European Review for Medical and Pharmacological Sciences 2021; 25: 108-115

LINC00641 regulates prostate cancer cell growth and apoptosis *via* the miR-365a-3p/VGLL4 axis

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Abstract. – OBJECTIVE: Long non-coding RNA (lncRNA) was frequently abnormally expressed in cancers. LINC00641 was reported to play crucial roles in regulating tumor progression. However, its role in prostate cancer (PCa) has not been fully explored.

PATIENTS AND METHODS: In this work, proliferation, invasion and apoptosis assays were performed to detect the biological roles of LINC00641 in PCa. Bioinformatic analyses, Luciferase activity reporter assay, and rescue experiments were performed to investigate the potential mechanisms of LINC00641 in PCa. Expression levels of LINC00641, microRNA-365a-3p (miR-365a-3p), and vestigial like family member 4 (VGLL4) in PCa tissues and normal tissues were analyzed at ENCORI.

RESULTS: We found LINC00641 and VGLL4 was reduced, while miR-365a-3p was elevated expression in PCa tissues compared with normal tissues. LINC00641 overexpression inhibited growth and invasion abilities of PCa cells in vitro. Functional assays revealed that miR-365a-3p/VGLL4 pair was the downstream targets of LINC00641.

CONCLUSIONS: The findings of our work provided evidence that LINC00641 serves as a tumor suppressive lncRNA in PCa by regulating miR-365a-3p/VGLL4 axis.

Key Words:
LINC00641, MiR-365a-3p, VGLL4, CeRNA, Prostate cancer.

Introduction

Prostate cancer (PCa) is a frequently occurred cancer type in male and a huge health threat to human worldwide[1]. In addition to the age and heredity factor, alterations in gene copy number, mutation, and methylation status also affect PCa progression[2].

98% of genomic transcripts are non-coding RNA (ncRNA) with limited protein coding capacity[3]. ncRNAs are reported could either stimulate or inhibit cancer progression[4]. Long non-coding RNA (lncRNA) is a type of ncRNA with a length of above 200 nucleotides[5]. LncRNA small nucleolar host gene 17 (SNHG17) stimulates PCa development *in vitro* and *in vivo* through positively regulate signal transducer and activator of transcription 5A via microRNA-339-5p (miR-339-5p)[6]. Silencing of SNHG15 inhibits PCa progression by suppressing cell proliferation, invasion and promoting cell apoptosis[7]. Upregulation expression status of lncRNA OGFRP1 was significantly correlated with advanced PCa tumor stages[8]. In addition, lncRNA OGFRP1 could promote PCa progression via upregulating SARM1 through completely bind miR-124-3p[8].

Recently, the roles of LINC00641 in cancers have attracted more and more attention. However, there is no study to explore the roles of LINC00641 in PCa until now. In this work, we aimed to investigate the roles and associated mechanisms of LINC00641 in PCa.

Patients and Methods

Clinical Patients

23 paired PCa tumor tissues and adjacent tissues were collected from patients who underwent resection at Beilun district people's hospital. Samples were snap-frozen in liquid nitrogen until further usage. Patients were classified into different tumor stage based on the 8th edition of American Joint Commission on Cancer (AJCC) and the Union for International Cancer Control (UICC). Study protocol was approved by the Ethics Committee of Beilun district people's hospital. Written informed consent was obtained from all enrolled patients. The patients were included if they were diagnosed as PCa and did not receive anti-cancer treatment before. In the meantime, the patients were excluded if they have other malignancies.

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Cell Culture

PCa cells (PC-3, C42B, and LNCaP) and normal prostate epithelial cells RWPE-1 were bought at American Type Culture Collection (ATCC; Manassas, VA, USA). Cells were incubated in Dulbecco's Modified Eagle's Medium (DMEM) contains 10% fetal bovine serum (FBS; Invitrogen, Carlsbad, CA, USA) at 37°C humidified incubator with 5 % CO_2.

Bioinformatic Analysis

ENCORI (http://starbase.sysu.edu.cn/index.php) was used to identify miRNA targets for LINC00641, and we found miR-365a-3p was a putative target. Furthermore, targets of miR-365a-3p were also analyzed at ENCORI and indicated vestigial like family member 4 (VGLL4) was a possible target.

Cell Transfection

Sequence of LINC00641 was inserted into pcDNA3.1 to construct recombinant vector pc-LINC00641. miRNAs used in this work including miR-365a-3p mimic and negative control (miR-NC) were supplied by GeneChem (Shanghai, China). Cell transfection was conducted using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA) according to the provided instructions.

