Mechanisms and functions of long non-coding RNAs in glioma (Review)

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Abstract. Glioma is one of the most common primary malignancies of the adult central nervous system with malignancy grades between I-IV. Among these four grades, glioblastoma is the most malignant and aggressive type of tumor and is characterized by a poor prognosis, high recurrence rate and short median survival time after initial diagnosis. Existing treatments, such as radiotherapy, chemotherapy and surgical resection, have poor therapeutic effects; therefore, it is necessary to discover novel targeted therapies to enhance the curative effect and improve prognosis. Recently, increasing evidence has shown that long non-coding RNAs (lncRNAs) participate in the vast majority of key physiological and pathological processes. Moreover, aberrant expression levels of lncRNAs are closely associated with the occurrence and development of glioma and other malignant phenotypes. The present review summarizes new insights into the functions and mechanisms of lncRNAs at the epigenetic, transcriptional and post-transcriptional levels, describes their ability to encode functional peptides in glioma and discusses their clinical potential as new biomarkers and prospective therapeutic targets.

Contents

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1. Introduction

Glioma, the most prevalent primary malignant cancer of the central nervous system of adults (1), is characterized by difficulty of early diagnosis, a high recurrence rate and a poor prognosis, especially for advanced and high-grade types (2-4). The World Health Organization has classified gliomas into four grades based on their histopathology and clinical prognosis: Grades I and II are routinely viewed as low-grade gliomas, while grades III and IV are deemed as high-grade gliomas (5). Glioblastoma multiforme (GBM), the most malignant and aggressive type, has a median survival time of 12-14 months after initial diagnosis, longer than that of only pancreatic and lung cancer (6). As research has progressed in recent years, medical technology has constantly improved. However, due to the rapid proliferation, high invasive potential and radio/chemotherapeutic resistance of GBM, current treatments, including surgical resection, radiotherapy and chemotherapy, do not have optimal effects, and patients with GBM still have a poor prognosis (7). Therefore, it is necessary to clarify in detail the pathogenetic mechanisms of glioma to achieve improved therapeutic effects and longer survival times in patients after initial diagnosis.

Long non-coding RNAs (lncRNAs) are transcripts that contain >200 nucleotides (nt), but lack protein-coding capacity (8). The structure of lncRNAs is typically similar to that of mRNAs, which have 5'-m7G caps and 3'-poly(A) tails (9), but they are more tissue-specific than mRNAs, indicating that lncRNAs may have specific biological roles and functional mechanisms (10). Recently, an increasing number of studies

has reported that lncRNAs participate in a variety of cellular physiological processes, including stemness, tumorigenesis, proliferation, invasion, angiogenesis and drug resistance, by regulating gene expression at the epigenetic, transcriptional and post-transcriptional levels (11,12). It has been demonstrated that most lncRNAs can recruit regulatory complexes through RNA-protein interactions to affect the expression levels of nearby genes, while some lncRNAs can also function as local regulators (13). Overexpression, deficiency or mutation of lncRNA genes has been reported to be associated with numerous human diseases, such as cancer, cardiovascular diseases, metabolic diseases and inflammation (14-17). Similarly, in glioma, progressive evidence has illustrated that abnormal expression levels of lncRNAs are closely associated with the occurrence and development of glioma and other malignant phenotypes (12).

Technological advancements, especially the completion of the human genome sequencing, have allowed the discovery of an increasing number of lncRNAs with different targets and functions (18); however, the specific mechanisms and functions of lncRNAs remain unclear. The present review summarizes the functions and mechanisms of lncRNAs at the molecular level in glioma and provides some prospects for their use in the therapy and diagnosis of glioma.

2. Classification of lncRNAs

Previous human genome studies have reported that lncRNAs are transcripts produced by RNA polymerase II (RNAPol II) that contain >200 nt, but lack an open reading frame (ORF) for translation into proteins (19,20). Accumulating studies have found that lncRNAs are important players at almost every level of gene function and regulation (11,14,21). Based on their genomic location relative to neighboring protein-coding genes and their molecular characteristics, lncRNAs can be classified into five categories: Sense, antisense, bidirectional (22), intronic (23) and intergenic [long intergenic ncRNAs (lincRNAs)] (8) (Fig. 1). Through the classification of unspliced and spliced lncRNAs from mouse and human embryonic stem cells (24), most lncRNAs are either localized to enhancer regions (~20%), called enhancer RNAs (eRNAs) (25,26), or associated with upstream antisense RNAs, which are derived from loci near transcription start sites (TSSs) of coding RNAs (60-70%) (24,27). The remaining lncRNAs are derived from transcripts that overlap with coding sequences (~5%) or from more distal, unannotated regions (~5%) (27). The latter lncRNAs are usually called lincRNAs (27,28). Moreover, eRNAs and promoter upstream transcripts, which are transcribed from enhancers and promoters, respectively, are functionally similar to regulatory DNA molecules (23). For example, eRNAs can promote the interactions of enhancers and promoters to activate target genes (29). However, although a number of lncRNAs are associated with annotated genomic regions, some intervening lncRNAs come from separate transcriptional elements that do not overlap with coding sequences or enhancers; these loci have their own promoters and can function through chromatin modifications as protein-coding genes (30). The lncRNAs metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) and nuclear enriched abundant transcript 1 (NEAT1), which are well-known structural intervening lncRNAs, belong to this category (14). Considering the close association between the structures and locations of lncRNAs and their stability and functional mechanisms (14), the identification of lncRNA secondary structures and classification is anticipated to serve a key role in the research and clinical application of lncRNAs (19).

