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CircRNA UBAP2 promotes the progression of ovarian cancer by sponging microRNA-144

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Abstract. – OBJECTIVE: This study aims to elucidate the regulatory effect of circular RNA UBAP2 (circUBAP2) on the progression of ovarian cancer (OC).

PATIENTS AND METHODS: Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) was used to detect the expressions of circUBAP2, microRNA-144 and CHD2 in OC tissues and adjacent normal tissues. The correlation between the expression levels of circUBAP2 and microRNA-144 with pathological parameters of OC patients was analyzed. Subcellular distribution of circUBAP2 was detected by chromatin fractionation assay. After overexpression of circUBAP2 in OC cells, changes in proliferative and migratory abilities were evaluated by Cell Counting Kit-8 (CCK-8) and transwell assay, respectively. In addition, the Dual-Luciferase reporter gene assay was used to verify the binding of circUBAP2 and microRNA-144, and the binding of CHD2 to microRNA-144.

RESULTS: QRT-PCR results showed that circUBAP2 was highly expressed in OC tissues, and its expression was negatively correlated with TMN stage and five-year survival of OC patients. CircUBAP2 was mainly distributed in the cytoplasm. Overexpression of circUBAP2 significantly promoted the proliferative and migratory abilities of OC cells. The Dual-Luciferase reporter gene assay demonstrated that circUBAP2 could bind to microRNA-144. Meanwhile, circUBAP2 negatively regulated microRNA-144 expression in OC cells. Besides, the promotive effects of circUBAP2 on the proliferation and migration of OC cells were reversed by microRNA-144 overexpression. MicroRNA-144 was lowly expressed in OC tissues, which was negatively correlated with TNM stage of OC patients. The Dual-Luciferase reporter gene assay confirmed the binding condition between CHD2 and microRNA-144. CHD2 expression was negatively regulated by microRNA-144 in OC cells. Moreover, CHD2 could bind to microRNA-144 and partially inhibited its activity, thereby promoting the proliferative and migratory abilities of OC cells.

CONCLUSIONS: CircUBAP2 promotes the progression of ovarian cancer by adsorbing microRNA-144.

Key Words:
CircUBAP2, MicroRNA-144, CHD2, Ovarian cancer, Proliferation, Migration.

Introduction

Ovarian cancer (OC) has become one of the most common malignancies threatening female health[1]. Early onset of OC is concealed, and effective diagnostic method in the early stage is lacked. More than 70% of OC patients are already in an advanced stage at the time of diagnosis. High rates of invasion and recurrence lead to the poor 5-year survival rate of OC patients with lower than 50%[2]. Therefore, explorations on specific and sensitive therapeutic targets for OC have become an urgent problem to be solved.

CircRNAs are a class of endogenous RNAs that are widely present in mammals, which was first discovered in RNA viruses in the 1970s[3]. However, circRNA was previously considered as a transcriptional waste by mis-splicing of exon transcripts[4]. With the rapid development of technologies such as RNA sequencing (RNA-seq) and bioinformatics, large-scale transcriptome data have identified abundant circRNAs in eukaryotic cells[5]. CircRNA in animals is mainly derived from cyclization of the 5' terminal end of the same exon and the downstream 3' terminal end in the splicing body[6]. Relative to traditional linear RNAs containing 5' and 3' terminal ends, circRNA is unlikely to be degraded by exonuclease owing to its closed-loop structure. There-

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fore, circRNA is more stable than linear RNA, which can serve as optimal tumor markers with a promising prospect[7]. CircRNA regulates gene expressions by competitively adsorbing endogenous RNAs (ceRNAs)[8,9]. Specifically, circRNA blocks the corresponding microRNA (miRNA) and abolishes its inhibitory effect on miRNA's target genes[10]. In addition, circRNA can act as a post-transcriptional regulator to mediate RNA expressions, protein activities and other functions[10]. In recent years, the expression profiles of some circRNAs have been elucidated in certain types of tumor tissues, such as colorectal cancer, hepatocellular carcinoma and gastric cancer[11-14]. CircRNA is a potential diagnostic and prognostic biomarker for tumors. However, the role of circRNA in the development of OC remains to be studied.

MiRNAs are a class of endogenous, small, non-coding RNAs that mediate target genes at the transcriptional level. They can specifically inhibit mRNA transcription by binding to the 3' untranslated region (3'UTR) of target genes, eventually regulating the expressions of functional genes. MiRNAs are involved in the regulation of malignant biological behaviors, such as proliferation and invasion of tumor cells[15]. High-frequency genomic variations of miRNA loci in the ovaries have been discovered through microarray analyses and sequencing technologies. It is suggested that miRNAs present good prospects in the diagnosis, prognosis and treatment of OC[16]. Low methylation level of miRNA let-7a-3 promoter results in abnormal expression of insulin growth factor IGF-II. This may, in turn, affects the prognosis of OC patients[17]. Meanwhile, downregulation of miRNA-31 leads to an increase in tyrosine kinase MET receptor and induces paclitaxel-resistance of OC cells[18]. Furthermore, miRNA-34c-5p inhibits amphiregulin-induced stemness characteristics and drug-resistance of OC cells by inactivating the amphiregulin (AREG)-epidermal growth factor receptor (EGFR)-extracellular-signal-regulated kinase (ERK) pathway[19].

To explore the interaction between circRNA and miRNA in OC, OC tissues and adjacent normal tissues were collected for analysis. Meanwhile, the expression level of circUBAP2 was detected. It was found that circUBAP2 was highly expressed in OC tissues and sponged microRNA-144, thereafter promoting the development of OC. Our results might provide a viable reference for clinical diagnosis and treatment of OC.

