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The m6A modification of LncRNA LINC00200 regulated by WTAP accelerates glioma tumorigenesis by regulating Wnt/β-catenin pathway

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Abstract

Background Several studies have delineated that dysregulated N6-methyladenosine (m6A) regulators participate in glioma progression. The objective of this study is to investigate the mechanism of Wilms' tumor 1-associating protein (WTAP)-mediated m6A modification of long noncoding RNA (lncRNA) LINC00200 in glioma.

Methods The LINC00200 expression in glioma was analyzed by qRT-PCR. The expressions of WTAP and Wnt/β-catenin pathway associated proteins were determined via qRT-PCR or western blotting. The levels of WTAP-mediated m6A modification of LINC00200 was ascertained by MeRIP-qPCR. Functionally, the effects of LINC00200 knockdown and the interaction of WTAP with LINC00200 on the glioma cell characteristics were examined by CCK8, colony formation, and transwell migration/invasion assays. In vivo experiments were performed to verify the effect of LINC00200 on tumor growth.

Results LINC00200 was overexpressed in glioma, and high LINC00200 level was related to higher-grade tumor. Moreover, its knockdown inhibited the malignant properties and expression of molecules related to Wnt/β-catenin pathway in glioma cell lines. In vivo, LINC00200 knockdown attenuated tumor growth. WTAP was also overexpressed in glioma tissues and demonstrated a positive association with LINC00200 expression. Furthermore, the relative enrichment of LINC00200 m6A was enhanced/reduced in a WTAP-dependent manner. Meanwhile, silencing LINC00200 partially reversed the malignant effects of WTAP overexpression in glioma.

Conclusion These results demonstrate that WTAP-mediated m6A modification of LINC00200 promotes glioma progression by modulating Wnt/β-catenin pathway.

Keywords Glioma, LINC00200, WTAP, M^6A modification, Wnt/β-catenin, LncRNA

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Introduction

Glioma is considered to be the most prevalent type of malignant tumor of the central nervous system (CNS), accounting for ~80% of the malignant primary brain tumors [1, 2]. In general, the gliomas are graded into 4 classes based on the amount and rate of the tumorous growth: I, II, III, and IV (I–II: *low grade*; III-IV: *high grade*). According to the WHO, grade IV gliomas are the worst malignant tumors because of their diffused cellular organization and high invasive and infiltration capacity [3]. The median time of survival for individuals diagnosed with grade IV gliomas is usually < 1.3 years, with just a tiny fraction (approximately 3–5%) living beyond 3 years [4]. Moreover, the prognosis for glioma patients has not substantially enhanced and the recurrence rate remains high [5, 6]. Hence, it is imperative to decipher the underlying molecular mechanisms of glioma development and its progression in order to uncover viable diagnostic and therapeutic targets.

Long noncoding RNAs (lncRNAs) are a class of RNA that do not code for proteins and usually have more than 200 nucleotides [7]. Numerous studies have delineated the significance of various lncRNAs in the recurrence and clinical outcome of gliomas when they are dysregulated by engaging in different cellular processes of glioma cells [8–10]. In this work, we looked into the significance of lncRNA LINC00200 in the tumorigenesis of glioma. Previous research on gastric cancer has revealed that LINC00200 is oncogenic, as it is implicated in tumor growth, metastasis, and resistance to oxaliplatin [11, 12]. Nonetheless, its biological significance and molecular mechanism in glioma remains obscure.

Interestingly, methylation-related lncRNAs have been implicated in cancer progression, but it is largely understudied in glioma [13]. In 1974, a group of researchers identified m6 A modification in the mRNA obtained from Novikoff hepatoma cells, which is methylation of adenosine at the N6-position [14]. Since then, m6 A modifications were found in RNAs other than mRNAs, including ribosomal RNAs, transfer RNAs, microRNAs, small nucleolar RNAs, circular RNAs, and lncRNAs [15]. Interestingly, the m6 A modifications regulated by methyltransferases ("writers"), demethylases ("erasers"), and binding proteins ("readers"), play vital roles in the pathogenesis of different cancers, including glioma [15, 16]. The "writers" include diverse m^6A methyltransferase proteins, including METTL3, METTL14, WTAP, KIAA1429, VIRMA, RBM15/15B, and METTL16, that collectively form the methyltransferase complex (MTC) [17]. Wilms tumor 1-associated protein (WTAP) is regarded as the regulatory subunit of MTC, as in its dearth, the methyltransferase's potential to bind RNA is significantly lowered [18]. Research has shown that WTAP has a significant impact in altering the progression of multiple diseases, including various degenerative disorders, cardiovascular diseases, and carcinoma [17]. However, its involvement in glioma has not been thoroughly examined, and the only study done on discerning its expression in glioblastoma found that it was overexpressed and that its overexpression made cancer cells more tumorigenic [19].

Therefore, we focused our current study to explore the effect of LINC00200 and its m6 A modification by WTAP on glioma cell malignancy. We additionally investigated molecules involved with Wnt/β-catenin pathway that serves a vital role in epithelial mesenchymal transition (EMT), a crucial event in the promotion of tumor cell invasion and metastasis [20]. We anticipate that our research might provide us a biomarker and possibly a therapeutic target for gliomas.

