Original paper

LncRNA-PVT1 enhances glucose metabolism of pediatric low-grade glioma cells through sponging miR-187-3p

Beibei Li, Zijian Feng, Yanyan Zheng

Department of Neonatology, Weifang Maternal and Child Health Hospital, China

Pediatric low-grade glioma (PLGG) is a heterogeneous group of primary central nervous system malignancies which represent the most frequent brain tumors in children. Although diagnosis and treatment of PLGG have been improved recently, the molecular mechanisms underlying the oncogenesis and progression of PLGG remain elusive. Studies have revealed critical roles of long non-coding RNAs (lncRNAs) in brain tumor progressions. Here, we aimed to investigate the clinical roles and molecular mechanisms of lncRNA PVT1 in PLGG. Expression of PVT1 was significantly upregulated in PLGG tissues compared with normal brain tissues. Blocking PVT1 effectively suppressed the glucose metabolism of PLGG-derived cells. MicroRNA-187-3p was detected to be remarkedly downregulated in PLGG tissues. Moreover, miR-187-3p is negatively correlated with PVT1 in PLGG tissues. We identified PVT1 sponged miR-187-3p to block its expression in PLGG cells. This association was further verified by RNA pull-down and luciferase assay. Subsequently, rescue experiments validated that inhibition of miR-187-3p in PVT1-silenced PLGG cells successfully overcame the low-PVT1-induced miR-187-3p upregulation and glucose metabolism. In summary, this study reports critical roles and molecular mechanisms of the lncRNA PVT1-accelarated glucose metabolism of PLGG cells.

Key words: pediatric low-grade glioma, lncRNA, PVT1, miR-187-3p, glucose metabolism.

Introduction

Pediatric low-grade glioma (PLGG) is a heterogeneous primary central nervous system (CNS) malignancy which represents the most frequent brain tumors in children [1]. In contrast to adult gliomas, which are mostly high-grade, children's gliomas are mainly low-grade [1, 2]. Symptoms of PLGG progress slowly or insidiously, depending on the location where glioma cells invaded [3]. Although the prognosis for PLGG has been improved recently, surgical resection was not applicable for specific locations of low-grade glioma in CNS [4], rendering PLGG a potential CNS disease with severe lethality and morbidity. Therefore, it is critical to investigate new molecular biomarkers and therapeutic targets for treatment of PLGG.

Long non-coding RNAs (lncRNAs) are a group of non-coding RNAs with relatively large size (> 200 nt) [5]. LncRNAs have attracted intensive attention recently, due to the fact that they play essential roles in tumorigenesis and progression of cancers through diverse molecular mechanisms [6, 7]. For instance, the lncRNA HOXA-AS2/miR-184/COL6A2 axis has been reported to act as a critical ceRNA network involved in low-grade glioma recurrence [8]. In addition, recent studies reported that hypoxia induced expression of lncRNAs LINC00941 and BASP1-AS1, which significantly affected the proliferation of low-grade glioma cells [9]. LncRNA plasmacytoma

Table I. PLGG patients are characterized and grouped by the 2021 WHO classification of PLGG/GNTs. Patients are subdivided into three families: pediatric-type diffuse low-grade gliomas, circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors

Tumor type	Gene/molecular profile/ Characteristically altered	Cases, $n = 35$
Paediatric-type diffuse low-grade gliomas		
Diffuse astrocytoma	MYB, MYBL1	6
Angiocentric glioma	MYB	4
PLNTY	BRAF, FGFR family	2
Diffuse low-grade glioma	BRAF, FGFR1, MAPK pathway	5
Circumscribed astrocytic gliomas		
Pilocytic astrocytoma	KIAA1549-BRAF, BRAF, NH	4
Pleomorphic xanthoastrocytoma	BRAF, CDKN2A/B	3
Subependymal giant cell astrocytoma	TSC1, TSC2	3
High-grade astrocytoma with piloid features	CDKN2A/B, ATRX, MAPK pathway	2
Chordoid glioma	PRKCA 1 Astroblastoma MN1, CDKN2A	0
Glioneuronal and neuronal tumors		
Ganglioglioma	BRAF	3
Desmoplastic infantile ganglioglioma/desmoplastic infantile astrocytoma		0
Dysembryoplastic neuroepithelial tumor	FGFR1	2

PLNTY – polymorphous low-grade neuroepithelial tumor of the young

variant translocation 1 (PVT1) has been revealed to be positively associated with various types of cancer [10]. A recent study reported that PVT1 promoted gallbladder tumor progressions by regulating the miR-143/*HK2* axis [11]. Moreover, PVT1 contributes to gemcitabine resistance of pancreatic cancer through sponging miR-619-5p [12], suggesting that PVT1 is a diagnostic biomarker and therapeutic target for cancers. Yet, the clinical roles and molecular mechanisms of lncRNA PVT1 in PLGG remain unknown.

Reprogramming of cellular metabolism has been emerging as a new cancer hallmark [13]. Warburg reported that cancer cells displayed enhanced conversion of glucose to pyruvate (anerobic glycolysis) despite the presence of abundant oxygen (aerobic glycolysis) [14]. Elevated glycolysis provides sustained biomass for cancer cell proliferation and oncogenic progression [15]. Moreover, recent studies suggested that targeting the dysregulated glucose metabolism could effectively suppress cancer cell growth, migration and chemosensitivity [16]. So far, the roles and molecular targets of PVT1 in glucose metabolism of PLGG cells have not been investigated. This study aimed to evaluate the functions and underlying mechanisms of PVT1 in regulating glucose metabolism of PLGG cells. The molecular target of PVT1 in PLGG was identified and validated.

