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Long non-coding RNA MALAT1 regulates ovarian cancer cell proliferation, migration and apoptosis through Wnt/β-catenin signaling pathway

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Abstract. – OBJECTIVE: Long non-coding RNA (LncRNA) MALAT1 is an important regulatory molecule in many diseases, especially in ovarian cancer. We aimed at exploring the function of MALAT1 in ovarian cancer and at clarifying its mechanisms.

PATIENTS AND METHODS: The expression level of MALAT1 in ovarian cancer tissues, para-carcinoma tissues and ovarian cancer cell lines were analyzed by Real-time polymerase chain reaction (RT-PCR). The cell proliferation rate was detected by CCK8 assay in SKOV3 and HO8910 cells. Transwell was used to detect the invasion and migration activities in SKOV3 and HO8910 cells. The cell cycle distribution and apoptosis rate were measured by flow cytometry analysis. The expression level of Dvl2, GSK-3β, β-catenin and cyclin D1 were detected by RT-PCR and Western blot.

RESULTS: The relative expression level of MALAT1 was identified to be aberrantly up-regulated in ovarian cancer tissues and cell lines. The high expression level of MALAT1 was associated with poor prognosis in ovarian cancer patients. The down-regulation of MALAT1 inhibited cell proliferation, invasion and migration, arrested cell cycle progression in S phase and induced cell apoptosis in ovarian cancer cell lines. Meanwhile, the down-regulation of MALAT1 decreased the expression level of DVL2, β-catenin and cyclin D1 and increased the expression level of GSK-3β in SKOV3 and HO8910 cells. Moreover, the inhibitory effect of MALAT1 down-regulation in cell invasion and migration was reversed by SKL2001 activating Wnt/β-catenin signal pathway and enhanced by XAV939 inhibiting Wnt/β-catenin signal pathway.

CONCLUSIONS: MALAT1 was overexpressed in ovarian cancer and associated to the poor prognosis. The down-regulation of MALAT1 inhibited cell proliferation, invasion and migration, arrested cell cycle progression in S phase and induced cell apoptosis by restraining the activation of Wnt/β-catenin signaling pathway in ovarian cancer cells.

Key Words:
MALAT1, Ovarian cancer, Proliferation, Invasion, Migration, Cell cycle, Wnt, β-catenin.

Introduction

Ovarian cancer is one of the three most common malignant tumors in the female reproductive system. Lacking effective screening and diagnostic methods, more than 70% of patients with this disease used to be diagnosed at advanced stages[1,2]. At present, the mainly effective treatments for ovarian cancer are surgical treatment and the chemotherapy of platinum combined paclitaxel[3]. In spite of initially high response rates to surgery and first line chemotherapy, approximately 75% of patients will eventually relapse because of drug resistance[4]. It has been a great challenge for gynecologists to treat recurrent ovarian cancer, thus, it is very important to explore the new drugs of targeted therapy of ovarian cancer.

Long noncoding RNAs (LncRNAs) are a new class of RNA, which are 200 nt to 200 kb in length and do not code proteins[5,6]. LncRNAs play a significant role in transcription and post-transcription, regulating genomic imprinting, the X chromosome

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silence, epigenetic modification, cell cycle, alternative splicing, cell fate decision, reprogramming, cell apoptosis, oncogenesis and nervous system development[7]. LncRNAs have been demonstrated to involve in a broad range of biological and pathological processes through interacting with proteins and/or nuclear acids[8]. Emerging evidence has found aberrant expression of lncRNAs in cancer cells, showing the crucial roles that lncRNAs play for the development of many cancers including ovarian cancer. However, the role of lncRNAs in ovarian cancer remain to be further explored[9,10].