Results

LINC00200 mRNA expression was markedly elevated in glioma samples

We first checked the difference in LINC00200 expression between tumors and normal tissues in various cancers from the TCGA database. The result of the analysis demonstrated that LINC00200 was upregulated in the glioma samples (Fig. 1A). In addition, the qRT-PCR analysis elucidated that the LINC00200 expression levels were notably higher in our glioma tissue samples as compared to healthy tissues (Fig. 1B). When the expression of LINC00200 was evaluated between grade I-II and grade III-IV tumors, it found that the levels were significantly higher in grade III-IV tumor tissues (Fig. 1C). These outcomes demonstrate that LINC00200 was upregulated in glioma samples, and its high expression is associated with high grades.

Silencing LINC00200 reduced the malignant properties of glioma cells in vitro and in vivo

LINC00200 expression was silenced in HS683 and T98G cells with the transfection of si-lnc#1/#2 to investigate the significance of LINC00200 in glioma. The results of the qRT-PCR clearly demonstrated the reduction in the expression of the lncRNA (Fig. 2A). The CCK-8 assay disclosed that LINC00200 silencing markedly suppressed glioma cell proliferation compared to the control (Fig. 2B). The colony formation assay similarly revealed that LINC00200 silencing reduced the colony numbers of glioma cells (Fig. 2C). Additionally, the glioma cell migration and invasion were substantially reduced upon silencing of LINC00200 expression, as assessed by transwell migration and invasion assays, respectively (Fig. 2D and E). In vivo, LINC00200 silencing also reduced the tumor volume, size, and weight, suggesting that tumor growth could be inhibited by silencing of LINC00200 expression (Fig. 2F). These outcomes reveal that inhibition of

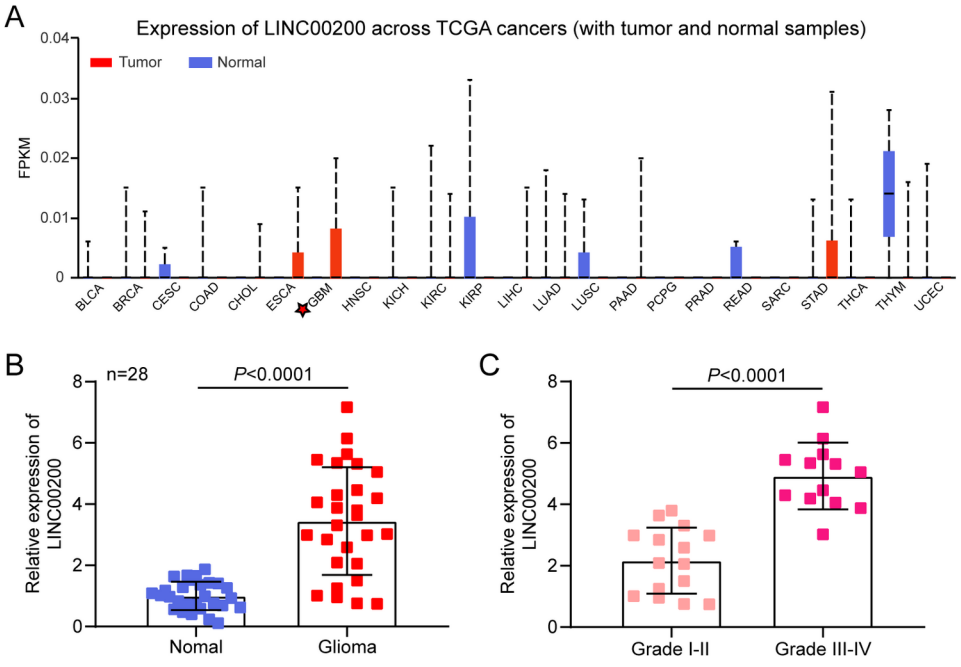

Fig. 1 Expression of LINC00200 was markedly elevated in glioma. **A** LINC00200 expression was analyzed in various human cancers from the data obtained from TCGA database. **B** LINC00200 expression was detected in 28 glioma tissue samples and 28 adjacent healthy tissue samples via qRT-PCR. **C** LINC00200 expression was compared between grade I–II and grade III–IV glioma tissue samples

LINC00200 expression reduces glioma cell proliferation, invasion and migration in vitro, as well as inhibited tumor growth in vivo.

Silencing LINC00200 restrained activation of Wnt/β-catenin pathway in glioma cells

miRDB database was used to predict 77 miRNAs binding to LINC00200. Then, FunRich was performed to enrich the key biological pathways of these miRNAs (Fig. 3A). Since Wnt signaling pathway plays pivotal role in tumor progression, and therefore, we further analyze the effects of LINC00200 on this signaling pathway. For this, western blotting was done to evaluate the relative expression levels of three proteins involved in Wnt/β-catenin pathway, including β-catenin, c-myc and cyclin-D1. The results demonstrated that in both cell lines, silencing LINC00200 markedly lowered the protein expression of the aforementioned molecules as compared to the controls (Fig. 3B). This suggests that LINC00200 silencing suppressed Wnt/β-catenin pathway in glioma cells.