3. Differential expression of lncRNAs in glioma

Aberrant expression levels of lncRNAs can mediate cell biological processes, such as proliferation, stemness, drug resistance and angiogenesis, and accelerate the progression of glioma malignancy (31). Therefore, an increasing number of studies have focused on the analysis of lncRNA gene expression profiles in GBM to identify the detailed mechanisms. By comparing the expression levels of mRNAs and lncRNAs between GBM and normal brain tissues, Han *et al* (32) found that 654 lncRNAs were upregulated and 654 lncRNAs were downregulated in GBM. Moreover, 104 matched lncRNA-mRNA pairs were identified, and 90 lncRNAs and 81 lncRNA-mRNA pairs were found to be differentially expressed (32). Chen *et al* (33) used the significant analysis of microarray (SAM) method in a training dataset to analyze the differential expression of lncRNAs between GBM and normal brain tissues, identifying 299 lncRNAs with differential expression, of which 133 were upregulated and 166 were downregulated in GBM compared with in normal brain tissues (33). The SAM method was then used to analyze the differential expression of lncRNAs between low-grade and high-grade gliomas in the training dataset, and 47 lncRNAs were found to be differentially expressed between low-grade and high-grade gliomas (33). By comparing the expression levels of mRNAs and lncRNAs between normal brain tissues and GBM, Li *et al* (34) found that 398 lncRNAs were differentially expressed and 1,995 mRNAs were dysregulated in GBM. Among these differentially expressed lncRNAs, 98 participated in 32 gene functions and 30 molecular pathways associated with tumorigenesis, development and metastasis of glioma (34,35).

Aberrant expression levels of lncRNAs in glioma have been identified to serve a crucial role in the tumorigenesis, proliferation and invasion of glioma cells (31). Moreover, abnormal lncRNA expression profiles in clinical glioma specimens are closely associated with histological differentiation and malignancy grade, which have crucial clinical significance in early glioma diagnosis of subclassifications and in patient prognosis (36).

4. lncRNAs regulate the expression of glioma genes at the epigenetic level

In glioma, lncRNAs can regulate gene expression at the epigenetic level before transcription by recruiting chromatin modifiers such as enhancer of zeste homolog 2 (EZH2)/polycomb repressive complex 2 (PRC2) (37) and WD repeat domain 5/trithorax group proteins (38) to a specific genomic location as scaffolds to regulate the trimethylation or acetylation of histone H3 (31). Therefore, lncRNAs can participate in the regulation of glioma phenotypes, such as tumorigenic behaviors, proliferation, invasion and drug resistance (37,39).

