Functional Roles of Long Non-Coding RNAs (LncRNAs) in Glioma Stem Cells

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Glioma, the most common and aggressive type of brain tumor, has a poor prognosis. Glioma stem cells (GSCs) are thought to be responsible for glioma genesis, proliferation, resistance to chemoradiotherapy, and recurrence. Long non-coding RNAs (lncRNAs) have been viewed as a prospective novel target in glioma therapy in recent years due to their functional roles in GSC biological processes. However, how lncRNAs interact with GSCs and the underlining mechanisms associated with these interactions are not yet clear. In this review, we briefly illustrate recent advancements in the functional roles of lncRNA and their potential mechanisms in GSCs.

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Background

Glioma is one of the most prevalent and aggressive primary malignant tumor in the central nervous system [1]. Despite treatment with a combination of surgery, chemotherapy and radiotherapy, patients typically have a poor prognosis [2]. Glioma stem cells (GSCs) are thought to be responsible for glioma genesis, proliferation, resistance to chemoradiotherapy, and recurrence because of their stem-like properties [3]. Therefore, GSCs have gained increasing attention as target cells for glioma therapy.

Recent studies have reported that non-coding RNAs (ncRNAs) play a key role in glioma cell proliferation, apoptosis, and cell invasion [4,5]. With the deepening and development of research, ncRNAs are expected to become a new biomarker for the diagnosis of glioma, and could also provide a more reliable theoretical basis for the prevention and targeted treatment of glioma [6]. Studies in recent years have accumulated evidence that ncRNAs possess critical regulatory roles in GSC biological processes. NcRNAs are usually classified into 2 categories according nucleotide length: short ncRNAs, whose length is <200 nucleotides, which include microRNAs (miRNAs, miRs) [7]; and long ncRNA (lncRNAs) whose length is >200 nucleotides long. In contrast to mRNA, lncRNA is not translated into protein because of the absence of uninterrupted open reading frames. Rather than being irrelevant transcriptional noise however, numerous studies have revealed that lncRNAs are associated with various biological roles such as oncogenesis, proliferation, differentiation, invasion, and metastasis in solid tumors [8]. Identifying regulatory roles of lncRNAs in GSC biological processes are therefore important for developing novel therapies for glioma. However, how lncRNAs interact with GSCs to affect glioma metastasis and recurrence is not yet clear. Therefore, this review highlights the functional roles of lncRNA and their potential mechanisms in GSCs.

Characteristics of GSC

GSCs are proposed to be a stem-like subpopulation within glioma tissue [9] that actively divide in response to radiotherapy and chemotherapy and thus limit the efficacy of these traditional therapies [10,11]. GSCs share many similar biological characteristics with neural stem cells (NSCs) and have the capacity to self-renew and differentiate into neural lineages. In addition, GSCs are able to form neurospheres in serum free medium and express specific NSCs markers such as nestin and CD133. Nestin is an intermediate filament protein specifically expressed in neuroepithelial stem cells while CD133 is a glycoprotein also known as prominin 1. Moreover, GCSs also express transcription factors characteristic of NSCs that are essential for maintaining self-renewal and pluripotency, such as Sox2, Oct4, and Nanog [12,13]. GSCs exhibit high tumorigenicity; only
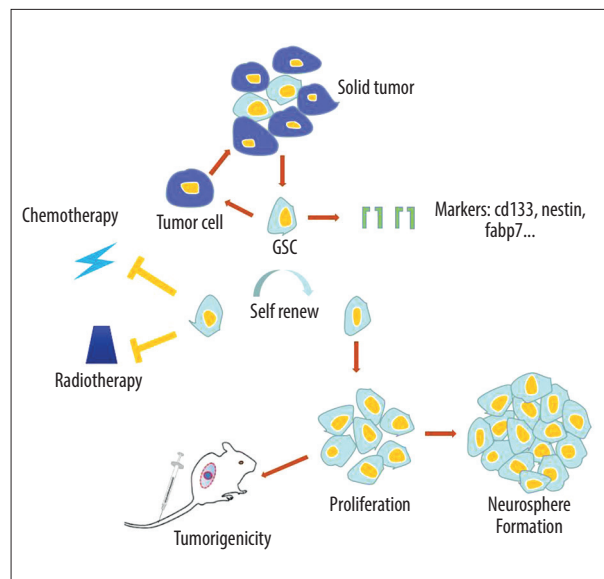

