], so lncRNAs may be more suitable biomarkers for glioma. In this review, we explore the potential use of lncRNAs as diagnostic and prognostic biomarkers, as well as their possible application in clinical treatment of glioma.

LncRNAs as biomarkers for glioma

lncRNA and glioma diagnosis

The current approach to diagnose glioma are mainly based on neuroimaging and biopsy. With the introduction of molecular parameters in the diagnosis of glioma [2], biopsy is of great significance for the treatment of glioma patients. However, the invasive procedure of tissue acquisition itself brings risks to the patients, and there is no way to know the subsequent mutation of tumor. Furthermore, the focal sampling of a lesion may not fully capture the intratumoral heterogeneity [14]. By contrast, liquid biopsy, referring to the replacement of surgical biopsy specimens with fluid samples such as blood and cerebrospinal fluid (CSF), may be the answer to these challenges. Liquid biopsy offers the promise of diagnosis and mutational analysis of glioma in a non-invasive manner [15], being available as an effective supplement to existing

solid biopsy. Liquid biopsies usually detect circulating tumor cells, extracellular vesicles, circulating tumor DNA (ctDNA) and circulating tumor RNA (ctRNA). As one of them, lncRNA is receiving more and more attention.

The best-known usage of lncRNA in cancer diagnosis is *Prostate cancer antigen 3 (PCA3)* in prostate cancer. *PCA3* is a specific lncRNA with an increased expression in more than 90% prostate tumors [16], which is already clinically used for prostate cancer detection and has been approved by the US Food and Drug Administration (FDA) [17]. Compared with prostate cancer, the most important characteristic of glioma is the existence of the blood–brain barrier, hinders the migration of glioma biomarkers to peripheral blood. Moreover, due to the presence of a large number of RNA enzymes in the blood, the half-life of free lncRNAs in the plasma is only 3 h and are easily decomposed. Nevertheless, lncRNAs can still exist stably in the peripheral blood attributed to the fact that exosomes serve as carriers for most lncRNAs [18]. The concentration of lncRNAs in exosomes can be even higher than that in derived cells [19]. Therefore, lncRNAs in peripheral blood and CSF could be suitable biomarkers for the diagnosis and prognosis of glioma.

At the molecular level, the lncRNA expression show considerable variation whether between glioma and normal tissue or among different glioma subtypes. Zhang et al. analyzed a cohort of gene expression data from the Gene Expression Omnibus (GEO) and found 129 lncRNAs, which showed a more than two-fold difference between gliomas and normal brain tissues [20]. Another analysis of glioma data based on The Cancer Genome Atlas (TCGA) showed that lncRNAs are extensively induced or repressed in both glioblastoma and low-grade glioma (LGG) [21]. Some differentially expressed lncRNAs were reported to have the potential function as biomarkers for glioma diagnosis (Table1).

It is worth mentioning that serum *lncRNA HOX transcript antisense RNA (HOTAIR)* can perform a diagnostic biomarker for glioblastoma, with a sensitivity of 86.1% and a specificity of 87.5%. According to the data in TCGA, glioblastoma can be classified into classical, mesenchymal, neural, and proneural subtypes based on gene expression [32]. Research has found that *HOTAIR* expression varied in different subtypes, which was markedly increased in the classical and mesenchymal subtypes compared with the neural and proneural subtypes [33]. Similarly, *HOXA11-AS* expression also showed great difference among the four glioblastoma subtypes. Specifically, the expression in the classical and mesenchymal subtypes was higher than that in the neural and proneural subtypes [34]. These results suggested that the expression level of some lncRNAs is closely related to tumor classification, and may even affect the malignant behavior of tumors.

lncRNA and glioma prognosis

Treatment for gliomas includes surgical resection, radiation and chemotherapy. The Response Assessment in Neuro-Oncology (RANO) criteria based on magnetic resonance imaging (MRI) is considered to be the gold standard for treatment efficacy evaluation [35]. The main problem in measuring treatment effectiveness is pseudoprogression [36, 37], which is caused by the response of brain tissue to chemotherapy and radiotherapy. The imaging feature of pseudoprogression is defined as increased enhancement and

