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Linc-UBC1 stimulates the metastasis and progression of ovarian cancer *via* downregulating p53 level

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Abstract. – OBJECTIVE: To elucidate the role of linc-UBC1 in regulating the metastasis and progression of ovarian cancer (OC) by downregulating the p53 level.

PATIENTS AND METHODS: Relative levels of linc-UBC1 in OC tissues and paracancerous tissues were determined by quantitative Real-Time Polymerase Chain Reaction (qRT-PCR). Differential expressions of linc-UBC1 in OC tissues with different tumor staging or tumor sizes were detected as well. Receiver operating characteristic (ROC) curves were introduced for assessing the diagnostic value of linc-UBC1 in OC. After silence of linc-UBC1, proliferative and migratory abilities of HO8910 and HEY cells were evaluated. Subcellular distribution of linc-UBC1 was analyzed. The interaction between linc-UBC1 and p53 was explored through the RNA immunoprecipitation (RIP) assay. At last, rescue experiments were conducted to uncover the role of linc-UBC1/p53 regulatory loop in influencing the progression of OC.

RESULTS: Linc-UBC1 was upregulated in OC and its level negatively correlated to that of p53. Linc-UBC1 level was higher in OC patients with advanced TNM staging or larger tumor size. Linc-UBC1 was mainly distributed in the nucleus. Silence of linc-UBC1 attenuated proliferative and migratory abilities of HO8910 and HEY cells. RIP assay verified that linc-UBC1 could inhibit the transcription of p53. Knockdown of p53 could partially reverse the regulatory effects of linc-UBC1 on regulating the progression of OC.

CONCLUSIONS: Linc-UBC1 is upregulated in OC tissues and cells. It stimulates the proliferation and metastasis of OC by downregulating p53 level, thus exerting a carcinogenic role.

Key Words:
Ovarian cancer, p53, Linc-UBC1, Progression.

Introduction

Ovarian cancer (OC) is one of the common malignancies in female reproductive organs. Its incidence is second only to cervical cancer and endometrial cancer[1]. Pathologically, epithelial cancer is the most common subtype in OC, followed by malignant germ cell tumor[2]. Notably, the mortality of ovarian epithelial cancer accounts the first in all kinds of gynecological tumors, posing a serious threat to females lives[3]. Due to the anatomical position in the pelvic cavity, the small volume of ovaries, and the atypical symptoms of OC, the detective rate of early-stage OC is low. Metastatic rate of ovarian epithelial cancer is very high, mainly affecting the pelvic and abdominal organs[4]. It is of great significance to search for diagnostic and therapeutic targets of OC[5].

Long non-coding RNAs (lncRNAs) are non-coding RNAs with over 200 nucleotides long[6]. Studies[7] have shown the important role of lncRNAs in epigenetics, cellular activities, and genetic information. Epigenetics is a condition where heritable changes occur in gene expressions, while the DNA sequence remains unchangeable. Epigenetics is essential for cell growth and differentiation, as well as tumor development[8]. Epigenetic regulation includes DNA methylation, histone modifications, and non-coding RNA regulation[9]. Non-coding RNAs are functional RNAs that cannot be translated into proteins[10]. Several reports[11] have shown the crucial functions of non-coding RNAs in tumor progression.

P53 is a tumor-suppressor gene in humans. Inactivation of p53 gene is of significance in tumorigenesis[12]. Wild-type p53 prevents canceration by inducing the apoptosis of tumor cells. It also contributes to DNA-repair[13]. Mutant p53 would result in canceration. P53 mutation occurs in about 50% of tumors[14]. P53-encoded proteins belong to transcriptional factors that control the initiation of cell cycle progression[15]. Under the

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normal circumstance, p53 slows down or monitors cell division[16]. As a crucial tumor-suppressor gene, p53 is well-analysed in tumor biology[17]. Imbalanced oncogenes and tumor-suppressor genes leads to tumorigenesis[18].

In this paper, upregulated linc-UBC1 aggravated the progression of OC by downregulating p53 level, indicating the oncogenic role of linc-UBC1 in OC. Our work provides new basis for clinical prevention and treatment of OC.

Patients and Methods

Sample Collection

OC tissues and paracancerous tissues were harvested from OC patients undergoing radical surgery. None of these patients were preoperatively treated with anti-tumor therapy. Samples were postoperatively diagnosed. This research was approved by the Medical Ethics Committee. Each subject obtained the informed consent.