Quantitative Real-Time PCR (RT-qPCR)

RNA from tissues and cells was isolated using TRIzol reagent (Invitrogen, Carlsbad, CA, USA) according to manufacturer's suggestions. RNA was reverse transcribed into complementary DNA with reverse transcription kit (TaKaRa, Dalian, Liaoning, China). RT-qPCR was conducted at ABI 7500 (Applied Biosystems, Foster City, CA, USA) using SYBR Green to detect expression levels of LINC00641, miR-365a-3p, and VGLL4. Primers used were as follows: LINC00641 forward, 5'-GTAACTCTATGTACAACGTTAA-3', LINC00641 reverse, 5'-TAGAAGTCAACTCATTATGCTGCTG-3'; VGLL4 forward, 5'-TTGTCCTAGGAAACGGGCTG-3', VGLL4 reverse, 5'-GGGCTTACTGGTAGACGGTG-3'; GAPDH forward: 5'-TCCCTGAGCTGAACGGGAAG-3', GAPDH reverse, 5'-GGAGGAGTGGGTGTCGCTGT-3'; miR-365a-3p forward, 5'-TAATGCCCCTAAAAATCCTTAT-3', miR-365a-3p reverse, 5'-CAGTGCGTGTCGTGGAGT-3'; U6 snRNA forward, 5'-GGAACGATACAGAGAAGATTAGC-3', U6 snRNA reverse, 5'-TGGAACGCTTCACGAATTTGCG-3'. Relative gene expression level was calculated with 2-ΔΔCT method.

Cell Proliferation Assay

Cell proliferation rate was analyzed using cell counting kit-8 (CCK-8, Beyotime, Haimen, Jiangsu, China). 2,000 cells were seeded in 96-well plate and incubated as described above. Optical density at 450 nm of each well was measured at 0, 24, 48, 72 h by adding CCK-8 reagent according to manufacturer's protocol.

Transwell Invasion Assay

For cell invasion assay, 1×10^6 cells were seeded into upper chamber of a 8 μm Matrigel coated 24-well transwell chamber (Corning, Corning, NY, USA). Medium contains FBS was added into bottom chamber. After 24 h incubation, invaded cells were fixed by methanol, stained by crystal violet, and counted under microscope.

Cell Apoptosis Assay

Cells after transfection were collected and washed with PBS. Cells were stained with Annexin V-FITC and PI (Beyotime, Shanghai, China) for 15 min in the dark. Cell samples were subjected to analysis at BD Bioscience FACSCalibur (Franklin Lakes, NJ, USA) and then analyzed using FlowJo 10 software.

Analysis of LINC00641, MiR-365a-3p, and VGLL4 Expression at ENCORI

ENCORI was used to analyze LINC00641, miR-365a-3p, and VGLL4 expression levels in PCa tissues and normal tissues. Expression correlation of LINC00641 and VGLL4 was also analyzed at ENCORI.

Dual-Luciferase Assay

LINC00641 or VGLL4 wild type and mutant Luciferase plasmids based on pGL3.0 were established by GeneChem. Cells were transfected with LINC00641/VGLL4-wt/mt and synthetic miRNAs using Lipofectamine 2000. After 48 h transfection, relative luciferase activity was measured using Dual-luciferase reporter assay system (Promega, Madison, WI, USA).

RNA Pull-Down Assay

The wild type and mutant miR-365a-3p sequences containing the LINC00641 and VGLL4 binding site were synthesized and labeled with biotin to obtain bio-miR-365a-3p-wt/mt. Cells were lysed and incubated with probes, and then incubated with streptavidin agarose magnetic beads in the appearance of RNase-free and yeast tRNA.

RNA was extracted with TRIzol and subjected to RT-qPCR analysis to calculate relative gene expression level.

Statistical Analysis

Data collected were displayed as mean±SD. Statistical difference was analyzed using Student's *t*-test or One-way analysis of variance and Tukey post-hoc test at SPSS 21.0 software (IBM Corp., Armonk, NY, USA). *p*-value less than 0.05 means statistically significant.

Results

LINC00641 was Decreased Expression in PCa

LINC00641 expression level in PCa tissues and normal tissues was firstly detected at ENCORI and the results showed LINC00641 expression level in PCa tissues was lower than that in normal tissues (Figure 1A). Results in Figure 1B also showed LINC00641 was decreased expression in PCa tumor tissues compared with normal tissues. Survival analysis showed patients with low LINC00641 expression tend to have lower survival rate than those with high expression (Figure 1C). Moreover, the expression level of LINC00641 in PCa cells was downregulated compared with normal cells (Figure 1D).

LINC00641 Overexpression inhibits PCa Cell Growth and Invasion

Expression level of LINC00641 in PCa cells transfected with pc-LINC00641 was significantly stimulated (Figure 2A). The effect of LINC00641 overexpression on cell growth was detected by CCK-8 assay and flow cytometry assay. We showed LINC00641 overexpression inhibited cell proliferation (Figure 2B) and promoted cell apoptosis (Figure 2C). Moreover, transwell invasion assay showed LINC00641 overexpression significantly inhibited cell invasion (Figure 2D).

