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Original Article

Exosomal miR-664a-5p as a therapeutic target biomarker for PARP inhibitor response in prostate cancer

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Abstract: This study investigated the role of urinary exosomal miR-664a-5p as a potential therapeutic target in prostate cancer (PCa). Small RNA sequencing of urinary exosomes from PCa patients with different responses to PARP inhibitors revealed that miR-664a-5p was significantly upregulated in responsive patients. Overexpression of miR-664a-5p enhanced the sensitivity of PCa cells to PARP inhibitors by directly targeting FOXM1, a transcription factor involved in DNA damage repair, leading to the downregulation of DNA damage response genes. Combined treatment with miR-664a-5p and olaparib synergistically inhibited tumor growth in a PC-3 xenograft mouse model. These findings suggest that urinary exosomal miR-664a-5p is a potential therapeutic biomarker for PARP inhibitor response in PCa patients, and targeting FOXM1 via miR-664a-5p represents a promising strategy for enhancing PARP inhibitor efficacy in PCa treatment.

Keywords: Prostate cancer, PARP inhibitor, miR-664a-5p, FOXM1

Introduction

Prostate cancer (PCa) is the most common cancer and the fifth leading cause of cancer-related deaths in men worldwide [1]. Despite advances in PCa treatment, patients with advanced or metastatic disease often develop resistance to conventional therapies, leading to poor prognosis [2]. Poly (ADP-ribose) polymerase (PARP) inhibitors have emerged as a promising therapeutic strategy for PCa, particularly in patients with defects in DNA damage reponse (DDR) genes, such as BRCA1/2 [3]. However, the clinical efficacy of PARP inhibitors is limited by the development of resistance, and there is a need to identify therapeutic targets that can enhance the response to these agents and overcome this limitation [4]. Identifying biomarkers that can predict response to PARP inhibitors and serve as potential therapeutic targets is crucial for improving treatment outcomes and developing personalized therapies for PCa patients.

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression post-transcriptionally by binding to the 3' untranslated region (UTR) of target mRNAs [5]. Accumulating evidence suggests that miRNAs play critical roles in PCa progression, metastasis, and therapeutic resistance [6]. Notably, several studies have reported that circulating miRNAs in blood or urine can serve as non-invasive biomarkers for PCa diagnosis and prognosis [7, 8]. However, the potential of urinary exosomal miRNAs as therapeutic targets and predictive biomarkers for PARP inhibitor response in PCa remains largely unexplored. The use of urinary exosomal miRNAs as biomarkers is particularly compelling due to the non-invasive nature of urine sampling, which offers an edge over other tissue-based biomarkers, typically requiring more invasive collection methods. This non-invasiveness aligns with the principles of precision medicine, aiming to reduce patient discomfort while providing tailored therapeutic strategies. Such an approach was effectively demonstrated by Jain et al., who validated urinary exosom-

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al miRNAs as reliable diagnostic and prognostic tools [8].

In this study, we aimed to identify urinary exosomal miRNAs that are differentially expressed in response to PARP inhibitors in metastatic castration-resistant prostate cancer (mCRPC) patients and investigate their potential as therapeutic targets. We hypothesized that certain miRNAs may regulate the expression of genes involved in DNA repair pathways, thereby influencing the sensitivity of PCa cells to PARP inhibitors. Furthermore, we sought to explore the molecular mechanisms underlying the interaction between the identified miRNAs and PARP inhibitor response, focusing on their potential roles in modulating the expression of DDR genes and forkhead box M1 (FOXM1).

Methods

Patients

The study protocol was approved and carried out in accordance with the approved guidelines by the Institutional Review Board at the Catholic University of Korea, Seoul St. Mary's Hospital (IRB approval No. MC20SNSI0161). Urine specimens of PCa patients who different responses to PARP inhibitors were obtained from the Korea Prostate Bank (Seoul, Republic of Korea) with informed consent.

Mid-stream urine specimens were collected before drug treatment, and were centrifuged at 2,500 rpm for 20 min at 4°C. The supernatant was transferred to new tubes and stored at -80°C.

Small RNA sequencing

Urinary exosome isolation, exosomal RNA extraction, library preparation, sequencing, and data analysis were performed as described in our previous study [9]. Briefly, urinary exosomes were isolated using ATPS (Exo2D, ExosomePlus, Gyeonggi, Republic of Korea) and exosomal total RNA was extracted using a miRNeasy Serum/Plasma Kit (Qiagen, Hilden, Germany). NEBNext Multiplex Small RNA Library Prep kit (New England BioLabs, Ipswich, MA, USA) was used for library construction, and high-throughput sequencing was performed on a NextSeq550 system (Illumina, San Diego, CA, USA). Sequence reads were mapped using Bowtie 2, and read counts were normalized using CPM + TMM method for comparison between samples.

Drugs and reagent

Olaparib (AZD2281, S1060), talazoparib (BMN 673, S7048), niraparib (MK-4827, S2741), and rucaparib (AG-014669, S1098) were purchased from Selleck Chemicals (Houston, TX, USA). Dimethyl sulfoxide (DMSO) and (2-hydroxypropyl)-β-cyclodextrin were purchased from Sigma-Aldrich (St. Louis, MO, USA). For *in vitro* experiments, all drugs were dissolved in DMSO and stored at -20°C. The final DMSO concentration did not exceed 0.1%.

MiR-664a-5p mimic (Assay ID: MC13213), miR-98-5p mimic (Assay ID: MC10426), miR-95-3p mimic (Assay ID: MC10147), and miRNA negative control (NC) mimic were purchased from Thermo Fisher Scientific (Waltham, MA, USA).