Material and methods

PLGG patient tissue collection

PLGG patients ($n = 35$) were histologically diagnosed at the Department of Pediatrics, Weifang Maternal and Child Health Hospital. PLGG patients were characterized according to the 2021 WHO classification of PLGG/GNTs (Table I). Tumor specimens and their adjacent normal brain tissues were dissected at Weifang Maternal and Child Health Hospital between July 2018 and March 2020. Tumor location was determined by MRI scan and PET, which determines the tumor region with the highest metabolic activity of the lesion. Brain tumor tissues were collected from patients by biopsy, which removes a small sample of brain tumor and normal brain tissues. Normal brain tissue was extracted around 5 cm near the tumor tissue. Patients did not receive radiotherapy before participating in this study. After dissection, tissues were immediately snap frozen and stored at –80°C. Written informed consent was obtained from all patients.

Cell culture

Human PLGG derived cell lines Res186 and BT66 were obtained from the Chinese Academy of Sciences (Shanghai, China). Res186 cells were cultured in

DMEM/F12 (Dulbecco modified Eagle medium/F12 Ham) medium supplemented with 10% FBS (fetal bovine serum) (Thermo Fisher Scientific, USA). BT66 cells were cultured in ABM basal medium (Lonza, US) supplemented with AGM SingleQuot Kit Supplements & Growth Factors (Lonza, US) plus 1 μg/ml doxycycline. Cells were maintained in an incubator with 5% CO_2 at 37°C.

Transfection

Transfections of siRNA, miR-187-3p, miR-187-3p inhibitor and their negative controls were performed using Lipofectamine 2000 (Thermo Fisher Scientific, USA) according to the manufacturer's protocols. Control siRNA (#A06001), siPVT1 (#A09005), miR-187-3p (#B02003) and inhibitor (#B03001) were obtained from GenePharma Co., Ltd. (Shanghai, China). Sequences of siRNAs and miRNAs were: control siRNA: 5′-UUCUCCGAACGUGUCACGUTT-3′; siPVT1: 5′-CACUACUGACCUUGCAGCUUAUUAU-3′; miR-187-3p: sense: 5'-UCGUGUCUUGUGUUGCAGCCGG-3', antisense: 5'-CCGGCUGCAACACAAGACACGA-3'; miR-187-3p inhibitor: 5'-CCGGCUGCAACACAAGACACGA-3'. Transfection of siRNA was conducted at 100 nM for 72 hours. Transfections of miRNA and inhibitor were conducted at 50 nM for 72 hours.

Bioinformatics analysis

The survival rates of PLGG patients with higher or lower PVT1 or miR-187-3p expression were analyzed by the Kaplan-Meier Plotter method, from https://kmplot.com. The association between PVT1 and miR-187-3p was predicted from starBase v2.0, https://starbase.sysu.edu.cn/ [17].

RNA isolation and quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNAs from PLGG tissues were extracted using TRIzol reagent (Thermo Fisher Scientific, USA) according to the manufacturer's instructions. Concentration and quality of RNA samples were determined using a spectrophotometer (Hitachi, Tokyo, Japan). The cDNA (complementary DNA) was synthesized from RNA samples by reverse transcription using a Prime Script RT Master Mix kit (Takara Bio, Japan). Primers used were: PVT1: forward, 5′-ATAGATCCTGCCCTGTTTGC-3′ and reverse, 5′-CATTTCCTGCTGCCGTTTTC-3′; *GAPDH*: forward, 5′-GGAGCGAGATCCCTCCAAAAT-3′ and reverse, 5′-GGCTGTTGTCATACTTCTCATGG-3′; miR-187-3p: forward, 5′-GCCGAGTCGTGTCTTGTGTT-3′ and reverse, 5′-CTCAACTGGTGTCGTGGA-3′; *U6*: forward, 5′-GCGCGTCGTGAAGCGTTC-3′ and reverse, 5′-GTGCAGGGTCCGAGGT-3′. PCR thermocycling reactions were conducted using SYBR Premix Ex Taq II (Takara Bio, Japan) with the following conditions: 95°C, 10 min, then 40 cycles at 95°C, 10 sec and 60°C, 1 min. Expression of lncRNA PVT1 was normalized to GAPDH and miR-187-3p expression was normalized to human U6. The relative expression levels were calculated using the $2^{-\Delta\Delta Ct}$ method.

RNA pull-down

The association between PVT1 and miR-187-3p was evaluated by RNA pull-down assay. Cell lysates were extracted using RIPA buffer (Thermo Fisher Scientific, USA) and were incubated with biotin-labeled scramble oligonucleotide control, PVT1 binding site sense or antisense probe at 4°C for 4 hours. Mixtures were incubated with streptavidin-coupled agarose beads for 2 hours at 4°C. The lncRNA-miRNA complex was washed out from beads and collected for qRT-PCR analysis. The binding capacity of miR-187-3p with PVT1 was assessed by detection of the amount of miR-187-3p in the complex.

Luciferase assay

The specific binding of PVT1 on miR-187-3p was assessed by dual luciferase assay. The wild type (WT) or miR-187-3p binding site mutant (Mut) sequence of PVT1 was amplified by PCR and cloned into the luciferase reporter vector pGL3 (Promega, USA). PLGG cells were co-transfected with control miRNA or miR-187-3p plus WT-PVT1 or Mut-PVT1 luciferase reporter. Luciferase activity was determined using the Dual-Luciferase Reporter Assay System (Promega, USA) according to the manufacturer's instructions.

Evaluation of glucose metabolism

The glucose metabolism of PLGG cells was evaluated by glucose uptake assay using the Glucose Uptake Colorimetric Assay Kit (MAK083, Sigma-Aldrich, Shanghai, China) and lactate product assay using the Lactate Assay Kit (MAK064, Sigma-Aldrich, Shanghai, China) according to the manufacturer's protocols. Experiments were performed in triplicate.

