Pathol. Oncol. Res. (2018) 24:385–391
DOI 10.1007/s12253-017-0254-y

ORIGINAL ARTICLE

MiR-1271 Inhibits Cell Growth in Prostate Cancer by Targeting ERG

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Received: 18 November 2016 / Accepted: 23 May 2017 / Published online: 27 May 2017

Abstract ETS-related gene (ERG) is an oncogene that is commonly found in prostate cancer (PCa). Several miRNAs have been reported to be associated with PCa. This study was undertaken to identify miRNAs that act as a tumor suppressor by targeting ERG. We collected 70 PCa and paired adjacent non-tumor (Adjacent-N) tissues and analyzed ERG expression by immunohistochemistry(IHC). Expression of 6 miRNAs (miR-21,-34a,-96,-125b,-150 and miR-1271) was analyzed by qRT-PCR. Luciferase reporter assay was performed to examine miRNA binding to the 3′-UTR of target genes. The effects of ectopic expression of miRNA on cell growth and MAPK signaling pathway were investigated in in PC-3 and LNCaP cell lines. Among 70 PCa cases, 13 (18.6%) were ERG positive. No significant difference of miR-34a, 96, 125b, and 150 expression was found between PCa and Adjacent-N tissues. Significantly higher level of miR-21 and lower level of miR-1271 expression were found in cancer tissues. Furthermore, miR-1271 was down-regulated in ERG-positive PCa cases ($p < 0.05$). Based on luciferase reporter assay, we identified ERG gene as a direct target gene for miR-1271. Transfection of a miR-1271 mimics into PC-3 and LNCaP cells repressed the ERG expression and significantly suppressed cell growth. Lastly, ectopic expression of miR-1271 inhibits AKT1, p38gama and CREB kinase activity. Our results suggested that reduced expression of miR-1271 may be involved in the ERG expression and that miR-1271 could be a therapeutic target for ERG-positive prostate cancer patients.

Keywords Prostate cancer · miR-1271 · ERG;miR-21

Introduction

Prostate cancer (PCa) is the leading cause of cancer death in males worldwide and its incidence rate in China is increasing. ERG (ETS-related gene) is an oncogene, which can fuse with TMPRSS2 to form an oncogenic fusion gene (TMPRSS2-ERG) that is commonly found in human PCa, especially in hormone-refractory patients [1]. The fusion gene resulting in ERG overexpression is critical to the progression of cancer by inhibiting androgen receptor expression. However, several studies showed that the incidence of ERG overexpression is significantly different in PCa among different ethnic groups [2, 3]. In western countries, ERG overexpression has been found in around 50% of PCa and is a very early event in tumorigenesis. However,only about 20% of PCa showed ERG overexpression in Asians. Future studies of the molecular pathways implicated in ERG may shed light on the disparity of PCa in different patients and help design better treatment strategies.

MicroRNAs (miRNAs) are highly conserved endogenous small 20–25 nucleotide non-coding RNAs that have been shown to participate in human tumorigenesis by directly targeting oncogenes or tumor suppressor genes [4]. Several studies showed that miRNA expression is deregulated in PCa and that this may have clinical significance. Shi et al. [5] showed that enforced expression of miR-125b promoted prostate tumor growth in nude mice. Yu et al. [6] found that over-expression of miR-96 induced proliferation and colony

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formation ability of LNCaP prostate cancer cells. Liu et al. [8]reported that miR-150 expression was significantly upregulated in prostate cancer stem cells and might participate in the development and progression of human PCas. Zhang et al. [7] showed that serum miR-21 levels were elevated in in patients with metastatic hormone-refractory prostate cancer. Kojima [8] et al. reported miR-34a over-expression attenuated paclitaxel resistance of hormone-refractory PC3 cells. However,Folini et al. [9]found that miR-21 knockdown in prostate cancer cells was not sufficient to affect the proliferative and invasive potential, or to modulate the expression of the tumor-suppressors PTEN.Thus, the oncogenic properties of miR-21 could be tissue dependent, which need to be further studied. MiR-1271 shares a common 'seed' sequence with miR-96 [10], and whether it had a significant function in PCas was in question. Thus, miRNA expression and the relevance of microRNAs in the development, progression and prognosis of prostate cancer need to be further studied.

