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SET7/9 promotes H3K4me3 at lncRNA DRAIC promoter to modulate growth and metastasis of glioma

C. LI, S.-Y. FENG, L. CHEN

Department of Neurosurgery, Chinese PLA General Hospital, Beijing City, China

Abstract. – OBJECTIVE: We aimed at investigating the expression levels of SET7/9 in glioma and the relationship between SET7/9 and LncRNA DRAIC. Further, we explored the relationship between SET7/9 and glioma cell metastasis and mood.

PATIENTS AND METHODS: The expression levels of DRAIC and miR-18a-3p in gastric cancer cells were measured by quantitative polymerase chain reaction (qPCR). The binding site of the promoter of DRAIC by H3K4me3 was confirmed by ChIP-Real-time PCR. The direct target of DRAIC and miR-18a-3p in gastric cancer cells was measured by a Luciferase reporter assay. Cell proliferation was detected by Cell counting kit-8 (CCK8), and cell invasion and migration were measured by transwell assays.

RESULTS: Compared with adjacent non-cancerous normal tissues, SET7/9 and DRAIC were both downregulated and miR-18a-3p was upregulated in glioma cells. Meanwhile, silencing of SET7/9 enhanced cell proliferation, migration, and invasion in U251 cells. H3K4me3 protein can bind to DRAIC promoter directly. Inhibition of SET7/9 and downregulation of DRAIC in U251 cells reversed the effect of SET7/9 silencing on the growth and metastasis of glioma cells. In U251 cells, SET7/9 and DRAIC overexpression inhibited cell proliferation, migration and invasion. In addition, miR-18a-3p interacts with DRAIC through direct binding. The inhibition of DRAIC promoted the growth and metastasis of U251 cells, while the co-transfection of si- DRAIC and miR-18a-3p further promoted the growth and metastasis of U251 cells. Overexpression of DRAIC inhibited the growth and metastasis of cells, completely reversing the co-transfection of Lnc-DRAIC and miR-18a-3p.

CONCLUSIONS: In this research, we discovered that the expression of SET7/9 was low in glioma cells and SET7/9-mediated H3K4me3 enrichment on the DRAIC promoter regulated the growth and metastasis of glioma cells by targeting miR-18a-3p. It potentially provides a new therapeutic marker targeting glioma.

Key Words:
H3K4me3, DRAIC, Metastasis, Glioma.

Introduction

Gliomas are the most common primary intracranial tumor, representing 81% of malignant brain tumors, although relatively rare, they cause significant mortality and morbidity[1,2]. Glioblastoma, the most common glioma histology (~45% of all gliomas), has a 5-year relative survival of ~5%[3]. Hence, glioma has fast growth rate, strong invasion ability and poor prognosis and it is vital to further reveal the pathogenesis of glioma and find a new drug target that more effectively blocks this progressive disease.

Histone is one of the major components of chromatin, and its amino acid residues can change the covalent modification of chromatin configuration, resulting in transcription activation or in addition to the simple regulation of gene expression[4]. Gene silencing histone modification can also raise protein complex, affect the downstream proteins which participate in cell division, cell apoptosis and memory formation, and even affect the immune system and inflammation[5]. Amino acid residues on histones that can be covalently modified are called modification sites which are usually located in four common histones (H2A, H2B, H3, H4), especially the free amino terminus of H3 and H4[6]. Common modifications include histone acetylation/deacetylation, methylation/demethylation, and phosphorylation[7]. Crosstalk between lysine methylation and other post-translational modifications is important for transcriptional gene regulation and epigenetic inheritance[8]. In addition to histones, several other cellular proteins, including transcription factors, tumor suppressors, and membrane related recep-

Corresponding Author: Chong Li, MD; e-mail: badlc301@126.com

tors, undergo lysine methylation[9]. SET7/9 plays an important role in the lysine methylation of histones and non-histones and is a known lysine methyltransferase involved in the monomethylation of lysine 20 of histone H3 (H3K4me3)[10]. Methyltransferase activity of this enzyme is involved in several basic cellular pathways, including DNA replication, cell cycle regulation, genomic instability, transcriptional regulation, and cell metabolism[11].

Long non-coding RNA (lncRNA) is a subclass of non-coding RNA, whose tissue specificity and cell specificity are stronger than that of coding RNA. LncRNAs are expressed in different cells and tissues and are closely related to the occurrence and development of many diseases[12-14]. LncRNA is considered to be a new epigenetic regulation and plays an important regulatory role in cell differentiation, proliferation, apoptosis and metabolism[15]. Histone methylation can regulate the expression of lncRNA and participate in a variety of important regulatory processes including chromatin remodeling, transcriptional activation, and transcriptional interference[16]. LncRNA maternal expression gene DRAIC has been shown to have anti-cancer effect and its expression in other cancer such as nasopharyngeal carcinoma significantly decreased[17], but the role of DRAIC in glioma and the relative mechanism is not clear.

The purpose of this study was to explore the interaction between DRAIC and H3K4me3-mediated miR-18a-3p in glioma cell proliferation, migration and invasion, to reveal the molecular mechanism of H3K4me3 in glioma progression, and to provide new ideas for glioma treatment.

