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DUXAP8 promotes the proliferation and migration of ovarian cancer cells *via* down-regulating microRNA-29a-3p expression

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Abstract. – OBJECTIVE: To study the role of long-chain non-coding RNA (lncRNA) DUXAP8 in ovarian cancer (OCa) and the underlying potential mechanism.

PATIENTS AND METHODS: The expression pattern of DUXAP8 in ovarian cancer was analyzed using the GEPIA database. Quantitative real-time polymerase chain reaction (qRT-PCR) was applied to determine the expression of DUXAP8 in OCa tissues; at the same time, OCa cell lines were cultured to complete functional experiments, including cell counting kit-8 (CCK-8), plate cloning experiments and transwell experiments to evaluate the effects of DUXAP8 on the proliferative and migration ability of OCa cell lines. Bioinformatics analysis and Dual-Luciferase reporter genes were used to determine the binding and expression of DUXAP8 to its downstream key gene microRNA-29a-3p in OCa cells. In addition, co-transfection technology and cell function recovery experiments were used to verify the important role of the DUXAP8/microRNA-29a-3p regulatory network in OCa.

RESULTS: DUXAP8 was abnormally highly up-regulated in OCa tissues and cell lines, besides, its expression was related to poor prognosis of patients. CCK-8 and plate cloning experiments showed that knockdown of DUXAP8 in OCa cells can significantly inhibit the proliferation of OCa cells. Transwell results suggested that knockdown of DUXAP8 can significantly inhibit OCa cell migration. In addition, it was found that DUXAP8 can bind and negatively regulate the expression of microRNA-29a-3p in OCa. Functional experiments in OCa cells also revealed that microRNA-29a-3p was a key downstream gene that mediated the regulation of DUXAP8 on OCa function.

CONCLUSIONS: DUXAP8 has abnormally high expression in OCa and can lead to malignant progression of the tumor.

Key Words:
DUXAP8, OCa, MicroRNA-29a-3p, Cell proliferation, Cell migration.

Introduction

Globally, ovarian cancer (OCa) is one of the most lethal cancers in women[1]. OCa is usually diagnosed at an advanced stage due to the lack of specific early symptoms[2]. The 5-year overall survival rate of OCa is only 40%[3]. Epithelial OCa (EOC) accounts for about 90% of all ovarian malignancies, and its 5-year survival rate is about 45%, while in patients with advanced OCa, the 5-year survival rate is further reduced to 35%[4]. Despite the optimization of surgical techniques and chemotherapy drugs over the past 20 years, the mortality and morbidity of EOC remain high. In particular, drug resistance is the main cause of high EOC mortality. Even after surgery and chemotherapy, most patients die within 5 years, mainly due to acquired resistance[5]. Therefore, it is necessary to further study the specific mechanism of malignant progression of OCa to guide the diagnosis and treatment of OCa.

Long-chain non-coding RNA (lncRNA) is a type of non-coding RNA with more than 200 nucleotide bases. Increasing evidence suggests that lncRNA participates in a variety of biological processes by regulating gene expression during and after transcription[6]. The hypothesis of competitive endogenous RNA (ceRNA) has received much attention in recent years. This hypothesis suggests that lncRNA acts as a competitive sponge for microRNAs to inhibit miRNA function and thereby regulate the expression of miRNA target genes[7]. Recently, there is evidence that abnormal expression of lncRNA in tumor tissues is involved in the occurrence, development and drug resistance of cancer *in vivo*. These results indicate that lncRNA might become a diagnostic biomarker and therapeutic target for human cancer[8,9]. LncRNA also participates in the progression of human tumor diseases, including regulating intracellular sig-