Many lncRNAs have been found to regulate the progression of ovarian cancer[11,12]. For example, LncRNA RP11-552M11.4 promoted the growth through suppressing BRCA2 in ovarian cancer[13]. Anti-sense lncRNA As-SLC7A11 inhibited ovarian cancer cells proliferation, migration and invasion by targeting BRCA2[14]. LncRNA CCAT1 contributed to ovarian cancer cells proliferation and metastasis via miR-1290[15]. Among them, little research about the effect of lncRNA MALAT1 on ovarian cancer has been identified[16]. Besides that, MALAT1 plays an important role in various cancers, such as lung cancer[17], glioblastoma[18], breast cancer[19], colorectal cancer[20] and osteosarcoma[21]. Although the effect of MALAT1 has been confirmed repeatedly, the regulatory mechanism of MALAT1 in ovarian cancer is still not clear.

This research was focused on the expression level of MALAT1 in ovarian cancer and the relationship with the prognosis. Meanwhile, the function of MALAT1 for the proliferation, invasion, migration and apoptosis in ovarian cancer was also determined. Finally, the regulatory mechanism of MALAT1 in ovarian cancer was illustrated through blockade or activation of Wnt/β-catenin signaling pathway.

Patients and Methods

Tissue Specimens

Sixty patients with ovarian cancer were collected from the Department of Obstetrics and Gynecology, Taihe Hospital, Hubei University of Medicine (Hubei, China). All patients received no treatment other than surgery and signed informed consent. Ethical Committee approval was granted by Taihe Hospital, Hubei University of Medicine (Shiyan, China). Sixty ovarian cancer tissues and para-carcinoma tissues were obtained from patients who were diagnosed histopathologically and subjected to surgical resection. All of the tissue samples were frozen in liquid nitrogen and then stored at -80°C refrigerator until use.

Cell Culture and Cell Transfection

A normal ovarian cell line (HOSEpiC) and four ovarian cancer cell lines (SKOV3, OVCAR3, 3AO and HO8910) were obtained from the American Type Culture Collection (Manassas, VA, USA). All of the cells were cultured in Roswell Park Memorial Institute-1640 (RPMI-1640) medium (Gibco, Rockville, MD, USA) supplemented with 10% fetal bovine serum (FBS; Gibco, Grand Island, NY, USA) at 37°C and 5% CO_2. Small interfering RNA against MALAT1 (si- MALAT1) and its negative control (si-NC) were synthesized by RiboBiotech (GuangZhou RiboBiotech, GuangZhou, China). si-MALAT1 and si-NC were transfected using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA), according to the manufacturer's instructions.

RNA Extraction and Quantitative Real-Time PCR

The total RNA from all samples and cultured cells was extracted using TRIzol (Invitrogen, Carlsbad, CA, USA). Reverse transcription was performed to generate the first-strand cDNA using M-MLV Reverse Transcriptase (Promega, Madison, WI, USA). Real-time PCR was carried out using the Power SYBR Gre-en PCR Master Mix (Applied Biosystems, Foster City, CA, USA) using the Bio-Rad System (Bio-Rad, Hercules, CA, USA). The primer sequences were: MALAT1 Fw-AGCGGAAGAACGAAT-GTA-AC and Rv-GAACAGAAGGAAGAGCCA-AG; GAPDH Fw-TGTTGCCATCAATGACCC-CTT and Rv-CTCCACGACGTACTCAGCG, Dvl2 Fw-AGGATACCACCCTTCCGTTG and Rv-G-GCGCCAAGTACTTTTTCAA, GSK-3β Fw-GACGCTCCCTGTGATTTATGTC and Rv-GTTAGTCGGGCAGTTGGTGTAT, β-catenin Fw-CGGTACATGCATGACTGAGAC and Rv-GTCACGTGGTACGACGTCAGAT, cyclinD1 Fw-GAGTAGTGCGAAGCATAGGTCT and Rv-CTAGCACGAGTAGTCGAGCGC,β-actin Fw-ACGAGACCIACCTTCAACTCCATC and Rv-TAGAAGCATTTGCGGTGGACGA. $2^{-\Delta\Delta CT}$ method was applied to determine the relative gene expression, and the expression levels of mRNA were normalized to U6 or β-actin.

