JBUON 2020; 25(4): 2028-2035
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

miR-19a promotes the metastasis and EMT through CUL5 in prostate cancer cell line PC3

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Summary

Purpose: *Prostate cancer is an epithelial malignancy that occurs in the prostate and metastasis is a challenge of the treatment of prostate cancer. MicroRNA (miR)-19a was usually upregulated in several cancers at the roles of miR-19a in the metastasis in prostate cancer are still unclear.*

Methods: *A normal prostate epithelial cell line P69 and two prostate cancer cell lines PC3 and DU145 were used in this study. The mRNA levels of miR-19a and CUL5 were measured using qRT-PCR assay. Transwell and Western blot assays were conducted to calculate cell metastasis and epithelial-mesenchymal transition (EMT) properties in PC3 cells. Luciferase reporter assay was applied to validate that miR-19a targeted to CUL5.*

Results: *The expression of miR-19a was high in prostate cancer and its overexpression predicted poor outcome of prostate cancer patients. miR-19a regulated the expression of CUL5 by directly targeting its mRNA 3'-UTR in PC3 cells. The expression of CUL5 was lower in prostate cancer tissues and cell lines than in non-tumor tissues and normal cells. Downregulation of CUL5 predicted worse outcome of prostate cancer patients. miR-19a promoted cell migration, invasion and EMT in prostate cancer by directly binding to CUL5 mRNA 3'-UTR. CUL5 partially reversed the roles of miR-19a on the metastasis in prostate cancer.*

Conclusions: *miR-19a promoted migratory, invasive and EMT abilities by binding to CUL5 in prostate cancer. The newly identified miR-19a/CUL5 axis provides novel insight into the pathogenesis of prostate cancer.*

Key words: *miR-19a, prostate cancer, CUL5, metastasis, EMT*

Introduction

Prostate cancer (PCa), an epithelial malignancy that occurs in the prostate, is one of the most common malignancies in men worldwide [1-3]. Although the initial growth is slow, it progresses rapidly and is easy to cause systemic metastases [3-5]. However, the molecular mechanisms underlying diagnosis and treatment of prostate cancer is still unclear. Therefore, it is urgent to explore new biomarkers for the metastasis of prostate cancer.

MicroRNAs (miRs), small non-coding RNAs with 19-25 nucleotides in length, can regulate gene expression by binding to 3'-UTR to degrade mRNA or suppress translation at the post-transcriptional level [6,7]. miR-19a usually upregulated and acted as oncogene in several cancers, including colorectal cancer, multiple myeloma, acute myelocytic leukemia and breast cancer [8-11]. This miR acted as oncogene in promoting tumor growth and me-

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Received: 03/01/2020; Accepted: 07/02/2020

tastasis in myeloma and lung cancer [12,13]. miR-19a improved the viability and inhibited cell apoptosis by directly targeting PTEN in osteosarcoma stem cells [14]. Similarly, Liu et al validated that miR-19a enhanced the proliferation, insulin secretion and suppressed the apoptosis through SOCS3 in pancreatic β cells [15]. Even in clear cell renal cell carcinoma, miR-19a promoted the growth, migration and inhibition of cell apoptosis [16]. Thus, we hypothesize that miR-19a may play a role in prostate cancer.

Cullin-5 (CUL5) is the least conserved member of the cullin family, forming the cullin-RING ubiquitin E3 ligase complexes (CRLs) [17,18]. The CUL5 gene polymorphisms are partially connected with HIV-1 infection and antiretroviral therapy in Brazilian populations [19]. CUL5, emerged as a biomarker, is associated with regulating cellular growth in multiple myeloma [20]. Moreover, low expression of CUL5 inhibited cell colony formation and induced cell cycle arrest in hepatocellular carcinoma [21]. The purpose of this study was to explore the functions of miR-19a and CUL5 in prostate cancer.

Methods

Patients and tumor samples

During 2014-2018, 48 operated prostate cancer patients were collected from The Second People's Hospital of Liaocheng, and we obtained 48 pairs of prostate cancer and corresponding non-tumor tissues. Before surgery, none of the patients had received chemotherapy or radiotherapy. The fresh tissues were stored at -80℃ in liquid nitrogen immediately after surgery. All patients signed the informed consent and the study was approved by the Ethical Committee of the Second People's Hospital of Liaocheng.

