European Review for Medical and Pharmacological Sciences 2020; 24: 4710-4718

MiR-219-5p inhibits prostate cancer cell growth and metastasis by targeting HMGA2

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Abstract. – OBJECTIVE: To investigate the expression of micro ribonucleic acid (miR)-219-5p in prostate cancer (PCa), its influences on the biological functions of PCa, and its mechanism.

PATIENTS AND METHODS: The expression differences of miR-219-5p and high mobility group protein A2 (HMGA2) in 30 pairs of PCa tissues and para-carcinoma tissues were detected via quantitative Real Time-Polymerase Chain Reaction (qRT-PCR), and the difference in miR-219-5p expression in PCa cell lines and normal prostatic epithelial cells was also determined *via* qRT-PCR. The human PC-3 cells were divided into negative control group and miR-219-5p overexpression group. Methyl thiazolyl tetrazolium (MTT) and colony formation assays were adopted to detect the cell proliferative ability, and flow cytometry was applied to determine the cell apoptosis. The expression of apoptosis-related proteins was measured via Western blotting, and the invasive and migratory abilities of the cells were examined through wound-healing and transwell assays. Bioinformatics prediction software and luciferase reporter assay were employed to verify the targets that might be controlled by miR-219-5p. Rescue experiment was conducted to clarify whether the inhibitory effects of miR-219-5p on the growth and metastasis of PC-3 cells depend on the inhibition of HMGA2.

RESULTS: It was shown in qRT-PCR results that the expression level of miR-219-5p was downregulated remarkably in PCa tissues and cell lines, but overexpressed miR-219-5p could repress the proliferation and promote the apoptosis of PC-3 cells notably. The results of wound-healing and transwell assays indicated that overexpressed miR-219-5p was able to suppress the invasion and metastasis of PC-3 cells. According to Western blotting results, overexpressed miR-219-5p could up-regulate the expressions of pro-apoptotic proteins [Bax, cleaved-caspase-3 and cleaved-poly-ADP-ribose-polymerase (PARP)] and reverse the epithelial-mesenchymal transition (EMT) of PCa cells. It was predicted *via* the bioinformatics software that HMGA2 gene might be a target gene of miR-219-5p. The Dual-Luciferase reporter assay confirmed that there was a direct regulatory relationship between miR-219-5p and HMGA2. The rescue experiment manifested that overexpressed HMGA2 could reverse the inhibition of miR-219-5p on the growth and metastasis of PC-3 cells.

CONCLUSIONS: MiR-219-5p suppresses the growth and metastasis abilities of prostate cancer cells by directly repressing the expression of HMGA2.

Key Words:
Prostate cancer (PCa), MiR-219-5p, HMGA2, Apoptosis, Epithelial-mesenchymal transition (EMT).

Introduction

Prostate cancer (PCa) is one of the ten major lethal tumors with an increasing morbidity rate in males[1]. Though radical prostatectomy and endocrine therapy can extend the survival time of the patients, the 10-year recurrence rate of moderate- and high-risk localized PCa is 54% and 71%, respectively[2]. At 18-24 months after endocrine therapy, PCa will develop into androgen-independent PCa in most patients. Although chemoradiotherapy can still be performed, the prognosis is poor and the disease progresses quickly. Therefore, it is urgent to find new therapeutic targets. As a category of newly-discovered endogenous small non-coding single-stranded ribonucleic acids (RNAs) with a length of 18-26 nt, micro RNAs (miRNAs) widely exist in eukaryotes and act on corresponding target messenger RNAs (mRNAs) by means of base pairing, thus inhibiting the degradation or post-transcriptional translation of mRNAs[3]. Scientific researchers discovered more

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than ten years ago that miRNAs are closely associated with carcinogenesis[4]. Dysregulated expression of miRNAs plays very important roles in the occurrence and development of multiple tumors[5]. The latest investigations suggest that miR-219-5p exerts crucial effects on the occurrence and development of tumors. Ma et al[6] reported that the expression of miR-219-5p declines in esophageal squamous cell carcinoma, while its up-regulation can repress the cell proliferation. However, Yang et al[7] revealed that miR-219-5p manifests the activity of oncogenes in hepatocellular carcinoma, thus facilitating the growth and metastasis of the disease. All those findings imply that miR-219-5p functions inconsistently in the occurrence and development of tumors, but the regulatory effect of miR-219-5p on biological characteristics of PCa has not been reported in literature yet.

This research aims to investigate the expression of miR-219-5p in PCa tissues and para-carcinoma tissues, elaborate its regulatory role in the biological behaviors of PCa cells, identify the downstream target genes of miR-219-5p, and reveal the molecular mechanism of miR-219-5p in modulating the incidence and progression of PCa.

Patients and Methods

Collection of PCa Samples

In this research, a total of 30 pairs of PCa and para-carcinoma tissue samples were collected from 30 PCa patients receiving surgery from January 2018 to June 2019 in our hospital. All the patients were definitely diagnosed through pathology, and they did not undergo chemotherapy, radiotherapy or any other forms of tumor-specific therapy before operation. The resection samples were frozen in liquid nitrogen, all the patients signed the informed consent, and this research was approved by the Ethics Committee of our Hospital.