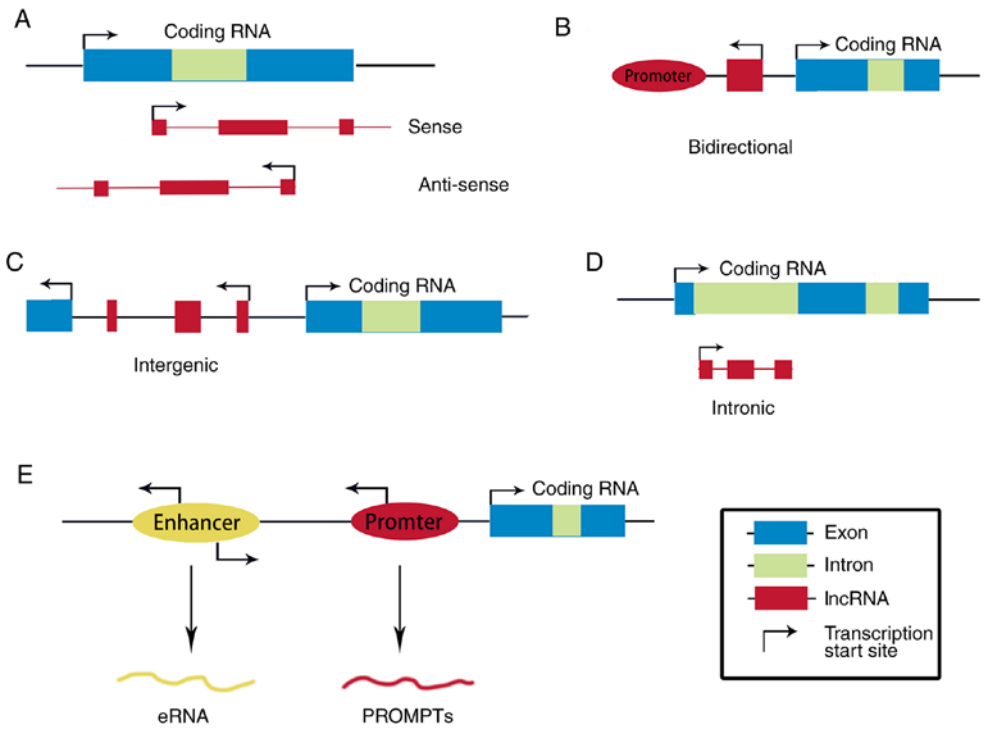

Figure 1. Classification of lncRNAs. (A) Sense lncRNAs and anti-sense lncRNAs, which are transcribed from protein-coding genes in the same or opposite direction. (B) Bidirectional lncRNAs, usually transcribed from the region between the promoter and protein-coding genes in the reverse direction. (C) Intergenic lncRNAs, transcribed from the region between two protein-coding genes. (D) Intronic lncRNAs, which are transcribed from introns. (E) eRNAs and PROMPTs, transcribed from enhancers and promoters. lncRNA, long non-coding RNA; eRNA, enhancer RNA; PROMPT, promoter upstream transcript.

The lncRNA NEAT1 is distributed mainly in the cell nucleus and has two transcripts, NEAT1_1 (3.7 kb) and NEAT1_2 (23 kb) (40). The lncRNA NEAT1 has been demonstrated to promote the occurrence of numerous types of cancer, such as colorectal cancer, breast cancer, liver cancer and glioma (41-44). A study on the detailed mechanism of lncRNAs have suggested that the lncRNA NEAT1 can be activated by the upstream EGFR signaling pathway; in addition, it can act as a scaffold to recruit and interact with the chromosome modification enzyme EZH2 (37). Moreover, the interaction between the lncRNA NEAT1 and EZH2 can promote histone H3 trimethylation in the promoter regions of Axin2, inhibitor of β-catenin and T-cell factor and glycogen synthase kinase 3β, which are negative regulatory factors of the WNT/β-catenin signaling pathway (45,46), to silence these downstream target genes, thereby activating the WNT/β-catenin signaling pathway to promote glioma tumorigenesis and proliferation (37) (Fig. 2A). Similarly, in neuroblastoma, the lncRNA neuroblastoma-associated transcript-1 (NBAT-1) functions as a scaffold to recruit and interact with EZH2 to downregulate the expression levels of NBAT-1/EZH2 target genes, such as SRY-box transcription factor 9 (SOX9), oncostatin M receptor and versican, to decrease the risk of neuroblastoma (47). The lncRNA temozolomide-associated lncRNA in GBM recurrence (TALC), with a total length of 418 nt and containing two exons, is highly expressed in temozolomide (TMZ)-resistant glioma cells (39). The lncRNA TALC, induced by AKT-mediated TMZ resistance in GBM, can control the acetylation of histone H3 on lysine 27 (H3K27) in the promoter regions of O6 methylguanine-DNA methyltransferase (MGMT) to trap microRNA (miRNA/miR)-20b-3p, activate c-MET and increase MGMT expression (39). The lncRNA ZFAT antisense RNA 1 (ZFAT-AS1), derived from an imprinted gene located on the long arm of the human genome, can bind to the relevant EZH2 subunit of the PRC2 complex to catalyze histone H3K27 methylation to inhibit transcription of the downstream gene caudal type homeobox 2 (CDX2), in turn promoting glioma cell proliferation, migration and invasion (48).

5. Transcriptional regulation by lncRNAs

Transcription is an important cellular physiological process that transfers DNA genetic material to the cytoplasm as RNA (49). Based on their patterns of interaction with proteins, lncRNAs regulate transcriptional processes via three mechanisms.