Given the therapeutic potential as biomarkers and highly tissue specific for miRNAs in PCas, we evaluated differentially expressed miRNAs from PCa and paired adjacent non-tumor tissues to study their potential roles in tumor pathogenesis.

Methods

Prostate Cancer Samples

Formalin-fixed and paraffin-embedded tissue samples of 70 PCa cases were obtained from patients who were diagnosed with PCa and treated by radical prostatectomy in the Department of Pathology at XuanWu Hospital from 2009 to 2016. All protocols for obtaining and studying human tissues and cells were approved by the institution's review board for human subject research. PCa diagnosis was based on clinical manifestation, morphology and immunophenotyping in accordance with the WHO classification guidelines [11].

RNA Isolation and qRT-PCR miRNA Analysis

Total RNA was extracted from Paraffin-embedded tissues using RecoverAll™ Total Nucleic Acid Isolation Kit (Catalog Number: AM1975; Applied Biosystems, Foster City, CA, USA) as reported previously [12]. qRT-PCR for mature miRNAs was performed as described by the manufacturer (TIANGEN, CHINA). U6 was used for normalization ($\Delta Ct = \Delta CtmiRNA- \Delta CtU6$) and to check the quality of the samples, i.e. only cases with a cycle threshold (Ct) value lower than 35 were used resulting in a total of 70 cases. MiR-21 miR-34a, miR-96,miR-125b, miR-150 and miR-1271 were analyzed by qRT-PCR. Relative expression levels were determined by using the formula $2^{-\Delta Ct}$.

Immunohistochemistry (IHC)

The slides were deparaffinized and endogenous peroxidase was blocked by incubation with 3% H_2O_2 for 10 min. Antigen retrieval was performed according to various protocols of the manufacturers. Immunostaining was performed using rabbit monoclonal antibody against ERG (Epitomics, California, USA) at a dilution of 1:100. Signals were amplified by incubation with the appropriate Horseradish Peroxidase-conjugated antibodies for 60 min and the reactivity was visualized by diaminobenzidin.

Luciferase Reporter Assay

A luciferase reporter plasmid containing the ERG 3′-UTR region was purchased from from RiboBio Co.,Ltd. (Guangzhou, China). Lipofectamine 2000 (Invitrogen;Life Technologies) was used as a transfection reagent. miRNA inhibitors (50 nmol/L), mimics (50 nmol/L), and reporter plasmid mixed with transfection reagent were added when cells were plated, followed by incubation for 48 h. A Dual-Luciferase assay (promega) and a Thermo Scientific Fluoroskan Ascent FL were used to analyze luciferase expression according to the manufacturer protocols.

Cell Culture and Transfection

PC cell line, PC-3, were cultured in F12 K and LNCaP were cultured in RPMI 1640,which are all supplemented with 10% fetal calf serum (GIBCO), 1% L-glutamine, and 1% penicillinstreptomycin in a 5% CO_2-humidified chamber. miRNA mimics control and miR-1271 mimics were purchased from RiboBio Co.,Ltd. (Guangzhou, China). For transfection, miRNA mimics control (50 nM final concentration), or miR-150 mimics (50 nM final concentration) were transfected into appropriate cells using lipofectamine 2000 (Invitrogen).24 h and 48 h after transfection cells were used for cell viability experiments.

Western Blot Analysis

PC-3 and LNCaP cell lysates were separated on polyacrylamide gels and electroblotted onto nitrocellulose membranes. Blots were blocked in blocking buffer (TBS with 0.05% Tween 20, pH 7.6 with 5% skimmed milk), washed and incubated with anti-ERG antibody (1:500 dilution) or monoclonal anti-beta-actin (1:1000) antibody at 4 °C overnight. Immunostaining was amplified by incubation with HRP-

conjugated antibodies and chemiluminescence was detected with ECL (Pierce, Rockford, USA).