Patients and Methods

Patients and Glioma Samples

In this work, 20 pairs of glioma tissue samples and adjacent normal ones were collected from surgically treated glioma cases and then stored at -80°C. All specimens were handled and made anonymous according to the ethical and legal standards. 20 cases of glioma patients based on accepted clinicopathological were enrolled in this study. This study was approved by the Ethics Committee of Nanchang University. Patients and their families had been fully informed that their specimens would be used for scientific research, and all participating patients had signed informed consent. Information of patients was included in Table I.

Cell Culture

Normal human glioma cell line (HEB) and human glioma cell lines (U251) were purchased from American Type Culture Collection (ATCC, Manassas, VA, USA). Cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM, HyClone, South Logan, UT, USA) supplemented with 10% fetal bovine serum (FBS; HyClone, GE Healthcare Life Science, South Logan, UT, USA), 100 U/mL penicillin and 100 μg/mL streptomycin (Invitrogen, Carlsbad, CA, USA) and incubated in a 5% CO_2 incubator at 37°C.

Cell Transfection

For cell transfection, cells in the logarithmic growth phase were transfected with corresponding constructs when the confluence was up to 80% following the instructions of Lipofectamine2000 (Life Technology, Carlsbad, CA, USA). At 6-h post-transfection, the culture medium was replenished with fresh DMEM containing 10% FBS. DRAIC-small interfering RNA (si-DRAIC), SET7/9-small interfering RNA (si-SET7/9), negative control (si-NC), DRAIC overexpression model (Lnc-DRAIC or Lnc-NC) and miR-18a-3p were constructed by Gene Pharma (Shanghai, China).

Chromatin Immunoprecipitation (ChIP)

The ChIP assay was performed using the ChIP assay kit (Sigma-Aldrich, St. Louis, MO, USA) according to the manufacturer's protocol. Cells were crosslinked with 1% formaldehyde for 10 min at room temperature and the reaction was terminated with 125 mM glycine treatment for 10 min. Chromatin extracts were immunoprecipitated with anti-H3K4me3 and anti-IgG antibodies

Table I. Demographic data.

Gender	Male	Female
Patients numbers	10	10
BMI (kg/m^2) ± SD	21.6 ± 3.6	20.3 ± 2.7
Age (years)		
< 45	4	5
≥ 45	6	5
TNM stage		
I-II	6	6
III-IV	4	4
Lymph node metastasis		
Negative	7	6
Positive	3	4

All the patients were selected randomly.

on Protein-A/G-Sepharose beads. After washing, elution, and de-crosslinking, PCR was performed using the primers spanning the putative H3K4me3-binding site on DRAIC.

RT-qPCR Assays

After taking out the culture plates, the cells were washed with PBS. After treatment, total RNA of cells was extracted by using TRIzol reagent (Life Technologies, Waltham, MA, USA) according to the manufacturer's instructions. Samples were stored at room temperature for 30 min. The reverse transcription of cDNA was performed with a PrimeScript™ RT reagent Kit (TaKaRa, Otsu, Shiga, Japan) according to the manufacturer's instructions. And for qRT-PCR, PCR primers were synthesized by GenePharma (ShangHai Gene Pharma, Shang-Hai, China) and sequences were listed in Table II. SYBR Premix Ex Taq II (TaKaRa, Otsu, Shiga, Japan) was used to detect the expression.

CCK-8 Assays

Cell proliferation capacity of treated U251 cells was evaluated using Cell Counting Kit-8 (CCK-8, CK04, Dojindo Molecular Technologies, Dojindo, Kumamoto, Japan) referring to the manufacturer's instructions at days 1, 2, 3 and 4 post-inoculation. Briefly, cells after transfection were seeded in 96-well plates in growth medium at approximately 6×10^3 cells/well. Then, 10 µl of CCK-8 solution was added into each well at each time-point and incubated at 37°C for 2 hours in dark. The optical density (OD) value (450 nm) was evaluated by a microplate reader (9200, Bio-Rad Laboratories, Hercules, CA, USA).

Transwell Assay

Transwell assay was used to investigate the invasion and migration of glioma cells. Cells were put on the upper the Matrigel-coated invasion chambers or non-coated migration chambers (BD Biosciences, Franklin Lakes, NJ, USA). 500 µl of DMEM medium containing 10% FBS was put in the lower chamber and serum-free medium was put in the upper chamber. The non-invasive cells were wiped off by cotton swabs after 48 hours of incubation. The invading or migrating cells were fixed with 95% ethanol, stained with 0.1% crystal violet. The number of invasive and migratory cells in the lower chamber were counted under an inverted microscope.

Luciferase Assays

Luciferase assay was used to investigate the interaction among DRAIC and miR-18a-3p with a Dual-Luciferase Reporter Assay System (Promega, Madison, WI, USA). The wild-type DRAIC and mutant DRAIC sequence (mutant in miR-18a-3p binding site) were cloned into pmirGLO plasmid. The pmirGLO-DRAIC or pmirGLO-DRAIC-mut was co-transfected with miR-18a-3p mimics or miR-NC by Lipofectamine 2000 (Life Technology, Carlsbad, CA, USA). Subsequently, the recombinant vectors were co-transfected with miR-NC or miR-18a-3p mimics into HEK 293 cells. Luciferase activity was detected by the Dual-Luciferase Reporter Assay System (Promega, Madison, WI, USA) according to the manufacturer's protocols after transfection for 48 h.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 5 V5.01 software (La Jolla, CA, USA). Statistical differences between the two groups were analyzed using the Student's *t*-test. The comparison between multiple groups was made using One-way ANOVA test followed by Post-Hoc Test (Least Significant Difference). Kaplan Meyer curves assay was performed using log-rank test. Independent experiments were repeated at least three times for each experiment and error bars were mean ± standard deviation ($\bar{x} \pm$ SD). $p<0.05$ was considered statistically significant.

