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Long non-coding RNA plasmacytoma variant translocation 1 (PVT1) promotes glioblastoma multiforme progression *via* regulating miR-1301-3p/TMBIM6 axis

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Abstract. – OBJECTIVE: To explore whether plasmacytoma variant translocation 1 (PVT1) could regulate glioblastoma multiforme (GBM) progression *via* microRNA-1301-3p (miR-1301-3p) and transmembrane BAX inhibitor motif containing 6 (TMBIM6) axis.

MATERIALS AND METHODS: Expression patterns of PVT1 and RMBIM6 in GBM patients were analyzed using GEPIA, an online gene expression analysis tool. Levels of PVT1 in GBM cells and normal cells were analyzed with quantitative real-time PCR method. Cell Counting Kit-8 (CCK-8), transwell invasion assay, and flow cytometry assay were applied to detect cell viability and apoptosis. Connections of PVT1 or TMBIM6 with miR-1301-3p were validated with bioinformatic tool and luciferase activity reporter assay.

RESULTS: PVT1 was significantly expressed in GBM tissues and cells. PVT1 promotes GBM cell proliferation and invasion but inhibits apoptosis *in vitro.* TMBIM6 was significantly expressed in GBM tissues. The knockdown of TMBIM6 reversed the stimulation effects of PVT1 on GBM cell malignancy behaviors with miR-1301-3p as a bridge.

CONCLUSIONS: Collectively, we showed PVT1 elevated TMBIM6 expression mediated by miR-1301-3p and thus to promote GBM progression.

Key Words:
PVT1, MiR-1301-3p, TMBIM6, Glioblastoma multiforme.

Introduction

Glioblastoma multiforme (GBM) is a highly malignancy central nervous system cancer type, which accounted for about 50% of all glioma cases[1]. GBM remains incurable although the improvements in GBM treatment methods and the main reason is we did not fully understand the mechanisms underlying GBM tumorigenesis[2].

Long non-coding RNA (lncRNA) belongs to non-coding RNA family and was previously regarded as transcript noise or "junk gene"[3,4]. In recent years, the importance of lncRNAs in regulating cancer progression has been gradually appreciated[5]. In particular, Ji et al[6] constructed a lncRNA/TF-mediated ceRNA network to identify core lncRNA that affect GBM carcinogenesis. LncRNA SNHG5 was found upregulated in GBM and correlated with poorer overall survival of GBM patients. Importantly, SNHG5 could regulate GBM carcinogenesis through miR-627-5p/CDK6 axis[7].

Plasmacytoma variant translocation 1 (PVT1), located at 8q24, is the first lncRNA identified in cancers[8]. PVT1 was found to serve as an oncogenic lncRNA to contribute tumorigenesis. Xu et al[9] found that PVT1 was increased expression in esophageal adenocarcinoma and correlated with shorter overall survival of cancer patients. Wang et al[10] indicated PVT1 was upregulated in nasopharyngeal carcinoma patients with shorter overall survival. Functional, PVT1 could regulate nasopharyngeal carcinoma cell growth, invasion, and tumorsphere formation[9,10].

LncRNAs act as ceRNA for miRNAs and indirectly regulating miRNA target genes and, in the end, to affect tumorigenesis[11]. We conducted *in vitro* experiments to determine how PVT1 modulates GBM cell proliferation, invasion, and apoptosis. Collectively, our results showed that PVT1 has a role in regulating GBM carcinogenesis and may provide a novel treatment strategy for GBM.

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Materials and Methods

Cells and Incubation

Human glioma cells (U87, U251, and T98G) were obtained from Cell Bank of China Academy Sciences (Shanghai, China). U87 and T98G cells were maintained in modified Eagle's medium (MEM, Invitrogen, Thermo Fisher Scientific, Inc., Waltham, MA, USA), while U251 cells were incubated at Dulbecco's Modified Eagle's Medium (DMEM, Invitrogen, Carlsbad, CA, USA). Normal Human Astrocyte (NHA) cells were obtained from American Type Cell Culture Collection (ATCC, Rockville, MD, USA) and plated in DMEM. The medium was supplemented with 10% fetal bovine serum (FBS, Invitrogen, Carlsbad, CA, USA) and placed in a 37°C humidified incubator contains 5% CO_2.

Cell Transfection

MiR-1301-3p mimic, negative control (NC-miR), small interfering RNA target PVT1 (si-PVT1) or TMBIM6 (si-TMBIM6), negative control (NC-siR) were purchased from GeneChem (Shanghai, China). pcDNA3.1 contains full sequence of PVT1 (pPVT1), and control was purchased from GenScript (Nanjing, Jiangsu, China). Cell transfection was performed using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA).