Table 1 LncRNA as diagnostic biomarkers in glioma

LncRNA	Levels	Cohort	AUC	Evaluation Criteria	Reference
ANRIL, SOX9	Upregulate	142 Patients, 120 Controls	0.930	Glioma Diagnosis	[22]
DLX6-AS1	Upregulate	36 Patients	0.795	Glioma Diagnosis	[23]
ELF3-AS1	Upregulate	182 Patients	0.8073	Glioma Diagnosis	[24]
GAS8-AS1	Downregulate	51 Patients, 51 Controls	0.88	Glioblastoma Diagnosis	[25]
HOTAIR	Upregulate	43 Patients, 40 Controls	0.913	Glioblastoma Diagnosis	[26]
HOTAIR	Upregulate	123 Patients	0.716	Grade I / Grade II-IV Glioma Discrimination	[27]
LINK-A	Upregulate	52 Patients, 38 Controls	0.8543	Glioma Diagnosis	[28]
NEAT1	Upregulate	51 Patients, 51 Controls	0.90	Glioblastoma Diagnosis	[25]
PSMG3-AS1	Upregulate	62 Patients, 62 Controls	0.9010	Glioblastoma Diagnosis	[29]
PVT1	Upregulate	59 Patients, 10 Controls	0.835	Glioma Diagnosis	[30]
ZNF667-AS1	Upregulate	155 Patients	0.8541	Glioma Diagnosis	[31]
ZNF667-AS1	Upregulate	155 Patients	0.7742	Grade I-II / Grade III-IV Glioma Discrimination	[31]

AUC area under the receiver operating characteristic (ROC) curve, *ANRIL* CDKN2B antisense RNA 1, *DLX6-AS1* Distal-less homeobox 6-antisense 1, *ELF3-AS1* ETS transcription factor 3-antisense RNA 1, *GAS8-AS1* growth arrest-specific 8-antisense 1, *HOTAIR* Hox transcript antisense intergenic RNA, *LINK-A* Long intergenic non-coding RNA for kinase activation, *NEAT1* Nuclear enriched abundant transcript 1, *PSMG3-AS1* Proteasome assembly chaperone 3-antisense 1, *PVT1* Plasmacytoma variant translocation gene 1, *SOX9* SRY-box transcription factor 9, *ZNF667-AS1* Zinc finger protein 667-antisense RNA 1

edema on MRI, hard to differ from tumor progression. This condition may be due to edema and increased vascular permeability caused by treatment-related local inflammation. Differential diagnosis is necessary because a combination of chemotherapy and radiotherapy may induce pseudoprogression in about 30% patients [38, 39]. Unfortunately, There is currently no effective radiological technique to distinguish pseudoprogression from tumor recurrence [40]. Several studies showed that lncRNA biomarkers may aid in the determination of glioma recurrence. For instance, *lncRNA family with sequence similarity 225 member B (FAM225B)* upregulates in recurrent glioblastoma, and is identified to be an independent prognostic factor for recurrent glioblastoma [41].

The multi-level involvement of lncRNAs in tumor biological process, makes them potential choices as prognostic biomarkers of glioma. Multiple lncRNAs have been confirmed to be closely related to the clinicopathological data and prognosis of glioma patients. A meta-analysis including 14 eligible studies and 1415 glioma patients indicated that lncRNA expression not only significantly correlated with overall survival (OS) in glioma patients but also associated with tumor diameter, tumor grade, and Karnofsky Performance Status Scale (KPS) [42]. According to another meta-analysis study, the expression of *urothelial carcinoma-associated (UCA1)* was positively associated with tumor size, while high *MALAT1* expression could predict short OS [43]. Compared with single lncRNA, lncRNA signature displayed stronger predictive effect for prognosis (Table 2). Most of these studies were based on lncRNAs in brain tissue, but some studies investigated the relationship between lncRNAs in serum and glioma prognosis. For example, Shen et al. found the expression level of *HOTAIR* and *growth arrest-specific transcript 5 (GAS5)* in serum were associated with survival, recurrence and progression in glioblastoma [44].

