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Long non-coding RNA LINC01128 affects proliferation, migration, and invasion of glioma cells by regulating miR-27b-3p

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Abstract

Introduction: *Glioma is a collective term for tumors derived from glial cells and neuronal cells in the nervous system, and is the most common malignant tumor in the brain. Nowadays, the problem of poor treatment effect and high recurrence rate of patients remains to be solved.*

Material and methods: *In this study, the expression levels of LINC01128 in glioma tissues, cells, and normal control group were determined by real-time quantitative PCR (RT-qPCR). Kaplan-Meier curve was used to evaluate the prognosis and survival. Multivariate Cox analysis was chosen to estimate the prognostic risk factors of glioma. Cell counting kit-8 (CCK-8) and Transwell methods were used to detect the effect of silencing LINC01128 on the proliferation, migration, and invasion of glioma cells, and the targeting effect of LINC01128 on miR-27b-3p was determined based on bio-informatics analysis and luciferase activity detection.*

Results: *LINC01128 was up-regulated in glioma tissues and cells. The possibility of LINC01128 as a prognostic factor of glioma was obtained through Kaplan-Meier's clinical data analysis and multivariate Cox analysis. Silencing LINC01128 targeting miR-27b-3p inhibited the proliferation, migration, and invasion activity of glioma cells. Moreover, there was a negative correlation between LINC01128 and miR-27b-3p.*

Conclusions: *Silencing LINC01128 inhibited the proliferation, migration, and invasion levels of glioma cells by targeting miR-27b-3p, thereby affecting the progression of gliomas.*

Key words: *glioma, prognosis, lncRNA LINC01128, miR-27b-3p.*

Introduction

As the most common neuro-epithelial cell primary intra-cranial tumor, glioma accounts for 40~50% of all brain tumors [8]. So far, the cause of glioma has not been fully determined, but it is considered to be triggered by carcino-genic factors in the environment, and also involves genetic factors [31,36]. Glioma can be divided into various types due to diversity of cell types, indicating that treatment and prognosis methods are also different [18,39]. Statistically, the onset age of glioma peaks at 30 to 40 years old, and the incidence rate is higher in males [11]. At present, treatment methods for glioma are mostly based on actual conditions of patient, such as drugs, surgery, chemical, and radiotherapy [10,13]. Due to shape and location of the tumor, it is difficult to completely remove it, unless multiple treatment methods are combined to achieve a better treatment effect [16]. However, these traditional treatment methods can only alleviate and control patient's condition as much as possible, and cannot achieve a complete cure. Therefore, on the basis of understanding the pathogenesis and prognosis of

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glioma, the involvement of biomarkers in the prognosis of glioma may provide better treatment for patients.

Long non-coding RNAs (lncRNAs) are RNA molecules, which length is > 200 nucleotides, and cannot be encoded [1,19]. LncRNAs have been proved to be involved in the growth, apoptosis, and other biological processes of tumor cells, and affects the progress of cancer as oncogenic or inhibitory genes of various cancers [27,28]. Studies in recent years have shown that glioma blood vessels could be promoted by lncRNA H19 [17] or MALAT1 [25]. Mu *et al*. also found that lncRNA BCYRN1 suppressed the occurrence of glioma by competitively binding with miR-619-5p [21]. It is noteworthy that miR-299-3p sponged by lncRNA LINC01128 can regulate osteosarcoma process [34]. LncRNA LINC01128 accelerated the development of cervical cancer by binding to miR-383-5p [9]. Moreover, LINC01128 promoted pancreatic cancer progression by targeting miR-561-5p [38]. However, the role of lncRNA LINC01128 in glioma has not been studied in detail, and it has certain research significance.

This study verified the regulation and clinical significance of LINC01128 on glioma by referring to previous theories and experiments, discussed the influence of abnormal expression of LINC01128 on glioma cells, and explored the possibility of LINC01128 as a prognostic biomarker of glioma.