Cell culture and treatment

A normal prostate epithelial cell line P69 and two prostate cancer cell lines PC3 and DU145 were obtained from American Type Culture Collection (ATCC; Rockville, MD, USA). All the cells were cultured in DMEM medium (Gibco, UK) supplemented with 10% fetal bovine serum (FBS; Gibco, UK) and incubated at 37°C in a humidified atmosphere with 5% CO_2.

Cell transfection

PC3 cells at a density of 70% were seeded into 6-well plates. miR-19a mimic or miR-19a inhibitor (Gene Pharma, China) were used to assess gain or loss miR-19a levels. According to the manufacturer's instructions, the transfection was carried out using Lipofectamine 2000 (Invitrogen; Thermo Fisher Scientific, Beijing, China), which was diluted in Opti-MEM medium. Next, the mixture was added to cells which were incubated at 37°C with 5% CO_2.

RNA extraction and real-time PCR

In accordance with the manufacturer's instructions, total RNAs or miRs were extracted using the TRIzol reagent (Invitrogen; Thermo Fisher Scientific, New York, USA) or the miRCURY RNA Isolation Kit (Exiqon, New York, USA), and quantified by a NanoDrop spectrophotometer (Thermo Fisher Scientific). Reverse transcription was performed to synthesize the first cDNA chain using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, New York, USA). The SYBR PrimeScript miR RT-PCR kit (Takara Bio, Dalian, China) or SYBR PrimeScript miR RT-PCR kit (Takara Bio, Otsu, Japan) was employed to calculate the expression of CUL5 or miR-19a with GAPDH and U6 as the internal reference. The nucleotide primers used for real-time PCR were as follows: miR-19a forward: 5'-TTTTTACTAATTTTGTGTACTTTTATTGTGTCGATGT-3'; reverse: 5'-CACTTTAGTGCTACAGAAGCTGTCA-3'; U6 snRNA forward: 5'-GCTTCGGCAGCACATATACTAAAAT-3'; reverse: 5'-CGCTTCACGAATTTGCGTGTCAT-3'; forward: 5'-GAACACAAGCACCCTCGTATT-3', reverse: 5'-TCAACGGAGTTACATTCTCGTCT-3'; GAPDH forward: 5'-GGGCTGCTTTTAACTCTGGTAA-3'; reverse: 5'-ATGGGTGGAATCATATTGGAAC-3'.

Western blotting

RIPA buffer (Beyotime Biotechnology, Shanghai, China) containing protease inhibitor (Sigma Aldrich, Shanghai, China) was applied to lyse the cells and extract total proteins. After centrifuging at 12,000 rpm for 15 min, the concentration of total protein was assessed using the bicinchoninic acid (BCA)/protein assay kit (Thermo Scientific, Yew York, USA). The proteins were separated using 10% SDS-PAGE followed by transfer onto PVDF membranes (Roche Applied Science, Basel, Switzerland) in accordance with the manufacturer's instructions. After blocking by incubating 5% skimmed milk at room temperature for 5 h, the membranes were incubated with primary antibodies. The primary antibodies were against CUL5 or GAPDH (Cell Signaling Technology, Shanghai, China). Then, the HRP-conjugated secondary antibody (1:5000, Cell Signaling Technology, USA) was performed to incubate the membranes. Western electrochemiluminescence Substrate (Bio-Rad, New York, USA) was applied to carry out the visualization.

Transwell assay

The migration and invasion in prostate cancer cells were assessed using Transwell chambers (Millipore, Bedford, MA, USA) with or without Matrigel coating. Before the experiment, transwell chambers were placed in 24-well plates and formed the upper and lower chamber. We seeded 200 μL cells' suspension in serum-free basal DMEM into the upper chamber, while 600 μL DMEM with 20% FBS was added into the lower chamber. The migrated or invaded cells were moved to the underside of the membranes. After 48-h culture, the cells still staying on the upper surface were removed using a cotton swab, while the migrated or invaded cells were fixed and stained using methanol and crystal violet. The number

of the migrated or invaded cells was counted with a microscope in five randomly chosen fields to get the average.