Cell lines and cell culture

C4-2B and 22Rv1 cells were obtained from the American Type Culture Collection (Manassas, VA, USA), and PC-3 cells were obtained from Korean Cell Line Bank (Seoul, Republic of Korea). All of three cell lines were cultured in RPMI 1640 medium (Gibco; Thermo Fisher Scientific, Inc.) supplemented with 10% fetal bovine serum (FBS; Gibco), 100 units/mL penicillin, and 0.1 mg/mL streptomycin (Gibco). Cultures were incubated at 37°C in a humidified atmosphere containing 5% CO_2. All cells were routinely tested and checked for the absence of mycoplasma.

MiRNA transfection and treatment

The cells were transfected with miR-664a-5p, miR-98-5p, miR-95-3p, and miR-NC using Lipofectamine™ RNAiMAX (Invitrogen; Thermo Fisher Scientific, Inc.) according to manufacturer's protocol. After 5 h of incubation, the medium was replaced and cell were treated with PARP inhibitors or DMSO. The PAPR inhibitor concentrations applied were as follows: for C4-2B cells, 2 μM olaparib, 20 nM talazoparib, 2 μM niraparib, and 10 μM rucaparib; for PC-3 cells, 5 μM olaparib and 0.2 μM talazoparib; and for 22Rv1 cells, 20 μM olaparib and 0.5 μM talazoparib.

Table 1. Sequence of primer for RT-qPCR

Gene	Forward sequence (5' to 3')	Reverse sequence (5' to 3')
FOXM1	TTCAGAACCCTTAGACCTCATC	GCTGAGGCTGTCATTCATTGTG
BRCA1	TCACAGTGTCCTTTATGTAAGAATG	ACTCCAAACCTGTGTCAAGC
BRCA2	CTTGCCCCTTTCGTCTATTTG	GTCGCCACTGGAGGTTGC
BRIP1	GGAAGAAGCAGGGAAAGCAG	GAGGCACTATTCTCTGATGACC
EXO1	CCTGCCCATTCAAGAAGTCATAG	TAATCACTCGTTCCACTCCCAC
RAD51	TTGTAGACAGTGCCACCGCC	AACATCGCTGCTCCATCCAC
B2M	TGCTGTCTCCATGTTTGATGTATCT	TCTCTGCTCCCCACCTCTAAGT

After the indicated time period, the cells were harvested and used for cellular and molecular analysis.

Cell viability assay

Cell viability was assessed using cell counting kit-8 (CCK-8, Dojindo, Rockville, MD, USA) according to the manufacturer's instructions. After 5 days of transfection and treatment, the supernatant was replaced with culture medium containing 10% CCK-8 reagent and incubated for an additional 1 h. Cell viability was indicated by the absorbance at 450 nm using a microplate reader (Molecular Devices, San Jose, CA, USA). All experiments were performed in triplicate.

Reverse transcription-quantitative polymerase chain reaction (RT-qPCR)

After 3 days of transfection and treatment, RNA extraction, cDNA synthesis and qPCR were carried out as previously described [10]. Relative gene expression was determined by normalizing to B2M using the $2^{-\Delta\Delta CT}$ method. Primer pairs used are listed in **Table 1**.

Western blot analyses

Cell lysates were prepared with PRO-PREP™ protein extraction solution (iNtRON Biotechnology Inc., Gyenggi, Republic of Korea). Proteins were separated by SDS-PAGE and transferred onto nitrocellulose membranes. The membranes were blocked and subsequently incubated overnight at 4°C with specific primary antibodies against FOXM1 (1:1000, Santa Cruz Biotechnology, Inc., Dallas, TX, USA) and β-actin (1:5000, Abcam, Cambridge, UK). The membranes were washed and then incubated with a horseradish peroxidase-conjugated horse anti-mouse or anti-rabbit IgG (GenDEPOT, Barker, TX, USA). The protein bands were visualized using an enhanced chemiluminescence detection kit (Thermo Fisher Scientific, Inc.), and detected using X-ray film [10].

Dual-luciferase reporter assays

The 3'UTR sequence of FOXM1 mRNA containing predicted target site of miR-664a-5p were chemically synthesized from Bioneer Corporation (Daejeon, Republic of Korea). Synthesized DNA fragments were inserted into the NheI and XbaI sites of pmirGLO (Promega Corporation, Madison, WI, USA), and identified by DNA sequencing assay. PC-3 cells were co-transfected with reporter plasmid and miRNA in 24-well plates using Lipofectamine® 2000 transfection reagent (Invitrogen). Luciferase activity was measured after incubation for 48 h using the Dual-Luciferase Reporter Assay System (Promega) according to the manufacturer's instructions. Firefly luciferase activity was normalized to renilla luciferase activity.

In vivo study

All experimental procedures were approved by the Institutional Animal Care and Use Committee of the Catholic University of Korea (CUMC-2022-0109-01). Five-week-old male BALB/c nude mice (body weight 20-25 g) were obtained from Orient Bio (Gyeonggi, Republic of Korea). The mice were injected subcutaneously in the flank with 1.5×10^6 PC-3 cells in 100 μL PBS with 100 μL Matrigel (Corning, NY, USA). When tumor volumes reached approximately 40 mm^3, the mice were randomly divided into four groups (n=6): (1) control group (vehicle + miR-NC); (2) olaparib group (olaparib + miR-NC); (3) miR-664a-5p group (vehicle + miR-664a-5p); (4) combination group (olaparib + miR-664a-5p).

For the *in vivo* experiments, olaparib was dissolved in 10% (2-hydroxypropyl)-β-cyclodextrin at a concentration of 50 mg/kg and administered via intraperitoneal injections 5 days a week. In vivo-jetPEI (Polyplus Transfection, Illkirch, France) was used as an *in vivo* delivery agent for miRNAs. The miRNA/in vivo-jetPEI complexes (miRNA 10 μg and in vivo-jetPEI reagent 1.2 μl for each mouse) were delivered intratumorally three times at 2-day intervals.

Tumor size was measured through the experimental period at 3-day intervals, and tumor volume was calculated as width^2 × length × 0.5. The mice were sacrificed after 10 days of treatment. Mice xenografts tissues were embedded in paraffin wax for immunohistochemical (IHC) assay using antibodies against Ki-67 (1:300, Abcam). Counter staining with hematoxylin was performed. Tissue sections were examined under a light microscope (Carl Zeiss Inc., Jena, Germany).

