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# LncRNA SNHG17 promotes proliferation and invasion of ovarian cancer cells through up-regulating FOXA1

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**Abstract. – OBJECTIVE: This study was designed to investigate the specific mechanism through which long non-coding RNA (lncRNA) SNHG17 promotes the proliferative capacity and invasiveness of ovarian tumor cells.**

**PATIENTS AND METHODS: Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) detected the expressions of SNHG17 and FOXA1 in 30 pairs of ovarian cancer tissue specimens and corresponding adjacent ones. Meanwhile, in ovarian cancer cell lines (A2780, OVCAR3, SKOV3, CAOV3) and normal ovarian epithelial cell line (IOSE80), SNHG17 and FOXA1 mRNA levels were also examined. In in vitro experiment, si-SNHG17, si-FOXA1, and their corresponding negative controls were transfected into ovarian cancer cell lines, respectively. After that, Cell Counting Kit-8 (CCK-8) and plate cloning experiments were carried out to examine cell proliferation ability, while transwell assay was performed for cell invasiveness detection. Lastly, the interplay between SNHG17 and FOXA1 was further assessed via qRT-PCR and Western blot.**

**RESULTS: qRT-PCR results indicated that SNHG17 expression was remarkably enhanced in ovarian cancer tissue samples compared with that in adjacent ones. In addition, ovarian cancer cells also contained higher expression of SNHG17 than the normal ovarian epithelial cells. However, down-regulating SNHG17 attenuated the cell proliferation and invasive ability. At the same time, compared with that in adjacent tissue samples, FOXA1 also showed a higher expression in ovarian cancer tissues, which was positively correlated with SNHG17. Silencing SNHG17 markedly downregulated FOXA1 expression at both mRNA and protein levels. Furthermore, downregulation of FOXA1 expression was found to be able to inhibit cell proliferation and invasion as well.**

**CONCLUSIONS: LncRNA SNHG17 can promote ovarian tumor cell proliferative ability and invasiveness by upregulating FOXA1, and serve as a potential therapeutic target for ovarian cancer.**

*Key Words:*
SNHG17, FOXA1, Ovarian cancer, Cell proliferation, Cell invasion.

## Introduction

Ovarian cancer is the leading killer of gynecological tumors[1], causing death of more than 100,000 women worldwide each year. For its insidious onset, rapid development, and poor prognosis, it has become the fifth cause leading to female death[2]. As the early symptoms of ovarian cancer are often insidious and non-specific, and there is a lack of specific indicators for early diagnosis, more than 70% of the newly diagnosed cases have reached advanced stage by the time of diagnosis[3]. Although surgical treatment and chemotherapy drugs have been applied clinically, the 5-year survival rate of advanced ovarian cancer patients is still relatively low, remaining at about 40%[4]. Therefore, it is of great significance to clarify the relationship between the functions of the new genes and the pathogenesis of ovarian cancer, to provide clues for designing reasonable therapeutic drugs and predicting prognosis. Long noncoding RNAs (lncRNAs) play a pivotal role in ovarian tumor progression, and are expected to become new tumor markers or targets for tumor therapy.

About 98% of the transcripts in the human genome are noncoding RNA, which can be divided into lncRNA and short chain lncRNA including microRNA, siRNA, and piRNA, according to their sizes. LncRNA accounts for 4%-9% of the human genome, which is a type of functional RNA molecule of more than 200 nucleotides (nt) in length, located in the nucleus or cytoplasm, regulating the expression and function of genes in various forms (e.g., epigenetic regulation, transcriptional regulation, post-transcriptional regulation, etc.)[5,6], thereby inducing



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the occurrence of diseases. Similar to microRNA, lncRNA also cannot be translated into protein, but is able to be widely engaged in almost all physiological and pathological activities of the human body, including the regulation of numerous tumors. The characteristics of lncRNA in gene expression regulation are mainly related to the length of its own molecules[7]. In addition, due to the long sequence, lncRNAs are generally less conserved and more tolerant to variation, so they are of great significance to the adaptability of species evolution[8]. Certain lncRNAs appear only at specific developmental stages[9] and are tissue-specific and/or cell-specific[10]. The specific expression level of lncRNA in some tumors can serve as diagnostic markers and/or potential therapeutic targets for tumors (such as DD3 in prostate cancer)[11]. Some lncRNAs are involved in the metastasis of many tumors. MALAT1 expression is remarkably increased if non-small-cell carcinoma progresses and metastases occur[12]. In addition, MALAT1 is also abnormally regulated in many human tumors, such as breast cancer and liver cancer[13].