Cell Culture and Transfection

PCa cell lines (LNCap, PC-3, and DU145) and normal prostatic epithelial cells (RWPE-1; Cell Bank of Type Culture Collection of Chinese Academy of Sciences, Shanghai, China) were cultured in Dulbecco's Modified Eagle's Medium (DMEM; HyClone, South Logan, UT, USA) containing 10% fetal bovine serum (FBS; HyClone, South Logan, UT, USA) at 37°C with 5% CO_2. MiR-219-5p mimic and negative control were purchased from GenePharma (Shanghai, China). The plasmid complementary deoxyribonucleic acid (pcDNA) 3.0-high mobility group protein A2 (HMGA2) plasmid was applied to overexpress HMGA2 using the vector designed and synthesized by Generay Biotech (Shanghai, China). Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA) was used for transfection according to the manufacturer's instructions.

Cell Viability Assay

The transfected cells were seeded into a 96-well plate (5,000 cells/well) and cultured with 200 μL of complete medium in each well for 24, 48, 72, and 96 h. After that, the cell proliferation was detected *via* a methyl thiazolyl tetrazolium (MTT) kit (Sigma-Aldrich, St. Louis, MO, USA), and the values at the absorption wavelength of 570 nm were read to plot the growth curves.

Colony Formation Assay

The transfected cells were harvested, inoculated into a 6-well plate at 600 cells/well, and cultured for 14 consecutive days, followed by washing with phosphate-buffered saline (PBS), fixation in 10% formaldehyde, staining with crystal violet and photography. The colony with over 50 cells formed was regarded as one clone.

Apoptosis Assay

After transfection, the cell concentration was adjusted to 5×10^3/mL, and 1 mL of cell suspension was subjected to Annexin V-fluorescein isothiocyanate (FITC)/propidium iodide (PI) double staining in accordance with the instructions of apoptosis kit and then examined by a flow cytometer (FACSCalibur; BD Biosciences, Detroit, MI, USA).

RNA Isolation and Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR)

The total RNA in tissues and cells was extracted using TRIzol reagent method (Invitrogen, Carlsbad, CA, USA), 1 g of which was reversely transcribed into complementary deoxyribonucleic acids (cDNAs). Next, fluorescence qPCR was performed to measure the content of miR-219-5p, with 2 μL of the product of reverse transcription as the template. The primer sequences of PCR are as follows: U6: forward: 5'-CTTCGGCAGCACATATAC-3', reverse: 5'-GAACGCTTCACGAATTTGC-3', miR-219-5p: forward: 5'-ACACTCCAGCTGGGTGATTGTCCAAACGCAAT-3', reverse: 5'-CTCAACTGGTGTCGTGGA-3'. With a 20 μL system, the PCR conditions are as follows: denaturation at 95°C for 10 s, annealing at 58°C for 10 s, and extension at

72°C for 10 s for 40 cycles. As for the detection of mRNA level of HMGA2, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as a reference gene, and the rest experimental system was the same as that of miR-219-5p. Primer sequences of PCR: HMGA2: forward: 5'-CGGCCAAGAGGCAGACCTAGG-3', reverse: 5'-GTTGGCGCCCCCTAGTCCTCT-3', GAPDH: forward: 5'-AGGTCGGTGTGAACGGATTTG-3', reverse: 5'-TGTAGACCATGTAGTTGAGGTCA-3'. GAPDH and U6 were used as loading controls for quantification of mRNAs and miRNAs, respectively. Relative gene expression was calculated using the $2^{-\Delta\Delta Ct}$ method.

Wound Healing Assay

The cells were seeded into the 6-well plate after transfection and cultured under appropriate conditions. When the cell fusion reached 90%, the medium was replaced with FBS-free medium for incubation for 24 h. Later, a wound was scratched evenly by virtue of a 200 μL sterile pipette tip that was perpendicular to the bottom of the 6-well plate, the floating cells scratched were washed away using PBS, and FBS-free medium was added for culture in an incubator. At 0 and 48 h after wound scratching, the distance of the cells migrating to the scratch area was observed and measured under a microscope.

Matrigel Invasion Assay

BD Biosciences (San Jose, CA, USA) Matrigel invasion chamber was adopted for the cell invasion assay. The lower membrane at the bottom of the chamber was evenly smeared with a layer of Matrigel. After the Matrigel was dried, 100 μL of serum-free medium and 2×10^5 cells were added into the chamber, followed by incubation in a well plate with 10% FBS medium as the inducer. 36 h later, the cells in the upper layer at the chamber bottom were brushed off. The cells on the surface of the lower membrane were fixed with methanol and stained with 0.1% crystal violet. After washing with PBS for three times, the cells were counted under a microscope.

