

Prognostic Value of miR-1826 in Prostate Cancer and Its Regulatory Effect on Tumor Progression

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Purpose: miRNAs can act as oncogenes or tumor suppressors and participate in the development and progression of tumors, thus affecting the prognosis and survival of cancer patients. In this paper, we mainly studied the role of miR-1826 in prostate cancer.

Patients and Methods: The expression of miR-1826 was studied by quantitative real-time PCR (qRT-PCR). Kaplan–Meier curves were used to analyze the relationship between the expression of miR-1826 and the survival rate of PC patients. Cox regression analysis was used to study the risk factors affecting the prognosis of PC patients. PC cells were transfected with miR-1826 mimic, mimic negative control (mimic NC), miR-1826 inhibitor, or inhibitor NC. The effect of miR-1826 on the proliferation of PC cells was studied by the CCK-8 method and colony formation assay. Transwell assays were used to detect the effect of miR-1826 on the migratory and invasive abilities of tumor cells.

Results: The expression of miR-1826 in PC tissues was lower than that in adjacent normal tissues, and that the expression levels of miR-1826 in four PC cell lines were all lower than normal human prostate epithelial cell lines. Patients with low expression of miR-1826 had shorter overall survival compared with those with high expression. The downregulation of miR-1826 promoted PC cell proliferation, migration, and invasion.

Conclusion: In summary, the low expression of miR-1826 may promote the progression of PC, and the low expression of miR-1826 is also associated with a poor prognosis in PC patients.

Keywords: miR-1826, prostate cancer, prognostic value, progression, treatment

Introduction

Prostate cancer (PC) is one of the most common malignant tumors in the male genitourinary system.^{1–3} PC is a malignant tumor with a high incidence in the United States, Canada, and other countries, accounting for approximately the second highest male malignant tumor mortality.⁴ Although the number of PC patients is relatively low in China, the incidence of PC increases year by year and ranks the third among male urogenital malignancies, due to adjustment of diet structure and the improvement of diagnostic techniques with the aging of the population.⁵ It has been reported that PC affects the quality of life and life expectancy of Chinese men over 50 years old.^{6,7} In recent years, due to the development of molecular biology, research on PC has progressed in many aspects, especially the tumor markers, mismatch repair-related genes, and tumor invasion and metastasis-related factors.⁸

MicroRNAs (miRNAs) are a class of endogenous, nonprotein-coding small molecular RNAs. Mature miRNAs are single-stranded RNAs containing about 22

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nucleotides (18–24).^{9,10} Studies have shown that miRNAs may be involved in the occurrence and development of human tumors.^{11–13} Many tumors have changes in miRNA expression levels, which may play a role in the occurrence and development of tumors as oncogenes or tumor suppressor genes. Exploring the mechanism of miRNA in PC may provide new ideas for the diagnosis and treatment of PC. Many studies have focused on the effect of abnormally expressed miRNAs on PC, such as miR-101,¹⁴ miR-26a,¹⁵ miR-153,¹⁶ and miR-9-5p.¹⁷ A previous study by Taha A Haj-Ahmad and coworkers investigated the potential of using the deregulation of urinary miRNAs to detect PC among cases of benign prostatic hyperplasia. In their study, they first suggested that miR-1826 was downregulated in PC compared with the healthy control group.¹⁸ However, until now, the expression level of miR-1826 in PC tissues or cells and its prognostic significance in PC have not been clear.

In the present study, we further investigated the clinical significance and functional roles of miR-1826 in PC, and its correlation with clinicopathological characteristics was analyzed to determine its prognostic significance in PC. The potential role of miR-1826 in PC was observed and explored by transfecting PC cells with miR-1826 mimic, mimic NC, miR-1826 inhibitor, or inhibitor NC into PC cells.

