

Protein arginine methyltransferase 7 regulates the cell cycle and promotes the progression of prostate cancer

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Abstract. Prostate cancer (PCa) is the second most common cancer in men worldwide. Protein arginine methyltransferase 7 (PRMT7) expression is associated with tumor growth, as it can drive tumor cell proliferation and promote its invasiveness in several types of cancer. However, its mechanism in PCa remains to be elucidated. In the present study, the function and associated mechanism of PRMT7 in PCa cells were investigated. The relationship between PRMT7 and PCa was analyzed using The Cancer Genome Atlas online database. Tissue chip techniques were used to identify the clinical relevance of PRMT7 expression. PRMT7 expression levels in PCa tissues and cells were verified using reverse transcription-quantitative PCR (RT-qPCR). Cell cycle, migration, proliferation and apoptosis of PC3 and DU145 cells were observed using flow cytometry, Cell Counting Kit-8, wound healing, plate cloning and cell invasion assays. Gene set enrichment analysis and chip expression profiles were used to predict the potential signaling pathway involved in the action of PRMT7 in PCa. First, The Cancer Genome Atlas database, tissue microarray analysis and RT-qPCR revealed that PRMT7 expression was increased in PCa tissues and

cells. Furthermore, small interfering RNA-mediated PRMT7 knockdown led to a notable reduction in the proliferation of cells, increased apoptosis, affected the cell cycle and decreased cell migration and invasion. Furthermore, PRMT7 regulated the functions of Yin Yang 1 (YY1), tumor protein p53 (TP53), cyclin D2 (CCND2), CDK6 and retinoblastoma 1 (RB1) in PCa. PRMT7 may promote proliferation, migration and metastasis in PCa cells by regulating the activity of YY1, TP53, CCND2, CDK6 and RB1 in the cell cycle signaling pathway.

Introduction

Prostate cancer (PCa) is one of the most common malignancies in men worldwide. According to the 2024 data from the American Cancer Society, PCa is the second leading cause of mortality in men, after lung cancer (1). Annually, there are ~1.5 million cases of PCa and it results in 396,700 mortalities globally (2). With increases in the global and aging populations, PCa has become a notable public health challenge in men worldwide (3). The incidence of PCa in China has markedly increased (4-6) and it has become one of the most common types of cancer in men in China. In 2020, in China, ~120,000 novel cases of PCa were reported, which accounted for 8.16% of cancer diagnoses in men. The number of PCa mortalities was ~50,000 making up 13.61% of cancer-related mortalities among men (7,8).

The 5- and 10-year survival rates for PCa depend on the stage and grade of the cancer at diagnosis. For localized or regional PCa, when the cancer is confined to the prostate or nearby areas, the 5-year relative survival rate is ~100%. For metastatic PCa, in which the cancer has spread to distant parts of the body, the 5-year survival rate is markedly reduced, ~37% (9). Recurrence is a concern with PCa, especially in advanced cases with increasing prostate-specific antigen (PSA) levels often indicating recurrence within 5-10 years in 20-30% of men treated for PCa. Recurrence is more likely in cases with aggressive tumor characteristics, increased initial PSA levels and advanced stage at diagnosis (10).

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The high risk of PCa is primarily attributed to its aggressive metastasis. In cases where cancer types are hidden, it is difficult for clinicians to diagnose and treat the disease early. In several cases, by the time PCa is diagnosed, tumor tissues have metastasized to areas outside the prostate, such as in the bone (11,12). PCa is associated with multiple genomic alterations, which result in a high degree of tumor heterogeneity. However, the specific mechanism underlying its malignancy remains unclear (13). Current progress in medical diagnostic imaging, surgery, chemotherapy and radiotherapy has improved the effective diagnosis, treatment and management of PCa. Androgen-blocking therapy (ADT), which targets androgen receptors (ARs), is the first-line treatment option in clinical practice, further to surgical excision. However, ~2 years of administering ADT to patients with advanced PCa results in the development of castration-resistant PCa; which is typically accompanied by elevated serum testosterone and PSA levels (14). Therefore, exploring the internal mechanisms and therapeutic targets of PCa and developing corresponding drugs is key to improve the survival and prognosis of patients and reduce the medical burden of searching for early diagnostic markers to supplement the diagnostic shortcomings of PSA.

Cytokines serve an important role in the development of cancer (15). Further to abnormal DNA methylation, histone post-translational modifications (PTMs) and changes in chromatin modification patterns are associated with carcinogenesis; the latter two have revealed to be key factors in cancer-related pathways (16). Histone methylation serves a regulatory role in various cancer cells; this process is catalyzed by histone methyltransferases (HMTs), which comprise different families of enzymes that methylate specific residues to alter gene transcription. For example, lysine HMT (protein lysine methyltransferase) methylates lysine residues, while histone arginine methyltransferase (PRMT) methylates arginine. The only type III PRMT among the nine members of the PRMT family is PRMT7, which contains only monomethyl arginine (17-22).

PTMs regulated by PRMT7 and its proteins are associated with tumor growth and metastasis (23). Specifically, PRMT7 expression is increased in clear cell renal cell carcinoma tissues and leads to renal cell carcinoma growth through the β -catenin/c-Myc axis (24). The upregulation of PRMT7 expression may promote breast cancer cell invasion by regulating MMP9 expression (25). Research on PRMT7 in breast cancer has indicated its potential as a biomarker and therapeutic target (26,27). Although PRMT7 has not been thoroughly studied in other cancer types, as a member of the PRMT family, it is known to regulate histone methylation, a PTM associated with cancer (28,29). In particular, as a member of the PRMT family, PRMT5 can promote the progression of PCa by influencing key regulatory factors, such as the AR. This influence on AR, a key regulator in PCa, suggests that PRMT5 serves a notable role in cancer development, which highlights its potential as a target for therapeutic intervention (30,31); therefore, PRMT7 is likely to serve a key role as an epigenetic regulator in PCa and ultimately affect tumor progression and prognosis.

In 2014, Vieira *et al* (32) studied the expression levels of partial HMT or demethylase in PCa and its relationship

with the occurrence and progression of cancer. Based on this and other previous studies (28-31) on the PRMT family and malignant tumors, the molecular mechanism of action of the PRMT7 in PCa were investigated. By validating the expression level of PRMT7 in prostate cancer cells and tissues, its correlation with clinicopathological features and patient survival was analyzed to further elucidate the potential mechanisms by which PRMT7 promotes prostate cancer progression.

Materials and methods

Patient samples. In the present study, 159 PCa samples were prospectively collected from patients diagnosed at the Affiliated Hospital of Jiangnan University (Wuxi, China) between December 2023 and June 2024. The tissue samples were obtained through standard hospital procedures. Patients were evaluated through clinical and histological analyses. The present study strictly adhered to the following predefined inclusion criteria: i) Histopathologically confirmed primary prostate adenocarcinoma [International Society of Urological Pathology (ISUP) grade ≥ 2]; ii) no prior history of radiotherapy or systemic therapy; and iii) availability of matched tumor-normal paired tissue samples for genomic analysis. The exclusion criteria comprised cases with metastasis at diagnosis (to avoid confounding by advanced disease biology) and specimens that did not meet tissue quality standards (RNA integrity number >7). The age distribution of the cohort (median, 68 years; range, 52-81 years), PSA levels and ISUP grades mirrored regional epidemiology. The tissue samples were collected for tissue microarray analysis and the correlation between PRMT7 and the age of the patients, Gleason score (33), PSA levels and TNM stage (34) in PCa were analyzed. Then, seven pairs of matched PCa clinical samples detected using reverse transcription-quantitative PCR (RT-qPCR) were also derived from the aforementioned tissues, with normal tissue samples collected 5 cm away from the tumor margin serving as negative controls. The present study was approved by the Ethics Committee of Affiliated Hospital of Jiangnan University (approval no. LS2023099; Wuxi, China). The present study was conducted in accordance with the Declaration of Helsinki. Each patient included in the present study signed a written informed consent form prior to sample collection.

Bioinformatics analysis. PRMT7 expression data were downloaded from The Cancer Genome Atlas (TCGA) online database (<http://tcga-data.nci.nih.gov/tcga/>). R software (version 4.3.0; <http://www.r-project.org>) and SPSS (version 17.0; SPSS Inc.) were used to analyze and process all data.