Table II. Primer sequences for qRT-PCR.

Genes	Forward	Reverse	Tm (°C)
SET7/9	5'-AGGCTCACTTATCGAATTGGC-3'	5'-GACATAGAACATCCGATGAA-3'	60
miR-18a-3p	5'-AGCGTACATAGAGGTACA-3'	5'-GGTACGGCCTACATTCCTG-3'	61
DRAIC	5'-GCATGGCTTACCTAACAGC-3'	5'-GTTCACTGAGGACCAGCCAAT-3'	62
GAPDH	5'-ACCGATTGGACACACGGCAT-3'	5'-AGACGATTAGCACTCGTACCG-3'	62
U6	5'-CGTTCGTTAGGCTTCGGCATC-3'	5'-TTCGGATGCGGAATGCCTGACG-3'	62

Results

SET7/9 and DRAIC Were Downregulated in Glioma

We first investigated the expressions of SET7/9 and DRAIC in glioma tissues and adjacent normal tissues to figure out the roles of SET7/9 and DRAIC in glioma progression by qRT-PCR. The results showed that the expressions of both SET7/9 and DRAIC were significantly downregulated in glioma tissues compared with adjacent normal tissues (Figure 1A and 1B). The mRNA expression level of SET7/9 was also significantly lower in glioma cell lines (U251) than that in a normal human glioma cell line as the same (HEB) (Figure 1C). DRAIC expression was decreased in U251 compared with HEB (Figure 1D). Meanwhile, Kaplan-Meier analysis suggested that low expression of SET7/9 was associated with reduced overall survival (Figure 1E). In summary, these data showed that SET7/9 is a potential oncogene in glioma and correlated with poor prognosis of glioma patients.

SET7/9 Inhibition in Glioma Cells Depressed Cell Proliferation, Invasion and Migration

To further explore the function of SET7/9 in glioma cells, we used si-SET7/9 to decrease the expression of SET7/9 in U251 cells and the transfection efficiency was tested using qRT-PCR and WB. The mRNA expression levels of SET7/9 were suppressed in U251 cells after transfection with si-SET7/9 (Figure 2A). The CCK8 showed that SET7/9 inhibition significantly decreased the proliferative ability of U251 cells (Figure 2B). We used transwell assays to detect the cell invasive and migratory abilities in si-SET7/9-transfected glioma cells, and SET7/9 inhibition significantly suppressed cell invasion (Figure 2C) and migration (Figure 2D) in U251 cells. Besides, qRT-PCR analysis showed that the expression of apoptotic related genes such as Bax and cleaved caspase-3 were significantly decreased whereas the expression of anti-apoptotic gene Bcl-2 was remarkably increased after downregulation of SET7/8 expression (Figure 2E-2G). These results indicat-

