Submitted: 29 August, 2022 Accepted: 29 November, 2022 Published: 15 February, 2024 DOI:10.22514/ejgo.2024.009

ORIGINAL RESEARCH

European Journal of Gynaecological Oncology

The mechanism of miR-143-3p regulating *FGF-9* in the proliferation, invasion

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Abstract

The study aimed at exploring the miR-143-3p expression and the mechanism involved in ovarian cancer development. RT-qPCR (Quantitative Real-time PCR) served for the detection of the miR-143-3p level in different ovarian carcinoma cells. Then miR-143-3p underwent transfection and presented overexpression in ovarian carcinoma cells. 3-(4,5)-dimethylthiahiazo (-z-y1)-3,5-di-phenytetrazoliumromide (MTT) assay, flat cloning experiment, Transwell invasion assay and scratch test served for the evaluation of the influences of miR-143-3p on ovarian cancer cell biological behavior. The candidate target genes were screened by using bioinformatics method. The double luciferase assay and Western blot together assessed the regulatory effect of miR-143-3p. Relative to the control group (NC), the overexpressed group presented significantly reduced ovarian cancer cell growth ($p < 0.01$). The results indicated the inhibitory impact of miR-143-3p overexpression on the invasion and migration of ovarian cancer 3AO and SKOV3 cells. Bioinformatics analysis confirmed *FGF-9* (Fibroblast Growth Factor 9) as one of target gene of miR-143-3p. Double luciferase assay also attested the direct negative regulatory impact of miR-143-3p on *FGF-9* ($p < 0.05$). The miR-143-3p overexpression significantly lowered the protein level of *FGF-9* in 3AO and SKOV3 cells ($p < 0.001$). miR-143-3p overexpression negatively regulated the proliferation, invasion and migration abilities of ovarian carcinoma cells, as well as the *FGF-9* protein expression.

Keywords

miR-143-3p; Ovarian carcinoma; Proliferation; Invasion; Migration; *FGF-9*

1. Introduction

Ovarian cancer is a representative malignancy regarding the reproductive system of females, responsible for the death of about 140,000 worldwide every year [1]. Ovarian cancer patients have a poor prognosis for several reasons, including its deep location in the pelvic cavity, which makes it difficult to be easily detected and unclear clinical symptoms in its early stage, resulting in most patients being diagnosed when the tumor has already progressed to its middle or late stages [2–4]. Additionally, the poor efficacies of clinical pharmacological treatments also contribute to poor cancer survival. In recent years, the rapid development of epigenetics has provided new ideas for diagnosing and treating malignant ovarian tumors [5, 6].

MicroRNA (miRNA), as one of the epigenetic regulatory mechanisms, has become a research hotspot. It is a newly discovered endogenous non-coding small single-stranded RNA. The miRNA length were 19–25 nucleotides. It specifically recognizes and binds to the 3' non-coding region of target mRNA *via* base-complementary pairing, causing the degradation of target genes or inhibiting protein synthesis, and participates in the regulation of the intracellular expression level of related genes after transcription [7–9]. According to many studies, the different expression of miRNA in ovarian cancer and normal tissues serve as an oncogene or tumor suppressor gene in ovarian cancer pathogenesis. According to a previous study, miR-424-5p inhibited ovarian cancer ferroptosis by targeting Acyl-CoA Synthetase Long Chain Family Member 4 (ACSL4) [10]. Another study revealed the obvious positive impact of miR-200c on the olaparib anti-cancer efficacy on ovarian cancer cells [11]. miR-143-3p is one of the most researched miRNAs. It was previously reported that follicular fluid-derived exosome miR-143-3p regulated glycolysis in Polycystic ovary syndrome (PCOS) granulosa cells, suggesting that miR-143-3p was involved in reproductive system diseases [12]. This study detected the miR-143-3p expression level in various ovarian cancer cell lines and explored its effects on the ovarian cancer cells.

2. Materials and methods

2.1 Materials

OVCAR3, ES-2, SKOV3, OV3-VGH, 3AO, OV2008 and A2780 cells were purchased from Tianjin Service Biotechnology (China). Fetal bovine serum (FBS), trypsin, Dulbecco's Modified Eagle Medium (DMEM) medium and Roswell Park Memorial Institute (RPMI) 1640 medium were provided by GIBCO (USA). Penicillin-Streptomycin solution was purchased from Wuhan Pnuosai Life Technology (China). miRNA mimics were synthesized by Shanghai Gima Genetics (China). Matrigel glue and Transwell chamber wwere purchased from BD (USA) and Millipore (USA), respectively. A dual luciferase test kit (RG027, Jiangsu, China) was purchased from Biyuntian.

2.2 Cell culture

SKOV3 and 3AO cells underwent culture in DMEM medium with 10% FBS and 1% Penicillin-Streptomycin solution. OVCAR3, ES-2, OV-3-VGH, OV2008 and A2780 cells received culturing in RPMI-1640 medium supplemented with 10% Gibco serum and 1% dual antibody. The cell incubator is set at a temperature of 37 ℃ and 5% carbon dioxide (CO_2).

