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PRINT: ISSN 0972-3757 ONLINE: ISSN 2456-6330
Int J Hum Genet, 23(4): 207-215 (2023)
DOI: 10.31901/24566322.2023/23.04.811

Role of miR-129-5p in Proliferation and Invasion of Prostate Cancer Cells

Yang Xu, Jing Wang, Bin Wang, Qingqiang Gao, Wen Yu and Zhipeng Xu*

Department of Andrology, Affiliated Drum Tower Hospital, Medical School of Nanjing University, Nanjing 210000, Jiangsu Province, P. R. China

KEYWORDS Invasion. miR-129-5p. Proliferation. Prostate Cancer

ABSTRACT The researchers were intended to inquire into the part of miR-129-5p in prostate cancer (PCa) cells. MiR-129-5p overexpression was achieved following transfection of miR-129-5p mimics into PCa PC-3 cells. Breeding as well as various treatments of nude mice was performed in a specific pathogen-free (SPF) environment. After successful construction of a transplanted tumour, 27 nude mice were randomly assigned into mimics-NC, control and miR-129-5p mimics groups (n=9). Following miR-129-5p overexpression, weakened invasion and migration abilities were noticed in PC-3 cells. The bioinformatics prediction results signified the existence of miR-129-5p binding sites in HOXC10. MiR-129-5p targeted and impeded HOXC10 expression. The miR-129-5p mimics group exhibited a notable diminution in the volume and weight of the transplanted tumour in contrast to the mimics-NC group ($P<0.05$). It shows the suppression of PCa PC-3 cell invasion and tumour tissue ontogenesis *in vivo* by miR-129-5p through regulating the protein level of HOXC10.

INTRODUCTION

As the second most common tumour in males in American and European countries (Lee et al. 2017), prostate cancer (PCa) displays lower incidence and mortality rates in China than those in European and American countries, but its incidence rate evidently rises along with the variations of diet, habits and lifestyle and the deterioration of environmental pollution (Han et al. 2013). In 2008, the crude incidence rate of PCa ranked seventh among all male malignancies in China (Peng et al. 2012). With the ageing population in China, more attention has been paid to the prevention and treatment of PCa. Hence, exploring the mechanisms of the onset and progression of PCa and finding effective and safe measures for its prevention and treatment are of great clinical significance.

As a class of small endogenous single-stranded non-coding RNAs containing 18-24 nucleotides, micro-ribonucleic acids (miRNAs) exert regulatory effects post-transcriptionally by dint of binding target messenger RNAs (mRNAs) (Böhm et al. 2020). MiRNAs are involved in the progression of PCa by regulating their downstream targets, as key regulators (Andresen et al. 2020; Injinari et al. 2021). As a member of the miR-129 family, miR-129-5p is the matured product of the 5' end of miR-129-1 and miR-129-2 that are precursors, and the major manifestation of their function (Yi et al. 2016). Furthermore, miR-129-5p has been affirmed in previous research to be aberrantly expressed in many tumours, which affects the biological behaviours of tumour cells, metastasis, proliferation, apoptosis and invasion, for instance (Fu et al. 2017; Wang and Yu 2018).

HOXC10 protein, as a transcription factor, is a member of the HOX family, which is situated on the human chromosome 12, with a size of 2017 bp (Enteghami et al. 2020). The unnatural expression of HOXC10 is closely implicated in the onset and progression of tumours (Miwa et al. 2019; Padam et al. 2021). However, the upstream modulating and controlling mechanism of HOXC10 or miR-129-5p binding site in HOXC10 stays unknown in the main.

Objectives

This study was intended to assess the impression on the proliferation of PCa cells by miR-129-5p as well as its mechanism of action.

