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MiR-494 Inhibits Epithelial Ovarian Cancer Growth by Targeting c-Myc

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Statistical Analysis C
Data Interpretation D
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Background: Epithelial ovarian cancer (EOC) is the most lethal malignant gynecological cancer. MicroRNAs (miRNAs) play important roles in the pathogenesis of ovarian cancer. The role of miR-494 in EOC has not been fully investigated.

Material/methods: MiR-494 levels in ovarian cancer tissues and cells were tested by qRT-PCR. Cells were transfected with miR-494 mimics or miR-494 ASO by Lipofectamine. Bioinformatics algorithms from TargetScanHuman were used to predict the target genes of miR-494. The c-Myc protein level was assayed by Western blot. The interaction between miR-494 and c-Myc was confirmed by dual luciferase assays.

Results: MiR-494 showed low levels in EOC tissues and cells. Overexpression of miR-494 inhibited cell growth and migration of EOC cells and vice versa. c-Myc is the targeted gene of miR-494.

Conclusions: MiR-494 has an anti-tumor role in EOC via c-Myc.

MeSH Keywords: Cell Growth Processes • Genes, myc • MicroRNAs • Ovarian Neoplasms

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Background

Ovarian cancer is the most lethal malignant gynecological cancer [1], and is a heterogeneous disease associated with family history of cancer, genetic risk, and the histopathology [2]. EOC is the most common type, accounting for 95% of invasive ovarian cancer cases. The standard treatment is aggressive surgery followed by platinum-taxane chemotherapy [3–7]. Although surgery and platinum-based chemotherapy currently are the cornerstone of standard ovarian cancer management pathways, new therapy strategies are urgently required to improve outcomes. Thus, understanding of the molecular pathogenesis of ovarian cancer is required.

MiRNAs are evolutionarily conserved small non-coding RNAs involved in the regulation of gene expression and protein translation [8]. miRNAs play roles in the pathogenesis of various cancers [9–14]. Similarly, many miRNAs in EOC are found at abnormal levels [15–21].

miR-494 has been studied in various tumors. In non-small cell lung cancer, miR-494 can induce tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) resistance and regulates the G1/S transition during liver tumorigenesis [22,23]. On the contrary, miR-494 showed low levels in gastric cancer, breast cancer, prostate cancer, and cholangiocarcinomas, and overexpression of miR-494 inhibited the cancer growth [24]. In gastric carcinoma, miR-494 acts as an anti-oncogene by targeting c-Myc [25]. However, the role of miR-494 in EOC remains unknown.

In the present study, we investigated the function of miR-494 and c-Myc in ovarian cancer, and found that miR-494 acts as an anti-oncogene by targeting c-Myc in e EOC. We hope our data may provide a better understanding of the pathogenesis of EOC.

Material and Methods

Patients

Fifteen EOC specimens were collected from the Department of Gynecology and Obstetrics, West China Second University Hospital, Sichuan University. Tissue samples were immediately frozen in liquid nitrogen after isolation. Informed consent was obtained from each patient. The Ethics Commitment of Sichuan Provincial Cancer Hospital and the Ethics Committee of Sichuan University approved this study. The senior pathologists of Sichuan Provincial Cancer Hospital evaluated the histological features of the specimens. The clinical information of the 15 EOC patients are provide in Supplementary Table 1.

Cell culture

EOC cell lines SKOV3, HO8910, and HEK293 were purchased from the American Type Culture Collection (ATCC, Rockville, MD, USA). SKOV3, HO8910, and HEK293 cells were maintained in DMEM with 10% fetal bovine serum (FBS) (Invitrogen Corp, Grand Island, NY, USA) [26].

Detection of miR-494 and c-Myc level in ovarian cancer tissues or cells

Total RNAs of EOC tissues and cells were extracted by TRIzol reagent (Invitrogen Corp, Grand Island, NY, USA) according the manufacturer's instructions. The total RNAs was reverse-transcribed to cDNA by using the All-in-one™ miRNA First-Strand cDNA Synthesis Kit (Invitrogen Corp, Grand Island, NY, USA). The primers were designed and synthesized by Shengong Company (Shengong, Shanghai, China). Real-time PCR assay was performed as described previously [12,27–29].