MiR-365a-3p was Increased in PCa and Could Directly Sponge with LINC00641

To further explore the acting mechanisms of LINC00641 in PCa, we analyzed the targets of

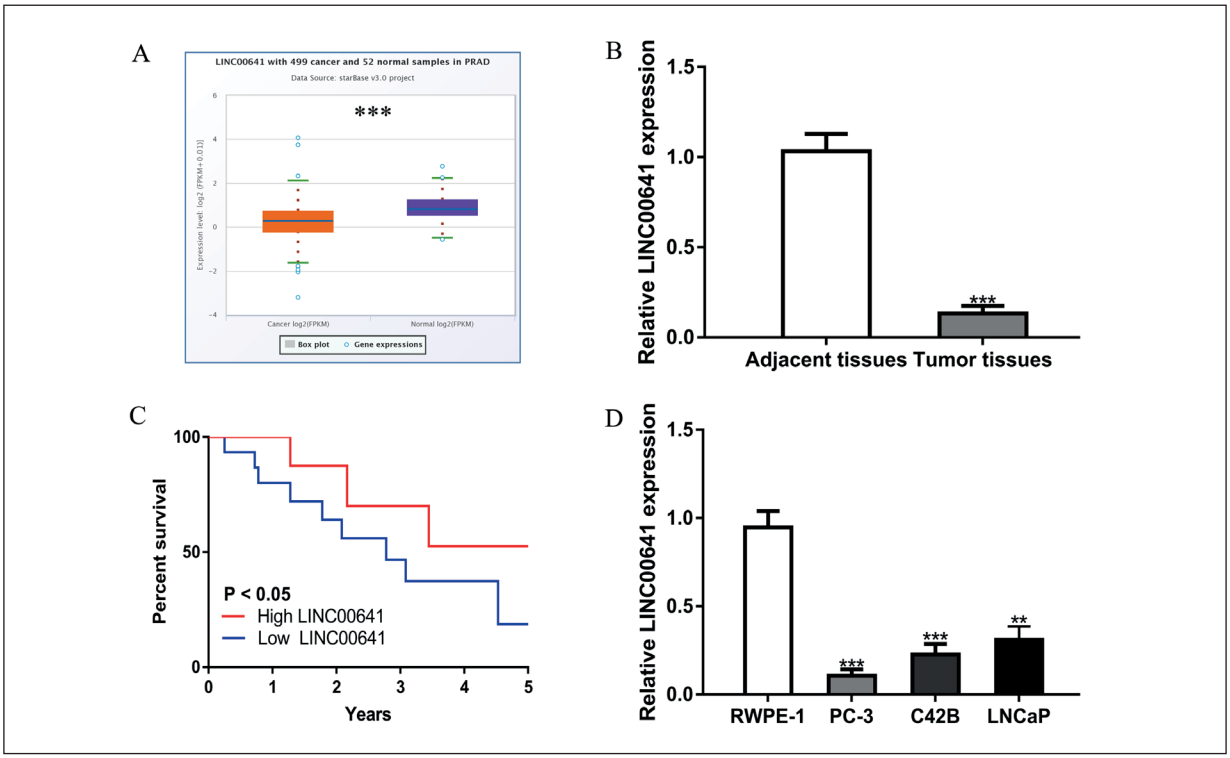

Figure 1. LINC00641 was decreased in PCa tissues and cells. **A,** LINC00641 expression in PCa tissues and normal tissues was detected by ENCORI. **B,** LINC00641 expression in PCa tissues and adjacent tissues was detected by RT-qPCR. **C,** Kaplan-Meier survival analysis was performed to assess effect of LINC00641 on PCa patients. **D,** LINC00641 expression in PCa cells and normal cell was indicated by RT-qPCR. PCa: prostate cancer; RT-qPCR: Quantitative real-time PCR.

