

# Association between long non-coding RNAs expression and pathogenesis and progression of gliomas (Review)

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**Abstract.** The incidence rate of gliomas is the highest among primary brain tumors. Although the understanding of the molecular pathology of glioma has improved during the previous two decades, effective therapies are not yet available to treat these tumors. Previous studies have indicated that long non-coding RNAs (lncRNAs) have a close association with glioma, suggesting that lncRNAs may be potential targets for the development of novel treatments for glioma. The present review summarized the latest studies on the dysregulation of lncRNAs in glioma, and discussed their potential use in the diagnosis, prognosis and therapies of glioma. The emergence of lncRNAs has revealed an additional facet to glioma oncogenesis. An improved understanding of their functions is important to advance lncRNA-based diagnosis, prognosis and therapeutic interventions of glioma.

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## 1. Introduction

Previous studies have identified that the human genome contains ~21,000 genes, and only <2% of them are protein-coding genes (1,2). In the previous decades, studies of protein-coding genes have led to improved understanding of their participation in tumorigenesis and tumor characteristics, consequentially establishing a number of protein prognostic markers and therapeutic targets in numerous types of cancer (3-6). Furthermore, larger numbers of non-coding RNAs (ncRNAs), including microRNAs (miRNAs), PIWI-interacting RNAs (piRNAs), small interfering RNAs (siRNAs), small nuclear RNAs (snRNAs), small nucleolar RNAs (snoRNAs) and lncRNAs are expressed at lower levels to fulfill regulatory functions to control complex physiopathological processes in humans (7,8). Therefore, it is important to characterize the functions of the large majority of ncRNAs.

ncRNAs may be classified by their biological functions: housekeeping ncRNAs and regulatory ncRNAs. Housekeeping ncRNAs are usually expressed constitutively, including ribosomal RNA (rRNAs), snRNAs, snoRNAs and transfer RNAs (tRNAs). Regulatory ncRNAs, according to their length, comprise short regulatory ncRNAs, including miRNAs, siRNAs and piRNAs and long regulatory ncRNAs (8-10).

lncRNAs are a class of ncRNAs with >200 nucleotides in length. It is now recognized that lncRNAs function as key regulatory players in a number of biological processes, including embryonic development, cellular differentiation and cancer (11). lncRNAs regulate their target genes at transcriptional or post-transcriptional levels. Previously, the dysregulation of lncRNAs has been closely associated with carcinogenesis and cancer progression. Compared with the protein-coding genes, lncRNAs exhibit more tissue- and time-specific expression patterns, and their expressions are more closely associated with their biological function and

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**Abbreviations:** CASC2, cancer susceptibility candidate 2; CNS, central nervous system; CRNDE, colorectal neoplasia differentially expressed; ceRNA, competing endogenous RNA; DNMT1, DNA methyltransferase 1; ERL, erlotinib; HOTAIR, HOX transcript antisense RNA; lncRNAs, long non-coding RNAs; MEG3, maternally expressed gene 3; MALAT1, metastasis associated lung adenocarcinoma transcript 1; miRNA, microRNA; ncRNA, non-coding RNA; piRNA, PIWI-interacting RNAs; rRNA, ribosomal RNA; siRNA, small interfering RNA; snRNA, small nuclear RNA; snoRNA, small nucleolar RNA; tRNA, transfer RNA; TMZ, temozolomide

**Key words:** biomarkers, function, glioma, long non-coding RNAs, therapeutic targets

tumor status, indicating enormous potential roles of lncRNAs as diagnostic and prognostic biomarkers, and as therapeutic targets in cancer (3,12-14). For example, the variant genotypes of rs7763881 in the hepatocellular carcinoma up-regulated long non-coding RNA gene may be responsible for the decreased susceptibility to hepatitis B virus-associated carcinogenesis in liver, suggesting that genetic variations in lncRNAs are associated with cancer susceptibility (15). In addition, aberrant expression of lncRNAs has been employed in cancer diagnosis and monitoring (16). H19 is upregulated in the plasma of patients with gastric cancer, and its expression enabled the differentiation of early stage gastric cancer from healthy controls (17). Subsequent studies have indicated that the level of H19 may be used to monitor and reflect the tumor dynamics in patients with gastric cancer (18). Furthermore, lncRNA expression profiles may also be used to identify clinically relevant cancer subtypes that predict tumor biological behavior, therapeutic responsiveness and clinical prognosis (19-23).