Material and methods

Sample of study participants and ethics

A total of 126 glioma patients, who attended Binzhou Medical University Hospital from June 2014 to June 2016 were recruited. According to average expression of lncRNA LINC01128, patients were divided into low expression groups (n = 59) and high expression groups (n = 67). Age, gender, tumor size, tumor location, tumor recurrence, Karnofsky performance status (KPS), and World Health Organization (WHO) grade of patients participating in the study are presented in Table I. Tissues obtained from all participants were stored at –80°C until use as required.

The research method complied with the standards stipulated in the Declaration of Helsinki. This study was approved by the Research Ethics Committee of Binzhou Medical University Hospital (No. 2014697). All participating patients understood the purpose of the study and related procedures, and signed an informed consent form approved by the ethics committee.

Table I. Correlation of the lncRNA LINC01128 expression with clinical characteristics in glioma

Parameters	Patients (N = 126)	lncRNA LINC01128 expression		P-value
		Low (n = 59)	High (n = 67)	
Age (years)				0.227
≤ 50	67	28	39	
> 50	59	31	28	
Gender				0.476
Male	77	38	39	
Female	49	21	28	
Tumor size (cm)				0.069
≤ 5	71	36	30	
> 5	55	23	37	
Tumor location				0.560
Supratentorial	67	33	34	
Sub-tentorial	59	26	33	
Tumor recurrence				0.048
Absent	76	41	35	
Present	50	18	32	
KPS				0.021
< 80	51	18	34	
≥ 80	75	41	33	
WHO grade				0.002
I, II	78	46	34	
III, IV	48	13	33	

Cell culture and transfection assay

The cells required for this study, including selected glioma cell lines (U87, T98G, U251MG, and A172) and control human astrocyte cell lines (HA) were all from BeNa Culture Collection (Beijing, China). Dulbecco's modified Eagle's medium (DMEM; Invitrogen, USA) was supplemented with 10% fetal bovine serum (FBS; Invitrogen, USA), and then used to culture all assay cells and placed at a 37°C incubator, containing 5% CO_2 [3].

The si-NC, si-LINC01128, miR-27b-3p mimic, mimic NC, miR-27b-3p inhibitor, and inhibitor NC needed for the study were purchased from GenePharma (Suzhou, China). Glioma cell lines (U87 and T98G) were inoculated into 6-well plates, and cell density was adjusted to 6×10^5 cells/well for 12 hours. Subsequently, transfection was performed with lipofectamine 3000 (Invitrogen, USA), and the cells were collected 48 hours later.

RT-qPCR assay

Total RNAs were extracted with TRIzol reagent (Invitrogen, USA), and quantified by NanoDrop™ (ThermoFisher Scientific). RNA was then reversely transcribed into cDNA using PrimeScript® RT reagent kit (Takara, Japan). According to the manufacturer's requirements, SYBR Premix Ex Taq kit (Takara, Japan) was configured with real-time quantitative PCR (RT-qPCR) reaction system. The initial denaturation was at 95°C for 30 s, then at 95°C for 5 s, and the optimal annealing temperature was 60°C for 30 s; the reaction was 40 cycles. RT-qPCR reactions were performed in a total volume of 10 µl, including 2.5 µl cDNA, 5 µl SYBR Premix, 0.25 µl each of paired primers, and 2 µl ddH_2O [22]. LINC01128 was normalized by glyceraldehyde phosphate dehydrogenase (GAPDH), and miR-27b-3p was normalized by U6 [32]. Expression levels of LINC01128 and miR-27b-3p were calculated by $2^{-\Delta\Delta Ct}$ method. Each assay was repeated in triplicate. Primers were summarized as the following: LINC-01128, 5'-CTGGGTCACAGTGTGATAGTGT-3' (forward) and 5'-TCCCTAAGAAAGAAGCTCAGAGA-3' (reverse). GAPDH, 5'-GGAGCGAGATCCCTCCAAAAT-3' (forward) and 5'-GGCTGTTGTCATACTTCTCATGG-3' (reverse). U6, 5'-GCTTCGGCAGCACATATACTAAAAT-3' (forward) and 5'-CGCTTCACGAATTTGCGTGTCAT-3' (reverse).

