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REVIEW

A critical overview of long non-coding RNA in glioma etiology 2016: an update

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Abstract With the development of whole genome and transcriptome sequencing technologies, a growing body of long non-coding RNAs (lncRNAs) has been identified and is receiving increasing attention. LncRNAs are non-protein encoding transcripts whose functions are crucial for advancing our comprehensive understanding of biological processes in human health and diseases, specifically glioma. It has been established that lncRNAs are differently expressed in the central nervous system and may play a vital role in glioma. As of June 2016, 20 lncRNAs have been identified that may play a role in glioma pathogenesis. Investigation into the role of lncRNAs in glioma may help to identify potential biomarkers which can improve the diagnosis and treatment of glioma. In this paper, we review current understanding of the function of lncRNAs in glioma initiation and progression.

Keywords Glioma · lncRNAs · Functional roles · Potential biomarkers and therapeutic targets

Introduction

Glioma is the most common malignant tumor in the central nervous system [1, 2]. Over 11 million individuals are diagnosed with cancer annually, and it is estimated that by the year 2020, this number will rise to 16 million [3, 4]. The World Health Organization (WHO) has divided gliomas into four grades. Generally speaking, grade I and II are typically considered low-grade gliomas (LGGs), while grade III and IV tumors are considered high-grade gliomas (HGGs) [5]. Genes that contribute to glioma development have been divided into two categories: oncogenes and tumor-suppressor genes. A number of oncogenes have been identified including EGFR [6–8], bFGF [9–11], and PDGF [12, 13]. Several tumor-suppressor genes have also been identified including: p53 [23], PTEN [28, 29], Rb [30], and E2F-1 [31, 32]. These functional genes are listed in Table 1. Although several genes that contribute to glioma development have been identified, very few researches are available on the relationship between them and an increasing popular novel target group: long non-coding RNAs (lncRNAs).

Mounting evidence indicates that lncRNAs are associated with glioma. Recent studies have shown that lncRNAs play a key role in a wide range of cellular physiological processes through interactions with key component proteins and that alteration of their expression and/or their primary or secondary structures could promote cell proliferation, invasion, and metastasis [33–35]. For example, MALAT1 and NEAT1 serve as molecular scaffolds for proteins within nuclear speckles (nuclear domains enriched in pre-mRNA splicing factors) and paraspeckles, respectively [33].

In this review, we explore the expression, functions, and known mechanisms of lncRNAs in gliomas and their potential for use as diagnostic and prognostic biomarkers and therapeutic targets. A summary of the review is provided in Fig. 1.

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Table 1 Oncogene and tumor suppressor gene in the process of glioma

	Gene	Features	Ref.
Oncogene	Epidermal growth factor receptor(EGFR)	Epidermal growth factor receptor of cell proliferation and signal transduction	[6–8]
	Basic fibroblast growth factor(bFGF)	Promotes cell division proliferation	[9–11]
	Platelet derived growth factor(PDGF)	Promoting mitosis factors	[12, 13]
	Vascular endothelial growth factor(VEGF)	Adjusts the development of blood vessels; increases the permeability	[14, 15]
	Insulin like growth factor-1(IGF-1)	Promotes cell differentiation	[16–18]
	Cyclin D	Relates to cell cycle	[19]
	Murine double minute 2 (MDM2)	Combines and adjusts the P53 protein	[20, 21]
	Cyclin dependent kinase 4 (CDK4)	Regulates cell from G1 phase to S phase	[22]
Tumor-suppressor gene	p53	Relates to cell apoptosis	[23]
	p16	Directly involved in cell cycle regulation	[24]
	p14ARF	Inhibiting MDM2	[25, 26]
	p73	Similar to the structure and function of p53	[27]
	PTEN/MMAC1/TEP1	Phosphatase activity of tumor-suppressor genes	[28, 29]
	Retinoblastoma tumor suppressor protein(Rb)	Makes cells stagnate in G1 phase	[30]
	E2F-1	The cell cycle-related transcription factors	[31, 32]