Figure 1. Characteristics of glioma stem cells (GSCs). Key properties that distinguish GSCs from the rest of the glioma cells include their ability to: a) self-renew, b) indefinitely proliferate, c) multipotency, d) share common NSC markers such as CD133 and nestin, e) form neurosphere-like structures *in vitro* culture, f) ability to generate tumors when injected *in vivo*, g) chemoradiation resistance.

100 GSCs (CD133-positive cells) were able to produce gliomas in immune deficient mice *in vivo* [14].

Despite previous in-depth research, many complexities exist in regard to the exact definition of a GSC and to the theory of GCS self-renewal; therefore, exact identification of these cells remains controversial [15,16]. Key properties that distinguish GSCs from other glioma cells include: their ability to self-renew and indefinitely proliferate; multipotent lineage differentiation capability; expression of NSC markers including nestin and CD133; ability to form neurosphere-like structures *in vitro* and to generate tumors when injected *in vivo*; and their chemoradiation resistance (Figure 1) [15–18].

Classical Oncogenic lncRNAs in GSCs

Aberrant expression of lncRNAs is thought to play a critical role in progression of various cancers. Several lncRNAs, which are upregulated in GSCs, may act as oncogenes to promote growth, migration, invasion, and chemo- and radio-resistance, while others may possess anti-tumor properties. Recently, numerous studies revealed that certain kinds of lncRNAs are thought to be associated with GSCs (Table 1, Figure 2). These lncRNAs may have an oncogenic role, which is directly involved in malignant biological properties [19–21].

Table 1. Functions and mechanisms of lncRNA in glioma stem cells.

LncRNA	Functions	Mechanisms
HOTAIR	Promoting the proliferation, invasion and *in vivo* tumorigenicity of GSCs	Si-HOTAIR reduced the recruitment of the EZH2 and LSD1 proteins, thereby upregulating the expression of PDCD4 at the epigenetic level
TALNEC2	Silencing of TALNEC2 decreased the self-renewal and mesenchymal transformation, increased sensitivity of these cells to radiation and prolonged survival of mice bearing GSC-derived xenografts	Two of the downregulated miRNAs, miR-21 and miR-191, mediated some of TALNEC2 effects on the stemness and mesenchymal transformation of GSCs.
H19	The expression of H19 was signifcantly higher in CD133+ glioblastoma cells than CD133- glioblastoma cells, H19 overexpressed GSCs exhibited greater ability of neurosphere formation	
NEAT1	Knockdown of NEAT1 inhibited GSCs proliferation, migration and invasion and promoted GSC apoptosis	By upregulating miR let-7e expression,let-7e functioned as a tumor suppressor
NEAT1	NEAT1 knockdown in the CD133+ U87 cells resulted in decreased colony formation, increased G1 cell cycle arrest and apoptosis	By miR-107 activation and inactivation of CDK6 protein
MALAT1	MALAT1 enhanced GSCs viability and proliferation abilities and promoted glioma tumorigenesis	Through suppressing miR-129 and facilitating SOX2 expressions
MALAT1	Maintains the stemness and regulated the proliferation of GSCs	The underlying mechanism was related to regulating the expression of Sox2 and Nestin and ERK/MAPK signaling activation
SOX2OT	Knockdown of SOX2OT inhibited the proliferation, migration and invasion of GSCs, and promoted GSCs apoptosis	SOX2OT-miR-194-5p/miR-122-SOX3-TDGF-1 pathway
CRNDE	Overexpression of CRNDE could promote the cellular proliferation, migration, invasion and inhibit the apoptosis in GSCs	Through the negative regulation of miR-186
lincRNAs p21	MiR-146b-5p overexpression increased apoptosis and radiosensitivity, and decreased cell viability, neurosphere formation capacity and stem cell marker expression in GSCs. knock-down lincRNA-p21 could rescue the phenotypic changes resulting from miR-146b-5p overexpression in GSCs	MiR-146b-5p/HuR/lincRNA-p21/β-catenin signaling pathway
GAS5	Overexpression could suppressed GSCs proliferation, migration and invasion	By binding to miR-196a-5p and upregulating the downstream FOXO1
lincRNAs 00152	Knockdown of linc00152 inhibited cell proliferation, migration and invasion, while promoted GSC apoptosis	Linc00152 regulated the malignant behavior of GSCs by binding to miR-103a-3p, which functions as a tumor suppressor