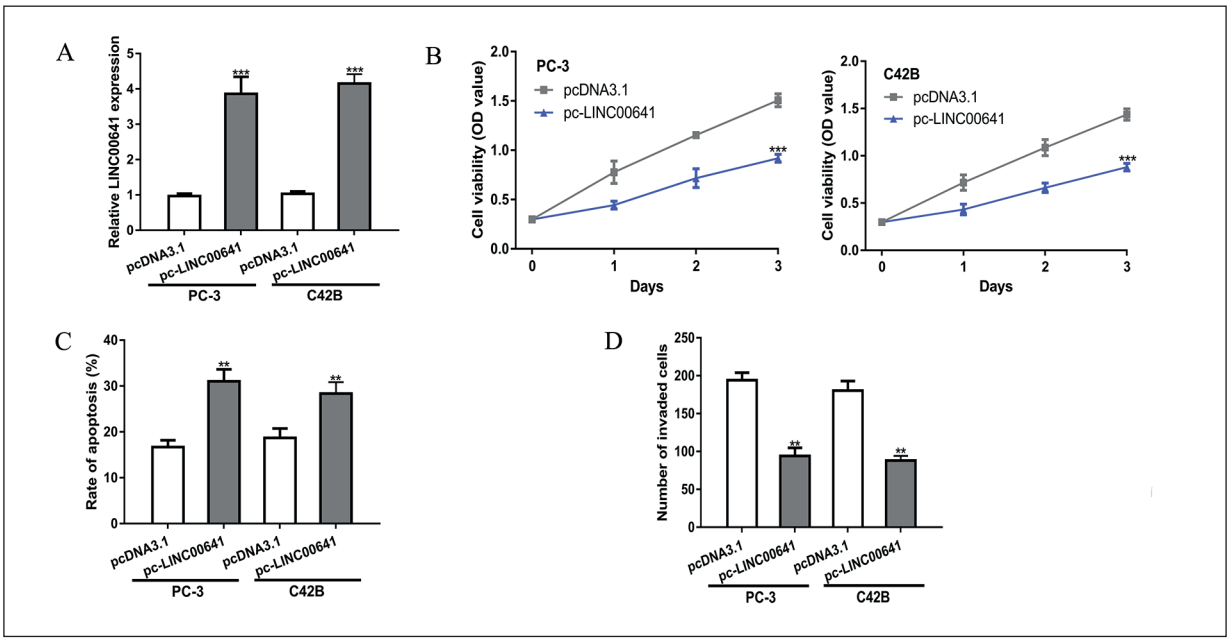

Figure 2. LINC00641 overexpression suppresses PCa cell growth and invasion. **A,** LINC00641 expression in PCa cells transfected with pc-LINC00641 and pcDNA3.1 was detected by RT-qPCR. **B,** Proliferation ability of PCa cells transfected with pc-LINC00641 and pcDNA3.1 was detected by CCK-8 assay. **C,** Apoptosis rate of PCa cells transfected with pc-LINC00641 and pcDNA3.1 was detected by flow cytometry assay. **D,** Invasion ability of PCa cells transfected with pc-LINC00641 and pcDNA3.1 was detected by transwell invasion assay. PCa: prostate cancer; RT-qPCR: Quantitative real-time PCR; CCK-8: cell counting kit-8.

LINC00641 and found miR-365a-3p was a possible target (Figure 3A). We found miR-365a-3p was increased expression in PCa tissues compared with normal tissues (Figure 3B and 3C). In addition, miR-365a-3p was negatively correlated with LINC00641 in PCa tissues (Figure 3D). Besides that, miR-365a-3p expression was significantly increased in PCa cells compared with normal cells (Figure 3E), and they were inhibited followingly LINC00641 overexpression (Figure 3F). To verify whether LINC00641 could interact with miR-365a-3p, Luciferase activity reporter assay was performed. Results showed that relative Luciferase activity in PCa cells harbor LINC00641-wt was significantly suppressed by miR-365a-3p mimic (Figure 3G).

MiR-365a-3p Overexpression Promotes PCa Cell Growth and Invasion

To investigate the roles of miR-365a-3p in PCa, miR-365a-3p mimic was transfected into PC-3 cells. We found miR-365a-3p expression level was significantly increased in miR-365a-3p mimic group (Figure 4A). CCK-8 assay and flow cytometry assay indicated that cell growth ability was stimulated following miR-365a-3p overexpression (Figure 4B and 4C). Transwell invasion assay revealed miR-365a-3p overexpression stimulated cell invasion (Figure 4D).

LINC00641 Regulates VGLL4 Expression Via MiR-365a-3p

To investigate how miR-365a-3p regulates PCa progression, targets of miR-365a-3p were predicted. We found VGLL4 was a potential target gene (Figure 5A). We then found VGLL4 was decreased expression in PCa tissues compared with normal tissues (Figure 5B and 5C). Correlation analyses showed VGLL4 was negatively correlated with miR-365a-3p (Figure 5D) and positively correlated with LINC00641 (Figure 5E and 5F) in PCa tissues. Furthermore, we found VGLL4 was decreased expression in PCa cells compared with normal cells (Figure 5G). Force the expression of miR-365a-3p decreased VGLL4 expression (Figure 5H). On the contrary, force the expression of LINC00641 significantly increased VGLL4 expression (Figure 5I). Luciferase reporter assay showed miR-365a-3p mimic significantly reduced Luciferase activity of VGLL4-wt but not VGLL4-mt (Figure 5J).