Immunohistochemistry staining and scoring. Paraformaldehyde (4%) was used to fix collected tissue samples at room temperature (25°C) for 24 h. Paraffin-embedded tissues were cut into 4- μ m-thick sections. Tissue sections were dewaxed, hydrated, then permeabilized with 0.5% Triton X-100 at room temperature (25°C) for 10 min, blocked with 3% H₂O₂ (25°C) for 30 min and 10% goat serum (25°C) for 30 min. Next, the samples were incubated with antibodies against PRMT7 from Merck KGaA (1:50; cat. no. HPA044241) at 4°C overnight. Thereafter, images of the sections were

taken using an Olympus IX73 inverted fluorescence microscope (Olympus Corporation). The subsequent steps were performed using the GTVision III Detection System/Mo&Rb (Gene Tech Co., Ltd.) (35,36). Immunohistochemistry results for healthy individuals were selected from the Human Protein Atlas database (<https://www.proteinatlas.org/ENSG00000132600-PRMT7/tissue/prostate#>).

Cell culture. Human PCa cell lines PC3, DU145, LNCAP, 22RV1 and WPMY-1 were purchased from the Cell Bank of the Chinese Academy of Science. DU145 and WPMY-1 cells were cultured in DMEM (Cytiva) supplemented with 10% FBS (Shenzhen Aipno Biomedical Technology Co., Ltd.). PC3, LNCAP and 22RV1 cells were cultured in RPMI-1640 (Cytiva) medium supplemented with 10% FBS (Shenzhen Aipno Biomedical Technology Co., Ltd.). All cells were incubated at 37°C with 5% CO₂.

RT-qPCR. RNA extraction from PC3, DU145, LNCAP, 22RV1 and WPMY-1 cells (each sample used 3x10⁶ cells) was carried out using a FastPure[®] Cell/Tissue Total RNA Isolation Kit V2 (cat. no. RC112-01; Vazyme Biotech Co., Ltd.) according to the manufacturer's protocol. RNA was reverse transcribed into cDNA using a HiScript[®] III RT SuperMix for qPCR (+gDNA wiper) (cat. no. R323-01; Vazyme Biotech Co. Ltd.). The primer sequences used for GAPDH and PRMT7 are listed in Table SI. qPCR was carried out in an Applied Biosystems 7500 PCR system (Thermo Fisher Scientific, Inc.) using a ChamQ Universal SYBR[®] qPCR Master Mix (cat. no. Q711-02/03, Vazyme Biotech Co. Ltd.). The RT-qPCR protocol consisted of: Initiation at 95°C for 30 sec, followed by 40 cycles at 95°C for 10 sec and 60°C for 30 sec. Relative quantification of gene expression was carried out using the 2^{-ΔΔC_q} method (35), with GAPDH as the endogenous control. Primer efficiencies were validated to be between 95-105% prior to analysis. The results were analyzed using a previously reported method (35).

Plasmid transfection. Small interfering (si)PRMT7 was designed based on the PRMT7 (NM_019023.5; *Infection*, https://www.ncbi.nlm.nih.gov/nuccore/NM_019023.5) target sequence. The sequences of the specific genes used in the present study were as follows: PRMT7-siRNA (43684-1) sense (S), 5'-CACAUCAUGGACGACAUGAUU-3' and antisense (AS), 5'-AAUCAUGUCGUCCAUGAUGUG-3'; PRMT7-siRNA (43685-1) S, 5'-GCUAACCACUUGGAA GAUAAA-3' and AS, 5'-UUUAUCUCCAAGUGGUU AGC-3'; PRMT7-siRNA (43686-1) S, 5'-CGAUGACUACUG CGUAUGGUA-3' and AS, 5'-UACCAUACGCAGUAGUCA UCG-3'; non-silencing siRNA S, 5'-UUCUCCGAACGUGUC ACGU-3' and AS, 5'-ACGUGACACGUUCGGAGAA-3'. They were synthesized and cloned into GV248 (11.5 kb) vector with *BsmBI* sites (purchased from Shanghai Genechem Co., Ltd.), recombinant vector was detected by DNA sequencing. The final products were then transfected into *Escherichia coli* (>1x10⁸ cfu/μg; purchased from Shanghai Genechem Co., Ltd.). The PRMT7-siRNA plasmid was then isolated/purified with the EndoFree Plasmid Mega Kit (Qiagen GmbH, Germany; Cat. #12381). Briefly, 4x10⁵ cells were seeded in each well of a 6-well plate. Upon reaching 60-70% confluency, transfections were carried out using Lipofectamine[®] 3000 reagent

(cat. no. L3000150, Thermo Fisher Scientific, Inc.) Cells were seeded in 6-well plates at a density of 1x10⁶ cells/well and cultured overnight to reach 70-80% confluency. For each well, 2.5 μg of plasmid DNA and 5 μl P3000[™] were diluted in 125 μl of Opti-MEM[®] Reduced-Serum Medium (Gibco; Thermo Fisher Scientific, Inc.) and mixed gently. Separately, 7.5 μl of Lipofectamine[™] 3000 was diluted in 125 μl of Opti-MEM[®]. The diluted DNA was then combined with the diluted Lipofectamine[®] 3000 (1:1 ratio) and incubated for 15 min at room temperature to form DNA-lipid complexes. The mixture was added dropwise to the cells, followed by gentle swirling. The cells were cultured at 37°C for an additional 48 h. The transfection efficiency was >80% based on green protein fluorescence.

Other assays. Western blot analysis, cell proliferation and colony formation assays, apoptosis analysis and cell cycle detection, wound healing, cell migration and invasion assays were carried out as previously described (35,36). The antibodies that were used are: anti-PRMT7 (1:1,000; cat. no. ab181214; Abcam), anti-GAPDH (1:2,500; cat. no. ab9485; Abcam), anti-β-actin (1:2,000; cat. no. GB12001; Wuhan Servicebio Technology); anti-cyclin D2 (CCND2; 1:2,000; cat. no. 67048-1-Ig) and anti-retinoblastoma (RB1; 1:2,000; cat. no. 67521-1-Ig) were purchased from Wuhan Sanying Biotechnology; anti-CDK6 (1:1,000; cat. no. A0705; Abclonal Biotech Co., Ltd.); and anti-Yin-yang 1 (YY1; 1:1,000; cat. no. GB111880), antitumor protein p53 (TP53; 1:1,000; cat. no. GB111740), anti-rabbit IgG (1:5,000; cat. no. GB23303) and anti-mouse IgG (1:5,000; cat. no. GB23301) were purchased from Wuhan Servicebio Technology Co., Ltd.

Transcriptome sequencing and analysis. Total RNA was isolated from all samples (4 PRMT7-KD replicates and 4 Control replicates) using TRIzol[™] reagent (cat. no. 15596026CN, Thermo Fisher Scientific, Inc.). RNA integrity was assessed using the Agilent Bioanalyzer 2100 system (RNA Nano 6000 Assay Kit; Agilent Technologies), and purity was confirmed using a NanoPhotometer[®] spectrophotometer (IMPLEN). Only high-quality RNA samples (RNA integrity Number >8.0; OD_{260/280} ratio ~2.0) were used for library construction. Sequencing libraries were prepared from 1 μg of total RNA per sample using the NEBNext[®] Ultra[™] RNA Library Prep Kit for Illumina[®] (New England BioLabs, Inc.) following the manufacturer's protocol. Briefly, poly(A)+ mRNA was enriched using poly-T oligo-attached magnetic beads and fragmented. First-strand cDNA synthesis was performed using random hexamer priming and M-MuLV Reverse Transcriptase (New England BioLabs, Inc.), followed by second-strand synthesis with DNA Polymerase I and RNase H. cDNA fragments were end-repaired, adenylated, and ligated to NEBNext adaptors. Libraries were size-selected (~250-300 bp) using AMPure XP beads (Beckman Coulter Inc.) and amplified by PCR with index primers. Library quality and concentration were validated using the Agilent Bioanalyzer 2100 system. Indexed libraries were pooled and clustered on a cBot Cluster Generation System (TruSeq PE Cluster Kit v3-cBot-HS; Illumina, Inc.). Paired-end sequencing (2x150 bp) was performed on an Illumina NovaSeq platform. Raw sequencing reads (FASTQ format) were quality-filtered

using custom Perl scripts to remove adapter sequences, poly-N reads, and low-quality reads ($Q < 20$), yielding clean reads. Quality metrics (Q_{20} , Q_{30} , GC content) were calculated for clean data. Clean reads were aligned to the human reference genome (GRCh38/hg38; https://www.ncbi.nlm.nih.gov/datasets/genome/GCF_000001405.26/) using HISAT2 (v2.0.5; <https://daehwankimlab.github.io/hisat2/>) with splice-site information derived from gene model annotations. Transcript assembly and read quantification per gene were performed using StringTie (v1.3.3b; <https://ccb.jhu.edu/software/stringtie/>). Gene expression levels were quantified as Fragments Per Kilobase of transcript per Million mapped reads (FPKM). Differentially expressed genes (DEGs) between PRMT7-KD and Control groups (4 vs. 4 replicates) were identified using DESeq2 (v1.16.1) in R. Genes with an adjusted P-value (Benjamini-Hochberg FDR) < 0.05 were considered statistically significant DEGs. Gene Ontology (GO) enrichment analysis (Biological Process, Molecular Function, Cellular Component), Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis, and Disease Ontology (DO) enrichment analysis of the identified DEGs were performed using the clusterProfiler R package. Gene length bias was corrected. Terms/pathways with a corrected P-value (FDR) < 0.05 were considered significantly enriched. The Search Tool for the Retrieval of Interacting Genes/Proteins database (<https://cn.string-db.org/>) was used to predict the possible cell cycle-related regulatory proteins downstream of PRMT7.