Proliferation Assay

A total of approximately 1×10^3 cells/well were cultured in 96-well plates either. Cell Counting Kit-8 (CCK-8, Dojindo Laboratories, Kumamoto, Japan) assay was added into cell at 37°C and 5% CO_2

for 4 h. Cell viability was detected in 6 wells per group and in blank controls. Afterward, 10 μL of the CCK-8 solution were added at 0, 24, 48, 72, and 96 h, and the resulting solution was incubated for 3 h at 37°C. The absorbance value at 450 nm of each well was measured. The cell growth curves were plotted using the absorbance value at each time point.

Migration and Invasion Assay

Transwell chambers (BD Biosciences, Franklin Lakes, NJ, USA) were applied to evaluate the migratory and invasive ability of ovarian cancer cells. 5×10^4 transfected cells without FBS were put into the top chamber on the non-coated membrane, and lower chamber was filled with 20% FBS to induce transfected cells to migrate or invade through the membrane. The cells were put in the upper chamber with the coated membrane for invasion assay. Next, these cells were incubated for migration and invasion assay, and stained with crystal violet. Three invasion chambers were utilized per condition, and five random fields were counted per chamber under an inverted microscope.

Flow Cytometry

Cells were cultured in 6-well plates with a concentration of 3×10^5 cells/well either and washed with phosphate-buffered saline (PBS). 5 μl FITC Annexin V and 5 μl PI were added into cell and stained for 15 min at darkness according to the manufacturer's instructions. Data acquisition and analyses were realized by Becton Dickinson (Franklin Lakes, NJ, USA) FACSCalibur using CellQuest software (Becton Dickinson, Franklin Lakes, NJ, USA).

Western Blot Analysis

Total protein was extracted from the cells or tissues by using a RIPA lysis buffer (Beyotime, Jiangsu, China). Proteins were separated through 10% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and incubated with 5% non-fat milk blocked membranes at room temperature. After blocking with 5% nonfat dry milk in Tris-buffered saline (TBS; 20 mM Tris-HCl, pH 7.5, 150 mM NaCl) containing 0.1% Tween 20, the membranes were incubated with primary antibody overnight at 4°C and subsequently incubated with matched secondary antibodies. Protein bands were detected through enhanced chemiluminescence (ECL) by utilizing a Pierce ECL Western blot substrate (Thermo Fisher Scientific, Waltham, MA, USA) and exposed to an X-ray film by using an ECL detection system (Thermo Fisher Scientific, Waltham, MA, USA).

Statistical Analysis

Statistical analysis was carried out with SPSS version 21.0 (IBM, Armonk, NY, USA). Data are presented means± SD. Statistical differences were carried out by using the Student's *t*-test between two groups and using one-way ANOVA followed by Student-Newman-Keuls post-hoc test between multiple groups. Kaplan-Meier method was used to perform the survival analysis. Differences were considered significant at $p<0.05$.

Results

MALAT1 was Upregulated in Ovarian Cancer Patients and Associated with the Prognosis

The expression level of MALAT1 in ovarian cancer tissues and para-carcinoma tissues was detected by RT-PCR. MALAT1 expression was upregulated in ovarian cancer tissues, compared with para-carcinoma tissues (Figure 1A) and the expression level of MALAT1 in ovarian cancer with metastasis was increased compared with ovarian cancer without metastasis (Figure 1B). After that, the level of MALAT1 in the tissue samples from patients of different TNM stage was examined. The expression of MALAT1 level in ovarian cancer patients with III-IV was higher than that of ovarian cancer patients with I-II (Figure 1C). Three-year survival rate in high expression of MALAT1 was lower than that in low expression of MALAT1 (Figure 1D).

MALAT1 was Upregulated in Ovarian Cancer Cell Lines

We detected MALAT1 expression in a normal ovarian cell line (HOSEpiC) and four ovarian cancer cell lines (SKOV3, OVCAR3, 3AO and HO8910) by RT-PCR. The results showed that MALAT1 expression level was significantly higher in ovarian cell lines than that in normal ovarian cell line, especially in HO8910 cell (Figure 2A). SKOV3 and HO8910 cells were transfected with si-MALAT1, the expression level of MALAT1 was significantly decreased, compared with cells transfected with si-NC (Figure 2B).

