miR-29c-3p regulates proliferation and migration in ovarian cancer by targeting KIF4A

Songwei Feng¹, Shanhui Luo¹, Chenchen Ji² and Jia Shi³*

Abstract

Background: Increasing evidence suggested that microRNA and kinesin superfamily proteins play an essential role in ovarian cancer. The association between KIF4A and ovarian cancer (OC) was investigated in this study.

Methods: We performed bioinformatics analysis in the GEO database to screen out the differentially expressed miRNAs (DEmiRNAs) associated with ovarian cancer prognosis. Upstream targeting prediction for KIF4A was acquired by using the mirDIP database. The potential regulatory factor miR-29c-3p for KIF4A was obtained from the intersection of the above all miRNAs. The prognosis of KIF4A and target-miRNA in OC was obtained in the subsequent analysis. qRT-PCR and Western blot detected KIF4A expression level in IOSE80 (human normal ovarian epithelial cell line). In the meantime, the gene expression level was detected in A2780, HO-8910PM, COC1, and SKOV3 cell lines (human ovarian carcinoma cell line). MTT and colony formation assays were used to detect cell proliferation of SKOV3 cell line. The following assays detected cell migration through the use of transwell and wound heal assays. Targeted binding relationship between KIF4A and miRNA was detected by using the dual-luciferase reporter assay.

Results: Both high expression of KIF4A and lower expression of miR-29c-3p could be used as biomarkers indicating poor prognosis in OC patients. Cellular function tests confirmed that when KIF4A was silenced, it inhibited the proliferation and migration of OC cells. In addition, 3'-UTR of KIF4A had a direct binding site with miR-29c-3p, which indicated that the expression of KIF4A could be regulated by miR-29c-3p. In subsequent assays, the proliferation and migration of OC cells were inhibited by the overexpression of miR-29c-3p. At the same time, rescue experiments also confirmed that the promotion of KIF4A could be reversed by miR-29c-3p.

Conclusion: In a word, our data revealed a new mechanism for the role of KIF4A in the occurrence and development of OC.

Keywords: Ovarian cancer, KIF4A, miR-29, Proliferation, Migration

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Introduction
Ovarian cancer (OC) has the lowest 5-year survival rate in female cancers because most patients are asymptomatic at an early stage and are already advanced when diagnosed. Therefore, it is extremely necessary to explore new diagnostic and therapeutic methods to improve the prognosis of OC patients. Early diagnosis of ovarian cancer through relevant basic research will maximize fertility preservation. This will significantly reduce the impact on sexual function, mental health, quality of life, and other aspects [1].

Taken together with current studies, more than 650 molecular motor members have been identified, collectively known as kinesin superfamily proteins (KIFs). Such proteins are critical players in the transport of intracellular vesicle and organelle transport along microtubules and cell division [2]. Rath et al. analyzed the motor domain’s phylogeny and identified 14 families containing 45 human and murine kinesin proteins [3]. Kinesin family member 4A (KIF4A), located in the cytoplasm and nucleus, is an important factor in tumorigenesis and development [4]. The KIF4A gene can play different roles in different cancers. It acts as an oncogene in most tumors, such as glioblastoma [5], liver cancer [6], and pancreatic cancer [7]. Interestingly, suppressor genes in gastric carcinoma include KIF4A [8]. Recent bioinformatics studies have shown that KIF4A expression is significantly different between normal ovarian samples and tumor samples, suggesting that KIF4A may be associated with the occurrence of OC [9]. However, the potential molecular mechanism of KIF4A in OC has never been explored.

MicroRNAs (miRNAs), non-coding small RNA with a length of 21–23 nt, play a role in regulating gene expression by loading into the RNA-induced silencing complex [10]. The target gene binding with miRNAs will result in colossal implications in a multitude of physiological processes and diseases [11]. It has been reported that miR-29c-3p can regulate the biological functions and processes and diseases [11]. It has been reported that miR-29c-3p and miRNAs can coregulate the process of tumorigenesis. Nevertheless, the molecular mechanism of KIF4A and miR-29c-3p in OC has never been evaluated.