WTAP was markedly upregulated and mediated m6A modification of LINC00200 in glioma cells

To investigate the potential m6 A modification of LINC00200 in glioma, qRT-PCR was performed to assess the expression levels of LINC00200 under overexpression of m6 A methyltransferases including METTL3, METTL14, WTAP, KIAA1429, ZC3H13, and RBM15 in glioma cells. Notably, only WTAP overexpression significantly increased LINC00200 expression in glioma cells (Supplementary Fig. 1). Then, we checked the WTAP expression in the glioma sample data from TCGA database and found that it was upregulated (Fig. 4A). Similar results were seen in our glioma tissue samples, wherein the WTAP expression was notably elevated in them than in healthy tissue samples (Fig. 4B). Furthermore, Pearson correlation analysis delineated positive correlation between the expressions of LINC00200 and WTAP in the glioma tissue samples (Fig. 4C). We then further explored the regulatory effect of WTAP on LINC00200 by silencing or overexpressing WTAP in HS683 and T98G cell lines. The outcomes of the western blotting clearly demonstrated the reduction and overexpression of WTAP protein after the transfections with the respective vectors (Fig. 4D). Moreover, the silencing and overexpression of WTAP in the glioma cells significantly reduced and elevated the expression of LINC01003, respectively (Fig. 4E). An anti-m6 A RIP assay together with RT-qPCR illustrated that the m6 A modification of LINC00200 was significantly increased in WTAP-overexpressed glioma cells (Fig. 4F). On the contrary, m6 A modification of LINC00200 was significantly reduced in WTAP-silenced glioma cells (Fig. 4G). Collectively, these findings implied that WTAP regulated the m6 A modification of LINC00200 in glioma cells.

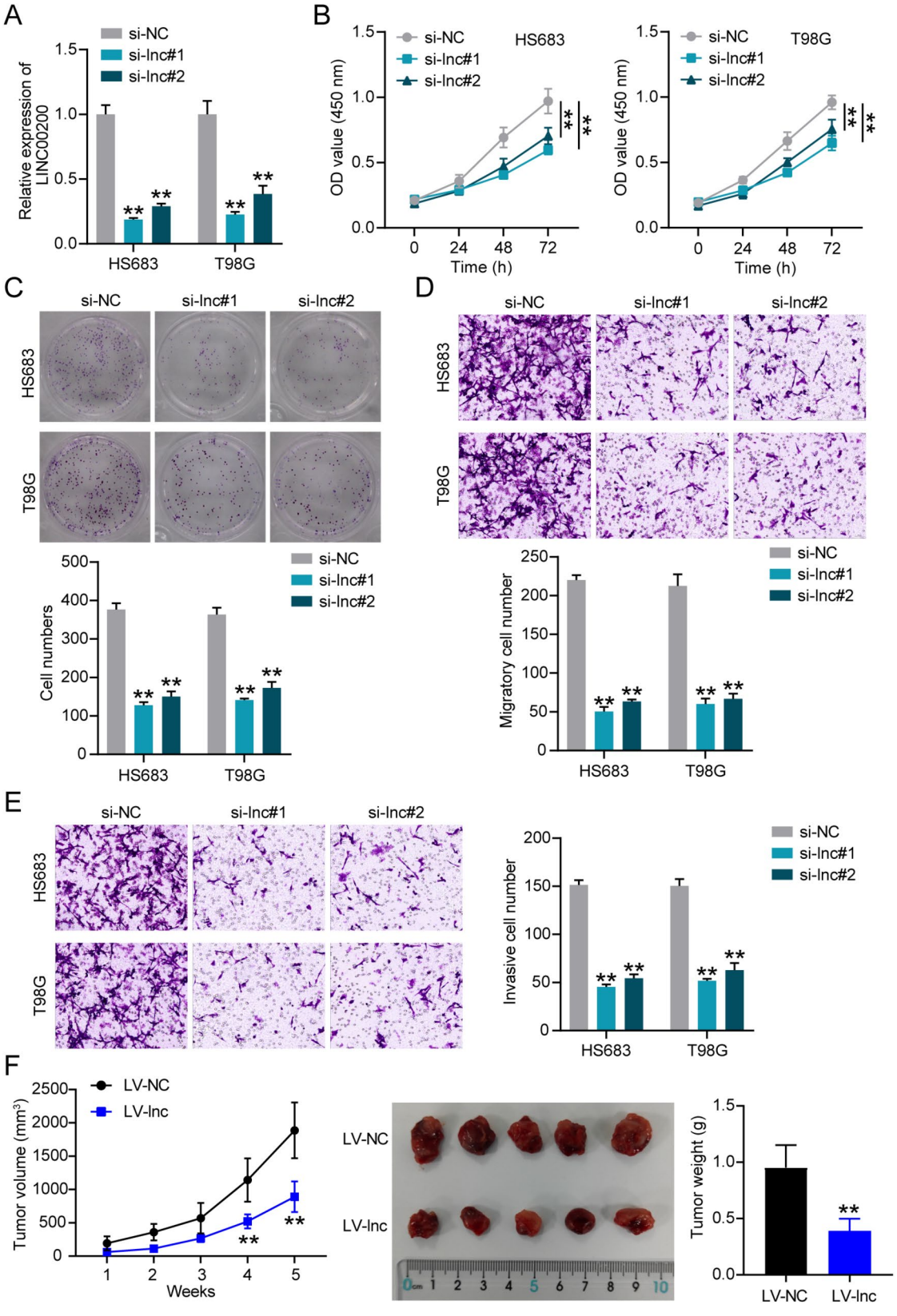

Fig. 2 (See legend on next page.)