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naling networks, maintaining tumor cell proliferation and anti-apoptotic capabilities, and regulating cell differentiation[10]. Consistently, Linc00460 was found to promote head and neck tumor progression by regulating the expression level of mir-206 and promoting tumor cell apoptosis and autophagy[11]. Besides, lncRNA RP1 has been found to enhance cell proliferative and migration ability by inactivating the p27/kip1 pathway and is considered to be one of the important oncogenes for breast cancer progression[12]. Recently, DUXAP8 has exhibited an oncogenic role in many tumors. DUXAP8 can regulate the mir-422a/PDK2 signal axis through the ceRNA mechanism, leading to the progression of liver cancer[13]. DUXAP8 is abnormally highly expressed in colon cancer and interacts with the transcription factor EZH2 to accelerate tumor cell proliferative, migrating and invasive progression[14]. DUXAP8 enhances the ability of tumor cells to progress in renal cancer by down-regulating mir-126, leading to cancer metastasis[15]. However, the important role of DUXAP8 in OCa is unknown.

Here, we used the TCGA database to analyze the expression of DUXAP8 in OCa tissue and detected its effect on OCa cell proliferative and migration ability through experimental biological techniques. Furthermore, through Dual-Luciferase reporter gene assay and functional reversal experiments, the interactions of DUXAP8 and the downstream molecular mechanism of DUXAP8 action were explored.

Patients and Methods

Tissue Specimens and Clinical Information

33 pairs of OCa tissues and adjacent normal tissues were collected from the Zaozhuang Mining Group Zaozhuang Hospital. The resected tissues were immediately stored in a liquid nitrogen tank (Ambion). Clinical data of patients were collected for subsequent experimental research. This investigation was approved by Zaozhuang Mining Group Zaozhuang Hospital Ethics Committee. Tumor pathological classification and staging criteria were performed in accordance with the Union for International Cancer Control (UICC) staging criteria. Inclusion criteria: patients with no severe diseases in other organs, and none of patients had preoperative chemotherapy/radiotherapy, endocrine or molecular targeted therapy. Exclusion criteria: patients with distant metastasis, those complicated with other malignancies, those with mental disease, those complicated with myocardial infarction, heart failure or other chronic diseases, or those previously exposed to radioactive rays. All procedures for the collection and use of the organization followed the ethical standards set out in the Helsinki Declaration.

Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR)

The total RNA was extracted using TRIzol reagent (TaKaRa, Komatsu, Japan). The complementary deoxyribose nucleic acid (cDNA) was synthesized using the reverse transcription kit (Invitrogen, Carlsbad, CA, USA), followed by the PCR reaction using SYBR Premix EX Taq ™ (TaKaRa, Komatsu, Japan) on the ABI 7500 real-time PCR system (ABI, Applied Biosystems, Foster City, CA, USA). The relative gene expression was calculated using $2^{-\Delta\Delta Ct}$. All primers used in the experiment were synthesized by Guangzhou Biotechnology Co., Ltd. (Guangzhou, China). Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as an internal control. The primes were listed below: DUXAP8 F: 5′-AGGATGGAGTCTCGCTGTATTGC-3′, R 5′-GGAGGTTTGTTTTCTTCTTTTTT-3′; GAPDH, F: 5′-AGAAGGCTGGGGCTCATTTG-3′, R: 5′-AGGGGCCATCCACAGTCTTC-3′; microRNA-29a-3p, F: 5’-CGTAGCACCATCTGAAATCG-3’; U6, F 5’-GCGCGTCGTGAAGCGTTC-3’; microRNA-29a-3p-RT, 5-GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGATAACCG-3’; U6-RT, 5’-GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACAAAATG-3’; Universal reverse primer, 5’-GTGCAGGGTCCG AGGT-3 ‘;

Cell Culture and Transfection

OCa cell lines (A2780, IGROV1, SKOV3, and ES-2) and normal epithelial cell lines were purchased from American Type Culture Collection (ATCC) (Manassas, VA, USA). Cells were maintained in modified media (Gibco, Rockville, MD, USA) containing 10% fetal bovine serum (FBS) (Gibco, Rockville, MD, USA) and cultured in a 37°C, 5% CO_2 incubator.

si-DUXAP8, microRNA-29a-3p mimics and their negative controls were transfected into cultured UM-UC-3 cells using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). These siRNAs or mimics and inhibitors were synthesized by

Shanghai Gima company (Shanghai, China). The siDUXAP8 sequence: 5′-AAGAUAA AGGUGGUUUCCACAAGAA-3′.