Enhancer-like activity. The transcription of most genes involves the interaction of a proximal promoter with more distant enhancer elements (50). Enhancers are usually located far from the transcriptional initiation site and interact with tissue-specific transcription factors that perform their function to modulate the differential expression of genes (51). Kim *et al* (52) found that some ncRNAs can be bidirectionally transcribed from activated enhancers, and the expression levels of these eRNAs are associated with the activity of the enhancer. Follow-up studies have shown that eRNAs may exert enhancer-like effects, such as remodeling chromatin, promoting chromatin accessibility (53) and bridging a distal enhancer with a proximal promoter (54). A class of lncRNAs similar to eRNAs is composed of activating ncRNAs (ncRNA-as), which have a transcriptional activation function; these lncRNAs are

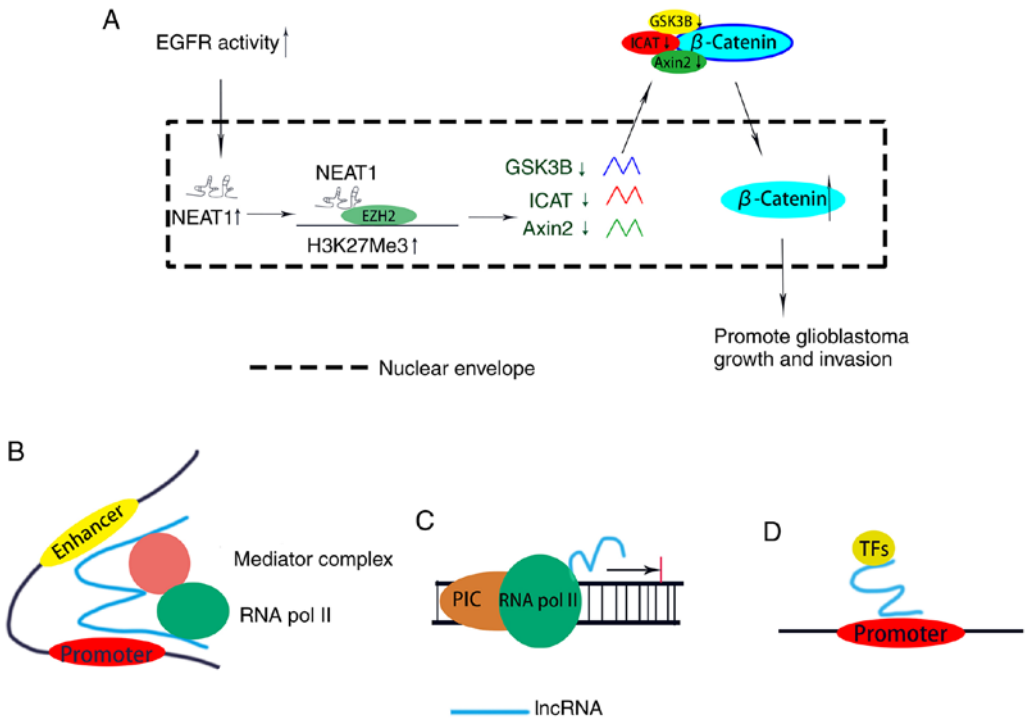

Figure 2. Functional mechanisms of lncRNAs at the epigenetic and transcriptional levels. (A) lncRNA NEAT1, driven by EGFR signaling pathway activity, can interact with the chromosome modification enzyme EZH2 to regulate the expression levels of the downstream genes to influence the progression of glioma. (B) Enhancer-like lncRNAs can bridge the enhancer and promoter elements by binding to RNAPol II and the mediator complex. (C) lncRNAs can bind to RNAPol II to prevent the formation of a PIC and dsDNA melting to interfere with transcription. (D) lncRNAs can interact with TFs in the promoter regions of genic RNA to regulate transcription. lncRNA, long non-coding RNA; RNAPol II, RNA polymerase II; PIC, preinitiation complex; TFs, transcription factors; NEAT1, nuclear enriched abundant transcript 1; H3K27Me3, trimethylation of histone 3 on lysine 27; EZH2, enhancer of zeste 2; GSK3B, glycogen synthase kinase 3β; ICAT, inhibitor of β-catenin and T-cell factor.

transcribed from independent loci, not from enhancers, and compose a class of functional molecules that can regulate the enhancing effect (25,55). Depletion of lncRNAs may lead to elevated expression levels of adjacent protein-coding genes at numerous loci in the human genome (25,55). This promotion of gene expression is mediated by RNA, and studies have shown that ncRNA-as can moderate this RNA-dependent transcriptional responsiveness in cis (25,55). These enhancer-like effects of lncRNAs may be functional mechanisms broadly used to modulate gene expression. Moreover, both eRNA and ncRNA-as can link the enhancer and promoter element of the coding gene as a scaffold for a protein complex, thereby regulating the transcription process (56) (Fig. 2B).

Binding to RNAPol II to interfere with transcription. lncRNAs can interfere with transcription by binding to RNAPol II (57). For example, the mRNA of the master regulator heat shock B2, which is transcribed from retrotransposons distributed broadly in the mouse genome (58) and is derived from the short interspersed nuclear element family (59), can induce transcriptional inhibition by interacting directly with RNAPol II and decreasing the production of a functional closed preinitiation complex (PIC) (60) (Fig. 2C).