MATERIAL AND METHODS

Cells, Animals and Main Reagents

PCa PC-3 cells were acquired from Xiehe Cell Bank of Chinese Academy of Sciences (China)

*Address for correspondence:
Zhipeng Xu
Telephone: +86-25-83106666
E-mail: 4515057@gmail.com

by means of a financial transaction. 4-5-week-old male BALB/c-nu nude mice were offered by Hunan SJA Laboratory Animal Co., Ltd. [licence number: SCXK (Hunan) 2016-0002, China]. Synthesis of PcDNA3-His C plasmids and miR-129-5p mimics plasmids overexpressing miR-129-5p was conducted by Shanghai Genechem Co., Ltd. (China). Roswell Park Memorial Institute (RPMI)-1640 (Gibco, USA), foetal bovine serum (FBS) (Thermo Fisher Scientific, USA), trypsin (Amersco, USA), a bicinchoninic acid protein assay kit from Beyotime Institute of Biotechnology, China, glyceraldehyde-3-phosphate dehydrogenase (GAPDH)-labelled goat anti-rabbit antibodies, HOXC10 and horseradish peroxidase (Cell Signalling, USA), Transwell chamber (Corning, USA), crystal violet and paraformaldehyde (PFA) (Soleibao Biotechnology Co., Ltd., China), Lipofectamine 2000 (Invitrogen, USA), and Trizol and reverse transcription kits (Thermo Fisher Scientific, USA) were used.

Cell Cultivation

After seeding into a culture flask, PC-3 cells were subjected to cultivation at 37°C with RPMI-l640 medium containing 100 U/mL penicillin, ten percent FBS and 100 U/mL streptomycin in a thermostat with five percent CO_2 and relative saturated humidity. The cells grew until adhering to the wall, during which refreshing of the medium for cultivation was conducted every two days. In the case that about ninety percent confluence was reached, they were digested with trypsin and passages about every 3 days. The harvesting of cells in the logarithmic growth phase was conducted for assays.

Cell Transfection and Grouping

Following seeding into 6-well plates at 5×10^5/well, the cells in the exponential growth phase in each well were added with 2 mL of preheated complete medium. After 24 hours of seeding, the cells grew to approximately fifty to sixty percent confluence. Next, gentle blending of serum-free RPMI-l640 medium (200 μL) and Lipofectamine 2000 reagent (5 μL) was performed, followed by standing in a wet room for 5 minutes. Afterwards, 100 pmol of miR-129-5p mimics (NC-mimics) was subjected to dilution with with 200 μL of serum-free RPMI-l640 medium through gentle blending. Later, the diluted miR-129-5p mimics (NC-mimics) was blended gently with Lipofectamine 2000 reagent and subjected to 20 minutes of standing at indoor temperature for the formation of the complex of miR-129-5p mimics (NC-mimics)/Lipofectamine 2000. Next, addition of solution (400 μL) containing the above complex into the wells with cells and complete medium (1600 μL) inside, followed by gentle shaking. Following 24-48 hour-cell incubation in the 37°C incubator with CO_2, the other post-transfection experimental operations were conducted. PC-3 cells were utilised as the control group, those transfected with NC-mimics were taken as the negative control group, and PC-3 cells subjected to transfection with miR-129-5p mimics were used as the miR-129-5p overexpression group.

Real-Time Polymerase Chain Reaction (PCR) for Detection of miR-129-5p mRNA Expression

Following digestion, cell centrifugation and harvesting were completed, and then the miRNA isolation kit of Thermo Fisher Scientific, USA, was employed for extracting miRNA. Thereafter, the TaqMan mRNA detection kit of Thermo Fisher Scientific, USA, was utilised for measurement of miR-129-5p expression. iQ5™ Real-Time PCR Detection System and SYBR Green II RNA gel stain (Bio-Rad, USA) were adopted for analyzing real-time PCR data. Correction was accomplished with U6RNA as an internal standard. $2^{-\Delta\Delta Ct}$ was exercised to evince the miR-129-5p relative expression, and the assay was conducted independently in triplicate.