Plate Clone Formation Experiment

The transfected cells were seeded in 6-well plates at a density of 2000 cells/well and cultured for 10 days. After harvested for fixation and staining, the cell colonies in the 6-well plate were photographed and counted.

Cell Counting Kit-8 (CCK-8) Test

Transfected cells were seeded in 96-well plates at a density of 2000 cells / well, and 3 replicates were set. Cell viability was detected by the CCK-8 kit (Dojindo Molecular Technologies, Kumamoto, Japan) at 0, 24, 48, 72, and 96 hours after cell culture, respectively.

Transwell Experiment

The migration of OCa cells was performed using a cell migration detection kit (BD Biosciences, Franklin Lakes, NJ, USA). Approximately 2×10^5 cells were plated into the upper chamber to make a serum-free cell suspension, and the lower layer was filled with the complete medium as a chemical attractant. After 24 hours of culture, cells were collected and fixed with pre-chilled methanol and stained with 2% staining solution. Finally, the stained cells were observed and photographed under a microscope.

Dual-Luciferase Assay

To determine the binding capacity of DUXAP8 and microRNA-29a-3p, we predicted the binding sites of the two, and based on the prediction results, we constructed the wild-type and mutant-type Luciferases reporter plasmid of DUXAP8, respectively. The cells were cultured in a 48-well plate for 24 hours, and then the constructed plasmid and microRNA-29a-3p mimic or negative control were transfected into OCa cells. After 24 hours, the Dual-Luciferase reporter gene assay was performed using the analytical systems (Promega, Madison, WI, USA).

Statistical Analysis

GraphPad Prism v7.0 software (La Jolla, CA, USA) was used for data analysis. All measurement data were in the form of mean ± standard deviation. The *t*-test and multiple comparison t-test were used for comparison between groups. The Pearson method was used to test the correlation of gene expression. A *p*-value of less than 0.05 was considered statistically significant.

Results

DUXAP8 Is Abnormally Overexpressed In OCa and Associated With Poor Prognosis

Comparative analysis from the TCGA database including a total of 426 OCa tissues and 88 normal ovarian tissues showed that DUXAP8 was remarkably overexpressed in OCa tissues (Figure 1A). Therefore, we collected clinical OCa tissues and normal ovarian tissues from a total of 33 OCa patients. The clinical information, including tumor staging and grading was shown in Table I. We found by qPCR that DUXAP8 was remarkably up-regulated in OCa tissues than that in normal ovarian tissues (Figure 1B). Meanwhile, DUXAP8 level was remarkably overexpressed in OCa cell lines A2780, OV2008, SKOV3, IGROV1 than in normal ovarian cell line ISOE80, (Figure 1C). We collected the prognosis information of recruited patients in the early stage and calculated the relationship between DUXAP8 and OCa prognosis using survival analysis, which suggested that patients with OCa with high DUXAP8 expression had a poorer survival prognosis, and their overall survival was remarkably shorter than that of patients with low DUXAP8 expression (Figure 1D). These above results demonstrated that DUXAP8 was remarkably overexpressed in OCa and was closely related to the poor prognosis of patients.

DUXAP8 Can Promote the Proliferation and Migration of OCa Cells

To further explore the role of DUXAP8 in the progression of OCa, we used loss of gene function to verify the effect of DUXAP8 on the proliferative and migration ability of OCa cells. First, we transfected si-DUXAP8 and corresponding negative controls in OCa cell lines, and verified the efficiency of transfection using qPCR (Figure 2A). Then, CCK-8 was applied to evaluate the proliferative ability of A2780 and SKOV3 cells, which showed that after silencing DUXAP8, the proliferative ability of OCa cell lines was remarkably inhibited (Figure 2B). The plate cloning experiment revealed that knocking down DUXAP8 in OCa cells remarkably reduced the cloning ability of OCa cell lines (Figure 2C). Besides, transwell experiments indicated that the migration ability was remarkably inhibited in OCa cell lines transfected with si-DUXAP8 (Figure 2D). The above experimental results confirmed that DUXAP8 can promote the proliferative and migration ability of OCa cells.