MTT Assay

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, Sigma) was added to cells and incubated for 4 h at 37 °C.The cells were centrifuged and the supernatant was removed. DMSO (Sigma) was added and absorption was measured at 540 nm in an ELISA reader.

MAPK Array Analysis

MAPK array was performed as reported previously [13].PC-3 cells were treated with or without miR-1271 mimics for 2 days. Cells were used for MAPK array detection by a commercially available kit (R&D).

Statistical Analysis

Statistical analysis was performed with a Student's t-test or F-test. All p values were two-sided and $p < 0.05$ were considered to be significant. Prism 5 software was used for the analysis.

Results

Clinical and Pathological Features

Among the 70 PCa cases included in this study, the median age at diagnosis was 70.5 years. In accordance with NCCN guidelines (version 2.2014), we classified patients as low risk (T1-T2, GS ≤ 6, PSA < 10 ng/mL), intermediate risk (T2b-T2c or GS = 7 or PSA 10-20 ng/mL), high risk (T3a or GS = 8–10; PSA > 20 ng/mL), very high risk (T3b, T4), and metastatic (any T, N1 and any T, any N, M1). Based on this classification, 30 (42.9%) were at low risk, 16 (22.9%) at intermediate risk, 20(28.5%) at high risk, 4(5.7%) was at very high risk, and no cases were metastasis.

ERG Expression in Prostate Cancer

To detect the ERG expression, immunohistochemistry was performed in 70 prostate cancer and paired adjacent non-tumor tissues. Positive immunohistochemical reaction was present mainly in the nuclear. ERG protein was only highly expressed in a subgroup of prostate tumors (13/70, 18.6%), but not expressed in adjacent non-tumor tissues (Fig. 1). Further analysis of the clinic pathological characteristics in 70 prostate tumors showed that no significant difference of ERG expression was observed in tumors with differentiation, Gleason score and risk status.

Upregulation of miR-21 and Downregulation of miR-1271 in PCa

To determine whether aberrant miRNAs expression is associated with PCa, we have examined 6 miRNAs expression in 70 pairs of prostate cancer tissues and their matched adjacent non-tumor tissues using real-time PCR. Of 6 miRNAs, miR-21 showed the highest expression level in prostate tissue samples. Five microRNAs (miR-34a, 96, 125b, 150, and 1271) showed very low expression in all samples. The expression level of miR-21 was higher in prostate cancer tissues than paired adjacent non-tumor tissues ($p < 0.05$, Fig. 2a). No significant difference of miR-34a, 96, 125b, and 150 expression was found between these two groups tissues ($p > 0.05$, Fig. 2b-e). MiR-1271 expression was lower in prostate cancer tissues than paired adjacent non-tumor tissues ($p < 0.05$, Fig. 2f).

ERG is a Direct Target of miR-1271

We did not find a significant correlation between the expression level of these 5 miRNAs (miR-21, 34a, 96, 125b, and 150) and ERG protein expression status in PCas. There was a significant reduction in miR-1271 expression in ERG positive PCa compared with ERG negative PCa tissues ($p < 0.001$,Fig. 3a). In order to verify that ERG might be a direct target of miR-1271, we not only constructed the reporter plasmid carrying the wild-type ERG 3′-UTR region, but also constructed a reporter plasmid carrying the mutant-type ERG 3′-UTR region (Fig. 3b). PC-3 and LNCaP cells were transfected with either miR-1271 mimics or miRNA control mimics. MiR-1271 mimics-transfected cells showed a marked reduction of wild-type reporter luciferase activity. Conversely, inhibition of luciferase activity by miR-1271 mimics was almost abolished in the mutant-type, suggesting that the predicted binding region was fully responsible for miR-1271 function (Fig.3c). By transfection with synthetic oligonucleotides (miR-1271 mimics), expression of miR-1271 was induced in PC-3 and LNCaP (confirmed by qRT-PCR, data not shown). Western blot analysis of cell lysates showed repression of ERG in the cells transfected with miR-1271 mimics (Fig. 3d).