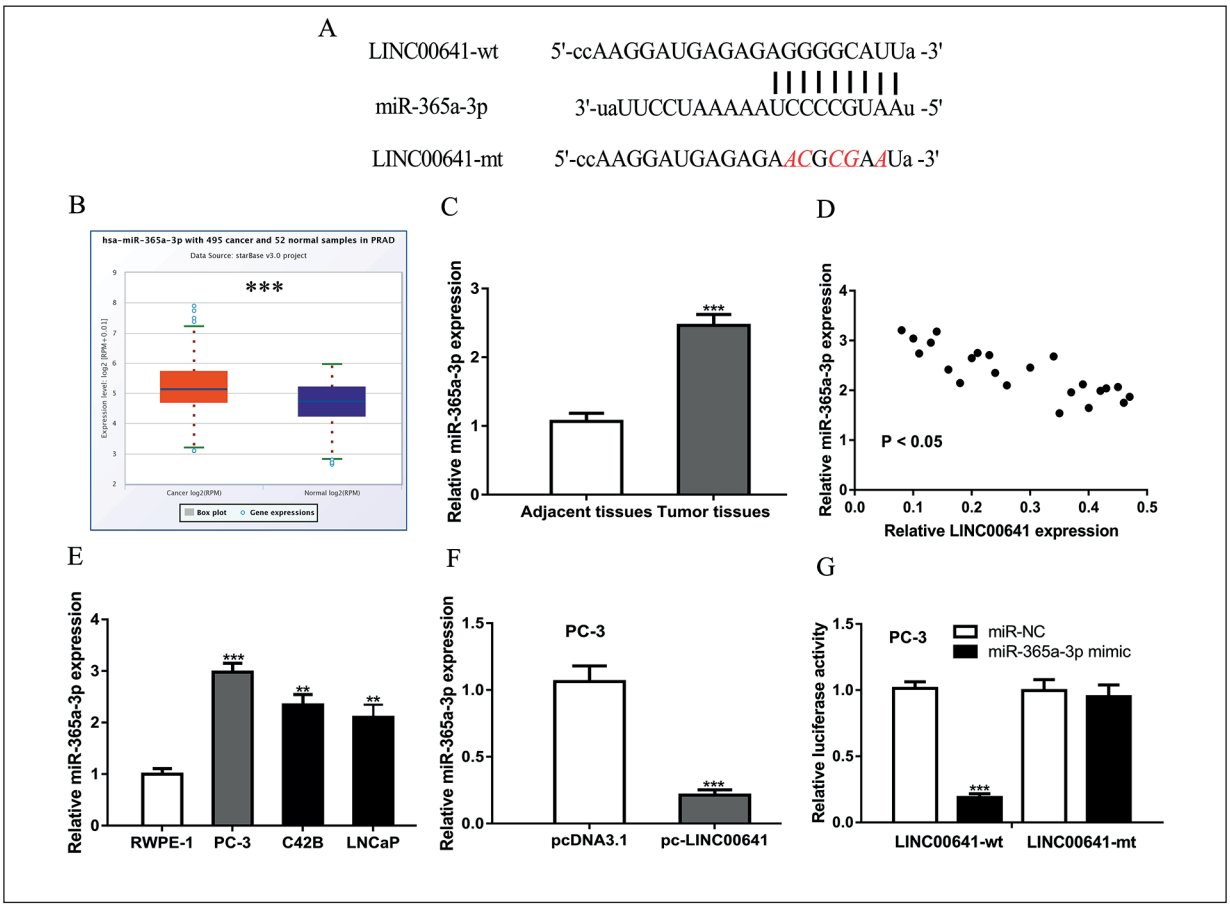

Figure 3. MiR-365a-3p was a target of LINC00641 in PCa. **A,** Binding module of LINC00641 and miR-365a-3p. **B,** miR-365a-3p expression in PCa tissues and normal tissues was detected by ENCORI. **C,** MiR-365a-3p expression in PCa tissues and adjacent tissues was detected by RT-qPCR. **D,** Expression correlation of LINC00641 and miR-365a-3p in PCa tissues. **E,** MiR-365a-3p expression in PCa cells and normal cell was detected by RT-qPCR. **F,** MiR-365a-3p expression in PCa cells transfected with pc-LINC00641 and pcDNA3.1 was detected by RT-qPCR. **G,** Relative luciferase activity in PCa cell transfected with LINC00641-wt/mt and miR-365a-3p mimic/miR-NC. PCa: prostate cancer; RT-qPCR: Quantitative real-time PCR; miR-365a-3p: microRNA-365a-3p; miR-NC: negative control microRNA; wt: wild type; mt: mutant.

RNA pull-down assay showed LINC00641 and VGLL4 could bind with miR-365a-3p in PCa cells (Figure 5K).