LncRNA HOTAIR (HOX transcript antisense RNA) was the first trans-acting lncRNA gene to be discovered in a range of cancers [22,23], and its upregulation is predictive of decreased survival in a variety of tumor cells [24,25]. Lysine specific de-methylase 1 (LSD1) and polycomb repressive complex 2 (PRC2) are functional targets of HOTAIR and it is thought that HOTAIR may serve as scaffold for LSD1 and PRC2. In glioma cells, upreg-ulation of lncRNA HOTAIR accelerates the glioma cell cycle period through interactions with PRC2 while its knockdown suppresses malignant biological properties of glioma cells via regulation of miR-326 [26,27]. Enhancer of zeste homolog 2 (EZH2) is the catalytic subunit of PRC2, which functions as a methyltransferase. In GSCs, HOTAIR downregulation reduces the recruitment of EZH2 and LSD1 proteins, thereby upregulat-ing the expression of the tumor repressor gene, *PDCD4*, at the epigenetic level [28]. *PDCD4* upregulation has been shown to inhibit the proliferation, invasion and tumorigenicity of hu-man GSCs *in vivo* [28].
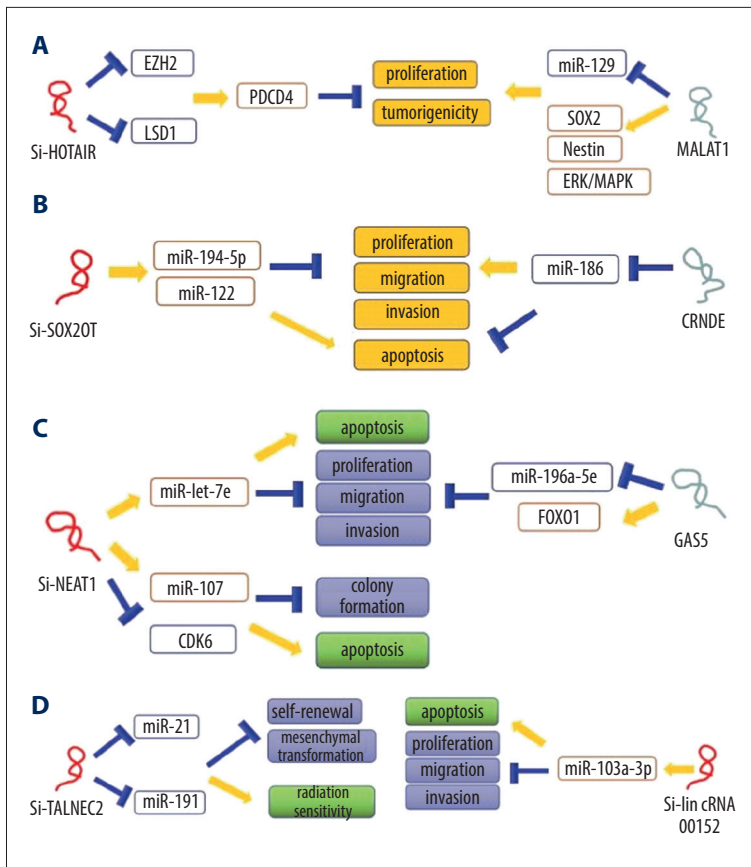
Figure 2. Representative figures of lncRNA interaction with key molecules or cellular processes in glioma stem cells (GSCs). (A) Si-HOTAIR reduced the recruitment of the EZH2 and LSD1 proteins, thereby upregulating the expression of PDCD4 at the epigenetic level. MALAT1 regulates the expression of SOX2 and Nestin and ERK/MAPK signaling activation. (B) SOX2OT can downregulate the expression of SOX3 by regulating miR-194-5p and miR-122. CRNDE could promote the proliferation, migration, and invasion, and inhibit the apoptosis in GSCs through the negative regulation of miR-186. (C) Knockdown of NEAT1 inhibited GSCs proliferation, migration, and invasion by upregulating miR let-7e expression. NEAT1 knockdown also resulted in decreased colony formation by miR-107 activation and inactivation of CDK6 protein. GAS5 overexpression could suppressed GSCs proliferation, migration, and invasion by binding to miR-196a-5p and upregulating the downstream FOXO1. (D) Silencing of TALNEC2 downregulated miR-21 and miR-191 mediated some of TALNEC2 effects on the stemness and mesenchymal transformation of GSCs. Linc00152 regulated the malignant behavior of GSCs by binding to miR-103a-3p, which functions as a tumor suppressor.