Materials and Methods

Patients and Tissue Samples

A total of 105 patients diagnosed with PC from 2012 to 2015 were selected, PC tissues and adjacent normal tissues were obtained by radical prostatectomy. All specimens obtained were immediately stored in liquid nitrogen. All patients signed informed consent. This study was approved by the Ethics Committee of Affiliated Hospital of Weifang Medical University (approval no.2012047). The exclusion criteria were as follows: patients who have received different treatments such as surgery, radiotherapy, and chemotherapy; or who had diseased of the heart, liver, brain, kidney, lung, and other organs or the blood system diseases. All patients were followed up for five years.

Cell Culture and Transfection

Cell culture: Prostate cancer cell lines (PC-3, VCaP, DU145, 22Rv1) and normal human prostate epithelial cells line (RWPE-1) were purchased from the Institute of Cell Research, Chinese Academy of Sciences (Shanghai,

China). All cells were cultured in RPMI 1640 (HyClone, Logan, UT, USA) culture medium containing 10% fetal bovine serum (HyClone) in a constant temperature incubator at 37°C and 5% CO₂, and the medium was changed every other day. The cell was subcultured when they reached more than 85% confluency.

Cell transfection: Cells (1×10^5 cells/well) were transfected with miR-1826 mimic, mimic NC, miR-1826 inhibitor, inhibitor NC (GenePharma; Shanghai, China) at a final concentration of 50 nM, and the untransfected cells were used as the blank control group. The cells were transfected according to the Lipofectamine 2000 manual (Thermo Fisher Scientific, Waltham, MA, USA), and the culture medium was replaced with a complete culture medium for 4–6 h. After 48 h of transfection, the efficiency was measured using quantitative real-time polymerase chain reaction (qRT-PCR).

RNA Extraction and qRT-PCR

The total RNA of all PC tissues or cells was extracted with TRIzol reagent (Thermo Fisher Scientific, Waltham, MA, USA), and the RNA quality and quantity were verified with a NanoDrop 1000 (Thermo Fisher Scientific). cDNA was synthesized with TaqMan miRNA reverse transcription kit (Thermo Fisher Scientific). PCR amplification and quantitative analysis were conducted with TaqMan miRNA quantitative PCR kit (Thermo Fisher Scientific) according to the kit instructions on an ABI 7500 PCR System. The RT-qPCR condition was as follows: 95°C for 2 min, 40 cycles of 95°C for 20 s, 60°C for 30 s, 72°C for 30 s, and then 72°C for 5 min. The sequences for RT-PCR were as follows: miR-1826, forward 5'-GCATTGATCATCGACACTTCGA-3' and reverse, 5'-AGTGCAGGGTCCGAGGTATTCGCACTG GAT-3'; U6, forward 5'-GCTTCGGCAGCACATATA CTAAAAT-3' and reverse 5'-CGCTTCACGAATTT GCGTGTCAT-3'. The $2^{-\Delta\Delta Ct}$ method was used to calculate the expression of miR-1826. The experiment was repeated at least 3 times.

Cell Proliferation Assay

The cells were incubated after transfection, and then the cell proliferation assay was conducted. The proliferative activity of the transfected PC cells was determined using a Cell Counting Kit-8 (CCK-8; Beyotime, Shanghai, China) at the time of 0, 24, 48, and 72 h. 10 μ L CCK-8 reagent was added to each well and incubated at 37°C for 2 h, after which the cell absorbance was detected at 450 nm using a microplate reader (Bio Tek).

Colony Formation Assays

Briefly, 100 cells at the log phase in the different groups were seeded in 6-well plates with a complete growth medium. After seeding and cultured for two weeks in a 5% CO₂ incubator, colonies were fixed with 4% paraformaldehyde and stained with 0.1% crystal violet for 1 h. Then the number of colonies was counted under a microscope.

Cell Migration and Invasion Assays

Cell invasion assays: The transfected PC cells were cultured in a serum-free medium for 12 h, and transwell chambers with Matrigel (BD Biosciences, San Jose, CA, USA) were used to determine the invasive ability. The cell density was 5×10^4 cells/well, and a normal cell culture medium containing fetal bovine serum was added to the lower layer of the chamber. After continuous culture for 24 h, cells in the lower compartment were stained with crystal violet, and 5 random fields were randomly selected for counting and statistics in each well.