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Fig. 2 Silencing LINC00200 reduced the malignant properties of glioma cells in vitro and in vivo. **A** The relative expression of LINC00200 was detected in HS683 and T98G cells by qRT-PCR at 48 h post-transfection with si-NC, si-lnc#1 and si-lnc#2. **B** The CCK-8 assay was done to determine the cell viability in the two transfected glioma cell lines. **C** The colony formation assay was done to check the cell number in the two transfected glioma cell lines. **D** The transwell migration assay was performed to assess the migrative ability in the two transfected glioma cell lines. **E** The transwell invasion assay was conducted to check the invasive ability in the two transfected glioma cell lines. **F** Tumor volume, size, and weight in mice after injecting HS683 cells with the transfection of LV-NC (negative control of lentiviral vector) and LV-lnc (LINC00200 knockdown lentiviral vector). $^{**}P < 0.001$ vs. si-NC or LV-NC

Silencing LINC00200 partially reversed the tumor-promoting effects of WTAP overexpression in glioma cells

Finally, we performed in vitro rescue experiments involving LINC00200 and WTAP in glioma cells to further understand their interactions. The CCK-8 and colony formation assays uncovered that WTAP overexpression markedly enhanced the cell proliferation capacity of glioma cells, which was partially reversed upon introduction of the si-lnc in these cells (Figs. 5A and B). Similarly, LINC00200 silencing partially reversed the migratory and invasive capacities of glioma cells that were upregulated by WTAP overexpression by the combined transfection of OE-WTAP + si-lnc (Fig. 5C and D). Hence, it is clear that LINC00200 enhances the progression of glioma via its WTAP-mediated m6 A modification, thereby revealing a targeted interaction between LINC00200 and WTAP.

Discussion

The occurrence and progression of glioma entails both genetic and epigenetic modifications [21]. Recently, there has been an increased emphasis on the role that lncRNAs play in tumor growth, and more and more lncRNAs have been identified that promote or inhibit the formation and progression of cancer [22]. Additionally, the biological importance of m6 A modifications has received a great deal of interest due to its robust regulation on mRNAs and noncoding RNAs [23, 24]. Therefore, this study focused on the role of LINC00200 and its m6 A methylation by WTAP in glioma progression. LINC00200 upregulation was observed in the tissue samples of glioma patients, and higher expression was related with high grade glioma. Furthermore, the LINC00200 silencing lowered the malignant properties of glioma cells and restrained Wnt/β-catenin signaling activation. Additionally, we also elucidated that the m6 A methylation of LINC00200 was mediated by WTAP, and their expressions were positively corelated in glioma. To our best knowledge, we are first to report the clinical value of LINC00200 and its m6 A methylation in glioma patients.

LINC00200 is a rarely studied lncRNA that is found on chromosome 10p15 and encoded by three exons [25]. It was first reported to be linked with the prognosis of hepatocellular carcinoma (HCC), in addition to four other lncRNAs [25]. The other two studies were done in gastric cancer, in which LINC00200 expression was upregulated and promoted the metastasis of gastric cancer as well as chemoresistance [11, 12]. As for the role of LINC00200 in glioma have not been reported. In our current study, we for the first time proved the upregulation of LINC00200 in glioma, and also revealed that LINC00200 is a tumor promotor in glioma by inhibiting proliferation, migration, and invasion. Our study innovatively confirmed that LINC00200 might be a prospective biomarker and therapeutic target for glioma.

Although contemporary studies have demonstrated the significance of m6 A modification as a regulator in cancer pathogenesis, it is still uncertain whether it operates in a lncRNA-dependent way during glioma tumorigenesis. The regulators of m6 A modification can render the malignancy of various types of tumors by altering particular lncRNAs [26]. However, few studies have been incurred to decipher the function of m6 A regulators affecting lncRNAs expression in glioma progression. The relevant literature, nevertheless suggests that m6 A-related lncRNAs are promising biological-markers for determining overall survival in individuals with low-grade glioma [27]. Among these m6 A modulators, WTAP has been extensively investigated in numerous malignancies but not in glioma, and the one study done on determining its expression in glioblastoma indicated that it was overexpressed, making cancer cells more tumorigenic [19]. Previous research has shown that WTAP acts as an oncogenic modulator of m6 A modification in HCC [28], osteosarcoma [29], and pancreatic cancer [30]. Similarly to earlier reports in glioma and other cancer, we also found that WTAP was elevated in glioma in the current investigation. Furthermore, it was shown that it mediated the m6 A regulation of LINC00200 and promoted the progression of glioma, which was different from the earlier reports. Therefore, our findings might enrich the regulatory mechanism of WTAP-mediated m6 A modification in glioma.

Our investigation also revealed that LINC00200 silencing markedly suppressed the Wnt/β-catenin signalling activation. This signalling pathway, which is thought to be one of the most evolutionarily conserved pathways, has been shown to perform vital functions in tumors [31]. This pathway has been implicated in serving a significant role in EMT, and any aberration in its activation impacts cell proliferation, invasion, migration, and apoptosis by regulating downstream molecules [20]. Therefore, an increasing number of efforts have been carried out to develop treatment techniques that explicitly target

