

RESEARCH ARTICLE

Anti-tumor Role of MicroRNA-4782-3p in Epithelial Ovarian Cancer

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Abstract: Ovarian cancer ranks fifth in cancer death among women. The 5-year relative survival of all stages ovarian cancer is 47%. Identification of new molecular targets is required for the development of targeted therapy. MicroRNA (miRNA) are small, highly conserved RNA molecules involved in the regulation of gene expression. miR-4782-3p has shown tumor-suppressive activities in non-small cell lung cancer. Thus, it is possible that miR-4782-3p may play a role in the development of ovarian cancer. Herein, we analyzed the levels of miR-4782-3p in ovarian cancer tissue and cell lines and tested the function of miR-4782-3p in cell proliferation and cell apoptosis. We found that miR-4782-3p plays an inhibitory role in ovarian cancer growth. The data showed that ovarian cancer tissue and cell lines showed lower levels of miR-4782-3p, which inhibited cell growth and increased cell apoptosis. Moreover, PDGFR α was identified as a direct target of miR-4782-3p. In conclusion, our data indicated that miR-4782-3p has an inhibitory impact on ovarian cancer.

Keywords: MiR-4782-3p, Ovarian cancer, Cell growth, Apoptosis

1. Introduction

Ovarian cancer (OC) contributed approximately 239,000 new cases and 152,000 deaths worldwide annually^[1]. It is the seventh most commonly diagnosed cancer among women worldwide^[2-6] and the tenth most common in China. Epithelial ovarian cancer (EOC), a common type of ovarian cancer, develops from the cells that cover the outer surface of the ovary. In most cancer, EOC is a type of treatable solid cancer, which respond to excision and chemotherapy drug. This disease, however, frequently persists and recurs, having the highest fatality-to-case ratio of all the gynecologic cancers^[7]. The identification of new molecular targets is required for the development of targeting therapy^[8].

MicroRNAs (miRNAs) are a class of small, endogenous RNAs of 21-25 nucleotides (nts) in length. MiRNAs regulate the gene expression by targeting specific mRNA for degradation to achieve translational repression^[9]. Aberrant expressions of miRNA are involved in tumorigenesis of various cancers^[10-16]. In OC, many miRNAs were aberrantly expressed. For example, specific miRNAs such as miR-21, miR-203, miR-205, miR-141, miR-200a, miR-200b, and miR-200c were significantly up-regulated in the cancer tissues in relative to in the normal ovarian tissues. Besides, subtypes of OC show different miRNAs profiles, the expression of miR-200a and miR-200c were enhanced in serous,

endometrioid, and clear cell, whereas the expression of miR-200b and miR-141 are increased in endometrioid and serous subtypes^[17].

MiR-4782-3p is a newly discovered microRNA. The function of miR-4782-3p has been investigated in hepatocellular carcinoma^[18] and non-small cell lung cancer^[19]. Two studies indicated that miR-4782-3p plays a tumor-suppressive role in hepatocellular carcinoma (HCC) and non-small cell lung cancer. Thus, it is possible that miR-4782-3p also plays an inhibitory role in OC.

Platelet-derived growth factor receptor alpha (PDGFR α) is a receptor located on the surface of various cell types^[20]. Significantly, the PDGFR α expression rate in malignant ovarian tumors was higher than that in normal ovarian tissues or benign ovarian tumor^[21]. Furthermore, a previous study showed that PDGFR α contributes to the progression of ovarian cancer^[22]. PDGFR α is a targeted gene of miR-34a^[23] in gastric cancer and was targeted by miR-219-5p in colorectal cancer^[24].

Here, we tested the effect of miR-4782-3p in ovarian cancer and revealed the anti-tumor function of miR-4782-3p. Our data also indicated miR-4782-3p targeted PDGFR α at least in SKOV3 cells.

2. Materials and methods

2.1. Patients and sample

Ten EOC tissue samples and adjacent normal tissue were acquired from the Department of Gynecology and Obstetrics, West China Second University Hospital, Sichuan University, Chengdu. Ethics committee of Sichuan University assessed and approved the use of human EOC tissues in this study. Informed consent of all patients was obtained in accordance with the regulation and law in China. The pathological diagnosis was performed by the senior pathologist of West China Second University Hospital.

2.2. Cell culture and reagent

The OC cell lines, such as SKOV3 and HO8910 cells, and normal human ovarian epithelial cells were obtained from the cell bank of Sichuan University. The SKOV3 cell line was derived from ovarian adenocarcinoma, whereas the HO8910 cell line was derived from ovarian serous cystadenocarcinoma. The cells were cultured in Dulbecco's Modified Eagle Medium (DMEM; cat. No. 11965092, Thermo Fisher, Waltham, MA) with fetal bovine serum (cat. no.10091155, Thermo Fisher, Waltham, MA). Cisplatin was purchased from BioChemPartner, Chengdu, China. The final concentration of cisplatin used was 25 μ M.

2.3. Quantitative reverse transcription-polymerase chain reaction (qRT-PCR)

The levels of miR-4782-3p in human EOC tissue samples, SKOV3, and HO8910 cells were analyzed by qRT-PCR.