Patients and Methods

General Information

A total of 24 OC patients treated in the Weifang Yidu Center Hospital from 2008 to 2016 were enrolled. OC tissues and adjacent normal tissues were resected during the surgery. None of the enrolled OC patients received preoperative treatment, and sample collection was approved by the patients. Tissues were preserved in liquid nitrogen. The study was approved by the Ethics Committee of Weifang Yidu Center Hospital. Clinical stage of OC was evaluated based on the criteria of FIGO.

Cell Culture

Five ovarian carcinoma cell lines (A2780, HEY, OVCAR3, HO8910, SKOV3) and one normal ovarian epithelial cell line (IOSE) were purchased from the American Type Culture Collection (ATCC; Manassas, VA, USA). Cells were cultured in Roswell Park Memorial Institute-1640 (RPMI-1640; Thermo Fisher Scientific, Waltham, MA, USA) medium containing 10% fetal bovine serum (FBS; Hyclone, South Logan, UT, USA), 100 IU/mL penicillin and 100 μg/mL streptomycin (Invitrogen, Carlsbad, CA, USA), and placed in a 37°C, 5% CO_2 incubator.

Cell Transfection

OC cells were seeded into 6-well plates with 6×10^5 cells per well and incubated overnight. Cells were transfected with overexpression plasmids of circUBAP2, microRNA-144, CDH2 or negative control according to the instructions of Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). Fresh medium was replaced 24 hours later. 48 hours after transfection, cells were harvested for the following experiments.

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

Total RNA in cells (2×10^6) or tissues (30 mg) were first extracted using RNAiso Reagent (TaKaRa, Otsu, Shiga, Japan). Extracted RNA was reversely transcribed into complementary deoxyribose nucleic acid (cDNA) for qRT-PCR. The relative expressions of circUBAP2 and microRNA-144 were calculated by the $2^{-\Delta\Delta CT}$ method. Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) reaction conditions were as follows: 94°C for 30 s, 55°C for 30 s and 72°C for 90 s, for a total of 40 cycles. Primers used in this study were as follows: CDH2, forward:

5′-CGGAGTCAACGGATTTGGTCGTAT-3′, CDH2, reverse: 5′-AGCCTTCTCCATGGTGGTGAAGAC-3′; circUBAP2, forward: 5′-AGCCTAGAGCCAACTCCTTTG-3′, circUBAP2, reverse: 5′-TCAGGTTGAGATTTGAAGTCAAGA-3′; microRNA-144, forward: 5′-TCCGATCATGTAGTAGATATTGACAT-3′, microRNA-144, reverse: 5′-GTGCAGGGTCCGAGGT-3′.

Western Blot

Total protein in OC cells was lysed with radioimmunoprecipitation assay (RIPA; Beyotime, Shanghai, China). The concentration of extracted protein was quantified using the bicinchoninic acid (BCA) protein assay kit (Pierce, Waltham, MA, USA). Protein samples were electrophoresed on polyacrylamide gels and then transferred to polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA). After blocking with 5% skimmed milk, the membranes were incubated with primary antibody (Cell Signaling Technology, Danvers, MA, USA) at 4°C overnight. The membrane was incubated with the secondary antibody at room temperature for 1 h after rinsing with the Tris-Buffered Salin and Tween buffer solution (TBST; Sigma-Aldrich, St. Louis, MO, USA). Chemiluminescence was used to expose the protein bands on the membrane.

Cell Proliferation Assay

OC cells were inoculated into 96-well plates at a density of 1×10^3 cells/well. After cell culture for 0 h, 24 h, 48 h, 72 h and 96 h, respectively, 10 μL of Cell Counting Kit-8 (CCK-8; Dojindo Molecular Technologies, Kumamoto, Japan) solution was added to each well, followed by incubation at 37°C for 1 h in the dark. The absorbance of each well at 450 nm was recorded by a microplate reader.

Cell Migration Assay

A total of 5×10^4 transfected OC cells were seeded into the upper chamber (8-μm) (Corning, Lowell, MA, USA). Meanwhile, the medium containing 10% fetal bovine serum (FBS; Gibco, Grand Island, NY, USA) was added as the chemotactic agent to the bottom chamber. The cells were maintained in a 37°C, 5% CO_2 incubator for 48 h. Penetrating cells to the bottom chamber were fixed in 70% ethanol for 30 min and stained with 0.1% crystal violet for 10 min. The number of penetrating cells was counted in five randomly selected fields per sample under an inverted microscope (magnification 100×).

RNA-Immunoprecipitation (RIP)

Nuclear proteins of cells at different time points were extracted according to the instructions. 10% of the total nuclear protein was used as input control. The remaining protein samples were incubated with anti-IgG and anti-Ago2 antibodies at 4°C for 3 h, followed by incubation with protein A/G plus-agarose (prewashed with IP lysate NETN100 three times) at 4°C overnight. At the other day, the proteins were centrifuged at 4°C, 2000 r/min for 1 min. The precipitate was finally re-suspended in NETN100. 10% of precipitate, input control and IgG sample were used for protein level determination. Meanwhile, the remaining samples were used for RNA isolation, purification and identification.

Chromatin Fractionation

Cytoplasmic and nuclear RNAs in OC cells were extracted according to the instructions of NE-PER kit (Thermo Fisher Scientific, Waltham, MA, USA). QRT-PCR was performed to detect cytoplasmic and nuclear expressions of UBAP2 and circUBAP2.