Ascertainment of impact of miR-129-5p on Proliferation Ability of PC-3 Cells by Methyl Thiazolyl Tetrazolium (MTT) Assay

Following harvesting, digestion and cell density adjustment were conducted for PC-3 cells in the exponential growth phase to acquire a suspension of 6×10^4/mL. Later, cell seeding into a sterile 96-well plate was performed at 100 μL/well, followed by 0-, 24-, 36-, 48- and 72-hour-cultivation in the incubator, respectively. At 4 hours before the end of culture, the medium for cultivation was carefully aspirated, followed by supplementation of MTT solution (20 μL) into each

well. Following 4 hour-cultivation at 37°C, addition of dimethyl sulfoxide (150 μL) into each well and 20 minutes of shaking were conducted. Lastly, a microplate reader was employed for optical density (OD) reading at 450 nm, followed by the plotting of the growth curve with OD value as the ordinate and time (hours) as the abscissa.

Ascertainment of Effects of miR-129-5p on Invasion and Migration Abilities of PC-3 Cells by Transwell Assays

Following dilution with FBS-free RPMI-1640 at 1:8, Matrigel was plated in the base of the upper Transwell chamber and hydrated. Thereafter, cell dilution was implemented using RPMI-1640 medium with serum deprived, with the concentration adjusted to 1×10^5/mL. Then addition of cell suspension (200 μL) into the upper Transwell chamber, as well as addition of 500 μM of RPMI-1640 containing twenty percent FBS into the lower Transwell chamber was conducted. Afterwards, 24 hours of further cell cultivation was completed in an incubator. After bringing out the upper Transwell chamber, it was rinsed with pre-cooled phosphate-buffered saline twice, followed by gentle wiping off of the cells on the supine surface of the upper chamber. Next, cell fixation was implemented on a membrane with four percent PFA for 15 minutes and subjected to 2 hours of crystal violet staining at indoor temperature. Finally, a high-power microscope was adopted for observation of the number of invading cells under the chamber. Five visual fields were picked out in a random manner for photography, and cell counting was implemented employing Image-Pro Plus 6.0 software from Media Cybernetics (USA). The identical procedures to those in the invasion assay, but without Matrigel, were conducted in the migration assay.

Ascertainment of Targeting of miR-129-5p to HOXC10 by Luciferase Reporter Assay

The bioinformatics prediction web site (http://starbase.sysu.edu.cn/index.php) was put to use for the prediction of the miR-129-5p binding fragment in HOXC10. The HOXC10 sequence was amplified from normal breast cell MCF-10A by RT-PCR and inserted into pMIR-REPORT to construct HOXC10 wild-type (WT) plasmids, whereas the construction of HOXC10 mutant (Mut) plasmids was performed via mutation as reported before (Peng et al. 2020). MiR-129-5 mimics, HOXC10 CASC2 WT plasmids and HOXC10 Mut plasmids were transfected into MCF-7 cells respectively or simultaneously. The dual luciferase reporter gene assay kit from Thermo Fisher Scientific (USA) was employed for ascertainment of luciferase activity, and the firefly luciferase/Renilla luciferase activity was the reporter gene activity.

Ascertainment of HOXC10 Expression by Western Blotting

The extraction and quantification of total protein of cells were implemented. Following addition of the protein sample to the loading buffer, denaturation at e+95°C for 10 minutes was conducted. Later, the sample was added into wells and subjected to SDS-PAGE at 80 V for 2 hours. Thereafter, product transfer onto a membrane (90 V for 60 minutes) was conducted, followed by blocking with two percent BSA overnight. Subsequently, product washing employing Tris-buffered saline-Tween 20 (TBST) was implemented 4 times, and then product incubation was performed at 4°C with primary antibody overnight. Next, product washing again with TBST 4 times was conducted, followed by 1-hour incubation with secondary antibody at 37°C. After it was washed with TBST 4 times and reacted for 30 seconds, the developer was added to the imaging system for exposure and image capture. Protein relative expression computation was carried out with β-Actin as the internal reference.