Cell Counting Kit-8 (CCK-8) Analysis

Cell proliferation rate was measured with CCK-8 assay (Beyotime, Haimen, Jiangsu, China). 5,000 cells were seeded at 96-well plates. CCK-8 reagent was added to the medium at the selected time and further incubated for 4 h. Optical density was measured at the wavelength of 450 nm using microplate reader.

Quantitative Real-Time PCR (qRT-PCR)

RNA was isolated with TRIzol reagent (Invitrogen, Carlsbad, CA, USA) and reverse transcribed into complementary DNA using PrimeScript RT kit (Takara, Dalian, Liaoning, China). qRT-PCR was conducted at QuantStudio 6 (Thermo Fisher Scientific, Inc., Waltham, MA, USA) using TB Green Fast qPCR Mix (Takara) with the following primer sequences: PVT1: F: 5'-TGAGAACTGTCCTTACGTGACC-3', R: 5'-AGAGCACCAAGACTGGCTCT-3'; TMBIM6: F: 5'-GAAGAGTGGAGACTGCTGCACG-3', R: 5'-TCAATATCAGGGAGCCCAAG-3'; GAPDH: F: 5'-AGGGCTGCTTTTAACTCTGGT-3', R: 5'-CCCCACTTGATTTTGGAGGGA-3'; miR-1301-3p: F: 5'-GCCCGCTTGCAGCTGCCTGGGAG-3', R: 5;-GTGCAGGGTCCGAGGT-3'; U6 snRNA: F: 5'-CGCCGGTATCGTTAATCCGTCT-3', R: 5'-GGATGTGAGAAGGTGTCGTC-3'. Expression levels of PVT1, miR-1301-3p, and TMBIM6 were calculated with the comparative Ct method.

Transwell Invasion Assays

Matrigel (BD Biosciences, San Jose, CA, USA) coated insert was used to measure cell invasion ability. Cells in FBS free medium were plated in the upper chamber, while FBS contained medium was filled into the lower chamber. After 24 h incubation, invaded cells were fixed, stained, and counted under a microscope.

Flow Cytometry Analysis

Flow cytometry was used to measure cell apoptosis rate. At first, cells were collected, washed, and incubated with Annexin V-FITC (Beyotime, Haimen, Jiangsu, China) for 5 min at 4°C away from light. Subsequently, cells were stained with PI (Beyotime, Haimen, Jiangsu, China) for 5 min. At last, the cell apoptosis rate was analyzed at BD LSRFortessa (BD Biosciences, San Jose, CA, USA).

Luciferase Reporter Assay

MiRNA target for PVT1 was analyzed at StarBase, while the miRNA target was also predicted on the same website. Wild-type (wt) or mutant (mt) sequences of PVT1 or TMBIM6 were synthesized by GenScipt and inserted into pmirGLO vector (Promega, Madison, WI, USA) to generate wt/mt-PVT1/TMBIM6 luciferase vectors. For luciferase activity analysis, cells were transfected with Luciferase constructs and miRNAs with Lipofectamine 2000. Luciferase activity was measured with Dual-Luciferase reporter kit (Promega, Madison, WI, USA) using Renilla Luciferase activity as internal control after 24 h transfection.

PVT1 and TMBIM6 Expression in GBM Tissues and Normal Tissues

The expression levels of PVT1 and TMBIM6 in GBM tissues and normal tissues were analyzed at GEPIA (http://gepia2.cancer-pku.cn/#index).

Xenograft Animal Model

Male nude mice were bought from Slac Laboratory Animal Center (Shanghai, China). The animal experiment was performed with a protocol approved by the Institutional Animal Care and

Use Committee of The first hospital of Jilin University. Cells with PVT1 knockdown or not were injected into the flank of the nude mice. After 4 weeks, mice were sacrificed to obtain tumor tissues and then photographed and weighted.

Statistical Analysis

Data collected from three independent experiments were analyzed with GraphPad Prism (La Jolla, CA, USA) and expressed as mean ± SD. Comparisons in groups were analyzed with Student's *t*-test and ANOVA and Tukey post-hoc test. Significant differences were considered significant when $p < 0.05$.

Results

PVT1 was highly expressed in GBM tissues and cells

We showed that PVT1 expression level was significantly higher in GBM tissues than in normal tissues through GEPIA analysis (Figure 1A). Moreover, we showed that PVT1 expression level was significantly elevated in GBM cells than NHA cells (Figure 1B).