Gliomas represent 31% of all central nervous system (CNS) tumors diagnosed in the United States, and 81% of all malignant CNS tumor types with high morbidity and mortality (2006-2010) (24). Despite the treatment options of surgical resection followed by radiotherapy and chemotherapy, the overall survival times of patients with glioma, particularly patients with malignant glioma, were low. The understanding of the genetic and molecular makeup of gliomas has been advanced during the previous decades. However, there remains a lack of effective therapies for these tumors. Therefore, an improved understanding of glioma pathogenesis is urgently required. Previous studies suggest that lncRNAs have a close association with glioma, but their roles and the underlying mechanisms remain elusive. In the present review, the recent progress on lncRNAs in the development of glioma was summarized, and their possible functions and pathogenesis mechanisms in regulating biological behaviors of glioma were discussed.

## 2. Classification and characteristics of lncRNAs

lncRNAs are a large and heterogeneous group of RNAs, reflecting indirectly their enormous variety and structural complexity. Based on its genomic location to protein-coding genes, an lncRNA may be placed broadly into several categories: i) bidirectional; ii) enhancer; iii) intergenic; iv) intronic; v) sense and vi) anti-sense lncRNAs. The expression of bidirectional lncRNAs is initiated within the vicinity (>1 kb) of a neighboring coding transcript of the opposite strand. Enhancer lncRNAs are located in the enhancer regions of the promoter of a coding transcript. Intergenic lncRNAs are transcribed from regions between two coding transcripts. Intronic lncRNAs are derived entirely from within the introns of a coding transcript. Sense lncRNAs overlap with a part of or the entire sense strand of a transcript. Anti-sense lncRNAs are transcribed from the anti-sense direction to the transcripts of a gene (Fig. 1) (25,26).

The ways in which lncRNAs regulate gene expression can also be grouped into three categories, which include transcriptional and post-transcription regulation, and other mechanisms. Transcriptional regulation is where lncRNAs regulate gene expression through transcriptional interference and chromatin remodeling (27). Post-transcription regulation involves the regulation of RNA splicing by modulating the functions of

splicing factors or by directly binding to pre-mRNA sequences. lncRNAs may also block translation through interaction with translation factors or ribosomes (28-30). Other mechanisms of gene expression by lncRNAs include protein localization, telomere replication and RNA interference (31,32).

lncRNAs may also be classified into four archetypes based on the molecular mechanisms of their functions: i) signal: lncRNAs may serve as molecular signals for gene regulation; ii) decoy: lncRNAs act as 'molecular sinks' that bind and sequester protein targets but do not exert any additional functions; iii) guide: lncRNAs interact with proteins and guide the localization of ribonucleoprotein complexes to specific targets; iv) scaffold: lncRNAs function as central platforms for multiple molecules to form scaffolding complexes to regulate their functions (33).

## 3. Dysregulation of lncRNAs in gliomas

Previous studies have suggested that several lncRNAs are involved in the development of gliomas and associated with various biological behaviors of tumors, including proliferation, migration, invasion and apoptosis. The lncRNAs that are associated with gliomas are summarized in Table I. In the following section, the potential roles of several lncRNAs in the development of glioma, and their potential for clinical applications for glioma treatment, are discussed.

### *Oncogenic lncRNAs*

**H19.** lncRNA H19, a paternally imprinted gene residing close to the telomeric region of chromosome 11p15.5, was first identified as a tumor suppressor (34,35). However, subsequent studies indicated that the function of H19 was tissue and developmental stage specific. H19 is oncogenic in thyroid cancer, hepatocellular and bladder carcinoma (36-38).

In gliomas, H19 contributes to tumorigenesis and tumor progression via several mechanisms. Jiang *et al* (39) identified that the increased expression of H19 lncRNA promoted the invasion and angiogenesis of glioblastoma cells in culture and increased the rate of growth of xenograft tumors in mice. Jia *et al* (40) revealed that H19, as a molecular sponge, promoted glioma-induced angiogenesis by downregulating miRNA-29a. Chen *et al* (41) demonstrated that H19 was upregulated in recurrent gliomas compared with primary gliomas, suggesting that it was associated the development of glioma. Shi *et al* (42) identified that H19 expression associated with tumor grade, that H19 promoted glioma progression via the H19-derived miR-675/CDH13 pathway, and that the suppression of H19 expression inhibited the invasion of glioma cells. Furthermore, H19 was expressed at high levels in the embryo and was hypothesized to serve an important role in the maintenance of the stemness in hematopoietic/embryonic stem cells (42-45). A previous study has demonstrated that H19 is upregulated in CD133<sup>+</sup> glioblastoma cells compared with CD133<sup>-</sup> tumor cells. The overexpression of H19 in CD133 tumor cells promoted tumor growth, indicating the importance of H19 in promoting stemness of glioblastoma cells (46). Li *et al* (47) reported that the knockdown of H19 was able to significantly reduce the expression of stem cell markers. A high expression of H19 was considered to transform normal astrocytes into glioma stem cells, suggesting that H19 may