E2F transcription factor 1 (E2F-1) belongs to the E2F family of transcription factors, and coordinates the expression of key genes involved in cell cycle regulation and progression. LncRNA H19 is a maternally expressed gene, which is regulated by the transcription factor E2F-1 [29]. The aberrant expression of H19 leads to the proliferation, migration, and molecular targeted drug resistance of various cancers [30,31]. The level of H19 expression is also known to be associated with glioma recurrence and poor patient prognosis [32,33]. Glioblastoma multiforme (GBM) cells with H19 knockdown displayed decreased cellular proliferation and a higher apoptosis rate when induced by temozolomide chemotherapy [34]. In addition, H19 knockdown suppressed the expression of the 4 stemness-related markers (CD133, NANOG, Oct4, and Sox2) in the U87MG and U251 cell lines [34]. In addition, overexpression of H19 promotes glioblastoma cell invasion and angiogenesis *in vitro*. Furthermore, the expression of H19 was found to be significantly higher in GSCs than in CD133 negative glioblastoma cells, and overexpression of H19 in GSCs induced greater neurosphere formation ability [35].

Recent studies have shown that lncRNA MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) is a crucial factor in colorectal cancer. MALAT1 promoted colorectal cancer cells metastasis, proliferation, and invasion. In contrast, silencing of MALAT1 was shown to inhibit the growth and metastasis and to promote drug sensitivity of colorectal cancer cells [36,37]. Significant upregulation of MALAT1 expression was observed in GSCs compared with non-stem glioma cells. MALAT1 was shown to maintain the stemness of GSCs by regulating the expression of Sox2 and nestin. Downregulation of MALAT1 also promoted the proliferation of the SHG139S GSC line, with results indicating that the underlying mechanism of proliferation was related to ERK/MAPK signaling activation [38]. The ERK/MAPK pathway is one of the most important signal transduction pathways involved in a variety of fundamental cellular processes such as proliferation, differentiation, motility, stress response, apoptosis, and survival. Another study showed that MALAT1 enhanced GSC viability and proliferation and promoted glioma tumorigenesis through suppressing miR-129 and facilitating SOX2 expression [39].

LncRNA NEAT1 (nuclear enriched abundant transcript 1) has been shown to be important mediator in a wide variety of tumors. NEAT1, as a downstream target of EGFR (epidermal growth factor receptor) pathway activity, has been shown

to participate in glioma cell invasion and growth via the WNT/β-catenin pathway which involved in early embryonic patterning and regulation of stem cell self-renewal and differentiation [40]. A study showed that NEAT1 expression was upregulated in GSCs where it was found to promote the proliferation, migration and invasion of GSCs via regulating let-7e expression [41]. Another separate study also indicated that NEAT1 knockdown resulted in decreased colony formation and increased G1 cell cycle arrest and apoptosis. Moreover, these effects were accompanied by miR-107 activation and inactivation of CDK6 protein [42].