Oligonucleotides and cell transfection

miR-494 antisense oligonucleotides (miR-494 ASO), miR-494 mimics, and negative control miRNA were purchased from RiboBio (Guangdong, China). MiR-494 ASO or MiR-494 mimics were transfected into cells by using Lipofectamine (Invitrogen, Shanghai, China), according to the manufacturer' s instructions [27].

Cell proliferation and migration assay

After 24 h of transfection of miR-494 mimics and miR-494 ASO, SKOV3 and HO8910 cells (5×10^3/well) were seeded into 96-well plates. Then MTT experiments were performed as previously described [30–32]. Absorbance in each well was measured by using a microplate reader set at 570 nm. To measure cell migration, 8-mm pore size culture inserts (Transwell; Falcon, BD Biosciences) were placed into wells of 24-well culture plates, separating the upper and lower chambers. In the lower chamber, 600 µL DMEM containing 10% FBS was added. Then 1×10^5/well cells were added to the upper chamber. After 24 h incubation, migrated cells were counted by use of a counting chamber (Shengong, Shanghai, China) [33].

MYC amplification and expression in different types of cancer analysis

MYC amplification data and graph were obtained from cBioPortal for Cancer Genomics [34,35]. The MYC expression in tumor data was from Gene Expression Omnibus (GEO) (*http://www.ncbi.nlm.nih.gov/geo/*).

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Supplementary Table 1. Clinical information.

No	Age (years)	Type	Stage	Differentiation
1	57	Epithelial ovarian cancer/serous	III	Low
2	59	Epithelial ovarian cancer/serous	IV	Moderate
3	57	Epithelial ovarian cancer/serous	III	Moderate
4	36	Epithelial ovarian cancer/serous	IV	Moderate
5	68	Epithelial ovarian cancer/serous	IV	Moderate
6	49	Epithelial ovarian cancer/serous	IV	Low
7	55	Epithelial ovarian cancer/serous	III	Moderate
8	66	Epithelial ovarian cancer/serous	IV	Low
9	65	Epithelial ovarian cancer/serous	III	Moderate
10	45	Epithelial ovarian cancer/serous	IV	Low
11	56	Epithelial ovarian cancer/serous	III	Low
12	59	Epithelial ovarian cancer/serous	III	Moderate
13	61	Epithelial ovarian cancer/serous	IV	Low
14	65	Epithelial ovarian cancer/serous	IV	Moderate
15	66	Epithelial ovarian cancer/serous	III	Moderate

Target prediction

Bioinformatics methods were applied for the prediction of the targeted genes of miR-494. In detail, the bioinformatics algorithms from TargetScanHuman were used [36–41].

Dual luciferase assays

To confirm whether c-Myc directly bind to miR-494, a dual luciferase assay was performed [42,43]. The 3'UTR of c-Myc was amplified by using PCR from genomic DNA. The production was inserted into the downstream of c-Myc 3'UTR reporter plasmids (pRL-c-Myc) (Biotech, Chengdu, China), and mutants of c-Myc 3'UTR were generated by use of a Site-Directed Mutagenesis kit (Shanghai, China). Then the whole plasmid was confirmed by sequencing. Mutation in the miR-494 binding site of the c-Myc 3'UTR were constructed by Shengong Company (Shengong, Chengdu, China). The luciferase reporter-containing mutant was constructed. For luciferase assays, HEK293 were transfected with luciferase reporter plasmid along with miR-494 mimics or negative control by using Lipofectamine 2000 (Invitrogen, Shanghai, China). At 24 h after transfection, these cells were analyzed by using a luciferase assay kit (Promega, Madison, WI, USA) [44].

Western blot

At 48 h after treatment, cells were washed with cold PBS and subjected to a lysis buffer. Protein lysates were separated using 8% SDS-polyacrylamide gel electrophoresis, then electrotransferred onto nitrocellulose filter membranes. The membranes were blocked with a buffer containing 5% non-fat milk in PBS with 0.05% Tween-20 for 2 h and incubated with primary antibody (anti-c-Myc) overnight. Then membranes were incubated with peroxidase-conjugated secondary antibodies (Milli-pore, Darmstadt, Germany) and developed with an enhanced chemiluminescence detection kit (Pierce, Rockford, IL). β-actin was used as blank control.