Cell migration assays: Chambers without Matrigel were used to determine the migration ability of PC cells. Other methods and procedures were consistent with the cell invasion experiment.

Statistical Analysis

SPSS 20.0 (SPSS Inc., Chicago, IL, USA) and GraphPad 5.0 (GraphPad Software, Inc., La Jolla, CA, USA) were used for statistical analysis of the experimental data. The experimental results were expressed as mean \pm standard deviation, and the differences between groups were detected by Student's t-tests or one-way analysis of variance (ANOVA). Kaplan-Meier method and Cox

regression analyses were used to analyze the prognostic significance. $P < 0.05$ was considered statistically significant.

Results

Expression of miR-1826 in PC Tissues and Cell Lines

The expression of miR-1826 in PC tissues and cell lines was studied by qRT-PCR. The results showed the relative expression of miR-1826 in PC tissues was lower than that in the adjacent tissues, and the difference was statistically significant ($P < 0.001$, Figure 1A). Meanwhile, the relative expression levels of miR-1826 in four PC cell lines (PC-3, VCaP, DU145, and 22RV1) were all lower than those in normal human prostate epithelial cells line (RWPE-1, $P < 0.001$, Figure 1B).

Relationship Between Clinicopathological Characteristics and miR-1826 Expression in PC Patients

Using the average expression level of miR-1826 in tissues as the cutoff point, 105 PC patients were divided into a group with a high expression of miR-1826 ($n = 45$) and a group with a low expression of miR-1826 ($n = 60$). The results showed that low expression of miR-1826 was significantly correlated with high Gleason score, lymph node metastasis, and high TNM stage (III and IV) ($P < 0.05$, Table 1). While the expression of miR-1826 was not significant with patient age, family history, and preoperative PSA.

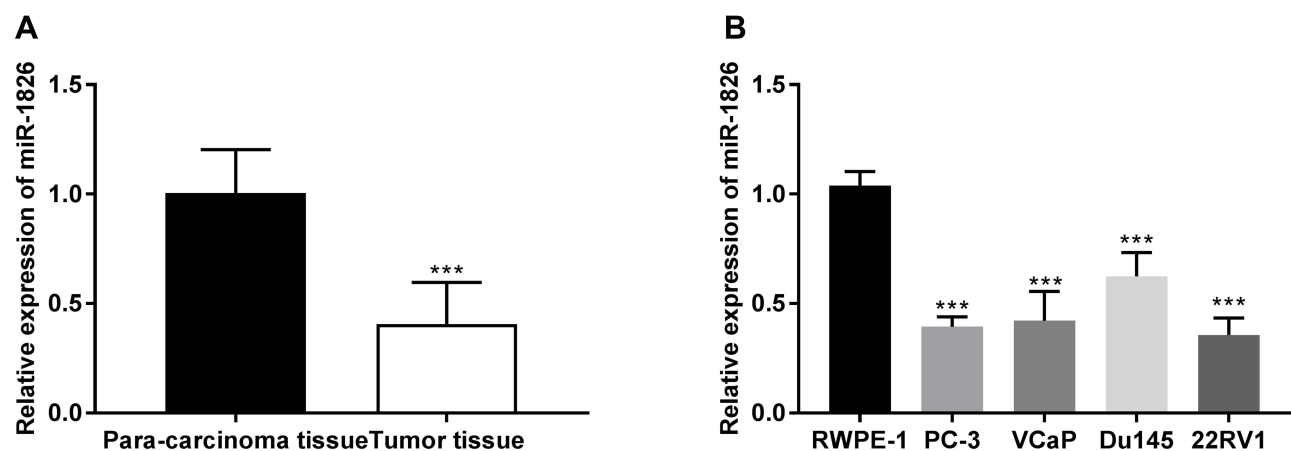


Figure 1 The expression of miR-1826 was reduced in PC tissues and cell lines. (A) The expression levels of miR-1826 in PC tissue samples and para-carcinoma tissues, *** $p < 0.001$. (B) The expression levels of miR-1826 in 4 PC cell lines, *** $p < 0.001$.