2.3 Cell transfection

The cells were digested for cell suspension at concentration of 200,000 cells/mL, followed by being inoculated into a six-well plate. The ovarian cancer cells underwent 18–24 h of culturing in a cell incubator. A sterile 1 × phosphate buffered saline (1 × PBS) solution was used to wash cells twice, and the solution was discarded. Transtaining solutions A and B were prepared in 1.5 mL sterile centrifuge tubes using the miRNA-NC mimics group. For solution A, 1 μL (20 μM) of miRNA-NC mimics was diluted and gently mixed with serum-free medium Opti-MEM to a final amount of 50 μL. For solution B, 1 μL of liposome Lip2000 was diluted and gently mixed with serum-free medium Opti-MEM to 50 μL. Solutions A and B were maintained at room temperature for five minutes. Then, solution B was added to solution A in a dropwise manner, and maintained at room temperature for 20 min after gentle mixing. The corresponding well was added with the dye transfer solution, the culture plate was gently shaken to distribute it evenly, and then placed in a cell incubator for culture at 5% CO_2 and 37 °C. 4 h later, the incubation solution of each group cell well was changed to 3 mL of 10% serum DMEM medium without Penicillin-Streptomycin solution, and the culture was continued in the cell incubator at the same condition.

2.4 MTT assay

Here, 100 μL cell suspension (about 1 × 10^4 cells) of transfected cells were placed to a 96-well plate, with three parallel wells in each group. The cells were cultured for 24 h. 1, 2 and 3 days of culture later, 10 μL of 5 mg/mL MTT solution was added to well, and then received another 4 h of culture. The culture medium was carefully aspirated, and added 100 μL Dimethyl sulfoxide (DMSO) to each well. The cell culture plate underwent 10 min of oscillation on shaker at low speed for fully dissolving the blue and purple crystals. An enzyme-linked immunodetector served for measuring the absorbance value at the wavelength of 490 nm. Cell proliferation inhibition rate was determined by: (optical delnsity of treatment group—blank well)/(optical delnsity of control group—blank well) × 100%.

2.5 Plate clone formation experiment

The transformed cells were digested to prepare the cell suspension. Then, 500 cells from each group were inoculated into 12-well plates, and an appropriate amount of complete medium was added to the final total volume of 2 mL. The cells were cultured for 1–2 weeks, followed by fixation in 4% paraformaldehyde, PBS wash, and 0.1% crystal violet staining. After the plates were allowed to dry, the cell-formed colonies were photographed and counted.

2.6 Transwell cell invasiveness assay

The Transwell chamber was pre-coated with artificial matrix glue. The transfected cells were digested, then counted using a cell counter after blowing and mixing. In the Transwell chamber, 200 μL of serum-free medium cell suspension was added, which contained approximately 10^5 cells. Then, 700 μL of complete medium with serum was added to a deep well in a Transwell chamber. The cells underwent one day of culture, followed by 15 min of 0.1% crystal violet staining. Lastly, the washed chamber was observed under a microscope and photographed.

2.7 Scratch assay

The digested transfected cells were inoculated in 6-well plates. When the cells are almost grown all over the bottom of the plate, a 200 μL pipette suction tip assisted in making scratches perpendicular to the well plate. The cell culture medium was discarded. The well plate received rinsing treatment in PBS for the removal of cell debris. Cell medium containing 2% serum was added, followed by cell culture at 37 ℃ and 5% CO_2 in a cell incubator and photographed at 0, 24, 48 and 72 h, respectively.

2.8 Dual-Luciferase Reporter

The reporter plasmid was constructed. The target fragment was inserted into a luciferase-expressed reporter gene vector. The reporter gene plasmid and the reference plasmid were co-transfected into the cells, followed by processing. The experimental method was conducted according to the double luciferase reporter gene system detection kit. Lastly, the relative luciferase activity of different treatment groups was calculated.

2.9 RT-qPCR

The miRNA extraction kit served for extracting miRNA from the cells of each group. Reverse transcription and RT-qPCR confirmed to the procedure of the corresponding kit.

RT Primer sequences:

U6, 5′-GTCGTATCCAGTGCAGGGTCCGAGGTATTCG CACTGGATACGACAAAATATGGAAC-3′.

miR-143-3p: 5′-GTCGTATCCAGTGCAGGGTCCGAGGTGCACTGGATACGACGAGCTAC-3′.

RT-qPCR primer sequences:

miR-143-3p-Fwd: 5′-TGCGGTGAGATGAAGCACTGTAG-3′.

U6-Fwd: 5′-TGCGGGTGCTCGCTTCGGCAGC-3′.

Reverse: 5′-CCAGTGCAGGGTCCGAGGT-3′.

2.10 Western blot

Two days after transfection, total cell protein was extracted. Subsequently, sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and membrane transformation were performed. The polyvinylidene fluoride (PVDF) membranes underwent the incubation of corresponding primary and secondary antibodies. The optical density of each band was detected using the chemiluminescence method.

