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MiR-203 over-expression promotes prostate cancer cell apoptosis and reduces ADM resistance

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Abstract. – OBJECTIVE: Extra-cellular signal regulated kinase (ERK)/mitogen activated protein kinase (MAPK) signaling pathway is widely involved in cell proliferation, apoptosis, and drug resistance. MAPK kinase 1 (MEK1) is the upstream protein kinase of ERK that can activate ERK/MAPK signaling pathway. microRNA 203 (MiR-203) down-regulation is found to be associated with prostate cancer pathogenesis. Bioinformatics analysis showed the complementary targeted relationship between miR-203 and the 3'-UTR of MEK1 mRNA. This study explored the role of miR-203 in regulating prostate cancer cell proliferation, apoptosis, and ADM resistance through affecting MEK1 expression.

MATERIALS AND METHODS: Dual-luciferase assay confirmed the targeted relationship between miR-203 and MEK1. MiR-203, MEK1, p-ERK1/2, and B cell lymphoma 2 (Bcl-2) expressions were compared in normal prostate epithelial cells PrEC, prostate cancer cells PC-3M, and drug resistance cells PC-3M/ADM. PC-3M, PC-3M/ADM cell apoptosis and proliferation were detected by using flow cytometry under ADM treatment at [illegible] concentration of PC-3M cells. PC-3M cells were cultured *in vitro* and divided into [illegible] groups including microRNA-normal control (miR-NC), miR-203 mimic, small interfere [illegible] (si-NC) and si-MEK1.

RESULTS: MiR-203 targeted and inhibited MEK1 expression. MiR-203 levels and cell apoptosis were significantly lower, while MEK1, p-ERK1/2, Bcl-2, and cell proliferation were significantly higher in PC-3M/ADM cells compared to the PC-3M cells. MiR-203 mimic and/or si-MEK1 transfection significantly reduced MEK1, p-ERK1/2, and Bcl-2 levels, attenuated cell proliferation, induced cell apoptosis, and decreased drug resistance.

CONCLUSIONS: MiR-203 elevation suppressed prostate cancer PC-3M cell proliferation, promoted apoptosis, and weakened ADM resistance through targeting [illegible] MEK1 expression to alleviate ERK/MAPK signaling pathway and Bcl-2 expression.

Key Words:
miR-203, MEK1, ERK/MAPK, ADM, Prostate cancer, Drug resistance.

Introduction

Prostate cancer (PC) refers to epithelium malignant tumor occurring in prostate. Though the incidence of PC is lower in China than Europe and the USA, it shows an increasing trend that accounts for the 6th in male and 3rd urinary system[1,2]. Chemotherapy is one of the most important measures in PC treatment. Chemotherapy resistance often affects the treatment effect and poor prognosis of PC.

Mitogen activated protein kinase (MAPK) signaling pathway is widely expressed in various tissues and cells, regulating multiple biological processes, including cell survival, proliferation, cycle, apoptosis, and drug resistance[3,4]. Extracellular signal regulated kinase (ERK) mediated MAPK signaling pathway is considered as a canonical MAPK signal transduction pathway. ERK/MAPK signaling pathway excessive activation induces cell abnormal proliferation, apoptosis, and differentiation, which are closely related to tumorigenesis[3-5]. Ras/Raf/MEK/ERK is the major mode of ERK/MAPK signaling pathway. MAPK kinase 1 (MEK1) phosphorylates the residue of Tyr/Thr on ERK protein to activate ERK/MAPK signaling pathway. MEK1 up-regulation

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is associated with tumor pathogenesis, progression, metastasis, and drug resistance[6-8]. MEK1 elevation plays a promoting role in PC occurrence and development[9,10]. MiRNA is a type of endogenous single stranded noncoding RNA at the length of 20-24 nt. It plays a degrading or inhibiting role on mRNA by binding with the 3'-UTR, thus negatively regulates gene expression at posttranscriptional level[11]. MiRNA abnormal expression plays an important role in tumorigenesis[12-14]. Multiple studies[15,16] revealed that miR-203 level significantly decreased in PC tissue and cell lines, suggesting that miR-203 plays a tumor suppressor role in PC. Bioinformatics analysis shows the complementary targeted relationship between miR-203 and the 3'-UTR of MEK1 mRNA. We explored the role of miR-203 in regulating MEK1 expression, ERK/MAPK signaling pathway activation, PC pathogenesis, progression, and ADM resistance.