Statistical analyses

The results of *in vitro* experiments are expressed as mean ± SD (standard deviation), whereas the results of *in vivo* experiments are expressed as mean ± SE (standard error). Differences between values were analyzed using Student's *t* test or one-way analysis of variance (ANOVA) test in GraphPad Prism 5 (GraphPad Software, San Diego, CA, USA). *P*-values <0.05 were considered statistically significant.

Results

Identification of urinary exosomal miRNAs associated with PARP inhibitor response in PCa patients

We performed small RNA sequencing on urine samples from PCa patients (n=8) who exhibited different responses to olaparib and talazoparib. Hierarchical clustering analysis revealed distinct miRNA expression profiles between the response and non-response groups for both olaparib (**Figure 1A**) and talazoparib (**Figure 1B**). MiR-664a-5p was significantly upregulated in the response group for both PARP inhibitors, while miR-98-5p and miR-95-3p were upregulated in the non-response group (**Figure 1C**).

MiR-664a-5p enhances PARP inhibitor sensitivity in PCa cells

To validate the functional role of the identified miRNAs in PARP inhibitor response, we transfected PCa cell lines (C4-2B, PC-3, and 22Rv1) with miRNA mimics and assessed their sensitivity to olaparib and talazoparib using cell viability assays. Overexpression of miR-664a-5p significantly increased the sensitivity of all three cell lines to both PARP inhibitors (**Figure 2A**). Overexpression of miR-98-5p and miR-95-3p significantly increased the sensitivity of the C4-2B cells to both PARP inhibitors. In contrast, the overexpression of miR-98-5p and miR-95-3p in PC-3 cells increased sensitivity to olaparib, but had no effect on talazoparib. In 22Rv1 cells, overexpression of miR-98-5p and miR-95-3p did not affect the sensitivity to both PARP inhibitors (**Figure 2B**, **2C**). Overexpression of miR-664a-5p significantly enhanced the sensitivity of C4-2B cells to all four PARP inhibitors (**Figure 3**), suggesting that miR-664a-5p plays a crucial role in modulating the response to various PARP inhibitors in PCa cells.

MiR-664a-5p downregulates FOXM1 expression by directly targeting its 3'UTR

To identify the target genes of miR-664a-5p, we explored the miRWalk database and found a putative binding site for miR-664a-5p in the 3'UTR of FOXM1 mRNA. We investigated whether miR-664a-5p regulates FOXM1 expression in PCa cells. The predicted binding site between miR-664a-5p and FOXM1 3'UTR is shown in **Figure 4A**. Dual-luciferase reporter assays using a vector containing the 3'UTR of FOXM1 showed that miR-664a-5p significantly suppressed the luciferase activity of the FOXM1 3'UTR construct (**Figure 4B**), indicating that miR-664a-5p directly binds to the 3'UTR of FOXM1 to downregulate its expression. Overexpression of miR-664a-5p significantly reduced FOXM1 mRNA (**Figure 4C**) and protein levels (**Figure 4D**) in C4-2B, PC-3, and 22Rv1 cells.

MiR-664a-5p and olaparib synergistically suppress DDR gene expression

We examined the expression of four genes (BRCA2, BRIP1, EXO1, and RAD51) that are both targets of FOXM1 and key DDR genes in PCa cells treated with miR-664a-5p, olaparib, or their combination. Combined treatment with miR-664a-5p and olaparib led to a significant reduction in the expression of all four DDR genes compared to either treatment alone (**Figure 5A-C**).

Combined treatment with miR-664a-5p and olaparib synergistically inhibits PCa tumor growth in vivo

We evaluated the efficacy of combined miR-664a-5p and olaparib treatment in a PC-3