Possible Role of miR-1271 in PCa

MTT analysis showed re-expression of miR-1271 by transfection with miR-1271 mimics significantly reduced proliferation of PC-3 and LNCaP cells ($p < 0.05$) (Fig. 4a). Especially after 24 h, the proliferation of PC-3 and LNCaP cells with miR-1271 mimics' transfection can reduce about 30% of cell growth. Extensive work by several groups has established that the Map kinases (MAPKs) pathway plays a critical role in the pathogenesis of PCa [14–16]. We therefore determined the effect of miR-1271 on the regulating of MAPKs signaling pathway in PC-3 and LNCaP cells by using MAPK array.

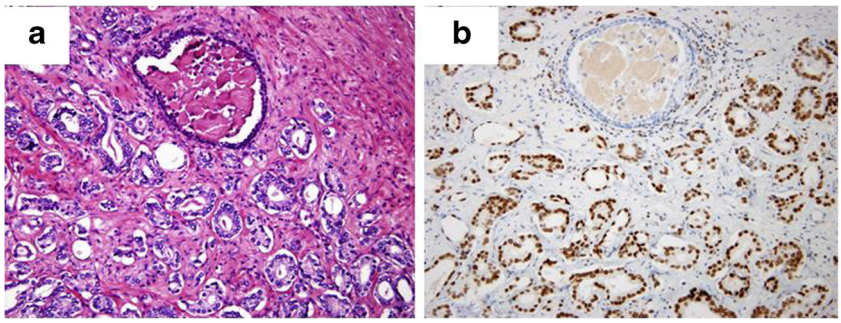

Fig. 1 Immunohistochemistry shows positive expression of ERG in PCa. **a:** Representative HE image of PCa. **b:** PCa tumor cells with ERG positivity in nuclear (both original magnification ×200)

From these 19 MAP kinases, ERK2 had the highest activity, and JNK pan and AKT1 an intermediate activity. AKT1,p38 gamma and CREB kinases have significantly down regulation of kinases activity after miR-1271 mimics transfection ($p < 0.05$). AKT3 and p38 beta showed a low activity in both samples.

Discussion

Early evidences suggest that ERG overexpression may be associated with PCa progression, and identification of miRNA signature in ERG-positive prostate cancer cells may help to identify novel molecular targets and pathways for personalized therapy [17, 18]. In this study, we analyzed 70 prostate cancer tissues and their matched adjacent non-tumor tissues. Our study is the first to show that extremely low miR-1271 is expressed in human prostate cancers, and is involved in the proliferation of the cancer. Our study is also the first to demonstrate that ERG is negatively regulated by miR-1271 via a specific target site (nt 285–292) within the 3′-UTR region of the ERG gene.

TMPRSS2- ERG gene fusion was first identified in PCa by Tomlins in 2005 [1] . In 2010, Park et al. [19]found that ERG