Statistical analysis

Statistical analyses were performed using the GraphPad Prism 7.0 software (GraphPad Software Inc., USA). Difference between two groups was analyzed by unpaired Student's *t*-test. Differences among three or more groups were analyzed by one-way analysis of variance (one-way ANOVA) followed by Bonferroni's post hoc test. Analyses with $p < 0.05$ were considered statistically significant.

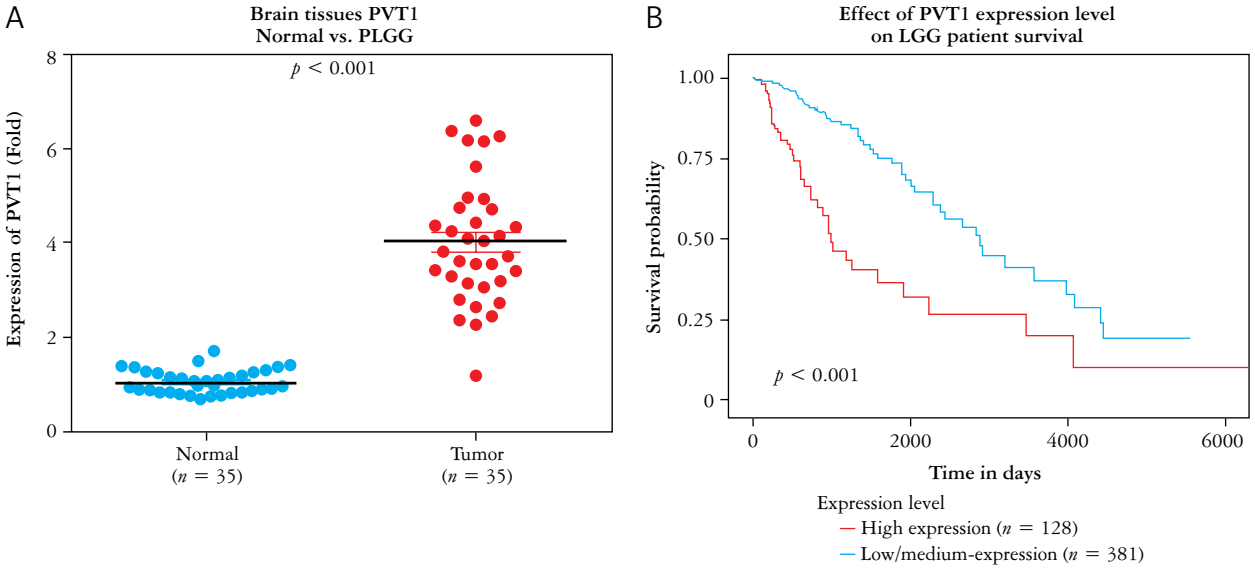

Fig. 1. lncPVT1 is positively associated with PLGG. **A**) Expression of lncRNA PVT1 in 35 PLGG tumor tissues and matched brain normal tissues. **B**) Survival rates of PLGG patients with lower or higher PVT1 expression levels were analyzed by KM Plotter analysis

Results

LncRNA-PVT1 is upregulated in pediatric low-grade glioma

Since the roles of lncRNA PVT1 in PLGG have not been investigated, we examined the expression of PVT1 in PLGG. A total of 35 human pediatric low-grade glioma and adjacent matched normal brain tissues were collected in this study. Results from qRT-PCR demonstrated that PVT1 was significantly upregulated ($p < 0.001$) in PLGG tissues compared with normal brain tissues (Fig. 1A). We then evaluated the clinical role of PVT1. PLGG patients with higher PVT1 expression levels showed significantly worse survival rates according to Kaplan-Meier plotter analysis ($p < 0.0001$) (Fig. 1B). These results suggest that lncRNA PVT1 is positively associated with PLGG progression.

miR-187-3p is downregulated in pediatric low-grade glioma

A number of studies revealed that miRNAs are critical regulators in cancer progression [18]. In addition, miRNAs are known to be blocked by lncRNAs [19]. We evaluated downregulated miRNAs which were potential downstream effectors of PVT1 in PLGG. Interestingly, miR-187-3p, which has been identified as a tumor suppressive molecule in various cancers [20, 21], showed significantly lower expression in PLGG tissues compared with adjacent normal brain tissues (Fig. 2). These analyses suggest that miR-187-3p is a potential tumor suppressor in PLGG.

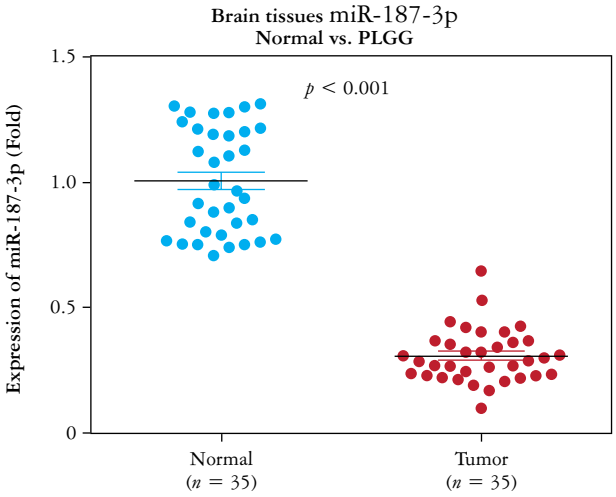

Fig. 2. miR-187-3p is negatively associated with PLGG. Expression of miR-187-3p in 35 PLGG tumor tissues and matched brain normal tissues

PVT1 and miR-187-3p reversely regulate glucose metabolism of pediatric low-grade glioma cell lines