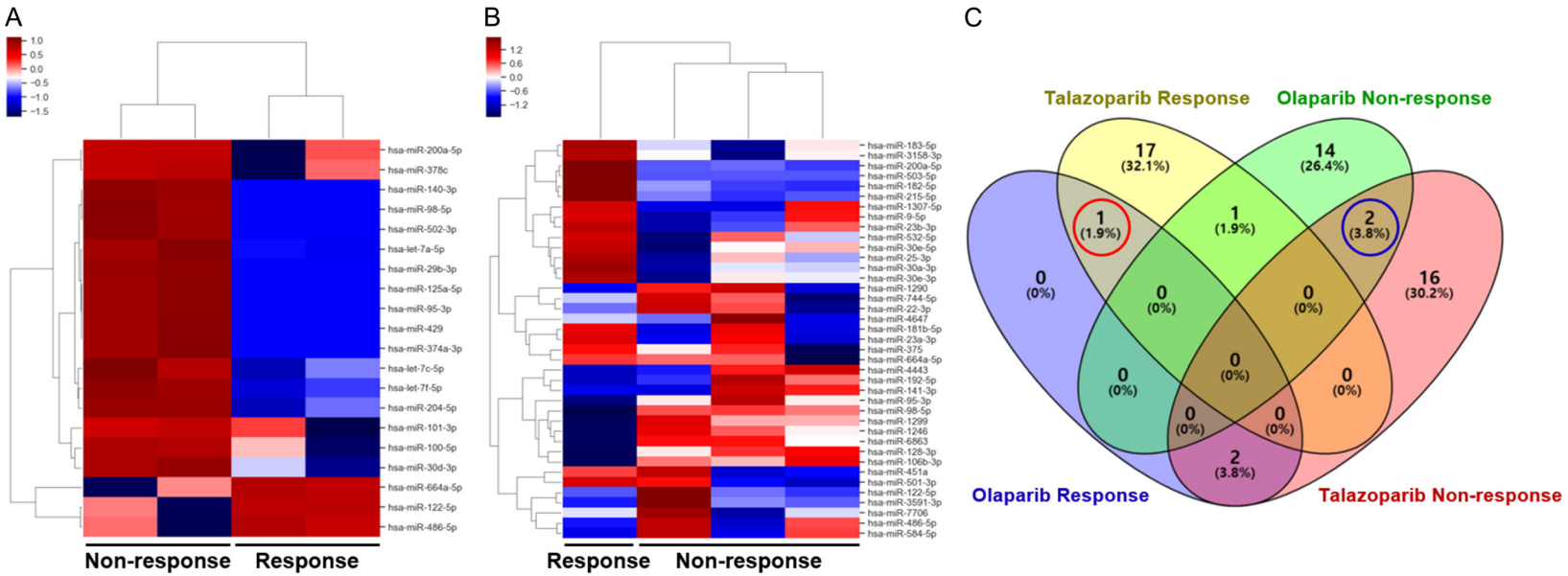

Figure 1. Small RNA sequencing for analysis of urinary exosomal miRNAs. A. Hierarchical clustering showing miRNAs differentially expressed in response to olaparib (fold-change >2, normalized read counts >6, *p*-value <0.05). B. Hierarchical clustering showing miRNAs differentially expressed in response to talazoparib (fold-change >2, normalized read counts >8). C. Venn diagram for the intersections between the four miRNA expression profiles. Red circle indicates miRNA that was found to be significantly upregulated in the response group of both olaparib and talazoparib. Blue circle indicates miRNA that was found to be significantly upregulated in the non-response group of both olaparib and talazoparib.

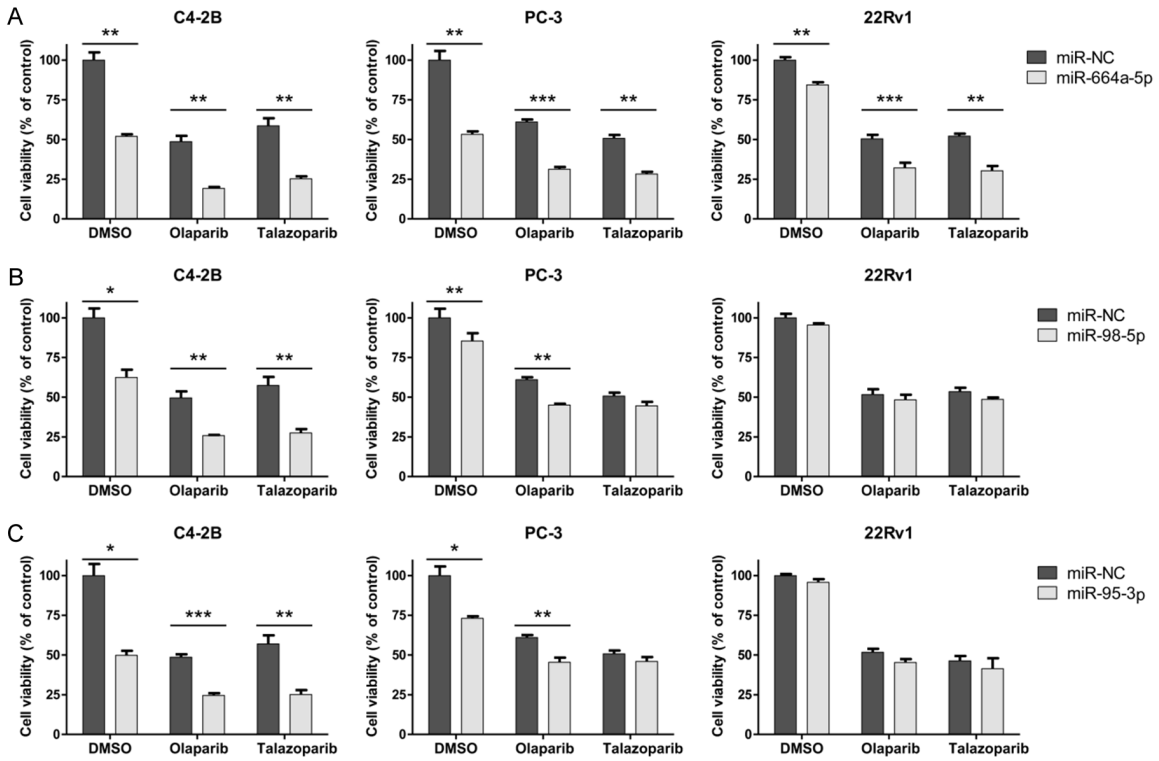

Figure 2. MiR-664a-5p increases sensitivity to a PARP inhibitor in prostate cancer cells. Three prostate cancer cells (C4-2B, PC-3, and 22Rv1) were transfected with miR-664a-5p mimic (A), miR-98-5p mimic (B), miR-95-3p mimic (C) or negative control miRNA mimic (miR-NC). Then, cells were incubated with olaparib or thalazoparib for 5 days, and cell viability was measured using the cell counting kit-8 assay. *P<0.05, **P<0.01, ***P<0.001. All data were presented as the mean ± SD of two experiments performed in triplicate.

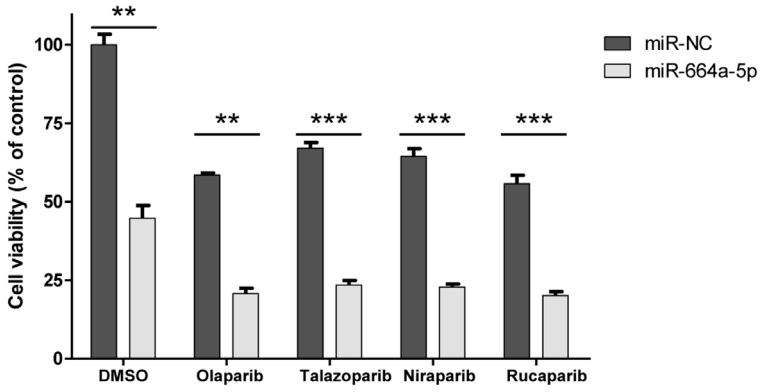

Figure 3. MiR-664a-5p enhances sensitivity to different PARP inhibitors. The C4-2B cells were transfected with miR-664a-5p mimic or negative control miRNA mimic (miR-NC), and then exposed to four different PARP inhibitors. After 5 days, cell viability was measured using the cell counting kit-8 assay. **P<0.01, ***P<0.001. Data was presented as the mean ± SD of two experiments performed in triplicate.

xenograft mouse model (**Figure 6A**). Mice treated with the combination therapy exhibited significantly reduced tumor growth compared to those treated with either miR-664a-5p or olaparib alone (**Figure 6B**). IHC analysis of the xenograft tumors revealed a significant decrease in Ki-67 positive cells in the combination treatment group (**Figure 6C**).