Statistical analysis. Data were analyzed using SPSS software (version 17.0; SPSS, Inc.). All data were presented as the mean $\pm$ SEM. The normality of the data was analyzed using the Shapiro-Wilk test. $P < 0.05$ was considered to indicate normally distributed data. Homogeneity of variance was assessed using Levene's test, with $P > 0.05$ considered to indicate homogenous data. For data that met normal distribution assumptions and equal variances, an unpaired Student's t-test was used to analyze the differences between two groups and one-way ANOVA and Bonferroni's post hoc test for multiple comparisons. All P-values derived from high-throughput analyses (for example, differential gene expression and pathway enrichment) were adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate (FDR) method with a significance threshold of FDR < 0.05 . $P < 0.05$ was considered to indicate a statistically significant difference. Images were generated using GraphPad Prism 8 (Dotmatics) and Illustrator CC 2018 software (v22.0; Adobe Systems, Inc.). Principal Component Analysis (PCA) was performed to reduce dimensionality and identify patterns. The raw dataset was standardized by mean-centering and scaling to unit variance. The covariance matrix of the standardized data was computed and decomposed into its eigenvalues and eigenvectors. Principal Components (PCs) were selected based on eigenvalues sorted in descending order, retaining components explaining $> 80\%$ cumulative variance. The standardized data was projected onto the orthogonal axes defined by the selected PCs. Analysis was implemented using: Python, scikit-learn (v1.2.2) with PCA(`svd_solver='auto'`); R, `stats::prcomp()` (R v4.3.0); MATLAB, `pca()` (MATLAB R2023a).

Results

PRMT7 is highly expressed in PCa. To explore whether there is a potential association between PRMT7 and PCa, relevant data were searched and analyzed in TCGA database. Significant differences in PRMT7 expression were identified in cancerous and adjacent tissues and in terms of the age of patients with PCa, Gleason score, PSA levels and TNM stage (Fig. 1A-H), which indicated that PRMT7 may be a key gene in PCa development. To further validate the aforementioned findings, tissues were collected from 159 patients with PCa and the correlation between PRMT7 expression and clinicopathological parameters were analyzed (including age, Gleason score, PSA level and TNM stage) using tissue microarray technology. PRMT7 was highly expressed in patients with PCa (Figs. 1I, SIA). Significant PRMT7 expression differences were also identified among different PSA levels in patients with PCa, although there were no significant differences in PRMT7 expression associated with age, Gleason score or TNM stage (Table I). This suggested that high PRMT7 expression is associated with worse prognosis in PCa.

To verify the differential upregulation of PRMT7 expression in PCa tissues, PRMT7 mRNA expression levels were measured in seven pairs of PCa clinical specimens. PRMT7 mRNA expression levels were elevated in PCa tissues (Fig. 1J). Furthermore, compared with those in WPMY-1 cells (a normal prostate cell line), PRMT7 mRNA levels were significantly increased in the PCa cell lines (PC3, DU145, LNCAP and 22RV1; Fig. 1K). Taken together, the present study results suggested that PRMT7 is highly expressed in PCa.

PRMT7 promotes PCa cell proliferation, migration and invasion, and affects the cell cycle and apoptosis. To explore the biological mechanism underlying the effect of PRMT7 expression on PCa cells, siRNA-mediated PRMT7 silencing was performed to observe the biological changes in cancer cells. A total of three siRNA-coding clones were designed based on the PRMT7 sequence; they could be used for both stable and transient expression in vertebrate cells to decrease the expression levels of PRMT7. Subsequently, RT-qPCR was performed to verify the silencing efficiency of the three siRNAs in PC3 and DU145 cells. Analysis suggested that after 3 days of siRNA (43684-1, 43685-1 and 43686-1) transfection, the mRNA and protein expression levels of PRMT7 in the experimental group (si-43686-1) was reduced (Fig. 2A). SiRNA 43686-1 demonstrated high silencing efficiency in PC3 and DU145 cells; therefore, siRNA 43686-1 was selected for subsequent experiments. Knockdown efficiency was also evaluated using western blotting (Fig. 2B).

CCK-8 assays indicated that the proliferation rates of PC3 and DU145 cells were significantly reduced after PRMT7 knockdown, which suggested that PRMT7 significantly affected cell proliferation (Fig. 2C). The results of wound healing and migration assays suggested that PRMT7 expression is significantly associated with the migratory ability of PC3 and DU145 cells (Fig. 2D). PRMT7 knockdown also significantly reduced the number of PC3 and DU145 cell clones (Fig. 2E). However, no effects associated with proliferation and colony formation were observed in the PRMT7-knockdown WPMY-1 cell line (Fig. S1B and C). The