We observed a negative expression pattern and clinical association between PVT1 and miR-187-3p in PLGG. Since reprogramming glucose metabolism has been emerging as a new hallmark of cancer cells [13], the roles of PVT1 and miR-187-3p in regulating glucose metabolism of PLGG-derived cells were assessed. PVT1 was silenced by siRNA in Res186 and BT66 PLGG-derived cell lines (Fig. 3A, 3B). Expectedly, blocking PVT1 effectively attenuated glucose uptake (Fig. 3C, 3D) and lactate product

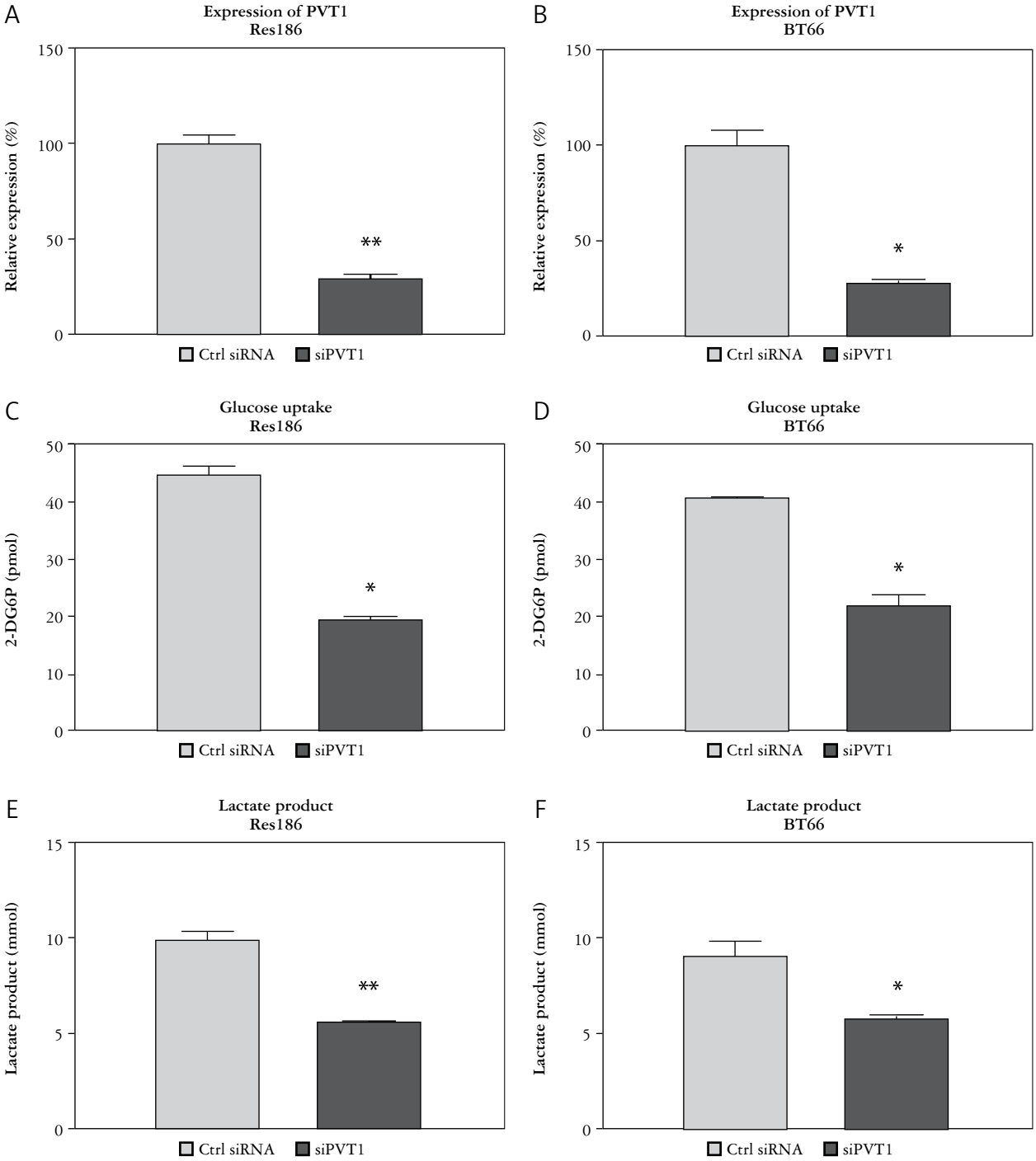

Fig. 3. PVT1 promotes glucose metabolism of PLGG cells. **A, B**) Control siRNA or siPVT1 was transfected into Res186 and BT66 cells. Expression of PVT1 was detected by qRT-PCR. Glucose uptake (**C, D**) and lactate product (E, F) from transfected cells were measured. *$p < 0.05$; **$p < 0.01$

(Fig. 3E, F), two glucose metabolism speed-limiting reactions [16] in PLGG cells, indicating that inhibiting the PVT1-promoted glucose metabolism could effectively limit PLGG growth. Expectedly, overexpression of miR-187-3p (Fig. 4A, B) significantly suppressed glucose metabolism (Fig. 4C–F). Summarizing the above results, we concluded that lncRNA PVT1 promotes and miR-187-3p inhibits glucose metabolism of PLGG cells.