Statistical analysis

The data are the mean ±S.D. from 3 independent experiments. When only 2 groups were compared, the difference between them was analyzed using a 2-tailed Student's t test. However, when 3 or more groups were compared, the difference among them was analyzed using ANOVA. Statistically significant differences in the expression of miR-494 between matched pairs were detected by the Wilcoxon matched-pairs signed rank test. SPSS software (version 17.0) was used to perform statistical analyses, in which $P<0.05$ was significant.

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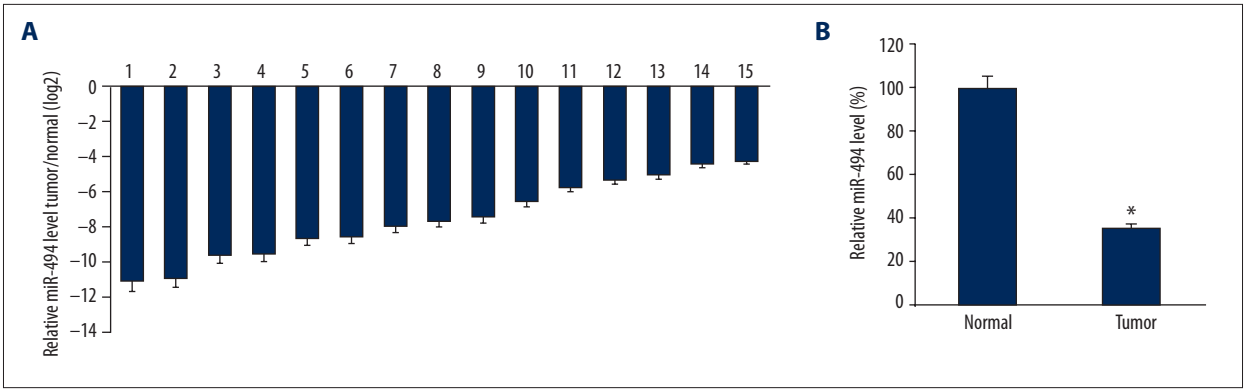

Figure 1. The miR-494 level in epithelial ovarian cancer tissues. The miR-494 levels in the 15 EOC tissues and matched adjacent normal cancer tissues were tested by qRT-PCR. U6 snRNA was used as blank control (**A**). The mean expression of miR-494 in the 15 EOC tissues and matched adjacent normal cancer tissues were calculated, and the mean level of 15 normal ovarian tissues were arbitrarily defined as 100% (**B**). The qRT-PCR experiments were performed 3 times. Data are mean ±S.D. * *P*<0.05