Prediction of Target MiRNA Binding to CircUBAP2

The CircUBAP2 sequence was compared with the database downloaded from miRanda (http://www.microrna.org/ microrna/ getMiran FOrm.do), PITA (http://genie.weizmann.ac.il/pubs/mir07/mir07_data.hyml) and RNAhybrid (http://Bibiserv.techfak.uni-bielefeld.de/rnahybrid/). Screening criteria were applied: (1) Total score ≥ 140, total energy < -17 kcal / mol; (2) Mutual binding energy $\Delta\Delta G$ < -10; (3) Minimum free energy (MFE) ≤ 20kcal / mol.

Dual-Luciferase Reporter Gene Assay

OC cells were digested with trypsin and inoculated into 24-well plates one day prior to transfection. At the other day, the serum-free medium was replaced. Transfection reagents were prepared as follows: Tube A: circUBAP2-WT plasmid and circUBAP2-MUT plasmid were mixed with culture medium; Tube B: CHD2-WT plasmid and CHD2-MUT plasmid were mixed with culture medium; Tube C: transfection reagent was mixed with culture medium. Tube C mixture was separately added into Tube A and B. Mixtures in Tube A and B were added in each well and incubated for 48 h. Transfection efficiency was observed by a fluorescence microscope (Leica, Wetzlar, Germany).

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 22.0 (Chicago, IL, USA) was used for all statistical analysis. GraphPad Prism (Version X; La Jolla, CA, USA) was introduced for figure processing. Experimental data were expressed as mean ± standard deviation (SD) ($\bar{x} \pm s$). Standard *t*-test was used to compare the differences between the two groups. Gene correlation was compared using Person analysis. Chi-square test was used for analyzing classification data. Kaplan-Meier was introduced to evaluate the prognosis of patients, and receiver operating characteristic (ROC) curve analysis was used for evaluating diagnostic sensitivity. $p<0.05$ was considered statistically significant.

Results

CircUBAP2 Was Highly Expressed in OC

To explore the role of circUBAP2 in the development of OC, we first detected the expression of circUBAP in OC tissues and adjacent normal tissues by qRT-PCR. Upregulated circUBAP2 was found in OC tissues relative to adjacent normal tissues (Figure 1A). In addition, circUBAP2 expression was positively correlated with TMN stage of OC patients (Figure 1B). Identically, circUBAP2 was highly expressed in OC cells than that of normal ovarian epithelial cells (Figure 1C). Among the five OC cell lines, OVCAR3 and HO8910 cells presented a relatively high expression of circUBAP2, which were selected for the following experiments. RNase treatment in OC cells markedly downregulated UBAP2 expression, whereas circUBAP2 expression was not altered, demonstrating the circRNA characteristics of circUBAP2 (Figure 1D and 1E). Chromatin fractionation assay showed that circUBAP2 was mainly distributed in the cytoplasm (Figure 1F and 1G). These data suggested that circUBAP2 might be closely related to the development of OC.

CircUBAP2 Promoted OC Development

To further explore the role of circUBAP2 in OC, we analyzed the potential of circUBAP2 to be a tumor marker for OC. CircUBAP2 effectively distinguished OC tissues from normal ovarian tissues (AUC = 0.8012 and cut-off value = 1.7, Figure 2A). Meanwhile, a negative correlation was found between the five-year survival rate of OC patients and circUBAP2 expression (p = 0.0209, Figure 2B). Subsequently, the circUBAP2 overexpression plasmid was constructed, and transfected into OVCAR3 and HO8910 cells. The results indicated that the mRNA level of circUBAP2 was markedly upregulated after transfection of the circUBAP2 overexpression plasmid (Figure 2C and 2D). The CCK-8 results showed that the proliferative potential of OC cells was remarkably enhanced by circUBAP2 overexpression (Figure 2E and 2F). Moreover, cell migration assay indicated a significant increase in the migratory rate of OC cells after circUBAP2 overexpression (Figure 2G).

CircUBAP2 Sponged MicroRNA-144

By online prediction at miRanda (http://www.microrna.org/ microrna/ getMiran FOrm.do), PITA (http://genie.weizmann.ac.il/pubs/mir07/mir07_data.hyml), RNAhybrid (http://Bibiserv.techfak.uni-bielefeld.de/rnahybrid/) and cross-correlation of circUBAP2, potential binding sequences were found between circUBAP2 and microRNA-144 (Figure 3A). The Luciferase reporter gene assay confirmed that circUBAP2 could bind to microRNA-144 (Figure 3B and 3C). Next, our results showed that overexpression of circUBAP2 in OC cells significantly downregulated microRNA-144 expression (Figure 3D). Besides, microRNA-144 was lowly expressed in OC tissues than that of the adjacent normal tissues (Figure 3E). Particularly, microRNA-144 expression gradually decreased with the progression of the disease. It presented the lowest level in OC tissues with stage III + IV (Figure 3F). Similarly, microRNA-144 was lowly expressed in OC cells as well (Figure 3G). A negative correlation was observed between circUBAP2 and microRNA-144 (R = -0.5732, p=0.0034, Figure 3H). Moreover, microRNA-144 was able to distinguish between normal ovarian tissues and OC tissues (AUC = 0.7344 and cut-off value = 1.261, Figure 3I).