PVT1 directly sponges miR-187-3p to block its expression in PLGG cells

Previous studies revealed that lncRNAs directly associate with miRNAs by forming a ceRNA network to downregulate miRNA expression [19]. We then asked whether PVT1 could sponge miR-187-3p in PLGG. The non-coding RNA server starBase identified that the sequence of PVT1 contains putative

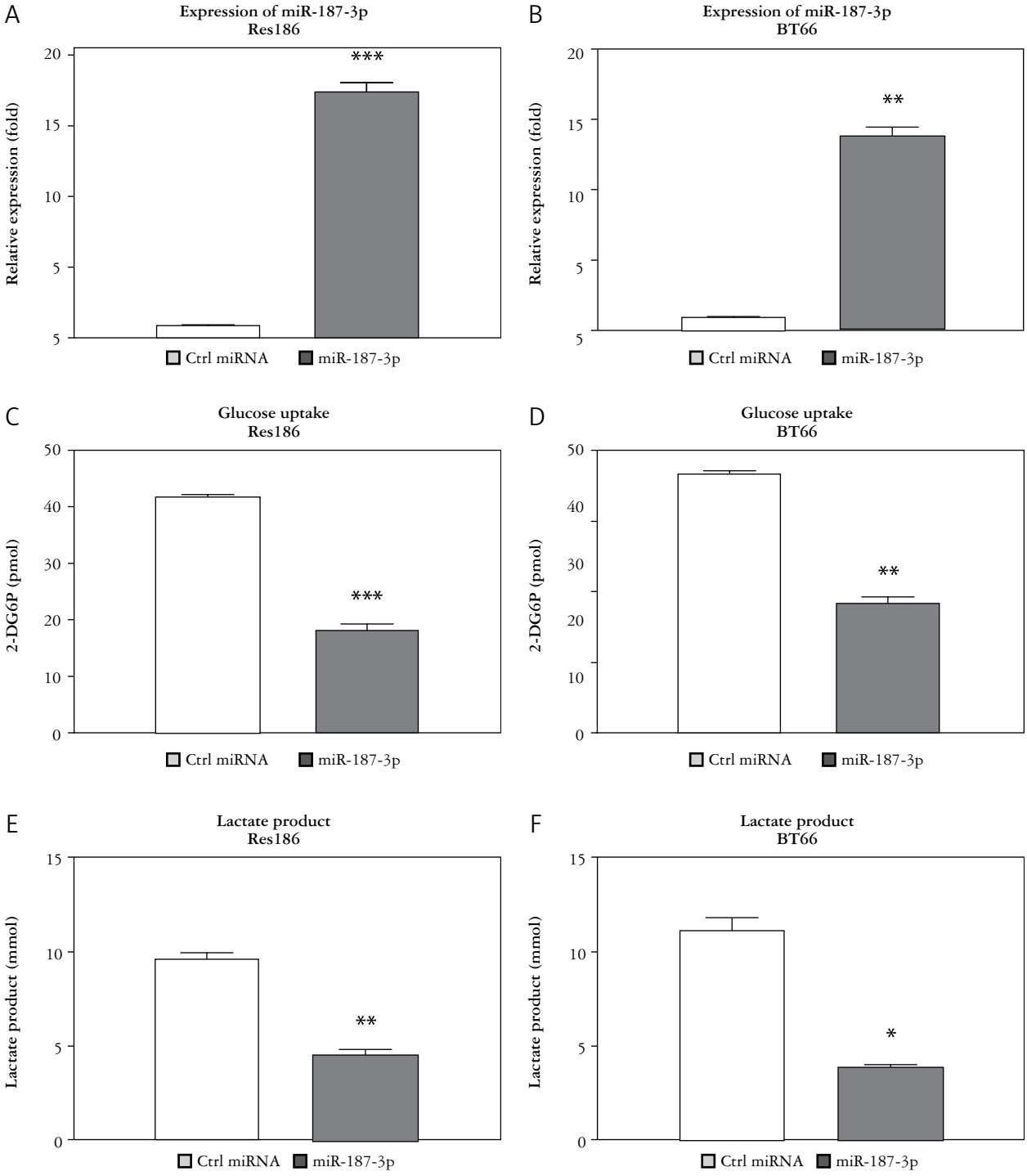

Fig. 4. miR-187-3p inhibits glucose metabolism of PLGG cells. (A, B) Control miRNA or miR-187-3p was transfected into Res186 and BT66 cells. The expression of miR-187-3p was detected by qRT-PCR. (C, D) Glucose uptake and (E, F) lactate product from transfected cells were measured. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

binding sites for miR-187-3p (Fig. 5A). Moreover, Pearson correlation coefficient analysis demonstrated a significantly negative correlation between PVT1 and miR-187-3p expression in PLGG tissues (Fig. 5B). We then tested whether PVT1 associated with miR-187-3p. RNA pull-down assay showed that only the biotin-labeled antisense PVT1 probe could bind and precipitate a sufficient amount of miR-187-3p in PLGG cells (Fig. 5C, D). The control probe and biotin-labeled sense PVT1 probe could not precipitate an enriched amount of miR-187-3p (Fig. 5C, D). Furthermore, the luciferase assay showed that PLGG cells which were co-transfected with luciferase vector containing wild type (WT) PVT1 plus miR-187-3p apparently blocked luciferase activity (Fig. 5E, F). Yet, inhibited luciferase activity was not detected in