2.11 Statistical analysis

SPSS 17.0 software (International Business Machines Corporation, New York, NY, USA) served for the data analysis. We repeated all experiments three times independently. Normal distribution data are described as mean ± standard deviation. Independent sample *t*-test assisted in comparing two independent samples, and the significance test level was set as two-sided $\alpha = 0.05$.

3. Results

3.1 miR-143-3p inhibited cell growth of ovarian cancer cells

According to RT-qPCR results, the miR-143-3p expression level in OVCAR3 cells was at the average level in 7 cell lines, so OVCAR3 was selected as the reference standard cell. Relative to the OVCAR3 cell line, SKOV3 and 3AO cell lines presented obviously lower miR-143-3p relative to OVCAR3 ($p < 0.001$, Fig. 1A). SKOV3 and 3AO were selected as research objects because of their strong proliferation and invasion characteristics.

Subsequently, miR-143-3p mimics and miR-143-3p NC were transfected into two cells, respectively. As found, relative to the expression levels of miR-143-3p in miR-NC group (NC), the two ovarian cancer cell lines were obviously higher ($p < 0.01$, Fig. 1B). As revealed by MTT assay, the cell vitality of 3AO cells overexpressing miR-143-3p were considerably less than miR-NC group at 48 h after transfection ($p < 0.01$, Fig. 1C). The results of SKOV3 cells were consistent in 3AO cells ($p < 0.01$, Fig. 1D).

3.2 miR-143-3p inhibited the proliferation of ovarian cancer cells

Relative to the NC, the miR-143-3p overexpression group presented obviously decreased rate of 3AO cell colony formations ($p < 0.001$, Fig. 2A). In the SKOV3 cell, the number of cell colony formation rates was also significantly reduced in the overexpression group ($p < 0.001$, Fig. 2B).

3.3 miR-143-3p inhibited the ovarian cancer cells invasion ability

After 24 hours of inoculation, the number of cells in the miR-143-3p mimics group crossing the basement membrane was greatly less than the NC group in ovarian cancer 3AO cell ($p < 0.001$, Fig. 3A) and SKOV3 cell ($p < 0.001$, Fig. 3A). Hence, miR-143-3p overexpression exerted an inhibitory impact on the invasion ability of ovarian cancer 3AO and SKOV3 cells.

3.4 miR-143-3p inhibited the ovarian cancer cells migration ability

Relative to the NC group, the miR-143-3p overexpression group possessed stronger migration ability in 3AO ($p < 0.001$, Fig. 4A) and SKOV3 cells ($p < 0.001$, Fig. 4B). Accordingly, miR-143-3p overexpression inhibited the migration ability of ovarian cancer 3AO and SKOV3 cells.

3.5 Target gene prediction and plasmid construction of miR-143-3p

For more deeply exploring the molecular mechanism of miR-143-3p on ovarian cancer, the bioinformatics software Targetminer and miRDB served for screening the miR-143-3p target genes. *FGF-9* was screened as a possible target gene (Fig. 5A). To confirm that *FGF-9* was the direct downstream miR-143-3p target gene, a dual luciferase reporter gene system which contained the 3′-untranslated region (3′UTR) binding site region of *FGF-9* wild type (WT) and mutant (Mut) was constructed (Fig. 5B). The corresponding firefly luciferase reporter gene plasmids were built respectively, and the recombinant plasmids were successfully identified by enzyme digestion (Fig. 5C).

3.6 FGF-9 is a direct target gene of miR-143-3p

Here, we explored whether miR-143-3p and *FGF-9* had direct target regulation effects in ovarian cancer cells. The dual-fluorescent reporter vector experiment suggested that the fluorescence signal intensity of 3AO cells overexpressing miR-143-3p in the 3′UTR region of *FGF-9* in the WT group was greatly lower relative to NC group ($p < 0.05$, Fig. 6A). However, miR-143-3p overexpression occurred in the *FGF-9* 3′UTR mutant group, and its fluorescence signal intensity did not show an obvious difference from that of NC group ($p > 0.05$, Fig. 6B). Accordingly, miR-143-3p was directly bound to the 3′UTR region of *FGF-9* for inhibiting the *FGF-9* expression. For further clarifying the inhibitory impact of miR-143-3p on *FGF-9* protein expression, Western blot was conducted, finding that the *FGF-9* protein level underwent obvious down-regulation after transfection of the miR-143-3p mimics ($p < 0.001$, Fig. 6C). Hence, miR-143-3p could be directly bound to the 3′UTR region of *FGF-9* to achieve the down-regulation of the *FGF-9* protein expression level.

4. Discussion

In recent years, as one of the epigenetic regulatory mechanisms, miRNA has become a hot topic in oncology research.