CircUBAP2 Exerted its Function by Sponging MicroRNA-144

To further verify the binding relationship between circUBAP2 and microRNA-144, the anti-Aog2 antibody was used to capture Ago2 protein and its binding RNAs. Subsequently, the expressions of circUBAP2 and microRNA-144 were determined by qRT-PCR. RIP assay demonstrated that circUBAP2 was capable of binding to microRNA-144 (Figure 4A and 4B). We specu-

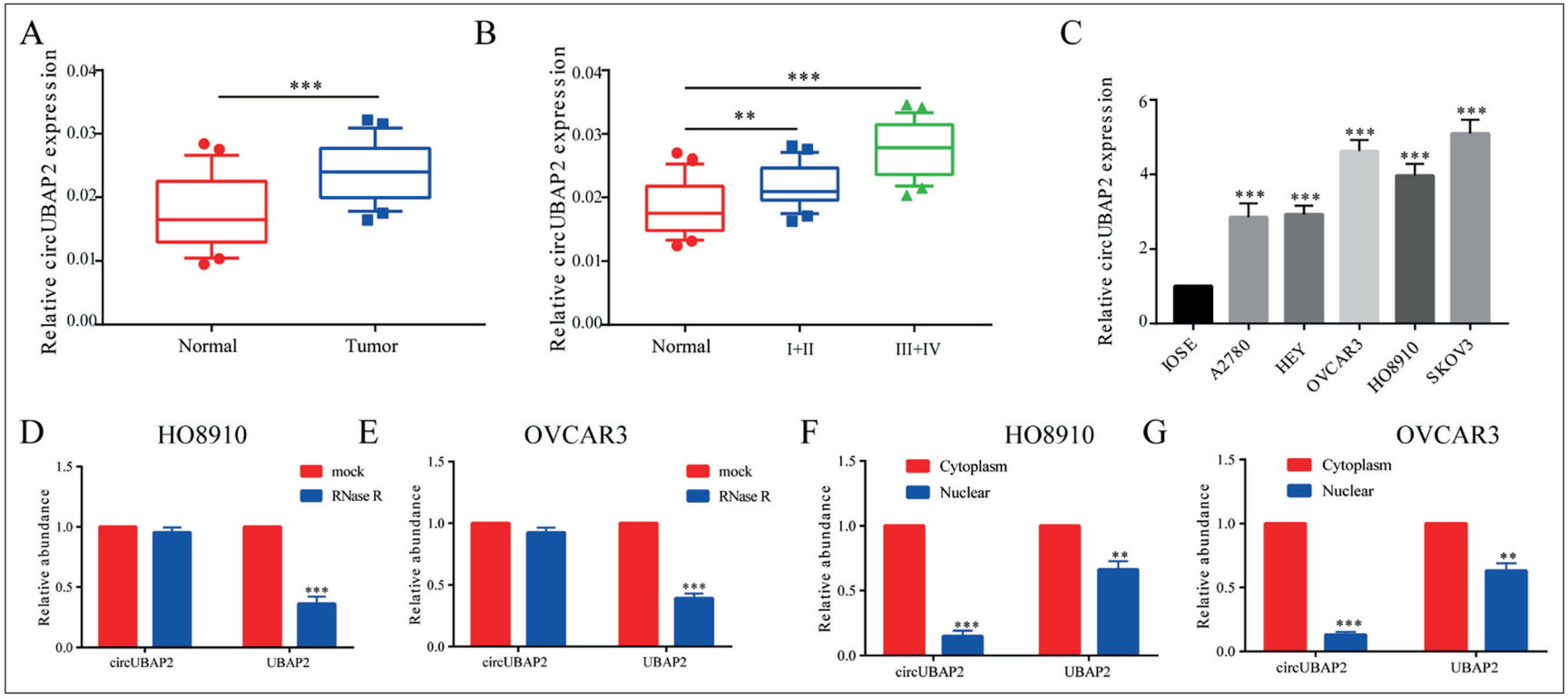

Figure 1. CircUBAP2 was highly expressed in OC. ***A,*** CircUBAP2 was highly expressed in OC tissues compared with adjacent normal tissues. ***B,*** CircUBAP2 expression was significantly higher in OC with stage III-IV than stage I + II. ***C,*** CircUBAP2 expression in OC cell lines. ***D, E,*** RNase treatment in OC cells markedly downregulated UBAP2 expression, whereas circUBAP2 expression did not alter. ***F, G,*** Chromatin fractionation assay showed that circUBAP2 mainly distributed in the cytoplasm of OC cells. *$p<0.05$, **$p < 0.01$, ***$p < 0.001$.