Effects of PVT1 on GBM Cell Proliferation, Invasion, and Apoptosis

Furthermore, gain-of and loss-of-function experiments were performed to explore the roles of PVT1. GBM cells with the lowest PVT1 expression level among the investigated cells were selected for gain-of-function analyses. The transfection of pPVT1 significantly increased PVT1 levels in U87 cells (Figure 2A). PVT1 overexpression increases U87 cell proliferation (Figure 2B) and cell invasion (Figure 2C) but decreases cell apoptosis (Figure 2D).

Moreover, loss-of-function experiments were conducted on T98G cells. The introduction of si-PVT1 significantly decreased the levels of PVT1 compared with NC-siR (Figure 3A). CCK-8 assay and transwell invasion assay revealed PVT1 silencing significantly decreased cell proliferation and invasion (Figure 3B and 3C). We also showed cells with si-PVT1 transfection displayed high cell apoptosis percentage compared with those with NC-siR (Figure 3D).

PVT1 Negatively Regulate MiR-1301-3p

Bioinformatic analysis showed that miR-1301-3p was a putative target for PVT1 (Figure 4A). MiR-1301-3p expression was found significantly decreased in GBM cells compared with NHA cells (Figure 4B). Moreover, we showed the transfection of pPVT1 significantly decreased the levels of miR-1301-3p (Figure 4C). Results of Dual-Luciferase activity reporter assay indicated miR-1301-3p overexpression inhibits Luciferase activity in GBM cells with wt-PVT1 transfection, suggesting the direct interaction of PVT1 and miR-1301-3p (Figure 4D).

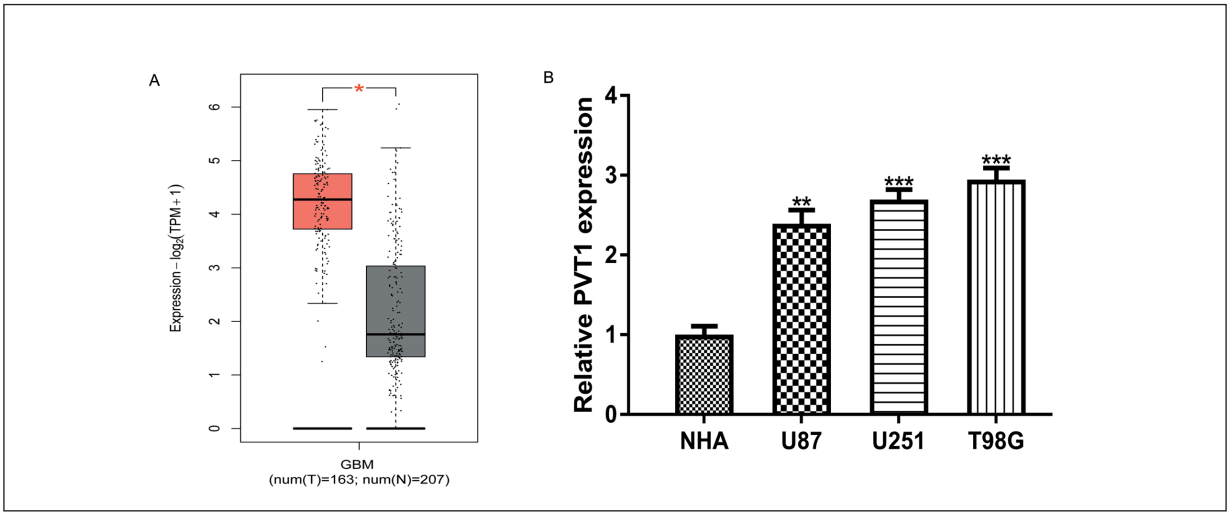

Figure 1. PVT1 was highly expressed in GBM tissues and cells. **A,** Expression of PVT1 in GBM tissues and normal tissues as examined at GEPIA. **B,** Expression of PVT1 in GBM cells and normal cell as examined by qRT-PCR. PVT1: plasmacytoma variant translocation 1; qRT-PCR: Quantitative real-time PCR; GBM: glioblastoma multiforme.