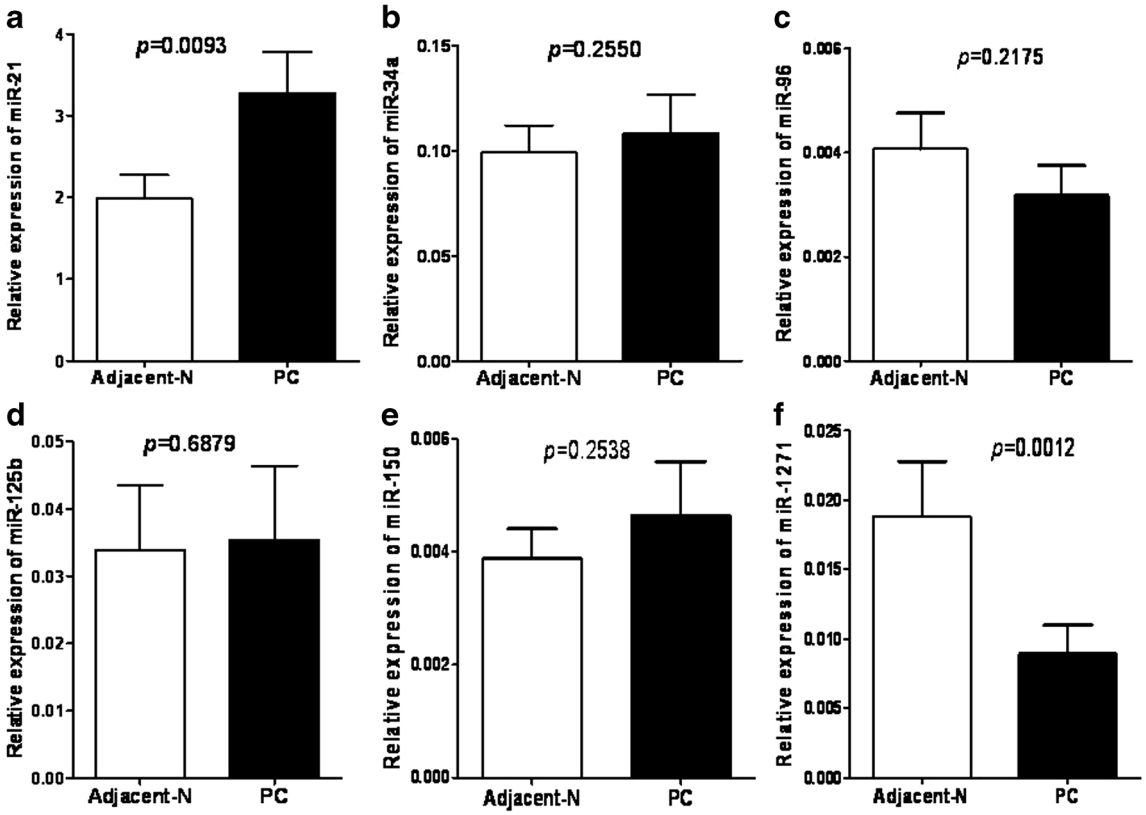

Fig. 2 Correlation of miRNA levels with prostate cancer and paired adjacent non-tumor tissues. **a:** Significantly higher level of miR-21 expression was found in cancer tissues. ($p = 0.0093$). **b-e:** No significant differences were observed between prostate cancer and paired adjacent non-tumor tissues cases for the four miRNAs(miR-34a,miR-96,miR-125b and miR-150). **f:** Significantly lower level of miR-1271 expression was found in cancer tissues. ($p = 0.0012$). Adjacent-N: adjacent non-tumor tissues; PC: prostate cancer tissues