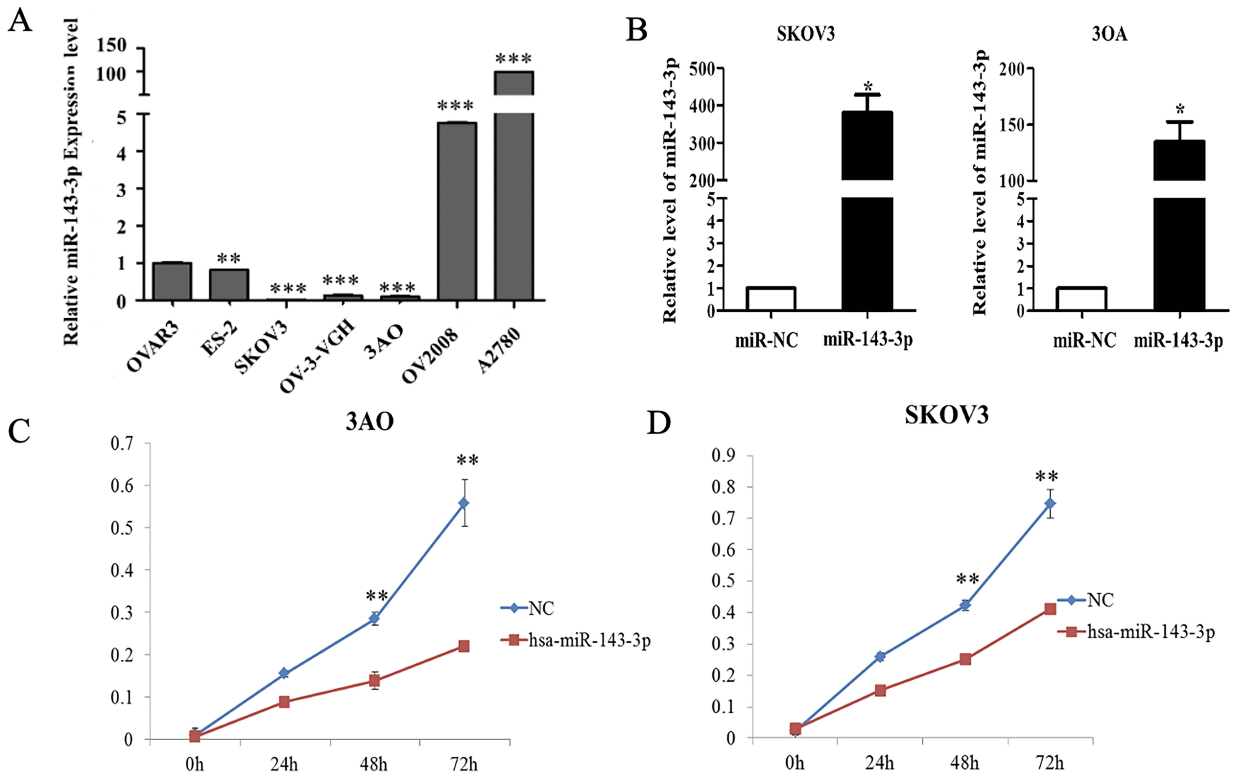

FIGURE 1. Overexpression of miR-143-3p inhibited ovarian cancer cells growth. (A) The expression levels of miR-143-3p in SKOV3 and 3AO cell lines were obviously lower (**$p < 0.01$, ***$p < 0.001$). (B) Relative to the transfection effect of miRNA-NC, miR-143-3p in the two types of cells receiving miR-143-3p mimics transfection presented considerably lower expression (*$p < 0.05$). (C) The overexpression of miR-143-3p resulted in significant inhibition of the viability of 3AO. Relative to the miRNA-NC group (Negative Control group, NC), miR-143-3p in the two types of cells transfected with miR-143-3p mimics (has-miR-143-3p) exhibited greatly elevated expression (**$p < 0.01$). (D) The overexpression of miR-143-3p resulted in significant inhibition of the viability of SKOV3. Relative to the miRNA-NC group (Negative Control group, NC), miR-143-3p in the two types of cells transfected with miR-143-3p mimics (has-miR-143-3p) exhibited greatly elevated expression (**$p < 0.01$).