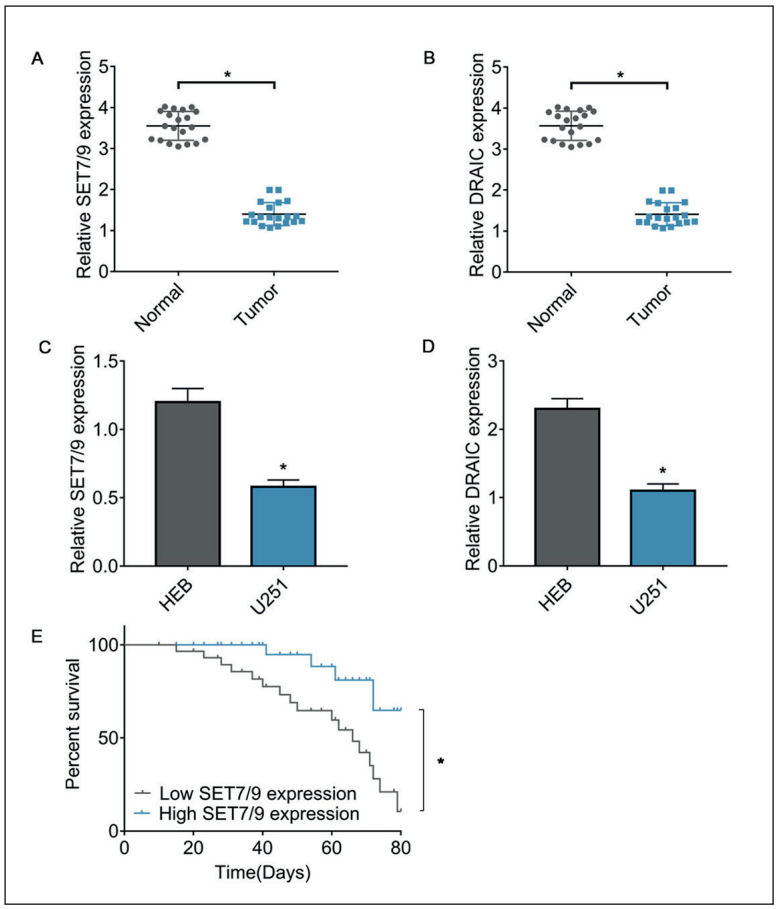

Figure 1. SET7/9 and DRAIC were downregulated in glioma. **A**, The mRNA expression levels of SET7/9 in human glioma tissues and adjacent tissues. **B**, Relative mRNA expression of DRAIC in human glioma tissues and adjacent tissues. **C**, The mRNA expressions of SET7/9 were measured by qRT-PCR in glioma tumor cell lines (HEB) and normal human glioma cell line (U251). **D**, The mRNA expressions of DRAIC were assessed by qRT-PCR in glioma tumor cell lines (HEB) and normal human glioma cell line (U251). **E**, The Kaplan-Meier survival curve of glioma patients based on SET7/9 expression. n=20,*$p<$ 0.05, log-rank test. The data in the figures represent the averages ± SD. Statistically significant differences between the treatment and control groups are indicated as * ($p < 0.05$) or ** ($p < 0.01$).

ed that SET7/9 can inhibit glioma cell proliferation, migration, invasion and regulate cell apoptosis.

SET7/9-Mediated H3K4me3 Enrichment on the DRAIC

SET7/9 is a specific H3K4me3 histone methyltransferase. To reveal whether SET7/9-mediated H3K4me3 enrichment on the DRAIC regulated the growth and metastasis of glioma, si-DRAIC or Lnc-DRAIC was introduced into si-SET7/9 transfected U251 cells. The expression level of H3K4me3 was decreased in U251 cells after transfection with si-SET7/9 (Figure 3A). ChIP assay was showed to evaluate the binding of H3K4me3 to the DRAIC. We observed an increase in the binding between H3K4me3 and DRAIC in U251 cells (Figure 3B). Furthermore, the silencing of SET7/9 dramatically reduced the expression level of DRAIC in U251 cells (Figure 3C). Besides, SET7/9 inhibition and DRAIC down-expression in U251 cells enhanced the effects of silencing of SET7/9 on glioma cell proliferation (Figure 3D), invasion (Figure 3F), and migration (Figure 3H). However, SET7/9 inhibition and DRAIC over-expression in U251 cells reversed the effects of silencing of SET7/9 on glioma cell proliferation (Figure 3E), invasion (Figure 3G), and migration (Figure 3I). These findings indicated that SET7/9-mediated H3K4me3 enrichment on the DRAIC regulated the growth and metastasis of glioma cells.