Materials and Methods

Main Reagents and Materials

PC-3M cells were purchased from Zeye Biotech Co., Ltd., (Shanghai, China). The human normal prostate epithelial cell line, PrEC, was purchased from Xuran Biotech Co., Ltd., (Shanghai, China). Dulbecco's Modified Eagle Medium (DMEM) and PrEGM medium were obtained from Lonza Inc. (Allendale, NJ, USA). Fetal bovine serum (FBS) was bought from Gibco (Grand Island, NY, USA). Total RNA extraction kit TRIzol Universal was purchased from Tiangen Biotech Co., Ltd., (Beijing, China). Real-time PCR TransScript Green One-Step qRT-PCR SuperMix was provided by Transgen (Beijing, China). The miR-203 mimic, miR-203 inhibitor, and miR-NC were purchased from Ribobio (Guangzhou, China). Transfection reagent FuGENE6 was purchased from Roche Diagnostics (Indianapolis, IN, USA). Rabbit anti-human MEK1, p-ERK1, p-ERK2, and horseradish peroxidase (HRP) conjugated secondary antibodies were derived from Abcam Biotech. (Cambridge, MA, USA). Mouse anti-human B cell lymphoma-2 (Bcl-2) and β-catenin antibodies, si-NC, and si-MEK1 were purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA). Annexin V/PI cell apoptosis detection kit was purchased from MultiSciences (Hangzhou, China). BeyoECL plus enhanced chemiluminescence (ECL) reagent and cell counting 8 (CCK-8) reagent were obtained from Beyotime (Shanghai, China). EdU cell proliferation detection kit was purchased from Molecular Probes (Eugene, OR, USA). Dual luciferase activity detection kit Dual-Glo Luciferase Assay System and pGL3 luciferase reporter gene vector were purchased from Promega (Madison, WI, USA). Adriamycin (ADM) was obtained from Wanle Pharmaceutical Industry (Shenzhen, China).

Cell Culture

The PC-3M cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) medium, while PrEC cells were cultured in PrEGM medium at 37°C and 5% CO_2. The cells were passaged at 1:4.

PC-3M/ADM Cell Model Establishment and Resistance Index Calculation

PC-3M cells at logarithmic phase were treated by using 5 ng/ml ADM for 24 h. Next, the medium was changed till cells grew and passaged in the medium stably. Next, the concentration of ADM was gradually increased to 10 ng/ml, 20 ng/ml, and 40 ng/ml, till the cell grew stably in 40 ng/ml ADM to establish cisplatin resistant PC-3M/ADM cell line.

PC-3M and PC-3M/ADM cells were treated by ADM at 0, 20, 40, 80, 160, 320, and 640 ng/ml. After 48 h, the cells were added with 10 µl CCK-8 for 4 h and tested at 450 nm to obtain the absorbance value (A450). Inhibitory rate = (1-ADM group A450)/control A450 × 100%. IC_{50} was calculated by SPSS software. Resistance index (RI) = IC_{50} of PC-3M/ADM / IC_{50} of PC-3M.

Flow Cytometry

The cells were added with 10 µM EdU solution at 37°C for 2 h. After the cells were incubated for 48 h, they were digested by trypsin and collected. After fixation and permeabilization, the cells were stained by reaction liquid containing Alexa Fluor 488 at room temperature avoiding light for 30 min and tested on CytoFLEX flow cytometry (Beckman Coulter Inc., Brea, CA, USA).