Luciferase reporter assay

Tagetscan was conducted to perform bioinformatics analysis to predict the putative target region of miR-19a on the 3'-UTR of CUL5 mRNA. To verify the miR-19a direct binding to the 3'-UTR of CUL5 mRNA, the binding sequences were mutated from UUGCAC to AACGUG. Both the wild type and the mutant sequences of CUL5 3'-UTR were amplified by PCR and then inserted into pmirGLO vector. The PC3 cells were seeded into 6-well plates and miR-19a mimic or NC together with wild type or mutant CUL5 mRNA were co-transfected into PC3 cells using Lipofectamine 2000 according to the manufacturer's instructions. Cells were harvested at 48h and the activity of Firefly luciferase was normalized to that of renilla luciferase.

Statistics

The results of multiple experiments are presented as the mean±SD. Statistical analyses were carried out by GraphPad Prism 7 software (GraphPad, San Diego, CA, USA). The comparisons between two or more groups were performed by Student's t-test and one-way analysis of variance (ANOVA). A p value <0.05 was considered to show a statistically significant difference.

Results

miR-19a upregulation predicted poor prognosis of prostate cancer

qRT-PCR was conducted to assess miR-19a expression in 48 pairs of prostate cancer and matched normal tissues. miR-19a was upregulated in prostate cancer tissues compared with the normal tissues ($p<0.05$) (Figure 1A). Kaplan-Meier analysis was employed to evaluate the correlation between the expression of miR-19a and the overall survival, and revealed that overexpression of miR-19a was associated with worse overall survival ($p<0.05$) (Figure 1B).

What's more, the expression of miR-19a was evaluated in prostate cancer cell lines PC3 and DU145 and a prostate epithelial cell line P69. The expression of miR-19a was higher in PC3 and DU145 cells than in P69 cells ($p<0.05$) (Figure 1C). miR-19a mimic or miR-19a inhibitor were applied to transfect in PC3 cells to gain or loss miR-19a, and its transfection efficiency was assessed by qRT-PCR ($p<0.05$) (Figure 1D).

miR-19a promoted the metastasis of PC3 cells

Transwell and western blot assays were conducted to assess cell migratory, invasive and EMT

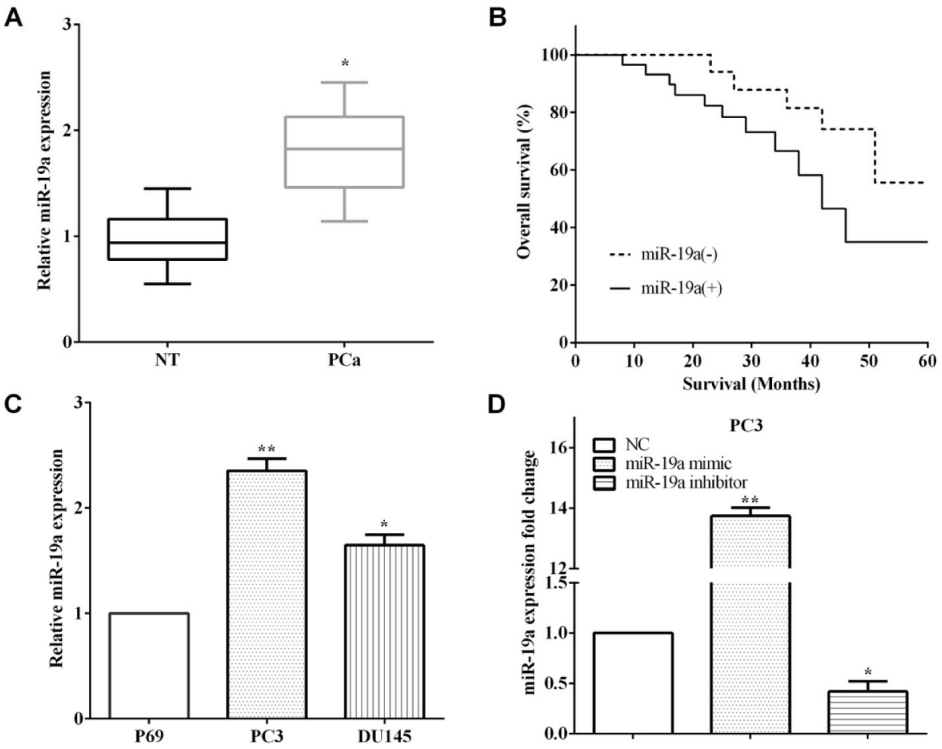

Figure 1. Upregulation of miR-19a predicted poor prognosis of prostate cancer. **A:** miR-19a was upregulated in prostate cancer tissues vs non-tumor tissues (*p<0.05). **B:** Overexpression of miR-19a predicted poor overall survival of prostate cancer (*p<0.05). **C:** The expression of miR-19a was lower significantly in PC3 and DU145 cells than in P69 cells (*p<0.05, **p<0.01). **D:** RT-qPCR was applied to measure the transfection efficiency of transfecting miR-19a mimic, miR-19a inhibitor in PC3 cells (*p<0.05, **p<0.01).