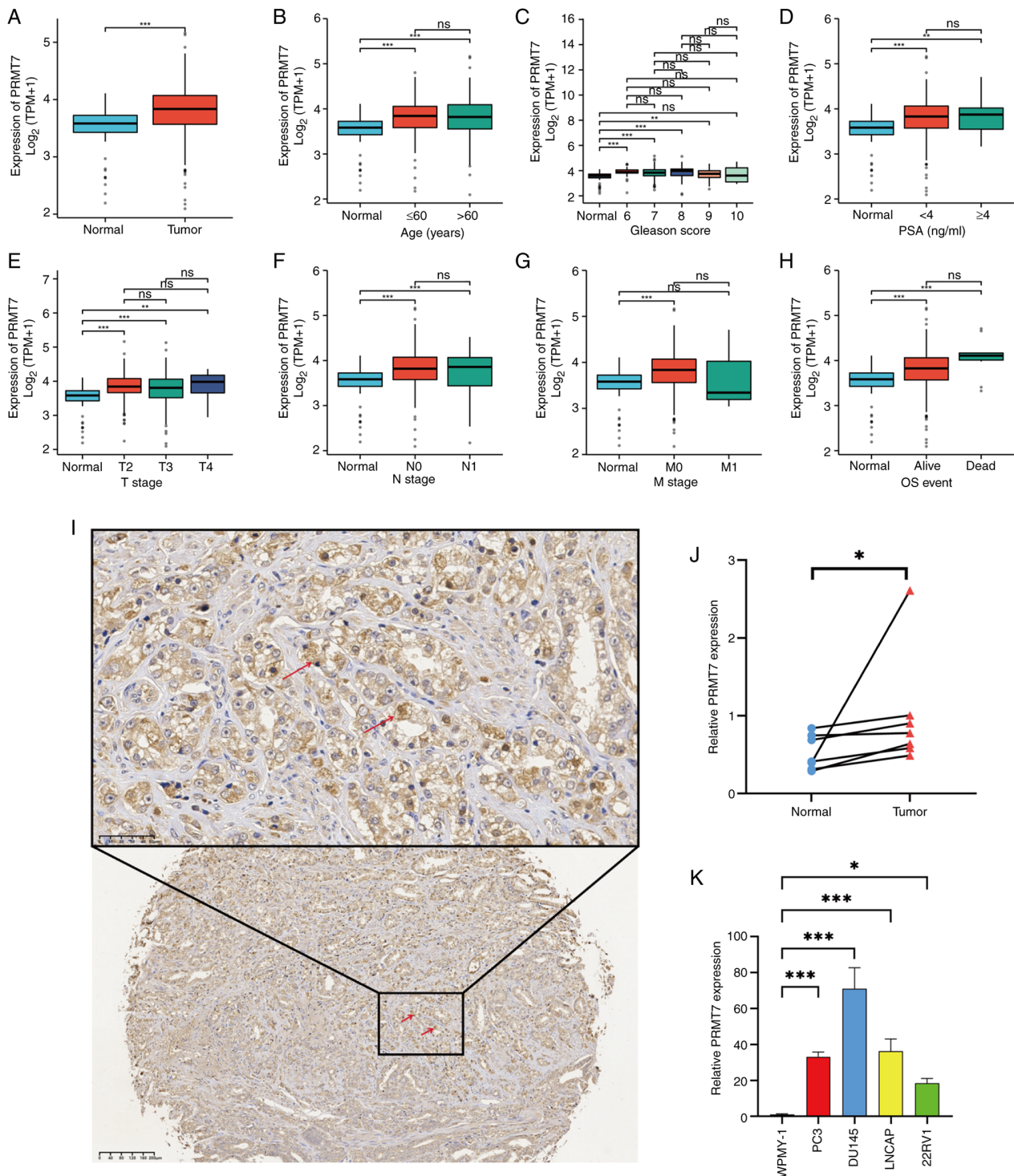


Figure 1. Differential gene expression patterns of PRMT7 in PCa. (A) The correlation between PRMT7 expression in cancerous and adjacent tissues of patients with PCa in TCGA database. (B) The correlation between PRMT7 expression and age of patients with PCa in TCGA database. (C) The correlation between PRMT7 expression and Gleason score of patients with PCa in TCGA database. (D) The correlation between PRMT7 expression and PSA levels of patients with PCa in TCGA database. (E) T, (F) N and (G) M stage of patients with PCa in TCGA database. (H) The correlation between PRMT7 expression and OS event of patients with PCa in TCGA database. (I) Representative image of PRMT7 immunohistochemical staining of PCa tissues and adjacent normal tissues (magnification, 50 and 100x; scale bar, 40 and 10 μm). The red arrows indicate the PRMT7 positive areas. (J) The expression levels of PRMT7 in PCa tissues was detected using RT-qPCR. The blue circle represents the normal tissue around the cancer, while the red arrow represents the tumor tissue. (K) The expression level of PRMT7 in PCa cell lines and normal prostate cells was detected using RT-qPCR. *P<0.05, **P<0.01 and ***P<0.001. PRMT7, protein arginine methyltransferase 7; PCa, prostate cancer; PSA, protein specific antigen; TPM, transcript per million; TCGA, The Cancer Genome Atlas; RT-qPCR, reverse transcription-quantitative PCR; ns, not significant.

results of the invasion assay suggested that the invasion and metastatic capacities of PC3 and DU145 cells in the experimental group were significantly inhibited 3 days after siRNA

infection, which suggested a significant association between these cell properties and PRMT7 expression (Fig. 2F and G). After PRMT7 knockdown, the number of PC2 cells in the

Table I. Correlation between PRMT7 expression and clinicopathological factors.

Covariates	Total, n (%)	PRMT7 expression		P-value	Statistical test
		Low, n (%)	High, n (%)		
Age, years					
<70	91 (57.23)	40 (56.34)	51 (57.95)	0.838	χ^2
≥70	68 (42.77)	31 (43.67)	37 (42.05)		
PSA value					
<10	64 (40.25)	22 (34.40)	42 (65.60)	0.032 ^a	χ^2
≥10	95 (59.75)	49 (51.60)	46 (48.40)		
Gleason score					
≤7	114 (71.70)	52 (73.24)	62 (70.45)	0.698	χ^2
>7	45 (28.30)	19 (26.76)	26 (29.55)		
TNM stage					
T1-T2	157 (98.74)	69 (97.18)	88 (100)	0.198	Fisher's exact test
T3-T4	2 (1.26)	2 (2.82)	0 (0.00)		

^aP<0.05. PRMT7, protein arginine methyltransferase 7; PSA, prostate-specific antigen.

G₁ phase increased (P<0.05), while that in the G₂/M phase decreased (P<0.01). Similarly, the proportion of DU145 cells in the G₁ phase increased (P<0.001), whereas that in the S-phase and G₂/M phases decreased (P<0.001 and P<0.05, respectively). These results suggested that PRMT7 expression is significantly associated with the cell cycle (Fig. 2H). Furthermore, the rate of apoptosis in PC3 and DU145 cells was significantly increased after transfection with siPRMT7 compared with that in the siCtrl group, which suggested a significant correlation between PCa with PRMT7 (Fig. 2I). These results confirmed that PRMT7 knockdown could inhibit PC3 and DU145 cell proliferation, migration and invasion, as well as the cell cycle and apoptosis.

PRMT7 influences the cell cycle in PCa cells. Next, the PRMT7 knockdown plasmid siPRMT7 was transfected into the PCa cell line PC3 (Fig. 3A). A total of four groups of siCtrl and siPRMT7 cells were selected for transcriptome sequencing (Fig. 3B), in which 13,006 genes were revealed to be co-expressed between the two groups of samples (Fig. 3C). Differential gene screening among samples revealed that the expression levels of 1,085 genes were upregulated and expression levels of 878 genes were downregulated in siPRMT7 cells compared with that in siCtrl cells (Fig. 3D and E). A differential gene set was formed by combining the differential genes after classification. Mainstream hierarchical clustering was used to perform cluster analysis on the FPKM values of the genes and conducted homogenization of rows (Z-score; Figs. S2 and S3).

To explore the functional characteristics of the differentially expressed genes and predict the downstream pathways of PRMT7, the differentially expressed genes were classified according to their functions and gene function enrichment analyses were carried out, including GO, KEGG, DO and other pathway analyses. DO analysis revealed that the differential genes were enriched in 'prostate

cancer' pathways, which confirmed the data presented in Fig. 4A. Furthermore, GO functional enrichment analysis demonstrated that the differentially expressed genes were enriched in the 'cell cycle' and 'cycle checkpoint' functions (Fig. 4B), which was confirmed by the KEGG pathway enrichment analysis results. KEGG is a comprehensive database that integrates genomic, chemical and system function information. A total of 33 DEGs in PC3 cells after PRMT7 knockdown regulate the 'cell cycle' function (Fig. 4C and D). Thus, PRMT7 is involved in cell cycle-related pathways in PCa cells, which could contribute to the malignant phenotype of PCa.

PRMT7 promotes the malignant progression of PCa through the YY1/TP53/CCND2/CDK6/RB1 signaling axis. To further explore the downstream mechanisms of PRMT7 in PCa, transcriptome sequencing data were used to map the differentially expressed genes associated with the cell cycle (Fig. 5A). We also predicted the potential cell cycle-related regulatory proteins downstream of PRMT7 (Fig. 5B). TP53 is an important cell cycle-related protein; mutations of TP53 have been reported to be important carcinogenic factors in PCa (12). To verify the validity of the predicted PRMT7 cell cycle-related pathways, proteins were collected and extracted from PC3 cells in the siPRMT7 and siCtrl groups and the expression levels of proteins involved in the aforementioned pathways between the two groups were compared using western blotting. The western blot data indicated that PRMT7 knockdown may modulate the activity of the aforementioned signaling pathways, as evidenced by altered expression levels of key pathway markers (Fig. S4). Collectively, the findings of the present study demonstrated that PRMT7 modulates the activity of key cell cycle regulators, including 'YY1', 'TP53', 'CCND2', 'CDK6' and 'RB1' in prostate carcinogenesis, which suggests its key role in driving cell cycle dysregulation.