Dual-Luciferase Reporter Gene Assay

The PCR products containing the full-length of MEK1 gene 3'-UTR or mutant segment were cloned to pGL3. Next, they were transformed to DH5α competent cells and sequenced to select the plasmid with correct sequence. After that, pGL3-MEK1-3'-UTR-wt (or pGL3-MEK1-3'-UTR-mut) was co-transfected to HEK293T cells using FuGENE6 together with miR-203 mimic (or miR-

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203 inhibitor, or miR-NC). The luciferase activity was detected according to the Dual-Glo Luciferase Assay System manual after cultured for 48 h.

Cell Transfection and Grouping

PC-3M/ADM cells were divided into four groups, including mimic-NC, miR-203 mimic, si-NC, and si-MEK1 groups. MiR-NC or miR-203 mimic at 30 nmol/l, si-NC or si-MEK1 at 10 nmol/l, and FuGENE6 at 10 µl were diluted in serum free DMEM medium at room temperature for 5 min. Then they were added to the cells and incubated for 72 h for the following experiments.

qRT-PCR

Total RNA was extracted using TRIzol Universal RNA Extraction Kit and adopted for PCR reaction by TransScript Green One-Step qRT-PCR SuperMix. The reaction system contained 1 µg template RNA, 0.3 µM primers, 10 µl 2 × TransStart Tip Green qPCR SuperMix, 0.4 µl One-Step RT Enzyme Mix, 0.4 µl Passive Reference Dye II, and RNase-free water. The PCR reaction was composed of 45°C for 5 min and 94°C for 30 s, followed by 40 cycles of 94°C for 5 s and 60°C for 30 s. Real-time PCR was performed on Bi[illegible] (Hercules, CA, USA) CFX96 to test the re[illegible]ve expression.

Western Blot

Total protein was extracte[illegible]y usin[illegible]istocetin-induced platelet aggregat[illegible] buff[illegible](RIPA) from cells. A total of 40 [illegible] protei[illegible]re separated by sodium dodecyl[illegible]ate-polya[illegible]mide gel electrophoresis (SD[illegible]PA[illegible]) and tra[illegible]rred to polyvinylidene f[illegible]oride (PV[illegible]) membrane. Next, the membran[illegible]as blocked by [illegible] skim milk and incubated i[illegible] primary antibody at 4°C overnight (MEK1, E[illegible]/2, [illegible]ERK1/2, Bcl-2, and β-actin at 1:3000, 1:1[illegible] 1:1000 [illegible]:2000, and 1:10000, res[illegible]). Th[illegible]rane was incubated in [illegible]seradis[illegible] peroxid[illegible] (HRP) labeled secondary a[illegible]ody [illegible]0000) for 1 h after washed by pha[illegible]ffere[illegible]line and tween 20 (PBST) for three [illegible]s. At last, the protein expression was detected [illegible] Beyo ECL Plus.

Cell Apoptosis Detection

The cells were digested by trypsin and resuspended in 100 µl Annexin V binding buffer. Next, the cells were incubated in 5 µl Annexin V-FITC and 5 µl PI. At last, the cells were tested on Beckman Coulter CytoFLEX flow cytometry to evaluate cell apoptosis.

Statistical Analysis

All data analyses were performed on SPSS 18.0 software (SPSS Inc., Chicago, IL, USA). The measurement data were depicted as mean ± standard deviation (SD). The Student's t-test was used to compare the differences between two groups. Tukey's post-hoc test was used to validate ANOVA for comparing measurement data between groups. $p < 0.05$ wa[illegible]sidered as statistical significance.