Western Blotting Assay

After the concentration was determined, 20 μg of total proteins were taken from each group for vertical electrophoresis using 11% separation gel for dodecyl sulfate, sodium salt-polyacrylamide gel electrophoresis (SDS-PAGE) under a voltage of 110 V for 90 min, followed by staining with Ponceau S, observation of the integrity of protein bands and membrane transfer under an electric current of 400 mA for 90 min. After that, the membrane was sealed in 5% skim milk for 2 h and incubated with Tris-buffered saline-Tween 20 (TBST)-diluted primary antibodies at 4°C overnight. Subsequently, the membrane was washed in TBST for 3 times, and secondary antibodies were added for incubation for 2 h, followed by washing with TBST again for 3 times, addition with chemiluminescent solution as the reaction substrate and exposure in a dark room. Finally, the exposed films were scanned to record the optical density of the objective bands and to calculate the relative content.

Luciferase Reporter Assay

TargetScan and PicTar were utilized to predict the potential target mRNAs of the target genes of miR-219-5p. It was shown in both databases that there was a latent binding sequence in the 3'-untranslated region (UTR) of HMGA2 mRNA that matched with miR-142-5p. The sequence fragments in the 3'-UTR of target gene HMGA2 that complementarily bind to mi-219-5p and the mutant (mut) HMGA2 3'-UTR sequence fragments were synthesized. Moreover, the mut HMGA2 3'-UTR fragments and predicted binding site of miR-219-5p in HMGA2 3'-UTR were cloned into the multiple cloning sites of downstream pGL3-Luciferase gene. Then, 293T cells were inoculated into a 24-well culture plate (1×10^5 cells/well) and co-transfected with Lipofectamine 2000 reagent, miR-219-5p mimic and luciferase plasmids containing HMGA2 3'-UTR or mut HMGA2 3'-UTR. The cells were harvested at 48 h after transfection to determine the activity of Dual-Luciferase as per the instructions of Dual-Luciferase reporter gene assay kit (Promega, Madison, WI, USA).

Statistical Analysis

All experiments were performed for at least three times independently. Data were expressed as mean ± standard deviation. Differences in means were compared using two-sided Student's *t*-tests. $p<0.05$ suggested a significant difference.

Results

MiR-219-5p Was Lowly Expressed in PCa Cell Lines and Human Tissues

To investigate the potential mechanism of miR-219-5p in PCa, the expression of miR-219-5p was detected by qRT-PCR in 30 pairs of PCa tissues

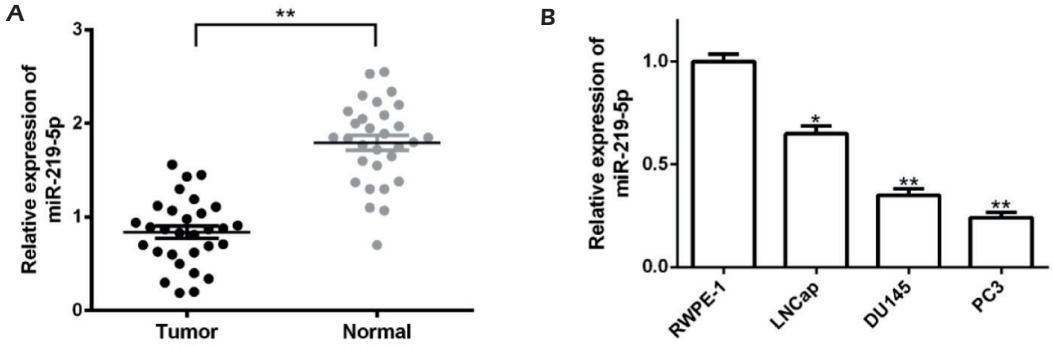

Figure 1. The expression of miR-219-5p in prostate cancer specimens and cell lines. **A,** Relative miR-219-5p expression in tumor and normal para-carcinoma tissues of 30 patients. **B,** Relative miR-219-5p expression of prostate cancer cell lines compared to that of normal prostatic epithelial cells (RWPE-1). Data are presented as means ± SD (n = 3). *$p < 0.05$, **$p < 0.01$ *vs.* control group.

cleaved-caspase-3, and cleaved-poly-ADP-ribose-polymerase (PARP) were further studied. Western blotting results revealed that the overexpressed miR-219-5p was able to up-regulate Bax, cleaved-caspase-3 and cleaved-PARP, and down-regulate Bcl-2 (Figure 2F).

MiR-219-5p Suppressed Migration and Invasion of PC-3 Cell Lines

Wound-healing and transwell assays were conducted to explore the regulatory effects of miR-219-5p on the invasive and migratory abilities of PC-3 cells. According to the results of wound-healing assay, the overexpression of miR-219-5p in the PC-3 cells could significantly suppress the migratory ability of the cells (Figure 3A, 3B). Similarly, it was displayed in the results of transwell assay that miR-219-5p overexpression could prominently restrain the invasive ability of PC-3 cells (Figure 3C). Huang et al[8] discovered that miR-219-5p is capable of inhibiting the metastasis of intestinal cancer by repressing epithelial-mesenchymal transition (EMT). Moreover, Western blotting was applied to detect the expressions of EMT-related proteins after overexpression of miR-219-5p, so as to study the regulatory role of miR-219-5 in EMT in the case of PCa. It was revealed that overexpressed miR-219-5p increased the expression of epithelial marker (E-cadherin) and decreased the expression of mesenchymal markers (N-cadherin and vimentin) distinctly (Figure 3D).