Down-Regulation of MALAT1 Inhibited Cell Proliferation, Invasion and Migration in Ovarian Cancer

In order to explore the effect of MALAT1 in ovarian cancer cell proliferation, invasion and migration, the cell proliferation, invasion and

migration were detected in SKOV3 and HO8910 cells after transfected with si-NC or si-MALAT1. Down-regulation of MALAT1 significantly inhibited ovarian cancer cells proliferation (Figure 3A). Meanwhile, the transwell assay showed that the ability of cells containing si-MALAT1 was lower than that of si-NC both for migration and invasion (Figure 3B). All data revealed that MALAT1 was a tumor promoter lncRNA for ovarian cancer through promoting cell proliferation, migration and invasion.

Down-Regulation of MALAT1 Arrested Cell Cycle Progression in S Phase and Induced Cell Apoptosis in Ovarian Cancer Cell Lines

We further examined whether down-regulation of MALAT1 affect cell cycle distribution and apoptosis rate in ovarian cancer. The results demonstrated that cell cycle was prominently shifted from G2/M phase to S phase, cell percentage in S phase was significantly increased and cell percentage in G2/M phase was significantly decreased in SKOV3 (Figure 4A-C) and HO8910 cells (Figure 4D-F). The rate of cellular apoptosis in SKOV3 and HO8910 cells was examined using flow cytometric analysis with Annexin V staining. Down-regulation of MALAT1 promoted cell apoptosis in SKOV3 (Figure 5A-C) and HO8910 cells (Figure 5D-F). All data revealed that down-regulation of MALAT1 arrested cell cycle progression in S phase and induced cell apoptosis in ovarian cancer cell lines

Down-Regulation of MALAT1 Regulated Wnt/β-Catenin Signaling Pathway in Ovarian Cancer Cell Lines

In order to confirm the mechanism of down-regulation of MALAT1 in ovarian cancer cell growth, apoptosis, the relative mRNA and protein