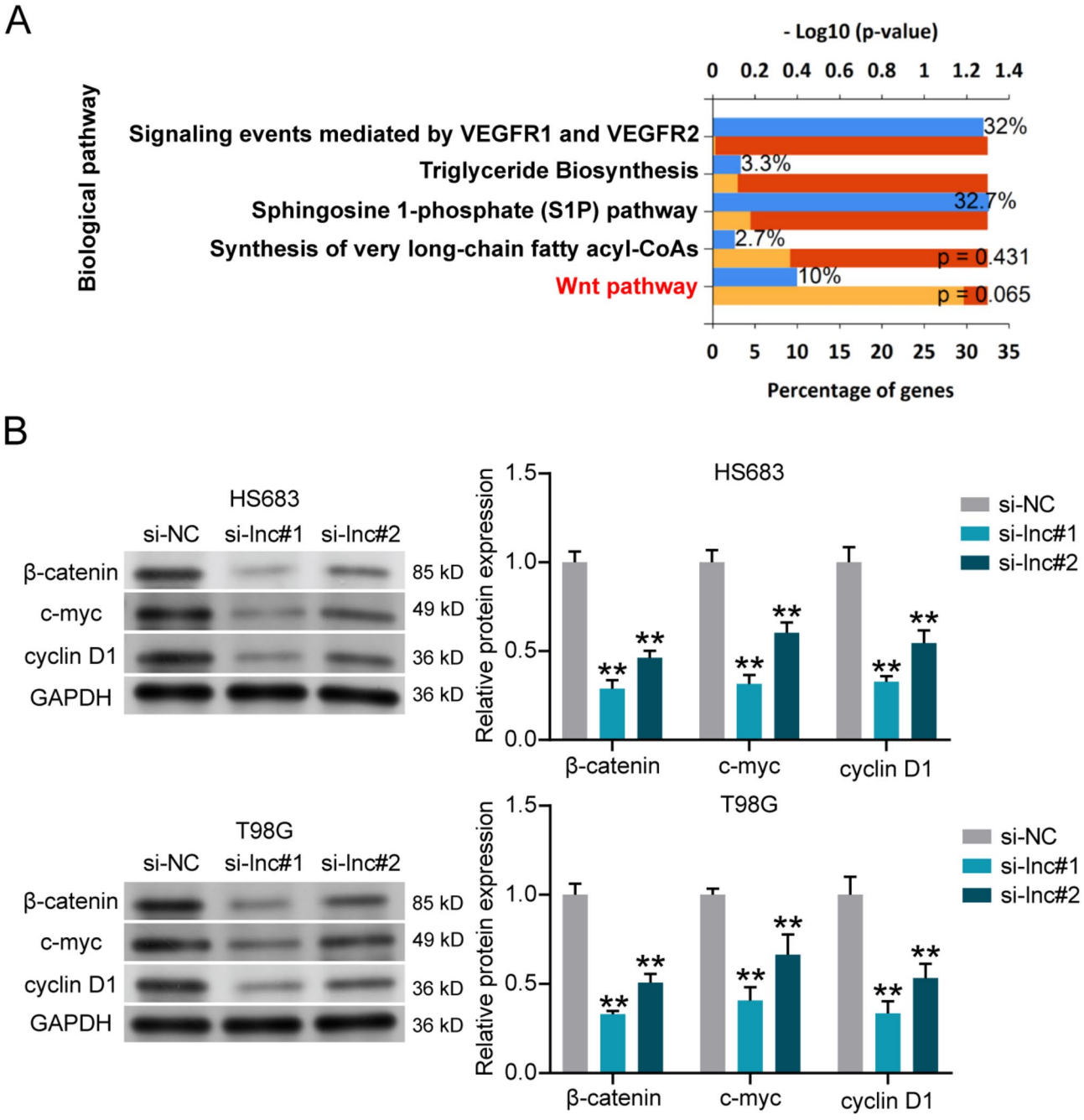

Fig. 3 LINC00200 silencing suppressed the Wnt/β-catenin signaling pathway in glioma cells. **A** The biological pathway of miRNAs binding to LINC00200 was enriched by FunRich. **B** The relative protein levels of β-catenin, c-myc and cyclin-D1 were analysed in HS683 and T98G cells transfected with si-NC, si-lnc#1 and si-lnc#2 by western blotting. $^{**}P < 0.001$ vs. si-NC

the Wnt/β-catenin pathway [32]. Previous work done in glioma has demonstrated aberrant Wnt/β-catenin pathway activation by various lncRNAs, such as LINC01503, BLACAT1, and LINC00839 [10, 33, 34]. Consistent with previous studies, our work also observed the activation of Wnt/β-catenin pathway in glioma cells. However, we found that silencing LINC00200 could suppress Wnt/β-catenin pathway in glioma, which was different from the previous studies.

There are some aspects that need to be addressed in future research. The prognostic significance of LINC00200 for glioma should be studied with a large sample set of patients with various stages and subtypes of gliomas. Additionally, the oncogenic role of