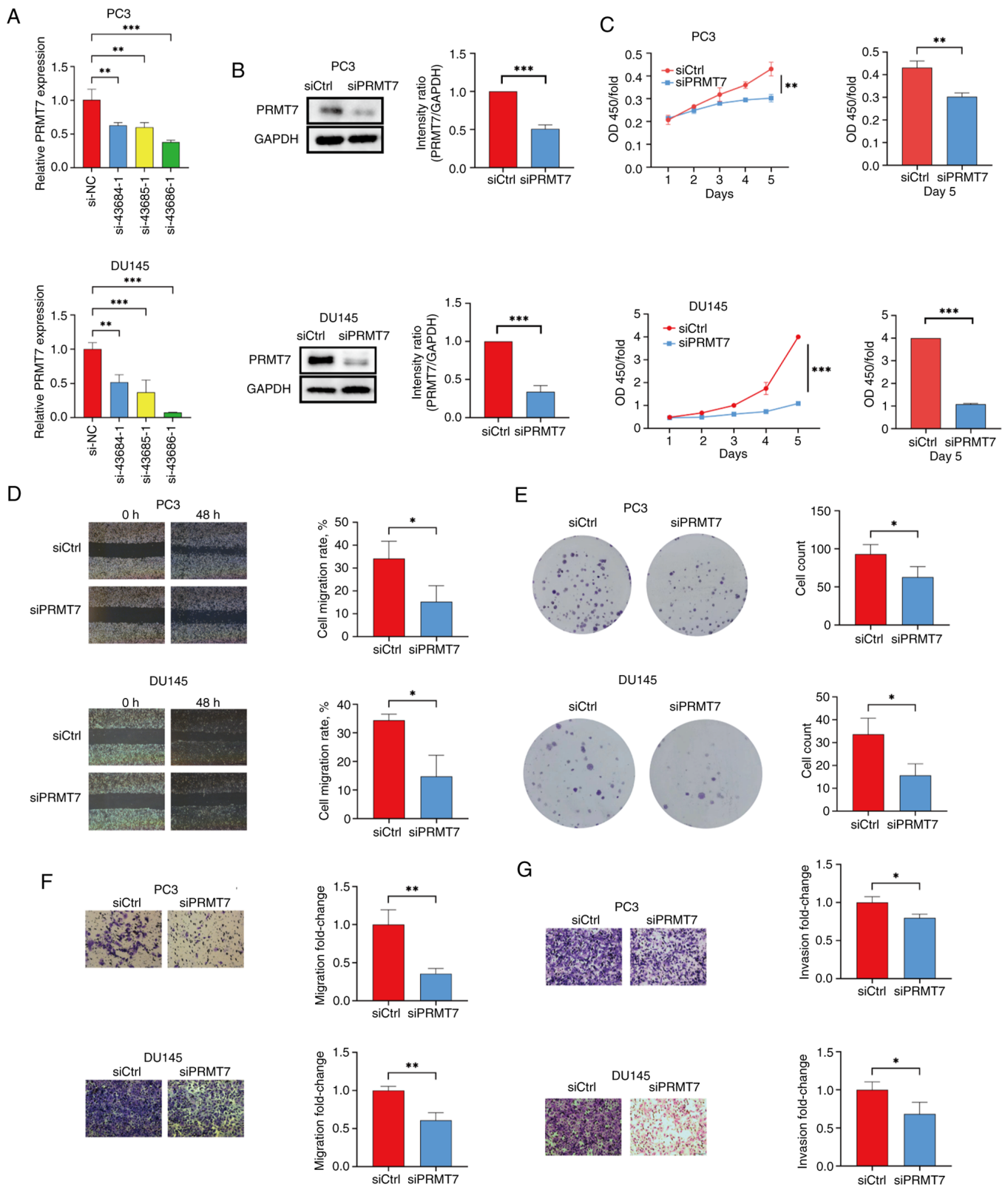


Figure 2. Continued.

Discussion

The occurrence and progression of cancer involves several cancer-promoting and cancer-suppressing genes. With the development of epigenetics, numerous tumor-related epigenetic changes have become the focus of research on cancer-related

mechanisms. PTMs involved in PCa are also a current research focus (37,38). Yao *et al* (30) suggested that PRMT5 inhibits the transcription of *CAMK2N1* and promotes PCa progression, which is regulated by the circSPON2/miR-331-3p axis. PRMT5 is recruited to AR promoters by the transcription factor Sp1 in LNCAP cell lines to promote tumor cell proliferation (39).

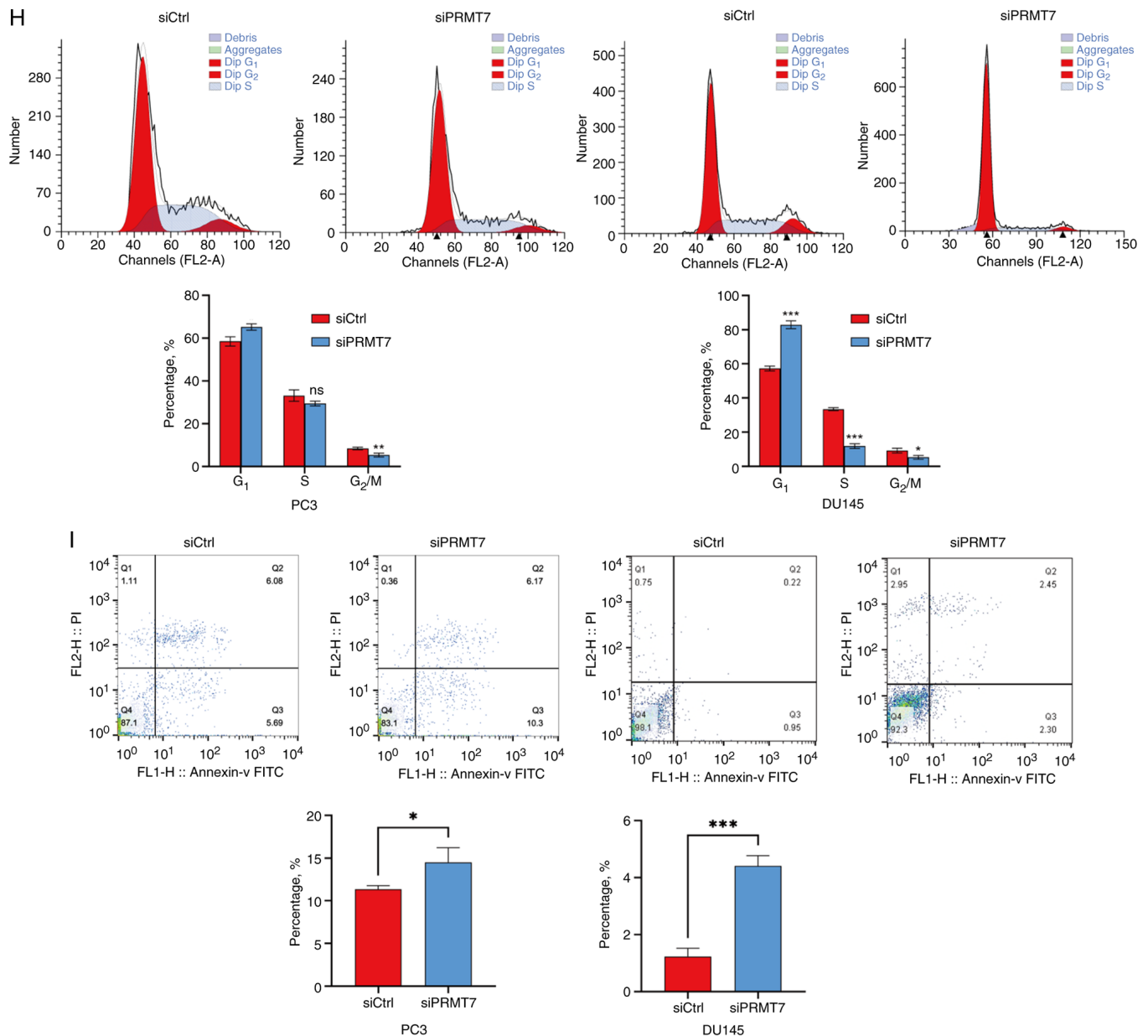


Figure 2. Function of PRMT7 in the PC3 and DU145 cell lines. (A) The inhibition efficiency of siPRMT7 in cell lines was determined using RT-qPCR. (B) Western blotting was used to detect the protein expression levels of PRMT7 in the siPRMT7 and siCtrl groups. (C) Cell proliferation in the siCtrl and siPRMT7 groups was assessed using a Cell Counting Kit-8 assay. (D) A wound healing assay was used to investigate the migratory ability of PCa cells after PRMT7 knockdown (scale bar, 500 μ m). (E) Plate colony formation assays were performed to determine the proliferation abilities of PC3 and DU145 cells treated with siCtrl and siPRMT7. (F) migration and (G) invasion of PC3 and DU145 cells were investigated using a Transwell assay after PRMT7 knockdown (scale bar, 100 μ m). (H) PI-FACS detection of the effect of PRMT7 knockdown on the PCa cell cycle. (I) The effect of PRMT7 knockdown on the apoptosis of PCa cells was detected using Annexin V-APC single staining. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$. PRMT7, protein arginine methyltransferase 7; PCa, prostate cancer; RT-qPCR, reverse transcription-quantitative PCR; siRNA, small interfering RNA; si, siRNA; Ctrl, control; NC, negative control; CCK-8, Cell Counting Kit-8.