Non-coding RNA

Non-coding RNAs or (ncRNAs) have been the subject of recent intense investigations. As the name suggests, ncRNAs are functional RNA molecules that are not translated into proteins. These molecules regulate gene expression at the epigenetic, transcriptional, and posttranscriptional level. Among ncRNAs are familial "housekeeping" RNAs and thousands of regulatory RNAs. NcRNAs are generally divided into two classes: small ncRNA and long ncRNA (Fig. 2). Small ncRNAs (sncRNAs) are less than 200 nucleotides (nt) and include subtypes such as tRNAs, snoRNAs, microRNA (miRNAs), siRNAs, snRNAs, exRNAs, piRNAs, scaRNAs, and rRNAs. Long ncRNAs (lncRNAs) are typically over 200 nt and lack an open reading frame. LncRNAs can reach over 100 kb in length. Because most sncRNAs are well below 200 nt and most lncRNAs are much longer, 200 nt is an arbitrary but convenient boundary used to distinguish between small and long RNAs [36, 37].

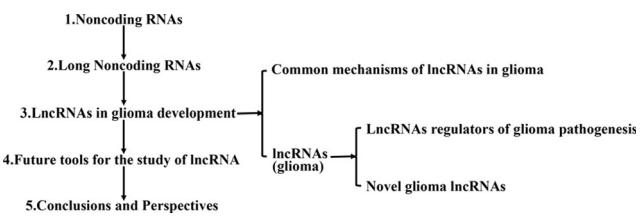

Fig. 1 Outline of the review

Long non-coding RNAs

LncRNAs, one of ncRNAs, are classified into several subtypes including antisense lncRNAs, intronic transcripts, long intergenic non-coding RNAs, promoter-associated lncRNAs, and untranslated region (UTR)-associated lncRNAs [38]. Many identified lncRNAs localize to the nucleus and cytoplasm [39]. Despite their high abundance in the cell, little is known about lncRNAs. LncRNAs are even more abundant than are protein-coding RNAs [38], but because many lncRNAs are processed into smaller non-coding RNAs, the number of lncRNAs could be significantly underestimated [40]. For the last few decades, lncRNAs were thought to be transcription "noises" or artifact [41]. However, recent studies have revealed that lncRNAs are involved in several biological processes and may even play a role in the development and progression of several diseases, including cancer [42, 43].

LncRNAs in glioma development

A growing number of studies have found an association between lncRNA expression and glioma grade and progression. For example, lncRNA microarrays revealed that lncRNAs ASLNC22381 and ASLNC20819 are differentially expressed between GBM and normal brain tissues, suggesting that ASLNC22381 and ASLNC20819 may play important roles in the recurrence and malignant progression of GBM via their target IGF-1 [44]. LncRNA

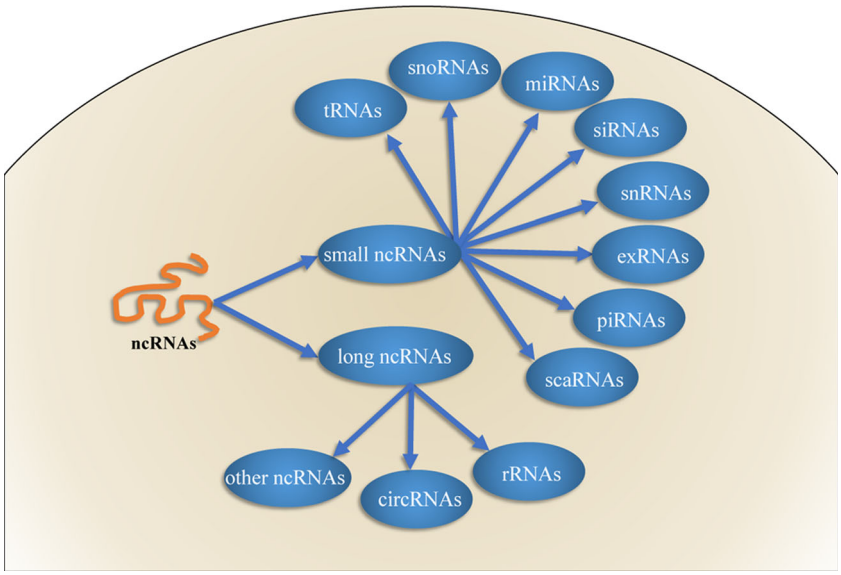

Fig. 2 Categories of ncRNAs. *tRNAs* transfer RNAs, *snoRNAs* small nucleolar RNAs, *miRNAs* microRNAs, *siRNAs* small interfering RNAs, *snRNAs* small nuclear RNA, *exRNAs* extracellular RNA, *piRNAs* piwi-interacting RNAs, *scaRNAs* small cajal body specific RNAs, *rRNAs* ribosomal RNAs, *circRNAs* circular RNAs