LncRNAs as therapeutic targets for glioma

lncRNA and signaling pathways

As mentioned above, the expression of lncRNAs in glioma differs greatly from that in normal tissues. Studies have confirmed that lncRNAs involved in various signaling pathways and play a role in diverse biological behaviors of glioma, such as proliferation, migration and invasion. Accordingly, lncRNAs can serve as therapeutic targets through regulating these signaling pathways (Fig. 2).

LncRNAs in PI3K/Akt signaling pathway

Phosphoinositide 3-kinase (PI3K) can be activated by some growth factor receptors such as epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR) as well as the insulin-like growth factor receptor (IGFR). The abnormal activation of PI3K and its downstream signaling pathways affects the apoptosis of cells, and has been suggested to be involved in the growth, metabolism, invasion and angiogenesis of glioma [59].

lncRNA LPP antisense RNA-2 (LPP-AS2) is a lncRNA, which is found upregulated in glioblastoma. It functions as a ceRNA and decoys for *miR-7-5p* to upregulate the expression of EGFR and activate the downstream PI3K/AKT/c-MYC pathway. Besides, *LPP-AS2* is both directly and transcriptionally regulated by c-MYC, forming a positive feedback loop and promote tumorigenesis [60]. Similarly, *lncRNA small nucleolar RNA host gene 16 (SNHG16)* binds to *miR-373-3p* to regulate EGFR expression [61].

Phosphatase and tension homolog (PTEN) is a major tumor suppressor gene, which depletes levels of.

phosphoinositol 3,4, 5-triphosphate (PIP3) and downregulate PI3K [59]. Studies found *lncRNA brain cytoplasmic RNA 1 (BCYRN1)* [62], and *DiGeorge Syndrome Critical Region Gene 5 (DGCR5)* [63] function as ceRNAs, regulate PTEN expression and therefore play a tumor-suppressive role via PI3K/Akt pathway.

LncRNAs in Wnt/β-catenin signaling pathway

Wnt is a group of secreted glycoproteins. When Wnt signal is lost, cytoplasmic β-catenin acts as an intercellular adhesion protein and degraded via the ubiquitination pathway. Once Wnt signal is activated, β-catenin translocates from cytoplasm to nucleus, functions as a transcriptional coactivator and then regulates the expressions of target genes, such as c-Myc and cyclin D1 [64]. Compared to normal tissues, expression of β-catenin is significantly higher in glioma tissues, which is also associated with higher histological malignancy grade and worse prognosis [65].

LncRNAs plays various roles in Wnt/β-catenin signaling pathway. *LncRNA solute carrier family 8 member A1 antisense RNA 1 (SLC8A1-AS1)* is highly upregulated in glioma tissues. It promotes proliferation, colony formation, migration, and invasion through activating Wnt/β-catenin signaling [66]. Consistently, *lncRNA ADAM Metallopeptidase with Thrombospondin Type 1 Motif 9 Antisense RNA 1 (ADAMTS9-AS1)* deficiency attenuates glioma cell proliferation and induced glioma cell apoptosis proliferation and migration of glioma cells by suppressing Wnt/β-catenin pathway [67]. Moreover, knockdown of *lncRNA RP5-821D11.7 (lncRNA-RP5)* negatively affects glioma proliferation, colony formation, migration and reduces epithelial-mesenchymal transition (EMT) through Wnt/β-catenin cascade [68]. Conversely, *lncRNA ST7 antisense RNA 1 (ST7-AS1)* expression is reduced in glioma tissues. *ST7-AS1*