Firstly, Trizol™ reagent (cat. No. 15596026, Thermo Fisher, Waltham, MA) was applied to isolate the total RNAs from OC tissue or SKOV3 and HO8910 cells. U6 small nuclear (sn) RNA was used as the internal control. qRT-PCR was performed using QuantStudio 3 Real-Time PCR System (Thermo Fisher, Waltham, MA). PCR was performed using 0.1 μ g of cDNA and SYBR-Green PCR Master Mix (Applied Biosystems, Grand Island, NY). Furthermore, appropriate primers were applied. The Applied Biosystems StepOnePlus Real-Time PCR System was used for transcription analysis with the StepOne software version 2.1. Comparative $\Delta\Delta$ CT method was used for data analysis. The primers were synthesized and tested by the ShengRui Company (ShengRui, Chengdu, China)^[25-28]. The primer sequences of miR-4782-3p were as follows: Forward 5'-TGCGGTGATTGTCTTCAT ATC-3'; reverse 5'-GTCGTATCCAG TGCAGGGTCCGAGGTGCAC TGGATACGACGTTCTAG-3'. The primer sequences of U6 snRNA were as follows: Forward 5'-CTCGCTTCGGCAGCATATACT-3'; reverse 5'-ACGCTTCACGAATTTGCGTG TC-3'. The primer sequences of PDGFR α were as follows: Forward 5'-CCCCACCGTGTT CTCGACA-3'; reverse 5'-CCGGATGGTCA CTCTTTAGGAAG-3'. The primer sequences of GAPDH were as follows: Forward 5'-CCTGCACCACCAACTGCTTA-3'; reverse 5'-GCCATCCACAGTCTTCTGAG-3'. The relative levels of miR-4782-3p were normalized to U6 snRNA, and the relative levels of PDGFR α were normalized to GAPDH.

2.4. miR-4782-3p mimics, miR-4782-3p ASO, and PDGFR α siRNA transfection in OC cells

The miR-4782-3p levels in SKOV3 and HO8910 cells were up-regulated and down-regulated by miR-4782-3p mimics and miR-4782-3p antisense oligonucleotides (ASO), separately. The miR-4782-3p mimics and ASO were designed and constructed by Sangon Biotech (Shanghai, China). PDGFR α siRNA was constructed by Sangon Biotech (Sangon, Shanghai, China). SKOV3 and HO8910 cells were seeded at a density of 1×10^6 per well into 6-well plates and cultured overnight. Then, miR-4782-3p mimics and ASO, PDGFR α siRNA were transfected into cells using the Lipofectamine 2000 (cat. no. 11668019, Thermo Fisher, Waltham, MA) according to the standard protocol.

2.5. Cell growth

The CyQUANT MTT Cell Viability Assay (cat. no. V13154) was applied to determine the cell growth. Briefly, the MTT stock solution and sodium dodecyl sulfate-hydrochloride (SDS-HCl solution) were prepared. In this experiment, we added 10 μ l of 12-mM MTT stock solution to each well. Then, the whole plates were incubated at 37°C for 4 h. Then, 100 μ l of SDS-HCl solution was added to each well and mixed well with a pipet. Then, the plates were incubated at 37°C for 4 h in a humidified chamber.

At last, optical density was measured using a microplate reader (Multiskan Fc, Thermo Scientific, Waltham, MA, USA) with a 570-nm filter^[29].

2.6. Annexin V staining protocol for flow cytometry

First, cell for apoptosis detection was digested and harvested. The cell apoptosis rate was analyzed using the Dead Cell Apoptosis Kit with Annexin V FITC and propidium iodide (PI) (cat. no. V13242, Thermo Fisher, Waltham, MA). Briefly, the cells were washed once in 1× phosphate-buffered saline (PBS), then once in 1× binding buffer. Next, the cells were suspended in 1× binding buffer at 1×10⁶ cells/ml, and annexin V-FITC was added. The mixture was incubated for 10-15 min at room temperature in the absence of light. Then, 2 ml of 1× binding buffer was added the mixture, which was then centrifuged at 400 ×g for 5 min. The supernatant was discarded afterward. Then, cell pellet was resuspended in 200 µl of 1× binding buffer containing 3 µl of PI and incubated for 5 min on ice. The apoptosis rate was analyzed with a BD FACSVerse™ flow cytometer (BD Biosciences, Franklin Lakes, NJ) with a 488-nm excitation laser. The data were analyzed using BD FACSuite™ version 1.01 (BD Biosciences). Cells in the right quadrant were chosen for apoptosis assay for quantification.

2.7. Prediction of the putative targets of miR-4782-3p

The putative target genes of miR-4782-3 were predicted by the bioinformatics method. Here, we used TargetScan (<http://www.targetscan.org/>)^[30] to calculate the possible mRNA targets of miRNAs by calculating the chance of conserved 8mer, 7mer, and 6mer sites that match the seed region of each miRNA.

2.8. Dual-luciferase reporter assays

The activity of PDGFRα was assayed by Dual-Luciferase® Reporter Assay System (cat. no. E1910, Promega, Madison, WI). Briefly, we cloned the 3'-untranslated region (3'-UTR) of PDGFRα genes and the mutated version of 3'-UTR of PDGFRα genes. The GeneArt™ Site-Directed Mutagenesis System (cat. no. A13282, Thermo Fisher, Waltham, MA) was used for the generation of the 3'-UTR of mutant PDGFRα. Then, these clones were inserted into the reporter plasmid and the control. Next, miR-4782-3p mimics were transfected to SKOV3 cells by lipofectamine 2000 according to the protocol. Twenty-four hours later, SKOV3 cells were collected for the luciferase activity measurement. Firefly luciferase activity was measured first, then Renilla luciferase assay buffer 2.0 was added to simultaneously quench firefly luciferase activity and measure Renilla luciferase activity. Then, the ratio of firefly luciferase/Renilla luciferase of each tube was calculated, and the value in control groups was arbitrarily defined as 100%.