MiR-219-5p Directly Regulated HMGA2 in PC3 Cell Lines

Based on the prediction by TargetScan and PicTar bioinformatics software, there was a latent binding sequence in the 3'-UTR of HMGA2 mRNA matched with miR-219-5p (Figure 4A). In this research, qRT-PCR was further adopted to examine the mRNA expression level of HMGA2 in PCa tissues and para-carcinoma tissues, and the results demonstrated that the level was elevated remarkably in PCa tissues, which is in line with the findings in previous reports (Figure 4B). To inquire the regulation of miR-219-5p on HMGA2 in PC-3 cells, the expression level of HMGA2 after overexpression of miR-219-5p was measured *via* qRT-PCR and Western blotting. The results manifested that overexpressed miR-219-5p was able to inhibit the mRNA and protein expressions of HMGA2 in PC-3 cells (Figure 4C, 4D). Subsequently, Dual-Luciferase reporter gene assay was performed to verify whether HMGA2 3'-UTR can bind to the sequences of miR-219-5p, and it was shown that the transfection with miR-219-5p mimic could repress the luciferase activity in HMGA2 3'-UTR but could not suppress the luciferase activity in the mut 3'-UTR (Figure 4E). All these results confirm that miR-219-5p directly acts on the 3'-UTR of HMGA2 and inhibits the expression of HMGA2.

MiR-219-5p Suppressed Cell Growth and Metastasis Through Targeting HMGA2

The aforementioned findings suggest that miR-219-5p can suppress HMGA2 expression in PC-3 cells, so rescue experiment was conducted to further elaborate whether the inhibition of miR-219-5p on the proliferation and invasion of PC-3 cells is dependent on its regulation on HMGA2. According to Western blotting, the transfection with HMGA2 overexpression vector could markedly up-regulate the expression of HMGA2 in the PC-3 cells (Fig-

and normal para-carcinoma tissues (Figure 1A). It was found that the expression of miR-219-5p was markedly down-regulated in LNCap, DU145, and PC-3 cell lines compared with that in human prostatic epithelial cell line RWPE-1 (Figure 1B), suggesting that miR-219-5p may inhibit the occurrence and development of tumors.

MiR-219-5p Suppressed Proliferation and Induced Apoptosis of PC-3 Cell Lines

The above investigation indicated that the PC-3 cell lines exhibited the lowest expression level of miR-219-5p, so they were selected for further study. The expression level of miR-219-5 in the cells was regulated through transfection with miR-219-5p mimic to explore the anti-cancer effect of miR-219-5p in PCa cells (Figure 2A). MTT assay results manifested that the proliferative ability of PC-3 cells was weakened evidently after the transfection with miR-219-5p mimic in comparison with that in control group (Figure 2B). Consistent with the MTT assay results, the results of colony formation assay also indicated that overexpressed miR-219-5p could notably repress the proliferation of PC-3 cells (Figure 2C, 2D). Furthermore, flow cytometry (Annexin V-FITC/PI) was adopted to investigate the effect of miR-219-5p on cell apoptosis, and it was found that overexpressed miR-219-5p could remarkably increase the percentage of apoptotic PC-3 cells (Figure 2E). Besides, the impacts of miR-219-5p on the levels of apoptosis-related proteins such as B-cell lymphoma-2 (Bcl-2), Bcl-2-associated X protein (Bax),