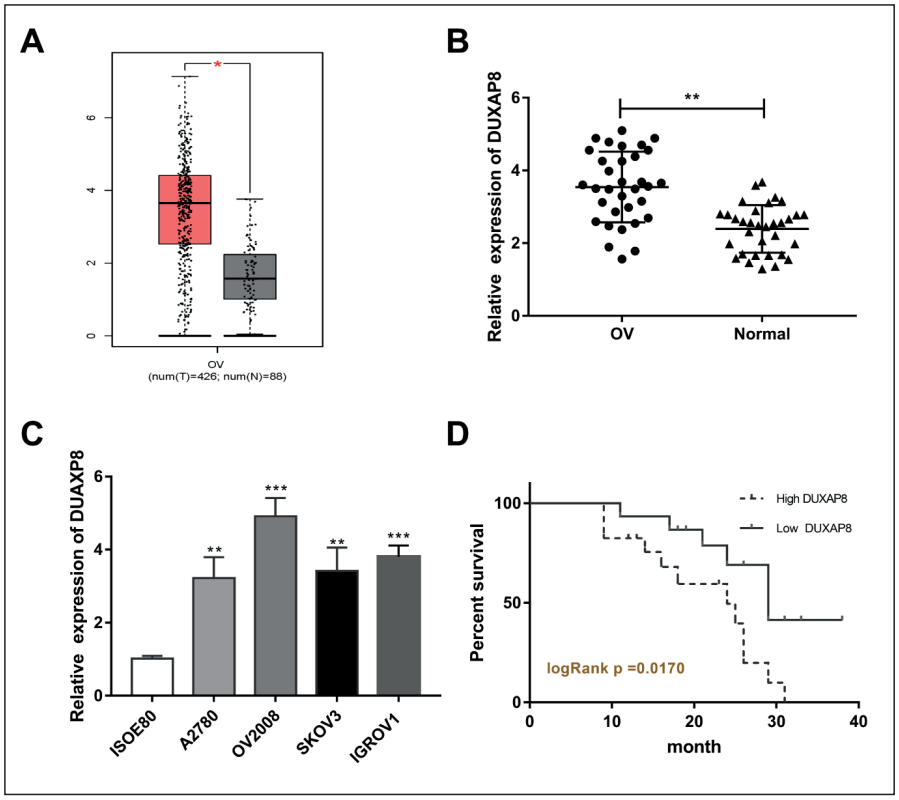

Figure 1. A, GEPIA database analysis was used to explore the expression level of DUXAP8 in ovarian cancer tissues and normal ovarian tissues; **B**, qRT-PCR was used to detect the expression level of DUXAP8 in clinical samples of ovarian cancer and normal samples; **C**, qRT-PCR was used to measure the expression level of DUXAP8 in ovarian cancer cell lines as well as normal cell lines; **D**, The generative analysis was applied to determine the survival prognosis of ovarian cancer patients with different DUXAP8 levels. *p<0.05, **p<0.01, ***p<0.001.