In this study, we confirmed through a series of experiments that KIF4A plays a vital role in the proliferation and migration of OC. And the relationship between miR-29c-3p and KIF4A was further found. These novel molecular mechanisms may play a crucial role in the future treatment of OC patients.

Materials and methods
Databases and bioinformatics analysis
The main databases used are Gene Expression Profiling Interactive Analysis (GEPIA) database (http://geopia.cancer-pku.cn), Kaplan-Meier Plotter (KM) database (http://kmplot.com/), Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/gds/), mirDIP database (http://ophid.utoronto.ca/mirDIP/index.jsp#r), starBase database (http://starbase.sysu.edu.cn), and genotype-tissue expression (GTEX) projects (http://www.gtexportal.org/home/index.html). The expression level of KIF4A and microRNA in OC were detected using the GEPIA database. We used KM database tools to evaluate the relationship between DEmiRNAs and prognosis, KIF4A, and prognosis, respectively. The log-rank P value, HR (95% CI), and survival curves were also calculated and displayed. The microRNA expression datasets used in this study (GEO: GSE83693 and GSE119055) were acquired from the GEO database. DEmiRNAs between healthy ovarian tissue and OC tissue in the datasets are screened by the GEO2R tool. DEmiRNAs were selected by the following criteria: |log2FC (foldchange)| > 2 and adjusted P value < 0.05. The upstream microRNAs of target KIF4A were predicted using the mirDIP database. We used the intersection of the DEmiRNAs from GEO and mirDIP to plot a Venn diagram. The starBase database was used for the correlation between miR-29c-3p and KIF4A gene in the OC cohort by using Pearson’s correlation coefficient.

Cell lines and transfection
All cell lines, including A2780, HO-8910PM, COC1, SKOV3, and IOSE80, were purchased from Suzhou Culture Collection (SCC, Suzhou, China). RPMI-1640 medium contained 20% FBS and penicillin (100 U/ml) and streptomycin (100 μg/ml). The above cell lines were all cultured here at 37°C and passaged for 2–4 passages after recovery. SKOV3 was thought of as low-grade serous cancer cells with wide type p53 derived from the...
ascites of a 64-year-old Caucasian female with an ovarian serous cystadenocarcinoma. Mimic NC, miR-29c-3p mimic, sh-NC, sh-KIF4A (sh-KIF4A-1, sh-KIF4A-2, sh-KIF4A-3), oe-NC, and oe-KIF4A were purchased from GenePharma (Shanghai, China). They were transfected into cell lines by Lipofectamine 2000 (Thermo Fisher Scientific, Inc.) according to the manufacturer’s instructions. The above cell lines rinsed with phosphate-buffered saline before transient transfection. All cells were cultured for at least 24 h before the above experiments.

Quantitative real-time PCR and Western blot
Trizol reagent (Invitrogen) was used to extract total RNA from cells. PrimeScript RT reagent kit (Jijia, Suzhou, China) was used for reverse transcription (RT). SYBR Prime Script RT PCR kit (Jijia, Suzhou, China) was used for qRT-PCR. miR-29c-3p and U6 and GAPDH were used as internal references, respectively. The primer sequences used were miR-29-F: TGCCAGGAGCTGGTGA TTTTCC, miR-29-R: ACGGGCGTACAGAGGATCCCC, U6-F: CTCGCTTCCGGCAGCACA, U6-R: AACGCTTTC AGGAATTTCGGT, KIF4A-F: TGAACCTCCAGTCC TCC, KIF4A-R: GCACTGATTACATTCTTCCC, GAPDH-F: GGAGGGAGATCCCTCCAAAAT, GAPDH-R: GGTCT GTGTGATACCTTCTCATGG. The results were calculated by the 2−ΔΔCt method, and the histogram was drawn.

Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was used to load the total proteins. The above proteins transferred to the nitrocellulose membranes (Amersham, USA) blocked with 5% skim milk powder at room temperature for 1 h. Then, KIF4A rabbit antibodies (ab122227, 1:1000, Abcam, Shanghai, China) and GAPDH rabbit antibodies (ab8245, 1:2500, Abcam, Shanghai, China) were used to incubate membranes at 4 °C overnight. Subsequently, PBST buffer (PBS buffer containing 0.1% Tween-20) was used to wash membranes for 10 min three times. Horseradish peroxidase-labeled secondary antibody goat anti-rabbit IgG (ab6721, 1:2000, abcam, Shanghai, China) was added to the membranes for incubation at room temperature for 1 h. The membranes were washed with PBST buffer for 10 min for 3 times. Immunoreactivity was detected by an Optical luminometer (Philips, Shanghai, China).

Dual-luciferase reporter assays
SKOV3 cells were seeded into 24-well plates. Then, above cells were co-transfected with KIF4A-WT/KIF4A-MUT vector and miR-29c-3p mimic/mimic NC using Lipofectamine 2000. For the vectors as mentioned above, they are based on psicheck2 and were constructed at binding sites of miR-29c-3p. A dual-luciferase reporter gene assay system was used to measure the luciferase activity from cell lysates after transfection for 48 h.

MTT and colony formation
At 24 h, 48 h, and 72 h, 10 μL MTT reagent with a concentration of 5 mg/ml was added into 96-well plates incubated at 37 °C for 4 h. The 96-well plates were incubated with the cells transfected for 48 h and digested with trypsin (5 × 10^3 cells/well). Then, all cells were exposed to 200 μL dimethyl sulfoxide (DMSO). Microplate readers measure the absorbance at 490 nm. In colony formation assay, cells were cultured in 500 cells/dish and incubation at 37 °C with 5% CO2 for 1–2 weeks. At room temperature, colonies were fixed with paraformaldehyde (4%), and dyed with crystal violet (0.1%) for 30 min each. Finally, the number of cell colonies was counted.

Transwell and wound healing assay
In transwell migration assay, transwell chambers with a polycarbonate membrane, the lower chambers contained 10% FBS and the upper chambers were used to seed 1 × 10^5 cells in serum-free DMEM. Under the condition that the upper chamber cells were removed and incubated for about 10 h, the lower chamber cells were stained with crystal violet for 1 min at 25 °C. The counts were then observed under a light microscope (Nikon, ×100): cell counts and averaged from within five regions.

Under the condition that floating cells were removed using PBS and cells were seeded in a 6-well plate at a density of 2 × 10^5 cells/well, a sterile 200-μL pipette tip generated a scratch wound. Scratches were photographed every 12 h and monitored for 48 h. The scratches were photographed using a microscope (Nikon, ×100) at 0 h and 24 h after scratching.

Statistical analysis
All histograms and line charts were plotted using Graphpad Prism 5.0. Mean ± SEM presents all the data. Differences among groups are analyzed by one-way analysis of variance. Comparisons were made between groups using the Student-Newman–Kuels test. All the above statistical analysis was carried out in Graphpad Prism 5.0 software. P value less than 0.05 was considered statistical significance. Relevant experimental indicators were detected at least 3 times.

Results
KIF4A is highly expressed in OC and is associated with poor progression
KIF4A expression by IOSE80 and four OC cell lines was detected. The results showed that cancer cell lines A2780 (5.532 ± 0.263), SKOV3 (6.565 ± 0.224), HO-8910PM (4.868 ± 0.311), and COCC1 (5.486 ± 0.458) express higher KIF4A compared with IOSE80 (P < 0.01), as shown in Fig. 1a and b. SKOV3 expressed highest KIF4A level; therefore, this line was selected for subsequent experiments. In addition, the survival analysis in the KM plot database is
Based on clinical data of TCGA and GEO. We plotted survival curve by following parameters by progression-free survival, optimal patients, serous ovarian carcinoma, and excluding outlier arrays. It was shown that high expression of KIF4A is associated with shorter progression-free survival in OC (HR = 1.57, \( P < 0.001 \)), as shown in Fig. 1c.

Combining with the clinical information of patients from the GEPIA database, which is based on gene expression profiles from TCGA and GTEx projects, demonstrated that the expression of KIF4A was significantly different in FIGO stage (\( F = 2.3, P < 0.05 \)), as shown in Fig. 1d. Through the analysis of DEMiRNAs expression in GEPIA database, we found that KIF4A was highly expressed in OC (\( P < 0.05 \)), as shown in Fig. 1e.