Cell Culture and Transfection

Ovarian epithelial cell line (IOSE) and OC cell lines (A2780, HO8910, OVCAR3, and HEY) were purchased from American Type Culture Collection (ATCC; Manassas, VA, USA). The cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM; Gibco, Rockville, MD, USA) containing 10% fetal bovine serum (FBS; Gibco, Grand Island, NY,USA) in an incubator with 5% CO_2 at 37°C.

Cells were inoculated in a 6-well plate with 1×10^4 cells per well. At 75-85% confluence, cells were cultured in 500 μL of Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA) containing transfection vectors. 1.5 mL of serum-free medium was applied in each well. At 4-6 h, complete medium was replaced.

RNA Extraction and Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR)

The total RNA in cells and tissues was extracted using the TRIzol method (Invitrogen, Carlsbad, CA, USA) for reverse transcription according to the instructions of PrimeScript RT reagent Kit (TaKaRa, Otsu, Shiga, Japan). RNA concentration was detected using a spectrometer. QRT-PCR was then performed based on the instructions of SYBR Premix Ex Taq™ (TaKaRa, Otsu, Shiga, Japan) at 94°C for 5 min, and 40 cycles at 94°C for 30 s, 55°C for 30 s and 72°C for 90 s. The relative level was calculated using the $2^{-\Delta\Delta Ct}$ method. Primer sequences used in this study were as follows: p53, F: 5'-CGAGTATCGAACTTCCTTTC-3', R: 5'-CATCGGCTGAAGTTGGAATGCA-3'; Linc-UBC1, F: 5'-GCTGCTACAACTCCTCGCACTG-3', R: 5'-GGATCGTGTACAGTGCGCTCAG-3'; U6: F: 5'- CTCGCTTCGGCAGCACA -3', R: 5'- AACGCTTCACGAATTTGCGT -3'; GAPDH: F: 5'-CGCTCTCTGCTCCTCCTGTTC -3', R: 5'-ATCCGTTGACTCCGACCTTCAC-3'.

RNA Immunoprecipitation (RIP)

Cells were treated according to the procedures of Millipore Magna RIP™ RNA-Binding Protein Immunoprecipitation Kit (Millipore, Billerica, MA, USA). Cell lysate was incubated with anti-IgG or anti-EZH2 at 4°C for 6 h. A protein-RNA complex was captured and digested with 0.5 mg/ml proteinase K containing 0.1% sodium dodecyl sulphate (SDS) to extract RNA. Non-specific adsorption was removed by repeat wash of magnetic beads in the RIP washing buffer. Finally, the extracted RNA was quantified by performing qRT-PCR.

Determination of Subcellular Distribution

Cytoplasmic and nuclear RNAs were extracted using the PARIS kit (Invitrogen, Carlsbad, CA, USA) and subjected to qRT-PCR. U6 was the internal reference of nucleus, and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was that of cytoplasm.

Cell Counting Kit-8 (CCK-8) Assay

Transfected cells were seeded into 96-well plates with 5.0×10^3 cells per well. At the established time points, 10 μL of CCK-8 solution (Cell Counting Kit-8; Dojindo Laboratories, Kumamoto, Japan) was added in each well. The absorbance at 450 nm of each sample was measured by a microplate reader (Bio-Rad, Hercules, CA, USA).

Transwell

Cell density was adjusted to 3×10^4 cells/ml. 100 μL of suspension was applied in the upper side of the transwell chamber (Corning, Corning, NY, USA). In the bottom side, 600 μL of

medium containing 20% fetal bovine serum (FBS) was applied. After 24 h of incubation, cells penetrated to the bottom side were fixed in methanol for 15 min, stained with crystal violet for 20 min, and counted using a microscope. The number of migratory cells was counted in 5 randomly selected fields per sample (magnification 200×).

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 18.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for data analysis. Data were expressed as mean ± standard deviation ($\bar{x}$±s). Data between the two groups were compared using the *t*-test. Receiver operating characteristic (ROC) curves were depicted to assess the prognostic value of linc-UBC1 in OC. Spearman correlation test was conducted for evaluating the relation between the two gene expressions. $p<0.05$ considered the difference was statistically significant.