Table 1 Correlation Between miR-1826 Expression and Clinical Characteristics of Prostate Cancer Patients

| Clinical Characteristics | Cases (n = 105) | Tissue miR-1826 Expression | | P-value |
|-----------------------------------|-----------------|----------------------------|---------------|---------|
| | | Low (n = 60) | High (n = 45) | |
| Age (years) | | | | 0.302 |
| < 50 | 62 | 38 | 24 | |
| ≥ 50 | 43 | 22 | 21 | |
| Preoperative PSA (ng/mL) | | | | 0.398 |
| < 10 | 54 | 33 | 21 | |
| ≥ 10 | 51 | 27 | 24 | |
| Gleason Score | | | | 0.027 |
| < 7 | 57 | 27 | 30 | |
| ≥ 7 | 48 | 33 | 15 | |
| Lymph node metastasis | | | | 0.005 |
| Negative | 76 | 37 | 39 | |
| Positive | 29 | 23 | 6 | |
| Family history of prostate cancer | | | | 0.458 |
| No | 45 | 28 | 17 | |
| Yes | 60 | 32 | 28 | |
| TNM stage | | | | 0.006 |
| I–II | 70 | 35 | 35 | |
| III–IV | 35 | 25 | 10 | |

Abbreviation: PSA, prostate-specific antigen.

Downregulation of miR-1826 is Associated with Poor Prognosis in PC Patients

The Kaplan-Meier survival curve was used to analyze the relationship between miR-1826 and the survival of patients. Figure 2 showed that the median survival time of the low-expression miR-1826 group was 48 months. The median survival time of the high expression miR-1826 group was 60 months ($P < 0.05$). The overall survival of patients in the low expression group was significantly lower than that in the high expression group. A multivariable Cox proportional regression model was established, and the dependent variable was the prognosis of patients with PC. The results showed that higher TNM stage, higher Gleason score, positive lymph node metastasis, and low expression of miR-1826 were all risk factors for poor prognosis in PC patients ($P < 0.05$), as shown in Table 2.

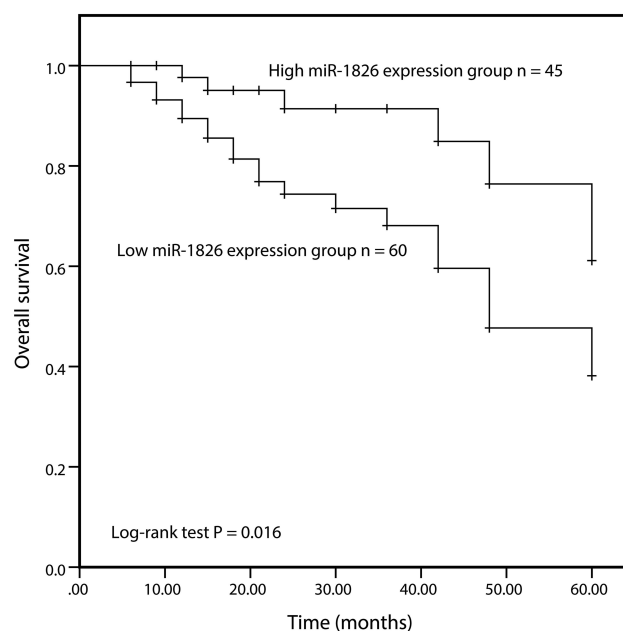


Figure 2 Kaplan-Meier survival curve in relation to the miR-1826 expression level in patients with PC. (Log rank test $P = 0.016$).