Evaluation of Effects of miR-129-5p Mimics on Subcutaneously Transplanted PC-3 Cells

Breeding as well as various treatments of the nude mice was performed in a SPF room. The super-clean bench was cleaned with seventy-five percent ethanol solution after routine ultraviolet disinfection for 30 minutes, and then the left abdomen of the mouse was disinfected with alcohol cotton balls. Then the collected PC-3 cell soliquoid was extracted using a 1-mL inspirator, 100 μL of which was subcutaneously injected into the mouse's left abdomen (number of inoculated cells: about 1×10^6). After cell inoculation, breeding of nude mice was conducted in

the SPF room again. The presence of tumours with a diameter of more than 5 mm in the left abdomen 2 weeks later indicated the successful construction of the transplanted tumour. Afterwards, 27 nude mice were grouped into miR-129-5p mimics, control and mimics-NC groups (n=9) using a random number table. Then incomplete medium, miR-129-5p mimics and mimics-NC were intratumorally injected, respectively at 1×10^{10} viral particles/time (titer of each type of virus: 2×10^{11} pfu/mL; injection volume: 50 μL) for each nude mouse, twice weekly for two consecutive weeks. For the control group, the same dose of normal saline was administered using the above-mentioned method. Following the first administration, recording of transplanted tumour short and long diameters was implemented every three days. Then, the long diameter was multiplied by short diameter^2 to acquire tumour volume, followed by plotting of a growth curve of the tumour volume. Two weeks after tumour transplantation, cervical dislocation was adopted for the sacrificing of mice, followed by weighing of the transplanted tumour.

Statistical Analysis

The statistical analysis was implemented employing SPSS 16.0 software (IBM, USA). The measurement data in keeping with normal distribution were delineated as mean ± standard deviation. With regard to comparisons between groups, the independent *t*-test was adopted. P<0.05 signified that the difference was of statistical significance.

RESULTS

Construction of PC-3 cells Stably Overexpressing miR-129-5p

It was disclosed in RT-PCR result in Figure 1 that in contrast with control and NC groups, the miR-129-5p mimics group manifested a significantly incremental miR-129-5p expression (P<0.05), signifying that succeeded construction of the cells stably overexpressing miR-129-5p (Fig. 1).

Impact on Proliferation of PC-3 Cells by miR-129-5p Overexpression

According to MTT assay results in Figure 2, the cell proliferation rates at 24 hours, 48 hours and 72 hours significantly lowered in miR-129-5p mimic group in contrast to those in NC and control groups (P<0.05), while these cell proliferation rates were comparable between the latter two groups (P>0.05) (Fig. 2).

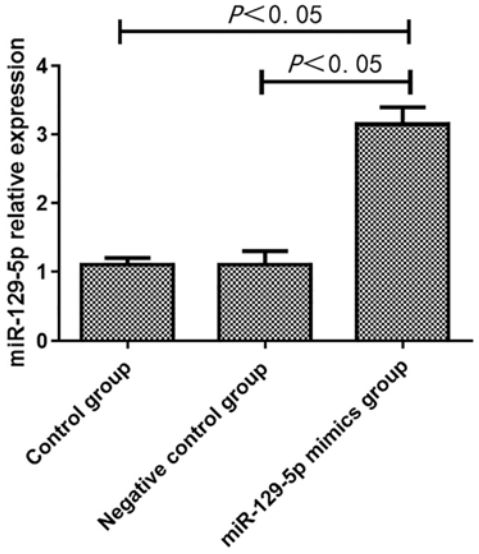

Fig. 1. mRNA expression of miR-129-5p in PC-3 cells ascertained by RT-PCR

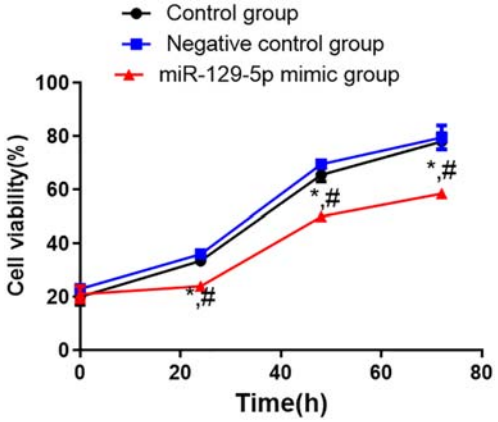

Fig. 2. Impact on proliferation of PC-3 cells by miR-29-5p overexpression. *P<0.05 *vs.* control group, #P<0.05 *vs.* control group

Impact on Migration and Invasion of PC-3 Cells by miR-129-5p Overexpression

The Transwell chamber assay results exhibited that the numbers of invasive and migrating

cells significantly declined in miR-129-5p overexpression group in contrast to those in NC and control groups (P<0.05), suggesting remarkable impediment on PC-3 cell invasion and migration by miR-129-5p overexpression (Fig. 3).