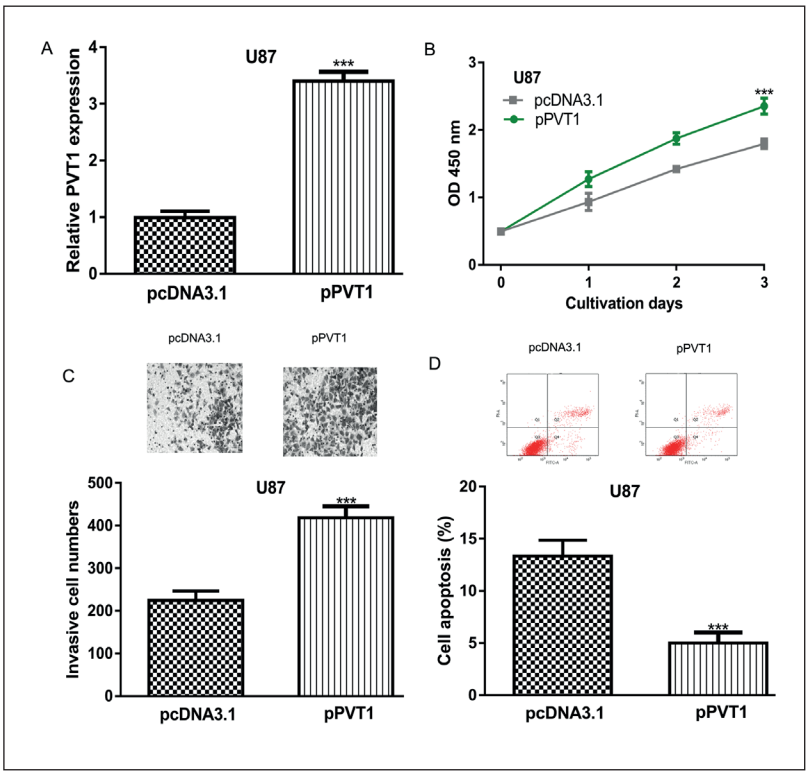

Figure 2. PVT1 overexpression promotes GBM cell proliferation and invasion but inhibits apoptosis. **A,** Expression level of PVT1 was determined by qRT-PCR in GBM cells with pPVT1 or pcDNA3.1 transfection. **B,** CCK-8 assay was used to measure proliferation of GBM cells with pPVT1 or pcDNA3.1 transfection. **C,** Transwell invasion assay was conducted to measure invasion of GBM cells with pPVT1 or pcDNA3.1 transfection (Magnification: 200×). **D,** Flow cytometry assay was used to determine apoptosis in GBM cells with pPVT1 or pcDNA3.1 transfection. PVT1: plasmacytoma variant translocation 1; qRT-PCR: Quantitative real-time PCR; GBM: glioblastoma multiforme; CCK-8: cell counting kit-8.

MiR-1301-3p Regulates TMBIM6 Expression in GBM

Subsequently, we analyzed the targets of miR-1301-3p and found that TMBIM6 was a putative target (Figure 5A). GEPIA analysis showed that TMBIM6 expression level was higher in GBM tissues than in normal tissues (Figure 5B). Moreover, we showed that TMBIM6 levels were