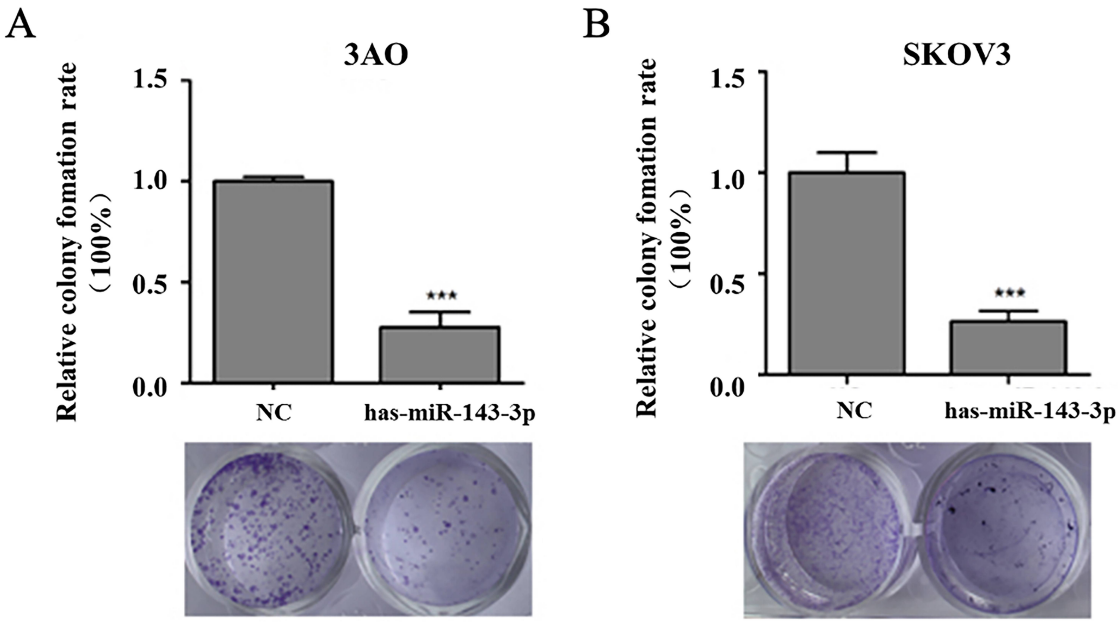

FIGURE 2. Overexpression of miR-143-3p inhibited ovarian cancer cells proliferation. (A) The number of cell colony formations of the miR-143-3p mimics group (has-miR-143-3p) was significantly lower than that of the miRNA-NC group (Negative Control group, NC) in 3AO cells (**$p < 0.001$). (B) The number of cell colony formations of the miR-143-3p mimics group (has-miR-143-3p) was significantly lower than that of the miRNA-NC group (Negative Control group, NC) in SKOV3 cell (**$p < 0.001$). The results suggested miR-143-3p overexpression restrained ovarian cancer cells proliferation.

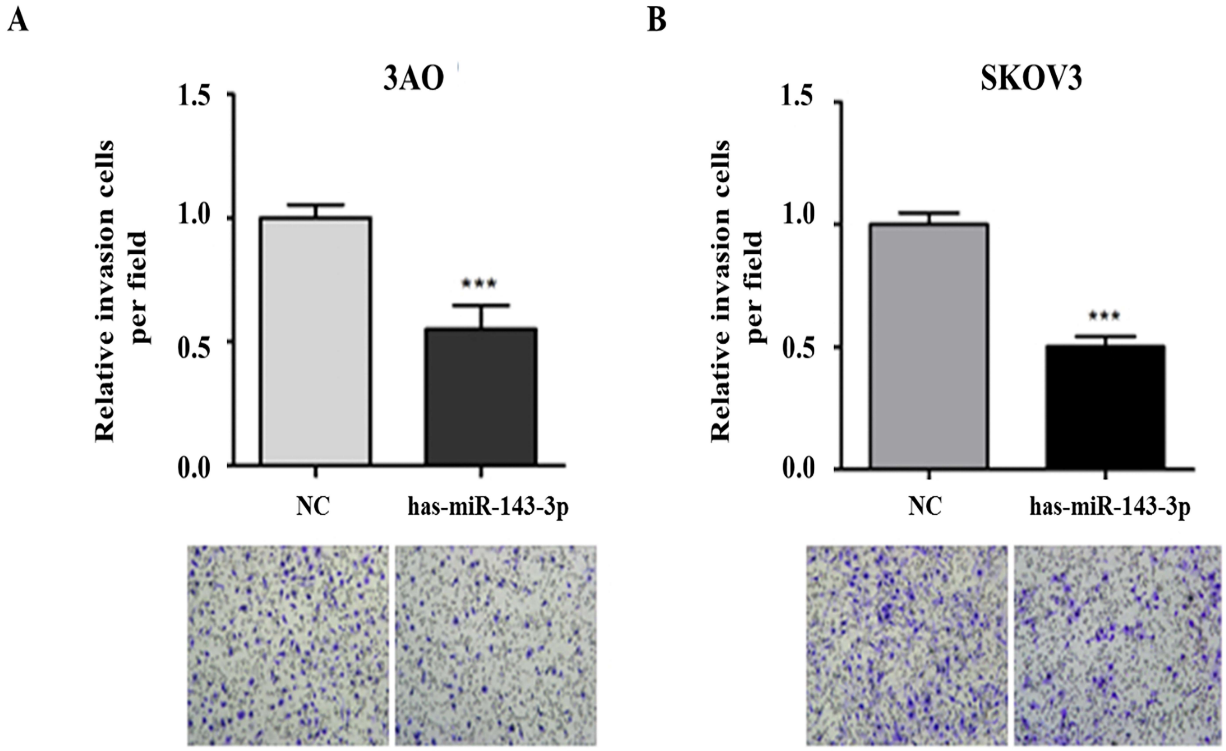

FIGURE 3. Overexpression of miR-143-3p inhibits ovarian cancer cells invasion. (A) The miR-143-3p mimics group (has-miR-143-3p) exerted an obvious inhibitory impact on the invasiveness of the miRNA-NC group (Negative Control group, NC) ovarian cancer 3AO cell (***$p < 0.001$). (B) The miR-143-3p mimics group (has-miR-143-3p) exerted an obvious inhibitory impact on the invasiveness of the miRNA-NC group (Negative Control group, NC) ovarian cancer SKOV3 cell (***$p < 0.001$). The results suggested that miR-143-3p overexpression restrained ovarian cancer cells invasion.