Taken together, our data have shown that KIF4A was significantly associated with prognosis and act as an oncogene in OC.

**Downregulation of KIF4A inhibits the proliferation and migration of OC cells**

SKOV3 cells transfected with 3 sets of sh-KIF4A have shown that expressions of KIF4A were significantly decreased (\( P < 0.01 \)), as shown in Fig. 2a and b. We did subsequent experiments selected by sh-KIF4A-3, because it was the most obvious decline in SKOV3 cells line. MTT and colony formation were used to study the effect of downregulation of KIF4A on proliferation. The results of the MTT assay showed that the OD values of the sh-KIF4A group (\( 0.239 \pm 0.020, 0.735 \pm 0.056, 1.611 \pm 0.001 \)) were significantly lower than those of the sh-NC group (\( 0.602 \pm 0.023, 1.632 \pm 0.025, 2.718 \pm 0.048 \)) at 24 h, 48 h, and 72 h, respectively (\( P < 0.05 \)). It was shown that downregulation of KIF4A can inhibit the proliferation in OC, as shown in Fig. 2c and d. Then, a transwell experiment was used to study the effect of KIF4A on migration, as shown in Fig. 2e; downregulation of KIF4A could inhibit migration in OC. The number of cells passing through the chamber filtration membrane was significantly less in the sh-KIF4A group (\( 65.325 \pm 4.663 \)) than in the sh-NC group (\( 180.718 \pm 5.876 \)) (\( P < 0.05 \)). As shown in Fig. 2f, this conclusion was further confirmed by wound heal assay.
Taken together, our data have shown that downregulation of KIF4A could inhibit the proliferation and migration of OC cells.

KIF4A is a target gene of miR-29c-3p

In order to further understand the mechanism of KIF4A in OC, we conducted experimental verification and bioinformatics analysis of its upstream regulatory components. Firstly, according to the data from the GEO database, including GSE83693 and GSE119055, we screened out 39 and 29 DEmiRNAs, which are shown in volcano plots, as shown in Fig. 3a. Then, we screened out and predicted the 78 miRNAs of KIF4A through mirDIPs. The potential regulatory factor miR-29c-3p of KIF4A was obtained from the intersection of the DEmiRNAs, as shown in the Fig. 3b. StarBase database was used to gain Pearson correlation analysis between miR-29c-3p and KIF4A in OC. The result showed a negative correlation ($r = -0.072$, $P < 0.05$), as shown in Fig. 3c. Through the analysis of DEmiRNAs expression in the GEPIA database, we found that miR-29c-3p was significantly low-expressed in OC, as shown in Fig. 3d. Also, survival analysis from the KM plot database also indicated that patients with high expression of miR-29c-3p survived considerably longer than those with low expression (HR = 0.74, $P < 0.05$), as shown in Fig. 3e. For the sake of proving the targeted regulatory relationship between miR-29c-3p and KIF4A, we detected the protein and mRNA expressions of KIF4A in miR-29c-3p mimic group and NC group in SKOV3. The results showed that the expression of KIF4A was significantly downregulated when miR-29c-3p was overexpressed ($P < 0.01$), as shown in Fig. 3f. Dual-luciferase reporter gene assay revealed that miR-29c-3p mimic significantly inhibited luciferase activity in KIF4A-WT group, as shown in Fig. 3g.

Taken together, our data have shown that KIF4A is a target gene of miR-29c-3p and a negative correlation between miR-29c-3p and KIF4A in OC.

Overexpression of miR-29c-3p inhibits proliferation and migration of OC cells which can be reversed by KIF4A

According to the above negative correlation between miR-29c-3p and KIF4A, we further investigated the effect of the expression of miR-29c-3p in OC. Firstly, we examined the overexpression efficiency of miR-29c-3p and KIF4A, as shown in Fig. 4a. Then, the results of MTT, colony formation, Transwell, and wound healing
assays showed that the overexpression of miR-29c-3p significantly inhibited cell activity, proliferation, and migration compared with NC group, as shown in Fig. 4a–d. In addition, rescue experiments also confirmed that the promotion of KIF4A could be reversed by miR-29c-3p.