Results

Linc-UBC1 Was Upregulated in OC and Correlated to Malignant Level

Compared with the paracancerous tissues, linc-UBC1 was upregulated in OC tissues (Figure 1A). Linc-UBC1 levels in OC patients with different staging and tumor sizes were detected. Its level gradually increased with the worsening of TNM staging of OC (Figure 1B). The ROC curves revealed certain diagnostic potential of linc-UBC1 in OC (Figure 1C). Moreover, the expression level of linc-UBC1 was lower in OC tissues smaller than 5 cm in size than those ≥ 5 cm (Figure 1D). The above data demonstrated the involvement of linc-UBC1 in the progression of OC.

Knockdown of Linc-UBC1 Suppressed the Proliferative and Migratory Abilities of OC

Relative levels of linc-UBC1 in OC cell lines were determined as well. Compared with ovarian epithelial cells, linc-UBC1 was highly expressed

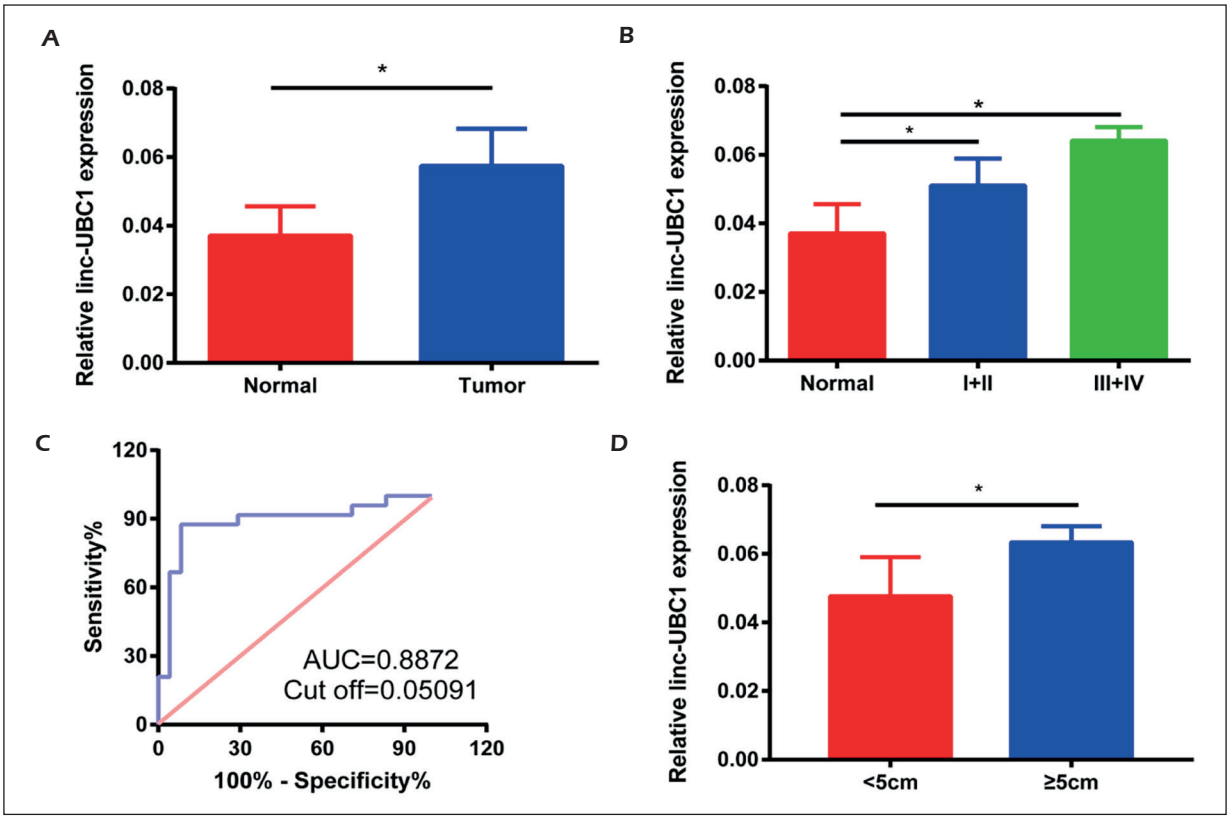

Figure 1. Linc-UBC1 was upregulated in ovarian cancer and correlated to malignant level. **A,** Relative level of linc-UBC1 in ovarian cancer tissues and paracancerous tissues. **B,** Relative level of linc-UBC1 in healthy people, ovarian cancer patients in stage I+II, and stage III+IV. **C,** ROC curves introduced for the prognostic value of linc-UBC1 in ovarian cancer (AUC=0.8872, cut-off value=0.05091). **D,** Relative level of linc-UBC1 in ovarian cancer tissues < 5 cm and ≥ 5 cm in tumor size.