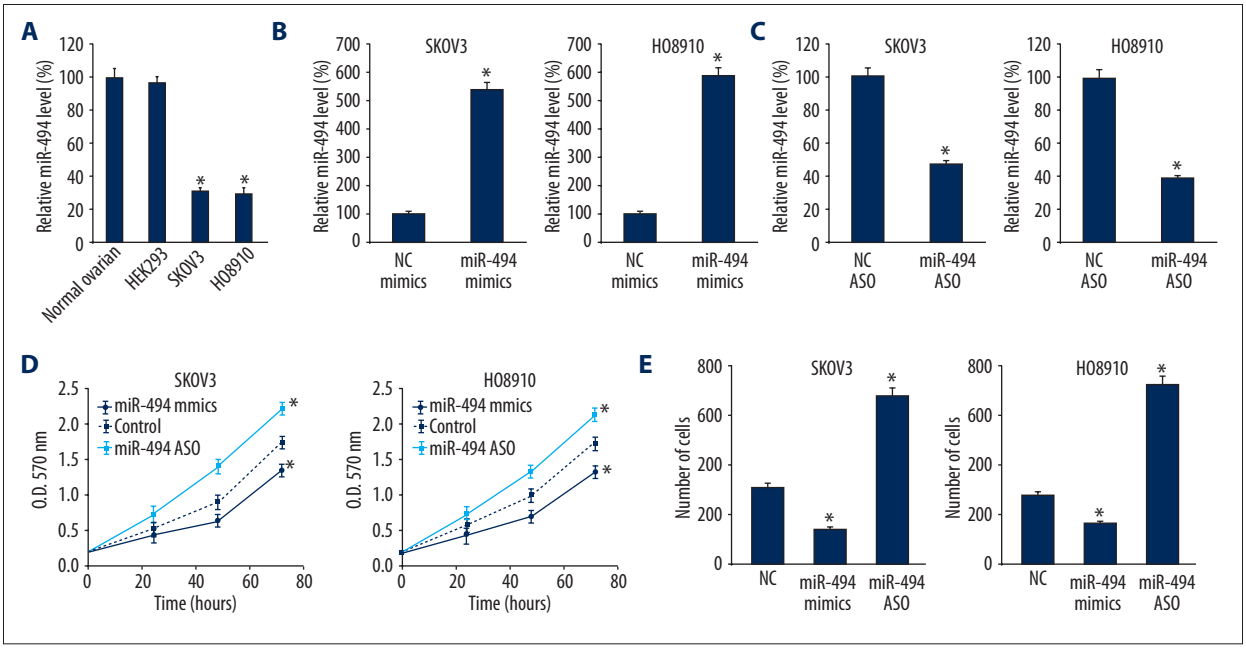

Figure 2. Overexpression of miR-494 inhibited cells growth and invasion and vice versa. The miR-494 levels in normal ovarian tissues, HEK293, SKOV3, and HO8910 cells were tested by qRT-PCR. The miR-494 level in normal ovarian tissues was deliberately treated as 100% (**A**). After miR-494 mimics transfection, the miR-494 levels in SKOV3 and HO8910 cells were examined. The miR-494 level in negative control was deliberately treated as 100% (**B**). After miR-494 ASO transfection, the miR-494 levels in SKOV3 and HO8910 cells were examined. The miR-494 level in negative control transfected cells was deliberately treated as 100% (**C**). After miR-494 mimics or miR-494 ASO transfection, the cellular proliferation of SKOV3 and HO8910 were tested by MTT analysis (**D**). After miR-494 mimics or miR-494 ASO transfection, cells were collected for migration test (E). The experiments were performed 3 times. Data are mean ±S.D. * *P*<0.05

Figure 3. c-Myc was targeted by miR-494. Alterations of c-Myc were visualized by cBioPortal for Cancer Genomics. Mutation, deletion, amplification, and other alterations are shown in different colors. The most frequent alteration of c-Myc in different types of cancer is amplification. The CAN data stand for copy number alteration data (**A**). The binding site for miR-494 in c-Myc was mutated (**B**). HEK293 cells were co-transfected with miR-494 mimics or control and reporter plasmid or the mutant 3'UTR of c-Myc, together with the controls. At 48 h after transfection, the luciferase activity was measured (**C**). MiR-494 mimics was transfected into HEK293 cells. At 48 h later, the c-Myc protein level was tested by Western blot (**D**). The mRNA levels of c-Myc in 15 EOC tissues were assayed by qRT-PCR (**E**). The experiments were performed 3 times. Data are mean±S.D. *P<0.05