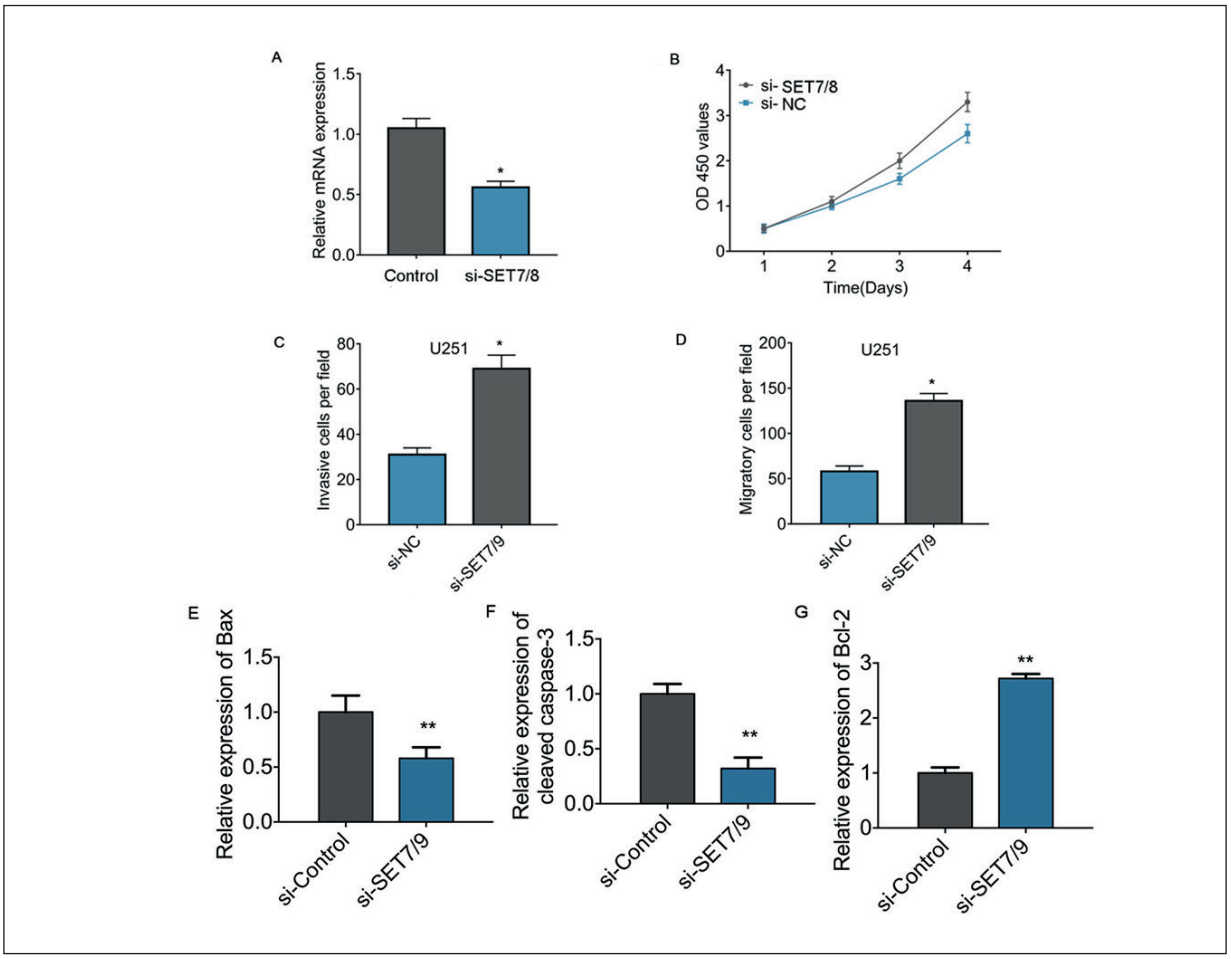

Figure 2. SET7/9 inhibition in glioma cells increased cell proliferation, invasion and migration. **A**, The mRNA expression levels of SET7/9 in U251 cells after transfection with si-SET7/9 were observed by qRT-PCR. **B**, The cell proliferation of U251 cells after transfection with si-SET7/9 was measured using CCK-8 assay. **C**, The cell invasion of U251 cells after transfection with si-SET7/9 was assessed using transwell assay. **D**, The cell migration of U251 cells after transfection with si-SET7/9 was measured using transwell assay. **E-G**, Relative expression of Bax, cleaved caspase-3 and bcl-2 in cells transfected with si-SET7/9. The data in the figures represent the averages ± SD. Statistically significant differences between the treatment and control groups are indicated as * ($p < 0.05$) or ** ($p < 0.01$).