Targeted Impact on HOXC10 Expression by miR-129-5p

It was discovered through bioinformatics prediction that there existed miR-129-5p binding sites to HOXC10. The luciferase reporter assay results affirmed the prominent weakening attributed to miR-129-5p mimic of the luciferase activity of HOXC10 wild-type plasmids (P<0.05), while the activity of HOXC10 mutant plasmids was subjected to no significant impact (P>0.05). The HOXC10 expression showed an evident reduction in miR-129-5p mimic group in contrast to that in NC group and control group (P<0.001) that, however, manifested comparable HOXC10 expressions (P>0.05) (Fig. 4).

Impact on Subcutaneously Transplanted PC-3 Cells by miR-129-5p Mimic

Two weeks after tumour transplantation, the tumour growth in miR-129-5p mimic group witnessed an observable slowing in contrast to that in control and mimic-NC groups (P<0.05) that, however, manifested similar tumour growth (P>0.05). The transplanted tumour weight varied considerably between mimic-NC group and miR-129-5p mimic group [(0.24±0.08) g *vs.* (0.67±0.12) g, P<0.05], while mimic-NC and control groups had similar weights [(0.68±0.11) g]. Taken together, the tumour growth of PCa was slowed down due to miR-129-5p overexpression (Fig. 5), with the lightest transplanted tumour weight in miR-129-5p mimic group, in keeping with the curve showing the slowest tumour growth in this group.

DISCUSSION

PCa frequently occurs in elderly males, and its incidence rate ranks top among all malignan-

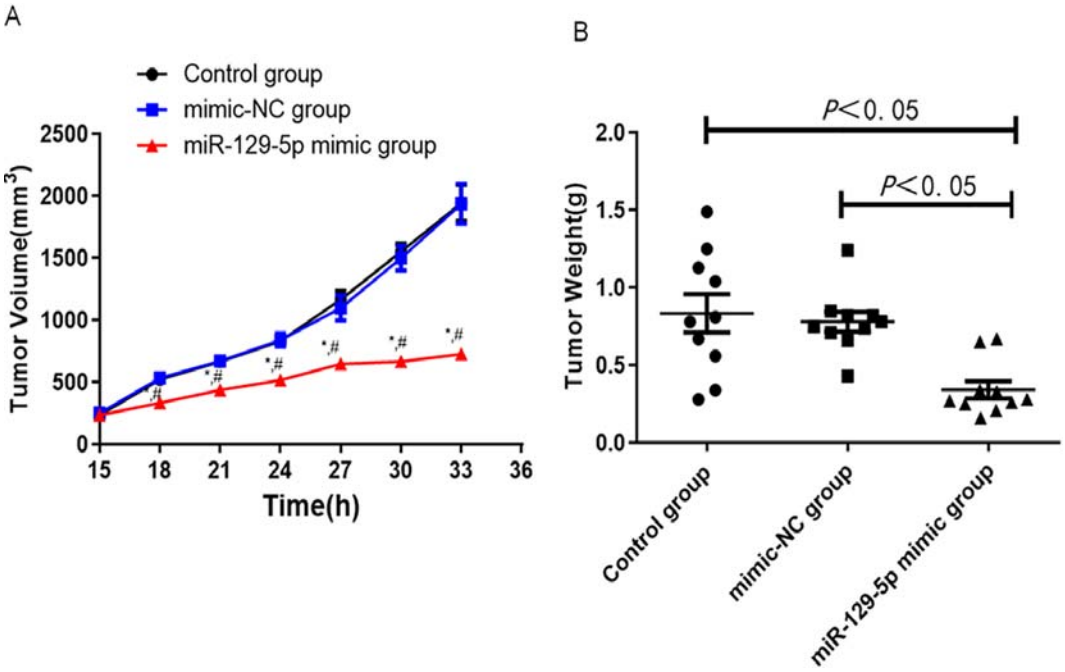

Fig. 5. Impact on subcutaneously transplanted PC-3 cells by miR-129-5p mimic
A: Growth curves of transplanted tumour
B: Transplanted tumour weights