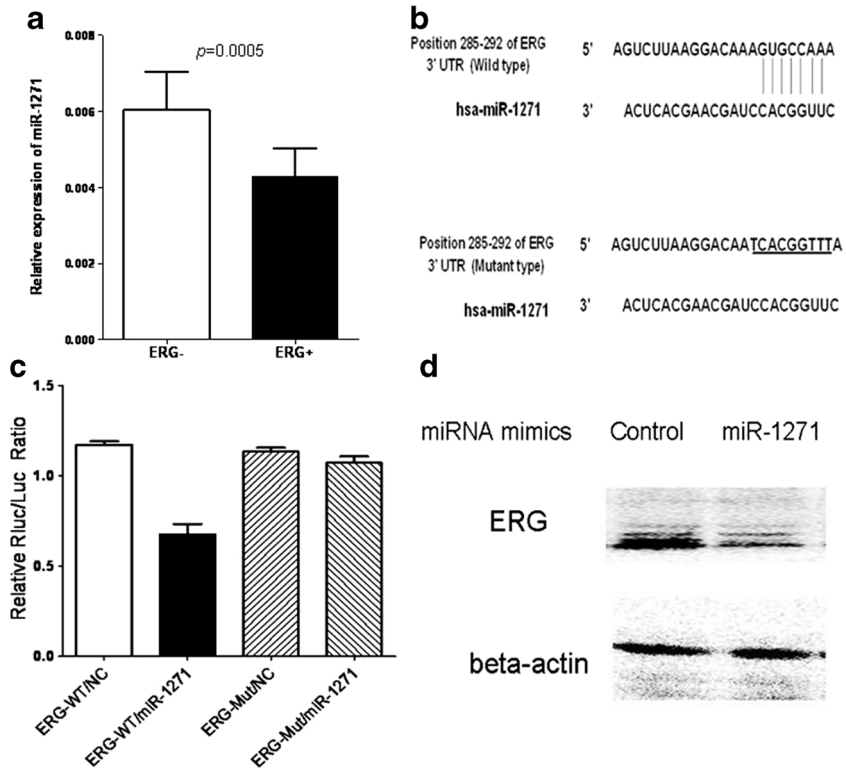

Fig. 3 ERG is a direct target of miR-1271 **a:**Significant difference was observed between ERG-positive and –negative cases for miR-1271 expression ($p = 0.0005$). **b:** Bioinformatics showed that miR-1271 potentially target the position 285–292 of ERG 3′ UTR (wild type). **c:** Two reporter plasmids were constructed, one carrying the wild-type ERG 3′-UTR region (ERG-WT), the other carrying the mutant-type ERG 3′-UTR region (ERG-Mut). The PC-3 and LNCaP cells were transfected with either miR-1271 mimics or miRNA control mimics (Negative Control:NT) for 2 days. miR-1271 mimics-transfected cells showed a marked reduction of wild-type reporter luciferase activity. **d:** Down regulation of ERG protein expression upon miR-1271 restoration in PC-3 and LNCaP cell lines

protein expression had 95.7%- 96.5% specificity for determining ERG rearrangement prostate cancer by using a combined immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) analysis. Thus, ERG protein expression may be useful for molecularly subtyping prostate cancer based on ERG rearrangement status. In accordance with several studies in Japanese and Koreans [3, 20], our results also showed that the percentage of ERG-positive cases is 18.6%, which is lower than the general findings reported involving western populations (approximately 50%) [1, 17]. Thus, the prevalence of ERG expression was significantly different amongst PCa patients of different ethnicities. ERG status analysis may help to better understand the differences in the etiology of PCa initiation and progression between ethnic groups.

MiR-21 was found to be over expressed in different human cancers (e.g. lung cancer, breast cancer) and was thought to be endowed with oncogenic properties by targeting tumor-suppressor genes [21, 22] (e.g. PTEN