Small nucleolar RNA host gene 17 (SNHG17, 1,186-nt lncRNA) was located at 20q11.23. As a newly discovered functional lncRNA, it has been reported to be abnormally expressed in gastric cancer and colorectal cancer tissues[14,15] to enhance the proliferation and migration of tumor cells by regulating p57 gene. However, no studies have reported the specific mechanism by which SNHG17 affect the progression of ovarian cancer. The purpose of this study was to further explore the expression of SNHG17 and its specific mechanism in the progression of ovarian cancer.

## Patients and Methods

### Sample Collection

A total of 30 pairs of tumor tissue specimens and adjacent normal ones collected from ovarian cancer patients in our hospital were stored in liquid nitrogen. All tissue samples were verified by pathology. Patients and their families signed informed consent. This research was approved by the Ethics Committee of our hospital.

### Cell Culture

Ovarian cancer cell lines (A2780, OVCAR3, SKOV3, CAOV39) and normal ovarian epithelial cells (IOSE80) were purchased from the Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences (Shanghai, China). All cells were cultured in complete medium Roswell Park Memorial Institute-1640 (RPMI-1640; Invitrogen, Carlsbad, CA, USA) containing 10% heat-inactivated fetal bovine serum (FBS; Invitrogen, Carlsbad, CA, USA), penicillin (100 U/mL)/streptomycin (100 μg/mL; Invitrogen, Carlsbad, CA, USA), and incubated in a humidified incubator at 37°C with 5% $CO_2$.

### Cell Transfection

The SNHG17 siRNA and FOXA1 siRNA used in this study and the corresponding negative controls were purchased from GenePharma (Shanghai, China). The cells used in the experiment ($5\times10^5$/well) were placed in a 6-well plate. After the cell density reached 80%, the transfection reagent was mixed with Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA), and incubated at room temperature for 30 minutes, and then, added to cells for 24-48 hours of transfection. Finally, the transfection efficiency was verified by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR).

### RNA Extraction and qPCR Detection

Purified total RNA was extracted from tissues and cells using a TRIzol (Invitrogen, Carlsbad, CA, USA) method. The complementary deoxyribose nucleic acid (cDNA) was obtained by reverse transcription using PrimeScript RT reagent Kit (TaKaRa, Otsu, Shiga, Japan). QRT-PCR analysis was carried out under the following conditions: 92°C for 10 minutes, then, 40 cycles of 10 seconds at 90°C and 1 minute at 60°C. The primer sequences were as follows: SNHG17 (F: 5'-TGCTTGTAAGGCAGGGTCTC-3', R: 5'-ACAGCCACTGAAAGCATGTG-3'); FOXA1 (F: 5'-GCAATACTCGCCTTACGGCT-3', R: 5'-TACACACCTTGGTAGTACGCC-3'); GAPDH (F: 5'-GGAATCCACTGGCGTCTTCA-3', R: 5'-GGTTCACGCCCATCACAAAC-3').

### Cell Counting Kit-8 (CCK-8) Assay

The cells in the medium were digested with 0.25% trypsin, and the cell suspension was seeded into 96-well plates. Each well contains at least $2\times10^3$ cells and 200 μL of medium. The cells were allowed to adhere to growth overnight, and then, the cell supernatant was washed with phosphate-buffered saline (PBS). A mixture containing 90 μL of RPMI-1640 medium and 10 μL of CCK-8 solution (Dojindo Molecular Technologies, Kumamoto, Japan) was added to each well. After 2 hours of incubation, the absorbance of each well was read at 450 nm by a microplate reader.

### Plate Cloning Experiment

After digesting the cells with 0.25% trypsin, the cell suspension was collected and adjusted to a concentration of $1\times10^3$/mL, and then, seeded into 6-well plates. Each well contained 100 μL of cell suspension and 2 mL of RPMI-1640 complete medium containing 10% fetal bovine serum. The cells were continuously cultured for 2 weeks, and the medium was changed every 5 to 7 days. After 2 weeks, the cells were photographed and counted.