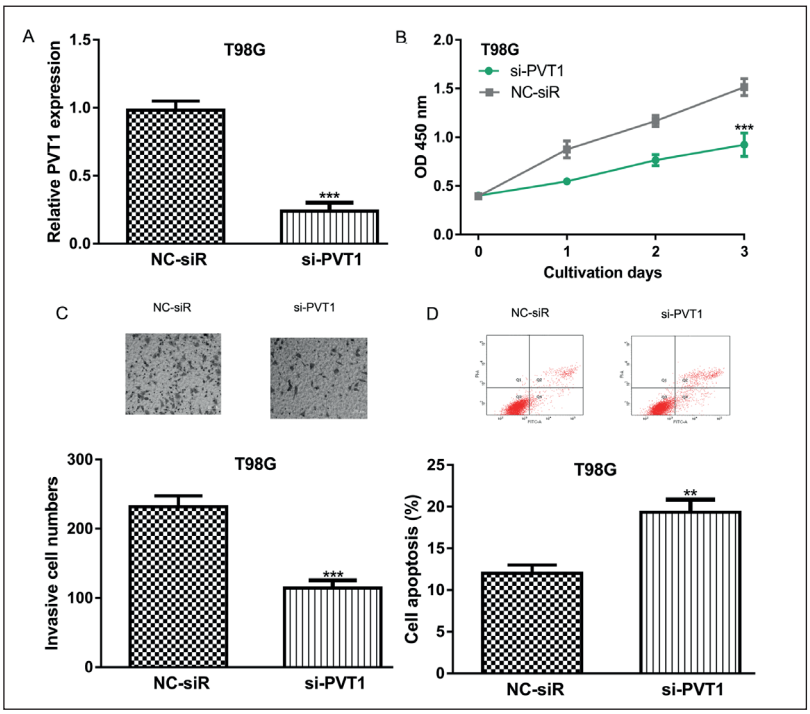

Figure 3. PVT1 overexpression inhibits GBM cell proliferation and invasion but promotes apoptosis. **A,** Expression level of PVT1 was determined by qRT-PCR in GBM cells with si-PVT1 or NC-siR transfection. **B,** CCK-8 assay was used to measure proliferation of GBM cells with si-PVT1 or NC-siR transfection. **C,** Transwell invasion assay was conducted to measure invasion of GBM cells with si-PVT1 or NC-siR transfection (Magnification: 200×). **D,** Flow cytometry assay was used to determine apoptosis in GBM cells with si-PVT1 or NC-siR transfection. PVT1: plasmacytoma variant translocation 1; qRT-PCR: Quantitative real-time PCR; GBM: glioblastoma multiforme; CCK-8: cell counting kit-8; si-PVT1: small interfering RNA targeting PVT1; NC-siR: negative control small interfering RNA.

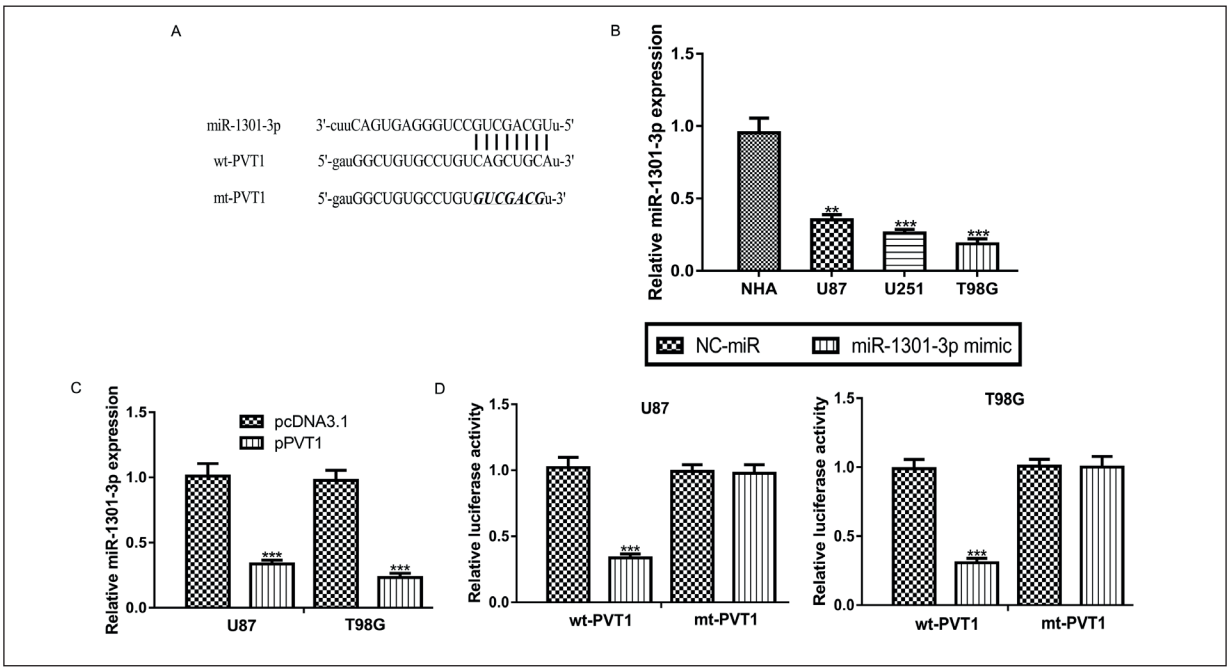

Figure 4. PVT1 binds and negatively regulate miR-1301-3p. **A,** Binding module between PVT1 and miR-1301-3p. **B,** Expression of miR-1301-3p in GBM cells and normal cell was examined by qRT-PCR. **C,** Expression of miR-1301-3p in GBM cells with pPVT1 transfection was detected by qRT-PCR. **D,** Luciferase activity of GBM cells with luciferase activity constructs or miRNAs transfection. PVT1: plasmacytoma variant translocation 1; qRT-PCR: Quantitative real-time PCR; GBM: glioblastoma multiforme; miR-1301-3p: microRNA-1301-3p; NC-miR: negative control miRNA; wt: wild-type; mt: mutant.