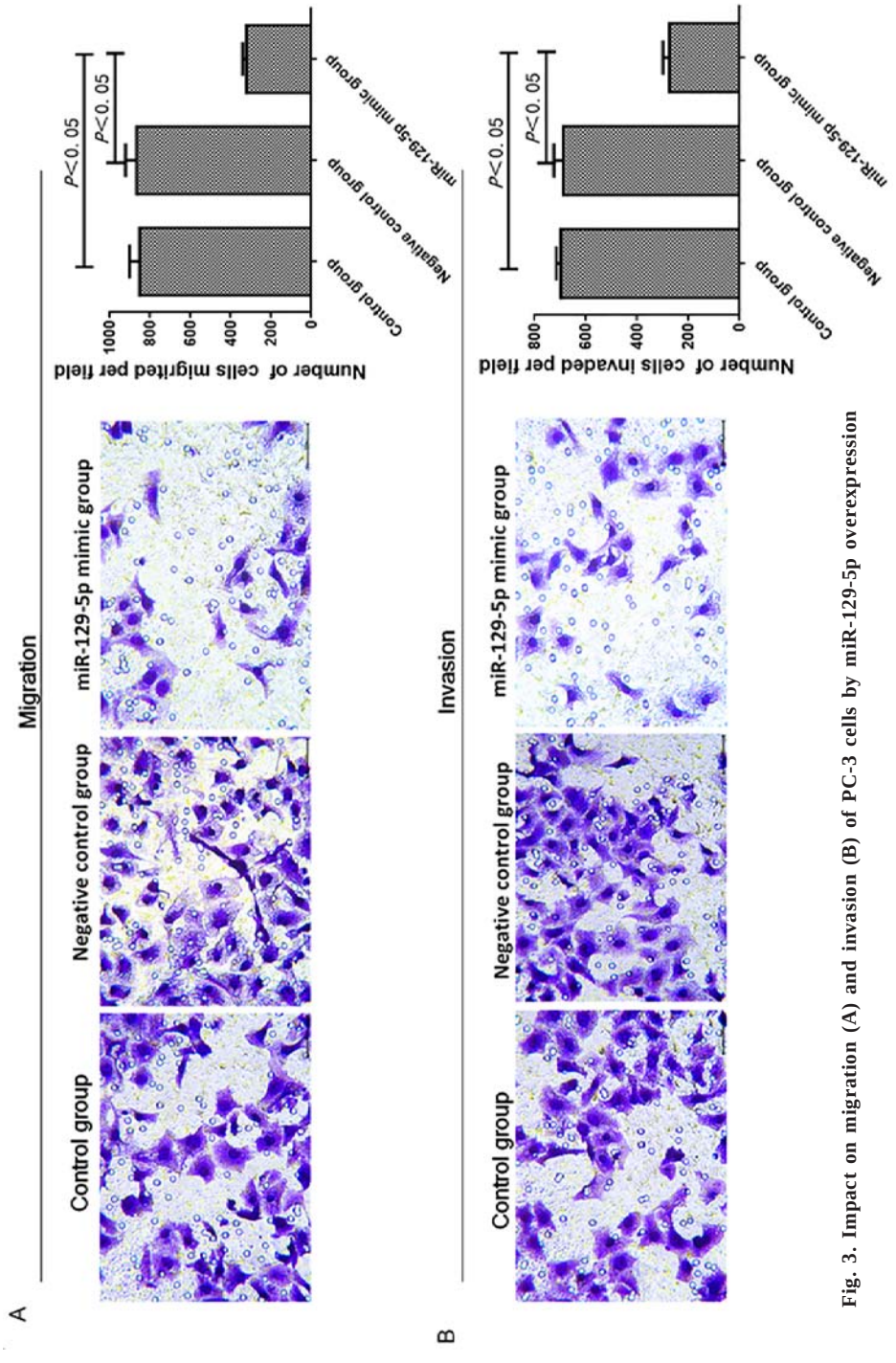

Fig. 3. Impact on migration (A) and invasion (B) of PC-3 cells by miR-129-5p overexpression