Novel LncRNAs in GSCs

Emerging evidence suggests that lncRNA TALNEC2 (tumor associated long non-coding RNA expressed on chromosome 2), is highly expressed in GBM with poor prognosis and plays a vital role in GSCs. TALNEC2 silencing attenuates mesenchymal transformation and self-renewal, increases radio-resistance and prolongs survival of mice bearing GSC-derived xenografts [43]. LncRNA SOX2OT (SOX overlapping transcript) is highly expressed in GSCs and glioma tissues. Silencing SOX2OT can inhibit the growth and invasion of GSCs by targeting the SOX2OT-miR-194-5p/miR-122-SOX3-TDGF-1 pathway [44]. In glioma cells, lncRNA CRNDE (colorectal neoplasia differentially expressed) was shown to regulate the proliferation and migration of GSCs by inhibiting the expression of miR-384 [45]. In GSCs, overexpression of CRNDE also facilitated malignant biological behavior by negatively regulating miR-186 [46].

Anti-Oncogenic LncRNAs in GSCs

LncRNAs have also been found to have a tumor suppressor role in GSCs. LncRNA GAS5 (growth arrest specific 5) exhibited significant anti-oncogenic capabilities in a variety of tumors. GAS5 has a relatively low expression in GSCs, and its overexpression suppressed GSC malignant biological behavior through upregulation of the downstream forkhead box protein (FOXO1) [47]. FOXO1 is a member of forkhead family of transcription factors that regulate a large number of genes involved in apoptosis, stress, angiogenesis and cell cycle arrest. Increased expression of FOXO1 was shown to inhibit GSC tumorigenicity, growth, migration and invasion.

Data suggests that lncRNA-p21 is a novel regulator of cell cycle, apoptosis and DNA repair. LncRNA-p2 has a relatively low expression in GBM tissues and GSCs but can negatively regulate β-catenin expression and activity. Indeed, knock-down of lncRNA-p21 rescued the decreased stemness and radio-resistance resulting from miR-146b-5p overexpression in GSCs [48].

Regulatory Mechanisms

The diverse mechanisms underlying the regulatory roles of lncRNAs include genome activity regulation, posttranscriptional regulation, protein modification, and anchoring and encoding functional micropeptides [49]. LncRNAs may function through interactions with their molecular partners including transcription factors [43]. It is thought that lncRNAs affect the transcription of genes and play a regulatory role in signaling, decoy, guidance, and scaffolding [8,50,51]. LncRNAs are also recognized as molecular signaling pathway regulators, modulating the expression of tumor related genes and their corresponding signaling pathways [38,40].

Recently, miRNAs have been definitively linked to glioma development. MiRNAs are thought to act as inhibitors by binding to specific region of their target mRNAs and by degrading them [52], thus modulating the expression of oncogenes or tumor suppressor-related miRNAs [44–46]. GSC-associated lncRNAs were shown to negatively regulate miRNA expression through their ability to act as "miRNA sponges". Long intergenic non-coding RNAs (lincRNAs) 00152 acts as a competing endogenous RNA, which affects expression of miR-103a-3p and positively modulates forebrain embryonic zinc finger protein 1 expression, a direct target of the GSC expressed oncogene, miR-103a-3p [53].

Conclusions and Perspectives

Research regarding the functional roles and underlying mechanisms of lncRNA and GSCs is still in the initial stages. Numerous studies have indicated that lncRNA signatures correlate with glioma malignancy grade, histological differentiation and prognosis [33]. Several GSC-associated lncRNAs have also been associated with the poor survival of patients with malignancies, such as the lncRNAs, MALAT1, H19, and HOTAIR [42,54,55]. These lncRNAs are significantly increased in GSCs and have direct correlation with tumor malignant status and are inversely proportional with overall survival in glioma patients. Studies have suggested that stemness-related lncRNAs in GSCs might serve as an independent prognostic factor in glioma, with their expression closely associated with grade and prognosis of glioma.