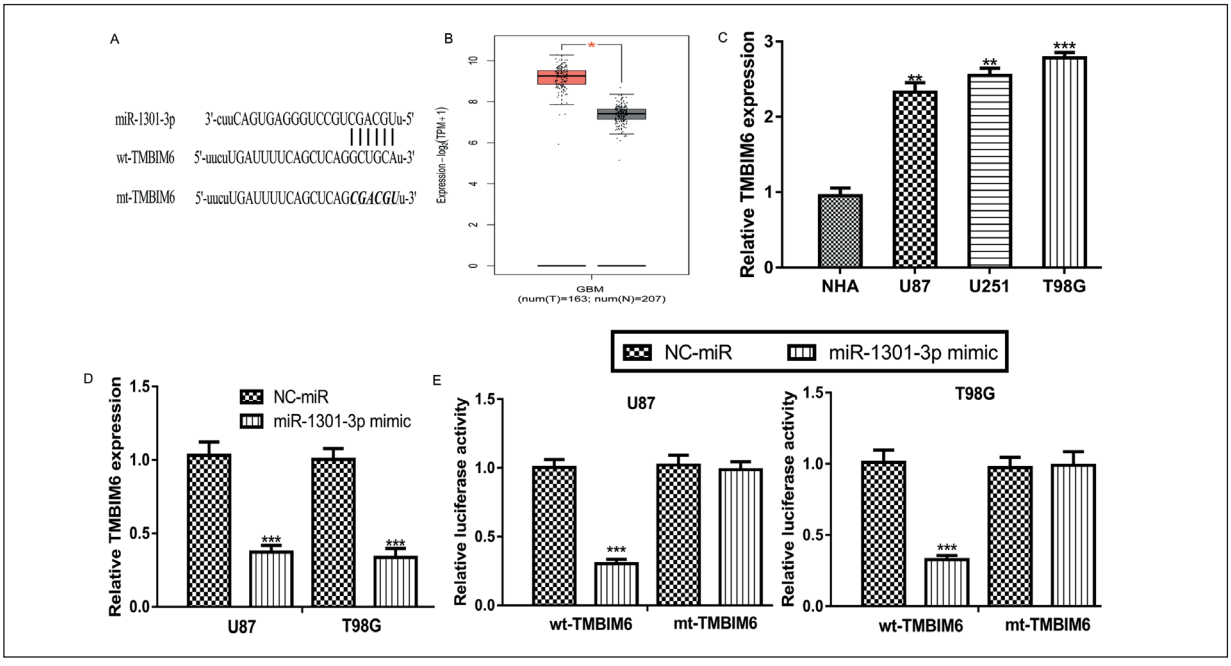

Figure 5. miR-1301-3p regulates TMBIM6 expression in GBM. **A,** Binding module between TMBIM6 and miR-1301-3p. **B,** Expression of TMBIM6 in GBM tissues and normal tissues as examined at GEPIA. **C,** Expression of TMBIM6 in GBM cells and normal cell was examined by qRT-PCR. **D,** Expression of TMBIM6 in GBM cells with miR-1301-3p mimic or NC-miR transfection was examined by qRT-PCR. **E,** Luciferase activity of GBM cells with luciferase activity constructs or miRNAs transfection. TMBIM6: transmembrane BAX inhibitor motif containing 6; qRT-PCR: Quantitative real-time PCR; GBM: glioblastoma multiforme; miR-1301-3p: microRNA-1301-3p; NC-miR: negative control miRNA; wt: wild-type; mt: mutant.

higher in GBM cells than in normal cells (Figure 5C). Besides, we showed that miR-1301-3p mimic transfection decreased TMBIM6 levels in GBM cells (Figure 5D). Luciferase activity reporter assay showed the introduction of miR-1301-3p mimic inhibited luciferase activity in cells with wt-TMBIM6 transfection (Figure 5E).

MiR-1301-3p/TMBIM6 Participates in he Role of PVT1 in GBM

As shown in Figure 6A, the levels of TMBIM6 in T98G was significantly increased by pPVT1, and miR-1301-3p mimic or si-TMBIM6 could abolish the effect of pPVT1 on TMBIM6 expression. Functional assays showed PVT1 overexpression could promote cell proliferation, invasion but inhibit apoptosis (Figure 6B-6D). The co-transfection of miR-1301-3p mimic attenuated the effects of pPVT1 (Figure 6B-6D). These results indicated miR-1301-3p/TMBIM6 axis was involved in the roles of PVT1 in GBM.