Cell proliferation and Transwell assay

Cell counting kit-8 (CCK-8; Dojindo, Japan) was chosen to measure cell proliferation, referring to the manufacturer's instructions. Glioma cells were inoculated with a density of 2×10^3 cells/ml on a 96-well plate. After 0, 24, 48, 72, and 96 hours, 10 µl of CCK-8 was added to each well and continued to culture for 2 hours at 37°C [6]. Absorbance of each well at 450 nm was detected by a microplate reader at least three times in each group, and average value was taken for analysis.

Migration and invasion ability of cells were detected by Transwell chamber. The cells were cultivated in 100 µl DMEM medium and placed in the upper chamber; 500 µl DMEM medium containing 10% FBS was placed in the lower chamber. Cell density was 5×10^5 cells/ml, cultured at 37°C for 6 hours, then 4% paraformaldehyde plasma cells was selected for fixation, and then stained with 0.1% crystal violet for 30 min [23]. The cells were observed under a microscope to analyze migration ability of the cells. Similarly, in the detection of glioma invasion levels, 50 µl Matrigel™ (Sigma-Aldrich, USA) was placed in the upper chamber, and remaining procedures were consistent with the migration method, ensuring that each set of assays was carried out at least three times.

Luciferase activity detection

LINC01128 sequence was cloned into a pmirGLO vector (Promega; Shanghai, China) and WT-LINC01128 and MUT-LINC01128 were constructed, respectively. T98G cells were co-transfected with WT-LINC01128 or MUT-LINC01128 and miR-27b-3p mimic, mimic NC, miR-27b-3p inhibitor, inhibitor NC, or control by lipofectamine 2000 (Invitrogen; USA). T98G cells were collected 48 hours after transfection, and luciferase activity was determined by a dual-luciferase reporter gene assay system (Program; USA).

Statistical analysis

All data obtained in the assay were expressed as mean ± standard deviation. Kaplan-Meier curve was used to evaluate the survival status of patients with glioma. Student *t*-test or one-way analyses of variance were applied to compare differences between two or more groups. Multivariate Cox analysis was to find prognostic factors of glioma. Data analysis software SPSS v. 20.0 (IBM, USA) and GraphPad 7.0 were applied, and $p < 0.05$ was considered statistically significant.

Results

LncRNA LINC01128 was increased in glioma tissues

Figure 1 shows the expression level of lncRNA LINC01128 in glioma tissues and normal tissues. The results implied that LINC01128 increased significantly in glioma tissues than in normal tissues, as determined by RT-qPCR. The correlation between the expression of lncRNA LINC01128 and clinical characteristics of glioma is demonstrated in Table I. It could be seen that among

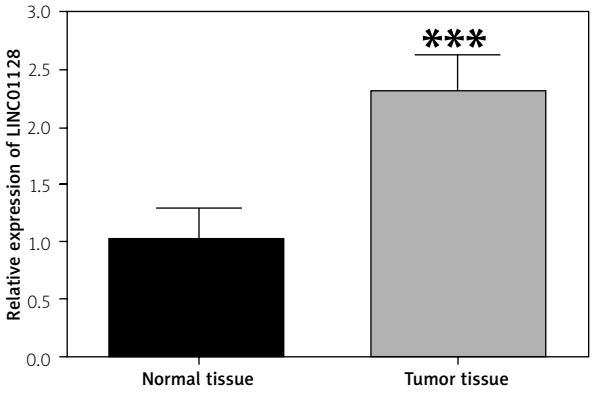

Fig. 1. Relative expression level of lncRNA LINC01128 in normal tissues and cancer tissues using RT-qPCR; ***$p < 0.001$.