2.9. Western blotting

SKOV3 cells were collected and washed by PBS for three times. Then, cells were transferred to cells lysis buffer (cat. no. ab152163, Abcam, Cambridge, UK). The protease inhibitor cocktail (cat. no. ab65621, Abcam, Cambridge, UK) was also added. The mixture was agitated for 30 min at 4°C. Then, the tube was centrifuged at 12,000 rpm. The supernatant was collected for protein amount determination by Pierce™ BCA Protein Assay Kit (cat. no. 23225, Thermo Fisher, Waltham, MA) according to the protocol. We of total protein from the cell lysate (30 µg) were loaded into each well of the stacking gel, and the SDS-PAGE was run for 2 h at 80 V. Upon completion of electrophoresis, the protein was transferred from the gel to the membrane. The membrane was blocked in a blocking buffer (cat. no. ab126587, Abcam, Cambridge, UK) for 1 h at room temperature. The primary antibodies used in this experiment were anti-PDGFRα (cat. no. ab5460, Abcam, Cambridge, UK) and anti-β-actin (cat. no. ab8227, Abcam, Cambridge, UK). The anti-PDGFRα and anti-β-actin antibodies were prepared in 1:1000 and 1:2000 dilutions, respectively. The membrane was incubated with the primary antibodies at 4°C overnight. Subsequently, the membrane was incubated with a secondary antibody (goat anti-rabbit IgG, 1:2000 dilution, cat. no. ab97080, Abcam, Cambridge, UK) for 1 h at room temperature. At last, the protein levels (PDGFRα and β-actin) were detected by ECL Western Blotting Substrate Kit (cat. no. ab65623, Abcam, Cambridge, UK).

2.10. Statistical analysis

Every experiments were performed at least three time. Data were presented as mean±standard deviation (SD). The means between the two groups were compared using the two-tailed *t*-test. Means among three groups were compared using one-way analysis of variance (ANOVA), with post-hoc Student-Newman-Keuls test. Results with *p*<0.05 were considered statistically significant. The statistical analyses were performed using the SPSS software (version 15.0).

3. Results

3.1. Low levels of miR-4782-3p in OC tissues samples

To test the role of miR-4782-3p in OC, we firstly determined the levels of miR-4782-3p in 10 OC tissues compared with that in adjacent normal tissue. The data showed that the expression of miR-4782-3p in tumor tissue is lower than the matched normal adjacent tissue (**Figure 1**). Furthermore, OC tissues showed lower miR-4782-3p mean levels.

3.2. miR-4782-3p inhibited cells growth and increased cell apoptosis rate

SKOV3, HO8910, and normal human ovarian epithelial cells were tested for the miR-4782-3p levels by

qRT-PCR. SKOV3 and HO8910 cells showed a lower level of miR-4782-3p (**Figure 2A**). Then, the miR-4782-3p mimics were transfected into SKOV3 and HO8910 cells to alter the miR-4782-3p levels (**Figure 2B**). We tested the cell growth and apoptosis following the transfection of miR-4782-3p mimics (**Figure 2C**). The data showed that miR-4782-3p mimics inhibited cell growth. Moreover, up-regulation of miR-4782-3p due to miR-4782-3p mimics increased the cell apoptotic rate (**Figure 2D and E**).

3.3. Down-regulation of miR-4782-3p promoted cell growth

Next, we tested the effect of down-regulation of miR-4782-3p by miR-4782-3p ASO transfection to SKOV3 and HO8910 cell. The decrease of miR-4782-3p was confirmed by qRT-PCR (**Figure 3A**). We found that down-regulation of miR-4782-3p increased cell growth (**Figure 3B**). Next, SKOV3 and HO8910 cells were treated with cisplatin following miR-4782-3p ASO transfection. We found that cisplatin increased the cell apoptosis rate and the down-regulation of miR-4782-3p decreased the rate of apoptosis induced by cisplatin (**Figure 3C and D**).

3.4. miR-4782-3p targeted PDGFR α

To elucidate the underlying mechanism of miR-4782-3p, the bioinformatics method was applied. Bioinformatics data showed that miR-4782-3p may bind the 3'-UTR of PDGFR α (**Figure 4A**). To confirm this, we cloned the 3'-UTR of PDGFR α genes and the mutated version of 3'-UTR of PDGFR α genes. Then, these clones were inserted into the reporter plasmid and the control. Luciferase activity was determined 48 h following transfection. We found that in the wild-type 3'-UTR of PDGFR α , miR-4782-3p mimics reduced the luciferase activity, indicating that miR-4782-3p mimics could bind the 3'-UTR of PDGFR α , whereas, in the mutant 3'-UTR of PDGFR α , miR-4782-3p mimics could not reduce the luciferase activity. This data indicated that PDGFR α is one of the targeted genes of miR-4782-3p (**Figure 4B**). Moreover, at 48 h post-transfection, PDGFR α protein levels were determined by Western blot analysis, and the results indicated that miR-4782-3p mimics could inhibit the expression of PDGFR α in SKOV3 cells (**Figure 4C**). Next, we tested the PDGFR α level in the normal adjacent tissues and tumor tissues and found that PDGFR α expression was increased in the latter (**Figure 4D**). Next, we transfected PDGFR α siRNA to SKOV3 and HO8910 cells. After 24 h, the levels of PDGFR α were tested by qRT-PCR, we found that PDGFR α siRNA decreased the PDGFR α levels (**Figure 4E**). Then, the cell growth was tested by MTT assay, and we found that PDGFR α siRNA decreased the cell growth of SKOV3 and HO8910 cells (**Figure 4F**).

4. Discussion

In this study, we tested the effect of miR-4782-3p in ovarian cancer and discovered that miR-4782-3p showed lower levels in tumor tissues. In addition, miR-4782-3p inhibited cellular proliferation and promoted cell apoptosis. We also found that PDGFR α is a direct target of miR-4782-3p.