DUXAP8 Binds and Down-Regulates MicroRNA-29a-3p In OCa

Since DUXAP8 participated in promoting tumor progression in OCa cells, we further explore the underlying molecular mechanisms. We used bioinformatics technology to predict its potential targets and found that the 3'UTR region of DUXAP8 had a binding site with microRNA-29a-3p (Figure 3A). Further researches revealed that microRNA-29a-3p was up-regulated in OCa cell lines A2780 and SKOV3 cells after transfection with si-DUXAP8 (Figure 3B). At the same time, we verified their binding relationship in OCa cells using the Dual-Luciferase reporter gene experiment. Besides, the probability of binding between DUXAP8 and microRNA-29a-3p was remarkably inhibited after the mutations of the binding site (Figure 3C-D). We then measured the expression relationship between the two in OCa tissues and performed correlation analysis using the Pearson algorithm. As a result, we found that there was a negative correlation between the expressions of DUXAP8 and microRNA-29a-3p in the OCa tissues (Figure 3E). These results indicated that DUXAP8 may regulate microRNA-29a-3p expression and participate in the process of OCa through the ceRNA mechanism.

Table I. Clinicopathological features of OV patients.

Characteristics	No. of cases
Age (years)	
≤50	11
>50	22
Tumor size	
≤5 cm	13
>5 cm	20
Stage	
I	8
II	7
III	13
IV	5
Histology type	
Serous adenocarcinoma	20
Mucoid adenocarcinoma	8
Endometrioid carcinoma	5
Pathological grade	
1	8
2	15
3	10
Lymph node metastasis	
0	19
1	14