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MiR-203 Targete[illegible]hi[illegible]ted MEK1 Expr[illegible]ion

Bioinfor[illegible]cs analys[illegible]ed the targeted binding [illegible]te b[illegible]een miR-[illegible]3 and 3'-UTR of MEK1 mRNA ([illegible]re 1A). Dual luciferase assa[illegible]aled that m[illegible]203 mimic transfection s[illegible]nificantly declined, while miR-203 inhibitor t[illegible]nsfection [illegible]nificantly elevated the relative lu[illegible]ferase ac[illegible]ity of HEK293T cells, indicating [illegible] reg[illegible]atory relationship between miR-203 and [illegible]EK1 mRNA (Figure 1B).

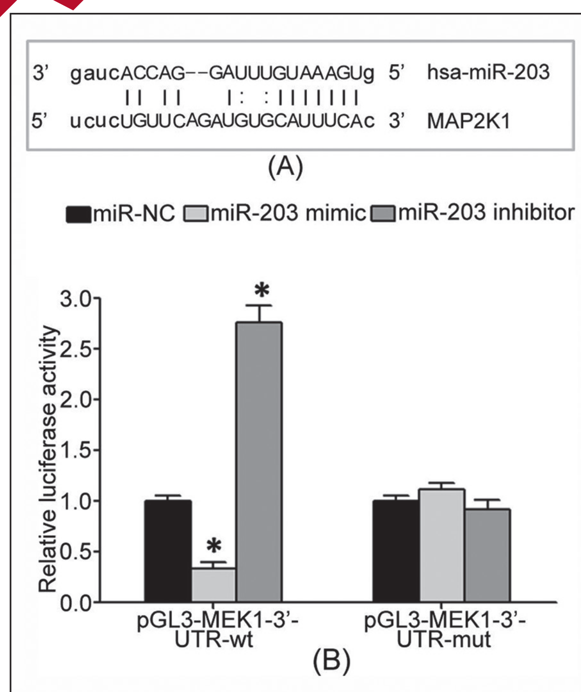

Figure 1. MiR-203 targeted inhibited MEK1 expression. **(A)** The binding site between miR-203 the 3'-UTR of MEK1 mRNA. **(B)** Dual luciferase assay. $*p < 0.05$, compared with mimic NC.

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MiR-203 Down-Regulated, while DJ-1 Overexpressed in PC-3M/ADM Cells

The IC_{50} of PC-3M cells was 32.63 ng/ml, while it was 412.77 ng/ml in PC-3M/ADM cells. The RI was 12.65. qRT-PCR showed that miR-203 was significantly lower in PC-3M/ADM cells compared with PC-3M cells, while it was significantly lower in PC-3M cells compared with PrEC cells. MEK1 and Bcl-2 mRNA levels were markedly higher in PC-3M/ADM cells compared with PC-3M cells (Figure 2A). Western blot revealed that MEK1, p-ERK1/2, and Bcl-2 protein levels were apparently higher in PC-3M/ADM cells compared with PC-3M cells and PrEC cells (Figure 2B). Flow cytometry demonstrated that the cell apoptotic rate was significantly lower (Figure 2C), while cell proliferation (Figure 2D) was significantly stronger in PC-3M/ADM cells than that in PC-3M cells treated by 32.63 ng/mL ADM.

MiR-203 Overexpression or MEK1 Down-Regulation Attenuated ADM Resistance in PC-3M/ADM Cells

Under the 40 ng/ml ADM was used to observe the impact of miR-203 on the ADM sensitivity of PC-3M/ADM cells. MiR-203 mimics and/or si-MEK1 transfection markedly reduced MEK1, p-ERK1/2, and Bcl-2 expressions (Figure 3A and B), attenuated cell proliferation (Figure 3C), enhanced cell apoptosis (Figure 3D) and weakened ADM resistance.