Several GSC-associated lncRNAs with oncogenic properties were observed in various cancer cell lines, with aberrant expression exhibiting different mechanisms in different cancer types. The underlying mechanisms of lncRNA expression in glioma remains elusive, and needs further study. Current research has been focused on the stemness of aberrant lncRNA expression in GSCs, but few studies have explored differentiation-related lncRNAs. Differentiation of GSCs might lead to

the inhibition of their selfrenewing ability and tumorigenic potential, as well as increasing their sensitivity to treatment [56]. A recent study, using a highthroughput microarray, identified a profile of 1545 lncRNAs and 2729 mRNAs that differed between GSCs and their non-differentiated counterparts [56]; therefore differentiation-related lncRNAs might become promising novel targets to eradicate GSCs.

A multitude of lncRNAs play regulatory roles in gene networks involved in NSC lineage specification and terminal differentiation, such as RMST, TUNA, and Malat1, among others [57,58]. Because of similar cell characteristics between NSCs and GSCs, these specification related lncRNAs in NSCs might also play important roles in GSC differentiation.

Conflict of interest

None.

References:

1. Ostrom QT, Gittleman H, Stetson L et al: Epidemiology of gliomas. Cancer Treat Res, 2015; 163: 1–14

2. Reni M, Mazza E, Zanon S et al: Central nervous system gliomas. Crit Rev Oncol Hematol, 2017; 113: 213–34

3. Auffinger B, Spencer D, Pytel P et al: The role of glioma stem cells in chemotherapy resistance and glioblastoma multiforme recurrence. Expert Rev Neurother, 2015; 15(7): 741–52

4. Xie G: Circular RNA hsa-circ-0012129 promotes cell proliferation and invasion in 30 cases of human glioma and human glioma cell lines U373, A172, and SHG44, by targeting microRNA-661 (miR-661). Med Sci Monit, 2018; 24: 2497–507

5. Bian A, Wang Y, Liu J et al: Circular RNA complement factor H (CFH) promotes glioma progression by sponging miR-149 and regulating AKT1. Med Sci Monit, 2018; 24: 5704–12

6. Xiao Y, Zhang L, Song Z et al: Potential diagnostic and prognostic value of plasma circulating microRNA-182 in human glioma. Med Sci Monit, 2016; 22: 855–62

7. Nagano T, Fraser P: No-nonsense functions for long noncoding RNAs. Cell, 2011; 145(2): 178–81

8. Huang X, Xiao R, Pan S et al: Uncovering the roles of long non-coding RNAs in cancer stem cells. J Hematol Oncol, 2017; 10(1): 62

9. Vescovi AL, Galli R, Reynolds BA: Brain tumour stem cells. Nat Rev Cancer, 2006; 6(6): 425–36

10. Lathia JD, Gallagher J, Myers JT et al: Direct *in vivo* evidence for tumor propagation by glioblastoma cancer stem cells. PLoS One, 2011; 6(9): e24807

11. Chen J, Li Y, Yu TS et al: A restricted cell population propagates glioblastoma growth after chemotherapy. Nature, 2012; 488(7412): 522–26

12. Thomas TM, Yu JS: Metabolic regulation of glioma stem-like cells in the tumor micro-environment. Cancer Lett, 2017; 408: 174–81

13. Liu T, Xu H, Huang M et al: Circulating glioma cells exhibit stem cell-like properties. Cancer Res, 2018; 78(23): 6632–42

14. Singh SK, Hawkins C, Clarke ID et al: Identification of human brain tumour initiating cells. Nature, 2004; 432(7015): 396–401

15. Ahmed AU, Auffinger B, Lesniak MS: Understanding glioma stem cells: Rationale, clinical relevance and therapeutic strategies. Expert Rev Neurother, 2013; 13(5): 545–55

16. Sampetrean O, Saya H: Characteristics of glioma stem cells. Brain Tumor Pathol, 2013; 30(4): 209–14

17. Najbauer J, Kraljik N, Németh P: Glioma stem cells: Markers, hallmarks and therapeutic targeting by metformin. Pathol Oncol Res, 2014; 20(4): 789–97

18. Zhang X, Kiang KM, Zhang GP, Leung GK: Long non-coding RNAs dysregulation and function in glioblastoma stem cells. Noncoding RNA, 2015; 1(1): 69–86