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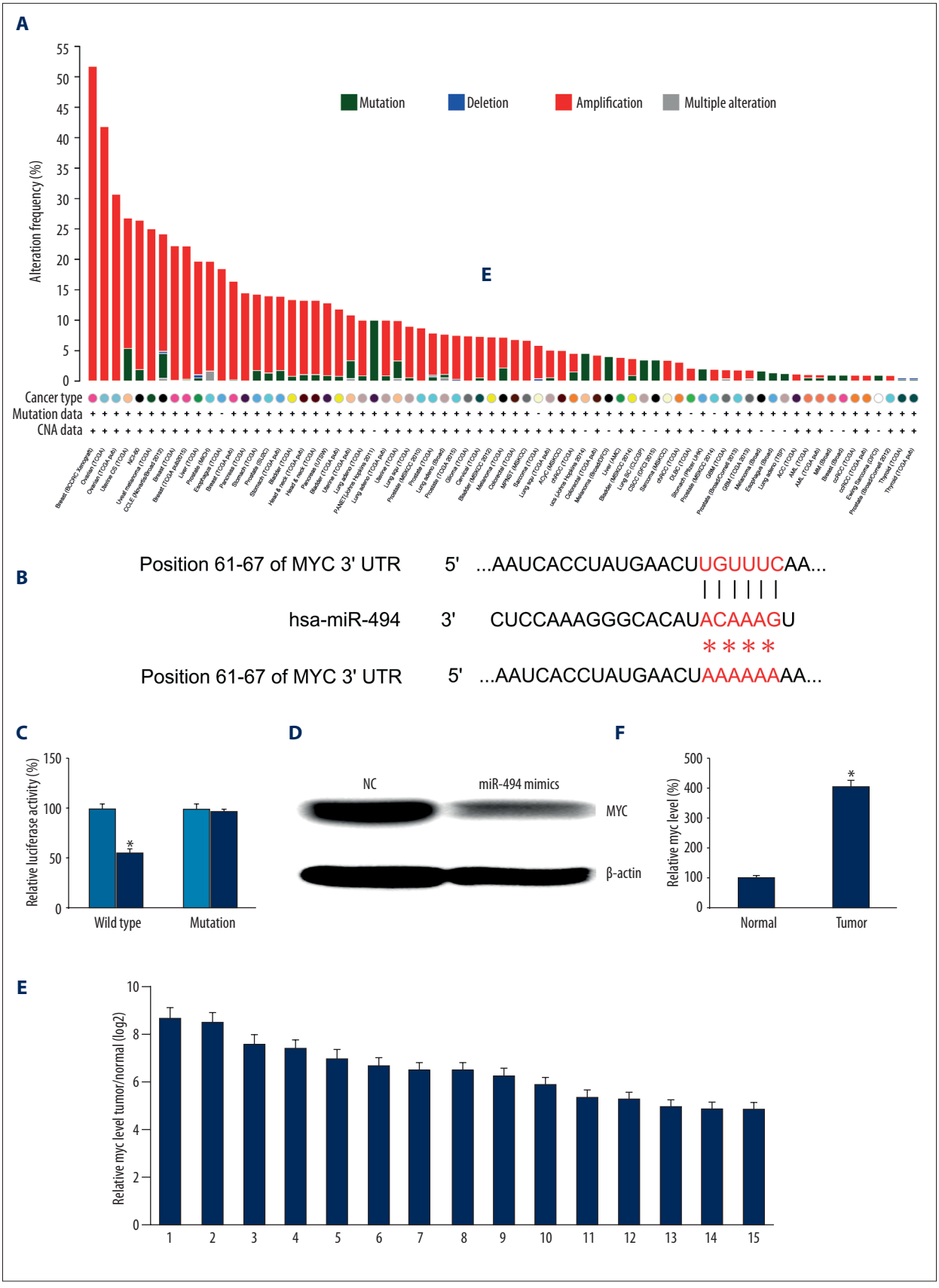

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Results

The lower expression of miR-494 in EOC tissues

We collected 15 EOC tissues from our hospital, then the miR-494 levels in each cancer tissue and matched adjacent normal tissue were assayed by qRT-PCR, and we found that all EOC tissues showed lower levels of miR-494 (Figure 1A). Then we calculated the mean level of miR-494 in the 15 cancer tissues and normal tissues, and found that the mean expression of miR-494 in the 15 cancer tissues was lower than the mean expression in normal tissues (Figure 1B).