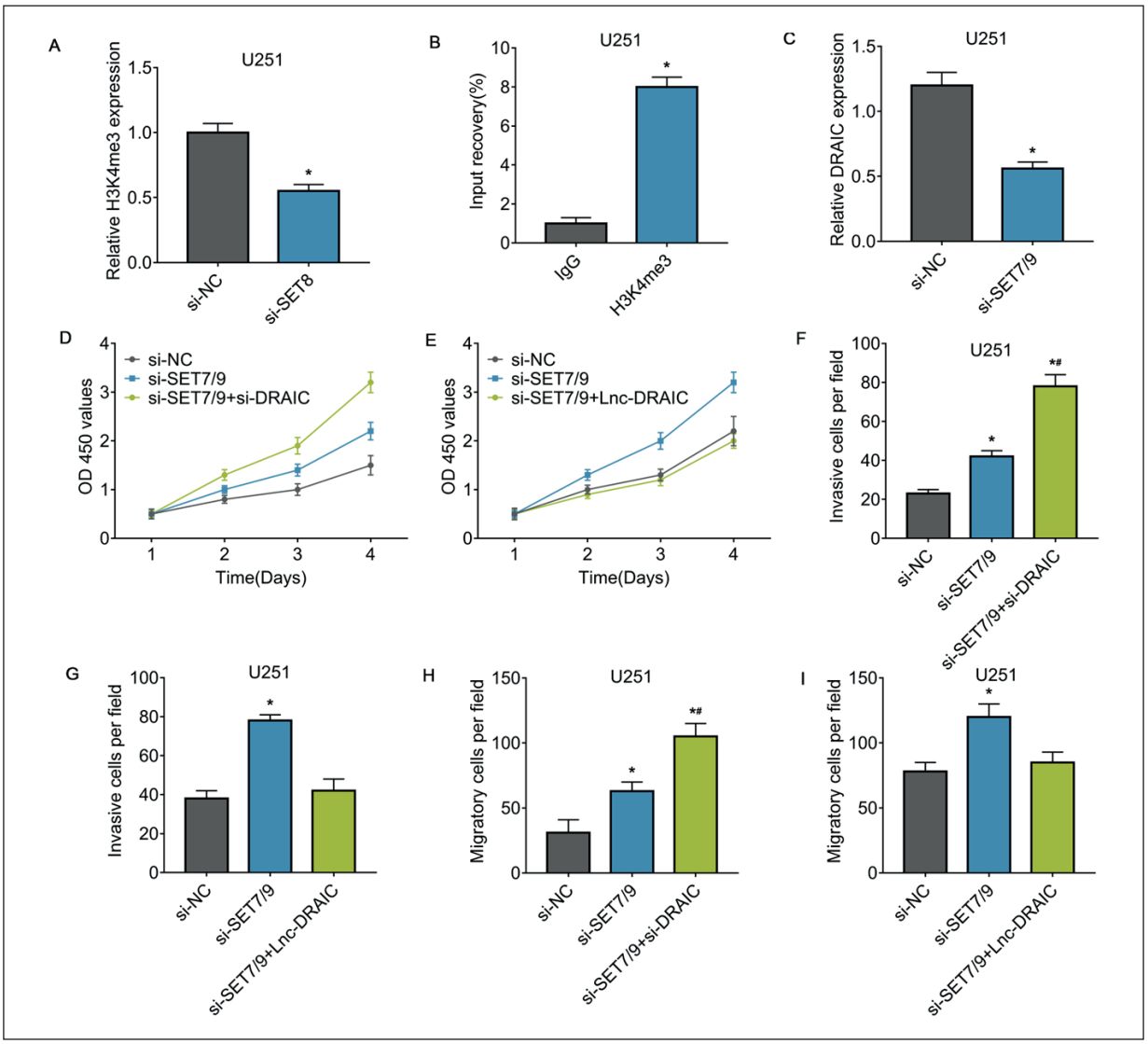

Figure 3. SET7/9-mediated H3K4me3 enrichment on the DRAIC. **A**, The expression level of H3K4me3 in U251 cells after transfection with si-SET7/9 was measured by qRT-PCR. **B**, The binding of H3K4me3 to the promoter region of DRAIC was performed by ChIP assay. **C**, The mRNA expression levels of DRAIC in U251 cells after transfection with si-SET7/9 were measured by qRT-PCR. **D**, The cell proliferation of U251 cells after transfection with si-SET7/9 or si-SET7/9 and si-DRAIC was measured using CCK-8 assay. **E**, The cell proliferation of U251 cells after transfection with si-SET7/9 or si-SET7/9 and Lnc-DRAIC was detected using CCK-8 assay. **F**, The cell invasion of U251 cells after transfection with si-SET7/9 or si-SET7/9 and si-DRAIC was measured using transwell assay. **G**, The cell invasion of U251 cells after transfection with si-SET7/9 or si-SET7/9 and si-DRAIC was measured using transwell assay. **H**, The cell migration of U251 cells after transfection with si-SET7/9 or si-SET7/9 and si-DRAIC was measured using transwell assay. **I**, The cell migration of U251 cells after transfection with si-SET7/9 or si-SET7/9 and Lnc-DRAIC was observed using transwell assay. The data in the figures represent the averages ± SD. Statistically significant differences between the treatment and control groups are indicated as * ($p < 0.05$) or ** ($p < 0.01$).

DRAIC Suppressed MiR-18a-3p Expression by Direct Interaction

To further investigate the effects of DRAIC in glioma progression, the putative binding site between DRAIC and miR-18a-3p was predicted by bioinformatics (Figure 4A). Luciferase reporter gene assay demonstrated that miR-18a-3p over-expression led to a significant decrease in Luciferase activity of DRAIC-WT, but not in DRAIC-MUT (Figure 4B). Moreover, the mRNA level of miR-18a-3p was remarkably elevated in U251 cells after transfection with si-DRAIC

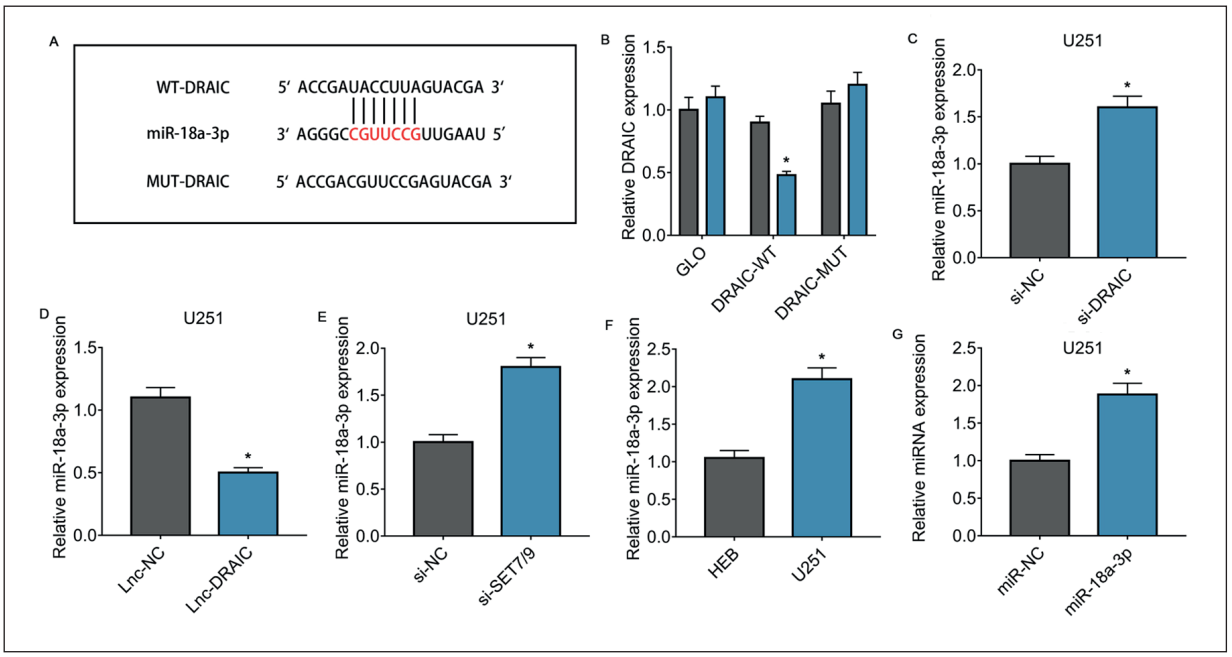

Figure 4. DRAIC suppressed miR-18a-3p expression by direct interaction. **A**, The predicted miR-18a-3p binging sites in DRAIC 3'-UTR. **B**, Effects of miR-18a-3p on the luciferase activity of DRAIC -WT and DRAIC -MUT reporter were detected by luciferase assays. **C**, The expression levels of miR-18a-3p were determined by qRT-PCR in U251 cells after transfection with si-DRAIC. **D**, The expression levels of miR-18a-3p were determined by qRT-PCR in U251 cells after transfection with Lnc-DRAIC. **E**, The expression levels of miR-18a-3p were determined by qRT-PCR in U251 cells after transfection with si-SET7/9. **F**, The mRNA expression levels of miR-18a-3p were measured by qRT-PCR in U251 and HEB cells. **G**, The mRNA expression levels of miR-18a-3p were measured by qRT-PCR in U251 cells after transfection with miR-18a-3p mimics. The data in the figures represent the averages ± SD. Statistically significant differences between the treatment and control groups are indicated as * ($p < 0.05$) or ** ($p < 0.01$).