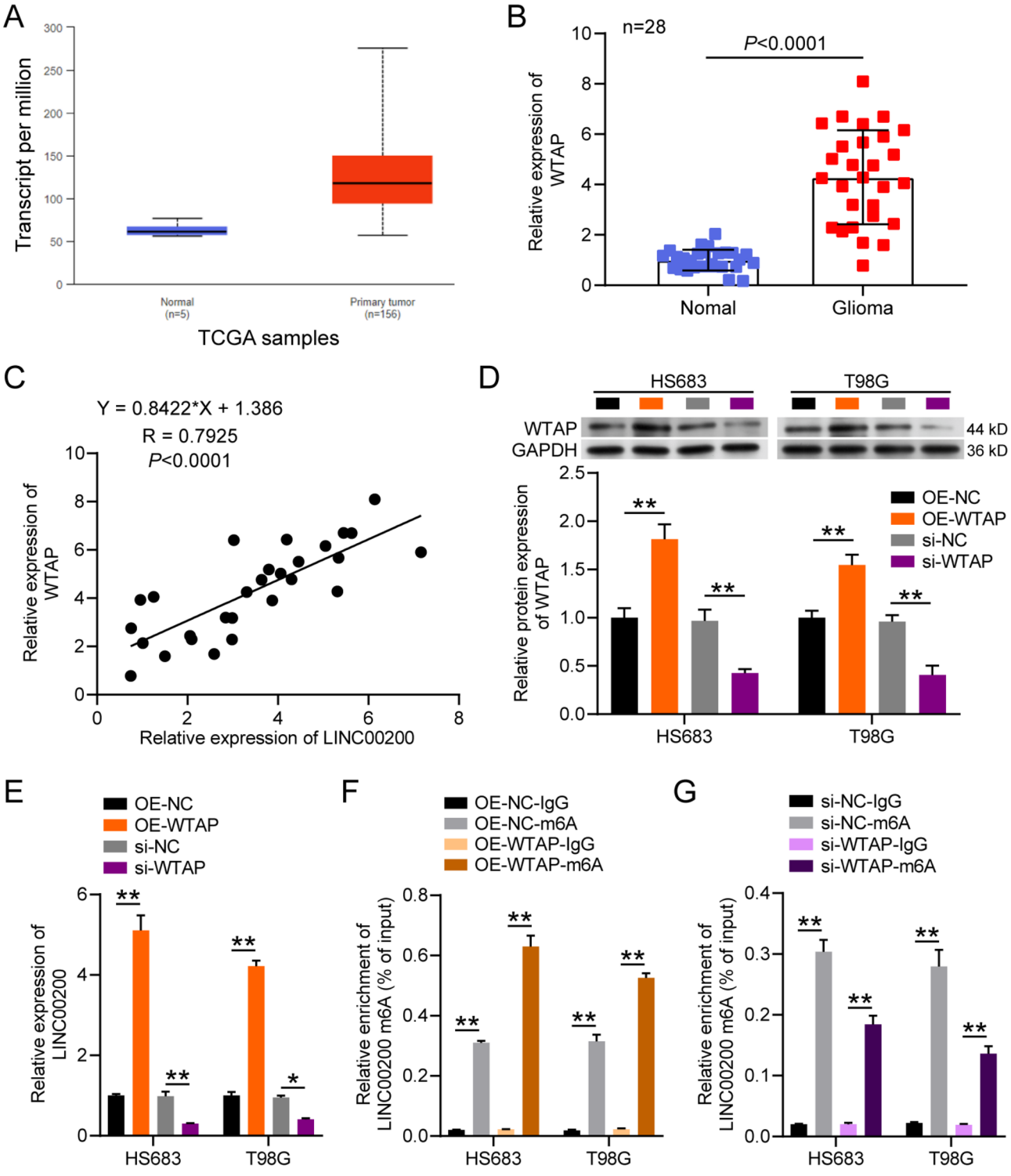

Fig. 4 WTAP expression was markedly elevated and mediated m6 A modification of LINC00200 in glioma cells. **A** WTAP expression was analyzed in glioma samples from the data obtained from TCGA database. **B** WTAP expression was detected in 28 glioma tissue samples and 28 adjacent healthy tissue samples via qRT-PCR. **C** The correlation of LINC00200 and WTAP expressions in glioma tissue samples was determined by Pearson correlation analysis. **D** The relative protein levels of WTAP were analysed in HS683 and T98G cells transfected with OE-NC, OE-WTAP, si-NC, and si-WTAP by western blotting. **E** The relative expression of LINC00200 was detected in HS683 and T98G cells by qRT-PCR at 48 h post-transfection with OE-NC, OE-WTAP, si-NC, and si-WTAP. **F** The status of m6 A methylation of LINC00200 between OE-NC and OE-WTAP transfected glioma cells was assessed using MeRIP-qPCR. **G** The status of m6 A methylation of LINC00200 between si-NC and si-WTAP transfected glioma cells was assessed using MeRIP-qPCR. $^{**}P < 0.001$