Discussion

PC is one of the most common malignant tumors in males in Western countries. Its incidence accounts as second among all malignant tumor with a rising trend linked to the age[17,18]. Though the incidence of PC in China is lower than West-

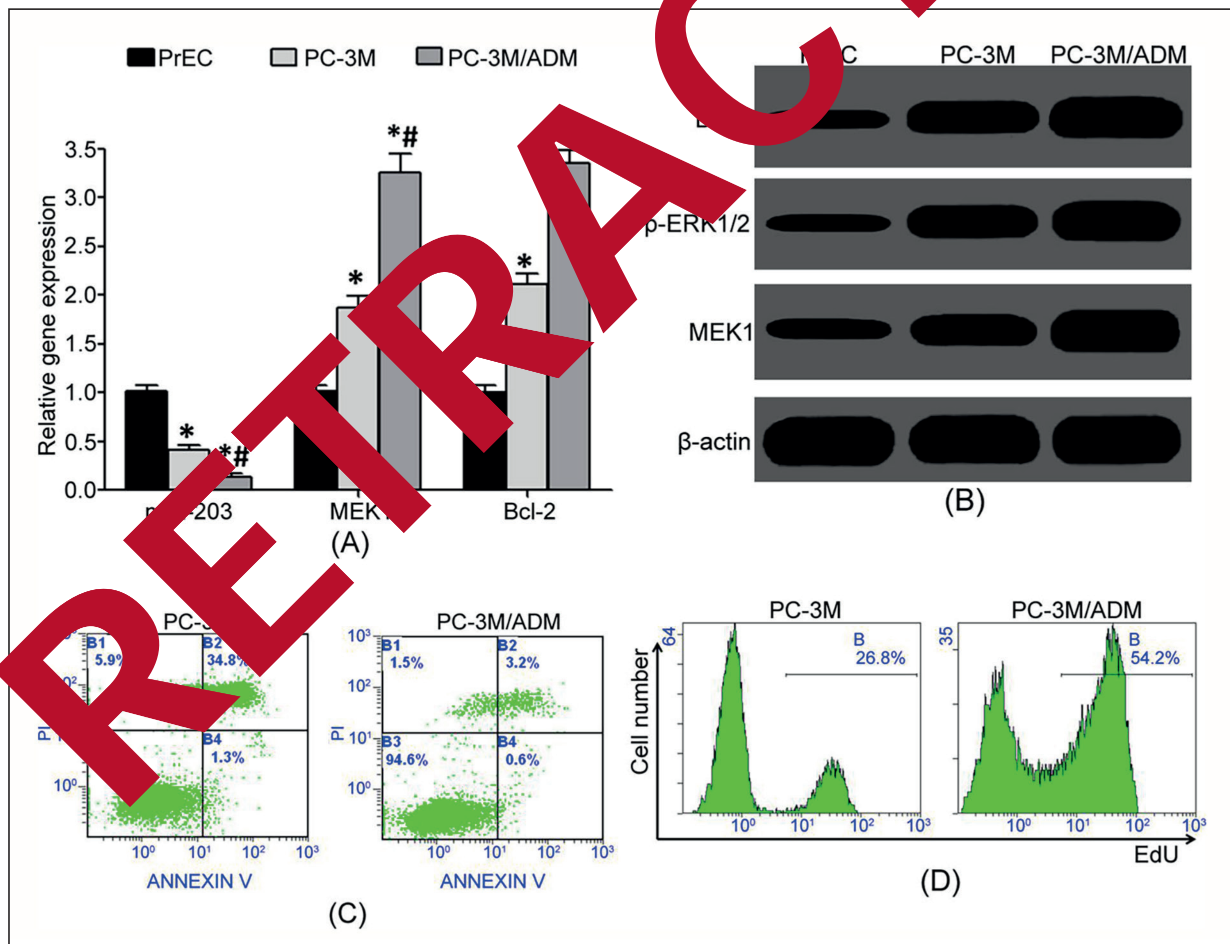

Figure 2. MiR-203 down-regulated, while DJ-1 over-expressed in PC-3M/ADM cells. **(A)** qRT-PCR detection of gene expression. **(B)** Western blot detection of protein expression. **(C)** Flow cytometry detection of cell apoptosis. **(D)** EdU staining detection of cell proliferation. $*p < 0.05$, compared with PrEC cells. $^{\#}p < 0.05$, compared with PC-3M cells.