in OC cells (Figure 2A). Among the four selected ovarian cancer cell lines, HO8910 and HEY cells expressed the highest level of linc-UBC1, and were chosen for the following studies. Transfection of si-UBC1 markedly downregulated linc-UBC1 level in HO8910 and HEY cells, presenting an effective transfection efficacy (Figure 2B). After transfection of si-UBC1, the viabilities in HO8910 and HEY cells were reduced (Figures 2C, 2D). Besides, migratory cell number was reduced after transfection of si-UBC1 (Figure 2E). Collectively, silence of linc-UBC1 could inhibit OC cells to proliferate and migrate.

Linc-UBC1 Bound to p53 and Negatively Regulated its Level

Subcellular distribution analysis revealed that linc-UBC1 was mainly expressed in the nuclear fraction, indicating the potential transcriptional or post-transcriptional function of linc-UBC1 (Figures 3A, 3B). P53 was lowly expressed in OC tissues than that of paracancerous tissues (Figure 3C). A negative correlation was identified between the expression levels of linc-UBC1 and p53 in OC tissues (Figure 3D). Moreover, transfection of si-UBC1 markedly upregulated p53 level in both HO8910 and HEY cells (Figures 3E, 3F). The potential interaction between p53 and linc-UBC1 was explored by performing the RIP assay. A higher enrichment of linc-UBC1 in anti-p53 was observed relative to that of anti-IgG, confirming the interaction between linc-UBC1 and p53 (Figures 3G, 3H).

Knockdown of p53 Reversed the Regulatory Effect of Linc-UBC1 on OC

Transfection of si-p53 markedly downregulated p53 level in HO8910 and HEY cells (Figures 4A, 4B). Transfection of si-UBC1 was proved to reduce the viability of OC cells, which was partially reversed by the co-transfection of si-p53 (Figures 4C, 4D). In addition, the decreased migratory cell number due to silenced UBC1 was reversed by the knockdown of p53 (Figure 4E). Therefore, linc-UBC1 aggravated the malignant progression of OC by downregulating p53.

Discussion

OC often occurs in perimenopausal women. Epithelial OC has the highest mortality rate in