(Figure 4C) and the mRNA level of miR-18a-3p was decreased in U251 cells after transfection with Lnc-DRAIC (Figure 4D). Furthermore, the silencing of SET7/9 significantly suppressed miR-18a-3p expression level in U251 cells (Figure 4E). To further verify the expression levels of miR-18a-3p in glioma cells, qPCR results showed miR-18a-3p expression was increased in U251 compared with RGM-1 (Figure 4F). To explore the function of miR-18a-3p in glioma cells, miR-18a-3p mimics were used to elevate the expression of miR-18a-3p in U251 cells and the transfection efficiency was tested using qRT-PCR.

MiR-18a-3p Was the Functional Target of DRAIC that Affects the Growth and Metastasis of Glioma Cells

To further explore whether the effects of DRAIC in glioma progression were mediated by miR-18a-3p, si-DRAIC mimics and miR-18a-3p were co-transfected into U251 cells and Lnc-DRAIC mimics and miR-18a-3p was co-transfected into U251 cells. DRAIC down-expression in U251 cells promoted cell proliferation (Figure 5A), invasion (Figure 5C), and migration (Figure 5E), which was further strengthened following the co-transfection of si-DRAIC and miR-18a-3p. DRAIC over-expression inhibited U251 cell proliferation (Figure 5B), invasion (Figure 5D), and migration (Figure 5F) and a complete reversal of the results seen in co-transfection of Lnc-DRAIC and miR-18a-3p. All these data suggested that DRAIC blocked glioma cell growth and metastasis via down-regulating miR-18a-3p. All conclusion revealed that SET7/9-mediated H3K4me3 enrichment on the lncRNA DRAIC regulated the proliferation, invasion, migration of glioma cells through targeting miR-18a-3p.

Discussion

Gliomas account for about 30% of all brain tumors and tumors of the central nervous system, and 80% of all malignant brain tumors[18]. Although the five-year survival rate for gliomas