LINC00641 Affects PCa Cell Growth and Invasion Via MiR-365a-3p/VGLL4 Axis

Based on these findings, we supposed LINC00641 may affect PCa progression via miR-365a-3p/VGLL4 axis. To validate this hypothesis, miR-365a-3p mimic was transfected into PC-3 cell along with pc-LINC00641. Results showed the stimulation effect of pc-LINC00641 on VGLL4 expression could be abolished by miR-365a-3p mimic (Figure 6A). *In vitro* functional assays showed miR-365a-3p mimic could reverse the inhibitory effects of pc-LINC00641 on PCa cell growth and invasion (Figure 6B-6D).

Discussion

Although improvements in the understanding of mechanisms related to PCa[6-8], several effects are still needed to understand molecules contributed PCa carcinogenesis. Hence, the further understanding of PCa is essential to develop novel treatment methods.

LINC00641 is reported to play crucial roles in regulating cancer progression. For example, LINC00641 was found highly expressed in acute myeloid leukemia and its knockdown could suppress cell growth and metastasis, indicating an oncogenic role of LINC00641[9]. On the contrary, LINC00641 was found decreased expression in breast cancer and its overexpression can suppress cancer growth and metastasis[10]. Moreover,

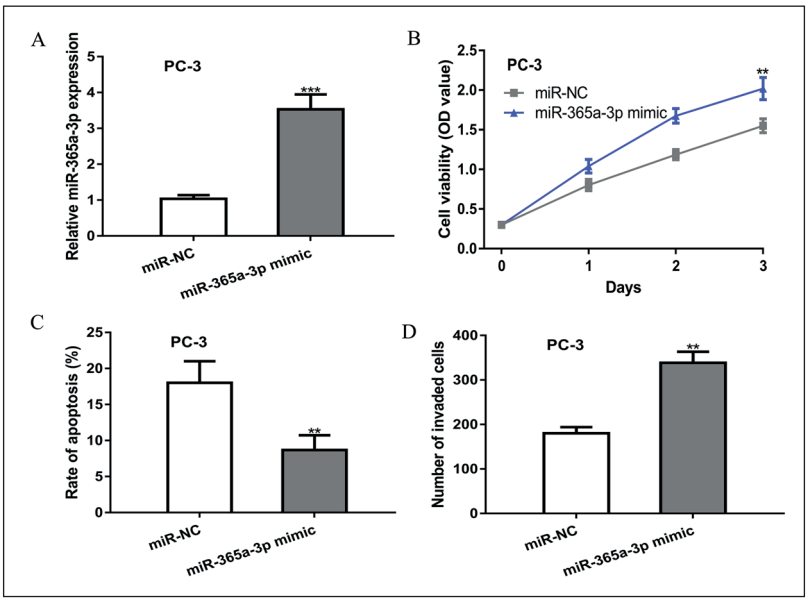

Figure 4. MiR-365a-3p overexpression stimulates PCa cell growth and invasion. **A,** MiR-365a-3p expression in PCa cells transfected with miR-365a-3p mimic and miR-NC was detected by RT-qPCR. **B,** Proliferation ability of PCa cells transfected with miR-365a-3p mimic and miR-NC was detected by CCK-8 assay. **C,** Apoptosis rate of PCa cells transfected with miR-365a-3p mimic and miR-NC was detected by flow cytometry assay. **D,** Invasion ability of PCa cells transfected with miR-365a-3p mimic and miR-NC was detected by transwell invasion assay. PCa: prostate cancer; RT-qPCR: Quantitative real-time PCR; CCK-8: cell counting kit-8; miR-365a-3p: microRNA-365a-3p; miR-NC: negative control microRNA.