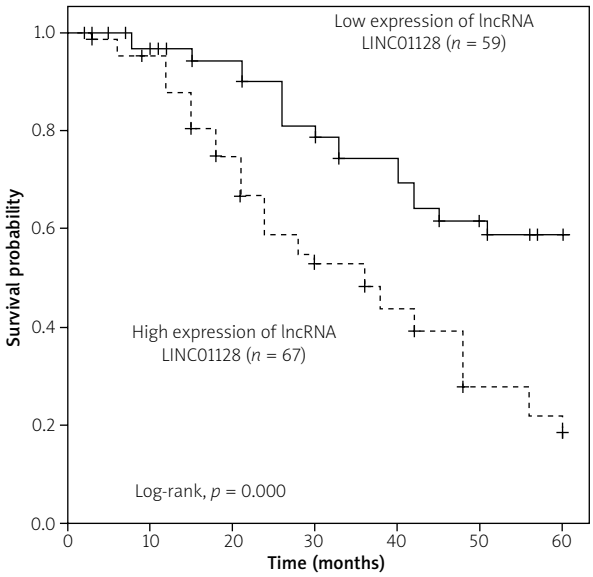

Fig. 2. Survival probability of low expressing lncRNA LINC01128 and high expressing lncRNA LINC01128 within five years was analyzed with Kaplan-Meier method (log-rank, $p = 0.000$).

the 126 glioma patients who participated in the study, the expression of LINC01128 was not related to the patient's age, gender, tumor size, and tumor location. However, the tumor recurrence, KPS, and WHO grade ($p < 0.05$) could affect the expression of LINC01128.

Analysis of survival and prognosis of glioma patients

The impact of high expression of LINC01128 and low expression of LINC01128 on the survival of glioma patients within five years was measured by Kaplan-Meier method (Fig. 2). Low expression of LINC01128 was compared with high expression of LINC01128; the patients had a higher probability of survival and better prognosis (log-rank, $p = 0.000$).

Multivariate Cox analysis of clinical features and overall survival are presented in Table II. LncRNA LINC01128 ($p < 0.001$) and WHO grade ($p = 0.014$) were indicated to be the factors affecting the survival of glioma patients. It could be interpreted that the possibility of LINC01128 as a prognostic biomarker of glioma was demonstrated by multivariate Cox analysis.

Silencing LINC01128 down-regulated the proliferation, migration, and invasion of glioma cells

To further explore the expression of LINC01128 in glioma cells, HA cells were compared with control; the expression of LINC01128 in glioma cells (U87, T98G, U251 MG, and A172) was significantly up-regulated by RT-qPCR (Fig. 3A). U87 and T98G cells with relatively higher LINC01128 expression and more obvious differences from the control group were selected to continue the subsequent assay. Figure 3B illustrates that LINC01128 in U87 and T98G cells were remarkably decreased after transfection of si-LINC01128 compared with the control group and si-NC. The CCK-8 reagent was selected to detect OD value at 450 nm in U87 and T98G cells, as shown in Figure 3C, D. Silencing LINC01128 inhibited the proliferation ability of glioma cells. At the same time, silencing LINC01128 also significantly inhibited the migration and invasion activities of U87 and T98G cells by Transwell method in Figure 3E and 3F, respectively. These results indicated that low expression of LINC01128 effectively affected the growth and proliferation of glioma cells and reduced cell viability.

Table II. Multivariate Cox analysis of clinical characteristics in relation to overall survival

Characteristics	Multivariate analysis		
	HR	95% CI	*p*-value
lncRNA LINC01128	3.293	1.740-6.230	< 0.001
Age	1.462	0.831-2.573	0.188
Gender	1.399	0.794-2.468	0.246
Tumor size	1.656	0.938-2.924	0.082
Tumor location	1.334	0.761-2.340	0.315
Tumor recurrence	1.647	0.918-2.953	0.094
KPS	1.721	0.975-3.038	0.061
WHO grade	2.174	1.171-4.035	0.014