Discussion

In this study, we identified urinary exosomal miR-664a-5p as a potential therapeutic target for PARP inhibitor response in PCa patients. The differential expression of miR-664a-5p in response versus non-response groups suggests its critical involvement in modulating PARP inhibitor efficacy. Our findings demonstrate that miR-664a-5p enhances the sensitivity of PCa cells to PARP inhibitors by directly targeting FOXM1, a transcription factor involved in DDR and chemoresistance. Overexpression of miR-

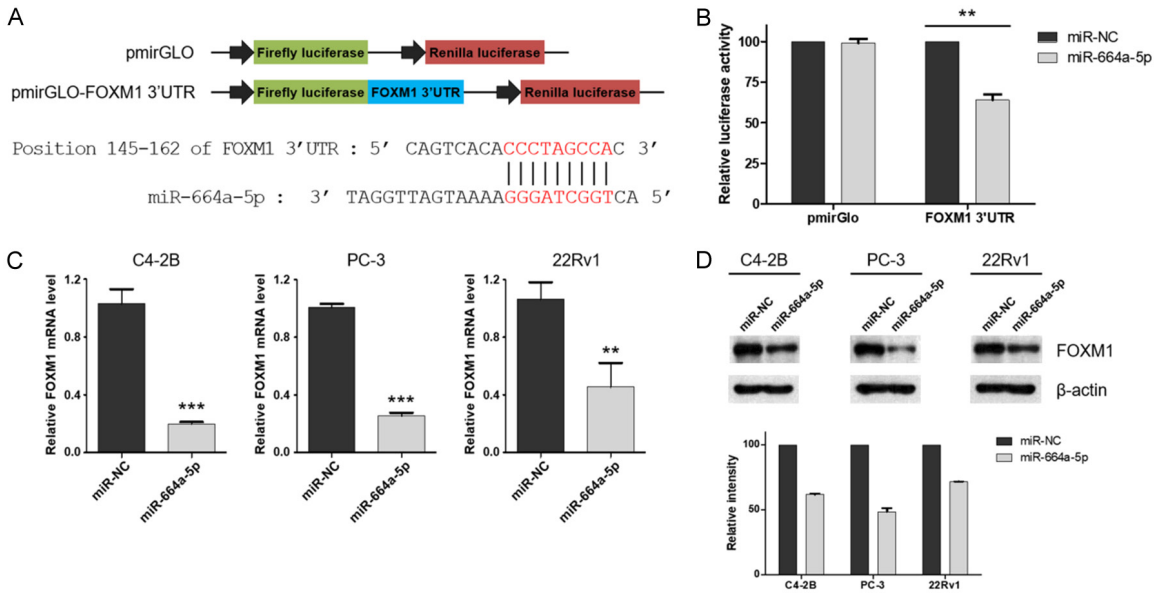

Figure 4. MiR-664a-5p directly targets to FOXM1. (A) Schematic structure of the dual luciferase reporter vector, and binding sites between miR-664a-5p and FOXM1 predicted through miRWalk. (B) PC-3 cells were co-transfected with FOXM1 3'UTR-luciferase reporter, and miR-664a-5p mimic or negative control miRNA mimic (miR-NC). After 48 h, relative luciferase activity of the reporter was evaluated by dual luciferase reporter analysis. 3'UTR: 3' untranslated region. (C, D) Three prostate cancer cells (C4-2B, PC-3, and 22Rv1) were transiently transfected with miR-664a-5p mimic or miR-NC mimic. After 3 days of transfection, FOXM1 mRNA (C) and protein (D) expression was determined by RT-qPCR and western blot analyses, respectively. β-actin was the loading control. **P<0.01, ***P<0.001. Data in (B and C) were presented as the mean ± SD of three experiments performed in triplicate.