Knockdown of PVT1 Inhibits Tumor Growth

To further explore the roles of PVT1 in GBM tumorigenesis, transfected cells were injected into nude mice. We found that the silence of PVT1 suppressed tumor growth in xenograft mice (Figure 7A and 7B). Moreover, we detected the expression level of PVT1, miR-1301-3p, and TMBIM6 in tumor tissues collected from xenograft mice. We found that PVT1 and TMBIM6 expression level was decreased, while miR-1301-3p expression level was increased by sh-PVT1 (Figure 7C).

Discussion

The importance of lncRNAs in regulating carcinogenesis has been appreciated[3,5]. PVT1 is found significantly elevated in cancers and hence exerted an oncogenic role[9,10]. In GBM, Zan et al[12] constructed a lncRNA mediated ceRNA network that was associated with GBM progression and found PVT1 was a hub gene for GBM carcinogenesis. However, the detailed roles of PVT1 in regulating GBM progression remain to be explored. With the GEPIA and RT-qPCR analyses, we found PVT1 expression was enhanced in GBM. *In vitro* researches showed PVT1 overexpression could promote GBM progression. On

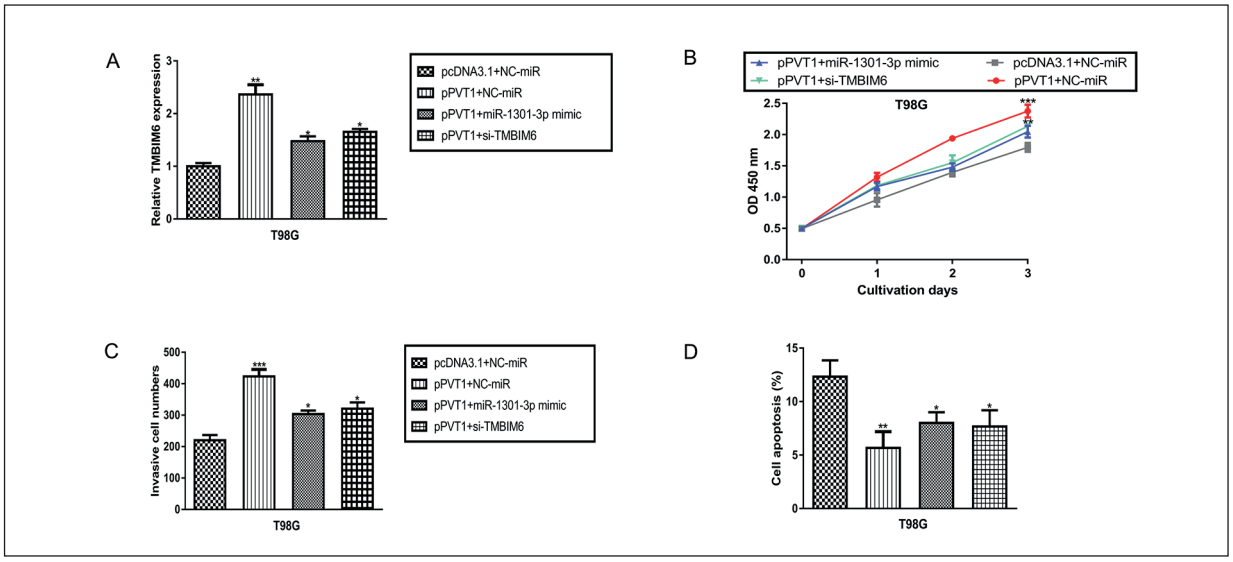

Figure 6. miR-1301-3p/TMBIM6 axis was involved in the PVT1 mediated GBM malignant behaviors. **A,** Expression of TMBIM6 in GBM cell with pPVT1+NC-miR, pcDNA3.1+NC-miR; pPVT1+miR-1301-3p mimic; pPVT1+si-TMBIM6 transfection was measured by qRT-PCR. **B,** CCK-8 assay was used to measure proliferation of GBM cells with pPVT1+NC-miR, pcDNA3.1+NC-miR; pPVT1+miR-1301-3p mimic; pPVT1+si-TMBIM6 transfection. **C,** Transwell invasion assay was conducted to measure invasion of GBM cells with pPVT1+NC-miR, pcDNA3.1+NC-miR; pPVT1+miR-1301-3p mimic; pPVT1+si-TMBIM6 transfection. **D,** Flow cytometry assay was used to determine apoptosis in GBM cells with pPVT1+NC-miR, pcDNA3.1+NC-miR; pPVT1+miR-1301-3p mimic; pPVT1+si-TMBIM6 transfection. PVT1: plasmacytoma variant translocation 1; qRT-PCR: Quantitative real-time PCR; GBM: glioblastoma multiforme; CCK-8: cell counting kit-8; TMBIM6: transmembrane BAX inhibitor motif containing 6; miR-1301-3p: microRNA-1301-3p; NC-miR: negative control miRNA; si-TMBIM6: small interfering RNA targeting TMBIM6.