may influence glioma maintenance by interacting with functional genes that regulate different oncogenic activities. In addition, a recent study identified 20 lncRNAs that are differently and uniquely expressed in glioma tumor tissue (Table 2), introducing the possibility that these lncRNAs could serve as molecular targets for cancer diagnosis and treatment.

Potential mechanisms of 20 lncRNAs in glioma

Epigenetic regulatory lncRNAs

Since it was discovered that lncRNAs can regulate gene expression, researchers have recognized that lncRNAs can control gene expression at the epigenetic level. Epigenetic regulation of gene expression can have a significant impact on glioma pathogenesis. For example, one of the defining epigenetic characteristics of glioma is DNA methylation. Multiple studies have implicated lncRNA in epigenetic regulation of genes that promote glioma pathogenesis. For example, it was shown that altered linc-POU3F3 expression could regulate methylation of the POU3F3 gene [67]. According to UCSC data, extensive DNA methylation can be found at the promoter of ADAMTS9-AS2 and ADAMTS9 [78]. LncRNAs also promote expression of chromatin modifier complexes and traffic them to specific locations along the chromosomes in order to modify DNA state. The most well-known lncRNA epigenetic gene regulator is HOTAIR. HOTAIR indirectly silences HOXD genes by upregulating chromatin modifier complex PRC2 and trafficking it to the HOXD gene cluster sites. There, the complex trimethylates the chromatin (at histone H3 on lysine 27) to transcriptionally silence HOXD gene expression [45–48]. Other lncRNAs, such as Xist, can facilitate expression of chromatin modifier complexes to modify DNA/RNA and histone stat [76].

Transcriptional regulatory lncRNAs

LncRNAs have also been shown to control gene transcription activities by complexing with transcription factors to modify RNA activity. For example, lncRNA TSLC1-AS1, an antisense transcript of tumor suppressor TSLC1, complexes with TSLC1 mRNA to silence TSLC1 expression. TSLC1-AS1 also positively correlated with other tumor suppressors including NF1, VHL, and PIK3R1 and negatively correlated with the oncogene BRAF [77]. In addition to complexing with transcription factors, lncRNAs may also contribute to glioma pathogenesis by contributing to other RNA regulatory processes, including gene splicing, RNA editing, and even protein translation. For instance, lncRNA HULC silencing decreased molecule eukaryotic initiation factor 4E (eIF4E) regulating other protein to suppresses angiogenesis [68].

LncRNA-miRNA interaction

As suggested by the hypothesis of competitive endogenous RNA (ceRNA), lncRNAs can also influence the expression of target genes by controlling microRNA (miRNA) expression. In both glioma and normal tissue, some lncRNAs can interact with miRNA to prevent the miRNAs from interacting with their target mRNAs. For instance, lncRNA NEAT1 promotes glioma pathogenesis by regulating miR-449b-5p [65]. Knockdown of lncRNA Xist exerts tumor-suppressive functions in human glioblastoma stem cells by upregulating miR-152 [76]. Researchers determined that lncRNA glioma tumor suppressor CASC2 overexpression decreased the expression