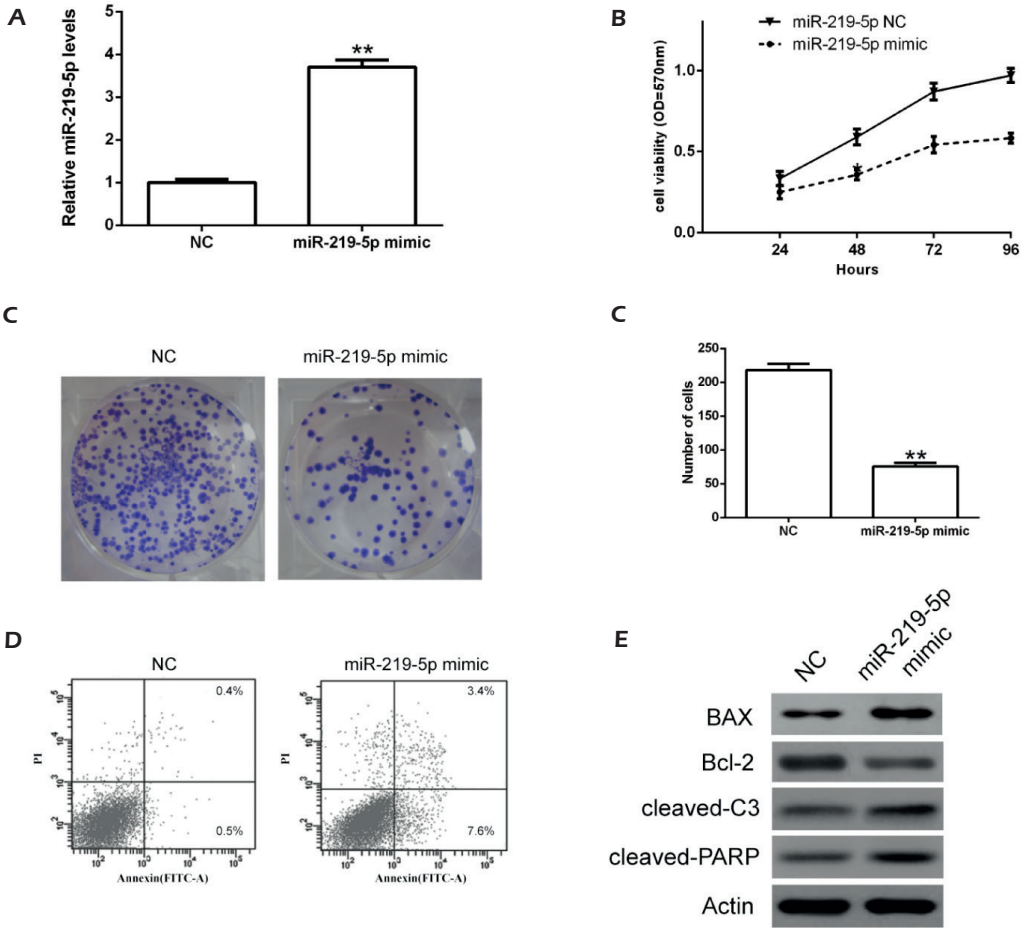

Figure 2. MiR-219-5p inhibits cell proliferation and induces apoptosis in PC-3 cells. **A,** Level of miR-219-5p in PC-3 cells transfected with miR-219-5p mimic or its negative control is detected using Real-time PCR analysis. **B,** Cell proliferation is detected after 24, 48, 72, and 96 h in two different groups by MTT. **C-D,** Cell proliferation is detected after 14 days in two different groups by colony formation assay (magnification: 10×). **E,** Percentage of apoptotic PC-3 cells in two different groups is detected by flow cytometry. **F,** Level of apoptosis-related proteins (Bcl-2, Bax, cleaved-caspase-3 and cleaved-PARP) in two different groups is detected by Western blotting. Data are presented as means ± SD (n = 3). *$p < 0.05$, **$p < 0.01$ *vs.* control group.