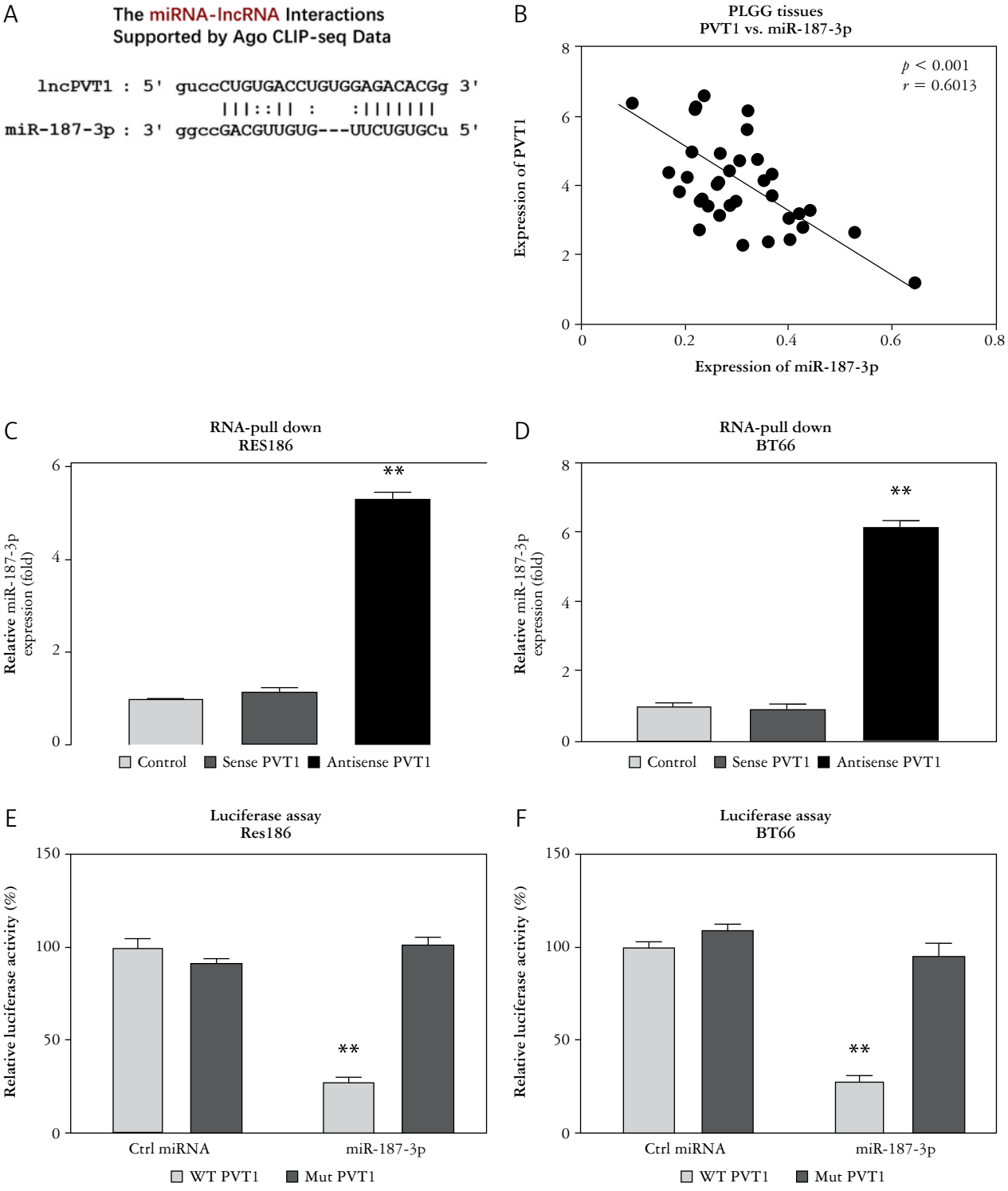

Fig. 5. PVT1 sponges miR-187-3p in PLGG cells. **A**) Prediction of the PVT1-miR-187-3p interaction by starBaseV2.0. **B**) Correlation between PVT1 and miR-187-3p in 35 PLGG tissues was analyzed by Pearson correlation coefficient analysis. **C, D**) RNA pull-down assay was performed to evaluate the binding of miR-187-3p on PLGG cell lines. **E, F**) Luciferase assay shows the specific binding of miR-187-3p on PVT1 in Res 186 and BT66 cells. $^{**}p < 0.01$

PLGG cells with co-transfection of luciferase vector containing the binding site mutant (Mut) PVT1 plus miR-187-3p (Fig. 5E, F). These results verified that PVT1 specifically sponged miR-187-3p in PLGG cells.

PVT1 promotes glucose metabolism of pediatric low-grade glioma cells through sponging miR-187-3p

Subsequently, we validated whether the PVT1-promoted glucose metabolism of PLGG cells occurred