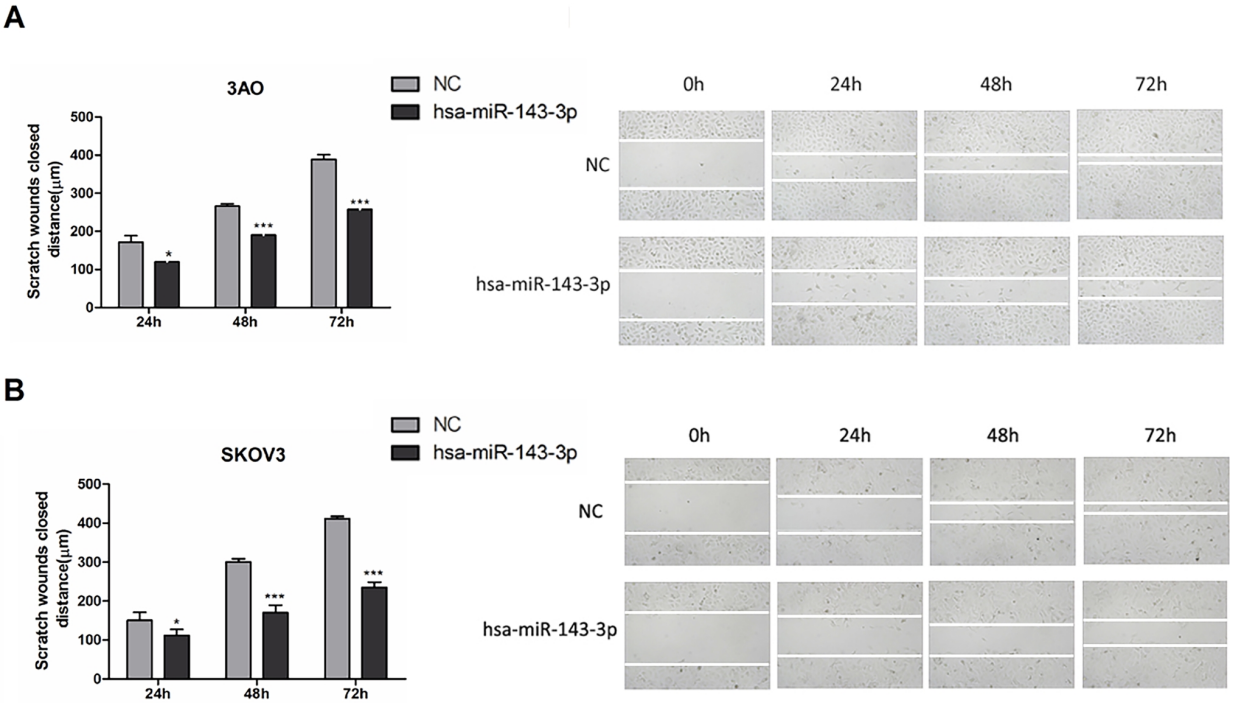

FIGURE 4. Overexpression of miR-143-3p inhibits 3AO and SKOV3 cells migration. (A) Scratch assay shows that the miR-143-3p mimics group (has-miR-143-3p) remarkably inhibited the migration ability of the NC group (Negative Control group, NC) ovarian cancer 3AO cells (*$p < 0.05$). (B) Scratch assay shows that the miR-143-3p mimics group (has-miR-143-3p) remarkably inhibited the migration ability of the NC group (Negative Control group, NC) ovarian cancer SKOV3 cell (***$p < 0.001$). Accordingly, miR-143-3p overexpression inhibited 3AO and SKOV3 cells migration.