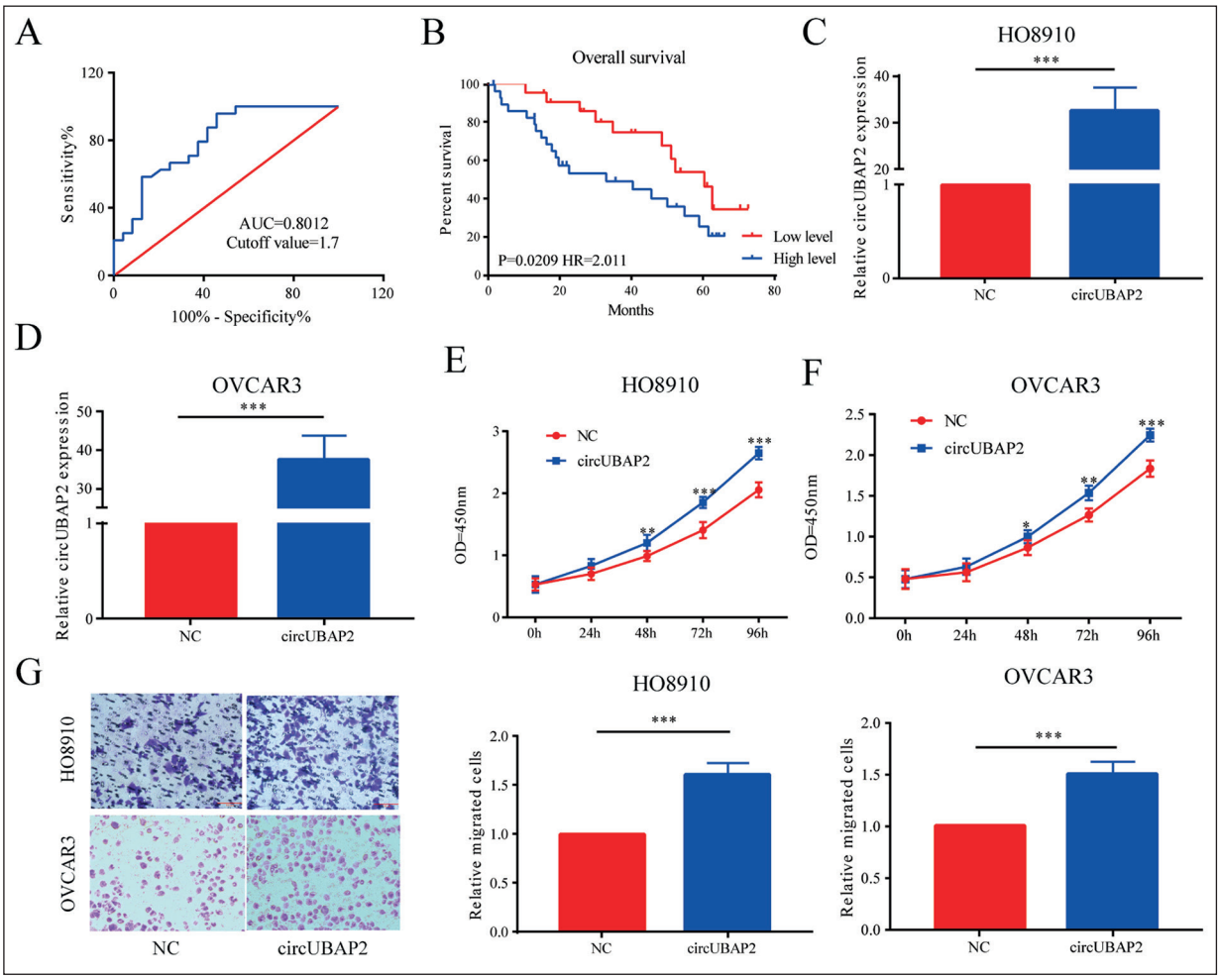

Figure 2. CircUBAP2 promoted OC development. ***A,*** AUV curves indicated that circUBAP2 effectively distinguished OC tissues from normal ovarian tissues (AUC = 0.8012 and cut-off value = 1.7). ***B,*** A negative correlation was found between the five-year survival rate of OC patients and circUBAP2 expression ($p = 0.0209$). ***C-D,*** The mRNA level of circUBAP2 was remarkably upregulated after transfection of the circUBAP2 overexpression plasmid in OVCAR3 and HO8910 cells. ***E-F,*** The CCK-8 results showed enhanced proliferative potentials of OVCAR3 and HO8910 cells by circUBAP2 overexpression. **G,** Cell migration assay indicated a significant increase in the migratory rate of OVCAR3 and HO8910 cells after circUBAP2 overexpression. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

lated that circUBAP2 exerted its biological functions by interacting with microRNA-144. Hence, OC cells were co-transfected with overexpression plasmids of circUBAP2 and microRNA-144. The results demonstrated that the promotive effect of circUBAP2 on the proliferation of OC cells was reversed by microRNA-144 overexpression (Figure 4C and 4D). Furthermore, the enhanced migratory ability of OC cells overexpressing circUBAP2 could be reversed by microRNA-144 overexpression (Figure 4E and 4F). These results indicated that circUBAP2 promoted the proliferative and migratory abilities of OC cells by sponging microRNA-144.

CDH2 Was the Target Gene of MicroRNA-144

By exploring the downstream targets of microRNA-144, we found that the sequences of CDH2 and microRNA-144 were complementary. Vectors containing wild-type (CDH2-WT) and mutant-type CDH2 (CDH2-MUT) were constructed. Dual-Luciferase reporter gene verified that CDH2-WT recombinant vector could bind to microRNA-144. However, CDH2-MUT was failed (Figure 5A). CDH2 expression was remarkably downregulated after microRNA-144 overexpression in OC cells (Figure 5B). Similarly, CHD2 expression in OC tissues was significantly