Acting as a 'decoy' for transcription factors. Transcription factors, which are a class of DNA binding proteins, can specifically bind to specific sequences in the TSS of protein-coding genes to modulate the transcription process (61). Accumulating evidence has demonstrated that lncRNAs can interact with transcription factors at the promoter regions of coding genes to regulate transcription (62). For instance, the lncRNA PANDA, transcribed from the CDKN1A promoter, interacts with the nuclear transcription factor Y subunit α or PRCs (PRC1 and PRC2) to either accelerate or suppress senescence (63) (Fig. 2D).

In glioma, lncRNAs generally bind to transcription factors at the promoter region of target genes to regulate transcription. For instance, the lncRNA paxillin interacting protein 1-antisense RNA 1 (PAXIP1-AS1), a critical mediator of cell death, has been found to recruit the transcription factor ETS proto-oncogene 1 (ETS1) to the promoter region of kinesin family member 14 (KIF14) to upregulate its expression (64). Thus, the lncRNA PAXIP1-AS1 promotes glioma cell migration, invasion and angiogenesis via the PAXIP1-AS1/ETS1/KIF14 axis (64). Furthermore, the lncRNA growth arrest-specific transcription 5 (GAS5), a member of the 5' terminal oligopyrimidine class of genes (65), can inhibit tumorigenesis by recruiting the transcription factor TFAP2A to its promoter region under physiological conditions (66). However, an indel genetic polymorphism of the lncRNA GAS5 increases glioma susceptibility by blocking the binding of the transcription factor TFAP2A (66).

6. Post-transcriptional regulation by lncRNAs

In addition to participating in transcriptional and epigenetic regulation, lncRNAs often modulate gene expression by post-transcriptional regulation (11). A number of published