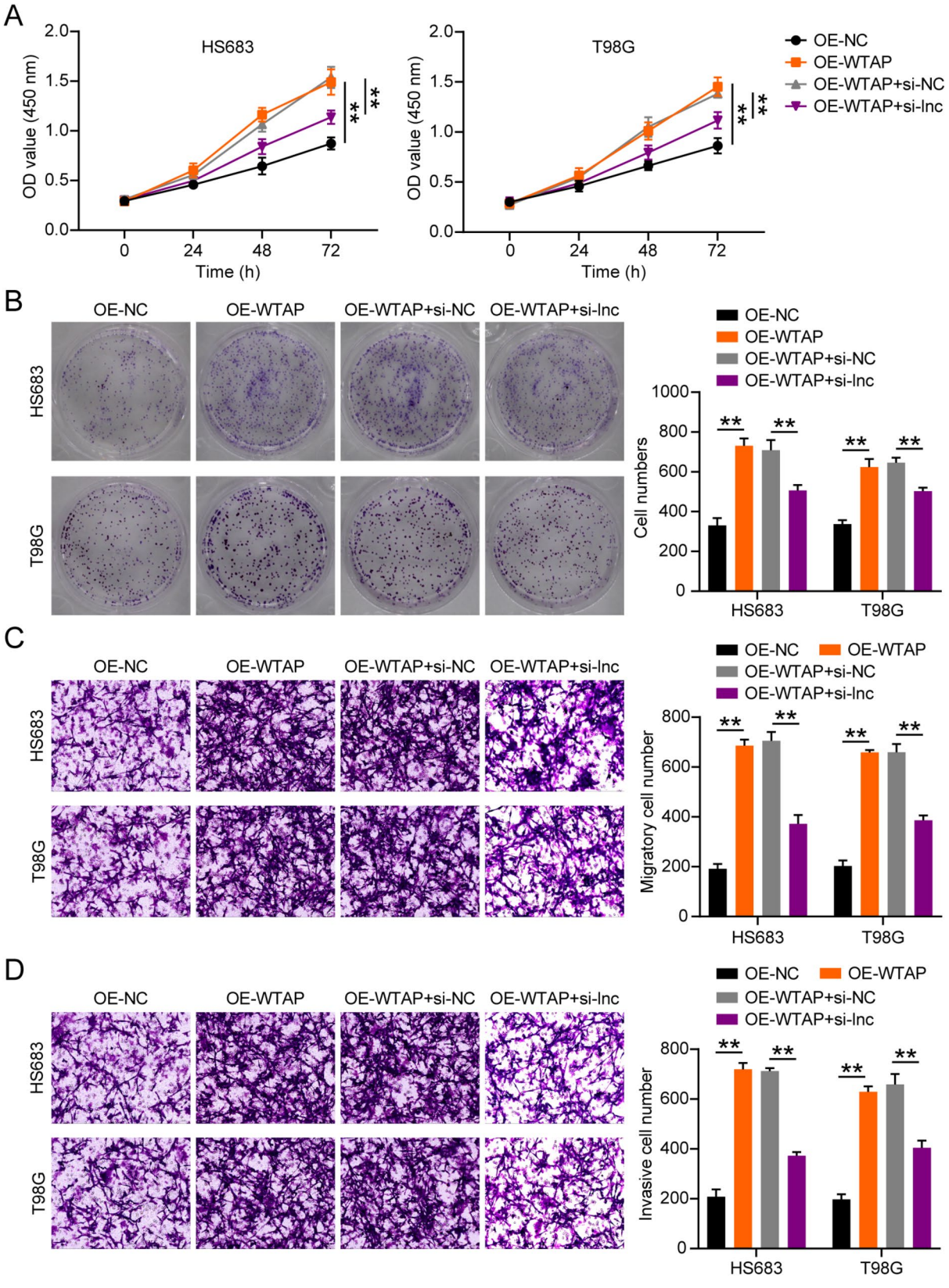

Fig. 5 (See legend on next page.)

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Fig. 5 Silencing LINC00200 partially reversed the tumor-promoting effects of WTAP overexpression in glioma cells. Rescue experiments were conducted on the glioma cell lines transfected with OE-NC, OE-WTAP, OE-WTAP + si-NC, and OE-WTAP + si-lnc. **A** The CCK-8 assay was done to determine the cell viability in various transfection groups of HS683 and T98G cells. **B** The colony formation assay was done to check the cell number in various transfection groups of HS683 and T98G cells. **C** The cell migration was assessed in the various transfection groups of HS683 and T98G cells by transwell migration assays. **D** The cell invasion was determined the various transfection groups of HS683 and T98G cells by transwell invasion assays. $^{**}P < 0.001$

LINC00200 for glioma warrants further testing in animal models.

In conclusion, this work highlights the oncogenic role of LINC00200 in promoting the malignancy of glioma via regulating Wnt/β-catenin pathway. We also elucidated the oncogenic role of WTAP and that it mediates the m6 A methylation of LINC00200 in glioma. Our findings add to the functional relevance of m6 A modification in glioma hallmarks and unlock new possibilities for investigating effective therapeutic options in glioma treatment.

Materials and methods

Clinical samples

28 pairs of glioma and neighboring non-tumor tissues were taken from the individuals with gliomas in our hospital. The participants of the study included 13 ♂ and 15 ♀ patients with 51.6 years old as mean age, all of whom signed an written informed consent form. The clinical characteristics describing tumor subtypes and grades of glioma patients used in this investigation are tabulated in Table 1. The samples were instantly flash-frozen by liquid N_2 after the surgical resection and kept at − 80 °C for future usage. The experiments were granted approval by the Ethics Committee of the Wuhan Fourth Hospital.

Cell culture and transfection

All glioma cell lines including HS683 and T98G were purchased from Procell (China). HS683 and T98G cell lines were cultured in DMEM medium + 10% FBS and MEM medium + 10% FBS, respectively, under the conditions of 5% CO_2 and 37 ℃. All vectors used for cell transfection were purchased from RiboBio (China). The transient transfection of cells was done with small-interfering RNA (siRNAs) for LINC00200 (si-lnc#1 and si-lnc#2) and WTAP (si-WTAP), and scramble siRNA oligonucleotides as the corresponding negative control (si-NC). The WTAP overexpression vector (OE-WTAP) and its empty vector (OE-NC) were also constructed using pcDNA3.1 vector. Lipo3000 (Invitrogen, USA) was used to transfect all the vectors into the cells as per the manufacturer's guide.

qRT-PCR

TRIzol LS reagent (abs60154, Absin, China) was used to extract the total RNA was from the glioma tissues/cells per the manufacturer's protocol. This was followed by reverse-transcripting the RNA into cDNA using MonScript RTIII Super Mix with dsDNase Kit (Monad, Suzhou, China). Then, the cDNA products were amplified using the MonAmp Fast SYBR Green qPCR Mix (Monad, Suzhou, China). The sequences of primers employed for the qPCR are displayed in Table 2. The relative quantification of expression was determined by $2^{-\Delta\Delta Ct}$ approach using GAPDH as internal control.

Methylated RNA immunoprecipitation (MeRIP) qPCR assay

The riboMeRIP m6 A Transcriptome Profiling Kit (RiboBio, China) was used to perform the assay. Briefly, 150 µg RNA from the transfected glioma cells was fragmented and diluted in immunoprecipitation buffer (IP) buffer. After that, the RNA was incubated either with beads coated in m6 A antibody or immunoglobulin G (lgG) antibody at 4 °C for overnight (O/N). After washing with the RIP wash buffer, the RNA was extracted, and the m6 A enrichment of LIN00200 was evaluated by qRT-PCR (as mentioned earlier).