Previous research indicated that miR-4782-3p plays a tumor-suppressive role in liver cancer^[18] and lung cancer^[19]. This study confirmed the suppressive role of miR-4782-3p in epithelial ovarian cancer. Previous studies showed that miR-4782-3p inhibits tumor growth through ubiquitin-specific protease 14 (USP14). Herein, obtained results indicate that miR-4782-3p inhibited EOC growth through PDGFR α . In our opinion, miR-4782-3p played anti-tumor role, not tumor-promoting role in three types of cancer. It is possible that miR-4782-3p may show tumor inhibitory roles in other types of cancer.

PDGFR and platelet-derived growth factor (PDGF) participate in multiple normal physiological processes, such as embryogenesis, wound healing, and the development of the vascular system^[31]. In addition, PDGF and PDGFR have been shown to participate in the progressive growth of ovarian cancer^[32]. Interestingly, a previous study showed that PDGF-D could promote ovarian cancer invasion by up-regulating matrix metalloproteinases^[33].

More importantly, PDGFR α is an independent indicator of a poor prognosis in epithelial ovarian neoplasms^[34]. PDGFR α and PDGF are an important novel potential target for ovarian cancer^[35]. Our data showed that inhibition of PDGFR α through siRNA could inhibit the cells growth of ovarian cancer cells, which is consistent with a previous study^[22]. Thus, our data indicated that inhibition of PDGFR α through siRNA or miR-4782-3p could both inhibit OC cell proliferation.

Interestingly, another study showed that inhibition of USP14 promotes connexin 32 internalization and

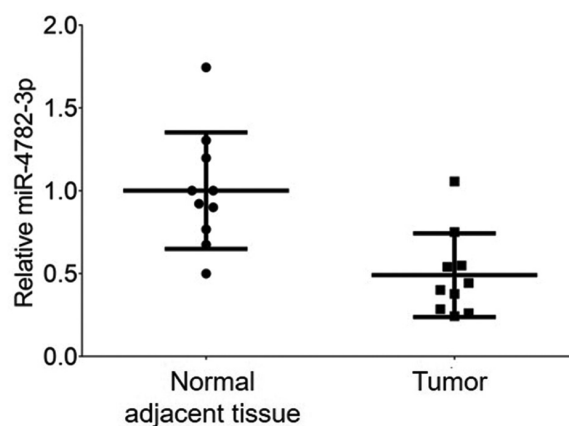


Figure 1. miR-4782-3p levels in OC tissues. miR-4782-3p levels in ten ovarian cancer tissue samples were analyzed by qRT-PCR. miR-4782-3p levels in adjacent normal tissue were arbitrarily normalized. Data are presented as mean \pm ea. Each experiment was performed at least for three times.

counteracts cisplatin cytotoxicity in human ovarian cancer cells^[36]. Remarkably, we found that USP14 negatively regulates lung tumorigenesis through not only apoptosis but also the autophagy pathway^[37]. Thus, it is possible that USP14 may be targeted by miR-4782-3p in ovarian cancer, and it is possible that miR-4782-3p could regulate autophagy. This warrants further investigation in future.

In this study, obtained results revealed that miR-4782-3p could target PDGFR α , indicating that miR-4782-3p is also a potential therapeutic target. It is known that USP14 is targeted by miR-4782-3p. Previous data showed that USP14 could promote cellular proliferation and inhibit apoptosis in ovarian cancer^[38]. Thus, we suspect that both PDGFR α and USP14 are targets of miR-4782-3p.

A growing number of studies revealed the importance of microRNAs in ovarian cancer and showed that differential expression profiles of miRNAs in the serum, plasma, exosomes in serum, ascites fluids, and tissues of ovarian cancer patients could help identify potential diagnostic and prognostic biomarkers^[39]. Furthermore, substantial evidence

showed the dysregulation of miRNA expression in the early stages of ovarian cancer transformation^[40-42]. It is also important to note that miRNAs also regulated proliferation, cell cycle, and survivability of ovarian carcinomas^[43-45].

In conclusion, our data showed the suppressive function of miR-4782-3p in ovarian cancer. Overexpression of miR-4782-3p leads to the inhibition of cancer cell growth and increased apoptosis rate, probably mediated by PDGFR α , the target of miR-4782-3p.

Acknowledgments

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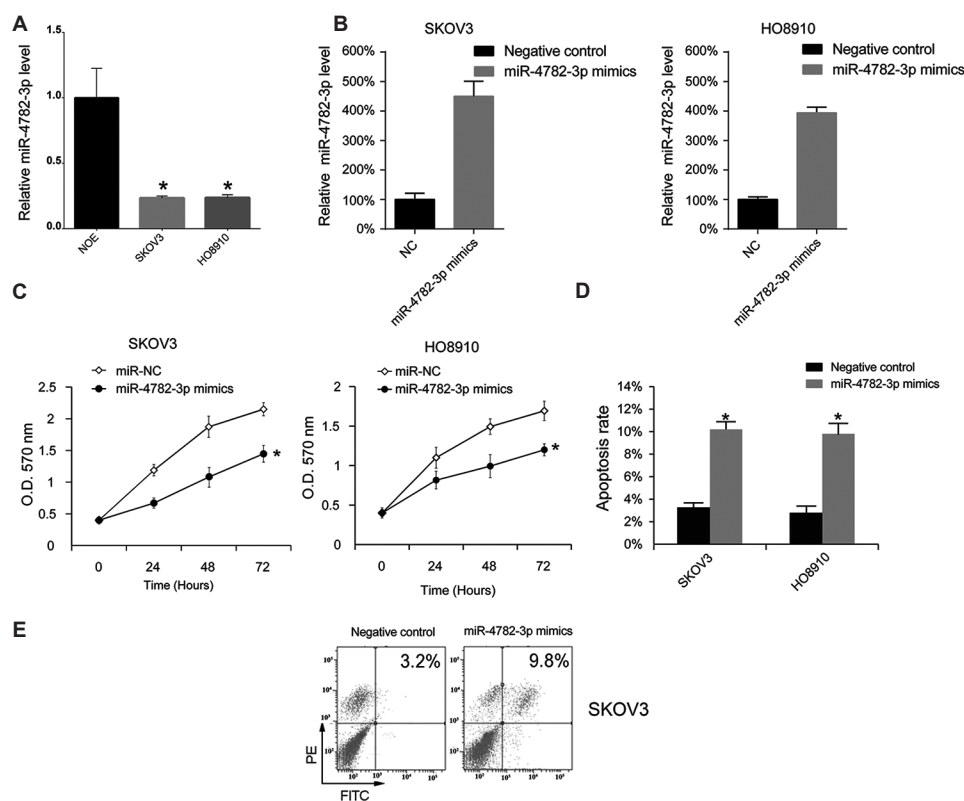