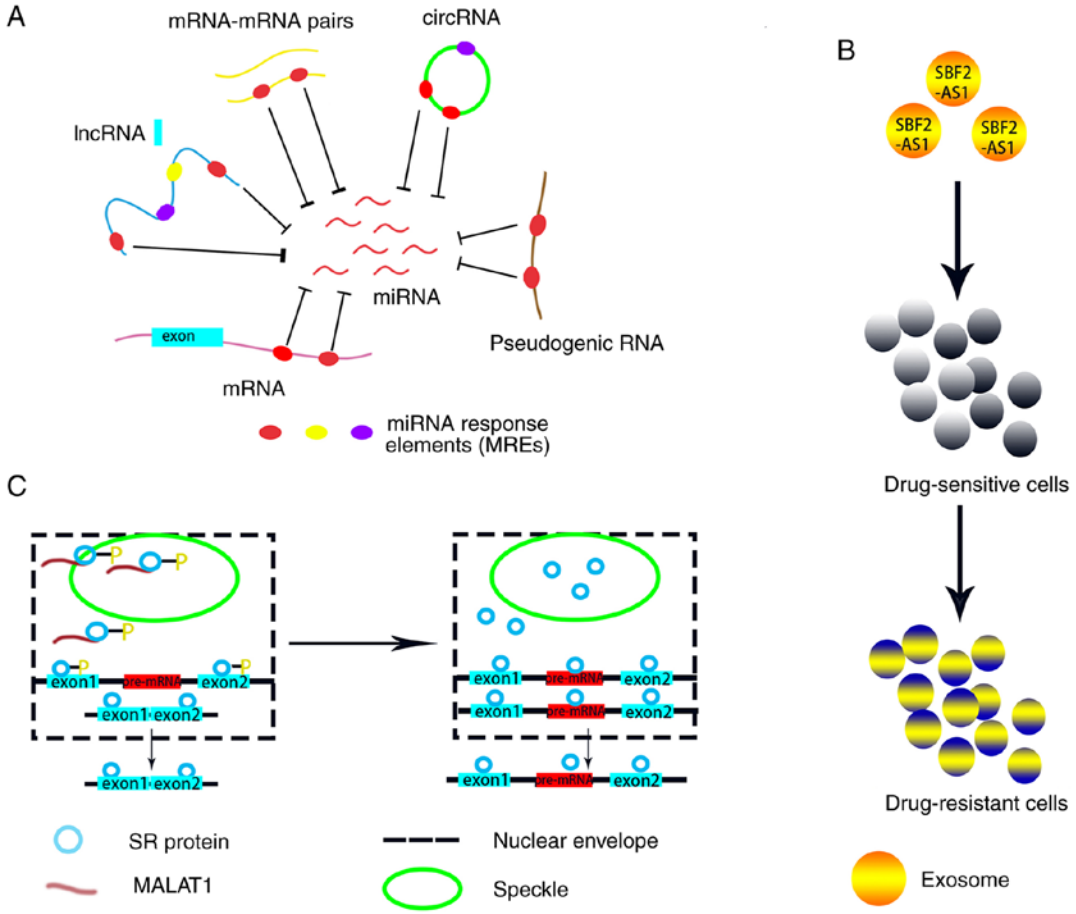

Figure 3. Functional mechanisms of lncRNAs at the post-transcriptional level. (A) ceRNA hypothesis: ceRNAs, including lncRNAs, circRNAs, pseudogenic RNAs and mRNA-mRNA pairs, contain MREs and can bind to miRNAs via the MREs to compete with mRNAs for a common miRNA pool (67). lncRNAs and circRNAs may have different specificity for MREs to sponge different miRNAs (shown as ovals of different colors). (B) lncSBF2-AS1 released from TMZ-resistant glioma cells via exosomes can endow a TMZ-resistant phenotype to neighboring TMZ-sensitive cells. (C) lncRNA MALAT1 can interact with SR protein in nuclear speckles and regulate its phosphorylation to influence the change in the alternative splicing of pre-mRNAs. lncRNA, long non-coding RNA; ceRNA, competing endogenous RNA; circRNA, circular RNA; miRNA, microRNA; MRE, miRNA response element; TMZ, temozolomide; SR, serine/arginine-rich; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; SBF2-AS1, SBF2 antisense RNA 1.

results have shown that lncRNAs can act as competing endogenous RNAs (ceRNAs) to decrease the expression levels of specific mRNAs (67), mediate alternative splicing (68) and affect mRNA stability (69) and intercellular communication (70). This section focusses on these functions to summarize the post-transcriptional mechanisms of lncRNAs in glioma.

ceRNAs. ceRNAs are a class of transcripts that can affect the expression levels of mRNAs at the post-transcriptional level by competing for binding to miRNAs (67). In 2011, a review proposed the ceRNA hypothesis, which states that mRNAs contain miRNA response elements (MREs) to which miRNAs can specifically bind, and that ncRNA species, including lncRNAs, circular RNAs (circRNAs), pseudogene RNAs and mRNA-mRNA pairs, also contain MREs and can potentially compete for a limited pool of miRNAs to regulate gene expression (71) (Fig. 3A). Subsequently, accumulating evidence has shown that lncRNAs may function as ceRNAs to sponge miRNAs and prevent them from interacting with their downstream target genes, thereby silencing these genes to affect the expression levels of the corresponding proteins (18,72-75).

The lncRNA CRNDE, encoded by the colorectal neoplasia differentially expressed gene, has been shown to be the most highly upregulated lncRNA among 129 differentially expressed lncRNAs in glioma (76). Li *et al* (75) demonstrated that the lncRNA CRNDE can act as a ceRNA to interact with miR-136-5p, thus competitively inhibiting miR-136-5p-mediated inhibition of Wnt-2 and Bcl-2. This event leads to an increase in the post-transcriptional expression levels of Wnt-2 and Bcl-2, and in the activation of the PI3K/AKT/mTOR signaling pathway (75). Moreover, Zheng *et al* (77,78) found that the lncRNA CRNDR can facilitate the proliferation, invasion and migration of glioma cells, and decrease their apoptosis through competitive inhibition of miR-384 and miR-186. Similarly, the lncRNA X-inactive specific transcript (XIST), transcribed from the X inactivation centre (79), can also act as a ceRNA of miR-126 to regulate the IRS1/PI3K/Akt signaling pathway in order to promote the viability, migration, invasion, apoptosis resistance and glucose metabolism of GBM cells (80). The lncRNAs HOTAIR and MEG3 can promote or suppress, respectively, the proliferation, invasion and migration of glioma cells by acting as ceRNAs of miR-141 and miR-19a (74).

In summary, lncRNAs act as ceRNAs through a ceRNA/miRNA/mRNA regulatory axis at the post-transcriptional level. The concept of a ceRNA/miRNA/mRNA regulatory pathway offers a novel concept for studying the underlying molecular mechanisms of glioma, as well as improves the understanding of lncRNAs and identifies a specific and sensitive profile of interactions between lncRNAs and mRNAs, which may contribute to the development of methods for both the earlier diagnosis and targeted therapy of glioma.

Alternative splicing. Alternative splicing of pre-mRNAs serves a crucial role in the regulation and diversity of gene functions, and is used by higher eukaryotes to increase the complexity of the transcriptome and proteome (81). Alternative splicing is mediated mainly by trans-acting protein factors, including serine/arginine-rich (SR)-associated proteins, heterogeneous nuclear ribonucleoproteins, the SR family of nuclear phosphoproteins (SR proteins) and small nuclear ribonucleoproteins (82). Among these factors, SR proteins, a class of proteins that can specifically bind to RNA, typically serve a key role in alternative splicing (83). Some results have shown that lncRNAs in glioma can modulate alternative splicing by controlling these trans-acting protein factors (68).