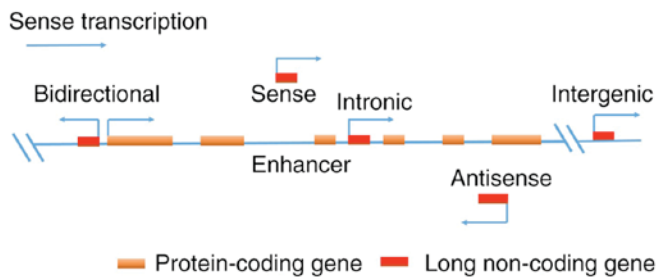


Figure 1. Long non-coding RNAs may be classified as bidirectional, enhancer, intergenic, intronic, sense or antisense based on their genomic location to neighboring protein-coding genes.

have role in contributing to the malignancy and stemness of glioblastoma cells. In addition, aberrant expression of H19 was observed in tumors from patients with temozolomide (TMZ) resistance, and TMZ-resistant cell lines (48). The silencing of H19 may regulate drug resistance genes, including multidrug resistance protein 1, multidrug resistant associated protein 1 and ATP-binding cassette subfamily G member 2; and may promote apoptosis in sensitized tumor cells in drug-resistant glioma (48). Furthermore, Jiang *et al* (39) also demonstrated that the stable overexpression of H19 in U87MG and U373MG cell lines promoted tumor formation and induced tumor cell proliferation and angiogenesis in an *in vivo* murine xenograft model.

**Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1).** MALAT1, an lncRNA with a length of 8.7 kb, is located on chromosome 11q13.1 (49). MALAT1 was originally identified as an lncRNA that is overexpressed in metastatic non-small cell lung cancer, and it is considered to be a potential therapeutic target for non-small cell lung cancer (50). The expression of MALAT1 is dynamically regulated to promote the development of various types of cancer, including ovarian, pancreatic, lung and cervical cancer (51-54). To date, MALAT1 has been reported to serve a pro-oncogenic role in the progression of gliomas. Ma *et al* (55) revealed that MALAT1 expression was associated with the malignant status of glioma and that high levels of MALAT1 expression were associated with poor prognosis in patients with glioma. Xiang *et al* (56) identified that the level of MALAT1 was increased in tumor tissues compared with normal brain tissues in glioma, and the knockdown of MALAT1 resulted in the downregulation of cyclin D1 and MYC, the inhibition of tumor growth and induction of cell apoptosis in gliomas. Vassallo *et al* (57) identified that MALAT1 was downregulated by WNT inhibitory factor 1 via the Wnt family member 5A/tumor protein 38-mitogen-activated protein kinase (MAPK)/Ca<sup>2+</sup> non-canonical WNT signaling axis, which led to an inhibition of migration and invasion of glioma cells. Ma *et al* (58) demonstrated that MALAT1 was upregulated in tumor endothelial cells compared with normal endothelial cells in glioma. Functional experiments indicated that MALAT1 acted as a competing endogenous RNA (ceRNA), which may interact with miR-140 to increase the permeability of the blood-tumor barrier. By contrast, Han *et al* (59) reported that MALAT1 served as a tumor suppressor gene in glioma. Han *et al* (59) demonstrated that the overexpression of MALAT1 caused a significant reduction

in cell proliferation and invasion by inactivating the extracellular signal-related kinase/MAPK signaling pathway *in vitro*, and in tumorigenicity in subcutaneous and intracranial human glioma xenograft models. Nucleotide sequences of MALAT1 are highly conserved throughout evolution, suggesting that it has an important cellular function (49). However, MALAT1 may not a good therapeutic candidate due to its high basal level of expression in normal brains. Therefore, additional studies are required to investigate the role of MALAT1 and its target genes in glioma.