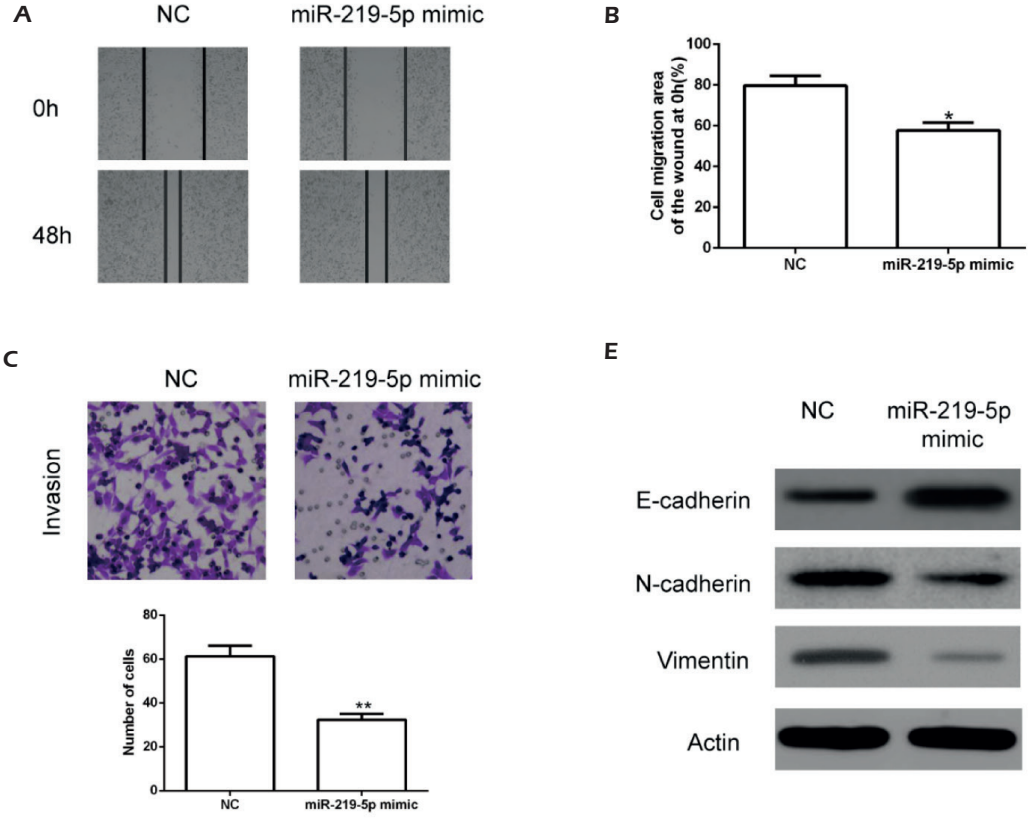

Figure 3. MiR-219-5p inhibits the migration and invasion of PC-3 cells. **A-C,** Migration and invasion capabilities of PC-3 cells transfected with miR-219-5p mimic or its negative control are detected by wound-healing and transwell assays (magnification: 40×). **D,** Expression of EMT-related proteins (E-cadherin, N-cadherin and vimentin) in two different groups is detected by Western blotting. Data are presented as means ± SD (n = 3). *$p < 0.05$, **$p < 0.01$ *vs.* control group.

ure 5A). The results of both MTT and colony formation assays displayed that overexpressed HMGA2 could evidently reverse the repression of miR-219-5p on the proliferation of PC-3 cells (Figure 5B, 5C). It was revealed in apoptosis assay that overexpressed HMGA2 could also reverse the apoptosis-inducing effect of miR-219-5p on PC-3 cells (Figure 5D). Consistent with the results of flow cytometry, the Western blotting results indicated that overexpressed HMGA2 reversed the up-regulation of Bax, cleaved-caspase-3 and cleaved-PARP, as well as the down-regulation of Bcl-2 by miR-219-5p (Figure 5D). According to the results of wound-healing and transwell assays, overexpressed HMGA2 partially reversed the inhibitory effects of miR-219-5p on PC-3 cell migration and invasion (Figure 5E). Interestingly, it was shown in the results of Western blotting that overexpressed HMGA2 equally reversed the up-regulation of E-cadherin, as well as the down-regulation of N-cadherin and vimentin by miR-219-5p (Figure 5F). All the above results demonstrate that miR-219-5p suppresses cell growth and metastasis by targeting HMGA2.

Discussion

MiR-219-5p has been proved to be related to the occurrence and development of multiple tumors, which is able to repress the proliferation and migration and accelerates the apoptosis of papillary thyroid carcinoma cells by targeting estrogen receptor[9]. It has also been reported that miR-219-5p can restrain the growth and metastasis of tongue squamous cell carcinoma cells by targeting PRKCI[10]. In this research, it was revealed that the expression levels of miR-219-5p in PCa tissues and cell lines were notably lower than those in normal para-carcinoma tissues and normal prostatic epithelial cell lines, implying that miR-219-5p

probably has correlations with the occurrence and development of PCa as a tumor suppressor. Next, miR-219-5p stable overexpression group was constructed and examined using MTT assay, colony formation assay, and apoptosis assay, and it was found that miR-219-5p overexpression could distinctly inhibit PC-3 cell proliferation and promote the apoptosis. Cell apoptosis is a process of programmed cell death, in which mitochondrion is a vital organelle, while Bax and Bcl-2 perform crucial functions in the modulation of mitochondrial apoptotic pathway. When the mitochondrion is affected by various stimulating factors, Bax can stimulate the opening of permeability transition pore to release cytochrome C and activate caspase cascade, thus leading to cell apoptosis. However, Bcl-2 can restrain the opening of permeability transition pore to antagonize the effects of Bax[11]. It was discovered in this research that miR-219-5p could up-regulate the expression of Bax and down-regulate that of Bcl-2, finally activating caspase-3 and PARP. It can be seen that miR-219-5p is able to facilitate PC-3 cell apoptosis by activating the mitochondrial pathway.

The EMT of tumor cells is the initial step and one of the most critical steps of invasion and metastasis. In the tumor cells with EMT, the expression of E-cadherin (an iconic protein of epithelial phenotype) is lowered, while those of N-cadherin and vimentin, proteins of