Downregulation of miR-1826 Promotes PC Cell Proliferation, Migration, and Invasion

In view of the imbalance of miR-1826 in PC patients, we further explored the biological function of miR-1826 in the process of PC. PC-3 and DU145 cells were transfected with miR-1826 mimic, mimic NC, miR-1826 inhibitor, or inhibitor NC. qRT-PCR was used to detect the expression of miR-1826. The result showed that miR-1826 mimic significantly increased the expression of miR-1826, while miR-1826 inhibitor decreased the expression of miR-1826, and the negative control group had no significant influence on the expression of miR-1826 ($P < 0.001$, Figure 3A). The effect of miR-1826 expression on the proliferation of PC cells was studied by the CCK-8 method and colony formation assay. The CCK-8 results showed that the low expression of miR-1826 could promote PC cell proliferation, while the high expression of miR-1826 inhibited PC cell proliferation compared with the negative control group ($P < 0.05$, Figure 3B). Moreover, the colony formation activity of cells that were treated with miR-1826 inhibitor was blocked, while was promoted in cells treated with miR-1826 mimic (Figure 3C).

Transwell assays were used to detect the effect of miR-1826 on the migratory and invasive ability of tumor cells. The experimental results showed that the low expression

Table 2 Multivariate Cox Regression Analysis for Independent Risk Factors of Overall Survival

| Variables | Multivariate Cox Analysis | | |
|-----------------------------------|---------------------------|--------------|---------|
| | HR | 95% CI | P-value |
| miR-1826 expression | 5.616 | 1.633–19.318 | 0.006 |
| Age | 1.088 | 0.471–2.514 | 0.843 |
| Preoperative PSA | 0.854 | 0.351–2.080 | 0.729 |
| Gleason Score | 0.322 | 0.122–0.847 | 0.022 |
| Lymph node metastasis | 4.048 | 1.504–10.890 | 0.006 |
| Family history of prostate cancer | 1.138 | 0.465–2.781 | 0.777 |
| TNM stage | 2.902 | 1.120–7.518 | 0.028 |

Abbreviations: PSA, prostate-specific antigen; HR, hazard ratio; CI, confidence interval.

of miR-1826 promoted the migratory and invasive abilities of cancer cells. In contrast, highly expressed miR-1826 reduced the ability of cancer cells to migrate and invade ($P < 0.01$, Figure 4A and B).

Discussion

PC is one of the most common male malignant tumors in men, and the prevalence of PC has been on the rise in China.¹⁸ The occurrence and development of tumors is a systemic disease involving multiple stages, multiple genes, and multiple signaling pathways, including abnormal expression of oncogenes, tumor suppressor genes, apoptosis-inducing genes and signal transduction genes. Studying the cause and mechanism of tumorigenesis and development is of great importance.¹⁹ miRNAs mainly exist in noncoding regions of eukaryotic genomes, which can regulate the expression of one or more genes after transcription and participate in cellular processes such as cell proliferation, apoptosis, differentiation and individual growth and development.^{20,21} miRNAs can act as oncogenes or tumor suppressor genes and participate in the regulation of target genes to affect the occurrence and development of tumors.²² The studies have shown that miRNAs can directly participate in the formation of human tumors such as lung cancer,²³ breast cancer,²⁴ and PC.^{25,26} In the study of PC, several examples of abnormal miRNA expression have been found to show a great influence on the occurrence, development and prognosis of PC. For example, miR-198 suppresses prostate tumorigenesis by targeting MIB1,²⁶ loss of miR-101 induces Glo-1-dependent EMT in PC,¹⁴ and miR-107 inhibits proliferation of PC cells by targeting cyclin E1.²⁷

miR-1826, an important miRNA, is abnormally expressed in colorectal cancer, kidney cancer, bladder cancer and adenoid cystic carcinoma.^{3,28–30} however, its