### Transwell Assay

After the cells were added to 200 μL of serum-free medium at a concentration of $3 \times 10^4$ cells/well, the cell suspension was added to an upper chamber coated with 200 mg/mL Matrigel. 500 μL of medium containing 10% FBS was added to the lower chamber. The cells were incubated for 24 hours at 37°C with 5% $CO_2$ for invasion analysis. After that, cells that transferred to the lower chamber were stained with 0.1% crystal violet, and then, observed under a microscope.

### Western Blot

Total protein was extracted from transfected OVCAR3 and SKOV3 cells. Then, the target proteins were separated using a 10% concentration gradient polyacrylamide gel and transferred to a 0.22 μm polyvinylidene difluoride (PVDF) membrane (Millipore, Billerica, MA, USA). All membranes were incubated for 2 h in blocking buffer (5% non-fat milk) and then incubated with primary antibody (Invitrogen, Carlsbad, CA, USA) overnight at 4°C. After incubation with the corresponding secondary antibody (Invitrogen, Carlsbad, CA, USA) for 2 h at room temperature, these protein bars were visualized by enhanced chemiluminescence reagents (ECL; Pierce, Rockford, IL, USA).

### Statistical Analysis

Data analysis was performed using Statistical Product and Service Solutions (SPSS) 17.0 statistical software (SPSS Inc., Chicago, IL, USA), and picture editing was performed using Graph-Pad Prism (Version X; La Jolla, CA, USA). Statistical analysis was performed using a *t*-test to assess the difference in experimental data. $p<0.05$ was considered to be statistically significant.

## Results

### High Expression of SNHG17 in Ovarian Cancer Tissues and Cells

qRT-PCR results revealed that SNHG17 level was remarkably increased in ovarian cancer tissue samples compared with that in adjacent normal ones (Figure 1A). In addition, ovarian cancer cell

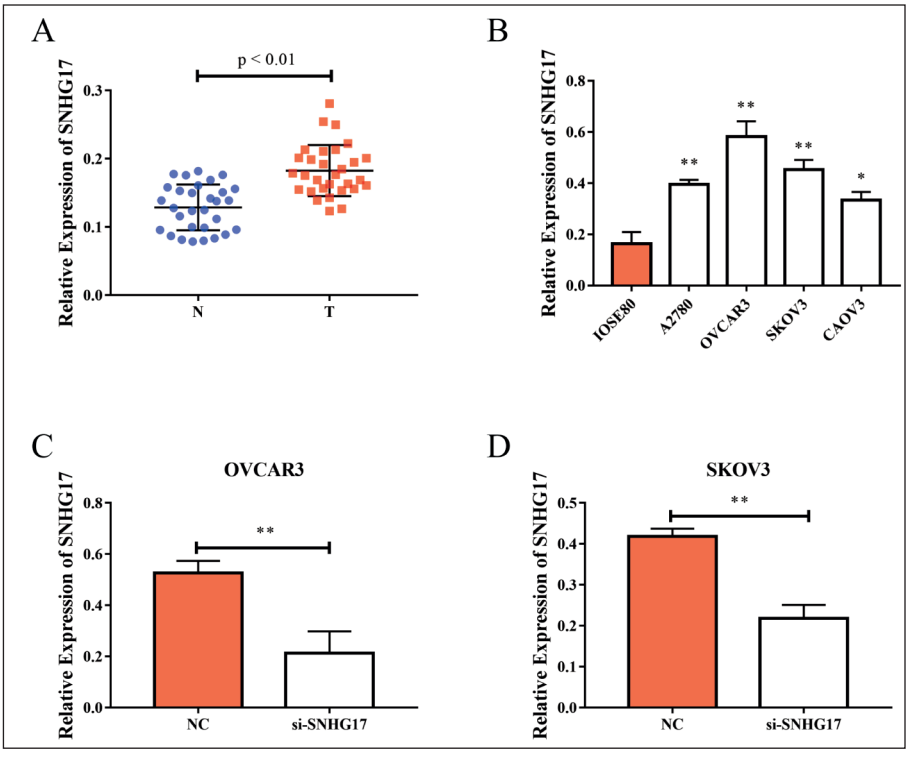


**Figure 1.** SNHG17 is highly expressed in ovarian cancer tissues and cells. **A**, qRT-PCR analysis shows that the expression of SNHG17 is significantly upregulated in ovarian cancer tissues compared with adjacent tissues. **B**, qRT-PCR assay shows that the expression level of SNHG17 is significantly increased in ovarian cancer cell lines (A2780, OVCAR3, SKOV3, CAOV3) compared with normal ovarian epithelial cells (IOSE80). **C**, Transfection efficiency of si-SNHG17 in OVCAR3 cells. **D**, Transfection efficiency of si-SNHG17 in SKOV3 cells. (**$p<0.01$).