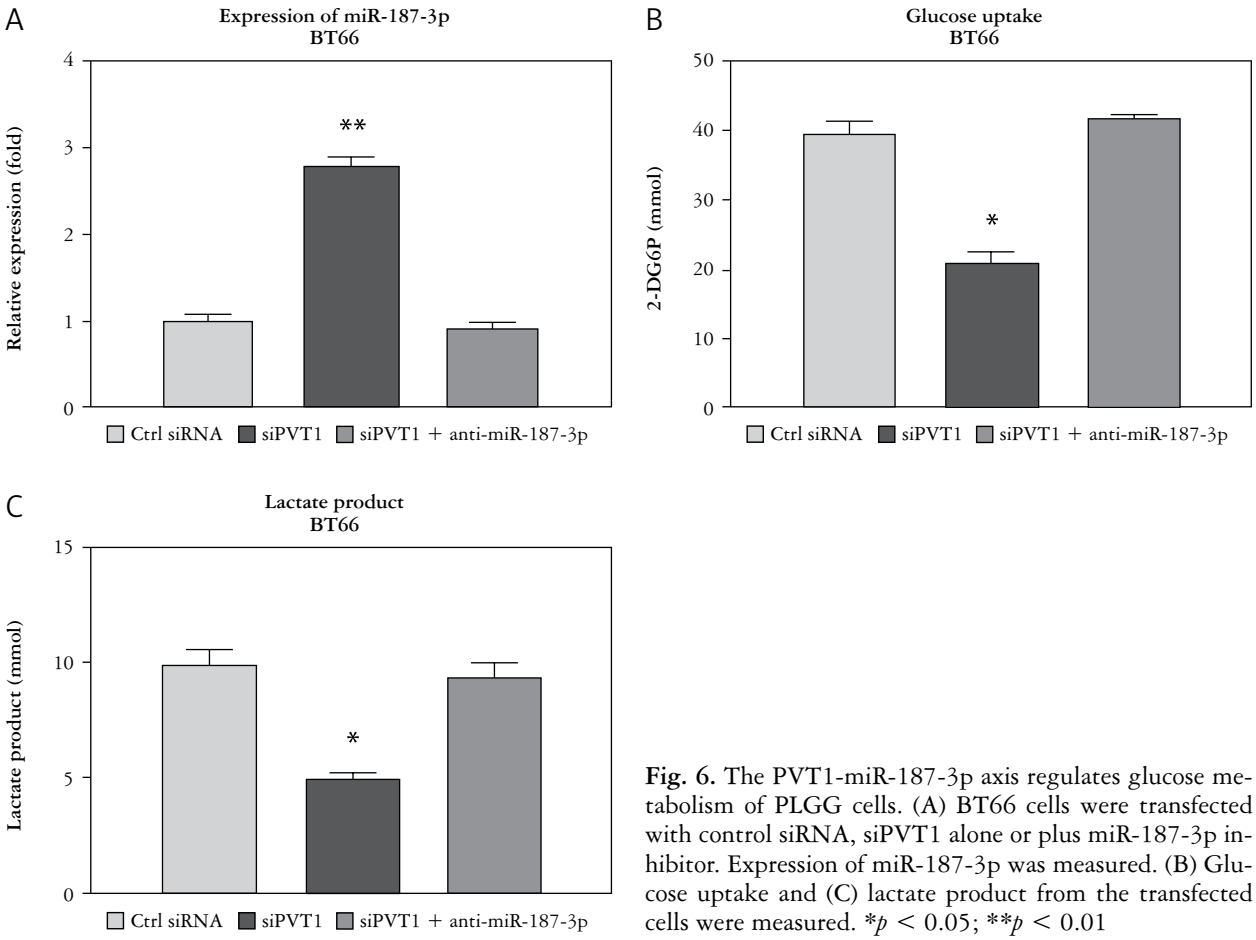

Fig. 6. The PVT1-miR-187-3p axis regulates glucose metabolism of PLGG cells. (A) BT66 cells were transfected with control siRNA, siPVT1 alone or plus miR-187-3p inhibitor. Expression of miR-187-3p was measured. (B) Glucose uptake and (C) lactate product from the transfected cells were measured. *$p < 0.05$; **$p < 0.01$

through sponging miR-187-3p. BT66 cells were transfected with control siRNA, siPVT1 or siPVT1 plus miR-187-3p inhibitor. Silencing of PVT1 led to significant recovery of miR-187-3p expression (Fig. 6A), which was further overridden by miR-187-3p inhibition (Fig. 6A). Expectedly, glucose uptake (Fig. 6B) and lactate product (Fig. 6C) were attenuated in PVT1-silenced cells. Moreover, glucose metabolism of BT66 cells with co-transfection of siPVT1 and miR-187-3p inhibitor were successfully recovered to levels from control cells (Fig. 6B, C). Taken together, rescue experiments validated that the PVT1-accelerated glucose metabolism of PLGG cells occurred through sponging miR-187-3p.

Discussion

Pediatric low-grade gliomas are the most common CNS malignancy in children, accounting for approximately 30% of pediatric brain tumors [1, 2]. The prognosis for PLGG is generally good and the 10-year overall survival was high (> 85%) [3]. The routine therapeutic treatment for progressive or symptomatic PLGG is surgical resection [4]. Moreover, radiotherapy, chemotherapy and targeted therapy are additional options for PLGG patients who were not found eligible for surgery [4]. The present study investigated the roles and molecular mechanisms of lncRNA PVT1 in PLGG. Clinically, expression of PVT1 was significantly elevated in PLGG tumors. Silencing of PVT1 effectively attenuated the glucose metabolism of PLGG cells, suggesting that PVT1 plays an oncogenic role in PLGG.

Accumulating evidence has revealed that lncRNAs are critical regulators in progression of various cancers [5]. Specifically, lncRNA PVT1 has been shown to play oncogenic roles in diverse cancers [10–12]. Our results firstly described the roles of PVT1 in PLGG indicating that PVT1 was negatively associated with survival rates of PLGG patients, consistent with previous studies [11, 12]. In addition, PVT1 functions to form a ceRNA network by direct association with miRNAs, resulting in blockage of target miRNAs' expression. Bioinformatics analysis indicated that the sequence of PVT1 contains a binding site for miR-187-3p, which has been reported to act as a tumor suppressor in multiple cancers [20, 21]. We found that miR-187-3p was significantly downregulated in PLGG tissues and positively associated with survival rate of PLGG patients. Overexpression of miR-187-3p significantly suppressed glucose metabolism of PLGG cells, suggesting that miR-187-3p plays reverse functions to PVT1. Furthermore, the predicted PVT1/miR-187-3p interaction was validated by RNA pull-down and luciferase assay. Taken together, these results revealed a PVT1-miR-187-3p ceRNA network in PLGG.

Cancer cells exhibited elevated glucose metabolism which provides essential energy and metabolic intermediates for growth of cancer cells [13, 14], suggesting that blocking the dysregulated glucose metabolism is an effective approach to limit cancer cell progression. The roles and underlying mechanisms of PVT1 in regulating glucose metabolism of PLGG cells were investigated in this study. We found that PVT1 promoted and miR-187-3p inhibited glucose metabolism of PLGG cells. Importantly, rescue experiments successfully validated the PVT1-accelerated glucose metabolism of PLGG cells was through direct sponging of miR-187-3p. Our findings revealed a PVT1-miR-187-3p ceRNA network in regulating glucose metabolism of PLGG. This study still has a limitation in that the conclusions were derived from *in vitro* experiments, which need further support and verification by an *in vivo* xenograft mouse experiment. Additionally, the downstream mRNA targets of miR-187-3p and precise signaling pathways which participated in regulating glucose metabolism of PLGG cells need to be further explored.