Figure 2. Up-regulation of miR-4782-3p suppressed proliferation and increased apoptosis in SKOV3 and HO8910 cells. (A) The expression value of miR-4782-3p in normal human ovarian epithelial cells (NOE) and SKOV3 and HO8910 cells were determined by qRT-PCR. The miR-4782-3p levels of SKOV3 and HO8910 cells were respectively compared with the miR-4782-3p levels of NOE. (B) The level of miR-4782-3p in NOE was normalized and defined as 100%. SKOV3 and HO8910 cells were placed in plate; 12 h later, miR-4782-3p mimic transfected was performed. After 24 h, miR-4782-3p levels in the SKOV3 and HO8910 cells were assayed by qRT-PCR. (C) miR-4782-3p levels in the control group were normalized as 100%. In addition, cellular proliferation was assessed by the MTT method. (D) Finally, SKOV3 and HO8910 cells were respectively pretreated with miR-4782-3p. Then, SKOV3 and HO8910 cells were stained with annexin V-FITC and PI and the cell apoptotic rate was evaluated by FACS analysis. (E) Representative images of flow cytometry for apoptosis of SKOV3 cells. Data are indicated as mean ap. Each experiment was performed for at least three times. * $P < 0.05$

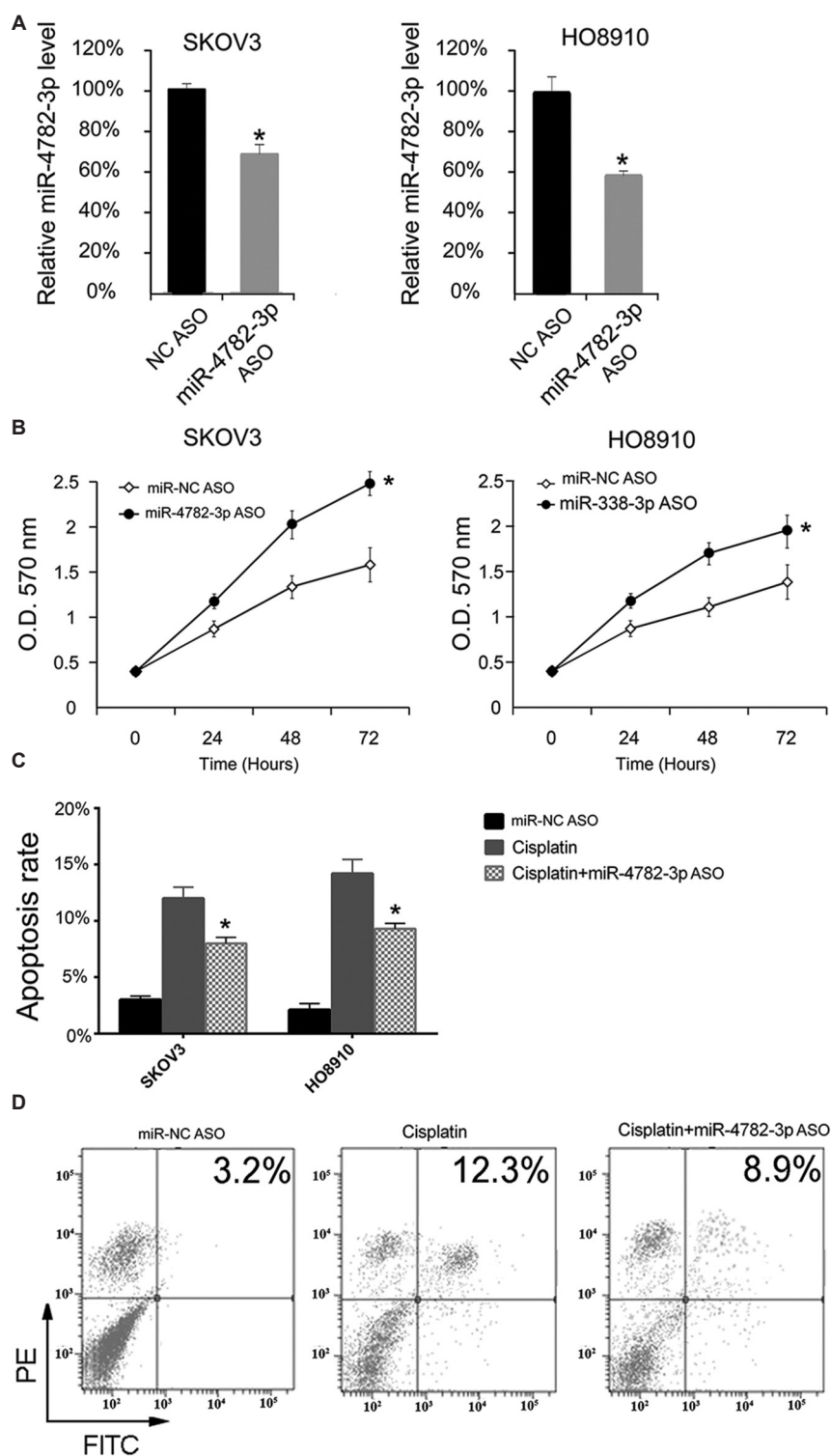


Figure 3. Suppression of miR-4782-3p promoted SKOV3 and HO8910 proliferation. (A) SKOV3 and HO8910 cells were placed into 6-well plates and then transfected with miR-4782-3p ASO. After 24 h, miR-4782-3p level was tested by qRT-PCR. miR-4782-3p levels in NC ASO were normalized as 100% in both SKOV3 and HO8910 cells. (B) After miR-4782-3p ASO transfection, MTT assay was performed to test the cell growth. Apoptosis rates were tested by annexin V-FITC/PI staining. (C) Twenty-four hours following miR-4782-3p ASO transfection, miR-NC ASO was used as control. (D) Representative images of flow cytometry for apoptosis of SKOV3 cells. The data are presented as mean \pm SD. Each experiment was performed for at least three times. * $P < 0.05$; NC, negative control.