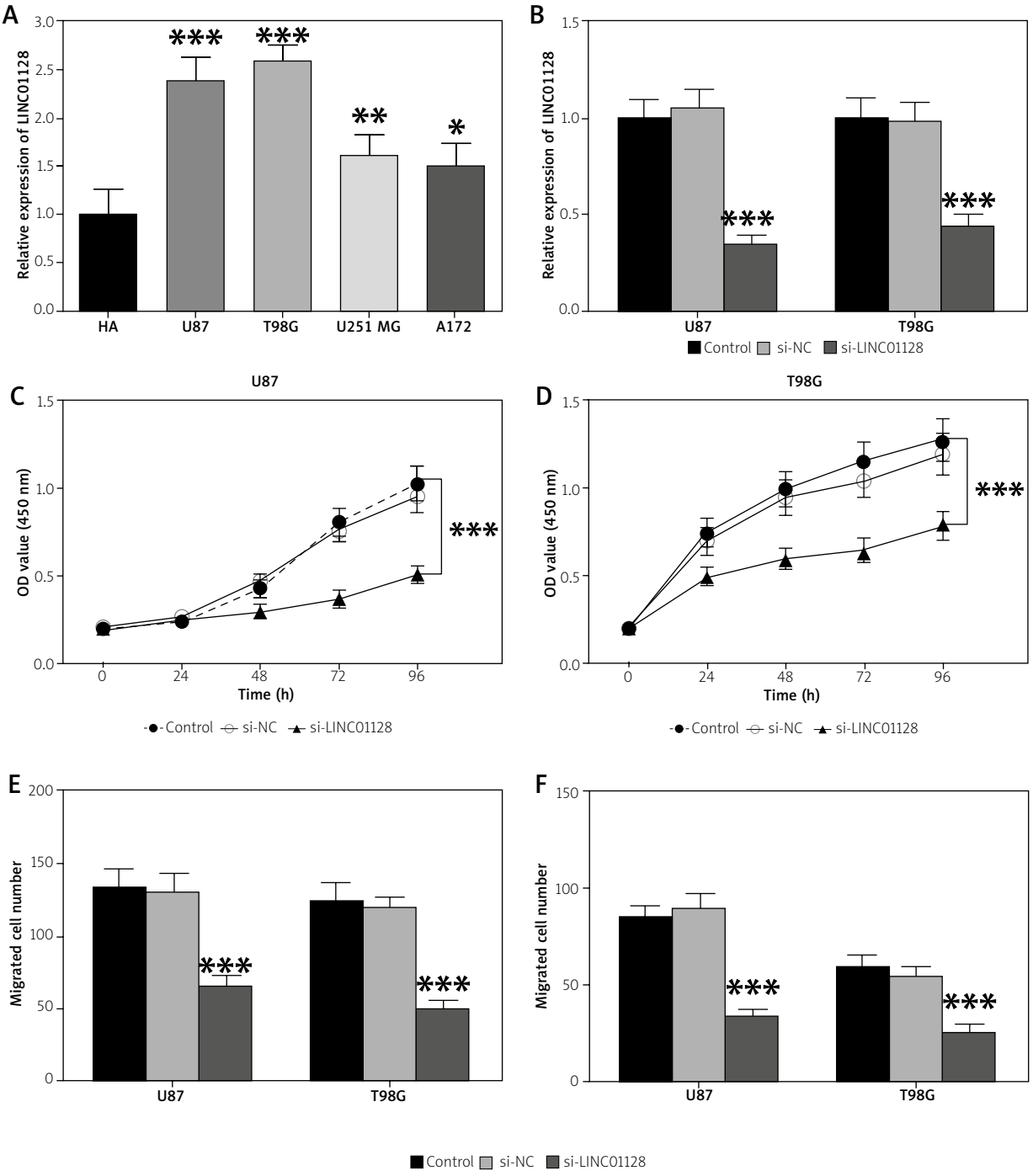

Fig. 3. Expression level of lncRNA LINC01128 in different glioma cell lines, and analysis of cell proliferation, migration, and invasion. **A**) Relative expression level of LINC01128 was up-regulated in different glioma cancer cells compared with HA cells; **B**) Relative expression level of LINC01128 in U87 and T98G cells transfected with si-LINC01128 was significantly down-regulated; **C**, **D**) Proliferative capacity of U87 and T98G cells were reduced, measured by CCK-8; **E**) Migration ability of U87 and T98G cells was down-regulated and measured by Transwell assay; **F**) Invasion levels of U87 and T98G cells were down-regulated and measured by Transwell assay; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