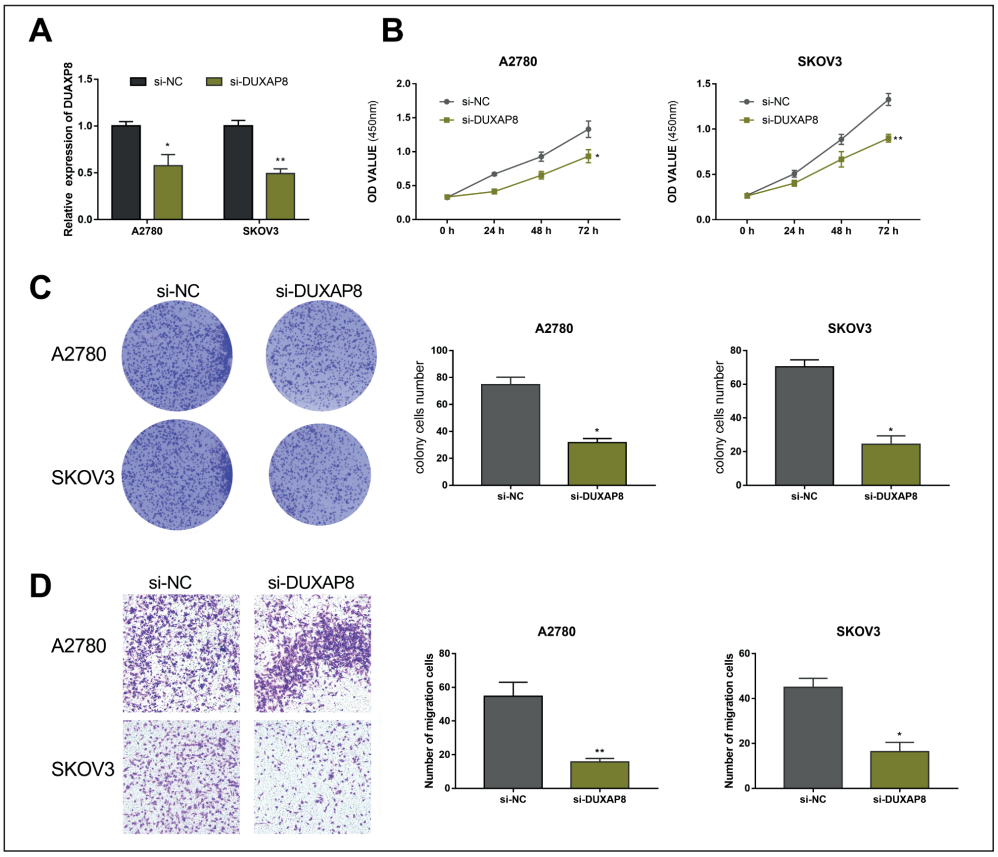

Figure 2. A, si-DUXAP8 and its negative controls were transfected in A2780 and SKOV3 cell lines and the DUXAP8 level was detected by q-PCR; **B**, CCK-8 experiments were applied to evaluate the proliferation ability of A2780 and SKOV3 cell lines after knocking down DUXAP8; **C**, Plate cloning experiments were applied to evaluate the the proliferation ability of A2780 and SKOV3 after knocking down DUXAP8 (magnification: 20×); **D**, The migration abilities of A2780 and SKOV3 cell lines after knocking down DUXAP8 was detected by transwell assay (magnification: 20×). *p<0.05, **p<0.01.

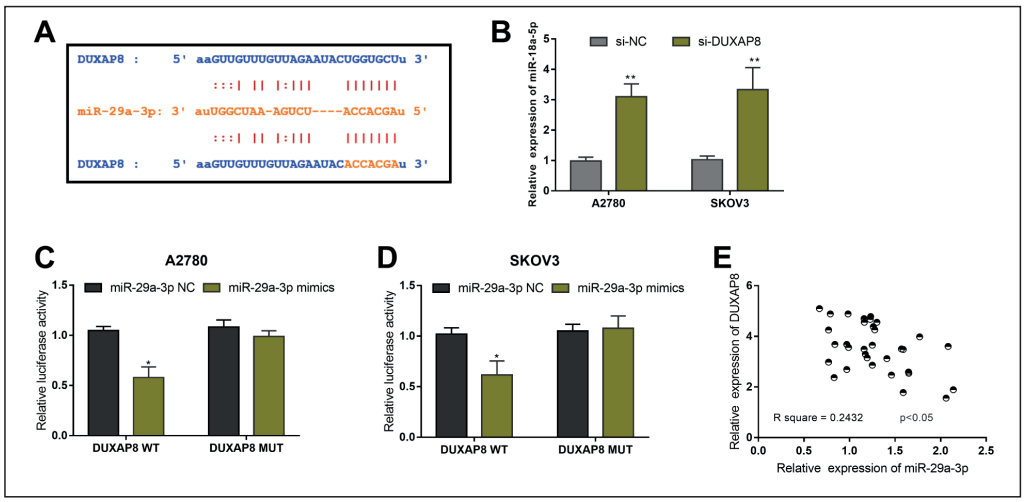

Figure 3. A, Bioinformatics predicted that the 3matics predictnocXAP8 had binding sites with microRNA-29a-3p; **B**, After knocking down DUXAP8 in ovarian cancer cells, microRNA-29a-3p expression in A2780 and SKOV3 cell lines was detected by q-PCR; **C-D**, Dual-Luciferase reporter gene experiment was used to determine the binding between Wt-DUXAP8(C)/ Mut-DUXAP8(C) and microRNA-29a-3p in ovarian cancer cells; **E**, Pearson algorithm correlation analysis was applied to evaluate the correlation between DUXAP8 and microRNA-29a-3p in 23 cases of ovarian cancer tissues; *p<0.05, **p<0.01.