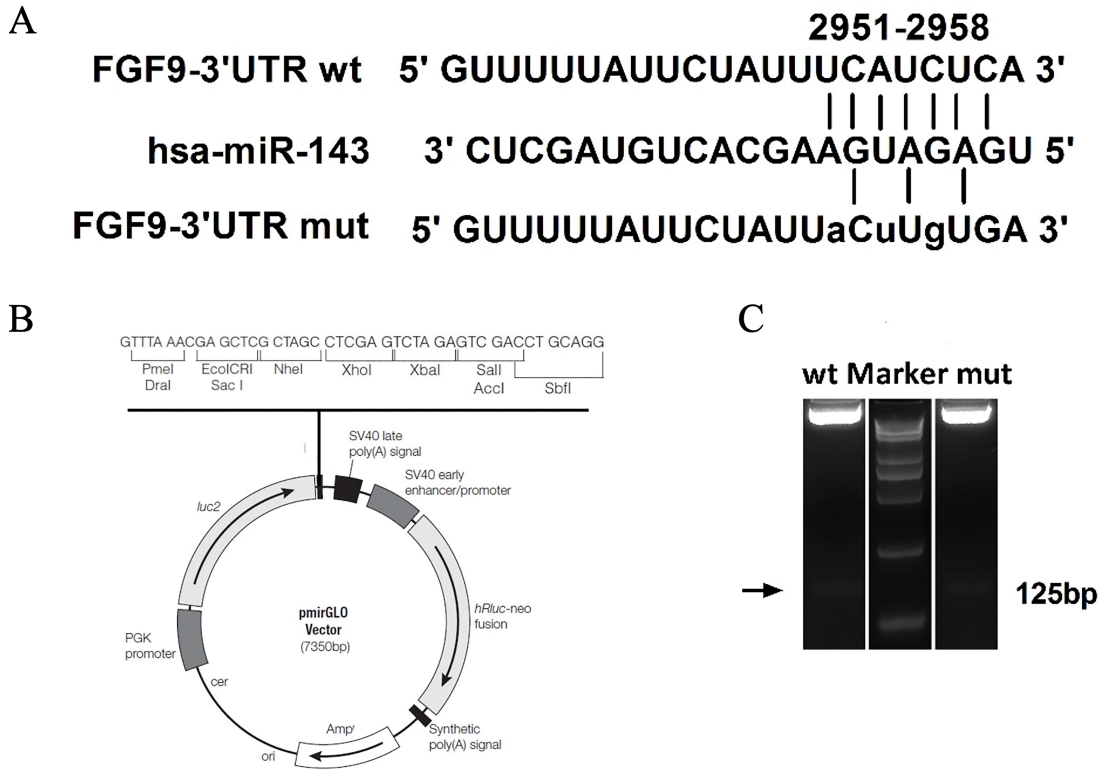

FIGURE 5. Construction of pmiGLO/FGF9-3′ UTR plasmid and pmiGLO/FGF9-3′ UTR mutant plasmid. (A) The nucleic acid sequence of wild type FGF-9 3′UTR, miR-143 and mutant type FGF-9 3′UTR. (B) The map of the pmirGLO Vector. (C) the nucleic acid expression product of recombinant plasmid.

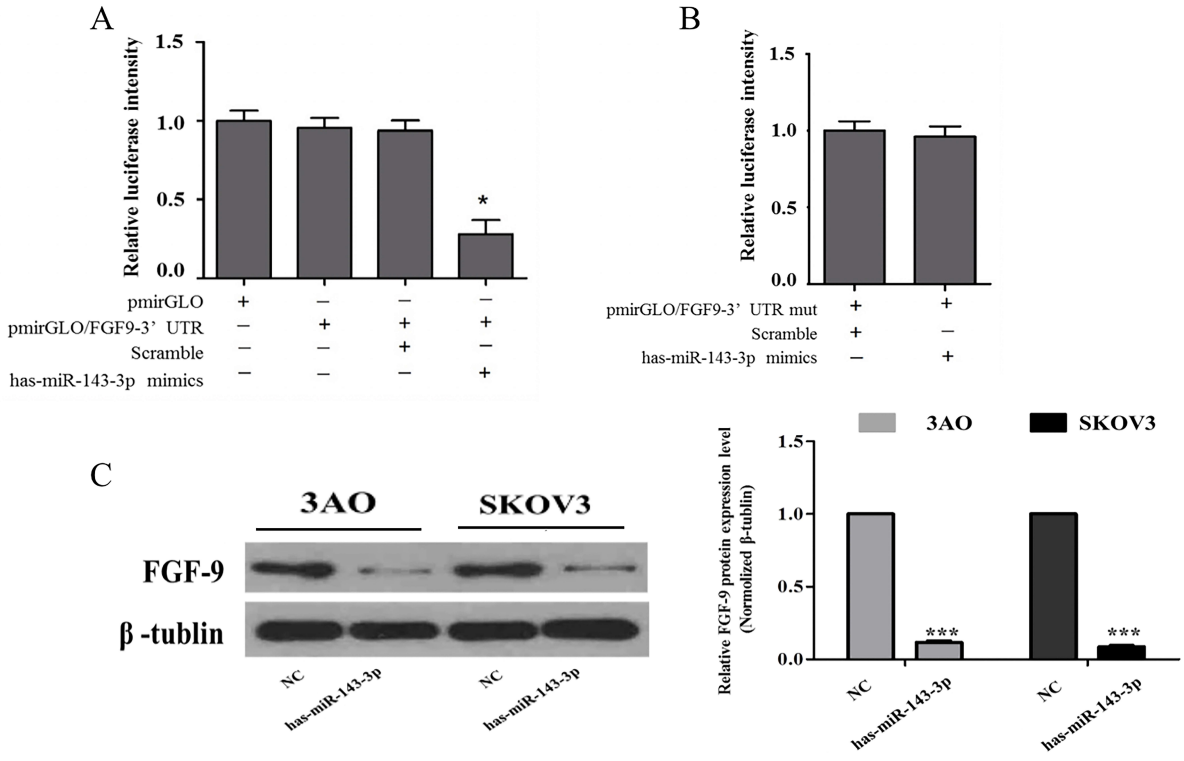

FIGURE 6. FGF9 is the direct target gene of miR-143-3p. (A) Dual luciferase reporter vector experiments confirmed the 3′ UTR region of *FGF-9* as a direct target gene of miR-143-3p (*$p < 0.05$, Fig. 6A), not the *FGF-9* 3′UTR mutant region. (B) the fluorescence signal intensity in each group ($p > 0.05$). (C) The expression of *FGF-9* protein level in the miR-143-3p mimics group (has-miR-143-3p) presented an obvious down-regulation relative to the miRNA-NC group (Negative Control group, NC) in ovarian cancer 3AO and SKOV3 cells (***$p < 0.001$).