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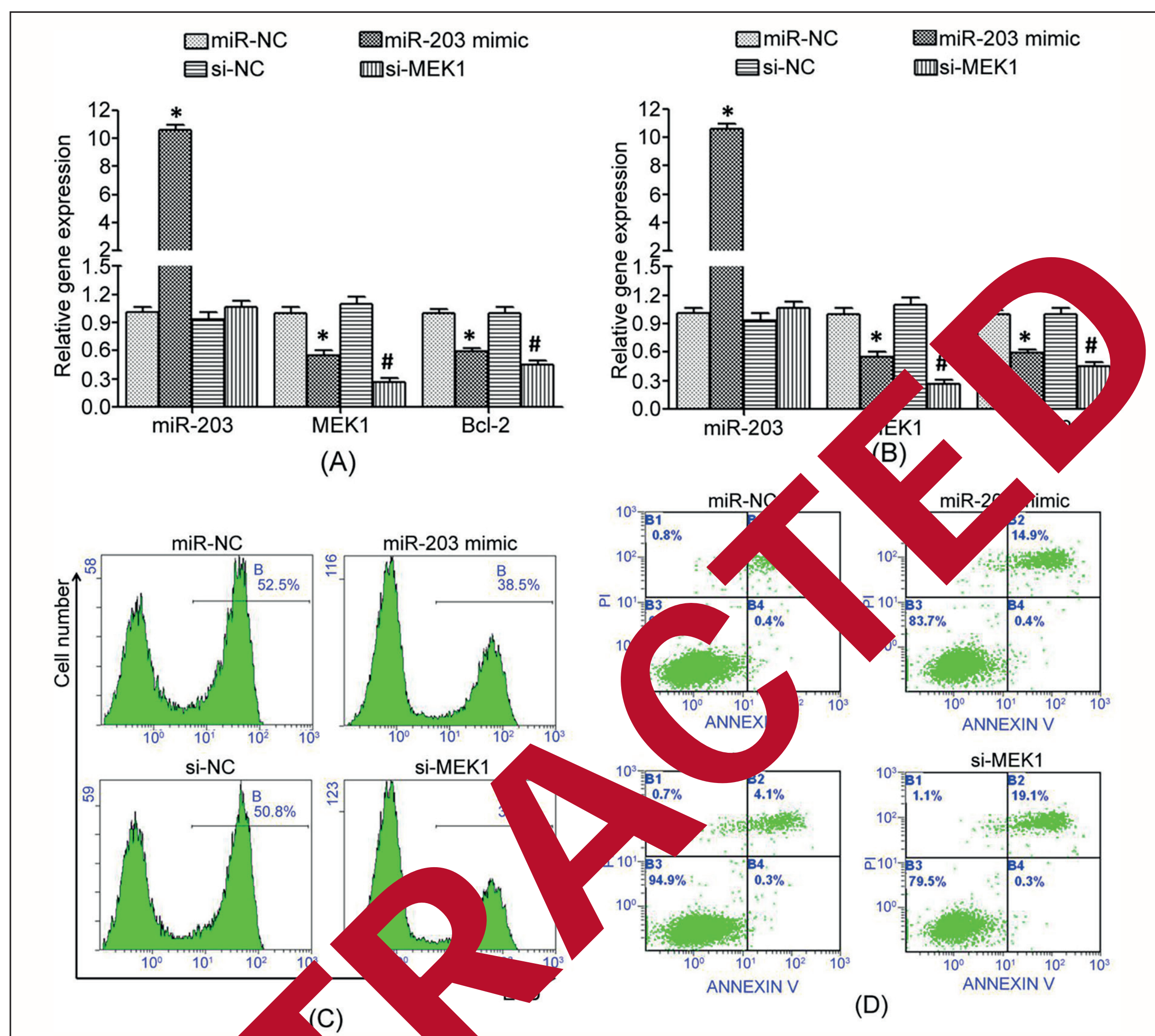

Figure 3. MiR-203 ...ver-expres... ...r MEK1 down-regulation attenuated ADM resistance in PC-3M/ADM cells. **(A)** qRT-PCR detection of ...ne expression. ... Western blot detection of protein expression. **(C)** Flow cytometry detection of cell apoptosis. **(D)** ...U staining detection o... ...ell proliferation. $^{a}p < 0.05$, compared with miR-NC. $^{b}p < 0.05$, compared with si-NC.