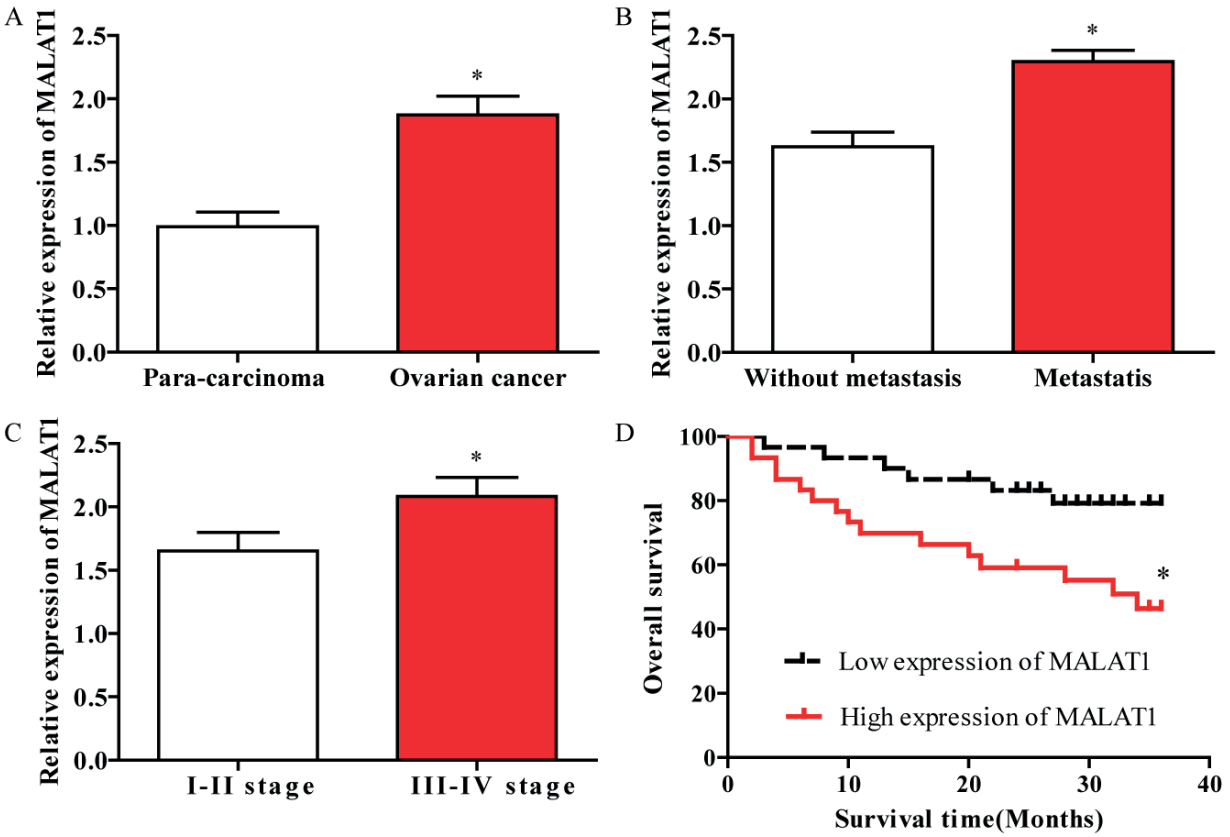

Figure 1. The expression level of MALAT1 in Ovarian cancer patients and associated with the prognosis ***A,*** The expression level of MALAT1 in ovarian cancer tissues and para-carcinoma tissues was detected by RT-PCR. ***B,*** The expression level of MALAT1 in ovarian cancer patients with metastasis and without metastasis was detected by RT-PCR. ***C,*** The expression level of MALAT1 in ovarian cancer patients with stage I-II and III-IV were detected by RT-PCR. ***D,*** Three-year survival rate were analyzed in ovarian cancer patients with low expression of MALAT1 and high expression of MALAT1. Data are shown as mean ± SD based on at least three independent experiments, *$p<0.05$.

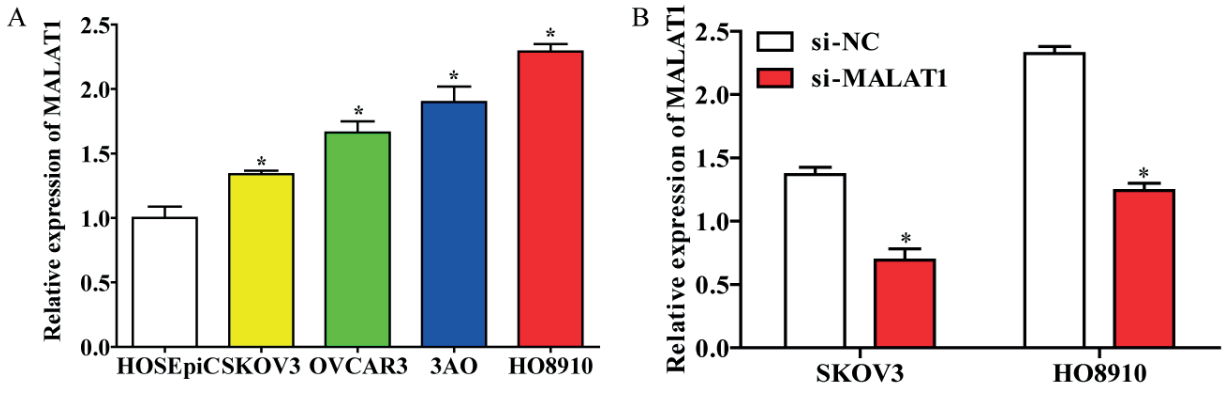

Figure 2. Up-regulation of MALAT1 in ovarian cancer cell lines ***A,*** The expression level of MALAT1 in SKOV3, OVCAR3, 3AO, HO8910 and HOSEpiC cells (control) was detected by RT-PCR. ***B,*** The expression level of MALAT1 in SKOV3 and HO8910 cells after transfected with si-NC or si- MALAT1 was detected by RT-PCR. Data are shown as mean ± SD based on at least three independent experiments, *$p<0.05$.