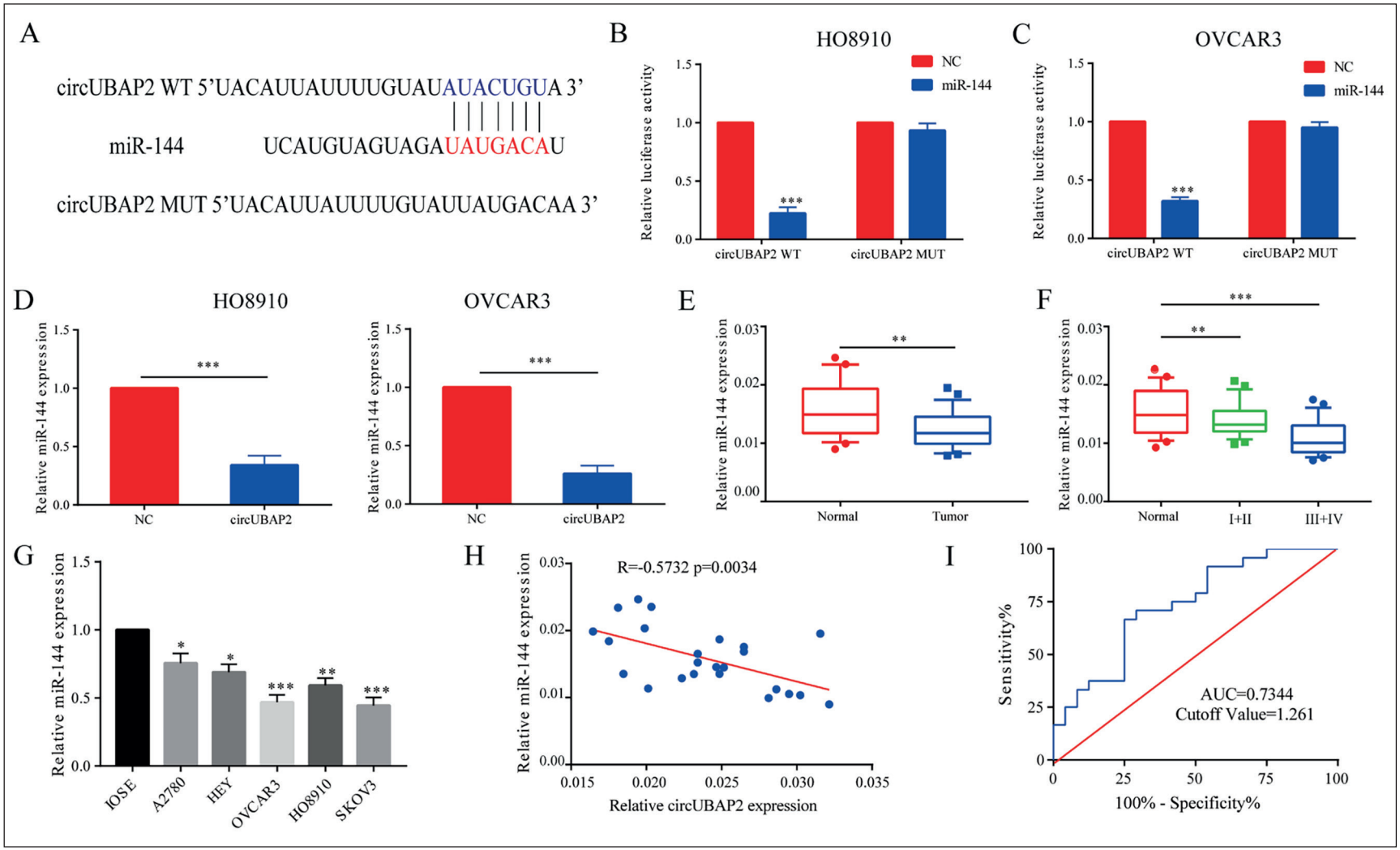

Figure 3. CircUBAP2 sponged microRNA-144. ***A,*** A potential binding site between circUBAP2 and microRNA-144. ***B-C,*** The Luciferase reporter gene assay confirmed that circUBAP2 could bind to microRNA-144. ***D,*** Overexpression of circUBAP2 in OVCAR3 and HO8910 cells significantly downregulated microRNA-144 expression. ***E,*** MicroRNA-144 lowly expressed in OC tissues than adjacent normal tissues. ***F,*** MicroRNA-144 expression gradually decreased with the disease progression, and presented the lowest level in OC tissues with stage III + IV. ***G,*** MicroRNA-144 lowly expressed in OC cell lines. ***H,*** A negative correlation was found between circUBAP2 and microRNA-144 (R = -0.5732, $p = 0.0034$). ***I,*** ROC curves indicated that microRNA-144 was also able to distinguish between normal ovarian tissues and OC tissues (AUC = 0.7344 and cut-off value = 1.261). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