lines (A2780, OVCAR3, SKOV3, CAOV39) contained a higher expression of SNHG17 than normal ovarian epithelial cells (IOSE80) (Figure 1B), and OVCAR3 and SKOV3 cells were selected for subsequent experiments. To further investigate the specific mechanism by which SNHG17 affects the progression of ovarian cancer, SNHG17 siRNA was transfected in OVCAR3 and SKOV3 cells, and the efficiency was verified by qRT-PCR detection (Figure 1C-1D).

### *Downregulation of SNHG17 Inhibits Invasiveness and Proliferative Capacity of Ovarian Cancer Cells*

CCK-8 assay revealed that cell proliferation was remarkably attenuated after downregulation of SNHG17 in OVCAR3 and SKOV3 cells (Figure 2A-2B), and the similar result was observed in plate cloning experiment (Figure 2C). At the same time, transwell cell invasion assay demonstrated that cell invasiveness was also significantly suppressed after downregulating SNHG17 (Figure 2D). The above observations indicate that the downregulation of SNHG17 is capable of inhibiting the proliferation, as well as invasion of ovarian cancer cells.

### *SNHG17 Can Upregulate FOXA1 Expression*

Using qRT-PCR, it was found that FOXA1 expression was also remarkably upregulated in ovarian cancer tissues when compared to that in adjacent ones (Figure 3A). Meanwhile, statistical tools were applied to confirm that FOXA1 and SNHG17 were positively correlated in ovarian cancer tissues (Figure 3B). To further investigate their intermodulation relationship, FOXA1 expression levels were detected after silencing SNHG17 in OVCAR3 and SKOV3 cells by qRT-PCR, which then revealed a significant decrease in FOXA1 expression (Figure 3C). Similarly, it was found that FOXA1 siRNA transfection simultaneously downregulated FOXA1 (Figure 3D) and SNHG17 (Figure 3E) in ovarian tumor cells,