...count...s, it has ...dually increased following a... of ...lation and the change of lifestyle[1,2]. Ch...erap... one of the most important measures ...C treatment. Chemotherapy resistance often aff... the treatment effect and poor prognosis of PC. It is of great significance to investigate the mechanism of PC chemotherapy resistance for improving therapeutic effect and prognosis.

MAPK signaling pathway is an important signal transduction system that widely exists in eukaryotes. It regulates various target genes expression and activation mediated by intracellular receptor tyrosine kinase, G-protein coupled receptor, and cytokine receptor under the effect of cytokines, growth factors, neurotransmitter, and G-protein coupled receptor, thus affecting cell survival, proliferation, migration, apoptosis, angiogenesis, and immune response[19,20]. ERK/MAPK signaling pathway excessive activation leads to cell abnormal proliferation, apoptosis, and differentiation, and promote malignant transformation. It is closely associated with various tumors pathogenesis, apoptosis escape, and differentiation capacity, such as gall bladder cancer[3], breast cancer[5], and thyroid cancer[4]. ERK/MAPK signaling pathway conforms to

the classic three-step enzymatic cascade, and presents the same activation mode under different stimulus. Ras/Raf/MEK/ERK is the major mode of ERK/MAPK signaling pathway. MEK1 is a type of kinase with dual specific protease that phosphorylates the Tyr/Thr residue of ERK protein, thus activating ERK/MAPK signaling pathway. MEK1 expression and functional activity are related to a variety of cancers pathogenesis, progression, metastasis, and drug resistance, including hepatic cancer[6], ovary cancer[7], and pancreatic cancer[8]. It was showed that MEK1 over-expression is related to PC pathogenesis and progression[9,10]. Scholars[15,16] revealed that miR-203 expression reduced in PC tissue and cell line, suggesting that miR-2031 may play a tumor suppressor role in the occurrence and development of PC. Bioinformatics analysis shows the complementary targeted relationship between miR-203 and the 3'-UTR of MEK1 mRNA. This investigation explores the role of miR-203 in regulating MEK1 expression, ERK/MAPK signaling pathway activation, and PC cell proliferation, apoptosis, and ADM resistance.