PRMT7, a member of the same family as PRMT5 and the only representative of the type III group, can monomethylate arginine. To the best of our knowledge, studies on the mechanism of action of PRMT7 in cancer are currently limited. Only a part of its mechanism of action in breast cancer has been identified and these previous findings suggested that it may be an important target for breast cancer treatment (27,40,41). However, due to its regulatory role in cancer stem cells (42,43), PRMT7 may also serve a key epigenetic regulatory role in several cancer types, including PCa. Rodrigo-Faus *et al* (44) proposed that in metastatic castration-resistant PCa cells, PRMT7 methylates

various transcription factors (such as forkhead box protein K1) to reprogram the expression of several adhesion molecules, which lead to the loss of adhesiveness in the primary tumor and increases its migratory ability. However, the experiments of the present study suggested a different conclusion. The present study suggested that PRMT7 was carcinogenic in PCa and may serve a role in cell cycle regulation of cancer cells. This was consistent with the results of other PRMT7 studies in renal cell carcinoma (24) and human non-small-cell lung cancer cells (45), which suggested that PRMT7 is likely a strong tumor-associated epigenetic factor.

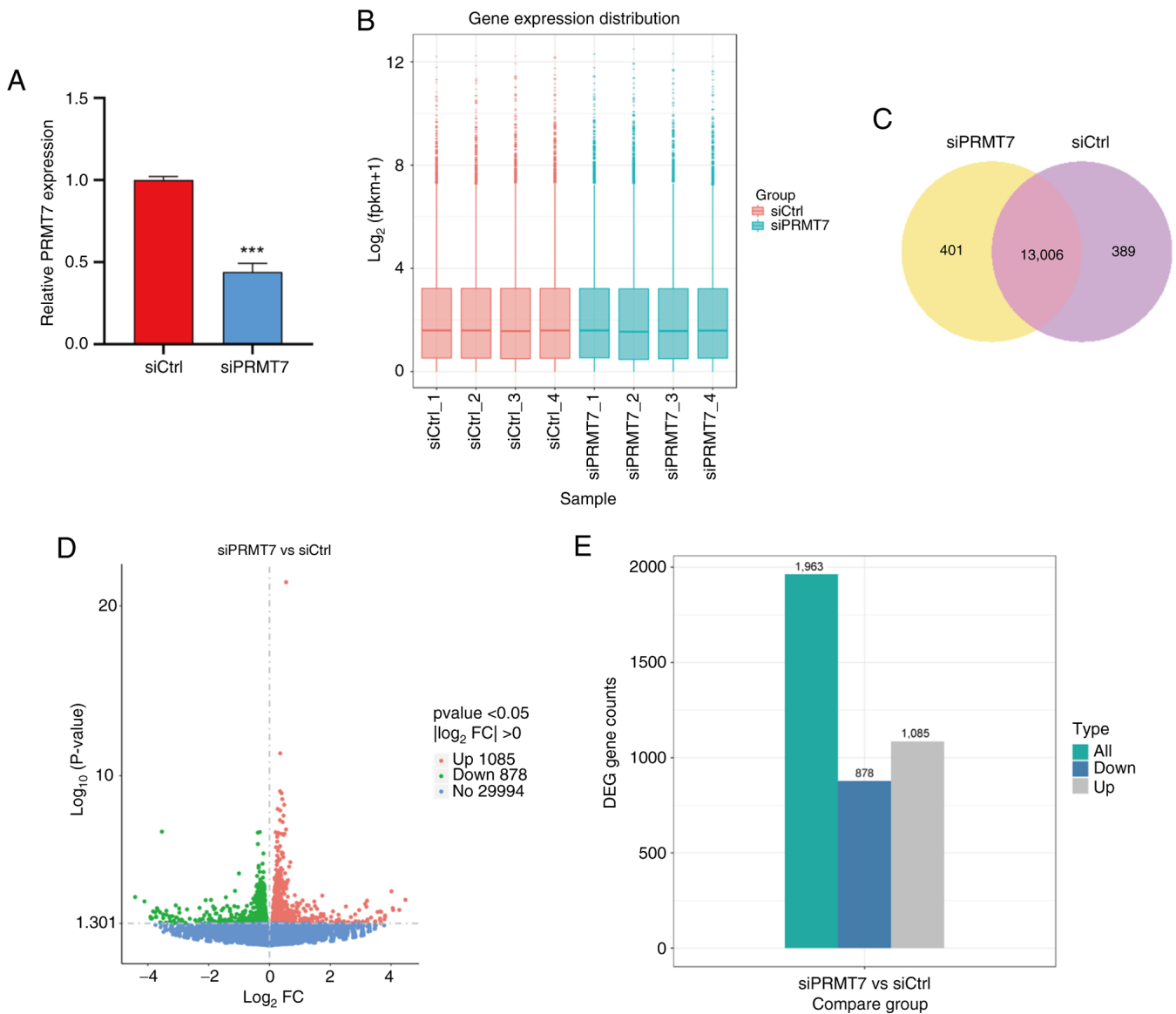


Figure 3. Transcriptome sequencing reveals differential gene expression after PRMT7 knockdown. (A) PRMT7 expression differences among transcriptome sequencing samples were detected using RT-qPCR. (B) Sample gene expression distribution box diagram. After calculating the FPKM values for all genes in each sample, the distribution of gene expression levels across different samples were visualized using boxplots. (C) Co-expression Venn diagram demonstrates the number of genes uniquely expressed in each group/sample. The overlapping regions indicate the number of co-expressed genes in two or more groups/samples. The comparison of the number of differentially expressed genes is displayed in the form of (D) volcano plot and (E) statistical histogram. Volcano plot displaying DEGs. The x-axis demonstrates log₂FC between the treatment and control groups and the y-axis represents the adjusted P-value (-log₁₀Adjusted P). Red dots denote significantly upregulated genes (log₂FC>1; Adjusted P<0.05), while green dots indicate downregulated genes (log₂FC<-1; Adjusted P<0.05). PRMT7, protein arginine methyltransferase 7; DEGs; differentially expressed genes; FPKM, fragments per KB of transcript per million mapped reads; log₂FC, log₂ fold change; RT-qPCR, reverse transcription-quantitative PCR; si, small interfering.

Based on a previous study by Vieira *et al* (32), the present study explored the specific molecular mechanism of PRMT7 in PCa to gain a more comprehensive understanding of the activity of PRMT7 and provide novel strategies for the clinical treatment and diagnosis of PCa. Tissues from 159 patients with PCa were collected and the correlation between PRMT7 expression and age, Gleason score, PSA and TNM stage were analyzed using tissue chip technology. PRMT7 expression significantly associated with PSA levels in patients with PCa. After analyzing the histochemical results of the patient samples, the present study demonstrated that PRMT7 was abnormally expressed in cancer tissues, which suggests that it may be associated with the occurrence and progression of PCa.

RT-qPCR results of paired PCa clinical specimens suggested that PRMT7 expression was also increased in PCa tissues. Similarly, PRMT7 expression was significantly increased in PCa cells compared with that in prostate epithelial cells.

Subsequently, siRNAs were used to knock down PRMT7 expression in PC3 and DU145 cells. PRMT7 promoted PCa cell proliferation, migration and invasion and affected the cell cycle and apoptosis. These results demonstrated that PRMT7 is an oncogene that contributes to the malignant phenotype of PCa.