Table 2 Long non-coding RNAs in glioma

LncRNA	Chromosome	Length(bp)	Dysregulation	Features	Ref.
HOTAIR	Chr12	12,649	Upregulated	Associates with invasion and metastasis	[45–48]
H19	Chr11	6308	Upregulated	A dual function of oncogene and tumor-suppressor gene	[49–57]
CRNDE	Chr16	10,327	Upregulated	A dual function, primarily oncogene	[58–61]
MALAT1	Chr11	8755	Upregulated	Promotes tumor cell proliferation and migration; functions as an oncogene	[62, 63]
NEAT1	Chr11	22,767	Upregulated	Promotes glioma pathogenesis	[64, 65]
HOXA11-AS	Chr7	4776	Upregulated	Transcribed from the HOXA transcript and promotes cell proliferation	[66]
linc-POU3F3	Chr2	47,759	Upregulated	Promotes tumor growth	[67]
HULC	Chr6	500	Upregulated	Suppresses angiogenesis by regulating ESM-1	[68]
SPRY4-1T1	Chr5	575	Upregulated	Suppresses cell proliferation, metastasis, and epithelial−mesenchymal transition	[69]
ATB	Chr14	161,837	Upregulated	Activated by TGF-β	[70]
AB073614	Chr3	1910	Upregulated	Increased AB073614 expression contributed to poor overall survival	[71]
MEG3	Chr14	81,622	Downregulated	Promotes the expression of P53 gene; functions as a tumor-suppressor gene	[72–75]
XIST	ChrX	32,103	Downregulated	Exerts tumor-suppressive functions	[76]
TSLC1-AS1	Chr11	1646	Downregulated	Correlated with NF1, VHL, and PIK3R1; functions as a tumor suppressor gene	[77]
ADAMTS9-AS2	Chr3	326,599	Downregulated	Regulated by DNMT1 and inhibits migration of glioma cells	[78]
MDC1-AS	Chr6	738	Downregulated	Attributed to upregulation of MDC1	[79]
TUG1	Chr22	9748	Downregulated	Promotes cell apoptosis	[80, 81]
ROR	Chr18	17,561	Downregulated	Inhibits the KLF4; functions as a tumor-suppressor gene	[82]
Gas5	Chr1	4983	Downregulated	Exerts tumor-suppressive functions	[83]
CASC2	Chr10	163,875	Downregulated	Inhibits cancer proliferation	[84]

of miR-21 significantly and that a reciprocal repression exists between CASC2 and miR-21 that is mediated by Argonaute2 [84] (Table 3).

In summary, many studies have identified interactions between lncRNAs and microRNAs; however, there are still many concerns on how these interactions influence glioma progression. For example, how do the cells regulate the expression of miRNAs and lncRNAs? How do lncRNAs mediate signal binding to miRNAs? With more in-depth research, more functions and mechanisms of lncRNAs will be elucidated.

Table 3 LncRNA-miRNA interaction in glioma

LncRNA	miRNA	Features	Ref.
HOTAIR	miR-326	Via modulation of miR-326	[48]
H19	miR-675	Deriving miR-675	[54, 55]
MALAT1	miR-140	Upregulating miR-140	[63]
NEAT1	miR-449b-5p/c	Regulating miR-449b-5p	[65]
ATB	miR-200a	A sink for miR-200a	[70]
XIST	miR-152	Upregulating miR-152	[76]
TUG1	miR-144	Targeting miR-144	[81]
Gas5	miR-222	Targeting miR-222	[83]
CASC2	miR-21	Via negative regulation of miR-21	[84]

LncRNA regulators of glioma pathogenesis

LncRNA HOTAIR

HOTAIR has previously been identified as a critical marker not only for tumor grade and outcome but also for molecular subtype in glioma [45, 46]. HOTAIR expression is low in low-grade gliomas (LGGs) and high in high-grade gliomas (HGGs) [46]. Glioma patients with high HOTAIR expression had a poorer prognosis for overall survival than did those with low HOTAIR expression. HOTAIR also plays an important role in glioma molecular classification and may serve as a novel therapeutic target for classical and mesenchymal glioma subtypes [47, 48].

LncRNA H19

H19 is one of the earliest discovered lncRNAs. It is an imprinted, maternally expressed gene in humans. The gene product of H19 is 6308 bp in length and lacks a clear open

reading frame [49]. At present, it has been reported that H19 might have a dual function as an oncogene and a tumor suppressor [50, 51]. The H19 gene serves as a marker of early recurrence in human bladder carcinoma [52], and H19 mRNA-like non-coding RNA promotes breast cancer cell proliferation through positive control by E2F1 [53].