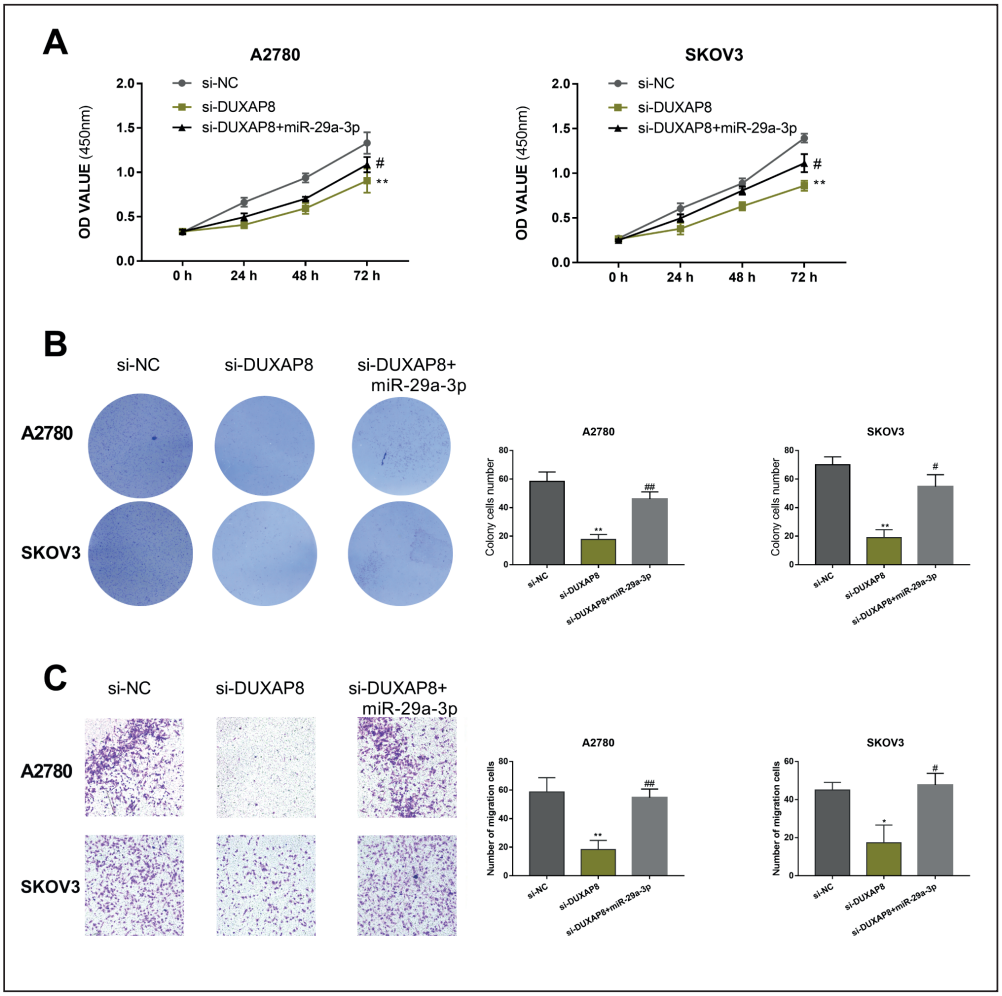

Figure 4. A, CCK-8 experiments were applied to evaluate the proliferation ability of A2780 and SKOV3 cell lines that co-transfected with si-DUXAP8+microRNA-29a-3p Inhibitor; **B**, Plate cloning experiments were applied to evaluate the proliferation ability of A2780 and SKOV3 that co-transfected with si-DUXAP8 + microRNA-29a-3p Inhibitor; **C**, The migration abilities of A2780 and SKOV3 cell lines after co-transfection of si-DUXAP8 + microRNA-29a-3p Inhibitor was detected by transwell assay (Magnification: 20×).*p<0.05, **p<0.01, $^{\#}p$<0.05, $^{\#\#}p$<0.01.

MicroRNA-29a-3p Is a Key Downstream Gene for DUXAP8

To further understand the role of microRNA-29a-3p in OCa, we performed functional recovery experiments in OCa cell lines. Through CCK-8 experiments, we found that transfection of microRNA-29a-3p inhibitor in A2780 and SKOV3 cell lines can restore the inhibitory effect of DUXAP8 on cell proliferation in OCa cells (Figure 4A). After microRNA-29a-3p inhibition, the number of colonies formed in A2780 and SKOV3 cell lines remarkably recovered (Figure 4B); transwell results showed that microRNA-29a-3p inhibition could revovery the migration ability of OCa cells after DUXAP8 knockdown (Figure 4C). The above experimental results further confirmed that microRNA-29a-3p exhibited a tumor suppressive effect in OCa, and the DUXAP8/microRNA-29a-3p signal axis played a key part in the progression of OCa.