**HOX transcript antisense RNA (HOTAIR).** HOTAIR, an lncRNA of >2,100-nucleotides in length, is transcribed from the antisense of the HOXC gene locus in chromosome 12 (60). It has been demonstrated that the overexpression of HOTAIR is associated with proliferation, invasion and chemoresistance of tumor cells. Therefore, HOTAIR is considered to be a poor prognostic factor in various types of cancer, including hepatocellular carcinoma, gastric and lung cancer (61,62). HOTAIR has been investigated as an important marker for molecular subtypes in glioma, which may serve as a potential therapeutic target for classical and mesenchymal gliomas (63). Zhou *et al* (64) reported that the expression of HOTAIR was associated with overall survival in patients with glioblastoma. Additionally, cell cycle arrest and attenuation of invasion in glioblastoma cells may be induced by HOTAIR depletion and subsequent inhibition of Nemo-like kinase/ $\beta$ -catenin axis. Similarly, Fang *et al* (65) suggested that the inhibition of HOTAIR by superparamagnetic iron oxide nanoparticles mediated siRNA transfection-induced programmed cell death 4 expression, which suppressed the proliferation, invasion and tumorigenicity of glioma stem cells. Recently, accumulating evidence has suggested that the reciprocal association between miRNA and lncRNA is actively involved in cancer pathogenesis (66). Ke *et al* (67) demonstrated that HOTAIR was significantly upregulated in glioma tissues and cell lines compared with normal controls. Furthermore, it was suggested that the knockdown of HOTAIR may lead to the inhibition of FGF1 by upregulating miR-326, which suppressed tumor growth *in vitro* and *in vivo*. Yang *et al* (68) also confirmed that the survival time of nude mice was extended in a short hairpin-HOTAIR group compared with that of control groups. A recent study indicated that HOTAIR, acting as an endogenous 'sponge', may bind with miR-141 to regulate the epigenetic modification of the miRNA-induced repression of spindle and kinetochore associated complex subunit 2 to promote the proliferation and invasion of glioma cells (69). Additionally, Wang *et al* (70) also demonstrated that miR-148b-3p may inhibit glioma cell growth by directly downregulating HOTAIR. These data suggest that the inhibition of HOTAIR activity may potentially be used as a novel therapy for the treatment of glioma.

**Colorectal neoplasia differentially expressed (CRNDE).** CRNDE, which is transcribed from the strand opposite to the adjacent iroquois homeobox 5 gene in chromosome 16, was initially regarded as a pro-oncogenic lncRNA that is upregulated in colorectal cancer (71). CRNDE serves a vital role in the development of numerous organs including breast, skin, and bronchial epithelium. Notably, an increased expression

Table I. Glioma-associated lncRNAs.

Type of lncRNA	Name of lncRNA	Expression in glioma tissues	Prognosis	Biological function	Targeted genes and pathways	(Refs.)
Oncogenic	AB073614	Up	Poor	Promotes proliferation and invasion	Unknown	(97)
Oncogenic	CRNDE	Up	-	Promotes growth and invasion	mTOR pathway; miR-384/PIWIL4/STAT3 Axis	(75,76)
Oncogenic	H19	Up	-	Promotes invasion, angiogenesis and recurrence	miRNA-29a, miR-675	(40,41,42)
Oncogenic	HOTAIR	Up	Poor	Promotes invasion and growth	NLK/ $\beta$ -catenin axis, miR-326	(64,67)
Oncogenic	HULC	Up	-	Promotes angiogenesis	PI3K/Akt/mTOR pathway	(98)
Oncogenic	MALAT1	Up	Poor	Promotes proliferation and inhibits apoptosis	Regulation of CCND1 and MYC	(56)
Oncogenic	NEAT1	Up	Poor	Promotes proliferation, invasion and migration	miR-449b-5p/c-Met axis	(99,100)
Oncogenic	POU3F3	Up	-	Promotes proliferation	Unknown	(101)
Oncogenic	SPRY4-IT1	Up	-	Promotes growth and migration	Induces EMT	(102)
Oncogenic	XIST	Up	-	Promotes proliferation, migration and invasion, and inhibits apoptosis	Reciprocal regulation between XIST and miR-152	(103)
Anti-oncogenic	ADAMTS9-AS2	Down	Good	Inhibits migration	Modulated by DNMT1	(104)
Anti-oncogenic	CASC2	Down	-	Inhibits proliferation, migration, and invasion, and promotes apoptosis	Reciprocal regulation between XIST and miR-21 in an Ago2-dependent manner	(78)
Anti-oncogenic	MEG3	Down	-	Inhibits proliferation and promotes apoptosis	Promoter methylation, P53 activation	(83,105)
Anti-oncogenic	TSLC1-AS1	Down	-	Inhibits proliferation, migration and invasion	Regulation of TSLC1	(106)