Cell proliferation assessment

The cell proliferation was checked using CCK-8 and colony formation assays.

CCK-8 assay: The plating of transfected cells (3×10^3/well) was done in the 96-well plates. Next, 10 µl/well of CCK-8 (Beyotime, China) was introduced to 96-well plates at 0, 24, 48 and 72 h, and a further incubation at 37 °C for 2 h was done. The absorbance was measured at 450 nm.

Colony formation assay: The transfected cells (1×10^3/well) were seeded into the 6-well plate and cultured for a period of 14 days. After that, the colonies were fixed with methanol and stained with 0.1% crystal violet (CV). The colonies were examined, counted and imaged under a light microscope (Nikon Corporation, Tokyo, Japan).

Transwell assays

Cell invasion/migration was evaluated by transwell assay using transwell chambers (Corning, USA). For invasion analysis, the transfected glioma cells were re-suspended in serum free DMEM medium at a density of 1×10^5 cells/mL and introduced to the upper chambers that were pre-covered with 8% Matrigel. The lower chambers were added 600 µL of DMEM medium having 10% FBS (as attractant). After a 24 h-incubation, 4% paraformaldehyde and 0.1% CV were added into the cells invading to lower surface of the membrane for fixing and staining. Finally, the invading cells were photographed by a light microscope. For migration analysis, the experimental

Table 1 Baseline characteristics of glioma patients in this study

Characteristic	*N* = 28
Age (years), mean	51.6
Sex	
Male	13
Female	15
Tumor subtype	
Astrocytoma	14
Glioblastoma	12
Oligoastrocytoma	2
Tumor location	
Frontal	15
Temporal	8
Parietal	3
Occipital	1
Infratentorial	1
Tumor stage	
I + II	15
III + IV	13

Table 2 Primer sequences used in this study

Primer names	Sequences
WTAP	Forward:5′-GACGCCATCAACACCGAGTT-3′
	Reverse:5′-CTTTGTCGTTGGTTAGCTGGT-3′
LINC00200	Forward: 5′-TTCCACACACAGGACCAAAG-3′
	Reverse:5′-GCCCGATACATCAAAGCTACA-3′
GAPDH	Forward:5′-TGACTTCAACAGCGACACCCA-3′
	Reverse:5′-CACCCTGTTGCTGTAGCCAAA-3′

procedure was the same as the invasion assay except for the upper chambers without 8% Matrigel.

In vivo experiments

LINC00200 knockdown lentiviral vector (LV-lnc) and its negative control (LV-NC) were constructed by OBiO Technology (China) to stably transfect HS683 cells. BALB/c nude mice (~ 20 g weight and 4-week-old) were purchased from Cyagen (China) and divided into two group (n = 5/group): LV-NC and LV-lnc. Then, the transfected HS683 cells were injected into each mouse according to corresponding group. The tumor volume was measured each week. After five weeks, all mice were performed euthanasia, and tumors were removed to photograph and weight. Ethics Committee of the Wuhan Fourth Hospital approved in vivo experiments.

Western blotting

Total protein was obtained by Radio Immunoprecipitation Assay lysis buffer (Beyotime, China) by lysing glioma cells in, and the concentration of isolated proteins was verified by BCA assay kit (Beyotime). The separation of proteins was done in SDS-PAGE and were transferred onto PVDF membrane. Then, the membrane was blocked using 5% skim-milk at room temperature and performed an overnight-incubation at 4 °C with the following primary antibodies: anti-β-catenin (AF0066, Beyotime, China), anti-c-Myc (AF6513, Beyotime), anti-Cyclin D1 (AF0126, Beyotime), anti-WTAP (abs133584, Absin, China) and anti-GAPDH (AF1186, Beyotime, loading control). On the following morning, secondary antibody (A0208, Beyotime) was added to the membrane for 60 min incubation. Finally, the protein-bands were analyzed with the help of BeyoECL Plus (P0018S, Beyotime).

Statistical analysis

The obtained data were analyzed using GraphPad Prism 8.0 (GraphPad, USA) and presented as mean ± standard deviation (SD). Student's t-test was carried out to the data in two groups. Analysis of variance together with Tukey's post hoc test was analyze the data in multiple groups. The correlation between the expressions of LINC00200 and WTAP was checked via Pearson's correlation analysis. A $P < 0.05$ was deemed to be statistically significant difference.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13008-025-00155-z.

Supplementary Material 1

Supplementary Figure 1 The relative expression of LINC00200 was detected in HS683 and T98G cells by qRT-PCR at 48 h post-transfection with OE-NC, OE-METTL3, OE-METTL14, OE-WTAP, OE-KIAA1429, OE-ZC3H13, and OE-RBM15. **P < 0.001

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None.

Author contributions

Zhiying Lu and Jing Chen designed this research, executed the experiments, performed data analysis, and wrote this manuscript. Chao Luo reviewed and edited this manuscript. All authors approved this manuscript.

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Data availability

The datasets generated and/or analyzed during this study can be obtained from the corresponding author upon reasonable request.

Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

The Ethics Committee of Wuhan Fourth Hospital (Wuhan, China) approved this study. All clinical samples were used in strict accordance with the ethical guideline of the Declaration of Helsinki. Informed consent was obtained from all participating patients.

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