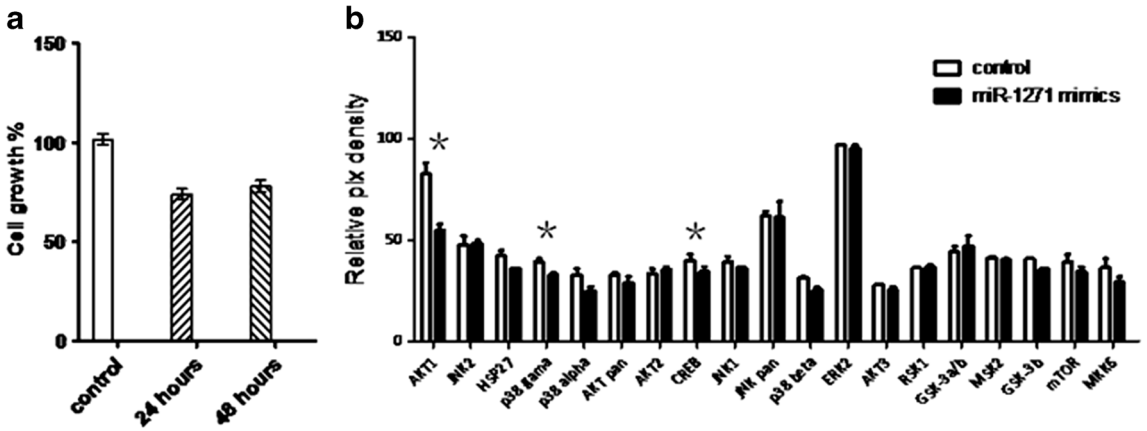

Fig. 4 Possible role of miR-1271 in PCa **a:** PC-3 and LNCaP cells were tranfected without or with 50 nM miR-1271 mimics and tested for cell growth by the MTT assay at 48 h after treatment. Results were expressed as percentage of cell growth in cells not treated with any inhibitor. Each bar represents the mean value for the 4 times experiment ± SD. $^{*}p < 0.05$ is significantly different from vehicle. **b:** Phosphorylation-MAPK array data (in duplicate) for PC-3 and LNCaP cells without or with 50 nM miR-1271 mimics transfection for 2 days. Each bar represents mean ± SD pixel density. $^{*}p < 0.05$ are significantly different from the control

and PDCD4,. Our study showed that miR-21 was significantly overexpressed in PCa than the adjacent non-tumor tissue, which is in agreement with the previous study that miR-21 was differently expressed in carcinomas and matched non-tumor tissues obtained from 85 advanced PCa patients [23]. They also found that PCa patients with high miR-21 expression have shorter progression-free survival than those with low miR-21 expression, which suggested that up-regulation of miR-21 may serve as an independent predictor of progress-free survival in PCas.However,Folini et al. [9] reported that miR-21 was not differently expressed in carcinomas and matched non-tumor tissues obtained from 36 untreated prostate cancer patients subjected to radical prostatectomy. Furthermore, it has been suggested that some miRNAs might have contradictory roles depending upon the tumor type. Indeed, it has been shown that miR-96 and miR-125 can function either as oncogene or tumor suppressor gene in different tumor types [24–26]. Thus, miRNA expression can be highly tissue specific and the relevance of microRNAs in the development, progression and prognosis of prostate cancer need to be further stuied.

Our results showed that the miR-1271 expression was not only significantly lower in PCa tissues compared to the adjacent non-tumor tissue, but also correlated with ERG expression in PCa. A computer search for miRNA targets in the ERG 3′-UTR sequence revealed several potential miRNAs complementary to this region, among which miR-1271 was the strongest candidate. Our in vitro luciferase assay study also showed that miR-1271 was regulator of the ERG gene. Furthermore, ERG protein levels are downregulated in PC-3 and LNCaP cells with miR-1271 mimics' transfection. Collectively, these data suggest that ERG is a direct target of miR-1271 in prostate cancer. Furthermore, we found that overexpression of miR-1271 significantly reduced proliferation of prostate cancer cells in vitro, which is in agreement with the previous study [27]. Our results indicated that miR-1271 was an important tumor suppressor miRNA in prostate cancer by targeting ERG oncogene. Previous studies also suggested that miR-1271 was a tumor suppressor by targeting GPC3, IGF1R, IRS1, mTOR, DIXDC1and BCL2 gene [27, 28]. By using MAPK array, we found that AKT1,p38 gamma and CREB kinases activity have significantly downregulated in PC-3 and LNCaP cells with miR-1271 restoration, which indicating that miR-1271 also play an important role in MAPK signaling pathway. The activation of AKT and p38 pathway appears to be characteristic of many aggressive prostate cancers and therapies will optimize targeting of this pathway to improve outcomes [15, 16]. Suarez et al. showed that CREB targeting can increase radiation-induced pre-mitotic apoptosis [14]. The mechanism of miR-1271 restoration attributing to downregulation of MAPK signaling need to be further studied to determine its biological relevance in PCa.

Conclusions

In summary, we observed downregulation of miR-1271 expression in ERG positive PCa. The overexpression of miR-1271 significantly inhibited proliferation and MAPK signaling in PCa cells. Targeting ERG by miR-1271 could be an effective approach for therapeutic strategy for ERG positive prostate cancer.

Acknowledgements This study was financially supported by the grants from Natural Science Foundation of China (81001054).

Author Contributions All authors carried out the experiments, participated in the design of the study and performed the statistical analysis, conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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