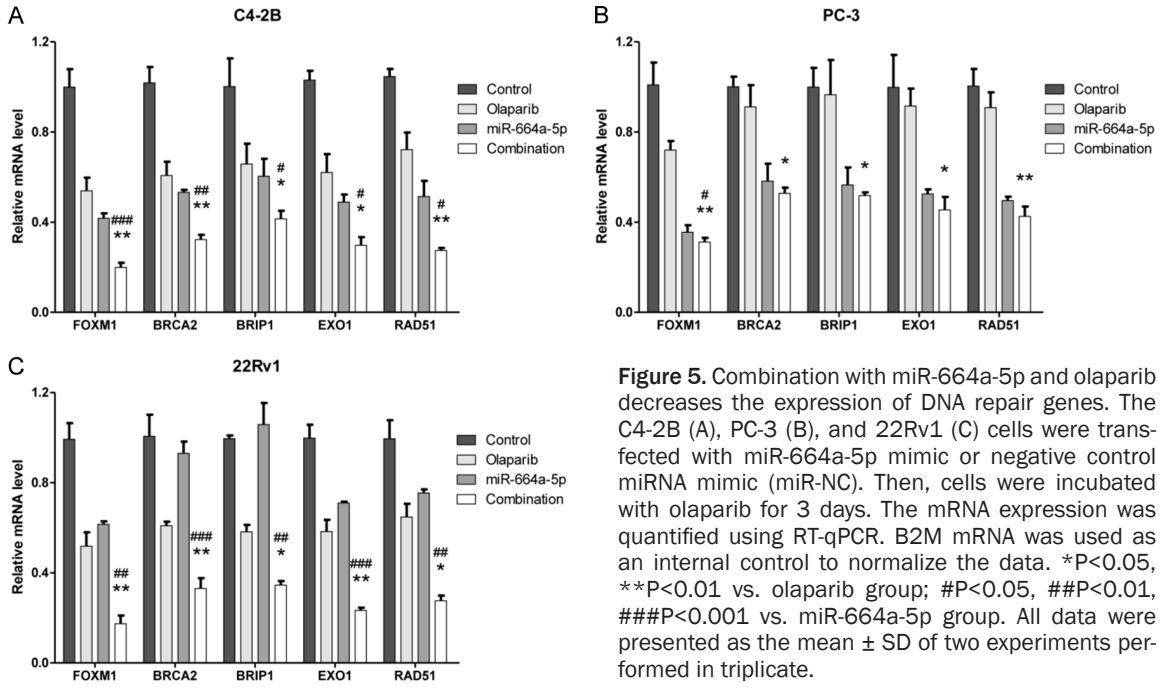

Figure 5. Combination with miR-664a-5p and olaparib decreases the expression of DNA repair genes. The C4-2B (A), PC-3 (B), and 22Rv1 (C) cells were transfected with miR-664a-5p mimic or negative control miRNA mimic (miR-NC). Then, cells were incubated with olaparib for 3 days. The mRNA expression was quantified using RT-qPCR. B2M mRNA was used as an internal control to normalize the data. *P<0.05, **P<0.01 vs. olaparib group; #P<0.05, ##P<0.01, ###P<0.001 vs. miR-664a-5p group. All data were presented as the mean ± SD of two experiments performed in triplicate.

664a-5p in PCa cells significantly reduced FOXM1 expression, leading to the downregulation of key DDR genes. Furthermore, combined treatment with miR-664a-5p and olaparib synergistically inhibited PCa tumor growth *in vivo*, suggesting that miR-664a-5p could be used as

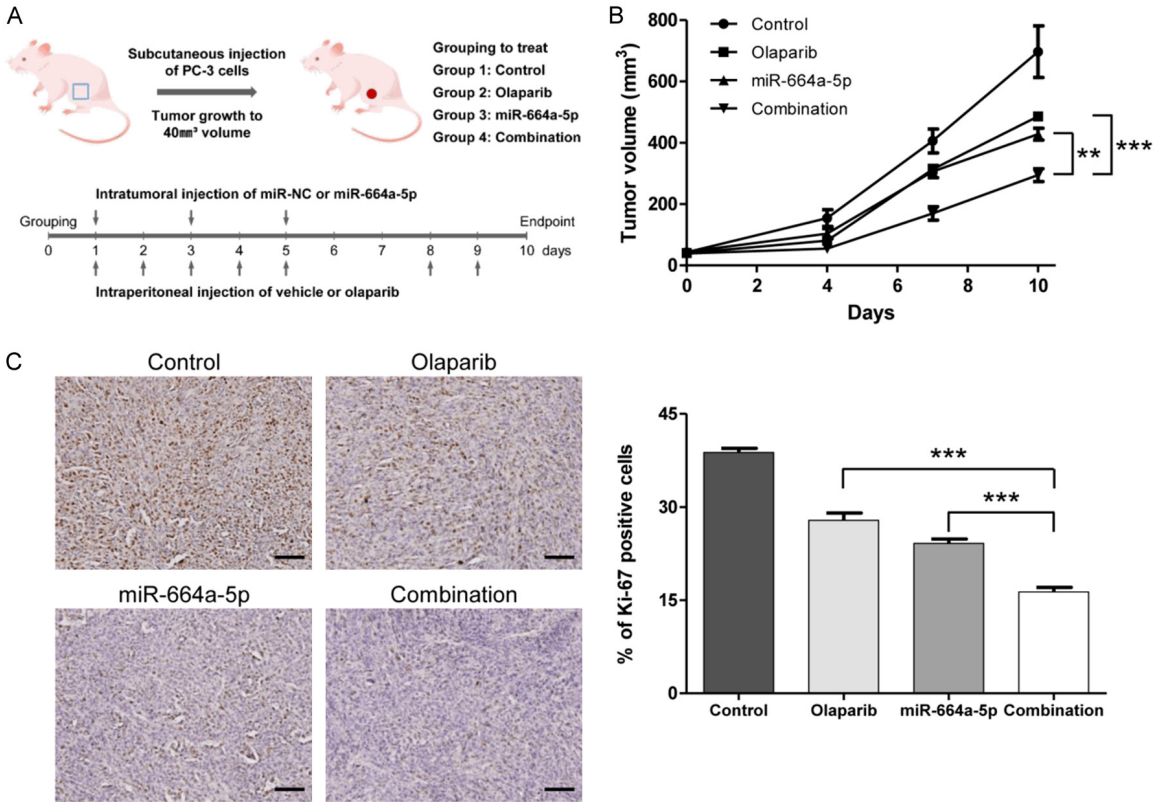

Figure 6. Combination with miR-664a-5p and olaparib inhibits tumor growth in vivo. A. Timeline of the establishment of PC-3 xenograft mouse model and combination treatment. B. Mean tumor volume of the four treatment groups (control, olaparib, miR-664a-5p, and combination) in the PC-3 xenograft model. C. Representative results of immunohistochemistry for Ki-67 in the four groups. The tumor tissues were stained using Ki-67 (brown), and the nuclei were counterstained with hematoxylin (blue). The bar graph represents the quantitative assessment of Ki-67 expression. Scale bar, 100 μm. **P<0.01, ***P<0.001. Data were presented as the mean ± SE (n=6).

a therapeutic agent in combination with PARP inhibitors.