lncRNA, long non-coding RNAs; miRNA, microRNA; CRNDE, colorectal neoplasia differentially expressed; HOTAIR, HOX transcript antisense RNA; HULC, Hepatocellular carcinoma up-regulated long non-coding RNA; MALAT-1, metastasis associated lung adenocarcinoma transcript 1; NEAT1, nuclear enriched abundant transcript 1; POU3F3, POU Class 3 homeobox 3; SPRY4-IT1, Sprouty RTK signaling antagonist 4-intronic transcript 1; XIST, X inactive specific transcript; ADAMTS9-AS2, ADAM metalloproteinase with thrombospondin type 1 motif 9-antisense 2; CASC2, cancer susceptibility candidate 2; MEG3, Maternally expressed gene 3; TSLC1-AS1, tumor suppressor in lung cancer 1-antisense 1; mTOR, mechanistic target of rapamycin; miR, microRNA; PIWIL4, Piwi-like RNA-mediated gene silencing 4; STAT3, Signal transducer and activator of transcription 3; NLK, Nemo-like kinase; EMT, epithelial-mesenchymal transition; XIST, X inactive specific transcript; CCND1, Cyclin D1; MYC, c-MYC; DNMT1, DNA methyltransferase 1; Ago2, Argonaute 2, RISC catalytic component.



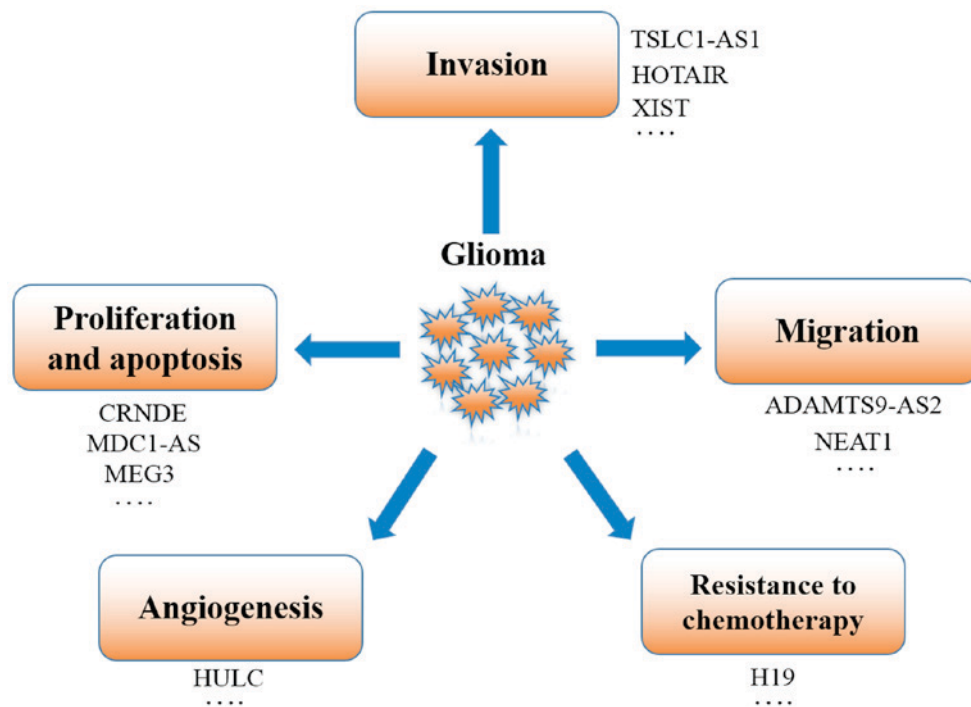


Figure 2. Long non-coding RNAs mediate various biological processes to regulate the progression of glioma. Certain representative lncRNAs function as oncogenes or tumor suppressors in specific biological process of glioma. TSLC1-AS1, tumor suppressor in lung cancer 1-antisense 1; HOTAIR, HOX transcript antisense RNA; XIST, X inactive specific transcript; CRNDE, colorectal neoplasia differentially expressed; MDC1-AS, Mediator of DNA damage checkpoint 1-antisense; MEG3, Maternally expressed gene 3; HULC, Hepatocellular carcinoma up-regulated long non-coding RNA; ADAMTS9-AS2, ADAM metalloproteinase with thrombospondin type 1 motif 9-antisense 2; NEAT1, nuclear enriched abundant transcript 1.