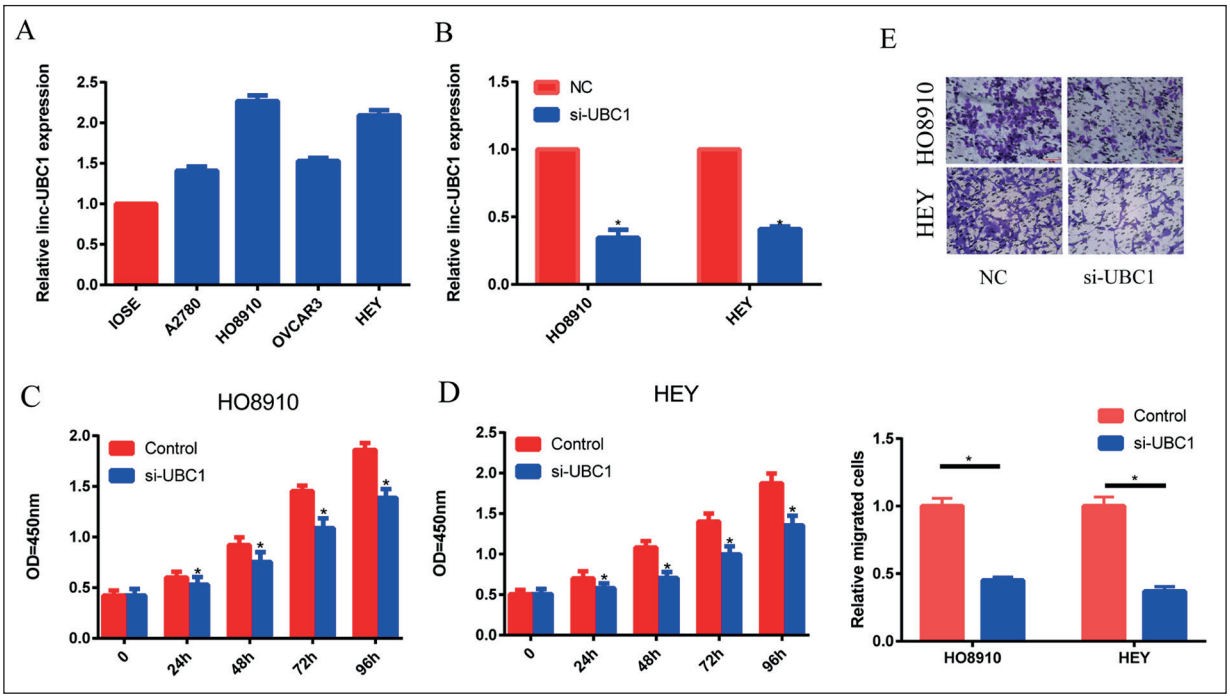

Figure 2. Knockdown of linc-UBC1 suppressed the proliferative and migratory abilities of ovarian cancer. **A,** Relative level of linc-UBC1 in IOSE, A2780, HO8910, OVCAR3, and HEY cells. **B,** Transfection efficacy of si-UBC1 in HO8910 and HEY cells. **C,** Viability in HO8910 cells transfected with control or si-UBC1. **D,** Viability in HEY cells transfected with control or si-UBC1. **E,** Migratory cell number in HO8910 and HEY cells transfected with control or si-UBC1 (magnification 200×).