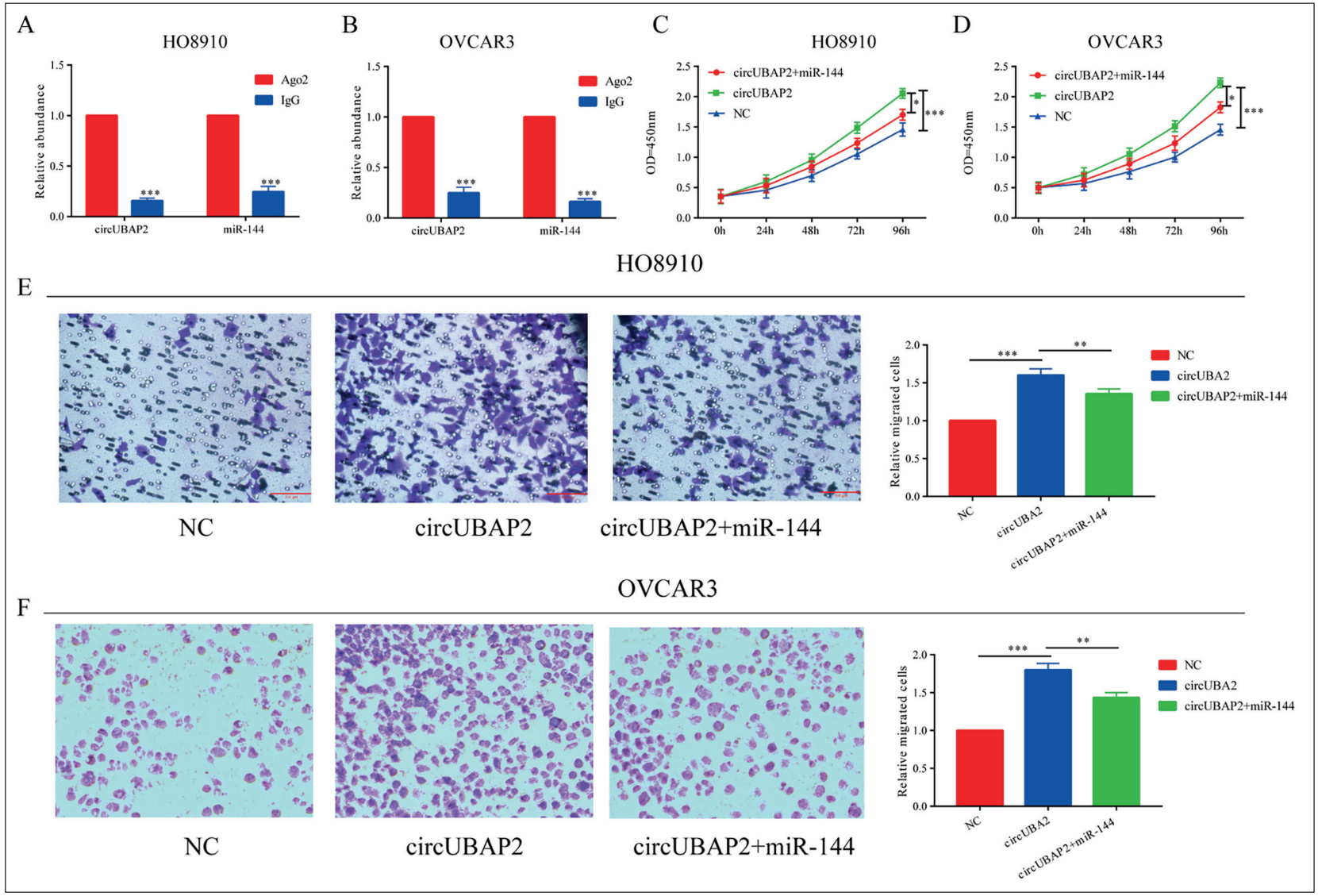

Figure 4. CircUBAP2 exerted its function by sponging microRNA-144. ***A, B,*** RIP assay demonstrated that circUBAP2 and microRNA-144 could bind to Ago2. ***C, D,*** The promotive effect of circUBAP2 on the proliferation of OVCAR3 and HO8910 cells was reversed by microRNA-144 overexpression. ***E, F,*** The enhanced migratory ability of OVCAR3 and HO8910 cells overexpressing circUBAP2 was reversed by overexpression of microRNA-144. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

higher than that of the adjacent normal tissues (Figure 5C). By detecting the relationship between CDH2 and microRNA-144, a significant negative correlation was found between the two molecules in OC tissues (R = -0.6717, $p = 0.0003$, Figure 5D). The potential regulatory effects of CDH2 on cellular performances of OC cells were determined. The results showed that the proliferative and migratory abilities of OC cells co-transfected with overexpression plasmids of microRNA-144 and CDH2 were markedly enhanced compared with those transfected with microRNA-144 mimics alone (Figure 5E).

Discussion

OC is a gynecological malignancy with extremely high mortality. Cytoreductive surgery and platinum-based chemotherapy are widely