H19 is also involved in the pathogenesis of a variety of central nervous system tumors. Some scholars found that H19 was closely correlated with tumor grade in three different glioma datasets [54]. Moreover, H19 interacts with miR-675 to regulate cadherin 13 (CDH13) —the direct target of miR-675—to influence glioma cell invasion. The oncogenic function of H19/miR-675 signaling may serve as a potential target for glioma therapy [54, 55]. H19 can also regulate GLI1 activity, which is a key protein astrocyte tumor progression [56]. High GLI1 expression increases proliferation index, histological grade, and recurrence of tumors in varying degrees. Additionally, H19 has an important impact on the biological behaviors of the glioma cells, such as cell cycle and apoptosis, and tolerance to chemotherapy and radiation [57].

LncRNA CRNDE

Colorectal neoplasia differentially expressed (CRNDE) is an lncRNA gene that expresses multiple splice variants and displays a tissue-specific pattern of expression [58]. A research identified a small group of 12 probe sets (10 lncRNA genes) that were closely associated with astrocytoma malignancy. Among these, CRNDE was upregulated with ascending malignancy grades, suggesting that CRNDE expression is elevated in gliomas [59]. This is particularly true for glioblastomas (high grade gliomas), astroblastomas, and astrocytomas, whereas oligodendrogliomas and oligoastrocytomas show less dramatic differences from normal tissue. Some studies revealed a positive correlation between CRNDE levels and epidermal growth factor receptor (EGFR) gene amplification, with elevated CRNDE levels associating with EGFR overexpression in high-grade oligodendrogliomas [58–60]. CRNDE has also been shown to promote glioma cell growth and invasion through the mTOR signaling pathway [61].

LncRNA MALAT1

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is highly conserved among mammals and highly expressed in the nucleus. It has been detected in a wide variety of human tumors, including glioma [62]. Ma J et al. showed that downregulation of MALAT1 suppressed the expression of glioma-associated factors Sox2 and Nestin while promoting proliferation in glioma cells and that downregulation of MALAT1 activates the ERK/MAPK signaling pathway [63]. They also determined that there was a reciprocal repression between MALAT1 and miR-140, suggesting that miR-140 mediated the effects that MALAT1 knockdown exerted [63].

LncRNA MEG3

Maternally expressed gene 3 (MEG3) is an imprinted gene highly expressed in the human pituitary. MEG3 was first discovered by Miyoshi et al. [72]. The MEG3 gene encodes a non-coding RNA of approximately 1700 nucleotides. There are 12 different MEG3 gene transcripts, generated by alternative splicing. MEG3 expression is lost in most human tumor cell lines and has been demonstrated to be markedly downregulated in glioma tissues compared with adjacent normal tissues [73]. Moreover, ectopic expression of MEG3 inhibited cell proliferation and promoted cell apoptosis in U251 and U87 MG human glioma cell lines [74]. MEG3 was also associated with p53 and this association was required for p53 activation [75].

Novel glioma lncRNAs

Oncogenesis (lncRNAs) in glioma

Several novel lncRNAs have been shown to be upregulated in glioma and to be directly involved in glioma initiation and development. These include HOXA11-AS, linc-POU3F3, HULC, SPRY4-1T1, ATB, and AB073614 [66–71]. Expression of many of these lncRNAs has also been shown to correlate with poorer outcomes in glioma patients.

HOXA11-AS

HOXA11-AS is the antisense transcript of HOX11. Expression of HOXA11-AS has been shown to closely associate with glioma grade and poor prognosis. Multivariate Cox regression analysis revealed that HOXA11-AS was an independent prognostic factor in glioblastoma multiforme patients, and its expression was correlated with the glioma molecular subtypes of The Cancer Genome Atlas (TCGA). HOXA1-AS may contribute to glioma pathogenesis by regulating cell growth. Overexpression of the HOXA11-AS transcript has been shown to promote cell proliferation in vitro, while knockdown of HOXA11-AS expression repressed cell proliferation via regulation of cell cycle progression. The growth-regulating effects of HOXA11-AS were also demonstrated in a xenograft mouse model [66].