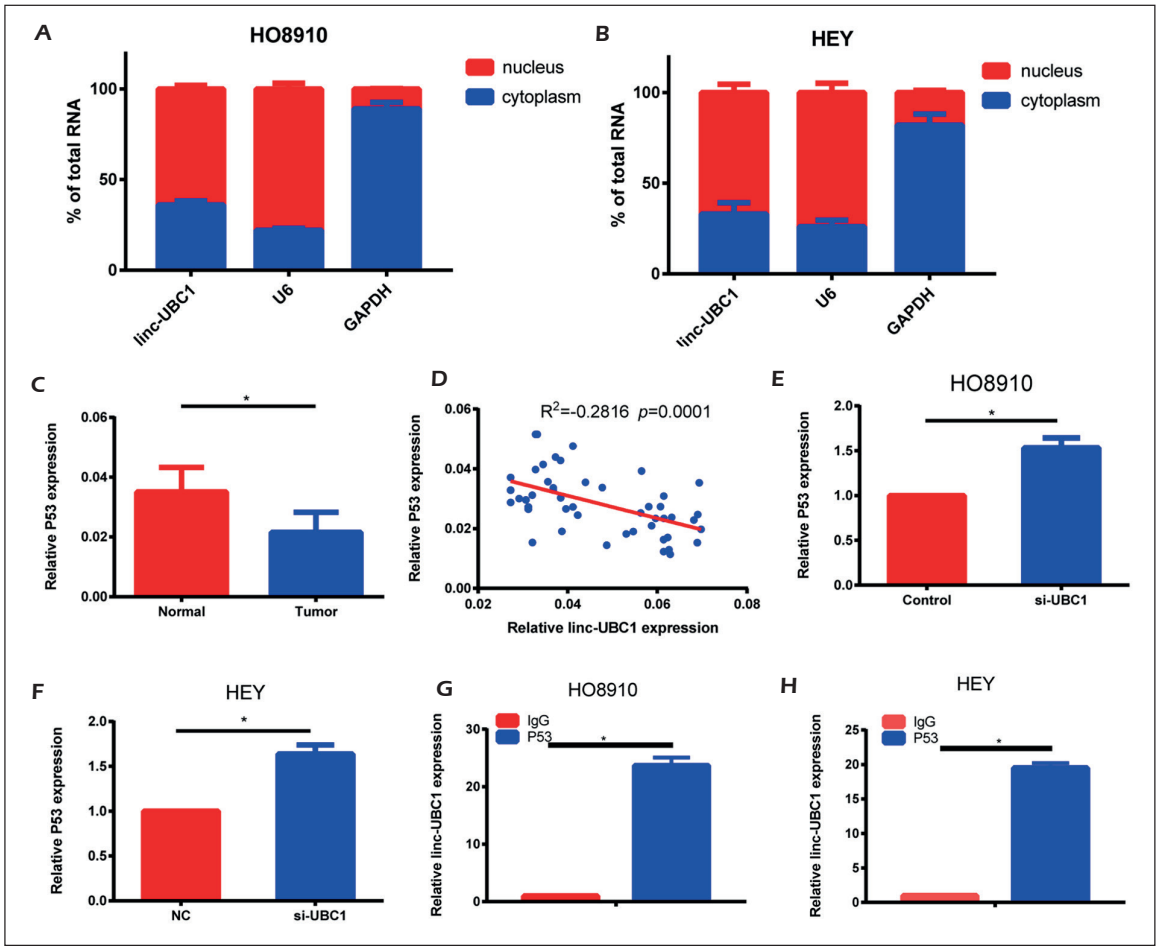

Figure 3. Linc-UBC1 bound to p53 and negatively regulated its level. **A,** Subcellular distribution of linc-UBC1 in HO8910 cells. U6 was the internal reference for nucleus and GAPDH was that for cytoplasm. **B,** Subcellular distribution of linc-UBC1 in HEY cells. U6 was the internal reference for nucleus and GAPDH was that for cytoplasm. **C,** Relative level of p53 in ovarian cancer tissues and paracancerous tissues. **D,** A negative correlation between expressions of p53 and linc-UBC1. **E,** Relative level of p53 in HO8910 cells transfected with control or si-UBC1. **F,** Relative level of p53 in HEY cells transfected with control or si-UBC1. **G,** Relative level of linc-UBC1 in anti-IgG and anti-p53 of HO8910 cells. **H,** Relative level of linc-UBC1 in anti-IgG and anti-p53 of HEY cells.

all gynecologic malignancies[19]. Globally, the five-year survival of OC is lower than 45%, resulting in a poor prognosis[20]. The mortality of OC ranks first among gynecologic cancers due to the atypical symptoms and lack of effective diagnostic methods[21]. Great advances achieved in microarray analyses, proteomics, immunohistochemistry, and other methods help to improve the diagnostic rate of OC. However, diversity in pathological subtypes and unclear pathogenesis of OC are thorny in enhancing the detective rate. Sensitive and specific hallmarks for OC are still lacking[22]. It is necessary to promote comprehensive screening of OC in females[23]. Recurrences of OC after radical surgery or chemotherapy severely influence the life quality of affected people[24]. In recent years, individualized therapies targeting cell cycle, signaling pathways, and immunity are promising approaches for enhancing the prognosis of OC patients[25].

LncRNAs are located in the nucleus or cytoplasm. They are involved in the regulation of gene expressions at transcriptional or post-transcriptional level[26]. In recent years, several researches have revealed the critical functions of lncRNAs in various biological processes[27]. Linc-UBC1 locates on chromosome 1q32.1, which has a transcription span of 2,616 bp[28]. It has been detected that linc-UBC1 is physically bound to polycomb inhibiting complex 2 (PRC2), wherein the core