The *in vitro* function of miR-494

Next we tested the function of miR-494 *in vitro*. EOC cell lines SKOV3 and HO8910 were tested by qRT-PCR for the miR-494 levels and the miR-494 levels in normal ovarian tissues, and HEK293 was used as negative control. Unsurprisingly, miR-494 levels in SKOV3 and HO8910 cells were lower than in miR-494 levels in normal ovarian and HEK293 cells (Figure 2A). Next, we overexpressed or suppressed miR-494 levels in SKOV3 and HO8910 by transfection of miR-494 mimics or miR-494 ASO. At 48 h following the transfection, the miR-494 levels in the 2 cell lines were tested, and we found that transfection of miR-494 mimics overexpressed the miR-494 levels and transfection of miR-494 ASO suppressed the miR-494 levels (Figure 2B, 2C). Next, proliferation of SKOV3 and HO8910 cells were assayed by MTT analysis. We found that overexpression of miR-494 inhibited cell proliferation and suppression of miR-494 promoted cell proliferation (Figure 2D). Migration assay showed that miR-494 mimics inhibited the migration of SKOV3 and HO8910 cells and miR-494 ASO promoted cell migration (Figure 2E).

c-Myc was targeted by miR-494

A previous study showed that c-Myc was targeted by miR-494 in gastric cancer [25], and we wondered whether miR-494 targeted c-Myc in ovarian cancer. To reveal the role of c-Myc, we queried The Cancer Genome Atlas (TCGA). The TCGA Project is a large-scale collaborative effort to characterize the genomic changes that occur in cancer. This project has profiled and analyzed large numbers of human tumors to discover and catalog molecular aberrations at the DNA, RNA, protein, and epigenetic levels [45]. We found c-Myc showed amplification in most types of cancer (Figure 3A). Next, we identified the binding sites between miR-494 and c-Myc, and the mutated version of c-Myc was also displayed (Figure 3B). The effect of miR-494 on the c-Myc translation was tested by luciferase reporter assay using luciferase reporter plasmid constructed with wild-type 3'UTR of c-Myc or mutant. We found that overexpression of miR-494 significantly reduced the luciferase activity of the reporter gene with wild-type 3'UTR of c-Myc, but not with the mutant (Figure 3C). Next, we tested the c-MYC protein level in HEK293 cells, and found the c-MYC protein level was suppressed following miR-494 transfection (Figure 3D). We then assayed the c-Myc mRNA levels in the 15 epithelial ovarian cancers, and found that in all cancer tissues, c-Myc showed higher levels (Figure 3E), and the mean expression of c-Myc in the 15 cancer tissues was higher than the mean expression in normal tissues (Figure 3F).

Discussion

In this study we tested the function of miR-494 in EOC. We found that miR-494 showed a lower level in cancer tissues, and overexpression of miR-494 suppressed the cellular proliferation and immigration. We also found that *c-Myc* can be targeted by miR-494 in EOC cells.

The *c-Myc* gene has been study for a long time. In 1983, Minna et al. found amplification and expression of the c-Myc oncogene in human lung cancer cell lines [46]. The oncogene role of *c-Myc* has been well studied. The *c-Myc* oncogene is activated in many types of cancer [47]. The c-Myc transcription factor regulates numerous processes, including epithelial-mesenchymal transition, metastasis, stemness, angiogenesis, and cell cycle progression [48]. Here, we found that miR-494 targeted *c-Myc* and miR-494 inhibited cellular proliferation; therefore, we hypothesized that miR-494 plays a role in ovarian cancer via *c-Myc*.

Interestingly, *c-Myc* can induce many miRNAs, including miR-9, miR-17, miR-18a, miR-19a, miR-20a, miR-22, and miR-25. These genes take part in many complicated processes, such as epithelial-mesenchymal transition, metastasis, angiogenesis, apoptosis, and heart development and reprogramming [48], suggesting that *c-Myc* stayed in the center of the molecular network.

The function of miR-494 has been revealed in various cancers. miR-494 is a tumor-suppressive miRNA in prostate cancer, pancreatic cancer, cholangiocarcinoma, ovarian cancer, and lung cancer [49–54], and showed oncogenic roles in hepatocellular carcinoma, retinoblastoma, and bronchial carcinogenesis [55–57]. The most common explanation is that miR-494 targets different genes in various cancers. However, why miR-494 targets certain genes in certain types of cancer needs further exploration.

Conclusions

Our study shows the role miR-494 in EOC. We found that miR-494 is a tumor suppressor in EOC by targeting *c-Myc*. We hoped

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that our data provide useful insights into a new mechanism of miR-494 in EOC.

Conflict of interest

The authors declare no conflicts interest.

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