Table 2 LncRNA as prognostic biomarkers in glioma

LncRNA	Cohort	AUC	Evaluation Criteria	Reference
6-lncRNA risk signature in LGG	529 LGG samples and 531 normal brain samples	0.884	1-year Survival	[45]
		0.857	3-year Survival	
		0.813	5-year Survival	
7 EMT-related lncRNAs	633 glioblastoma samples and 28 normal brain samples	0.624	1-year Survival	[46]
		0.650	2-year Survival	
		0.657	3-year Survival	
8 immune-associated lncRNAs in LGG	529 LGG samples and 5 normal brain samples	0.81	3-year Survival	[47]
		0.738	5-year Survival	
8 mutant-derived lncRNAs signature in LGG	714 LGG samples	0.919	1-year Survival	[48]
		0.913	3-year Survival	
		0.851	5-year Survival	
9 immune-associated lncRNAs of LGG	529 LGG samples and 1152 normal brain samples	0.87	OS Prediction	[49]
10 MES-related lncRNAs	1284 glioma samples	0.762	OS Prediction	[50]
10 immune-related lncRNAs	629 glioma samples	0.866	1-year Survival	[51]
		0.734	3-year Survival	
		0.64	5-year Survival	
10-lncRNA-based Classifier	1094 glioma samples	0.892	3-year Survival	[52]
		0.836	5-year Survival	
11 immune-related lncRNAs of LGG	529 LGG samples	0.866	3-year Survival	[53]
		0.762	5-year Survival	
Ferroptosis-related lncRNAs Signature	1904 glioma samples	0.869	1-year Survival	[54]
		0.914	3-year Survival	
		0.879	5-year Survival	
Glycolysis-related lncRNA Signature	685 glioma samples	0.851	3-year Survival	[55]
		0.879	5-year Survival	
Metabolism-related lncRNA-mRNA Signature	951 glioma samples	0.806	OS Prediction	[56]
PCG-lncRNA signature	233 glioma samples	0.69	1-year Survival	[57]
		0.72	2-year Survival	
		0.81	3-year Survival	
AC064875.2	995 glioma samples	0.8961	OS Prediction	[58]
HOTAIRM1		0.8893		
LINC00908,		0.9142		
RP11-84A19.3		0.9000		

AUC area under the receiver operating characteristic (ROC) curve, *MES* mesenchymal subtype, *OS* Overall Survival, *LGG* low-grade glioma, *PCG* protein coding gene

overexpression downregulates polypyrimidine tract-binding protein 1 (PTBP1) expression, suppresses Wnt/β-catenin pathway and inhibits glioma progression, which might be a promising therapeutic target [69].

LncRNAs in Notch signaling pathway

Notch signaling consists of transmembrane receptors, transmembrane ligands and DNA binding proteins. Notch is hydrolyzed by proteases and releases Notch protein fragment such as Notch intracellular domain (NICD), and then binds to transcription factor CSL (CBF1, Suppressor of Hairless, Lag-1) to regulate downstream gene expression of both normal cells and tumor cells [70]. The most important physiological implication of the Notch pathway in glioma lies in its maintenance of glioma stem cells (GSCs). Activation of the Notch pathway can produce more NICD and then induce GSC differentiation and contribute to intra-tumor heterogeneity [71]. *Long intergenic non-protein coding RNA 1410 (LINC01410)* motivates Notch signaling pathway and accelerates the progression of glioma by sponging *miR-506-3p* and promoting NOTCH2 receptor [72]. *Prostate cancer-up-regulated long noncoding RNA 1(PlncRNA-1)* promotes cell proliferation and inhibits cell apoptosis via modulation of Notch pathway, indicating that lncRNAs play vital roles in the regulatory of Notch