19. Bhan A, Soleimani M, Mandal SS: Long noncoding RNA and cancer: A new paradigm. Cancer Res, 2017; 77(15): 3965–81

20. de Oliveira JC, Oliveira LC, Mathias C et al: Long non-coding RNAs in cancer: Another layer of complexity. J Gene Med, 2019; 21(1): e3065

21. Rafiee A, Riazi-Rad F, Havaskary M, Nuri F: Long noncoding RNAs: Regulation, function and cancer. Biotechnol Genet Eng Rev, 2018; 34(2): 153–80

22. Botti G, Marra L, Malzone MG et al: LncRNA HOTAIR as prognostic circulating marker and potential therapeutic target in patients with tumor diseases. Curr Drug Targets, 2017; 18(1): 27–34

23. Li J, Wang J, Zhong Y et al: HOTAIR: A key regulator in gynecologic cancers. Cancer Cell Int, 2017; 17: 65

24. Tsai MC, Spitale RC, Chang HY: Long intergenic noncoding RNAs: New links in cancer progression. Cancer Res, 2011; 71(1): 3–7

25. Gupta RA, Shah N, Wang KC et al: Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature, 2010; 464(7291): 1071–76

26. Zhang K, Sun X, Zhou X et al: Long non-coding RNA HOTAIR promotes glioblastoma cell cycle progression in an EZH2 dependent manner. Oncotarget, 2015; 6(1): 537–46

27. Ke J, Yao YL, Zheng J et al: Knockdown of long non-coding RNA HOTAIR inhibits malignant biological behaviors of human glioma cells via modulation of miR-326. Oncotarget, 2015; 6(26): 21934–49

28. Fang K, Liu P, Dong S et al: Magnetofection based on superparamagnetic iron oxide nanoparticle-mediated low lncRNA HOTAIR expression decreases the proliferation and invasion of glioma stem cells. Int J Oncol, 2016; 49(2): 509–18

29. Berteaux N, Lottin S, Monté D et al: H19 mRNA-like noncoding RNA promotes breast cancer cell proliferation through positive control by E2F1. J Biol Chem, 2005; 280(33): 29625–36

30. Lin Y, Xu L, Wei W et al: Long noncoding RNA H19 in digestive system cancers: A meta-analysis of its association with pathological features. Biomed Res Int, 2016; 2016: 4863609

31. Lei Y, Guo W, Chen B et al: Tumor-released lncRNA H19 promotes gefitinib resistance via packaging into exosomes in non-small cell lung cancer. Oncol Rep, 2018; 40(6): 3438–46

32. Shi Y, Wang Y, Luan W et al: Long non-coding RNA H19 promotes glioma cell invasion by deriving miR-675. PLoS One, 2014; 9(1): e86295

33. Wang L, Yu Z, Sun S et al: Long non-coding RNAs: Potential molecular biomarkers for gliomas diagnosis and prognosis. Rev Neurosci, 2017; 28(4): 375–80

34. Li W, Jiang P, Sun X et al: Suppressing H19 modulates tumorigenicity and stemness in U251 and U87MG glioma cells. Cell Mol Neurobiol, 2016; 36(8): 1219–27

35. Jiang X, Yan Y, Hu M et al: Increased level of H19 long noncoding RNA promotes invasion, angiogenesis, and stemness of glioblastoma cells. J Neurosurg, 2016; 2016(1): 129–36

36. Xu Y, Zhang X, Hu X et al: The effects of lncRNA MALAT1 on proliferation, invasion and migration in colorectal cancer through regulating SOX9. Mol Med, 2018; 24(1): 52

37. Tang D, Yang Z, Long F et al: Inhibition of MALAT1 reduces tumor growth and metastasis and promotes drug sensitivity in colorectal cancer. Cell Signal, 2019; 57: 21–28

38. Han Y, Zhou L, Wu T et al: Downregulation of lncRNA-MALAT1 affects proliferation and the expression of stemness markers in glioma stem cell line SHG139S. Cell Mol Neurobiol, 2016; 36(7): 1097–107

39. Xiong Z, Wang L, Wang Q, Yuan Y: LncRNA MALAT1/miR-129 axis promotes glioma tumorigenesis by targeting SOX2. J Cell Mol Med, 2018 [Epub ahead of print]