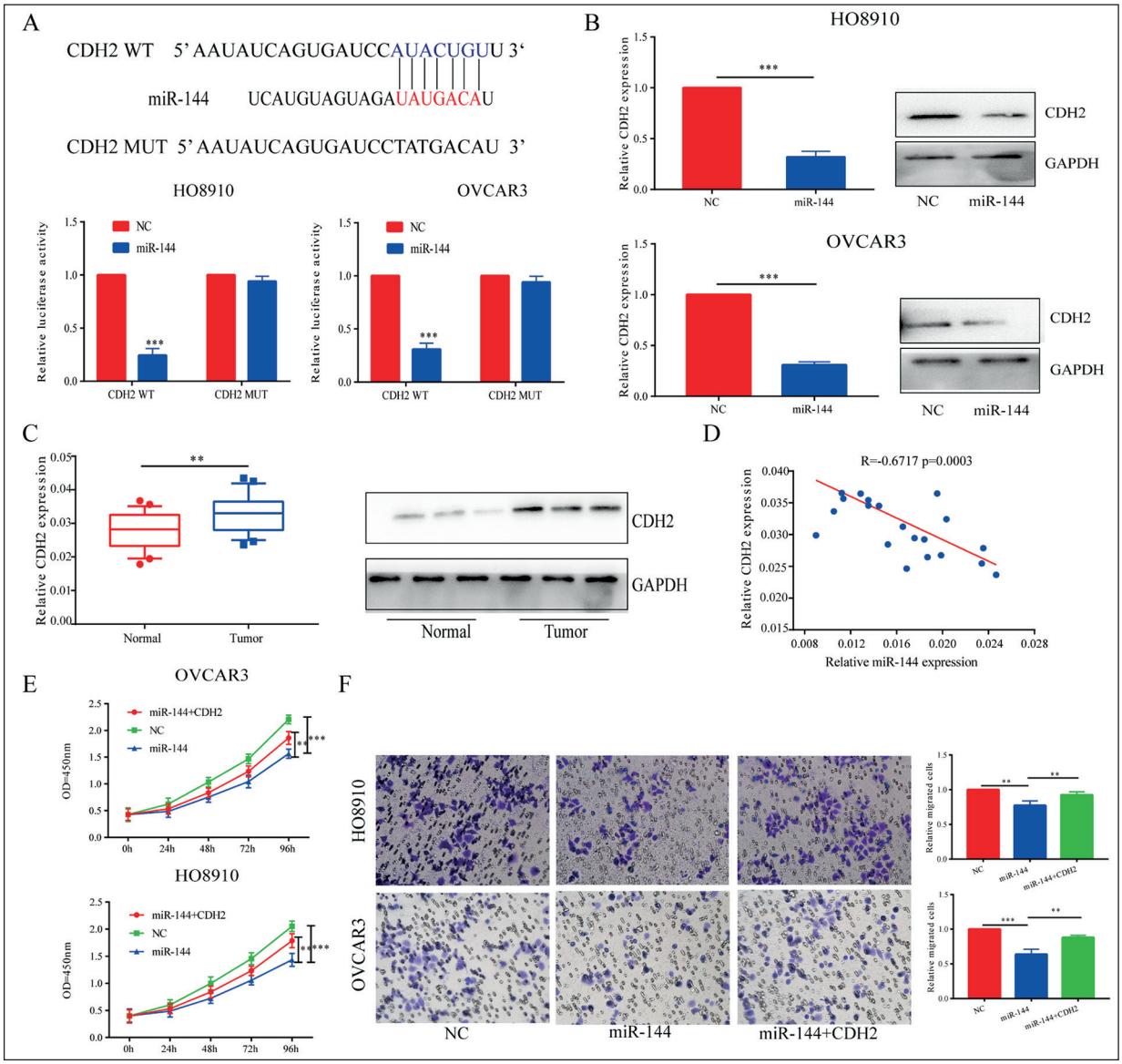

Figure 5. CDH2 was the target gene of microRNA-144. ***A,*** The Dual-Luciferase reporter gene verified that CDH2 could bind to microRNA-144. ***B,*** CDH2 expression was remarkably downregulated after microRNA-144 overexpression in OVCAR3 and HO8910 cells. ***C,*** CHD2 expression in OC tissues was significantly higher than that of the adjacent normal tissues. ***D,*** A negative correlation was found between CDH2 and microRNA-144 in OC tissues (R = -0.6717, $p = 0.0003$). ***E,*** The proliferative and migratory abilities of OC cells co-transfected with overexpression plasmids of microRNA-144 and CDH2 were markedly enhanced compared with those transfected with microRNA-144 mimics alone. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

applied in the treatment of OC. Unfortunately, advanced OC patients are prone to experience tumor recurrence and chemotherapy resistance. Therefore, it is urgent to search for novel biological hallmarks and therapeutic targets for OC. Some certain ncRNAs, including miRNAs and circRNAs, have been identified to be crucial during the development and progression of OC. In this study, circUBAP2 expression was significantly upregulated in OC tissues and cell lines. CicrUBAP2 promoted the proliferative and migratory abilities of OC cells. Therefore, we proposed that cicrUBAP2 might be a potential diagnostic and therapeutic marker for OC.

MicroRNA-144 was first identified as being differentiated from mature erythroid cells[20]. It directly aggravates the degree of anemia, reduces regeneration and antioxidant of glutathione by regulating the cellular response to oxidative stress[21]. With the conduction of in-depth researches, the potential roles of microRNA-144 in the development of various tumors have emerged. For example, upregulation of microRNA-144 promotes the proliferation of cervical cancer cells[22]. MiR-144-3p inhibits the proliferation and metastasis of pediatric Wilms' tumor cells by regulating Girdin[23]. As a potential prognostic marker, microRNA-144-5p directly targets CCNE1/2 in bladder cancer[24]. MicroRNA-144 regulates the proliferation and cell cycle of acute lymphoblastic leukemia through the interaction with FMN2[25]. By modulating C-X-C motif chemokine ligand 11, microRNA-144 mediates chronic inflammation and tumorigenesis of rectal cancer[26]. Meanwhile, the role of microRNA-144 in OC has also been reported. MicroRNA-144 inhibits the proliferation and migration of OC cells by targeting RUNX1[27]. However, the underlying mechanism of microRNA-144 in OC has not been fully elucidated. In the present work, microRNA-144 was lowly expressed in OC tissues. With the progression of the disease, OC patients in stage III + IV showed a significantly lower level of microRNA-144 than those in stage I + II. Meanwhile, overexpression of cicrUBAP2 in OC cells markedly inhibited the expression of microRNA-144, showing a negative correlation. It is suggested that microRNA-144 level in OC was negatively regulated by circUBAP2.

CDH2 is a member of the cadherin family, which is mainly expressed in the nervous system. Meanwhile, CDH2 is crucial in neuronal development and differentiation[28]. Recently Marfella et al[24] have found that CDH2 is a widely distributed calcium-dependent cell adhesion molecule. In addition to nerve tissues, it is found in hematopoietic tissues, muscles and bone tissues. CDH2 mediates intercellular adhesion, signal transduction, as well as cell proliferation and migration. It exerts a vital role in cell recognition, growth differentiation and signal response. Besides normal development, CDH2 is involved in the cellular behaviors of malignant tumors[30,31]. Our study found that CHD2 expression was markedly reduced in OC cells overexpressing microRNA-144. CDH2 inhibited microRNA-144 expression by binding to its 3'UTR, thereby attenuating proliferation and migration of OC cells.

Some limitations in this work should be identified. *In vivo* biological functions of circUBAP2 are needed to be explored by establishing animal models of OC. Besides, the underlying mechanism of circUBAP2 upregulation in OC remains unclear and requires further exploration.

Conclusions

This study first explored the regulatory role of cicrUBAP2 on the development of OC. CicrUBAP2 was highly expressed in OC tissues and cell lines, and was positively correlated with TMN stage. In addition, cicrUBAP2 acted as a sponge to adsorb microRNA-144. Overexpression of microRNA-144 in OC cells reversed the promotive effect of circUBAP2 on cell proliferation and migration. We believed that circUBAP2 was an oncogene in OC, which was expected to be a new therapeutic target. In summary, circUBAP2 promoted the progression of ovarian cancer by adsorbing microRNA-144.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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