Conclusions

The results of this study support the conclusion that lncRNA PVT1 promotes glucose metabolism of PLGG cells by sponging miR-187-3p. This provides an experimental basis for the future clinical application of the PVT1-miR-187-3p axis in the treatment of PLGG.

Disclosures

1. The study received approval from the Ethics Committee of Weifang Maternal and Child Health Hospital (#20210302).
2. Assistance with the article: None.
3. Financial support and sponsorship: This study was supported by an internal funding resource from Weifang Maternal and Child Health Hospital.
4. Conflicts of interest: None.

References

1. Ryall S, Tabori U, Hawkins C. Pediatric low-grade glioma in the era of molecular diagnostics. Acta Neuropathol Commun 2020; 8: 30. DOI: 10.1186/s40478-020-00902-z.
2. Bale TA, Rosenblum MK. The 2021 WHO Classification of Tumors of the Central Nervous System: an update on pediatric low-grade gliomas and glioneuronal tumors. Brain Pathol 2022; 32: e13060. DOI: 10.1111/bpa.13060.
3. Pérez JPM, Muchart J, López VS, et al. Targeted therapy for pediatric low-grade glioma. Childs Nerv Syst 2021; 37: 2511-2520.
4. Fangusaro J, Bandopadhayay P. The "Risk" in Pediatric Low-Grade Glioma. Cancer Cell 2020; 37: 424-425.
5. Statello L, Guo CJ, Chen LL, Huarte M. Gene regulation by long non-coding RNAs and its biological functions. Nat Rev Mol Cell Biol 2021; 22: 96-118.
6. Goodall GJ, Wickramasinghe VO. RNA in cancer. Nat Rev Cancer 2021; 21: 22-36.
7. Tan YT, Lin JF, Li T, et al. LncRNA-mediated posttranslational modifications and reprogramming of energy metabolism in cancer. Cancer Commun (Lond) 2021; 41: 109-120.
8. Chen PY, Li XD, Ma WN, et al. Comprehensive transcriptomic analysis and experimental validation identify lncRNA HOXA-AS2/miR-184/COL6A2 as the critical ceRNA regulation involved in low-grade glioma recurrence. Onco Targets Ther 2020; 13: 4999-5016.
9. Xu S, Tang L, Liu Z, ET AL. Hypoxia-related lncRNA correlates with prognosis and immune microenvironment in lower-grade glioma. Front Immunol 2021; 12: 731048. DOI: 10.3389/fimmu.2021.731048
10. Lu D, Luo P, Wang Q, et al. lncRNA PVT1 in cancer: a review and meta-analysis. Clin Chim Acta 2017; 474: 1-7.
11. Zhou C, Yi C, Yi Y, et al. LncRNA PVT1 promotes gemcitabine resistance of pancreatic cancer via activating Wnt/β-catenin and autophagy pathway through modulating the miR-619-5p/Pygo2 and miR-619-5p/ATG14 axes. Mol Cancer 2020; 19: 118. DOI: 10.1186/s12943-020-01237-y.
12. Chen J, Yu Y, Li H, et al. Long non-coding RNA PVT1 promotes tumor progression by regulating the miR-143/HK2 axis in gallbladder cancer. Mol Cancer 2019; 18: 33. DOI: 10.1186/s12943-019-0947-9.
13. Pavlova NN, Zhu J, Thompson CB. The hallmarks of cancer metabolism: still emerging. Cell Metab 2022; 34: 355-377.
14. Stine ZE, Schug ZT, Salvino JM, Dang CV. Targeting cancer metabolism in the era of precision oncology. Nat Rev Drug Discov 2022; 21: 141-162.
15. Koppenol WH, Bounds PL, Dang CV. Otto Warburg's contributions to current concepts of cancer metabolism. Nat Rev Cancer 2011; 11: 325-337.
16. Ghanavat M, Shahrouzian M, Deris Zayeri Z, et al. Digging deeper through glucose metabolism and its regulators in cancer and metastasis. Life Sci 2021; 264: 118603. DOI: 10.1016/j.lfs.2020.118603.
17. Li JH, Liu S, Zhou H, et al. starBase v2.0: decoding miRNA-ceRNA, miRNA-ncRNA and protein-RNA interaction networks from large-scale CLIP-Seq data. Nucleic Acids Res 2014; 42 (Database issue): D92-D97. DOI: 10.1093/nar/gkt1248.
18. Ali Syeda Z, Langden SSS, Munkhzul C, et al. Regulatory mechanism of microRNA expression in cancer. Int J Mol Sci 2020; 21: 1723. DOI: 10.3390/ijms21051723.
19. Wang L, Cho KB, Li Y, et al. Long noncoding RNA (lncRNA)-mediated competing endogenous RNA networks provide novel potential biomarkers and therapeutic targets for colorectal cancer. Int J Mol Sci 2019; 20: 5758. DOI: 10.3390/ijms20225758.
20. Wu Y, Tao L, Liang J, et al. miR-187-3p increases gemcitabine sensitivity in breast cancer cells by targeting FGF9 expression. Exp Ther Med 2020; 20: 952-960.
21. Geng J, Yang K. circCCND1 regulates oxidative stress and FGF9 to Enhance chemoresistance of non-small cell lung cancer via sponging miR-187-3p. DNA Cell Biol 2021; 40: 675-682.

Address for correspondence:

Yanyan Zheng
Department of Neonatology
Weifang Maternal and Child Health Hospital
407 Qingnian Road, Weicheng District
Weifang City, Shandong Province
China, 261000
e-mail: zhengyyweifang@163.com