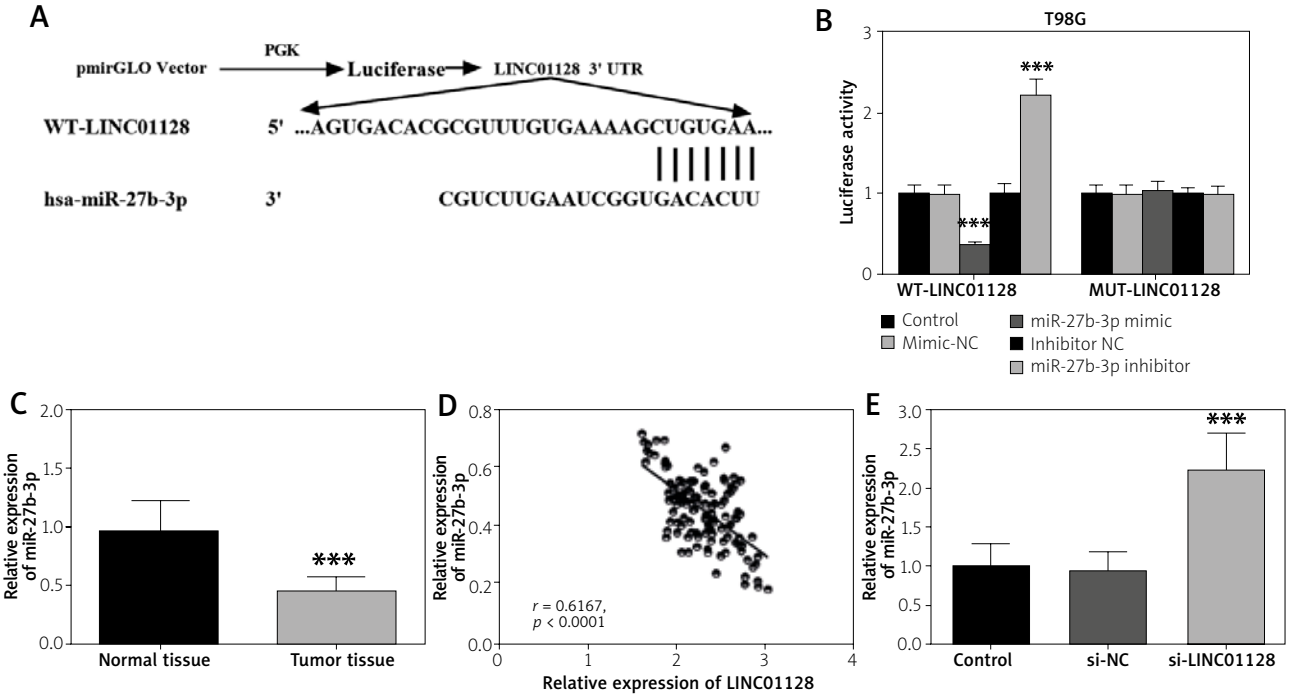

Fig. 4. LncRNA LINC01128 targeting miR-27b-3p was analyzed and studied. **A**) Complementary binding site of lncRNA LINC01128 and miR-27b-3p; **B**) Luciferase activity of WT-LINC01128 and MUT-LINC01128 in T98G cells; **C**) Relative expression level of miR-27b-3p in normal tissues and cancer tissues using RT-qPCR; **D**) Expression levels of LINC01128 and miR-27b-3p were negatively correlated; **E**) si-LINC01128 in T98G cells increased the expression level of miR-27b-3p; ***$p < 0.001$.

LncRNA LINC01128 targeted miR-27b-3p

There was a potential binding region of lncRNA LINC01128 on miR-27b-3p, which was predicted by bioinformatics. In Figure 4A, WT-LINC01128 have a binding site with miR-27b-3p. To reveal the regulatory mechanism of LINC01128 on miR-27b-3p, WT-LINC01128 and MUT-LINC01128 were constructed. As shown in Figure 4B, MUT-LINC01128 had no effect on luciferase activity in T98G cells. However, miR-27b-3p mimic reduced the luciferase activity of WT-LINC01128, and miR-27b-3p inhibitor promoted the luciferase activity. This suggested that LINC01128 interacted directly with miR-27b-3p. By comparing the expression of miR-27b-3p in glioma tissues and normal tissues, as can be seen in Figure 4C, the expression of miR-27b-3p in glioma tissues had decreased, which was much lower than that in normal tissues. Meanwhile, the expression of LINC01128 and miR-27b-3p negatively interacted, that is, miR-27b-3p was negatively adjusted by LINC01128 (Fig. 4D). Further studies on the effect of low expression of miR-27b-3p in glioma cells T98G found that low expression of LINC01128 regulated the expression of miR-27b-3p markedly up-regulated (Fig. 4E), speculating that si-LINC01128 promoted the expression of miR-27b-3p in glioma cells.