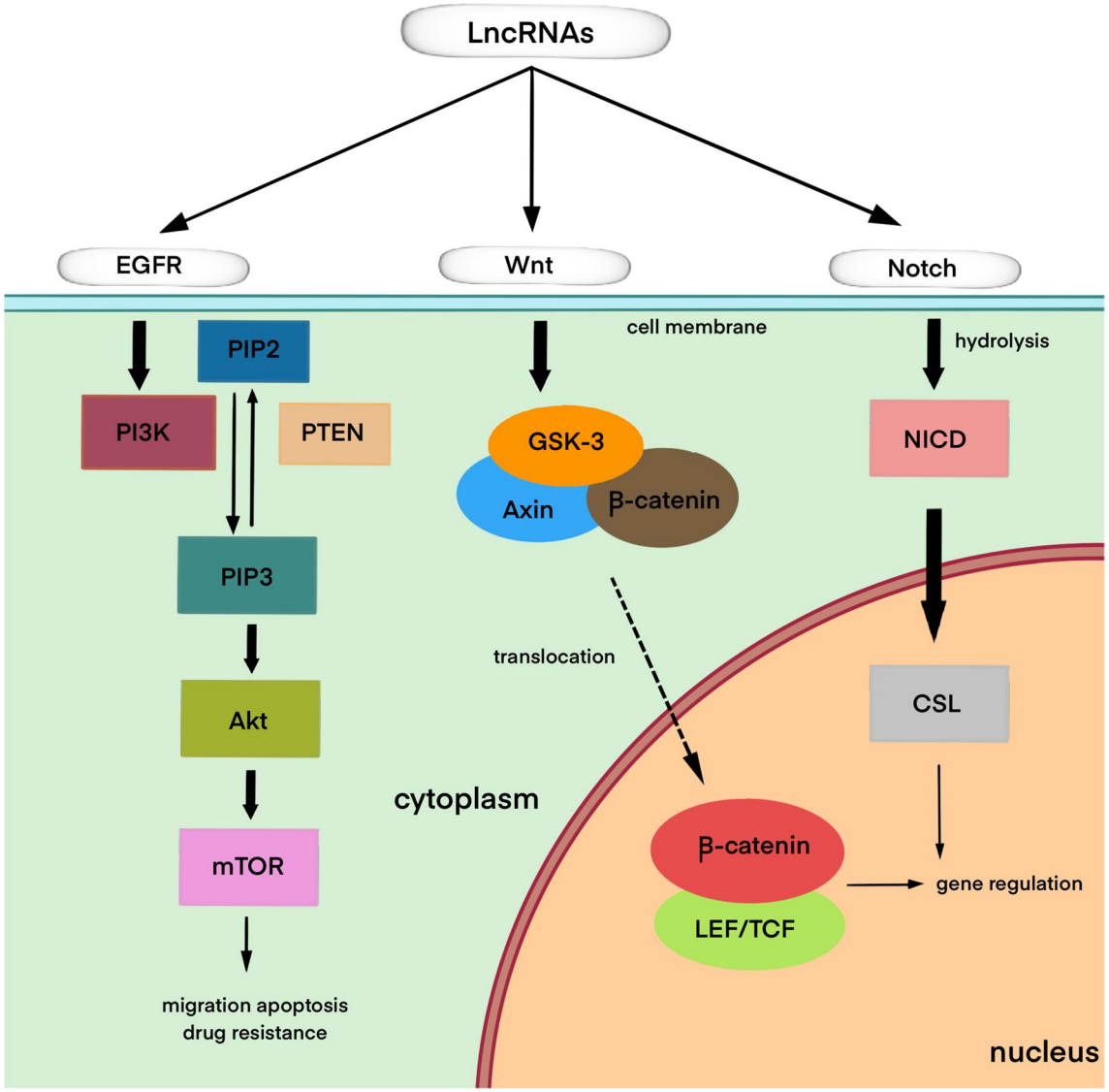

Fig. 2 LncRNAs regulating important signaling pathways in glioma. lncRNAs can not only upregulate or activate the receptors on the surface of the cell membrane but also affect key moleculesin the signaling pathways, influecing the biological behavior of glioma. *mTOR* mammalian target of rapamycin, *GSK-3* glycogen synthase kinase-3, *LEF* lymphoid enhancer factor; TCF, T-cell factor

signaling pathway and have potential of becoming therapeutic targets.