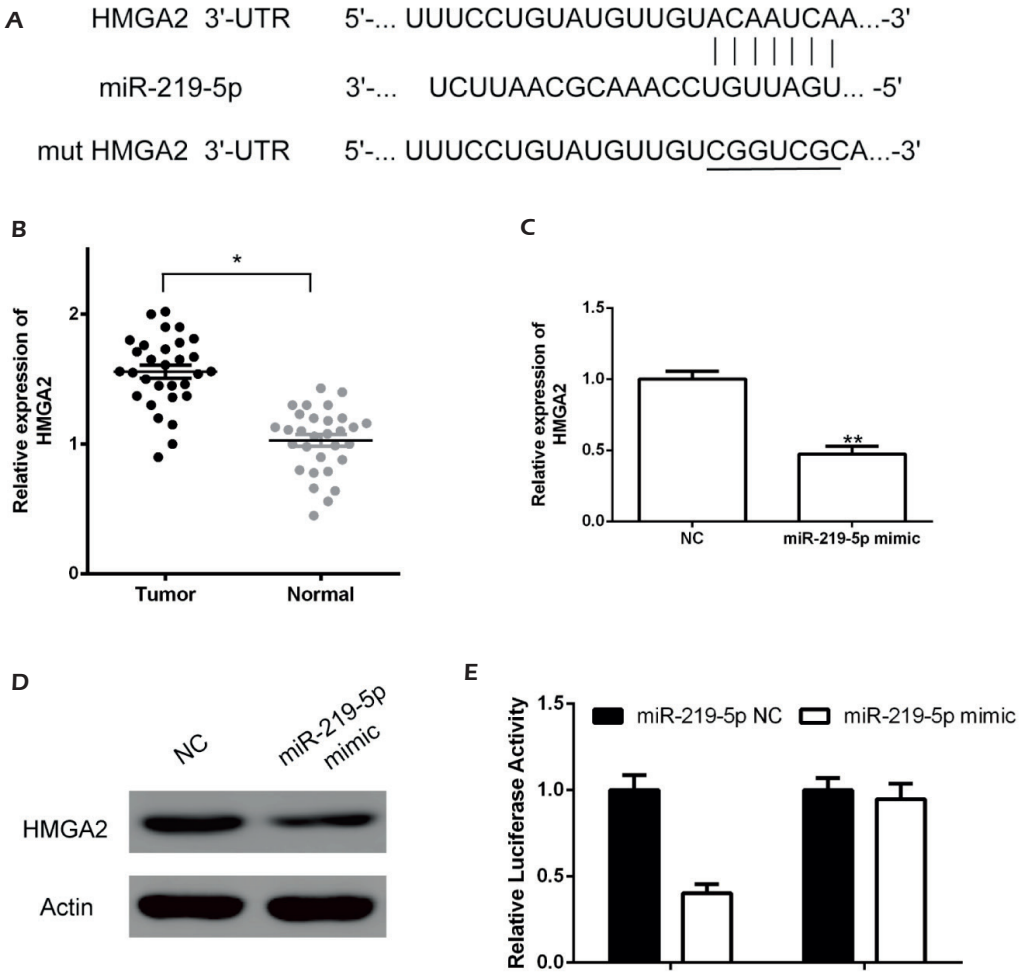

Figure 4. MiR-219-5p directly targets HMGA2. **A,** Predicted binding site of miR-219-5p in the 3'-UTR of HMGA2. **B,** Relative HMGA2 expression in tumor and normal para-carcinoma tissues of 30 patients. **C-D,** Expression of HMGA2 in PC-3 cells transfected with miR-219 mimic or its negative control. **E,** Luciferase activity of mimic group co-transfected with wild 3'-UTR construct is inhibited significantly compared to that of mutant construct groups. Data are presented as means ± SD (n = 3). *$p < 0.05$, **$p < 0.01$ *vs.* control group.