Taken together, our data have shown that overexpression of miR-29c-3p inhibits proliferation and migration of OC cells, which can be reversed by KIF4A.

**Discussion**

In this study, we confirmed that the upregulation of KIF4A in OC cells compared with normal ovarian epithelial cells. And the study showed that silencing KIF4A could inhibit the proliferation and migration in OC. In addition, this study revealed that miR-29c-3p could regulate the expression of KIF4A.

KIF4A has been reported to be upregulated in many tumors, such as renal cell carcinoma [18], endometrial cancer [16], and prostate cancer [19]. In this study, through bioinformatics analysis in the GEPIA database, we discovered significant differences in KIF4A expression in OC. Meanwhile, Western blot and qRT-PCR also confirmed that KIF4A in OC was highly expressed. Previous studies have shown that KIF4A may be a potential biomarker for poor prognosis of hepatocellular carcinoma [20], and breast cancer [21]. Therefore, we used “The Kaplan-Meier plotter” for survival analysis of KIF4A, and we observed that patients with higher KIF4A expression had poorer prognosis. Then, we used the GEPIA database to find that
KIF4A also had significant differences in different FIGO stages. Combined with the above analysis, it suggested that KIF4A could be used as a diagnostic marker for the prognosis in OC. In addition, we validated the effect of KIF4A on cell proliferation and migration by silencing the expression of this gene in SKVO3 cell lines. We found that silencing KIF4A could significantly inhibit cell function. The above data further confirmed that KIF4 played an important role in OC.

miRNAs play a crucial role in migration, differentiation, apoptosis, and other processes. Target gene mRNA suppressed translation and degraded posttranscriptional by miRNAs binding to the 3'UTR of the mRNA [22]. For in-depth upstream mechanisms for KIF4A, we went a step further to analyze the DEmiRNAs of ovarian cancer in the GEO database and predicted the targeting miRNAs of KIF4A through the Mirdip database. Finally, we obtained the miR-29c-3p, which had a targeted binding site with KIF4A, which was downregulation in OC patients. Our data suggested that miR-29c-3p may be a suppressor in the development of OC, and it could target the downregulation of KIF4A in OC. MiR-29 has been related to types of cancer. miR-29 restrains proliferation, migration, and invasion in breast cancer cells through downregulating PDCD-4 [23]. miR-29 targeting PTEN inhibits proliferation and migration of osteosarcoma cells [24]. And miR-29 inhibits the progression of lung cancer via peripheral myelin protein 22 [25].

In this study, we also verified that miR-29c-3p could regulate the expression of KIF4A at the cellular level. Our data showed that overexpression of miR-29c-3p significantly inhibited the proliferation and migration of OC cell lines. When KIF4A was overexpressed, its inhibitory impact on miR-29c-3p could be reversed. However, this study only analyzed the effects of KIF4A and miR-29c-3p on ovarian cancer cells in terms of cell proliferation and migration, and their impact on other cell functions and specific mechanisms of action need further to study.

In the future, we can also use the miR-29c-3p/KIF4A axis as a target site for OC molecular therapy, in order
to improve the therapeutic effects and prognosis of OC patients.

Conclusions

As a member of the kinin superfamily, KIF4A has an important influence on the proliferation and migration of cancer cells. This study explored the mechanism of KIF4A as a target gene of miR-29c-3p in regulating OC process. In the future, KIF4A may not only serve as a diagnostic marker for KIF4A, but also be a therapeutic site for OC patients. This may be a new direction for our future research. In conclusion, this study provides a new theoretical basis for molecular targeted therapy of OC in the future.

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Authors’ contributions

S.F. and J.S. conceived and designed the study. S.F. and S.L. did the main experiments. S.F. analyzed and interpreted the data. S.L. revised the article critically. All authors had final approval of the submitted versions.

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Availability of data and materials

The following information was supplied regarding data availability: Data is available at NCBI GEO database, TCGA database, GEPIA database, and Kaplan-Meier Plotter database.

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study compiled with the Declaration of Helsinki and was approved by the Ethics Committees of the Second Affiliated Hospital of Soochow University.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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