lncRNA and therapeutic resistance

In all treatments of glioma like surgical resection, radiation and chemotherapy, therapeutic resistance is an inevitable problem. The therapeutic tolerance of gliomas is closely related to GSCs. GSCs have features of pluripotency and self-renewal and are capable of producing a variety of cell types that constitute the bulk of tumor [73]. After surgical resection, GSCs remaining are considered to be the main cause of glioma recurrence [74]. Similarly, CSCs are believed to be responsible for temozolomide (TMZ) resistance and become a source of new tumor cells [75]. CD133-expressing GSCs are enriched in glioma after radiation therapy, which were found to promote radiation resistance through various pathways such as the DNA damage checkpoint [76], Notch [77] and NF-κB [78].

There are a number of lncRNAs involving the self-renewal, proliferation and differentiation of GSCs. Fritah et al. analyzed the transcriptome changes of GSCs under the standard chemotherapy by TMZ and found that TMZ induced the expression of a large number of lncRNAs. The researchers also integrated thousands of molecular associations in databases and generate a gene regulatory network. 22 lncRNAs were extracted from the network,

which involve in regulatory loops of drug response and have prognostic value in gliomas [79].

Notch signaling has received a lot of attention in promoting GSC self-renewal and suppressing GSC differentiation. It was found that Notch signaling regulates *lncRNA taurine-upregulated gene 1(TUG1)* expression in glioma, while *TUG1* helps maintain the stemness of GSCs through antagonizing *miR-145*. Additionally, *TUG1* targeting treatment induces GSC differentiation and inhibits cell proliferation in vivo [80]. Moreover, Several r lncRNAs such as *SOX2 overlapping transcript (SOX2OT)* [81], *LINK00152* [82], *TP73-AS1* [83] and *HOTAIRM1* [84] also play critical roles in the malignant behavior of GSCs and considered to be potential therapeutic targets for glioma.

TMZ, as a kind of alkylating agent, is the first-line therapy for glioma. Unlike many other chemotherapeutic drugs, TMZ can readily cross the blood–brain barrier [85]. Its metabolic products can methylate the guanine residues, The methylated guanine, which cannot be repaired by DNA mismatch repair (MMR), and leads to replication-associated double-stranded DNA breaks, G2/M cell cycle arrest, and eventl apoptosis [86].

Unfortunately, temozolomide only extends survival by two months [87], and gliomas are always resistant to TMZ. The most classic mechanism of resistance to TMZ therapy is upregulation of the enzyme methylguanine-DNA methyltransferase (MGMT), which directly repairs methylated guanine. Several lncRNAs involved in the regulation of MGMT expression. Oncogene transforming growth factor beta1 (TGF-β1) is able to upregulate *lncRNA H19* and *HOXD-AS2*, decrease *miR-198* expression, and then promote temozolomide resistance and MGMT expression. [88]. *Temozolomide-associated lncRNA in glioblastoma recurrence (lnc-TALC)* can also increase MGMT expression by mediating the acetylation of H3K9, H3K27 and H3K36 in MGMT promoter regions through the c-Met/Stat3/p300 axis [89].

Extensive studies reported alterations in the DNA mismatch repair (MMR) system also conferred resistance to temozolomide [90, 91]. One research found that *lncRNA X-inactive Specific Transcript (XIST)* coregulates MMR and MGMT pathways at the same time. *XIST* directly targets *miR-29c* to regulate one of the key MMR proteins, MSH6, and downregulates MGMT expression simultaneously [92].