expression level of Dvl2, GSK-3β, β-catenin and cyclinD1 in SKOV3 and HO8910 cells after transfected with si-NC or si- MALAT1, were analyzed. Down-regulation of MALAT1 decreased Dvl2, β-catenin and cyclinD1 mRNA expression and increased GSK-3β mRNA expression in SKOV3 (Figure 6A) and HO8910 cells (Figure 6B), compared with control group. Meanwhile, the protein expression of Dvl2, β-catenin and cyclinD1 was significantly decreased and the protein expression of GSK-3β was significantly increased in SKOV3 (Figure 7A-B) and HO8910 cells (Figure 7C-D) after transfected with si- MALAT1. These results indicated that Wnt/β-catenin signaling is important in the function of MALAT1 on ovarian cancer cell growth.

*Blockade or Activation of Wnt/*β*-Catenin Signaling Pathway in Ovarian Cancer Cell Lines after Transfected with si-MALAT1 Affected Cell Invasion and Migration*

To further confirm the role of Wnt/β-catenin signaling pathway in the function of MALAT1 on cell growth in ovarian cancer, SKL201 and XAV939 were used to activate and block Wnt/β-catenin signaling pathway. Transwell assay showed that the ability of cells containing si-MALAT1 and activation of Wnt/β-catenin signaling pathway was close to that of si-NC both for migration and invasion. The ability of cells containing si-MALAT1 and blockade of Wnt/β-catenin signaling pathway was lower than that of si-NC both for migration and invasion in SKOV3 (Figure 8A) and HO8910 cells (Figure 8B). This suggests that down-regulation of MALAT1 may inhibit the activation of the Wnt/ beta-catenin signaling pathway to inhibit the invasion and migration in ovarian cancer cells.

Discussion

LncRNAs are a member of ncRNAs and they are frequently observed in cancers involved in carcinogenesis and progression[22]. Increasing evidence showed that aberrant expression of lncRNAs has been identified in several human cancers, including ovarian cancer[23]. They may provide us with new biomarkers for the diagnosis and prognosis of cancers. The upregulation of MALAT1 promotes tumor metastasis in lung cancer[17] and glioblastoma[18]. Although previous researches showed that overexpression of MALAT1 acted as an oncogene in many cancers, the mechanism of MALAT1 in ovarian cancer has not yet been investigated. We detected the expression level of MALAT1 in ovarian cancer tissues, para-carcinoma tissues and ovarian cancer cell lines. The cell proliferation rate, invasion, migration activities, cell cycle distribution and apoptosis in SKOV3 and HO8910 cells after transfected with si-MALAT1 were measured. Moreover, blockade or activation of Wnt/β-catenin signaling pathway was used to analyze the effect on cell invasion and migration in ovarian cancer cell lines after transfected with si-MALAT1.

In our investigation, we found that MALAT1 was up-regulated in ovarian cancer tissues and