abilities in PC3 cells. As expected, cell migratory and invasive abilities were improved by miR-19a mimic ($p<0.05$), whereas they were impaired by miR-19a inhibitor ($p<0.05$) (Figure 2A and B). For EMT ability, miR-19a mimic improved the expression of N-cadherin while suppressed the expression of E-cadherin (Figure 2C). On the contrary, the expression of N-cadherin was decreased by miR-19a inhibitor whereas E-cadherin expression was enhanced (Figure 2D), revealing that miR-19a enhanced the metastatic ability in PC3 cells.

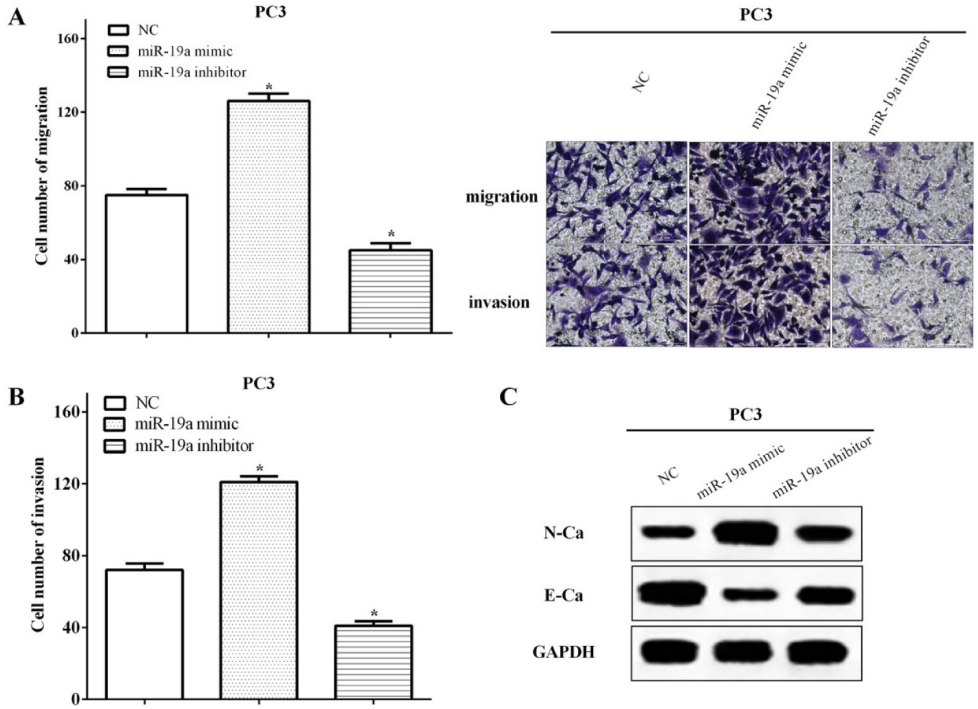

Figure 2. miR-19a impaired cell metastasis of PC3 cells **A:** miR-19a regulated cell migratory capacity in PC3 cells (*$p<0.05$). **B:** miR-19a mimic inhibited invasion, whereas it was inhibited by miR-19a inhibitor (*$p<0.05$). **C:** miR-19a improved the EMT ability in PC3 cells.