Given to their extensive involvement in transcriptional and post-transcriptional regulatory, lncRNAs may also regulate drug-resistance pathways independent from MGMT. *LncRNA small nucleolar RNA host gene 12 (SNHG12)* acts as a sponge for *miR-129-5p*, leading to anti-apoptosis and G1/S transition via the MAPK/ERK pathway [93]. *CACS2* is a tumor-suppressive lncRNA that inhibits the proliferation of glioma cells and amplifies TMZ-induced repression of cell proliferation [94]. *SET-binding factor 2 antisense RNA1 (SBF2-AS1)* [95] and *MALAT1* [96] also enhances chemoresistance to temozolomide.

As stated above, the resistance of glioblastoma to radiotherapy is similarly complex. Multiple signaling pathways collectively maintain the intrinsically-radioresistant glioma stem cell populations. [97]. In other tumors, lncRNAs meditate radioresistance through various mechanisms including repair of DNA damage, cell cycle arrest, apoptosis, CSCs regulation, EMT, and autophagy [98]. Liu et al. use clustered regularly interspaced short palindromic repeat interference (CRISPRi) to screen out nine lncRNAs sensitizing cells to radiation, named as *lncRNA Glioma Radiation Sensitizers (lncGRS)* [99]. The expression of *lncRNA antisense hypoxia-inducible factor (AHIF)* in glioblastoma augments under radiation, conferring the ability of vitality, invasion and radiation resistance on tumor cells. More importantly, the ability can be transmitted between tumor cells through exosomes [100]. *Lnc-RI* acts as a ceRNA by competitively binding to *miR-193a-3p*, stabilizes RAD51 mRNA and increases spontaneous DNA double-strand break (DSBs) repair levels [101]. Furthermore, *TPTEP1* competitively interacting with *mir-106a-5p* to upregulate MaPK14 expression, thereby activating the P38 MaPK signaling pathway, and suppressing glioma stemness and radioresistance [102]. *LINK-RA1* can stabilize the level of H2B K120 monoubiquitylation (H2Bub1), thus inhibiting the activation of autophagy and contributing to the radioresistance of glioma cells [103] (Fig. 3).

Conclusions and future prospects

Since been discovered in the last century, lncRNAs were once thought to be transcriptional noise for a long time. With the report [104] of *HOTAIR*, the regulation of lncRNAs on gene expression has become a focus of research. In the field of glioma, researchers have explored many lncRNAs with diagnostic and therapeutic potential. Glioma lncRNAs can be transported by exosomes, cross the blood–brain barrier and easily detected in peripheral circulation. Moreover, lncRNAs have the features of disease specificity and cell type specificity.

Although substantial experimental evidence and bioinformatics analysis suggest that lncRNAs have great potential as biomarkers in glioma, translating basic research into clinical practice still faces many difficulties, which is also the direction for future investigation. Firstly, to date, none of the lncRNA specificity is sufficiently high to pass the requirements of the Tumor Marker Utility Grading System Levels of Evidence/NCCN for clinical application [105]. Secondly, technical standards for the extraction of lncRNA samples need to be established, and there is an absence of clinical research to obtain biological correlation, sensitivity,