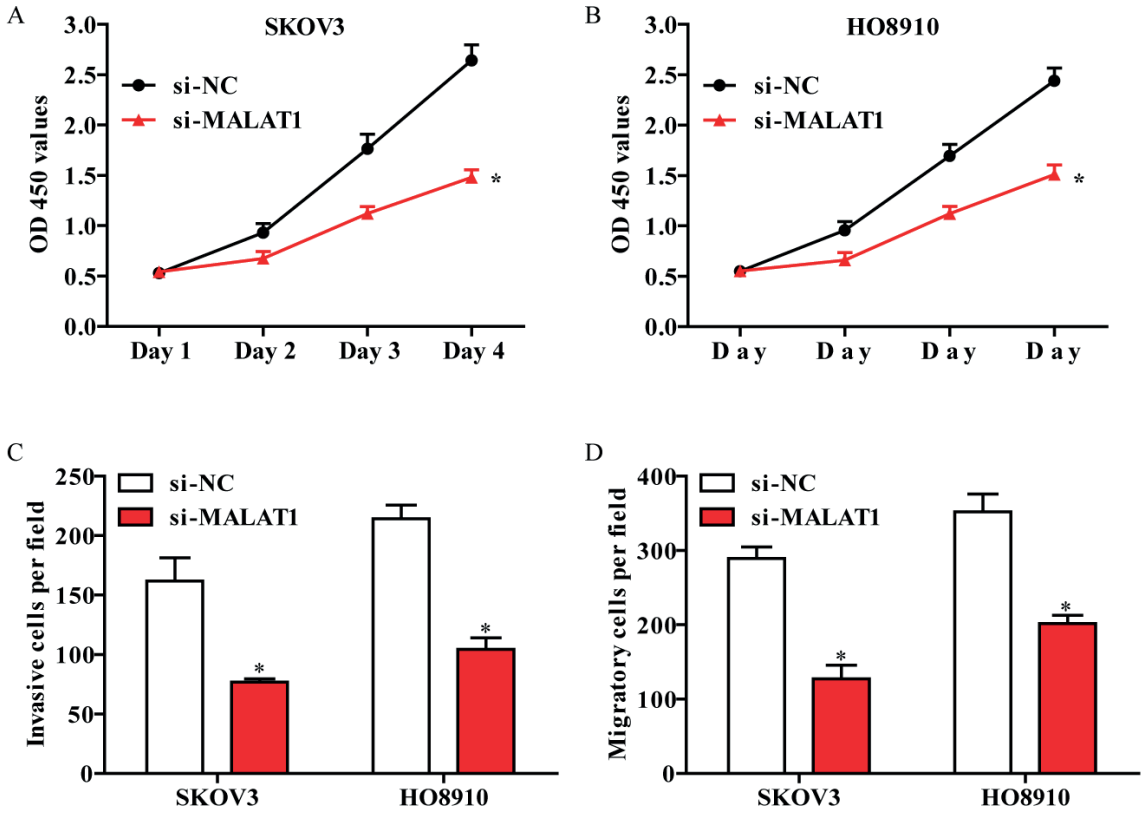

Figure 3. Down-regulation of MALAT1 inhibited cell proliferation, invasion and migration in ovarian cancer cell lines. ***A,*** The cell proliferation rate was detected by CCK8 assay in SKOV3 cells after transfected with si-NC or si- MALAT1. ***B,*** The cell proliferation rate was detected by CCK8 assay in HO8910 cells after transfected with si-NC or si- MALAT1. ***C,*** Down-regulation of MALAT1 inhibited cell invasion in SKOV3 and HO8910 cells. ***D,*** Down-regulation of MALAT1 inhibited cell migration in SKOV3 and HO8910 cells. Data are shown as mean ± SD based on at least three independent experiments, *$p<0.05$.

cell lines and that it was associated with the poor prognosis in ovarian cancer patients. The down-regulation of MALAT1 inhibited cell proliferation, invasion and migration, arrested cell cycle progression in S-phase and induced cell apoptosis in ovarian cancer cell lines. Meanwhile, the down-regulation of MALAT1 decreased the expression level of DVL2, β-catenin and cyclin D1 and increased the expression level of GSK-3β in SKOV3 and HO8910 cells. Moreover, the inhibitory effect of MALAT1 down-regulation in cell invasion and migration was reversed by SKL2001 activating Wnt/β-catenin signal pathway and enhanced by XAV939 inhibiting Wnt/β-catenin signal pathway.

Increasing evidence showed that MALAT1 may contribute to the development of cancers, gastric cancer proliferation and metastasis via miR-23b-3p[24]. Antisense MALAT1 inhibited choriocarcinoma cells proliferation, migration and invasion by targeting miR-218[25]. However, little research about the effect of lncRNA MALAT1 on ovarian cancer has been identified[16]. Liu et al[26] reported that the inhibition of MALAT1 inhibited tumorigenicity and induced apoptosis in human ovarian cancer SKOV3 cell line, but the mechanism was unclear.