prognostic value and regulatory effect on tumor progression in PC have not been studied. In this study, we investigated the expression level of miR-1826 in PC tissues and cell lines, and it was found that the expression level of miR-1826 in PC tissues and cell lines were significantly lower than that in adjacent tissues and normal human prostate epithelial cells line, respectively. Our findings were similar to previous studies that showed that miR-1826 expression was much lower in three bladder cancer cell lines than in a normal bladder cell line.³ Moreover, a low miR-1826 expression was correlated with higher TNM stage, higher Gleason score and lymph node metastasis. The results suggested that the abnormally low expression of miR-1826 maybe was involved in the occurrence and development of PC. The results of Kaplan-Meier and multivariate Cox analyses showed that the patients with the low expression of miR-1826 might have a poor prognosis. The above outcomes indicated that miR-1826 might be a direct influencing factor on the poor prognosis of PC patients. The prognostic significance of miR-1826 for other cancers has also been previously reported. For instance, in locally advanced gastric cancer, downregulation of miR-1826 also indicates a poor prognosis in patients and may be a candidate biomarker for prognosis of osteosarcoma.³¹

In addition, we further investigated the effect of abnormally expressed miR-1826 on the biological behavior of PC cells by cell transfection. The results showed that the low expression of miR-1826 could promote the proliferation, metastasis, and invasion of PC cells. Instead, upregulation of miR-1826 inhibits proliferation, metastasis, and invasion. This seems to indicate that miR-1826 is a tumor suppressor gene for PC and the lower expression of miR-1826 may promote PC progression. Similar to this