The lncRNA MALAT1 is one of the most abundant lncRNAs in normal human physiological tissues (84). Initially, lncRNA MALAT1 was known as a prognostic molecular marker of advanced lung cancer (85); however, previous studies have found an association between MALAT1 and other types of cancer, such as pancreatic cancer, prostate cancer, breast cancer, glioma and leukemia (86-90). Tripathi *et al* (91) reported that the lncRNA MALAT1 can bind to SR proteins and act as a molecular sponge to modulate the phosphorylation levels of SR proteins. By regulating the phosphorylation status of SR proteins, the lncRNA MALAT1 can indirectly mediate the intranuclear transfer of SR proteins between nuclear speckles and transcription sites to control their distribution to nuclear speckles, thereby regulating alternative splicing (91) (Fig. 3C). Furthermore, by modulating the activation levels of SR proteins, MALAT1 regulates alternative splicing, as well as controlling other post-transcriptional gene regulatory mechanisms associated with SR proteins, such as translation, nonsense-mediated decay and RNA export (92,93).

mRNA stability and protein modification. Regulation of mRNA stability and protein modification are important processes in post-transcriptional regulation. From the perspective of modulating mRNA stability, lncRNAs can either enhance mRNA stability by forming protective lncRNA-mRNA duplexes (94) or accelerate mRNA degradation by recruiting RNA-binding proteins, such as polypyrimidine tract binding protein 1 (PTBP1), to target pre-mRNAs in order to promote mRNA degradation (95). For instance, the lncRNA PTB-AS can directly bind to the PTBP1 3'-untranslated region via staphylococcal nuclease domain-containing 1 to stabilize PTBP1 mRNA, which significantly promotes the proliferation and migration of glioma cells (96). The lncRNA FMR1 autosomal homolog 1 can maintain the stability of miR-17-92a-1 cluster host gene mRNA to upregulate the downstream protein TAL bHLH transcription factor 1 in order to regulate the biological behavior of glioma cells (97).

Moreover, lncRNAs can directly interact with key proteins of signaling pathways, thus influencing their expression levels and regulating their functions (31). For example, in addition to acting as a ceRNA, the lncRNA CRNDE can also bind to the P70S6K protein, a direct downstream effector of the mTOR signaling pathway, and enhance its phosphorylation level, suggesting that CRNDE may modulate the mTOR signaling pathway by modifying this downstream protein (98).

Intercellular communication. Previous studies have shown that lncRNAs can serve important roles in intercellular communication. Barile and Vassalli (99) found that lncRNAs can be incorporated into exosomes and secreted into recipient cells passing through blood vessels, thereby controlling target signaling pathways and regulating cell phenotypes. Exosomes are the most clearly defined vesicles known to date; these vesicles have diameters ranging between 40 and 150 nm, and can be secreted by numerous different types of cells (100). Their promising diagnostic and therapeutic potential and value have received increasing attention, particularly in cancer, such as glioma, breast cancer, prostate cancer and pancreatic cancer (101-106). Accumulated evidence has demonstrated that exosomes can decelerate lncRNA degradation in the circulation and that exosomal lncRNAs can be utilized for early diagnosis of cancer (107). Moreover, a number of studies have confirmed that exosomal lncRNAs can function as intercellular carriers to transmit cellular messenger molecules, including lncRNAs (108-110).

For instance, a recent study identified a lncRNA, lncSBF2-AS1 (ENSG00000246273), that can be activated by the transcription factor ZEB1 and promote the TMZ resistance of glioma cells (110). Zhang *et al* (110) revealed that lncSBF2-AS1 released from TMZ-resistant glioma cells via exosomes can endow neighboring TMZ-sensitive cells with a TMZ-resistant phenotype; by contrast, deficiency of exosomal lncSBF2-AS1 can partially reverse the drug resistance phenotype of the parental cells, suggesting that exosomal lncSBF2-AS1 can induce TMZ resistance via intercellular communication (Fig. 3B). Similarly, the lncRNA HOTAIR can be secreted into adjacent cells via serum exosomes and modulate TMZ resistance through the miR-519a-3p/ribonucleotide reductase catalytic subunit M1 axis (111).