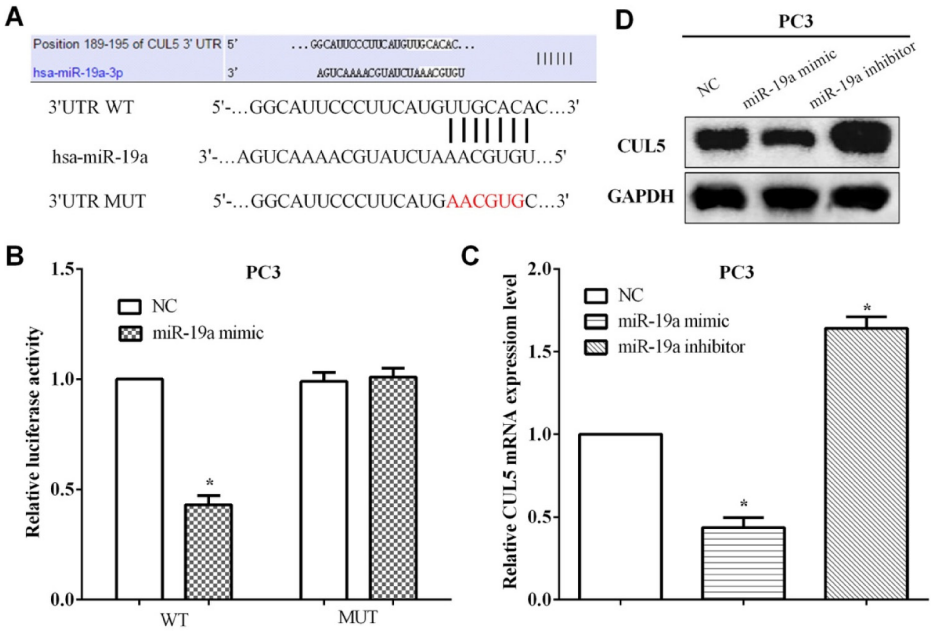

Figure 3. miR-19a regulated the expression of CUL5 **A:** TargetScan predicted that CUL5 was a target gene of miR-19a. **B:** miR-19a mimic inhibited the luciferase activity of cells transfected with wild type 3'-UTR of CUL5 (*$p<0.05$). **C:** The expression of CUL5 was reduced by miR-19a mimic, while it was improved by miR-19a inhibitor in PC3 cells (*$p<0.05$).

miR-19a regulated the expression of CUL5 via directly binding to the 3'-UTR of its mRNA

The potential target genes of miR-19a were predicted by TargetScan, and CUL5 was discovered to be a candidate. To investigate miR-19a direct binding to the 3'-UTR CUL5 mRNA, the conjectural binding sequences were mutated from UUGCAC to AACGUG (Figure 3A). Compared to the NC mimic, the luciferase ability was suppressed by miR-19a mimic in cells transfected with the wild type CUL5 3'-UTR ($p<0.05$). However, miR-19a mimic did not alter the luciferase activity of cells transfected the mutated CUL5 3'-UTR ($p>0.05$) (Figure 3B). What's more, the mRNA and protein levels of CUL5 were evaluated after transfection with miR-19a mimic or miR-19a inhibitor in PC3 cells. As expected, miR-19a mimic reduced the mRNA level of CUL5 ($p<0.05$), while miR-19a inhibitor improved CUL5 mRNA level in PC3 cells ($p<0.05$) (Figure 3C). Also, the protein level of CUL5 was reduced after overexpression of miR-19a, whereas miR-19a inhibitor increased the expression of CUL5 in PC3 cells (Figure 3D). All these findings elucidated that CUL5 expression was regulated by miR-19a by binding to 3'-UTR in PC3 cells.

Downregulation of CUL5 predicted poor prognosis of prostate cancer patients

To explore the functions of CUL5 on miR-19a, the expression of CUL5 was calculated by qRT-PCR assay, which revealed that CUL5 was lowly expressed in prostate cancer tissue compared with the matched normal tissues ($p<0.05$) (Figure 4A). Similarly, the expression of CUL5 was lower in prostate cancer cell lines PC3 and DU145 than the normal cells P69 ($p<0.01$) (Figure 4B). In addition, Kaplan-Meier method revealed that upregulation of CUL5 was related to poor overall survival of prostate cancer patients ($p<0.05$) (Figure 4C).