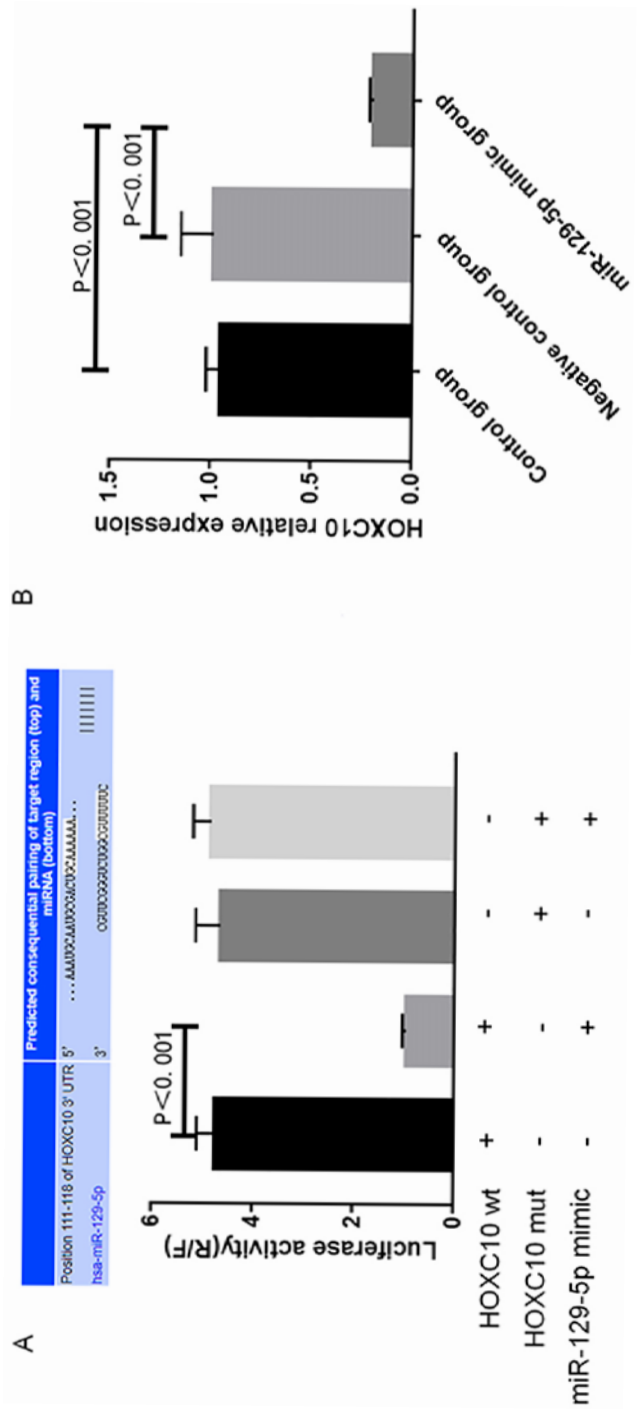

Fig. 4. Targeted impact on HOXC10 expression by miR-129-5p
A: Detection of miR-129-5p targeted binding to HOXC10 by means of luciferase assay

cies in developed countries (Wah et al. 2021). Novel targeted therapy that can selectively kill tumour cells and abate normal cell injury has been highlighted currently. MiRNAs have been proven to widely take part in the onset and progression of tumours, which have been closely related with the biological modulations of PCa (Xu et al. 2018).