7. lncRNAs encode tumor-associated functional polypeptides

In addition to the aforementioned functional mechanisms, lncRNAs have been proven to have other functions in normal and cancer tissues, such as encoding functional peptides. As mass spectrometry, deep RNA sequencing and bioinformatics techniques have improved, accumulating evidence suggests that lncRNAs that were previously considered non-coding may have the ability to encode small biologically active peptides (112). lncRNAs may have small ORFs (sORFs) that can be translated into small peptides containing <100 amino acids (aa) (113). Some studies have identified that these functional peptides encoded by lncRNA sORFs can regulate

biological processes and influence tumorigenesis, proliferation, invasion and metastasis.

Wang *et al* (114) identified that the lncRNA LINC00908 can encode a 60-aa functional peptide known as ASPRS and is differentially expressed in normal and triple-negative breast cancer tissues. ASPRS is a small regulatory peptide of STAT3 and can directly bind to STAT3 and downregulate its phosphorylation to decrease VEGF expression (114). Through regulation of VEGF, the ASPRS protein can decrease angiogenesis and suppress tumorigenesis in breast cancer (114). Moreover, in glioma, the circRNA SNF2 histone linker PHD RING helicase (SHPRH) can be translated into SHPRH-146-aa; this protein protects the full-length SHPRH from degradation by ubiquitin proteases to inhibit cell proliferation and tumorigenicity (115,116). The lncRNA LINC-PINT can form the circular molecule circPINT by self-cyclization, which contains an sORF that encodes the functional peptide PINT-78-aa; this peptide can directly interact with polymerase-associated factor 1 (PAF1) to regulate the PAF1/POLII complex, inhibit transcriptional elongation of downstream oncogenes, including c-Myc, sox-2, cyclin D1 and cpeb1, and suppress the proliferation and tumorigenesis of GBM cells (117).

8. Clinical potential of lncRNAs

Based on these functional mechanisms of lncRNAs, we speculate that lncRNAs may function as novel biomarkers and therapeutic targets in glioma to improve patient prognosis. For example, lncRNAs have highly specific expression patterns in different cells and tissues; thus, they may be used to distinguish different subtypes of glioma and evaluate patient prognosis (10). A previous study revealed that using small interfering RNAs to target tumor-associated lncRNAs achieves therapeutic effects (118). Moreover, given that lncRNAs always interact with other molecules to regulate gene expression, the binding sites of these interactions may become new therapeutic targets using methods such as a peptide nuclein acid-based strategy, which can block the interaction between lncRNA HOTAIR and EZH2, subsequently decreasing HOTAIR-EZH2 complex activity (119). Based on the differential expression of lncRNAs between normal and glioma tissues, we speculate that lncRNAs may act as potential biomarkers to diagnose glioma in early stages. Considering that exosomes are extremely stable and are readily accessible in nearly all types of human biofluids, and that lncRNAs can be secreted into the circulation through packaging into exosomes (120), exosomal lncRNAs may be one of the most promising biomarkers. Since exosomes can cross the blood-brain barrier, the strategy of exploiting exosomes to deliver glioma-suppressive lncRNAs to target sites may be a promising therapeutic option for glioma (121).

9. Conclusions

Currently, accumulating evidence has proven that lncRNAs are closely associated with the malignant progression of cancer and serve important roles in the onset and progression of glioma. Therefore, the present review described the classification of lncRNAs, the functional mechanisms of lncRNAs in glioma at the epigenetic, transcriptional and post-transcriptional levels, and the ability of lncRNAs to encode functional peptides. However, numerous questions about lncRNAs remain unanswered. Considering the significance of lncRNAs in numerous physiological processes and their close association with the occurrence of diseases, research on lncRNAs is expected to grow exponentially in the future. We predict that further exploration will focus on the following aspects: Detecting the secondary structures of lncRNA interaction sites; investigating lncRNA binding patterns to seek new RNA-based targets; establishing complete ceRNA/miRNA/mRNA regulatory networks and translating these findings from theories to clinical applications; improving the identification and isolation of tumor-specific exosomal lncRNAs, further revealing the detailed mechanism underlying the intercellular transfer of exosomal lncRNAs; increasing the intracellular uptake efficiency and the relative stability of lncRNA-based drugs; accurately delivering lncRNAs to target sites to enhance the therapeutic effects of lncRNA-associated drugs; further studying the encoding function of lncRNAs; and evaluating the clinical potential of functional polypeptides. The understanding of lncRNAs remains incomplete, but the clinical potential of lncRNAs is worth exploring. The present review summarized new insights into the functional mechanisms of lncRNAs from different aspects and may be useful for future research in similar areas.

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Authors' contributions

XC was a major contributor in writing the manuscript. GG provided the major ideas and outlines, and gave the final approval of the version to be published. YL contributed to conception and design, and acquisition of data. SW contributed to acquisition of data and revision of the text. YZ contributed to acquisition of data and revision of the figures. YL and QH confirmed the authenticity of the data. QH was the corresponding author and primarily responsible for revision of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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