Discussion

As one of the malignant primary brain tumors, glioma has a very high mortality and morbidity rate [5,14,37]. The symptoms and signs caused by glioma are affected by the location of the tumor, such as headache, nausea, vomiting, epilepsy, blurred vision, and other symptoms [7,26]. In addition, increased intra-cranial pressure, brain edema, epilepsy, psychiatric symptoms, and a series of complications also occur [24]. However, the difference in malignant degree of glioma affects the speed of patient's disease progression. Moreover, it is difficult to achieve complete treatment of glioma, and it often recurs after surgery, which seriously affects the survival of patients [12]. Based on the above, it is necessary to analyze the pathogenesis of gliomas and use biomarkers for timely prognosis of patients to achieve more accurate treatment.

As mentioned earlier, a variety of lncRNAs play a regulatory role and prognostic value in the development of gliomas [29]. LncRNA LINC01128 has also been confirmed to be involved in tumor progression. It was known that LINC01128 has been found to increase expression in cervical cancer tissues and cells [9]. LINC01128 was obtained higher than the control group

in osteosarcoma tissues and cells as well [34]. In this study, the expression of LINC01128 was significantly upregulated in glioma tissues and cells by RT-qPCR analysis, which was consistent with the trend in previous studies. In order to further understand the potential mechanism and regulation of LINC01128 in glioma, the expression and clinical characteristics of LINC01128 were discussed. This study proved that silencing LINC01128 reduced the proliferation, migration, and invasion ability of glioma cells in-vitro, that is, LINC01128 promoted the development of glioma. This was similar to results that of Hu et al. study, who found that LINC01128 can enhance cell proliferation, migration, and invasion by binding to miR-383-5p [9], and indicated that our assay results had a certain reference value. Meanwhile, Yao *et al*. verified the effect of LINC01128 on the development of osteosarcoma, and clarified that LINC01128 accelerated the occurrence and development of osteosarcoma as well. Also, the survival of patients was evaluated based on log-rank test and Kaplan-Meier method to analyze the prognostic value of LINC01128 [34]. In this study, the same method was used and combined with multivariate Cox analysis to show that LINC01128 have the potential as a prognostic biomarker of glioma.

It has been demonstrated and confirmed in many studies that lncRNAs can affect the development of gliomas by combining with miRNAs [30,35]. Some literatures have confirmed that miR-27b-3p was related to the development of a variety of tumors, including glioma, colorectal cancer, and endometrial cancer [2,15,20,33]. Miao and his colleagues found that miR-27b-3p inhibited the development of glioma by targeting YAP1. Bioinformatics analysis revealed that LINC01128 might bind to miR-27b-3p in this study. Based on this bold speculation, LINC01128 might play a role in glioma by targeting miR-27b-3p. In order to explore the specific mechanism of LINC01128 and miR-27b-3p in gliomas, luciferase activity detection and clinical *in vitro* cell experiments explained that LINC01128 and miR-27b-3p had complementary sites, and LINC01128 was negatively correlated with miR-27b-3p. Furthermore, Chang *et al*. reported that lncRNA TTN-AS1 up-regulated RUNX1 through sponge miR-27b-3p to enhance glioma progression [4]. Combined with this study, it was suggested that LINC01128 may affect the development of glioma by targeting miR-27b-3p. Inevitably, there are still some deficiencies in the current research. For example, the number of participants should be increased, and in-depth clinical exploration before LINC01128 may be used as a prognostic treatment.

In general, lncRNA LINC01128 was highly expressed in gliomas. Silencing LINC01128 may inhibit the proliferation, migration, and invasion levels of glioma cells by targeting miR-27b-3p, thus affecting the progression of gliomas and benefiting the treatment and survival of patients. LINC01128 may be a new prognostic biomarker for glioma.

Disclosure

The authors report no conflict of interest.

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