Linc-POU3F3

Linc-POU3F3 is a highly conserved functional transcription regulator that contributes to glioblastoma progression. Linc-POU3F3 levels associate with tumor grade. Overexpression of linc-POU3F3 has also been found to

Table 4 Key database of long noncoding RNAs

Data name	URL	Features	Ref.
C-It-Loci	http://c-it-loci.uni-frankfurt.de/	Uses positionally conserved regions (loci)	[85]
Co-LncRNA	http://www.bio-bigdata.com/Co-LncRNA/	Provides analysis of lncRNAs for coexpression, GO, and KEGG	[86]
CHIPbase	http://deepbase.sysu.edu.cn/chipbase/	Uses chromatin immunoprecipitation with deep sequencing (ChIP-seq) data	[87]
NONCODE	http://www.noncode.org/	Integrates experimental data for pairwise homology and feature recognition	[88, 89]
LncRBase	http://bicresources.jcbose.ac.in/zhumur/lncrbase/	Designed to analyze the influence of different regulatory elements	[90]
LncRNAdb	http://www.lncrnadb.org/	Dedicated to eukaryotic cell lncRNA	[91, 92]
LncRNome	http://genome.igib.res.in/lncRNome/	Search for lncRNAs using multiple criteria	[93]
Starbase 2.0v	http://starbase.sysu.edu.cn/rbpLncRNA.php	Focuses on interaction analysis of pan-cancer data and interaction networks	[94, 95]
LNCipedia	http://www.lncipedia.org/	Resolve redundancies present in the HUGO nomenclature	[96, 97]
LncRNA2Function	http://mlg.hit.edu.cn/lncrna2function/	Uses lncRNA–mRNA gene pairs to annotate the function of lncRNAs	[98]
lncRNASNP	http://bioinfo.life.hust.edu.cn/lncRNASNP/	LncRNA-impacting SNPs	[99]
LncRNADisease	http://210.73.221.6/lncrnadisease	LncRNA relationship with disease	[100]
Lnc2Cancer	http://www.bio-bigdata.com/lnc2cancer/	LncRNA relationship with disease	[101]
Linc2GO	http://www.bioinfo.tsinghua.edu.cn/~liuke/Linc2GO/index.html	Focuses on the ceRNA hypothesis	[102]
miRcode	http://www.mircode.org	Focuses on the ceRNA hypothesis	[103]
DIANA-LncBase	http://www.mircoma.gr/LncBase	Focuses on the ceRNA hypothesis	[104, 105]
LncACTdb	http://www.bio-bigdata.net/LncACTdb/	Focuses on the ceRNA hypothesis	[106]
RegRNA2.0	http://regrna2.mbc.nctu.edu.tw/	Focuses on the ceRNA hypothesis	[107]

promote cell viability and proliferation in glioma cells, whereas knockdown of linc-POU3F3 showed the opposite effect. As expected, linc-POU3F3 expression negatively correlates with the mRNA level of POU3F3, suggesting that linc-POU3F3 might affect glioma development via altering expression level of POU3F3 [67].

HULC

LncRNA HULC positively correlates with grade dependency in glioma patient tissues. Its silencing suppresses angiogenesis by inhibiting glioma cell proliferation and invasion. HULC knockdown also induces anoikis and blocks the cell cycle at G1/S phase via the PI3K/Akt/mTOR signaling pathway, thus regulating the tumor-related genes involved in the above biological behavior in human glioma U87MG and U251 cells. However, these effects were reversed by ESM-1 overexpression, suggesting a mediating role of ESM-1 in the pro-angiogenesis effect of HULC [68].

SPRY4-1T1

Like many of the previously mentioned lncRNAs, SPRY4-IT1 was found to be upregulated in human glioma tissues and cell lines. Thus, knockdown of SPRY4-IT1 could inhibit glioma cell growth and migration and epithelial-mesenchymal transition (EMT) phenotype in glioma cells. Based on these findings, SPRY4-IT1 may be used as a new target for diagnosis and treatment of glioma [69].

ATB

ATB is abnormally upregulated in glioma tissues and cell lines compared with normal brain tissues. Glioma patients with high ATB expression had shorter overall survival time. Furthermore, knockdown of ATB significantly inhibits glioma malignancy, including cell proliferation, colony formation, migration, invasion in vitro, and the xenograft tumor formation in vivo, suggesting that it may support glioma cell behavior [70].