Our findings are consistent with the emerging literature that underscores the role of miRNAs in cancer therapy resistance. Fabris et al. [7] highlighted the potential of miRNAs to influence drug resistance mechanisms in prostate cancer and emphasized the need to validate their translational potential in clinical management. This provided a basis for our study, where we identified that miR-664a-5p modulates sensitivity to PARP inhibitors by targeting and downregulating FOXM1, a known regulator of DDR genes. FOXM1 is a transcription factor that regulates cell cycle progression, DDR, and chemoresistance in various cancers, including PCa [11-13]. Recent studies have shown that FOXM1 overexpression is associated with poor prognosis and resistance to chemotherapy and radiotherapy in PCa [10, 14, 15]. Moreover, FOXM1 has been implicated in the regulation of DDR genes, such as BRCA1/2 and RAD51, suggesting its potential involvement in PARP inhibitor resistance [16, 17].

Various studies have highlighted the role of different miRNAs in PCa, emphasizing their potential as diagnostic, prognostic, and therapeutic targets. For example, miR-301a has been identified as strongly correlated with PCa recurrence and metastasis, making it a promising biomarker for tracking disease progression [18]. Similarly, miR-375 and miR-141 are significantly upregulated in PCa and are associated with high-risk tumors and advanced disease stages, which suggests their potential utility in clinical assessments of PCa severity and progression [19]. In addition, Duca et al. recently reported that miR-19b-3p and miR-101-3p were differentially expressed in prostate cancer tissues and their altered levels were associated with various clinical parameters, suggesting their potential as non-invasive biomarkers for

prostate cancer diagnosis and prognosis [20]. Another study highlights the differential expression of miRNAs like miR-130a, miR-181, and miR-328, which are associated with drug resistance and epithelial-to-mesenchymal transition in PCa. This indicates that certain miRNAs can influence the cellular mechanisms underlying therapy resistance and metastatic potential, presenting a targeted approach for therapeutic intervention [21].

In addition to the aforementioned miRNAs, recent studies have highlighted the involvement of miR-664a-5p in diverse biological processes and diseases, including cancer. While the direct association between miR-664a-5p and PCa has not been studied, its involvement in other cancer types and cellular processes suggests that it may also play a role in PCa. For instance, a study by Xiao et al. suggested that plasma miR-664a-5p levels were associated with lung cancer risk in a Chinese case-control study, indicating its potential as a biomarker for cancer diagnosis [22]. Additionally, miR-664a-5p has been implicated in the regulation of cellular processes such as neuronal differentiation [23], apoptosis, and mitochondrial homeostasis in vascular smooth muscle cells [24], as well as osteogenic differentiation of human bone marrow-derived mesenchymal stem cells [25]. These findings suggest that miR-664a-5p may have a broader impact on cellular mechanisms that are also relevant to cancer progression, such as cell differentiation, apoptosis, and cellular homeostasis.

However, several limitations must be acknowledged. The sample size of our study was relatively small, which may affect the generalizability of our results. Furthermore, while our study focused on mCRPC patients, the variability in treatment backgrounds across studies can complicate direct comparisons of biomarker efficacy. Additionally, the miRNA regulatory networks are immensely complex, and the roles of other miRNAs and their potential interactions were not explored in depth in this study. Future studies should aim to delineate these networks more comprehensively and include larger, more diverse patient cohorts to validate the clinical utility of miR-664a-5p and other miRNAs.

In conclusion, our study identifies urinary exosomal miR-664a-5p as a potential therapeutic target for PARP inhibitor response in PCa patients. The synergistic effect of miR-664a-5p and olaparib in suppressing PCa tumor growth provides a rationale for the development of miRNA-based therapies in combination with PARP inhibitors for the treatment of PCa.

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Disclosure of conflict of interest

None.

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References

[1] Leslie SW, Soon-Sutton TL, R IA, Sajjad H and Skelton WP. Prostate Cancer. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Taylor Soon-Sutton declares no relevant financial relationships with ineligible companies. Disclosure: Anu R I declares no relevant financial relationships with ineligible companies. Disclosure: Hussain Sajjad declares no relevant financial relationships with ineligible companies. Disclosure: William Skelton declares no relevant financial relationships with ineligible companies.: StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC.; 2024.

[2] Nuhn P, De Bono JS, Fizazi K, Freedland SJ, Grilli M, Kantoff PW, Sonpavde G, Sternberg CN, Yegnasubramanian S and Antonarakis ES. Update on systemic prostate cancer therapies: management of metastatic castration-resistant prostate cancer in the era of precision oncology. Eur Urol 2019; 75: 88-99.

[3] Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, Nava Rodrigues D, Robinson D, Omlin A, Tunariu N, Boysen G, Porta N, Flohr P, Gillman A, Figueiredo I, Paulding C, Seed G, Jain S, Ralph C, Protheroe A,

Hussain S, Jones R, Elliott T, McGovern U, Bianchini D, Goodall J, Zafeiriou Z, Williamson CT, Ferraldeschi R, Riisnaes R, Ebbs B, Fowler G, Roda D, Yuan W, Wu YM, Cao X, Brough R, Pemberton H, A'Hern R, Swain A, Kunju LP, Eeles R, Attard G, Lord CJ, Ashworth A, Rubin MA, Knudsen KE, Feng FY, Chinnaiyan AM, Hall E and de Bono JS. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015; 373: 1697-1708.

[4] Olivieri M, Cho T, Álvarez-Quilón A, Li K, Schellenberg MJ, Zimmermann M, Hustedt N, Rossi SE, Adam S, Melo H, Heijink AM, Sastre-Moreno G, Moatti N, Szilard RK, McEwan A, Ling AK, Serrano-Benitez A, Ubhi T, Feng S, Pawling J, Delgado-Sainz I, Ferguson MW, Dennis JW, Brown GW, Cortés-Ledesma F, Williams RS, Martin A, Xu D and Durocher D. A genetic map of the response to DNA damage in human cells. Cell 2020; 182: 481-496, e421.