Discussion

Ovarian cancer causes a large number of deaths in female populations and is the main tumor of the reproductive system that threatens public health[16,17]. Significant progress has been made in the diagnosis and treatment of ovarian cancer. Recently, new molecularly targeted drugs have been used to treat ovarian cancer. However, the mortality and recurrence rate of ovarian cancer are still high[18].

With the development of high-throughput sequencing and RNA analysis technology, the possible role of long non-coding RNA (lncRNA) in cancer has been fully studied[19]. LncRNAs regulate tumors progression and mediate genetic modification at the transcriptional and post-transcriptional levels. Imbalance of lncRNA is considered to be an important link in tumorigenesis and development[20]. Previous studies have suggested that up-regulated DUXAP8 promoted the progression of tumors such as liver cancer and colorectal cancer through miRNA adsorption mechanisms[21,22]. However, the association about DUXAP8 and OCa still remains unclear. Our study investigated its possible mechanisms in OCa for the first time. We found that DUXAP8 was abnormally highly expressed in OCa, but its specific role in OCa has not been studied. Therefore, we recruited patients with clinical OCa, collected tissue samples during surgery, and followed up the patients' long-term survival. We found that DUXAP8 level was remarkably higher in OCa tissues than that in normal ones. In addition, we found that OCa patients that overexpressing DUXAP8 had shorter survival time, suggesting that DUXAP8 may play a role in the risk of poor prognosis of OCa. We speculated that DUXAP8 may affect carcinogenic in OCa. We validated this hypothesis through experimental cell models of OCa. Comparing the expression level of DUXAP8 in the cells, we found that the expression of DUXAP8 in tumor cells also increased significantly. We then performed CCK-8, plate cloning experiments, and transwell experiments to determine the effect of changes in DUXAP8 expression on cell proliferative and migration capacity. The results demonstrated that DUXAP8 may be involved in tumor development by promoting the proliferative and migration ability of OCa cells.

To clarify the specific mechanism of DUXAP8 on carcinogenesis, we selected the LncRNA target gene prediction website starbase to predict the downstream genes of DUXAP8. The prediction results found that microRNA-29a-3p was a potential downstream target of DUXAP8. microRNA-29a-3p is an important tumor suppressor gene. Previous studies have confirmed that its target gene COL4A2 is anchored in LMH cells and regulates tumor cell proliferation, migration and invasion[23]. In colorectal tumors, microRNA-29a-3p could inhibit the growth of tumors by down-regulating the oncogene RPS15A[24]. Related studies have found that microRNA-29a-3p may have an impact on the diagnosis and treatment of OCa and the administration of microRNA-29a-3p by exosomes could induce cells to resist tumor differentiation[25,26]. In this study, to confirm whether DUXAP8 could regulate microRNA-29a-3p, we silenced DUXAP8 and detected the expression of microRNA-29a-3p. We found that there was a negative correlation between their expressions. The Luciferase reporter gene experiment directly indicated the binding relationship between DUXAP8 and microRNA-29a-3p. Besides, Pearson correlation analysis revealed that DUXAP8 can negatively regulate the expression of microRNA-29a-3p in clinical cancer tissues. Subsequent functional reversal experiments further revealed that inhibiting microRNA-29a-3p expression in OCa cells can reverse the restriction of DUXAP8 on the proliferative and migration ability of OCa cells. Our study confirmed the important effect of the DUXAP8/microRNA-29a-3p signal axis on the progression of OCa, and the regulatory network might be a new target for the diagnosis and treatment of OCa.

Conclusions

Altogether, these results demonstrated for the first time that DUXAP8 is abnormally highly expressed in OCa tissues and cell lines and can lead to tumor malignancy. DUXAP8 may negatively regulate microRNA-29a-3p, thereby mediating the tumorigenesis of OCa.

Conflict of Interests

The authors declare that they have no conflict of interests.

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