Dual luciferase assay revealed that miR-2[illegible] mimic transfection significantly declined, [illegible] miR-203 inhibitor transfection significantly [illegible]vated the relative luciferase activity of HEK2[illegible] cells, indicating the regulatory rela[illegible]nship b[illegible]tween miR-203 and MEK1 m[illegible]K ca[illegible] activate anti-apoptotic factor [illegible]-2 exp[illegible]sion to promote cell proliferation and [illegible]uce[illegible]opotosis[21,22]. MiR-203 was [illegible]gnific[illegible] lowe[illegible] in PC-3M/ADM cells co[illegible]red with [illegible]3M cells, while it was signif[illegible]ntl[illegible]wer in P[illegible]M cells compared with [illegible]EC cells[illegible]EK1, p-ERK1/2, and Bcl-2 pr[illegible]n levels were [illegible]parently higher in PC-3[illegible]ADM cells compared with PC-3M cells and [illegible] c[illegible]s. It revealed that miR-203 downr[illegible]latio[illegible]ay pl[illegible]a role in increasing M[illegible]press[illegible]ancing ERK/MAPK [illegible]naling [illegible]thway [illegible]ivity, and facilitating PC p[illegible]ogen[illegible]and drug resistance. Boll et al[23] repo[illegible]at [illegible]203 level significantly declined in PC[illegible]ue compared with normal prostate tissue, fol[illegible]ng pathological grading. MiR-203 expression was significantly lower in PC cell lines LNCaP, PC3, and DU-145 compared with normal prostate epithelial cell RWPE-1. Hailer et al[24] showed that miR-203 markedly declined in PC tissue compared with benign hyperplastic prostate tissue, and that was related to lymph node metastasis. Saini et al[16] suggested that miR-203 expression was more reduced in PC tissue and cell lines LNCaP, DU145, and PC3 than that in benign prostate tissue and normal prostate epithelial cell line RWPE-1[16]. Siu et al[25] demonstrated that miR-203 level apparently decreased in PC tissue compared with normal prostate tissue, while it was significantly lower in metastatic PC. In this study, miR-203 expression significantly reduced in PC cells, indicating that its downregulation may be involved i[illegible] patho-genesis, which was similar wi[illegible]Bo[illegible] al[23], Saini et al[16], and Siu et al[25] fi[illegible]gs. Amata[illegible]lo et al[9] showed that MEK1 en[illegible]ement play[illegible] a crucial role in promoti[illegible]PC c[illegible]MT an[illegible]invasion, revealing the [illegible]mor-prom[illegible] a[illegible]on of MEK1 in PC, whic[illegible]as in [illegible]ccordan[illegible]vith our results. Siu et al[25] [illegible]o[illegible]rated that miR-203 down-regulat[illegible] in PC [illegible]esista[illegible]e to tyrosine kinase inhi[illegible]s (TKIs). [illegible]l[26] revealed that miR-203 [illegible]vel [illegible]lined in h[illegible]mone resistant PC cells LNCaP-abl [illegible]mpared with LNCaP cells. Th[illegible]dy showe[illegible]at miR-203 significantl[illegible]reduced in drug resistant PC cells compared w[illegible]h parent d[illegible]g sensitive cells, suggesting that m[illegible]203 dow[illegible]egulation may play a role in PC cell [illegible]g re[illegible]stance, which was in accordance with Siu et al[25] and Sun et al[26]. MiR-203 mimics [illegible]/or si-MEK1 transfection markedly reduced ME[illegible], p-ERK1/2, and Bcl-2 expressions, attenuated cell proliferation, enhanced cell apoptosis, and weakened ADM resistance. Fragni et al[27] reported that the effect of zoledronic acid on suppressing PC cell proliferation and inducing cell apoptosis was related to miR-203 enhancement and survivin decrease, confirming the tumor suppressor role of miR-203 on PC. Boll et al[23] demonstrated that miR-203 over-expression significantly arrested PC cell cycle[23]. Saini et al[16] exhibited that miR-203 up-regulation significantly attenuated ZEB2, RUNX2, DLX5, SmMAD4, and Survivin expressions, inhibited EMT process, migration, and invasion, alleviated cell proliferation, and induced cell apoptosis in PC-3 cells. Siu et al[25] revealed that the inhibition of miR-203 enhanced PC drug resistance to TKIs. In this study, miR-203 over-expression reduced PC cell drug resistance, which verified the result of Siu et al[25]. This work revealed the role of miR-203 in targeting MEK1, regulating ERK/MAPK signaling pathway, and in affecting ADM resistance. We only explored the impact of miR-203 on MEK1, ERK/MAPK signaling pathway, and PC cell proliferation, apoptosis, and ADM resistance. However, we did not test the corresponding mechanism in clinical samples.

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Conclusions

We showed that down-regulation of miR-203 was associated with ADM resistance in PC-3M cells. MiR-203 elevation suppressed prostate cancer PC-3M cell proliferation, promoted apoptosis, and weakened ADM resistance through targeted inhibiting MEK1 expression to alleviate ERK/MAPK signaling pathway and Bcl-2 expression.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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