CUL5 partially reversed the promoting function of miR-19a

To investigate the roles of CUL5 in prostate cancer cells, pcDNA3.1-CUL5 plasmid was re-transfected into miR-19a overexpressed PC3 cells, and the transfection efficiency was measured by qRT-PCR ($p<0.05$) (Figure 5A). Transwell assay was performed to evaluate the migratory and invasive abilities in PC3 cells. Compared with cells transfected with miR-19a mimic only, miR-19a overexpressing cells had decreased migratory and invasive abil-

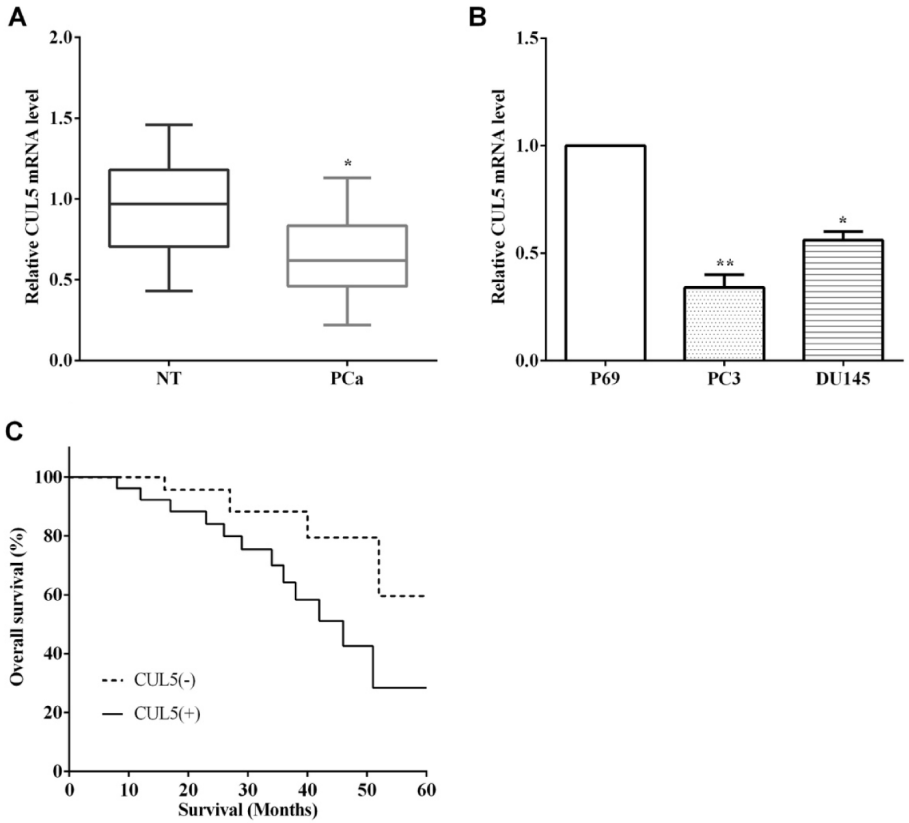

Figure 4. Downregulation of CUL5 predicted poor prognosis of prostate cancer patients **A:** The expression of CUL5 was lower in prostate cancer tissue than in normal tissues (*$p<0.05$). **B:** CUL5 was lowly expressed in PC3 cells vs prostate P69 cells (*$p<0.05$, **$p<0.01$). **C:** Downregulation of CUL5 predicted poor overall survival of prostate cancer patients ($p<0.05$).