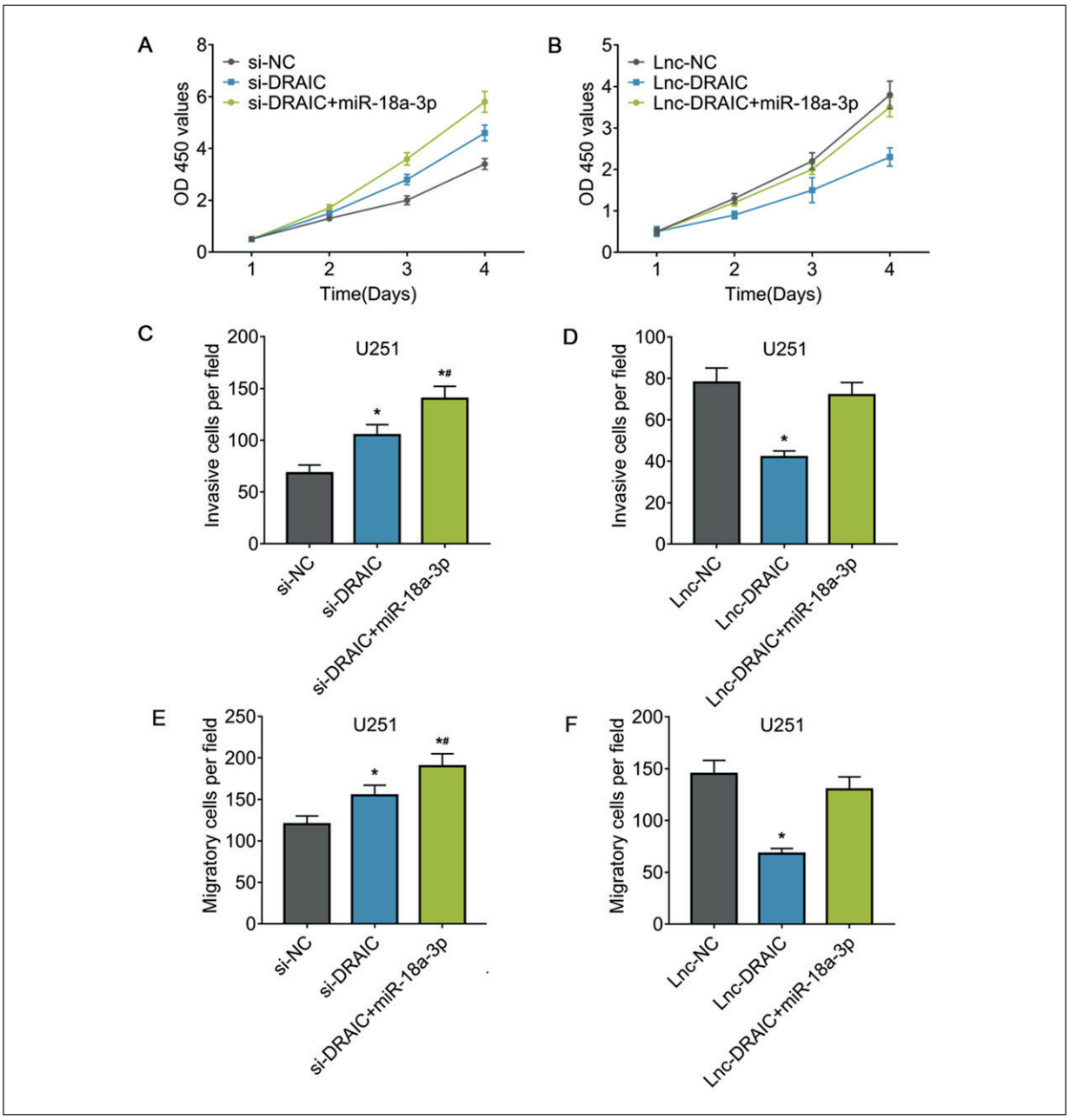

Figure 5. MiR-18a-3p was the functional target of DRAIC that affect the growth and metastasis of glioma cells. **A**, The cell proliferation of U251 cells after transfection with si-DRAIC or si-DRAIC and miR-18a-3p mimics was measured using CCK-8 assay. **B**, The cell proliferation of U251 cells after transfection with Lnc-DRAIC or Lnc-DRAIC and miR-18a-3p mimics was detected using CCK-8 assay. **C**, The cell invasion of U251 cells after transfection with si-DRAIC or si-DRAIC and miR-18a-3p mimics was observed using transwell assay. **D**, The cell invasion of U251 cells after transfection with Lnc-DRAIC or Lnc-DRAIC and miR-18a-3p mimics was indicated using transwell assay. **E,** The cell migration of U251 cells after transfection with si-DRAIC or si-DRAIC and miR-18a-3p mimics was disclosed using transwell assay. **F,** The cell migration of U251 cells after transfection with Lnc-DRAIC or Lnc-DRAIC and miR-18a-3p mimics was revealed using transwell assay. The data in the figures represent the averages ± SD. Statistically significant differences between the treatment and control groups are indicated as * ($p < 0.05$) or ** ($p < 0.01$).

has improved in recent years, it is still not encouraging. Therefore, our study aims to find a feasible alternative to the treatment of glioma. Epigenetics plays an important role in biological cytology by regulating gene expression without changing the encoding gene sequence whose regulation includes DNA methylation, histone modification, non-coding RNA regula-

tion, and chromatin remodeling[5,19-23]. At present, histone modification is closely related to the occurrence and development of tumors[24]. Through studies, we found that set7/9 is related to the proliferation, invasion and migration of glioma cells, with high expression in normal cells and low expression in glioma cells.

MicroRNAs regulate the expression of other genes[25]. miRNAs bind to target messenger RNA (mRNA) to inhibit post-transcriptional gene expression and play an important role in regulating gene expression, cell cycle, and timing of organism development[26]. They have been found to act as oncogenes or suppressor genes in human cancer by regulating processes associated with tumorigenesis[27]. In this study, we observed miR-18a-3p as one of the oncogene miRNAs associated with glioma progression, and DRAIC, as the molecular sponge of miR-18a-3p, which can regulate the growth and metastasis of glioma cells. To further explore whether the effect of DRAIC on glioma progression was mediated by miR-18a-3p, si-DRAIC mimics and miR-18a-3p were co-transfected into U251 cells; meanwhile, Lnc-DRAIC mimics and miR-18a-3p were co-transfected into U251 cells. The results showed that the down-regulated expression of DRAIC in U251 cells promoted cell proliferation, invasion and migration, and was further enhanced after co-transfection of si-DRAIC and miR-18a-3p. Overexpressed DRAIC inhibited the growth and metastasis of U251 cells and completely reversed the results seen in the co-transfection of Lnc-DRAIC and miR-18a-3p. All these data suggest that DRAIC blocks the growth and metastasis of glioma cells by down-regulating miR-18a-3p.

Histone methylation, a type of histone post-translational modification, is a hallmark of epigenetic and transcriptional regulation of gene expression. In particular, methylation at histone H3 lysine 4 (H3K4) is associated with active expression or poised bivalent states of genes at the genome-wide level. Broad H3K4me3 is an epigenomic signature that occupies the transcription start sites in tumor suppressor genes and cell identity genes. Our findings showed that SET7/9 loss caused decreases of broad H3K4me3 and induced glioma tumors. Notably, SET7/9 loss diminished broad H3K4me3 and tumor suppressor genes DRAIC, thus activating the invasion and proliferation of glioma tumor cells. Limitations in this research were the lack of the study of EMT *in vitro* and that of tumor progression *in vivo* xenograft nude mice.

Conclusions

Nowadays, it is important to figure out the molecular changes that induce the migration of tumor cells in glioma to improve prognosis and diagnosis. However, the detailed molecular mechanisms of lncRNA and histone methylation in cell migration and invasion remain poorly understood. In our study, we found that both SET7/9 and DRAIC were poorly expressed in glioma cells, while SET7/9-mediated enrichment of H3K4me3 in DRAIC regulated the growth and metastasis of glioma cells by targeting miR-18a-3p. Therefore, our study provides valuable clues for understanding the SET7/9 epigenetic regulation of the expression of LncRNA DRAIC to promote glioma proliferation and invasion.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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