AB073614

Another potential prognostic factor is lncRNA AB073614. AB073614 expression is significantly upregulated in cancerous brain tissues compared with normal brain tissues, and it was positively correlated with tumor grade in glioma patients. Kaplan-Meier analysis

demonstrated that increased AB073614 expression contributed to poor overall survival [71].

LncRNA tumor suppressors in glioma

Here, we describe lncRNAs that are downregulated in glioma and their potential role as tumor suppressors in the disease.

TSLC1-AS1, ADAMTS9-AS2, and MDC1-AS

LncRNAs-TSLC1-AS1, ADAMTS9-AS2, and MDC1-AS are antisense lncRNAs [77–79] (Table 2). Their biological functions are related to their maternal genes. For example, recent findings suggest that MDC1-AS can upregulate coding gene MDC1 on both an mRNA and protein level, thus verifying its assumed role as the antisense of MDC1 [79].

Taurine upregulated gene 1

Taurine upregulated gene 1 (TUG1) expression was significantly inhibited in glioma and showed significant correlation with tumor grade, tumor size, and overall survival. Additional studies revealed that the dysregulation of TUG1 affected the apoptosis and cell proliferation of glioma cells. Moreover, TUG1 promoted cell apoptosis of glioma cells by activating caspase-3- and caspase-9-mediated intrinsic pathways and inhibiting Bcl-2-mediated antiapoptotic pathways, supporting a tumor suppressor function for the lncRNA in human glioma [80, 81].

LincRNA-ROR

Previous studies found that the lncRNA-ROR expression was significantly lower in glioma tissues than in adjacent normal tissues. Knockdown of lncRNA-ROR expression significantly elevated cell proliferation and enhanced CD133 expression and glioma cell sphere-forming capacity in U87 cells. Overexpression of lncRNA-ROR, on the other hand, showed the opposite effect. LncRNA-ROR expression was also found to negatively correlate with stem cell factor KLF4 [82].

Gas5

LncRNA Gas5 was reported to be a negative regulator for survival and proliferation of several cancers, including in glioma cell lines. Overexpression of Gas5 has been shown to increase the expression of tumor suppressors bmf and Plexin C1 (PLXN C1) via directly targeting and reducing the expression of miR-222 in glioma cells. Combining the expression of Gas5 with the knockdown of miR-222 resulted in small tumor volumes and long survival in nude mouse models of glioma [83].

CASC2

CASC2 is expressed at a low level in glioma tissue and glioma cell lines and has been shown to inhibit glioma cell malignancy by reducing proliferation, migration, and invasion and by promoting cell apoptosis when overexpressed. Furthermore, bioinformatics, luciferase reporter assays, and pull-down assay confirmed that miR-21 binds to CASC2 in a sequence-specific manner. Introduction of miR-21 largely abrogated CASC2-mediated inhibition of glioma cell proliferation, migration, and invasion and promotion of cell apoptosis [84].

Future tools for the study of lncRNA

A growing number of lncRNA databases are being developed to aid in the study of lncRNAs and their function in the normal and disease state. A summary of 18 databases pertaining to the biology of lncRNAs are detailed in Table 4. LncRNADisease [100] and Lnc2Cancer [101] provide information on the relationship between lncRNAs and diseases. Linc2GO, miRcode, DIANA-LncBase, LncACTdb, CHIPBase, and RegRNA2.0 facilitate the study of lncRNA-miRNA interactions [102–107]. These databases will significantly contribute to a better understanding of lncRNAs and miRNAs, which are essential members of epigenetic regulation.

Conclusions and perspectives

The unique expression and function of lncRNAs in glioma can potentially be used to as novel biomarkers and targets for cancer therapies. However, many key questions need to be investigated: (1) the relationship between lncRNAs and genes (Table 1), (2) the role of this relationship in glioma development and prognosis, and (3) the role of miRNA and lncRNA regulation in glioma. Because lncRNA research is still in its infancy, more research in this area is needed in order to fully understand the role of lncRNAs in gliomas and their potential as glioma diagnostic and clinical targets. Although the molecular mechanisms of lncRNAs have not been completely elucidated, lncRNAs could potentially revolutionize diagnosis and treatment of glioma in the near future.

Compliance with ethical standards

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Conflicts of interest None

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