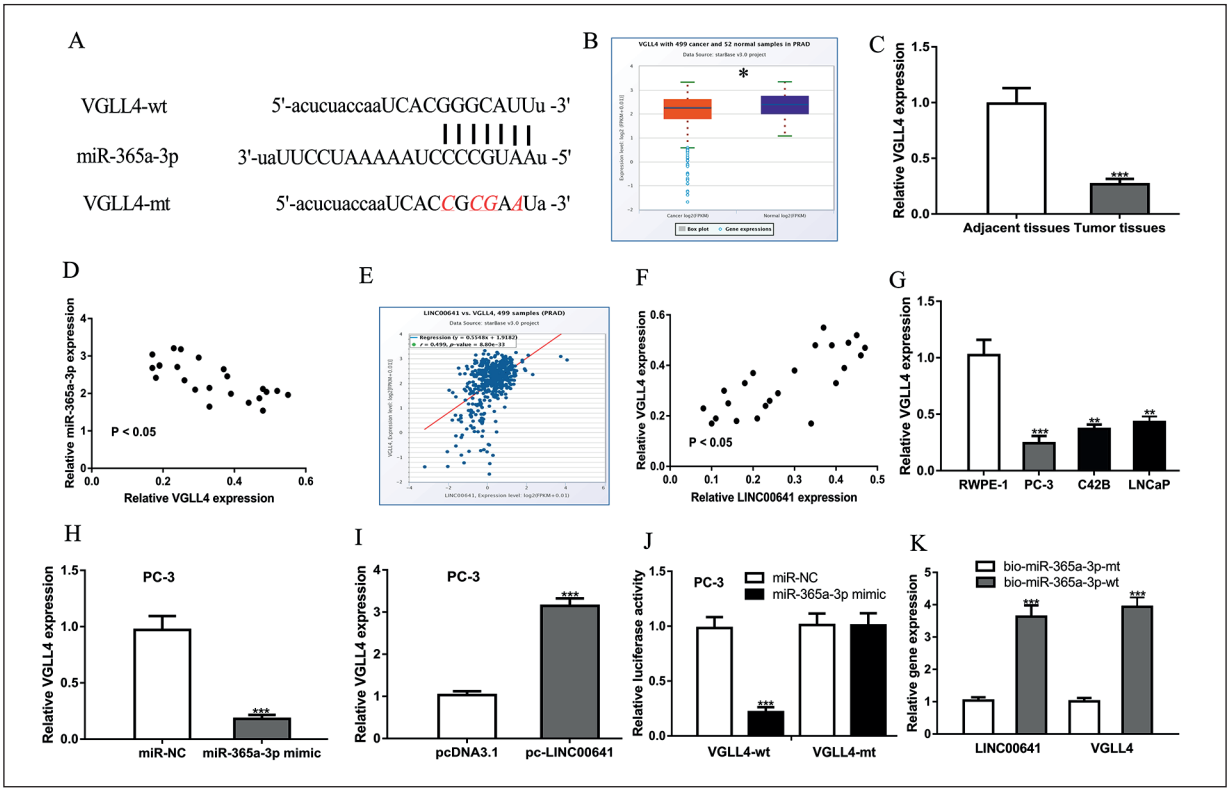

Figure 5. LINC00641 regulates VGLL4 expression via miR-365a-3p. **A,** Binding module of VGLL4 and miR-365a-3p. **B,** VGLL4 expression in PCa tissues and normal tissues was detected by ENCORI. **C,** VGLL4 expression in PCa tissues and adjacent tissues was detected by RT-qPCR. **D,** Expression correlation of VGLL4 and miR-365a-3p in PCa tissues. **E,** Expression correlation of VGLL4 and LINC00641 in PCa tissues detected by ENCORI. **F,** Expression correlation of VGLL4 and LINC00641 in PCa tissues. **G,** VGLL4 expression in PCa cells and normal cell was detected by RT-qPCR. **H,** VGLL4 expression in PCa cells transfected with miR-365a-3p mimic and miR-NC was detected by RT-qPCR. **I,** VGLL4 expression in PCa cells transfected with pc-LINC00641 and pcDNA3.1 was detected by RT-qPCR. **J,** Relative luciferase activity in PCa cell transfected with VGLL4-wt/mt and miR-365a-3p mimic/miR-NC. **K,** RNA pull-down assay to analyze the co-enrichment of LINC00641, miR-365a-3p, and VGLL4. PCa: prostate cancer; RT-qPCR: Quantitative real-time PCR; miR-365a-3p: microRNA-365a-3p; VGLL4: vestigial like family member 4; miR-NC: negative control microRNA; wt: wild type; mt: mutant.