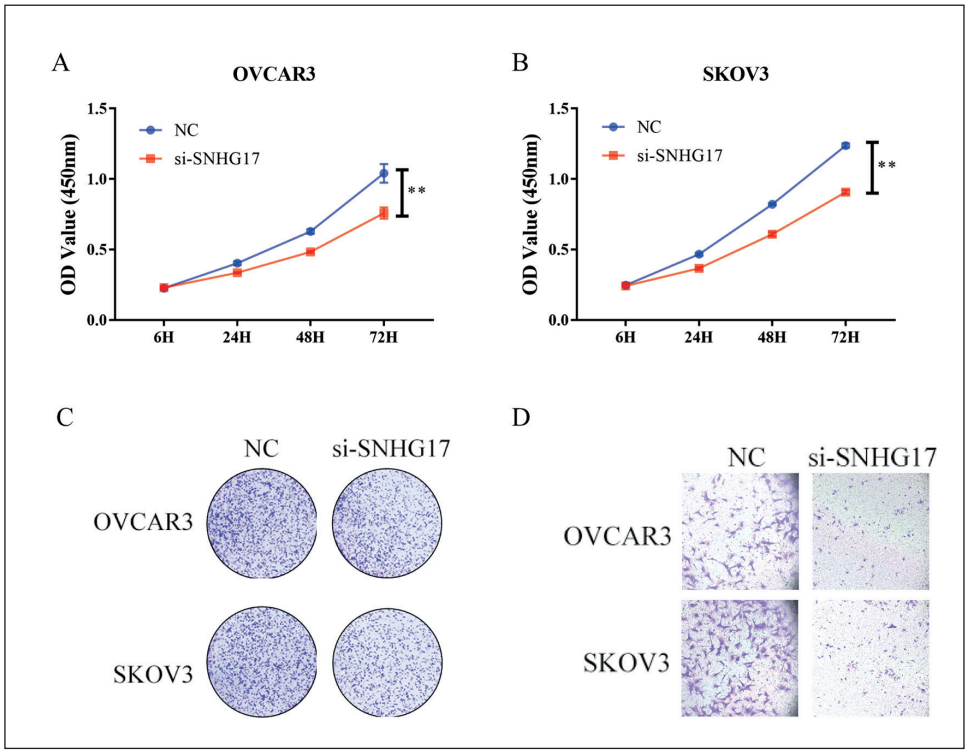


**Figure 2.** Downregulation of SNHG17 inhibits cell proliferation and cell invasion. **A**, The results of CCK-8 show that the expression of SNHG17 is down-regulated in OVCAR3 cells, and the cell proliferation ability is weakened. **B**, Downregulation of SNHG17 expression in SKOV3 cells decreased cell proliferation ability. **C**, The results of plate cloning experiments show that down-regulation of SNHG17 expression in OVCAR3 and SKOV3 cells weakens the cell proliferation ability (magnification: 40×). **D**, Transwell cell invasion assay shows that downregulation of SNHG17 expression in OVCAR3 and SKOV3 cells significantly attenuates the cell invasion ability (magnification: 40×) (**$p$<0.01).