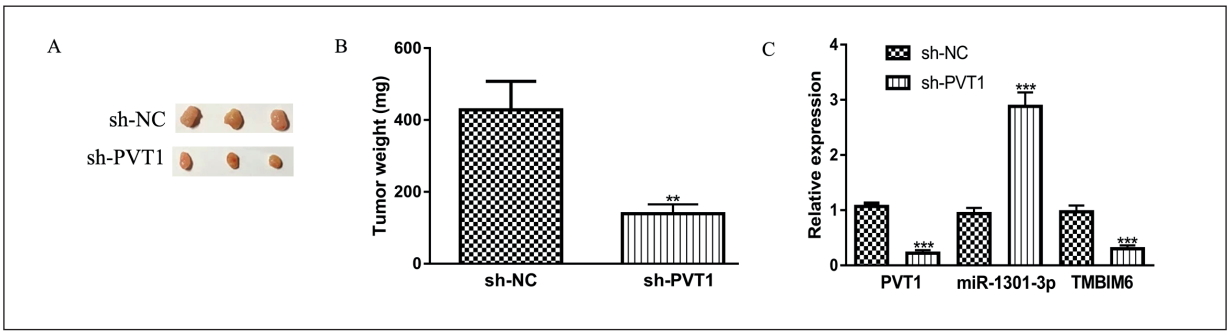

Figure 7. lncRNA PVT1 knockdown inhibits tumor growth in xenograft mouse model. **A, B,** Xenograft tumor was photographed and tumor weight was measured. **C,** Relative PVT1, miR-1301-3p, and TMBIM6 expression level in the xenograft tissues. PVT1: plasmacytoma variant translocation 1; TMBIM6: transmembrane BAX inhibitor motif containing 6; miR-1301-3p: microRNA-1301-3p; sh-PVT1: short hairpin RNA targeting PVT1; sh-NC: negative control shRNA.

the contrary, we found that the silencing of PVT1 inhibits GBM progression. *In vivo* experiments showed that silence of PVT1 inhibits tumor growth. According to the previous studies[9,10], our results also suggested PVT1 may serve an oncogenic lncRNA in GBM.

MiRNAs are downstream targets of lncRNAs, which is also referred to the competing endogenous (ceRNA) theory[7,13-16]. It was found that lncRNA GAPLINC serves as ceRNA for miR-331-3p in GBM[15]. Geng et al[16] indicated that lncRNA SNHG11 could regulate GBM progression *via* sponging miR-154-5p. Hence, miRNA targets for PVT1 were predicted at StarBase, and we found that miR-1301-3p was a putative target. MiR-1301-3p is a miRNA that is reported to have diverse biological roles in cancers. For instance, Peng et al[17] reported that miR-1301-3p was decreased in breast cancer tissues and correlated with large tumor size and late tumor stage. Functional assays showed that miR-1301-3p overexpression inhibits breast cancer cell growth by arresting cell cycle and promoting apoptosis[13]. Besides, Song et al[18] reported that miR-1301-3p was elevated in prostate cancer, and its overexpression was revealed to promote cancer stem cell expansion *via* targeting SFRP1 and GSK3β. In this work, we showed that miR-1301-3p was reduced expression in cancer cells, and its overexpression could inhibit cancer cell proliferation and invasion but promote apoptosis. The direct interaction of PVT1 and miR-1301-3p was validated by Luciferase activity reporter assay.

Furthermore, targets for miR-1301-3p were predicted at StarBase to help us understand the roles of PVT1 in GBM. We showed that TMBIM6, upregulated in GBM tissues and cells, was a possible target of miR-1301-3p. TMBIM6 was previously reported to be upregulated in cancers and promote metastasis[19,20]. Here, we showed that TMBIM6 was a direct target for miR-1301-3p using a Dual-Luciferase activity reporter assay. Moreover, we found that miR-1301-3p/TMBIM6 axis was involved in the roles of PVT1 in regulating GBM behaviors.

Conclusions

To sum up, our work identified a novel PVT1/miR-1301-3p/TMBIM6 triplet in regulating GBM progression. Our work will advance our understanding regarding the mechanisms behind GBM progression.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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