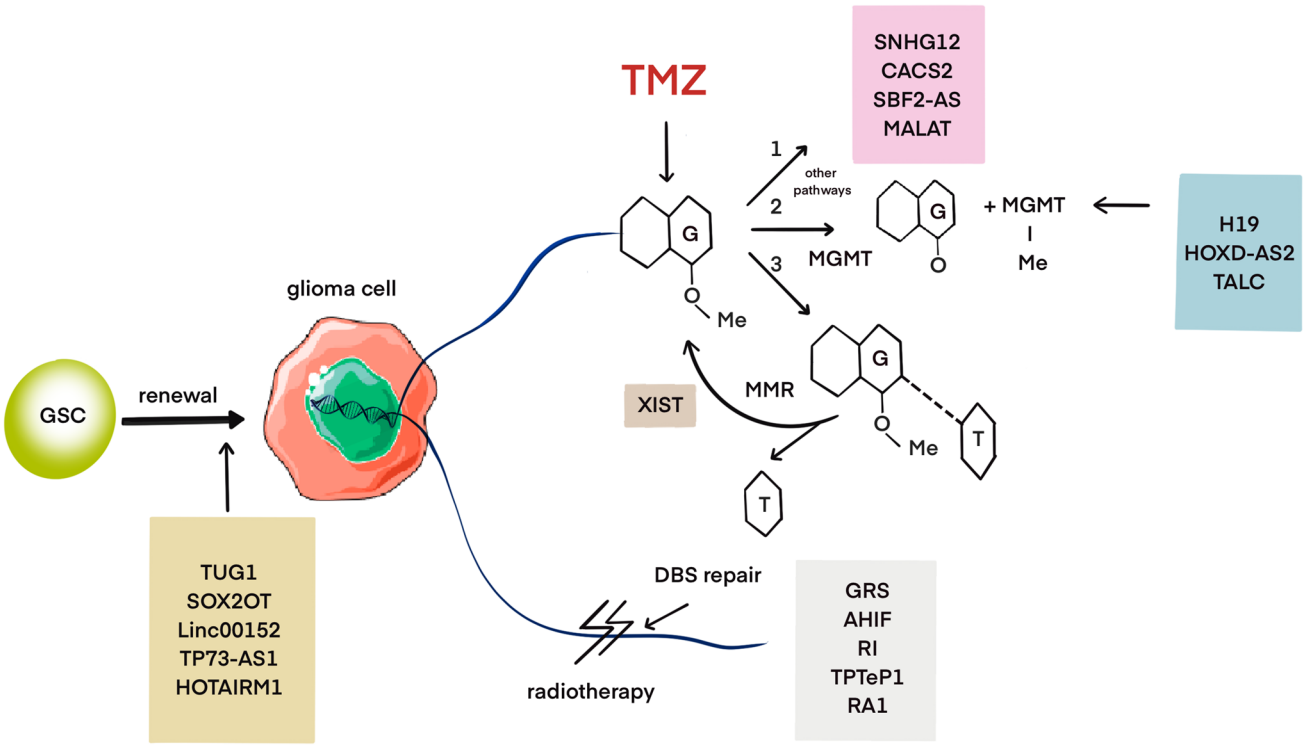

Fig. 3 Role of lncRNAs in resistance to radiotherapy and chemotherapy in glioma. Role of lncRNAs in resistance to radiotherapy and chemotherapy in glioma. LncRNAs can mediate drug resistance of glioma through regulating the production of MGMT and the MMR system respectively. In radiotherapy, lncRNAs contribute to radiotherapy resistance by participating in double-strand break (DSBs) repair. The self-renewal of GSC is regulated by multiple lncRNAs, which have substantial effects in treatment resistance

specificity, etc. Lastly, the concentration of lncRNA in peripheral blood is too low, and there lacks a rapid, economical and efficient approach for detection. Real-time polymerase chain reaction (RT-PCR) is the gold standard for RNA level measurement, but it requires expensive equipment and is highly sensitive to genomic DNA contamination [106]. Microarray-based method is not easily interfered by contamination, but does not involve the amplification of samples, resulting in low sensitivity [107]. New detection methods like nanosensors are highly anticipated. It's also required to determine whether the dysregulated lncRNA expression can be used as a predictor of tumorigenesis rather than just prognosis.

It's exciting to make therapeutic targeting of lncRNAs in the clinic a reality. Nevertheless, better understanding of the off-target effects of nucleic acid therapeutics and potential toxicity is needed. CRISPR-Cas9 is another exciting technology that can be used to target lncRNAs, however, further research is needed to fully understand its effects and application.

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

Code availability Not applicable.

Declarations

Conflict of interest The authors confirm that this article content has no conflict of interest.

Consent to participate Not applicable.

Consent for publication Not applicable.

Ethical approval Not applicable.

Humans and animal rights Not applicable.

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