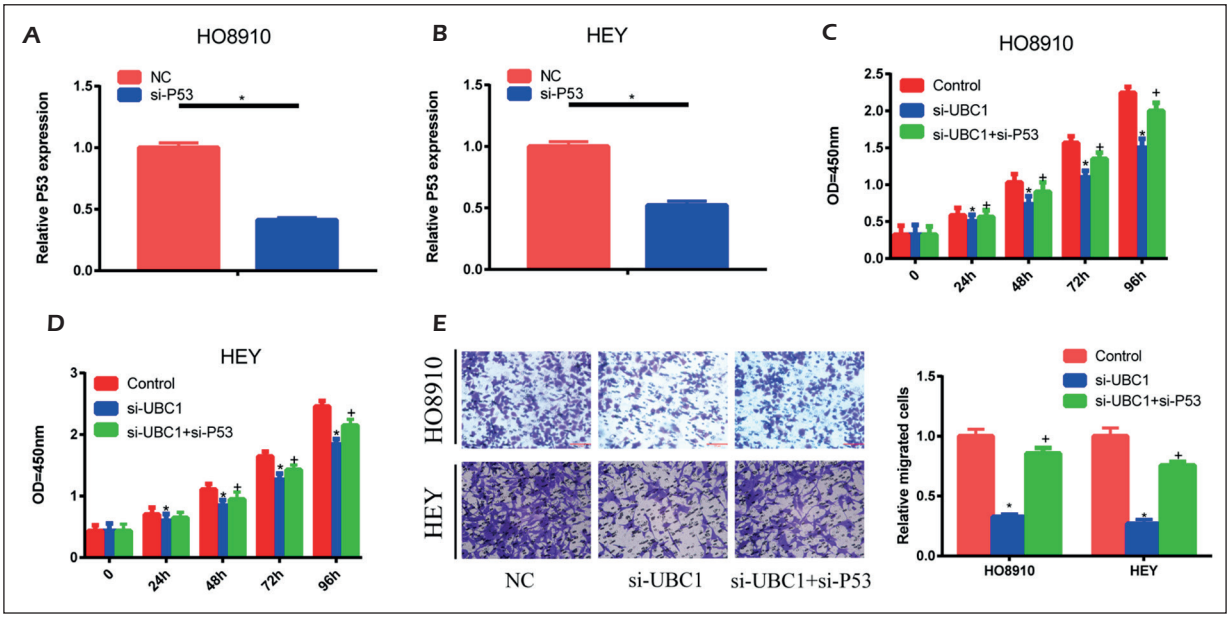

Figure 4. Knockdown of p53 reversed the regulatory effect of linc-UBC1 on OC. **A,** Transfection efficacy of si-p53 in HO8910 cells. **B,** Transfection efficacy of si-p53 in HEY cells. **C,** Viability in HO8910 cells transfected with control, si-UBC1 or si-UBC1+si-p53. **D,** Viability in HEY cells transfected with control, si-UBC1 or si-UBC1+si-p53. **E,** Migratory cell number in HO8910 and HEY cells transfected with control, si-UBC1, or si-UBC1+si-p53 (magnification 200×).

components are EZH2 enhancers[29,30]. Linc-UBC1 dysregulation has been identified as a potential biological marker of tumorigenesis. Moreover, linc-UBC1 promotes tumor invasion and metastasis by downregulating E-cadherin through the EZH2 recruitment in esophageal squamous cell carcinoma[31]. Upregulated linc-UBC1 is associated with poor prognosis of colorectal cancer, which promotes proliferation and metastasis of tumor cells[32]. Linc-UBC1 physically binds to PRC2 and serves as a negative prognostic factor for lymph node metastasis and survival in bladder cancer[30]. Nevertheless, the role of linc-UBC1 in OC is unclear.

P53 gene could arrest cell cycle progression, induce apoptosis, maintain genomic stability, and inhibit tumor angiogenesis[33]. After the occurrence of p53 mutation, spatial conformation changes lead to the transformation of p53 from a tumor-suppressor gene to an oncogene[34,35]. LncRNA LINP1 promotes the malignant progression of prostate cancer by regulating p53[36]. LncRNA PICART1 mediates cancer cell proliferation and migration by targeting p53[37]. LncRNA WT1-AS inhibits the invasiveness of cervical cancer cells by adsorbing miR-330-5p to regulate the p53 expression[38]. LOC572558 inhibits the growth of bladder cancer by modulating the AKT-MDM2-p53 axis[39].

In this paper, linc-UBC1 was upregulated in OC and negatively correlated to the p53 level. In OC patients, their linc-UBC1 levels gradually increased with the worsen of TNM staging and enlargement of tumor size. Linc-UBC1 was mainly distributed in the nucleus. Silence of linc-UBC1 attenuated proliferative and migratory abilities of HO8910 and HEY cells. RIP assay verified that the transcription of p53 was inhibited by linc-UBC1. The knockdown of p53 could partially reverse the regulatory effects of linc-UBC1 on mediating the progression of OC. As a result, we believed that linc-UBC1 aggravated the progression of OC by downregulating p53.

Conclusions

We demonstrated that linc-UBC1 was upregulated in OC tissues and cells. Linc-UBC1 stimulated the proliferation and metastasis of OC by inhibiting p53 level, thus exerting a carcinogenic role.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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