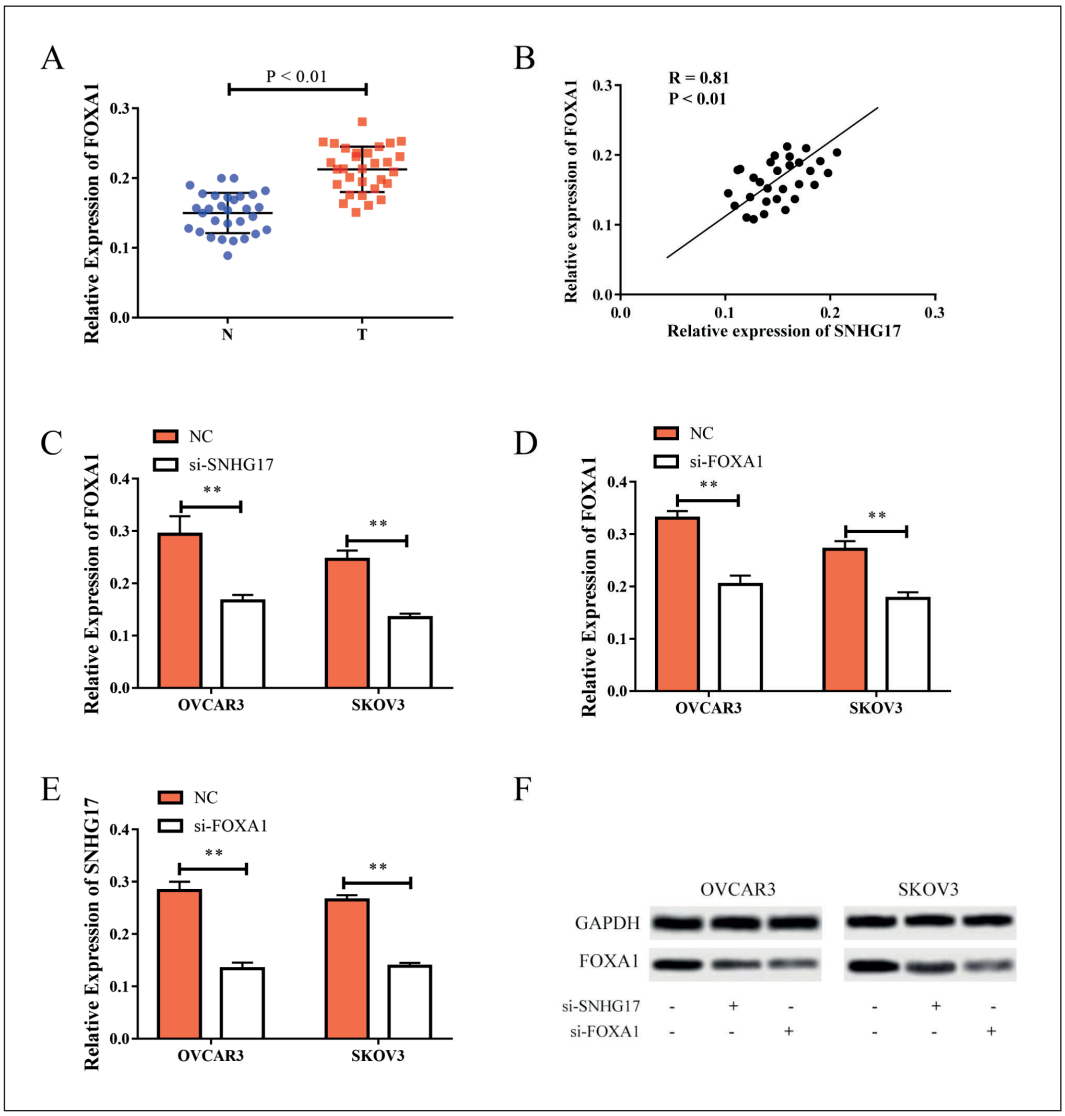


**Figure 3.** SNHG17 upregulates FOXA1 expression. **A**, qRT-PCR assay shows that FOXA1 expression is significantly up-regulated in ovarian cancer tissues relative to adjacent tissues. **B**, There was a positive correlation between FOXA1 expression and SNHG17 expression in ovarian cancer tissues. **C**, qRT-PCR assay showed that down-regulation of SNHG17 inhibited FOXA1 expression. **D**, Transfection efficiency of si-FOXA1 in OVCAR3 and SKOV3 cells. **E**, qRT-PCR assay showed that the expression level of SNHG17 was also significantly decreased after down-regulation of FOXA1 expression. **F**, Western blot analysis showed that FOXA1 protein levels were decreased after downregulation of SNHG17 expression or transfection of si-FOXA1 in OVCAR3 and SKOV3 cells. (**$p$<0.01).

both in mRNA and protein levels (Figure 3F). Taken together, it can be concluded that SNHG17 is able to positively modulate FOXA1 expression in ovarian tumor cell lines.

### *Downregulation of FOXA1 Inhibits Proliferation Capacity and Invasiveness of Ovarian Cancer Cells*

Subsequently, CCK-8 and plate cloning experiments were further carried out to explore the changes in cell proliferation after knocking down FOXA1 in OVCAR3 and SKOV3 cells. As a result, it was found that FOXA1 downregulation dramatically weakened cell proliferative capacity (Figure 4A-4C). At the same time, as for the changes in cell invasive ability, transwell assay detected a significant reduction (Figure 4D). Therefore, it can be concluded that the downregulation of FOXA1 is capable of repressing the invasive and proliferative capacity of ovarian cancer cells.