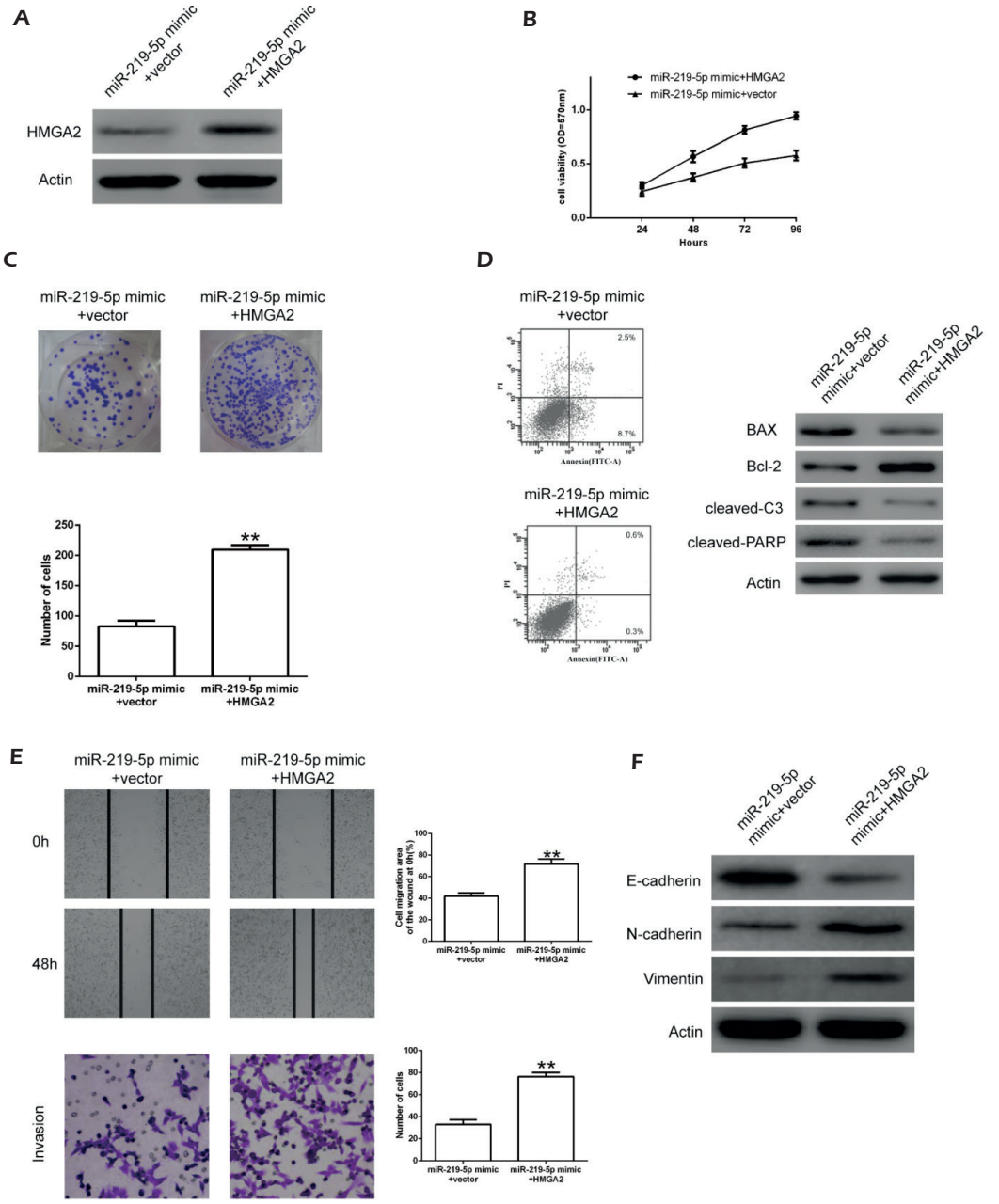

Figure 5. MiR-219-5p suppresses cell growth and metastasis through targeting HMGA2. **A,** Expression of HMGA2 in PC-3 cells after transfection with miR-219-5p mimic and HMGA2 vectors, or miR-219-5p mimic and empty vector control is analyzed through Western blotting. **B,** Cell proliferation is detected after 24, 48, 72 and 96 h in two different groups by MTT. **C,** Cell proliferation is detected after 14 days in two different groups by colony formation assay (magnification: 10×). **D,** Apoptotic PC-3 cells and apoptosis-related proteins (Bcl-2, Bax, cleaved-caspase-3, and cleaved-PARP) in two different groups are detected by flow cytometry or Western blotting. **E,** Wound-healing and transwell assays are conducted to analyze the migration and invasion capabilities of PC-3 cells in two different groups (magnification: 40×). **F,** Expression of EMT-related proteins in two different groups is detected by Western blotting. Data are presented as means ± SD (n = 3). $^{**}p < 0.01$ *vs.* control group.

mesenchymal phenotype, are raised, thereby attenuating the adhesion ability of tumor cells, enhancing the migratory ability and easily triggering distant metastasis[12]. Indeed, Huang et al[8] have reported the inhibition of miR-219-5p on EMT process in their study, that is, miR-219-5p can suppress the EMT of intestinal cancer cells through controlling lymphoid enhancer-binding factor 1. Based on the findings of this research, miR-219-5p was capable of repressing the inva-

sion and migration of PC-3 cells prominently. In addition, it was interesting that miR-219-5p could reverse the EMT of PC-3 cells, suggesting that miR-219-5p can inhibit the invasion and migration of tumor by reversing the EMT.

MiRNAs play their roles *via* the post-transcriptional regulation of corresponding target genes. Sun et al[13] revealed that miR-219-5p inhibits the proliferation and metastasis of non-small cell lung cancer cells through targeted inhibition of HMGA2 expression. Similarly, the prediction on basis of TargeTscan and PicTar indicated that HMGA2 might be one of the potential target genes of miR-219-5p. Furthermore, the Dual-Luciferase reporter assay results confirmed that HMGA2 was the target gene of miR-129-5p. HMGA2 exhibits high expression in a variety of malignant tumors and participates in the modulation of tumor proliferation, invasion, metastasis, drug resistance, etc[14,15]. It was clarified in this research that PCa tissues manifested higher expression of HMGA2 than normal prostatic tissues, which is consistent with the previous reports[16]. The subsequent function study indicated that overexpressed HMGA2 could reverse the inhibitory effects of miR-219-5p on the proliferation, invasion, and migration of PC-3 cells, further verifying that miR-219-5p exerts such inhibitory effects based on the targeted inhibition of HMGA2.

Conclusions

In summary, it was discovered in this research that the expression level of miR-219-5p is downregulated prominently in PCa tissues and cell lines. Interestingly, it was further found that miR-219-5p can suppress the proliferative, invasive, and migratory abilities and promote the apoptosis of PC-3 cells by repressing the expression of HMGA2. The anti-tumor effects of miR-219-5p on PCa and the possible mechanism were also revealed in this research, suggesting that miR-219-5p has the potential to become a target of gene therapy for PCa.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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