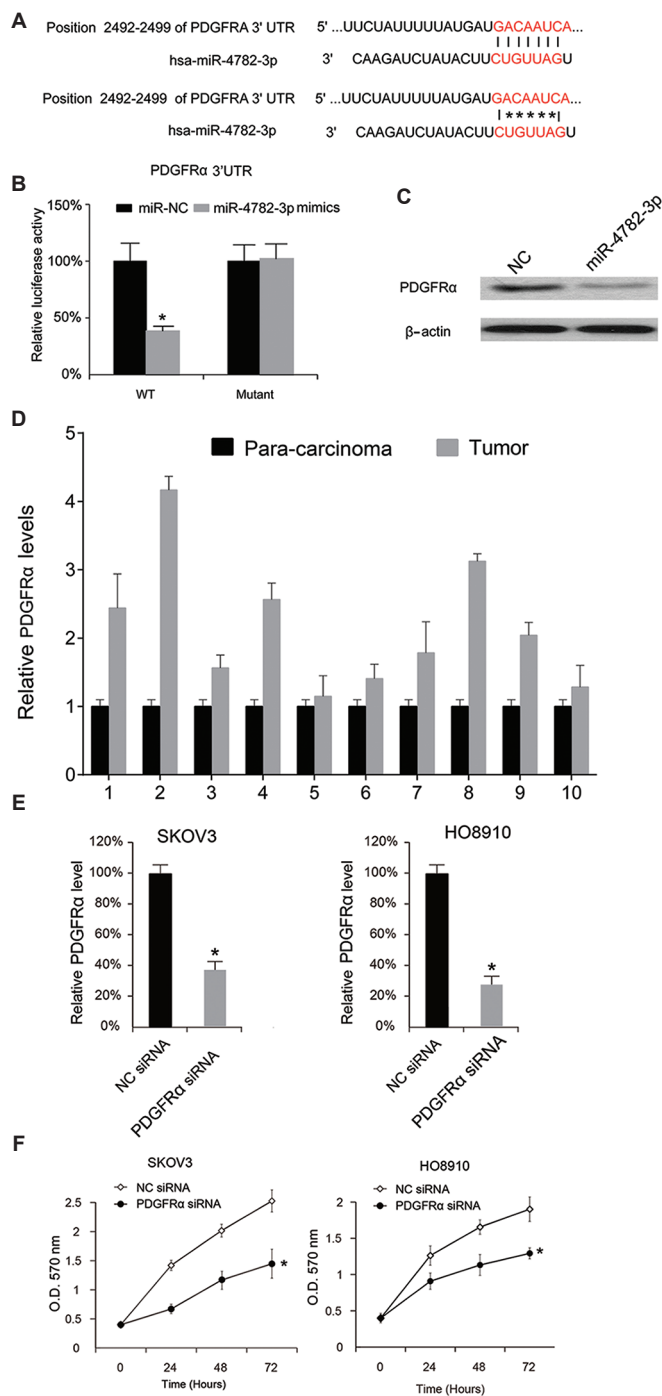


Figure 4. PDGFR α was targeted by miR-4782-3p in SKOV3 cells. (A) The binding site of miR-4782-3p in PDGFR α and its mutated version is listed. miR-4782-3p mimics and plasmids containing the mutated 3'-UTR sequence of PDGFR α were transfected to SKOV3, whereas miR-NC and plasmids containing wild-type transfection were used as controls. (B) 48 h later, the luciferase activity was analyzed. (C) miR-4782-3p mimics were transfected into SKOV3 cells, and the level of PDGFR α protein was determined by Western blotting. PDGFR α levels in ten OC tissue samples were analyzed by qRT-PCR. (D) PDGFR α levels in adjacent normal tissue were arbitrarily normalized as 1. SKOV3 and HO8910 cells were seeded separately and then transfected with PDGFR α siRNA. After 24 h, PDGFR α expression was tested by qRT-PCR. (E) PDGFR α levels in NC ASO were normalized as 100% in control. (F) The cellular proliferation was tested by MTT assay following PDGFR α siRNA transfection. Each experiment was performed for at least three times. * $P < 0.05$; NC, negative control.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Author contributions

T.A. and J.L. collected patient data. T.A., J.L., and Q.Y. performed PCR, Western blotting, and other molecular experiments. L.X. and X.J. conceived the idea of the study design and wrote the manuscript. X.J. analyzed data and revised the manuscript for important intellectual content. All the authors have read and approved the manuscript.