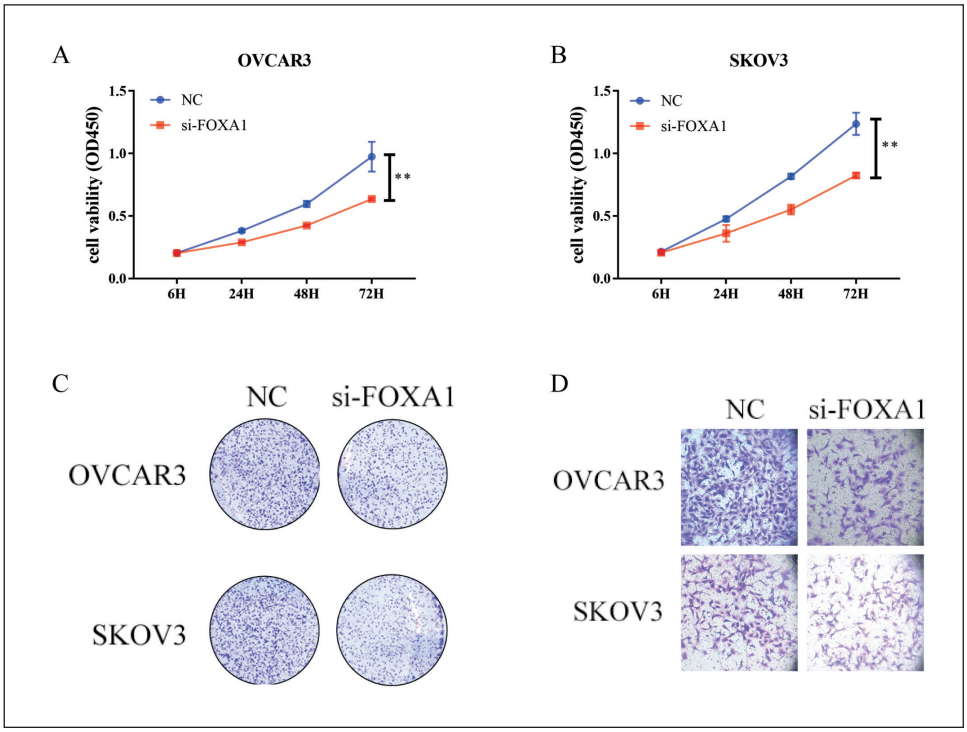


**Figure 4.** Downregulation of FOXA1 inhibits cell proliferation and cell invasion. **A**, The results of CCK-8 assay show that downregulation of FOXA1 inhibited cell proliferation ability. **B**, Downregulation of FOXA1 expression in SKOV3 cells decreases cell proliferation. **C**, The results of plate cloning experiments show that down-regulation of FOXA1 expression in OVCAR3 and SKOV3 cells weakens cell proliferation ability (magnification: 40×). **D**, Transwell cell invasion assay shows that downregulation of FOXA1 in OVCAR3 and SKOV3 cells inhibits cell invasive ability. (magnification: 40×) (**$p$<0.01).

## Discussion

As one of the six gynecological tumors, ovarian cancer is a common tumor in female reproductive system[16-18]. Epithelial ovarian carcinoma accounts for 85%-90% of all ovarian tumors, which is the most common pathological type[19]. Worldwide, more than 230,000 new cases of ovarian epithelial cancer occur each year and about 14,000 patients die, and in China, the number of new cases is about 154,000 every year. What makes it terrible is that most patients with ovarian cancer have developed to advanced stage when they visit doctor, and most of them are accompanied by local or distant metastasis[20]. Due to the insidious onset, the difficulty in early diagnosis, and the strong resistance to chemotherapy drugs, the 3-year survival rate of ovarian cancer patients is only about 50%, while the 5-year survival rate is less than 30%[21]. Although the prognosis of ovarian cancer patients has been advanced with the progress of surgical level and the extensive application of platinum-based combined chemotherapy, the long-term survival rate is still unsatisfactory[22]. Therefore, the search for biomarkers related to the prognosis of disease has become an urgent problem to be solved.

The FOX protein family can be divided into 17 subclasses according to the amino acid sequence of the forkhead domain[23]. This protein family can be involved in many physiological processes, such as embryonic development, cell proliferation, and cell cycle regulation. Gene mutations of this family may induce certain developmental diseases, metabolic diseases, and even tumors[24]. As a member of FOX protein family, FOXA1 is mainly engaged in regulating the signaling pathway of nuclear steroid receptors and controlling the activation of estrogen or testosterone receptors[23]. FOXA1 can be detected in many tissues and organs, such as breast, liver, kidney, prostate, digestive tract, lung, and bladder, and directly participates in the growth and development of embryos, cell proliferation, and differentiation[25,26]. In addition, FOXA1 can achieve sex differences in the incidence of pan-

creatic cancer, lung cancer, liver cancer, and other solid tumors by regulating AR and ER signaling pathways[27]. Meanwhile, the expression of FOXA1 is able to affect patients' liver cancer susceptibility, invasion, and metastasis of pancreatic cancer and lung cancer[28,29]. Moreover, in addition to the above solid tumors, FOXA1 also plays a pivotal role in regulating the activity of nuclear steroid receptors in breast and prostate cancer, which is necessary for the estrogen signaling pathway in breast cancer cells[30]. Some studies[24] have explored the correlation between ovarian epithelial carcinoma and patients' survival time from both the RNA and protein levels[31,32]. In this research, a regulatory relationship was discovered between FOXA1 and SNHG17 expression, and its mechanism of action was further explored.

In this study, it was found that both the ovarian cancer tissues and cell lines contained a significantly high expression of SNHG17 and FOXA1. Downregulation of SNHG17 markedly inhibited the proliferation and invasive ability of ovarian cells. At the same time, FOXA1 mRNA and protein levels both showed significant reduction after the knockdown of SNHG17, revealing a positive correlation between SNHG17 and FOXA1. Similarly, in ovarian cancer cells, SNHG17 expression also showed a decrease when FOXA1 expression was downregulated. Moreover, further studies revealed that the downregulation of FOXA1 could also attenuate cell proliferation and invasive ability, just like SNHG17. Thus, it can be concluded that SNHG17 can promote the progression of ovarian cancer by upregulating FOXA1 expression, which accelerates cell proliferation and invasion.

## Conclusions

In short, SNHG17 can upregulate FOXA1 expression to promote cell proliferative capacity, as well as invasiveness, and thus participate in the development of ovarian cancer.

### Conflict of Interests

The authors declare that they have no conflict of interest.

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