Furthermore, the present study explored the specific regulatory mechanisms by which PRMT7 exerts oncogenic effects in PCa. Bioinformatics analysis and transcriptome sequencing

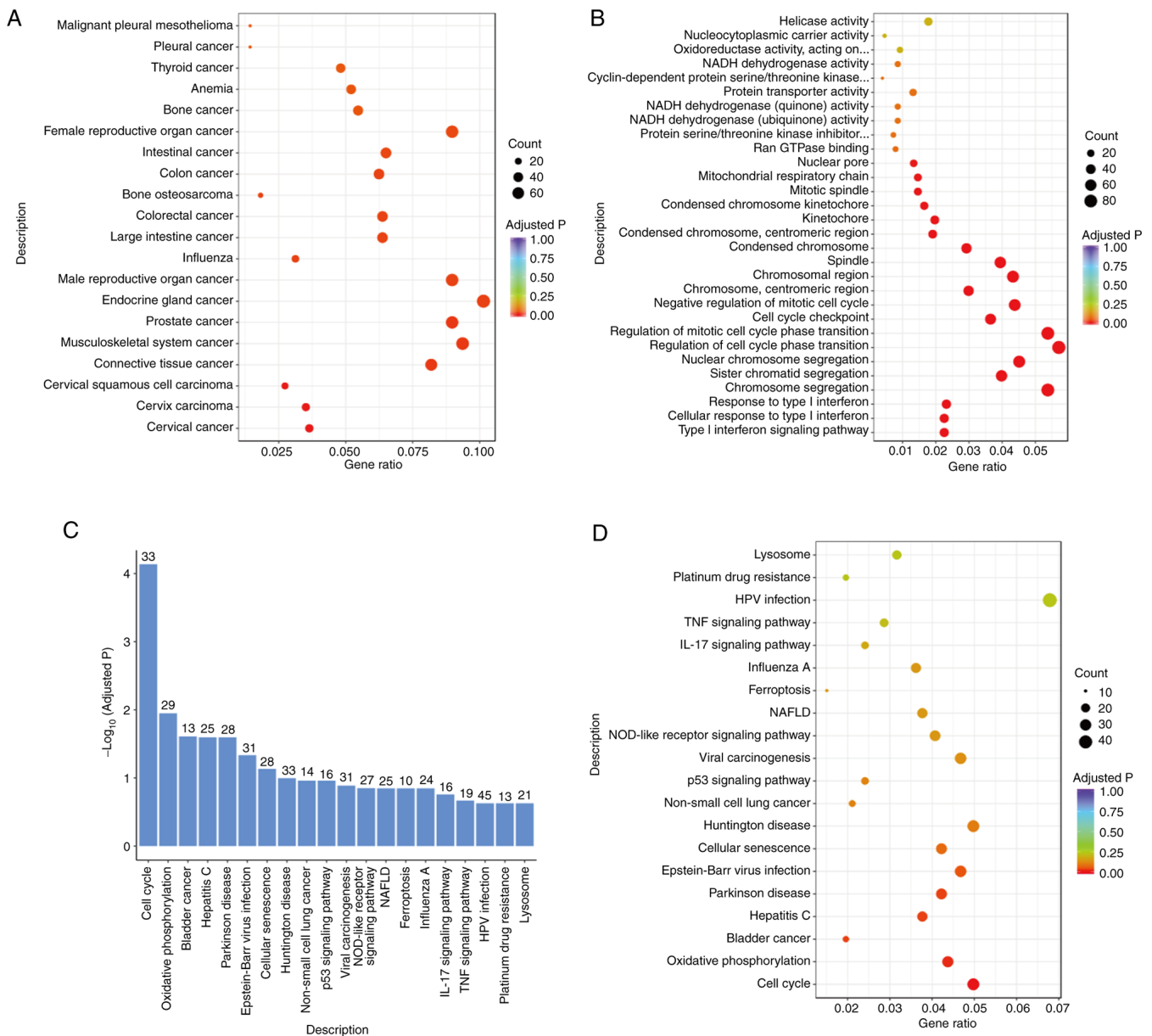


Figure 4. PRMT7 is involved in the regulation of cell cycle-related pathways and affects the cell cycle in PCa. (A) The DO enrichment distribution map of the DEGs associated with PRMT7. DO is a biomedical database that systematically annotates associations between human gene functions and diseases, providing standardized disease descriptors for functional genomics research. (B) Map of the GO enrichment sites of the DEGs associated with PRMT7. GO is a comprehensive bioinformatics resource that systematically characterizes gene functions through three orthogonal categories: Biological processes, cellular components and molecular functions. (C) KEGG enrichment analysis of the DEGs associated with PRMT7. KEGG is an integrated database that systematically consolidates genomic, chemical and systems functional information to facilitate biological pathway analysis and network modeling. (D) KEGG enrichment and distribution map of the PRMT7 differential genes. PRMT7, protein arginine methyltransferase 7; DEGs, Differentially expressed genes; log₂FC, log₂ fold change; DO, Disease Ontology; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; NAFLD, Non-alcoholic fatty liver disease; NOD, Nucleotide-binding Oligomerization Domain.

were used to search for PRMT7-related differentially expressed genes in PCa and predict the potential downstream cancer-promoting signaling molecules. The present study determined that PRMT7 may be involved in cell cycle control pathways, particularly the YY1/TP53/CCND2/CDK6/RB1 signaling pathway.

p53 is a stress-activated transcription factor that regulates the expression of target genes involved in DNA repair, cell cycle arrest, and apoptosis to maintain genomic stability and suppress tumorigenesis (46). Mutations in the p53 gene have been reported in 50% of all human malignancies, including

breast, colon, lung, liver, prostate, bladder and skin cancer (47). p53 orchestrates cell cycle checkpoints (G1/S, G2/M arrest), senescence, and metabolic adaptation to preserve genomic integrity. As a tumor suppressor, it is indispensable for eliminating damaged normal cells, while its dysfunction in cancer promotes genomic instability, therapy resistance, and metastasis (46,48-52). However, the results of the present study indicated that PRMT7 depletion did not significantly affect TP53 protein expression levels. PC3 cells harbor homozygous deletion of TP53, which explains the lack of detectable changes. This confirms that the pro-proliferative effects of

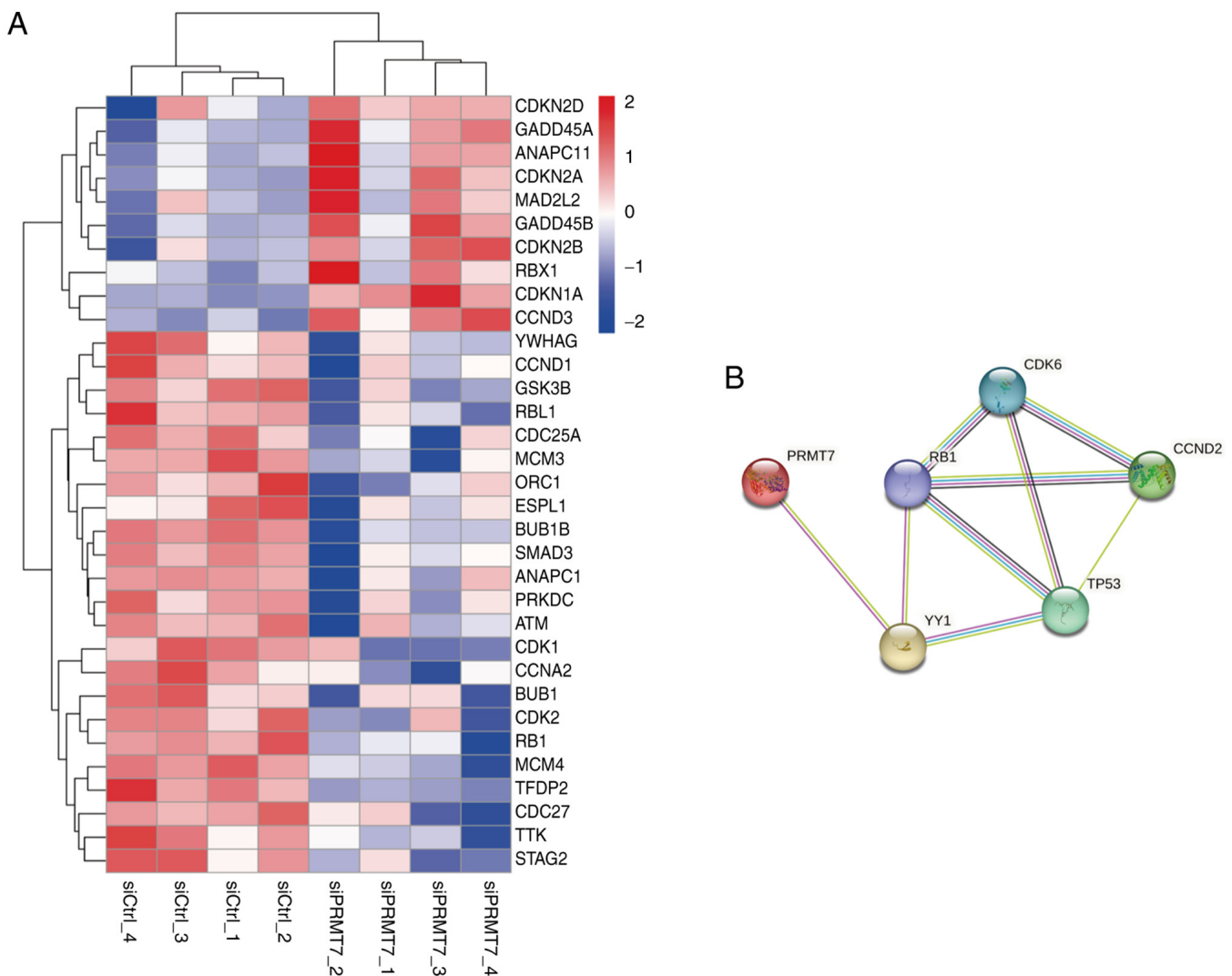


Figure 5. PRMT7 is involved in the YY1/TP53/CCND2/CDK6/RB1 cell cycle signaling axis. (A) Heatmaps of cell cycle-related differential genes identified using transcriptome sequencing. (B) Cell cycle-related regulatory proteins predicted in the STRING database and their component signaling axes. PRMT7, protein arginine methyltransferase 7; YY1, Yin Yang 1; TP53, tumor protein p53; CCND2, cyclin D2; RB1, retinoblastoma 1; STRING, Search Tool for the Retrieval of Interacting Genes/Proteins.