[5] Bartel DP. Metazoan microRNAs. Cell 2018; 173: 20-51.

[6] Lo UG, Yang D and Hsieh JT. The role of microRNAs in prostate cancer progression. Transl Androl Urol 2013; 2: 228-241.

[7] Fabris L, Ceder Y, Chinnaiyan AM, Jenster GW, Sorensen KD, Tomlins S, Visakorpi T and Calin GA. The potential of microRNAs as prostate cancer biomarkers. Eur Urol 2016; 70: 312-322.

[8] Jain G, Das P, Ranjan P, Neha, Valderrama F and Cieza-Borrella C. Urinary extracellular vesicles miRNA-A new era of prostate cancer biomarkers. Front Genet 2023; 14: 1065757.

[9] Kim MY, Shin H, Moon HW, Park YH, Park J and Lee JY. Urinary exosomal microRNA profiling in intermediate-risk prostate cancer. Sci Rep 2021; 11: 7355.

[10] Kim MY, Jung AR, Shin D, Kwon H, Cho HJ, Ha US, Hong SH, Lee JY, Kim SW and Park YH. Niclosamide exerts anticancer effects through inhibition of the FOXM1-mediated DNA damage response in prostate cancer. Am J Cancer Res 2021; 11: 2944-2959.

[11] Liao GB, Li XZ, Zeng S, Liu C, Yang SM, Yang L, Hu CJ and Bai JY. Regulation of the master regulator FOXM1 in cancer. Cell Commun Signal 2018; 16: 57.

[12] Park YY, Jung SY, Jennings NB, Rodriguez-Aguayo C, Peng G, Lee SR, Kim SB, Kim K, Leem SH, Lin SY, Lopez-Berestein G, Sood AK and Lee JS. FOXM1 mediates Dox resistance in breast cancer by enhancing DNA repair. Carcinogenesis 2012; 33: 1843-1853.

[13] Chen L, Wu M, Ji C, Yuan M, Liu C and Yin Q. Silencing transcription factor FOXM1 represses proliferation, migration, and invasion while inducing apoptosis of liver cancer stem cells by regulating the expression of ALDH2. IUBMB Life 2020; 72: 285-295.

[14] Aytes A, Mitrofanova A, Lefebvre C, Alvarez MJ, Castillo-Martin M, Zheng T, Eastham JA, Gopalan A, Pienta KJ, Shen MM, Califano A and Abate-Shen C. Cross-species regulatory network analysis identifies a synergistic interaction between FOXM1 and CENPF that drives prostate cancer malignancy. Cancer Cell 2014; 25: 638-651.

[15] Lin JZ, Wang ZJ, De W, Zheng M, Xu WZ, Wu HF, Armstrong A and Zhu JG. Targeting AXL overcomes resistance to docetaxel therapy in advanced prostate cancer. Oncotarget 2017; 8: 41064-41077.

[16] Fang P, Madden JA, Neums L, Moulder RK, Forrest ML and Chien J. Olaparib-induced adaptive response is disrupted by FOXM1 targeting that enhances sensitivity to PARP inhibition. Mol Cancer Res 2018; 16: 961-973.

[17] Hegan DC, Lu Y, Stachelek GC, Crosby ME, Bindra RS and Glazer PM. Inhibition of poly(ADP-ribose) polymerase down-regulates BRCA1 and RAD51 in a pathway mediated by E2F4 and p130. Proc Natl Acad Sci U S A 2010; 107: 2201-2206.

[18] Nam RK, Benatar T, Wallis CJ, Amemiya Y, Yang W, Garbens A, Naeim M, Sherman C, Sugar L and Seth A. MiR-301a regulates E-cadherin expression and is predictive of prostate cancer recurrence. Prostate 2016; 76: 869-884.

[19] Brase JC, Johannes M, Schlomm T, Fälth M, Haese A, Steuber T, Beissbarth T, Kuner R and Sültmann H. Circulating miRNAs are correlated with tumor progression in prostate cancer. Int J Cancer 2011; 128: 608-616.

[20] Duca RB, Massillo C, Dalton GN, Farré PL, Graña KD, Gardner K and De Siervi A. MiR-19b-3p and miR-101-3p as potential biomarkers for prostate cancer diagnosis and prognosis. Am J Cancer Res 2021; 11: 2802-2820.

[21] Verma S, Pandey M, Shukla GC, Singh V and Gupta S. Integrated analysis of miRNA landscape and cellular networking pathways in stage-specific prostate cancer. PLoS One 2019; 14: e0224071.

[22] Xiao Y, Liu C, Fu Y, Zhong G, Guan X, Li W, Wang C, Hong S, Fu M, Zhou Y, You Y, Wu T, Zhang X, He M, Li Y and Guo H. Mediation of association between benzo[a]pyrene exposure and lung cancer risk by plasma microRNAs: a Chinese case-control study. Ecotoxicol Environ Saf 2024; 271: 115980.

[23] Watanabe K, Yamaji R and Ohtsuki T. MicroRNA-664a-5p promotes neuronal differentiation of SH-SY5Y cells. Genes Cells 2018; 23: 225-233.

[24] Yang Y, Li M, Liu Y, Wang Z, Fu X, He X, Wang Q, Li XX, Ma H, Wang K, Zou L, Wang JX and Yu T. The lncRNA punisher regulates apoptosis and mitochondrial homeostasis of vascular smooth muscle cells via targeting miR-664a-5p and OPA1. Oxid Med Cell Longev 2022; 2022: 5477024.

[25] Zhang Y, Liu Y, Wu M, Wang H, Wu L, Xu B, Zhou W, Fan X, Shao J and Yang T. MicroRNA-664a-5p promotes osteogenic differentiation of human bone marrow-derived mesenchymal stem cells by directly downregulating HMGA2. Biochem Biophys Res Commun 2020; 521: 9-14.