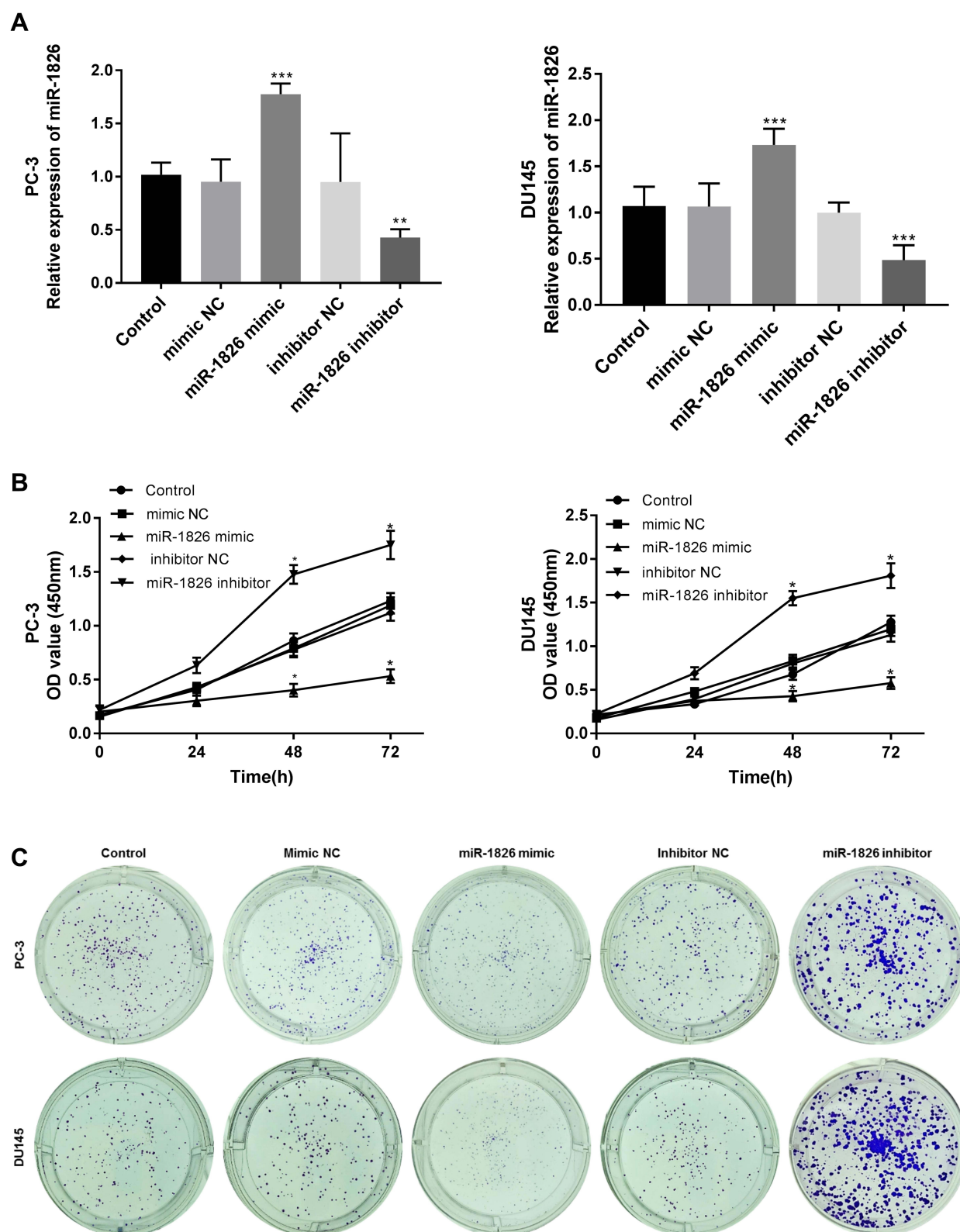


Figure 3 Effects of miR-1826 expression levels on proliferation in PC-3 and DU145 cells. **(A)** The expression level of miR-1826 was analyzed by qRT-PCR after transient transfection with miR-1826 mimic/inhibitor (or mimic/inhibitor NC). **(B)** The CCK-8 assay was performed to study cell proliferation. **(C)** Colony formation capacity was measured. * $P < 0.05$, ** $P < 0.01$ *** $P < 0.001$.