References

- Reid BM, Permuth JB, Sellers TA, 2017, Epidemiology of Ovarian Cancer: A Review. *Cancer Biol Med*, 14:9–32.
- Holschneider CH, Berek JS, editors, 2000, Ovarian Cancer: Epidemiology, Biology, and Prognostic Factors. In: Seminars in Surgical Oncology. Hoboken, New Jersey: Wiley Online Library.
- Permuth-Wey J, Sellers TA, 2009, Epidemiology of Ovarian Cancer. In: Cancer Epidemiology. Berlin: Springer, pp.413–37. DOI: 10.1007/978-1-60327-492-0_20.
- Nagle CM, 2011, Ovarian Cancer Epidemiology. In: Encyclopedia of Cancer: Berlin: Springer, pp.2686–9.
- Lacey JV Jr., Mink PJ, Lubin JH, *et al.*, 2002, Menopausal Hormone Replacement Therapy and Risk of Ovarian Cancer. *JAMA*, 288:334–41. DOI: 10.1001/jama.288.3.334.
- Greene MH, Clark JW, Blayney DW, editors, 1984, The Epidemiology of Ovarian Cancer. In: Seminars in Oncology. Amsterdam, Netherlands: Elsevier.
- Momenimovahed Z, Tiznobaik A, Taheri S, *et al.*, 2019, Ovarian Cancer in the World: Epidemiology and Risk Factors. *Int J Womens Health*, 11:287. DOI: 10.2147/ijwh.s197604.
- Yap TA, Carden CP, Kaye SB, 2009, Beyond Chemotherapy: Targeted Therapies in Ovarian Cancer. *Nat Rev Cancer*, 9:167. DOI: 10.1038/nrc2583.
- Bartel DP, 2009, MicroRNAs: Target Recognition and Regulatory Functions. *Cell*, 136:215–33. DOI: 10.1016/j.cell.2009.01.002.
- Cortez MA, Anfossi S, Ramapriyan R, *et al.*, 2019, Role of miRNAs in Immune Responses and Immunotherapy in Cancer. *Genes Chromosomes Cancer*, 58:244–53. DOI: 10.1002/gcc.22725.
- Hu W, Tan C, He Y, *et al.*, 2018, Functional miRNAs in Breast Cancer Drug Resistance. *Oncol Ther*, 11:1529–41.
- O'Bryan S, Dong S, Mathis JM, *et al.*, 2017, The Roles of Oncogenic miRNAs and their Therapeutic Importance in Breast Cancer. *Eur J Cancer*, 72:1–11. DOI: 10.1016/j.ejca.2016.11.004.
- Slattery ML, Mullany LE, Sakoda LC, *et al.*, 2018, Dysregulated Genes and miRNAs in the Apoptosis Pathway in Colorectal Cancer Patients. *Apoptosis*, 23:237–50. DOI: 10.1007/s10495-018-1451-1.
- Yang F, Ning Z, Ma L, *et al.*, 2017, Exosomal miRNAs and miRNA Dysregulation in Cancer-associated Fibroblasts. *Mol Cancer*, 16:1–10. DOI: 10.1186/s12943-017-0718-4.
- Hirschberger S, Hinske LC, Kreth S, 2018, MiRNAs: Dynamic Regulators of Immune Cell Functions in Inflammation and Cancer. *Cancer Lett*, 431:11–21. DOI: 10.1016/j.canlet.2018.05.020.
- Florczuk M, Szpechcinski A, Chorostowska-Wynimko J, 2017, miRNAs as Biomarkers and Therapeutic Targets in Non-small Cell Lung Cancer: Current Perspectives. *Target Oncol*, 12:179–200. DOI: 10.1007/s11523-017-0478-5.
- Taylor DD, Gercel-Taylor C, 2008, MicroRNA Signatures of Tumor-derived Exosomes as Diagnostic Biomarkers of Ovarian Cancer. *Gynecol Oncol*, 110:13–21. DOI: 10.1016/j.ygyno.2008.04.033.
- Bo W, Hu Y, Feng X, *et al.*, 2016, The Tumor Suppressor Role of miR-4782-3p in Hepatocellular Carcinoma. *Oncol Rep*, 35:2107–12. DOI: 10.3892/or.2016.4568.
- Wu N, Zhang C, Bai C, *et al.*, 2014, MiR-4782-3p Inhibited Non-small Cell Lung Cancer Growth via USP14. *Cell Physiol Biochem*, 33:457–67. DOI: 10.1159/000358626.
- Ding H, Wu X, Boström H, *et al.*, 2004, A Specific Requirement for PDGF-C in Palate Formation and PDGFR- α Signaling. *Nat Genet*, 36:1111. DOI: 10.1038/ng1415.
- Yi C, Li L, Chen K, *et al.*, 2012, Expression of c-Kit and PDGFR α in Epithelial Ovarian Tumors and Tumor Stroma. *Oncol Lett*, 3:369–72.
- Matei D, Emerson R, Lai Y, *et al.*, 2006, Autocrine Activation of PDGFR α Promotes the Progression of Ovarian Cancer. *Oncogene*, 25:2060. DOI: 10.1038/sj.onc.1209232.
- Peng Y, Guo JJ, Liu YM, *et al.*, 2014, MicroRNA-34A Inhibits the Growth, Invasion and Metastasis of Gastric Cancer by Targeting PDGFR and MET Expression. *Biosci Rep*, 34:e00112. DOI: 10.1042/bsr20140020.
- Xiong GB, Zhang GN, Xiao Y, *et al.*, 2015, MicroRNA-219-5p Functions as a Tumor Suppressor Partially by Targeting Platelet-derived Growth Factor Receptor Alpha in Colorectal Cancer. *Neoplasia*, 62:855–63. DOI: 10.4149/neo_2015_104.
- Li D, Liu X, Lin L, *et al.*, 2011, MicroRNA-99a Inhibits Hepatocellular Carcinoma Growth and Correlates with Prognosis of Patients with Hepatocellular Carcinoma. *J Biol*