miRNAs play different roles in different tumors and are reported to be tissue specific. They could impact tumorigenesis, cell cycle, apoptosis, proliferation, invasion and metastasis, chemotherapy resistance and other biological functions [13], indicating their potentially important role in tumor diagnosis and treatment. By now, researchers have not well explored the function and mechanism of many miRNAs in ovarian cancer, such as miRNA10a, miRNA20a, miRNA26a, miRNA29a, miRNA214, miRNA145 and other genes. As found in previous studies, miR-143-3p could affect the occurrence and development of lung cancer, liver cancer, cervical cancer and other malignant tumors [14–16] and played an important biological regulatory role. Nevertheless, researchers failed to well explore the function and mechanism of miR-143-3p in ovarian cancer.

In our reaserch, miR-143-3p was different expression in different ovarian cancer cells, and the expression of miR-143-3p in 3AO and SKOV3 cells with strong proliferation and invasion characteristics was lower than in other cells with weak proliferation and invasion. The overexpression of miR-143-3p in 3AO and SKOV3 cells restrained their proliferation, invasion and metastasis, suggesting the negative regulatory impact of miR-143-3p overexpression on ovarian cancer cells in terms of the activity, proliferation, invasion and invasion metastasis. According to Jiang *et al*. [17], miR-143-3p suppressed the metastasis of OS cells from human osteosarcoma cells to the lung, and further studies identified the target genes regulated by miR-143-3p as monoclonal antibody (ASAP3) and monoclonal antibody (MSI2). The mechanism of action was elucidated and confirmed by animal experiments. miR-143-3p was a new target for diagnosing and treating lung metastasis of human osteosarcoma. Based on the study by He *et al*. [18], miR-143-3p regulated the QUAKING-5 (QKI-5)expression to participate the proliferation, invasion and Emergency Medical Technician (EMT) process of esophageal squamous cell carcinoma . The above research conclusions were consistent with our research results, both of which play a role in regulating related target genes.

Fibroblast Growth Factors (FGF) are a class of small secreted polypeptide growth factors that participate in the biological processes of cell differentiation, proliferation, cycle, apoptosis, migration, invasion and so on. As one of the 22 members of FGF, FGF9 is a ligand effector protein, which plays corresponding biological roles by binding to downstream receptors FGFRs [19]. Previous studies confirmed that FGF9 was closely related to the differentiation of ovarian and follicle cells. FGF9 is involved in the sorting process of ovarian cells and follicle cells by regulating tumor cyclin D1 and Cyclin dependent kinase 4 (CDK4) [20]. Abnormal differentiation of cells is an important cause of tumorigenesis. Zhang *et al*. [21] found that FGF9 involved in the occurrence of ovarian cancer. In addition, as found in the study by Abdel-Rahman *et al*. [22], *FGF-9* activated the mitogen-activated protein kinase (MAPK)/extracellular regulated protein kinases (ERK) signaling pathway in tumor cells, over-phosphorylate ERK, and eventually lead to the development of tumors. These results suggested that the *FGF-9* gene plays an irreplaceable role in tumors. We used bioinformatics technology to predict a variety of target genes of miR-143-3p, thereinto the *FGF-9* gene was selected as the research object, and the *FGF-9* gene was involved in the process of proliferation and invasion of tumor cells. In ovarian cancer, miR-143-3p overexpression could negatively regulate the *FGF-9* gene and inhibit the *FGF-9* protein expression. Our study also confirmed that *FGF-9*, a direct target gene of miR-143-3p, could inhibit the ovarian cancer.

5. Conclusions

In conclusion, miR-143-3p overexpression inhibited ovarian cancer cells in terms of the proliferation, invasion and migration by negatively regulating its target gene *FGF-9*. However, there were still some shortcomings in this study. The detailed underlying mechanism of miR-143-3p in regulating target gene *FGF-9* to inhibit ovarian cancer cells should be further elucidated. Next, the relationship of miR-143-3p with pathological stage, classification and survival of ovarian cancer patients will be further explored and analyzed. Meantimie, whether overexpression of miR-143-3p inhibits ovarian cancer *in vivo* should also be determined. Altogether the findings of this powerful evidence for elucidating the invasion and metastasis mechanism of ovarian cancer.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

WY—designed the research study, performed the research, analyzed the data and wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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How to cite this article: Wang Yan. The mechanism of miR-143-3p regulating *FGF-9* in the proliferation, invasion. European Journal of Gynaecological Oncology. 2024; 45(1): 55-62. doi: 10.22514/ejgo.2024.009.