40. Chen Q, Cai J, Wang Q et al: Long noncoding RNA NEAT1, regulated by the EGFR pathway, contributes to glioblastoma progression through the WNT/β-catenin pathway by scaffolding EZH2. Clin Cancer Res, 2018; 24(3): 684–95

41. Gong W, Zheng J, Liu X et al: Knockdown of NEAT1 restrained the malignant progression of glioma stem cells by activating microRNA let-7e. Oncotarget, 2016; 7(38): 62208–23

42. Yang X, Xiao Z, Du X et al: Silencing of the long non-coding RNA NEAT1 suppresses glioma stem-like properties through modulation of the miR-107/CDK6 pathway. Oncol Rep, 2017; 37(1): 555–62

43. Brodie S, Lee HK, Jiang W et al: The novel long non-coding RNA TALNEC2, regulates tumor cell growth and the stemness and radiation response of glioma stem cells. Oncotarget, 2017; 8(19): 31785–801

44. Su R, Cao S, Ma J et al: Knockdown of SOX2OT inhibits the malignant biological behaviors of glioblastoma stem cells via up-regulating the expression of miR-194-5p and miR-122. Mol Cancer, 2017; 16(1): 171

45. Zheng J, Liu X, Wang P et al: CRNDE promotes malignant progression of glioma by attenuating miR-384/PIWIL4/STAT3 axis. Mol Ther, 2016; 24(7): 1199–215

46. Zheng J, Li XD, Wang P et al: CRNDE affects the malignant biological characteristics of human glioma stem cells by negatively regulating miR-186. Oncotarget, 2015; 6(28): 25339–55

47. Zhao X, Liu Y, Zheng J et al: GAS5 suppresses malignancy of human glioma stem cells via a miR-196a-5p/FOXO1 feedback loop. Biochim Biophys Acta Mol Cell Res, 2017; 1864(10): 1605–17

48. Yang W, Yu H, Shen Y et al: MiR-146b-5p overexpression attenuates stemness and radio-resistance of glioma stem cells by targeting HuR/lincRNA-p21/β-catenin pathway. Oncotarget, 2016; 7(27): 41505–26

49. Peng Z, Liu C, Wu M: New insights into long noncoding RNAs and their roles in glioma. Mol Cancer, 2018; 17(1): 61

50. Wang KC, Chang HY: Molecular mechanisms of long noncoding RNAs. Mol Cell, 2011; 43(6): 904–14

51. Zhang C, Peng G: Non-coding RNAs: An emerging player in DNA damage response. Mutat Res Rev Mutat Res, 2015; 763: 202–11

52. Meister G: miRNAs get an early start on translational silencing. Cell, 2007; 131(1): 25–28

53. Yu M, Xue Y, Zheng J et al: Linc00152 promotes malignant progression of glioma stem cells by regulating miR-103a-3p/FEZF1/CDC25A pathway. Mol Cancer, 2017; 16(1): 110

54. Jia P, Cai H, Liu X et al: Long non-coding RNA H19 regulates glioma angiogenesis and the biological behavior of glioma-associated endothelial cells by inhibiting microRNA-29a. Cancer Lett, 2016; 381(2): 359–69

55. Zhang JX, Han L, Bao ZS et al: HOTAIR, a cell cycle-associated long noncoding RNA and a strong predictor of survival, is preferentially expressed in classical and mesenchymal glioma. Neuro Oncol, 2013; 15(12): 1595–603

56. Li H, Li H, Hao Y et al: Differential long non-coding RNA and mRNA expression in differentiated human glioblastoma stem cells. Mol Med Rep, 2016; 14(3): 2067–76

57. Wang L, Liu Y, Sun S et al: Regulation of neuronal-glial fate specification by long non-coding RNAs. Rev Neurosci, 2016; 27(5): 491–99

58. Wang L, Deng Y, Duan D et al: Hyperthermia influences fate determination of neural stem cells with lncRNAs alterations in the early differentiation. PLoS One, 2017; 12(2): e0171359