- Chem*, 286:36677–85. DOI: 10.1074/jbc.m111.270561.
26. Song B, Zhang C, Li G, *et al.*, MiR-940 Inhibited Pancreatic Ductal Adenocarcinoma Growth by Targeting MyD88. *Cell Physiol Biochem*, 35:1167–77. DOI: 10.1159/000373941.
 27. Zhou Q, Yu Y, 2015, Upregulated CDK16 Expression in Serous Epithelial Ovarian Cancer Cells. *Med Sci Monit*, 21:3409–14. DOI: 10.12659/msm.894990.
 28. Li H, Xu Y, Qiu W, *et al.*, 2015, Tissue miR-193b as a Novel Biomarker for Patients with Ovarian Cancer. *Med Sci Monit*, 21:3929. DOI: 10.12659/msm.895407.
 29. Mosmann T, 1983, Rapid Colorimetric Assay for Cellular Growth and Survival: Application to Proliferation and Cytotoxicity Assays. *J Immunol Methods*, 65:55–63. DOI: 10.1016/0022-1759(83)90303-4.
 30. Agarwal V, Bell GW, Nam JW, *et al.*, 2015, Predicting Effective microRNA Target Sites in Mammalian mRNAs. *Elife*, 4:e05005. DOI: 10.7554/elife.05005.
 31. Heldin CH, Westermark B, 1999, Mechanism of Action and *In Vivo* Role of Platelet-derived Growth Factor. *Physiol Rev*, 79:1283–316. DOI: 10.1152/physrev.1999.79.4.1283.
 32. Dabrow MB, Francesco MR, McBrearty FX, *et al.*, 1998, The Effects of Platelet-derived Growth Factor and Receptor on Normal and Neoplastic Human Ovarian Surface Epithelium. *Gynecol Oncol*, 71:29–37. DOI: 10.1006/gyno.1998.5121.
 33. Wang Y, Hu C, Dong R, *et al.*, 2011, Platelet-derived Growth Factor-D Promotes Ovarian Cancer Invasion by Regulating Matrix Metalloproteinases 2 and 9. *Asian Pac J Cancer Prev*, 12:3367–70. DOI: 10.1016/j.ygyno.2003.12.041.
 34. Henriksen R, Funa K, Wilander E, *et al.*, 1993, Expression and Prognostic Significance of Platelet-derived Growth Factor and its Receptors in Epithelial Ovarian Neoplasms. *Cancer Res*, 53:4550–4.
 35. Apte SM, Bucana CD, Killion JJ, *et al.*, Expression of Platelet-derived Growth Factor and Activated Receptor in Clinical Specimens of Epithelial Ovarian Cancer and Ovarian Carcinoma Cell Lines. *Gynecol Oncol*, 93:78–86.
 36. Luo H, Wang X, Ge H, *et al.*, 2019, Inhibition of Ubiquitinspecific Protease 14 Promotes Connexin 32 Internalization and Counteracts Cisplatin Cytotoxicity in Human Ovarian Cancer Cells. *Oncol Rep*, 42:1237–47. DOI: 10.3892/or.2019.7232.
 37. Han KH, Kwak M, Lee TH, *et al.*, 2019, USP14 Inhibition Regulates Tumorigenesis by Inducing Autophagy in Lung Cancer *In Vitro*. *Int J Mol Sci*, 20:5300.
 38. Wang Y, Wang J, Zhong J, *et al.*, 2015, Ubiquitin-specific Protease 14 (USP14) Regulates Cellular Proliferation and Apoptosis in Epithelial Ovarian Cancer. *Med Oncol*, 32:379. DOI: 10.1007/s12032-014-0379-8.
 39. Alshamrani AA. Roles of microRNAs in Ovarian Cancer Tumorigenesis: Two Decades Later, What Have We Learned? *Front Oncol*, 10:1084. DOI: 10.3389/fonc.2020.01084.
 40. Lee YS, Dutta A, 2007, The Tumor Suppressor MicroRNA let-7 Represses the HMGA2 Oncogene. *Genes Dev*, 21:1025–30. DOI: 10.1101/gad.1540407.
 41. Mayr C, Hemann MT, Bartel DP, 2007, Disrupting the Pairing between let-7 and Hmga2 Enhances Oncogenic Transformation. *Science*, 315:1576–9. DOI: 10.1126/science.1137999.
 42. Park SM, Shell S, Radjabi AR, *et al.*, 2007, Let-7 Prevents Early Cancer Progression by Suppressing Expression of the Embryonic Gene HMGA2. *Cell Cycle*, 6:2585–90. DOI: 10.4161/cc.6.21.4845.
 43. Liu G, Sun Y, Ji P, *et al.*, 2014, MiR-506 Suppresses Proliferation and Induces Senescence by Directly Targeting the CDK4/6-FOXM1 Axis in Ovarian Cancer. *J Pathol*, 233:308–18. DOI: 10.1002/path.4348.
 44. Xia B, Yang S, Liu T, *et al.*, 2015, miR-211 Suppresses Epithelial Ovarian Cancer Proliferation and Cell-cycle Progression by Targeting Cyclin D1 and CDK6. *Mol Cancer*, 14:57. DOI: 10.1186/s12943-015-0322-4.
 45. Li J, Shao W, Feng H, 2019, MiR-542-3p, a microRNA Targeting CDK14, Suppresses Cell Proliferation, Invasiveness, and Tumorigenesis of Epithelial Ovarian Cancer. *Biomed Pharmacother*, 110:850–6. DOI: 10.1016/j.biopha.2018.11.104.