of CRNDE has been identified in a variety of solid tumors, including brain tumors (72). Previous studies indicated that the expression of CRNDE was markedly increased in primary and recurrent gliomas (73). Zhang *et al* (74) identified that CRNDE was significantly overexpressed in glioma tissues, and that the expression level of CRNDE was positively associated with the pathological grades of glioma. Similarly, Zheng *et al* (75) demonstrated that CRNDE promoted migration, invasion and proliferation, and inhibited apoptosis in glioma cells through regulating the expression levels of the miR-384/Piwi-like RNA-mediated gene silencing 4/signal transducer and activator of transcription 3 axis. Consistent with these data, Wang *et al* (76) demonstrated that CRNDE was upregulated lncRNA in glioma compared with normal tissues in their study, and that the overexpression of CRNDE promoted proliferation and invasion in glioma through the mechanistic target of rapamycin pathway *in vitro* and *in vivo*. These results suggest that understanding the underlying mechanisms whereby CRNDE functions in glioma may reveal a novel therapeutic strategy for the treatment of glioma in future.

#### Tumor-suppressive lncRNAs

**Cancer susceptibility candidate 2 (CASC2).** CASC2 has been identified as a tumor suppressor in numerous types of solid tumors (77). The role of CASC2 in glioma pathogenesis has been examined by several studies. Wang *et al* (77) indicated that a low level of CASC2 expression was detected in gliomas. The findings of Wang *et al* (78) suggested that CASC2 served as a tumor suppressor role via regulation of miR-21 in an Ago2-dependent manner in gliomas. Furthermore, a study by Liao *et al* (79) demonstrated that the low expression of CASC2

was associated with malignant characteristics and poor clinical prognosis in glioma. The overexpression of CASC2 inhibits the proliferation of glioma cells and amplifies TMZ-induced repression of cell proliferation through the direct inhibition of miR-181a. However, whether CASC2 has the same effect *in vivo* has not been reported in glioma. Therefore, the role of CASC2 in a mouse model of glioma requires additional investigation.

**Maternally expressed gene 3 (MEG3).** MEG3 is a maternal imprinting gene at the delta like non-canonical notch ligand 1-MEG3 locus on chromosome 14q32.3 in humans (80). A number of previous studies demonstrated that MEG3 was expressed in a number of normal tissues, with particularly marked expression in the brain, but absent or low expression in multiple types of tumors, including cervical carcinoma, breast adenocarcinoma, meningioma and glioma (81,82). Wang *et al* (83) demonstrated that the expression of MEG3 was decreased in tumor tissues compared with adjacent non-tumor tissues in gliomas. Furthermore, ectopic expression of MEG3 inhibited the growth of glioma cells by activation of the p53 signaling pathway. Liu *et al* (84) also suggested that MEG3 served an important role in genotoxic stress-induced glioma cell death. Similarly, Li *et al* (84) indicated that a low level of MEG3 expression was observed in glioma tissues. This low expression of MEG3 was due to DNA methyltransferase 1 (DNMT1), which is mediated by hypermethylation of the MEG3 promoter. Furthermore, the inhibition of DNMT1 repressed the growth and resulted in apoptosis of glioma cells in a p53-dependent manner. Additionally, Zhang *et al* (85) also demonstrated that MEG3 markedly reduced tumor volume and

the expression of Ki-67 and proliferating cell nuclear antigen *in vivo*.