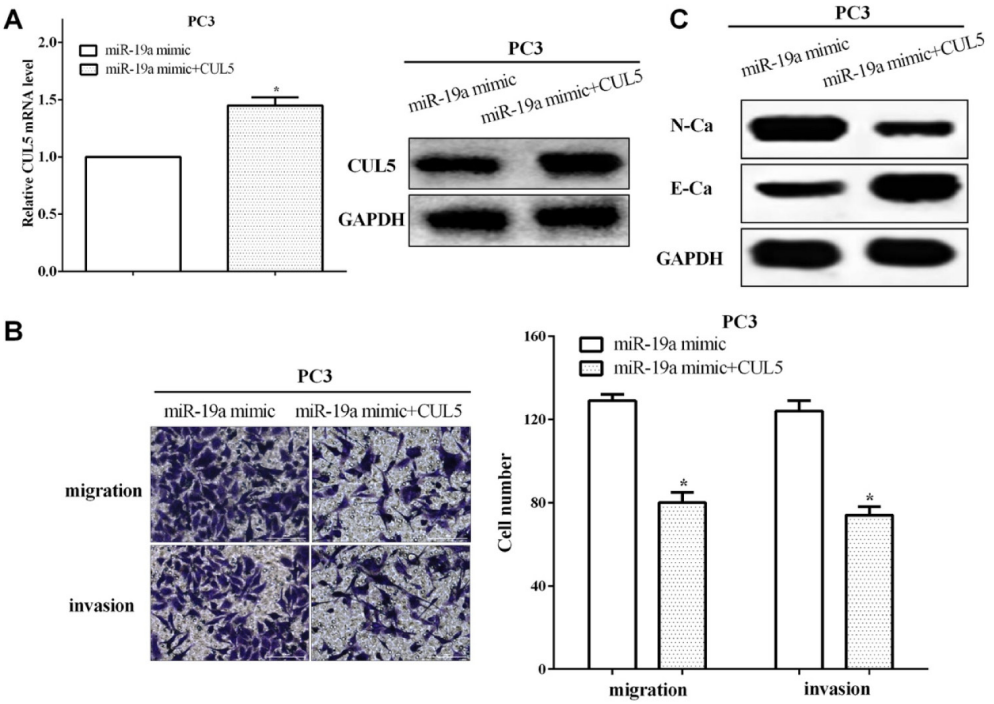

Figure 5. CUL5 partially reversed roles of miR-19a. **A:** After overexpressing CUL5 in cells overexpressing miR-19a mimic, the mRNA and protein levels of CUL5 increased. **B:** Re-transfecting CUL5 inhibited significantly cell migratory and invasive abilities in miR-19a overexpressed cells. **C:** CUL5 could partially reverse the roles of miR-19a on the EMT capacity in PC3 cells (*p<0.05).

ity after re-transfected CUL5 (p<0.05) (Figure 5B). In addition, overexpression of CUL5 inhibited the expression of N-cadherin while E-cadherin expression was promoted in miR-19a overexpressed PC3 cells (Figure 5C), which indicated that CUL5 partially reversed the effects of miR-19a on cell migration, invasion and EMT in PC3 cells.

Discussion

Prostate cancer is one of the most non-cutaneous malignancies diagnosed in males [22]. In both developed and developing countries, the incidence and recurrence rate of prostate cancer have increased [23]. Therefore, it is urgent to investigate the mechanisms of miRs, and provide new ideas for further research on the treatment strategy of this disease.

miR-19a served as an oncogene and acted as a prognostic marker of prostate cancer [24]. Consistent with a previous study [24], we discovered that the expression of miR-19a was higher in prostate cancer tissues and cell lines, and upregulation of miR-19a was correlated with worse outcome of prostate cancer patients. miR-19a also improved cell viability and invasion by TGFβR2 in nasopharyngeal carcinoma [25]. miR-19a promoted cell proliferation and metastasis via TIA1 in colorectal cancer [26]. Similarly, miR-19a mediated cell viability and invasion via β-catenin/Tcf-4 pathway in glioma [27]. Consistent with all the findings, we found that miR-19a promoted the migration, invasion and EMT in prostate cancer cells.

In renal cell carcinoma, CUL5 acted as a novel candidate tumor suppressor to maintain genome stability [28]. In addition, CUL5 was lowly expressed in endometrial adenocarcinoma and was associated with prognosis [29]. Consistent with the above findings [28,29], we discovered that low expression of CUL5 was correlated with worse outcome of prostate cancer patients. Moreover, knockdown of CUL5 enhanced cell metastasis in small-cell lung cancer [30]. Consistent with all the findings [30], we found that CUL5 was downregulated in prostate cancer tissues and cell lines compared to corresponding non-tumor tissues and normal cells. We also discovered that CUL5 was a target gene of miR-19a, which was consistent with the findings in gastric cancer [31]. In addition, miR-19a regulated the expression of CUL5 by binding to the 3'-UTR of its mRNA in prostate cancer cells. CUL5 partially reversed the promoting function of miR-19a on migration, invasion and EMT.

Conclusion

The expression of miR-19a was higher while of CUL5 was lower in prostate cancer tissues and cell

lines vs normal tissues and normal cell line. Upregulation of miR-19a or downregulation of CUL5 was connected with worse outcome of prostate cancer patients. miR-19a promoted cell migration, invasion and EMT in prostate cancer by directly binding to the 3'-UTR of CUL5 mRNA. CUL5 partially reversed the roles of miR-19a on metastasis in prostate cancer.

Conflict of interests

The authors declare no conflict of interests.

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