In lung cancer, miR-129-5p works as a tumour suppresser and its increment in expression can suppress cell multiplication and promote programmed cell death (Li et al. 2019). In cervical cancer, targeted binding of miR-129-5p to Zic2 enables its repression on the Hedgehog signalling pathway, cell invasion and migration (Wang et al. 2018). In addition, in gastric cancer, miR-129-5p serves as a tumour suppresser gene, and its overexpression is capable of weakening the resistance of gastric cancer cell line SGC7901/ADR to chemotherapy (Wu et al. 2014). In gastric cancer tissues, miR-129-5p is expressed at a low level and targets interleukin-8 to take part in cell migration and invasion (Jiang et al. 2016). Moreover, miR-129-5p overexpression targets SPOCK1 by dint of binding the 3'-untranslated region, thus suppressing the viability, invasion and migration of SGC-7901 cells (Yan et al. 2017). Nevertheless, the part of miR-129-5p in PCa has seldom been reported. In this work, hence, miR-129-5p overexpression in PC-3 cells was achieved by lentiviral transfection. It was disclosed in the MTT assay that miR-129-5p overexpression impeded the growth of PC-3 cells. Besides, it was uncovered in the Transwell chamber assay that miR-129-5p overexpression group manifested a signal falling in numbers of cell invasion and migration in contrast to NC and control groups, indicating that such overexpression remarkably hindered PC-3 cell invasion and migration. In addition, a mouse transplanted tumour model was constructed to further validate the impression on tumour growth by miR-129-5p using *in vivo* experiments. After intratumoral injection of miR-129-5p, the tumour volume growth in this group following treatment was slowed down notably, and the tumour volume significantly dropped in this group in contrast with that in control and mimic-NC groups until the end of the experiment. Likewise, miR-129-5p mimic group manifested a marked drop in the weight of transplanted tumours in contrast to mimic-NC and control groups.

The rapid development of biological and computer-analytic technologies in recent years has greatly contributed to the analysis and identification of the target genes of miRNAs (Xu et al. 2020). In this work, prediction of the underlying target genes of miR-129-5p was conducted employing starBase, followed by selection of candidate genes from the intersection. Based on the TCGA database of gene expression profiling, the expressions of candidate genes in PCa were analysed. The findings revealed that compared with other candidate genes, HOXC10 was highly expressed in PCa. Thus, HOXC10 was used as the target gene for validation.

The HOXC10 promoter incorporates numerous G-tracts in its negative strand and possesses high potentiality of G-quadruplex structure formation, of which mutation or deletion affects the expression of HOXC10 (Zhang et al. 2018). Chromatin remodelling protein CHD7 of DNA helicase activity is capable of binding the HOXC10 promoter, possibly opening the G-quadruplex structure to give rise to an elevated gene expression (Dai et al. 2019). From the perspective of miRNAs, Zheng et al. (2017) reported that miR-136 targeted HOXC10 to impede peritoneal metastasis specific in gastric cancer. However, the mechanism through which HOXC10 boosts abnormal cell proliferation stays unknown. The results of luciferase reporter assay in this work affirmed the miR-129-5p's targeted binding to HOXC10, and the impediment on HOXC10 expression by up-regulating miR-129-5p expression.

CONCLUSION

MiR-129-5p impedes PCa PC-3 cell invasion and tumour tissue ontogenesis *in vivo* by modulating the level of HOXC10 protein. Thus, miR-129-5p acts as an underlying target for treating PCa.

RECOMMENDATIONS

Further animal and clinical studies are required to affirm the results of this study.

ABBREVIATIONS

- FBS: foetal bovine serum
- GAPDH: glyceraldehyde-3-phosphate dehydrogenase

- miRNA: micro-ribonucleic acid
- mRNA: messenger RNA
- MTT: methyl thiazolyl tetrazolium
- Mut: mutant
- OD: optical density
- PCa: prostate cancer
- PCR: polymerase chain reaction
- PFA: paraformaldehyde
- RPMI: Roswell Park Memorial Institute
- SPF: specific pathogen-free
- TBST: Tris-buffered saline-Tween 20
- WT: wild-type

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Paper received for publication in February, 2022
Paper accepted for publication in March, 2022