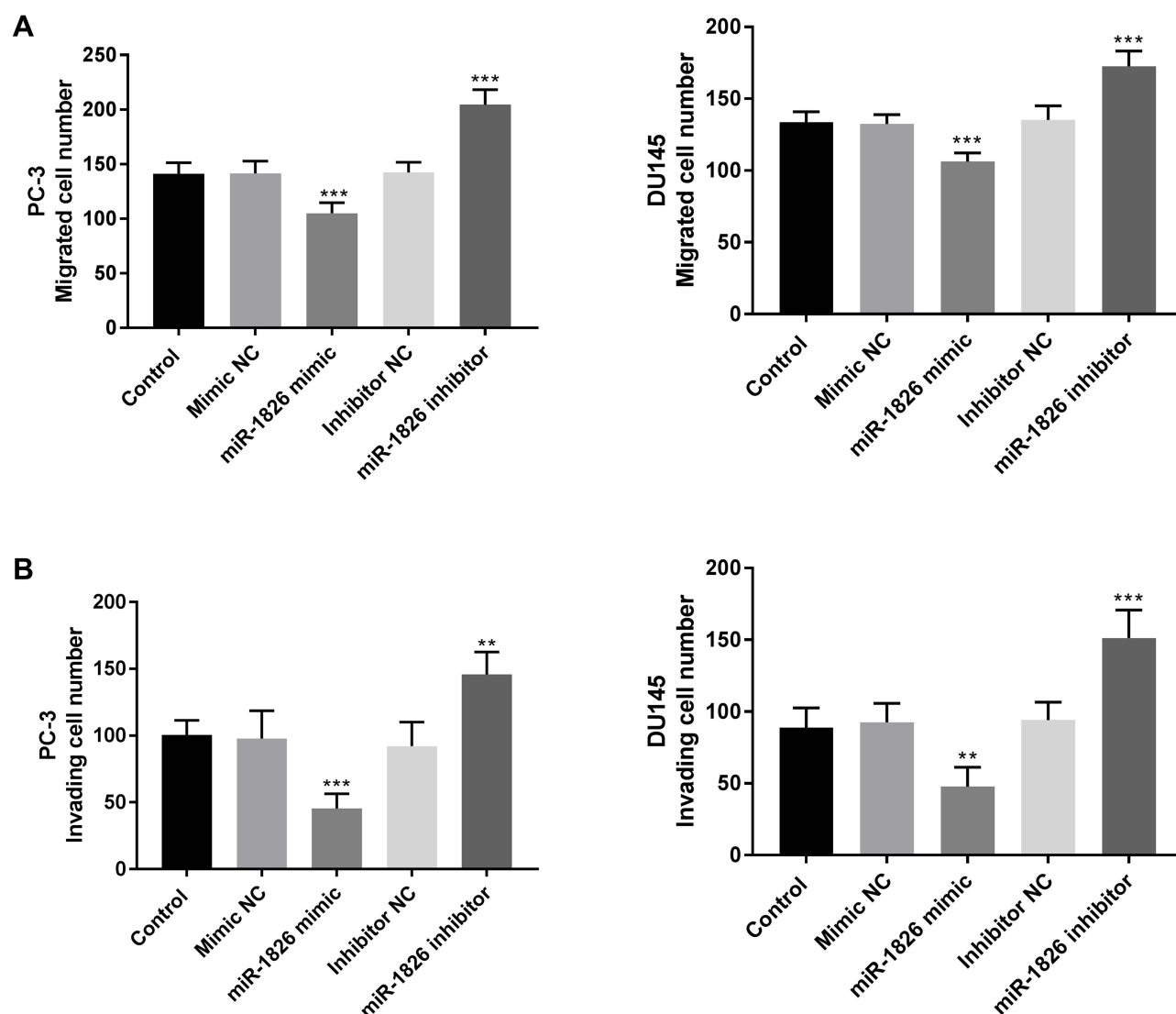


Figure 4 Effects of miR-1826 on cell migratory and invasive abilities in PC-3 and DU145 cells. (A) Cell migratory and (B) invasive abilities were assessed with Transwell assay. ** $P < 0.01$, *** $P < 0.001$.

result, a study showed miR-1826 inhibits VHL-inactivated renal cancer tumor by downregulating beta-catenin (CTNNB1) and MEK1, which suggests that miR-1826 may play an important therapeutic role in renal cancer patients.²⁸ In human bladder cancer, the miR-1826 also plays an important role as a tumor suppressor via CTNNB1/MEK1/VEGFC downregulation in bladder cancer.³ CTNNB1 was upregulated and involved in the progression of PC, which also had a crucial role in the Wnt pathway.³² From the above results and studies, miR-1826 may play a tumor-suppressive role in PC through downregulating CTNNB1.

There are several limitations in the present study. For instance, a lack of in vivo data is a limitation. Latest

studies by Parashar D and co-workers indicated that 3-D Spheroid formation assay is an alternative approach for the pre-clinical model.^{33,34} Further studies will also try to prove the hypothesis through enhancing the technical skills on in vivo and 3-D Spheroid formation assay. In the other hand, the detailed mechanism of miR-1826 in PC will also be explored in future studies.

Conclusion

In summary, miR-1826 has a lower expression in PC tissues than in adjacent tissues and has abnormally low expression in prostate cells. Furthermore, the low expression of miR-1826 is related to the poor prognosis and shorter survival time of PC. In addition, the research results also show that the low

expression of miR-1826 can promote the proliferation, metastasis, and invasion of PC cancer cells. These results speculate that miR-1826 may be a tumor suppressor gene for PC, and targeting the upregulation of miR-1826 expression may become a new idea for the treatment of prostate cancer in the future.

Ethics Statement

All patients signed informed consent. This study was approved by the Ethics Committee of Affiliated Hospital of Weifang Medical University (approval no.2012047). The guidelines outlined in the Declaration of Helsinki were followed.

Disclosure

The authors report no conflicts of interest in this work.

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