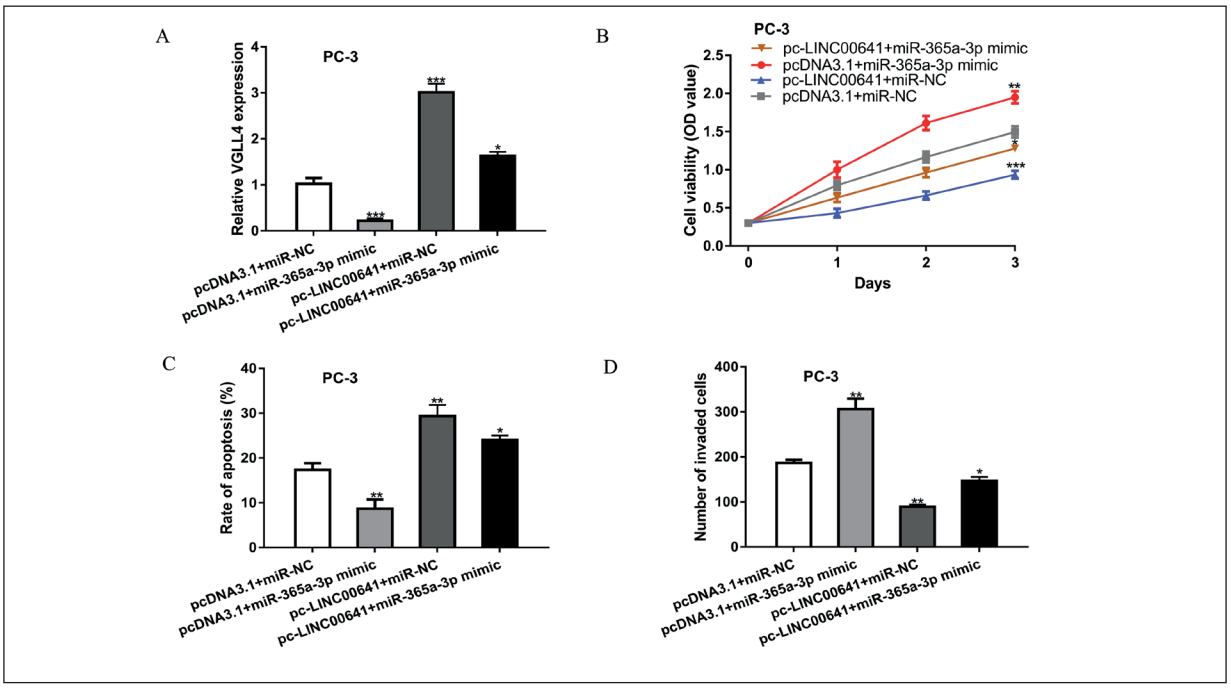

Figure 6. LINC00641 regulates PCa cell growth and invasion via miR-365a-3p/VGLL4 axis. **A,** VGLL4 expression in PCa cells transfected with pcDNA3.1+miR-NC, pcDNA3.1+miR-365a-3p mimic. Pc-LINC00641+miR-NC, and pc-LINC00641+miR-365a-3p mimic was detected by RT-qPCR. **B,** Proliferation ability of PCa cells transfected with pcDNA3.1+miR-NC, pcDNA3.1+miR-365a-3p mimic. Pc-LINC00641+miR-NC, and pc-LINC00641+miR-365a-3p mimic was detected by CCK-8 assay. **C,** Apoptosis rate of PCa cells transfected with pcDNA3.1+miR-NC, pcDNA3.1+miR-365a-3p mimic. Pc-LINC00641+miR-NC, and pc-LINC00641+miR-365a-3p mimic was detected by flow cytometry assay. **D,** Invasion ability of PCa cells transfected with pcDNA3.1+miR-NC, pcDNA3.1+miR-365a-3p mimic. Pc-LINC00641+miR-NC, and pc-LINC00641+miR-365a-3p mimic was detected by transwell invasion assay. PCa: prostate cancer; RT-qPCR: Quantitative real-time PCR; miR-365a-3p: microRNA-365a-3p; VGLL4: vestigial like family member 4; miR-NC: negative control microRNA.

LINC00641 was identified expressed at a low level in non-small cell lung cancer and it could suppress cell proliferation by inducing cell apoptosis[11]. In our work, we launched investigations to explore the functions of LINC00641 in PCa. We showed LINC00641 was decreased expression in both PCa tissues and cells, and its low expression could predict shorter overall survival of PCa patients. Functionally, LINC00641 overexpression could suppress PCa cell proliferation and invasion and induced cell apoptosis, suggesting LINC00641 exerts a tumor suppressive role in PCa.

MiRNA is another type of ncRNA with a length of 18-25 nucleotides and can affect cancer progression, including PCa[12,13]. LncRNA can bind with miRNA to regulate cancer behaviors, which is also termed as competing endogenous RNA (ceRNA) theory[14]. MiR-365a-3p was reported to play both tumor suppressive and oncogenic roles in cancers[15,16]. It was reported miR-365a-3p was increased expression in colorectal cancer and correlated with poorer prognosis[15]. In addition, miR-365a-3p was shown to promote laryngeal squamous cell carcinoma growth and metastasis through PI3K/AKT pathway[16]. We provided evidence that miR-365a-3p was increased expression in PCa and it could promote tumor progression. Furthermore, we analyzed the target of miR-365a-3p. VGLL4 is found expressed at low levels in triple-negative breast cancer and negatively correlated with ki67 expression and tumor size[17]. Silencing of VGLL4 is shown to stimulate triple-negative breast cancer cell growth, indicating tumor suppressive role of VGLL4[17]. Our work also found VGLL4 was expressed at low levels in PCa tissues and cells. Rescue experiments showed LINC00641 regulates PCa progression via miR-365a-3p/VGLL4 axis.

Conclusions

According to the limited of our knowledge, we for the first time revealed that LINC00641 was

significantly decreased expression in PCa and correlated with worser overall survival of cancer patients. Of note, we showed force the expression of LINC00641 could suppress PCa cell growth and invasion via miR-365a-3p/VGLL4 axis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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