PRMT7 in PC3 cells are independent of canonical p53 pathways. However, PRMT7 may still engage alternative survival pathways (for example, MDM2 and AKT) in p53-null cells to bypass p53-mediated cell cycle checkpoints.

YY1 is a member of the GLI-Kruppel zinc finger protein family that has two opposing abilities: Inhibiting and activating gene transcription (53). PRMT7 interacts with YY1, which leads to breast cancer cell migration and invasion (26). In the present study, YY1 exhibited a small yet statistically significant decrease in expression upon PRMT7 knockdown. PRMT7 may methylate YY1 to stabilize its protein or enhance its transcriptional activity. Loss of PRMT7-dependent methylation could impair the ability of YY1 to activate downstream targets, including cell cycle regulators such as CCND2/CDK6 (54-56). In indirect regulation, YY1 downregulation might reflect secondary effects of PRMT7 knockdown, such as altered chromatin accessibility at YY1-binding loci or dysregulation of upstream signaling pathways (56,57). This mild reduction suggests YY1 is not the primary effector of PRMT7 in PC3 cells, but its partial loss may synergize with other pathways to amplify CCND2/CDK6 suppression.

CCND2 is a member of the cyclin family that encodes cyclin D2. It regulates cancer cell processes through the cell cycle. Cyclin D2 reduces the inhibitory effect of miR-615 on the proliferation, migration and invasion of PCa cells (58). The expression levels of E2F transcription factor 2 and CCND2 was downregulated by let-7a; the latter may inhibit PCa growth in an *in vivo* PCa xenograft model (59). CCND2 promotes PCa development and CDK6 and RB1 are well-known cell cycle regulators; several studies have reported that targeting them can affect the cell cycle of PCa cells and inhibit their proliferation (60-63). Analysis of the western blotting experiments in the present study demonstrated that CCND2 and CDK6 levels were markedly downregulated following PRMT7 depletion. PRMT7-mediated symmetric dimethylation of histone H4R3 (H4R3me2s) is key for maintaining an active chromatin state at the CCND2 promoter. PRMT7 knockdown may induce heterochromatin formation, which represses transcription. PRMT7 might methylate RNA-binding proteins to stabilize CCND2 mRNA; its absence could accelerate mRNA degradation. PRMT7 may methylate histones (for example,

H3R2me2s) at the CDK6 promoter to facilitate transcriptional elongation by RNA Polymerase II. Furthermore, YY1 has been reported to bind the CDK6 promoter (64). The concurrent downregulation of YY1 and CDK6 expression suggests a PRMT7-YY1-CDK6 regulatory axis. In the present study, total RB1 protein levels demonstrated no significant alteration after PRMT7 knockdown. RB1 function is primarily governed by phosphorylation status compared with total protein abundance. The observed CCND2/CDK6 downregulation likely reduces RB1 phosphorylation, activating its growth-suppressive function without altering total RB1 levels. PRMT7 may methylate RB1 to modulate its interaction with E2F or chromatin remodelers. However, such modifications might not affect total RB1 stability, which necessitates phospho-specific assays. Therefore, these results suggested that PRMT7 likely serves a role in TP53-related cell cycle pathways, ultimately contributing to PCa progression.

Previous studies on blocking AR resistance have indicated the role of AR-related cell cycle pathways in PCa (65–67). The binding of androgens to their receptors induces cell cycle progression by directly affecting the transcription-regulated expression of cell cycle regulatory proteins (68). This involves ligand-activated AR signaling regulation of the cell cycle, which causes androgen-deprived ADT-sensitive cells to exit the cell cycle and stall in the G₀ phase (69–71). As CDK complexes control transition within the cell cycle and maintain progression from the G₁ phase to mitosis (72–74), AR can promote tumor cell proliferation by affecting the activity of CDKs and CDK inhibitors. After androgen blocking, the expression of major D-type cyclin is inhibited in ADT-reactive PCa cells, which results in cell cycle arrest and the inhibition of cell proliferation (71,75). The growth factor-mediated accumulation of D-type cyclins in cells further induces CDK4/6 activity and maintains the cell cycle (74), which initiates the phosphorylation/inactivation of the RB tumor suppressor and blocking the RB-mediated negative regulation of cell cycle transition and DNA replication (76). These results suggested that further research on cell cycle changes in PCa could help to elucidate the possible mechanism of androgen-blocking drug resistance and tumorigenesis.

The present study had several limitations. For instance, the sample collection period was relatively short (~6 months). Although an adequate sample size was achieved from this high-volume tertiary hospital (Affiliated Hospital of Jiangnan University; Wuxi, China), the potential for temporal bias requires consideration. Furthermore, the present study primarily relied on *in vitro* experiments. Future research should validate these findings through multicenter cohorts and further investigate the molecular mechanisms underlying PRMT7-mediated cell cycle regulation. Ideally, a larger and directly matched control group would enhance the reliability of the findings. Furthermore, future collaborations with other institutions aim to obtain a more comprehensive dataset, thereby improving the external validity of the present study results. Although the present study revealed that PRMT7 modulates cell cycle progression in PCa cells through a specific signaling axis, the mechanisms underlying cell cycle G₀ arrest and the downstream phosphorylation of associated factors remains

to be elucidated. Relying on bioinformatics prediction methods, specific research directions were identified to study the mechanism by which PRMT7 promotes PCa. These findings suggested a functional involvement of PRMT7 in modulating PCa cell cycle progression, but more rigorous mechanistic investigations are required to fully delineate its underlying molecular actions. However, due to the lack of further evidence, the present study was unable to confirm the precise mechanism by which PRMT7 affected cell cycle-related factors such as YY1, TP53, CCND2, CDK6 and RB1 in PCa. As members of the same enzyme family, PRMT7 and other PRMTs may exhibit synergistic or antagonistic interactions *in vivo*. Notably, studies have reported that PRMT7-mediated monomethylation of histone H4 at Arg-17 can directly modulate PRMT5-catalyzed symmetric dimethylation at Arg-3 within the same histone protein (77,78). Therefore, investigating the functional role of PRMT7 in PCa progression must account for the coordinated or competitive activities of other PRMT family members, particularly in regulating cell cycle checkpoints through key effectors such as RB1 phosphorylation and CDK6 activation. These mechanisms require further investigation in future studies. Future experiments will include exploring the specific mechanism of PRMT7 in the PCa cell cycle and identifying effective molecularly targeted drugs associated with PRMT7 to provide research directions for the precise treatment of PCa.

The present study confirmed that PRMT7 was involved in the proliferation and invasion of PCa cells and potentially promoted the malignant progression through the YY1/TP53/CCND2/CDK6/RB1 cell cycle signaling axis.

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Availability of data and materials

The data generated in the present study may be found in the Gene Expression Omnibus under accession number (GSE302155) or at the following URL: <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE302155>. The remaining data generated in the present study may be requested from the corresponding author.

Authors' contributions

HW, HZ, JG, NF and DY conceived and designed the present study; HW, RW, JN and YM performed the experiments and acquired the data. SW, YQ, QQ and LZ contributed to data analysis. HW and YM confirm the authenticity of all the raw data. All authors were involved in drafting and revising the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Affiliated Hospital of Jiangnan University (approval no. LS2023099; Wuxi, China) and written informed consent was obtained from all patients prior to sample collection.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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