#### 4. Clinical applications in gliomas

With an improved understanding of their functions, lncRNAs are becoming an important focus of study as a novel type of cancer biomarker for diagnosis, treatment and prognostic prediction. At present, certain lncRNAs have been examined for their potential clinical applications. It has been demonstrated that specific lncRNA profiles are associated with tumor subtypes, mutational status and the survival time of patients with glioma, based on the analysis of RNA-seq datasets from The Cancer Genome Atlas (86). Gliomas with oxalosuccinate decarboxylase (IDH1) mutations exhibited a unique lncRNA gene expression signature that was different from that of tumors exhibiting the wild-type IDH1 gene (87). As prognostic markers, the four lncRNAs (AGAP2-AS1, TPT1-AS1, LINC01198 and MIR155HG) were suggested to have prognostic value for patients with anaplastic gliomas (88). Furthermore, lncRNAs have demonstrated potential in applications for non-invasive detection of cancer. Zhou *et al* (18) identified that the level of H19 in the plasma of patients with gastric cancer was significantly increased compared with healthy controls. In addition, the plasma level of H19 was decreased markedly in postoperative patients compared with that in preoperative patients. The plasma level of H19 may be used as a non-invasive method to evaluate glioma progression in the future.

lncRNAs, due to their highly tissue-specific expression in cancer phenotypes, are potential targets for cancer therapy. Preclinical studies have demonstrated the therapeutic efficacy of antisense oligonucleotides targeting cancer-associated lncRNAs, including MALAT-1 and H19 (89,90). At present, certain lncRNAs have been identified to be associated with glioma therapy. Amit *et al* (91) revealed that a construct expressing the diphtheria toxin A-fragment, under the control of H19 and insulin-like growth factor 2 P4 promoters, demonstrated anti-tumoral efficacy against glioblastoma *in vitro* and *in vivo*. The BET bromodomain inhibitor, I-BET151 inhibited the growth of glioblastoma cells *in vitro* and *in vivo* by directly reducing HOTAIR expression (92). Similarly, Ke *et al* (67) also reported that HOTAIR knockdown inhibited tumor growth. In addition, aberrant expression of growth arrest specific transcript 5 (GAS5) lncRNA has also been associated with chemoresistance in glioma. García-Claver *et al* (93) revealed that the GAS5 lncRNA was markedly upregulated following treatment with erlotinib (ERL) in ERL-sensitive and -resistant glioma. The knockdown of GAS5 sensitized U87MG cells to ERL treatment. Similarly, in tumor tissues and cell lines from patients with TMZ resistance, H19 was significantly upregulated (48). The silencing of H19 may decrease the half-maximal inhibitory concentration values for TMZ, and increase the apoptotic rate of glioma cells (48). In summary, these results provide experimental basis for the use of lncRNAs as novel therapeutic targets in gliomas. lncRNA-based therapeutics may represent a novel direction for the treatment of glioma, although studies concerning their safety, efficacy and more efficient delivery systems are required.

#### 5. Conclusion and future perspectives

lncRNAs may be regulators in the determination of the development of particular organs, rather than simply functioning as housekeeping genes. In contrast to other tissues, the brain expresses high levels of numerous lncRNAs, which are involved in neuro-development (94). Their deregulation may cause neurological disorders and brain tumors (95). As aforementioned, lncRNAs function as oncogenes or tumor suppressors by interacting with DNA, mRNA, ncRNA and proteins, and regulate the proliferation, migration, invasion, apoptosis, angiogenesis and stemness of glioma cells (Fig. 2). Recent studies of lncRNAs have highlighted their vital roles in the pathogenesis and progression of glioma. Furthermore, the sensitivity and reliability of RNA-based molecular technologies and tools to detect and target lncRNAs in glioma have improved (96). However, it should be noted that the current knowledge base regarding the biological roles of lncRNAs in glioma is primarily concerned with the identification and quantification of the expression levels of different lncRNAs and associated molecules in tumor and normal tissues. To date, the *in vivo* functions of a large proportion of the identified lncRNAs remain unknown. Therefore, a short-term goal would be to investigate the molecular, cellular and physiological functions of lncRNAs and their roles in pathogenesis of glioma, which will provide a foundation for developing novel medical therapies that target lncRNAs. High throughput technologies and massively parallel sequencing tools, in combination with bioinformatics methods, would assist in identifying lncRNA candidate targets whose dysregulation serves a pivotal role in the pathogenesis and progression of glioma. Genetically engineered mouse models would also be an indispensable tool to elucidate the functions and mechanisms of lncRNA genes in glioma *in vivo*. In summary, the identification of lncRNAs has revealed an additional facet of glioma tumorigenesis. Understanding the precise molecular mechanisms whereby lncRNAs function is important to advance lncRNA-based diagnosis, prognosis and therapeutic interventions against glioma.

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