The Wnt/β-catenin signaling pathway is involved in regulating cell proliferation, cell polarity and cell adhesion and other cellular activities[27]. Researches[28] have found that Wnt/β-catenin signaling pathway plays a key role in the occurrence and development of colorectal cancer, breast cancer, liver cancer and other malignant tumors. Abnormal activation of Wnt/β-catenin signaling pathway in cancer cells was related to the abnormal expression of Wnt protein and the nuclear transfer of β-catenin protein. In the nucleus, the combination of β-catenin and t-cell factors promotes the transcription of target genes, activates downstream genes, promotes the proliferation and inhibits apoptosis in tumor cells. At the same

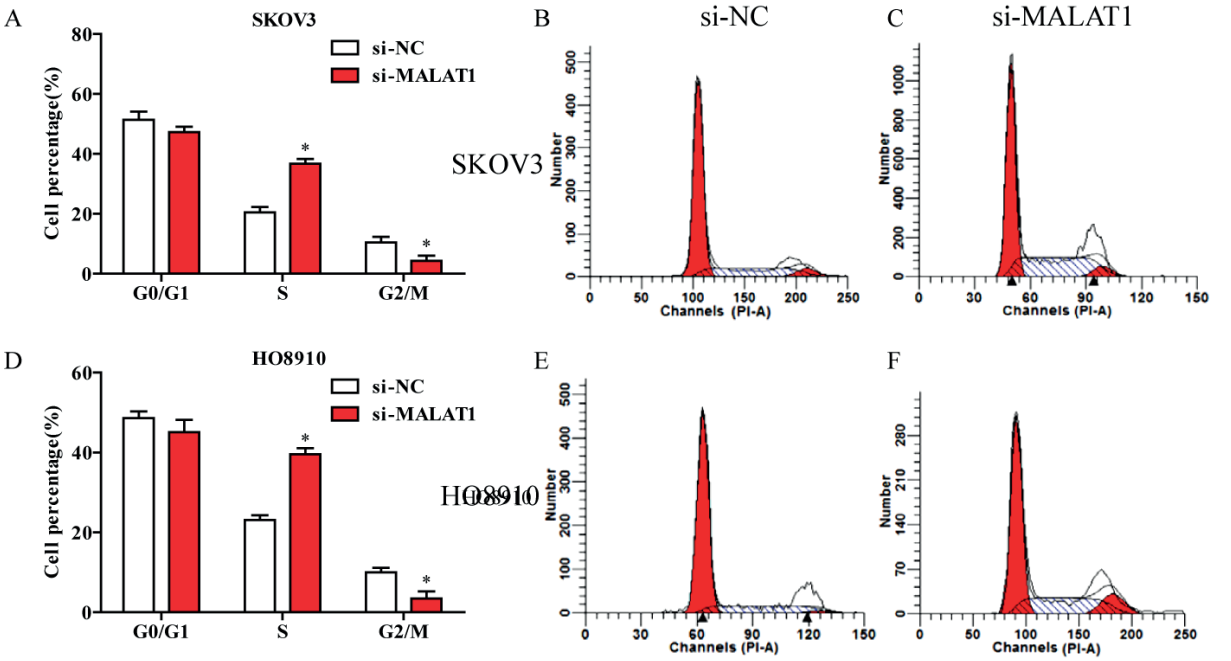

Figure 4. Down-regulation of MALAT1 arrested cell cycle progression in S-phase in ovarian cancer cell lines. A and *C*, The cell cycle distribution was detected by flow cytometry analysis in SKOV3 cells after transfected with si-NC or si- MALAT1. ***B*** and ***D*.** The cell cycle distribution was detected by flow cytometry analysis in HO8910 cells after transfected with si-NC or si- MALAT1. Data are shown as mean ± SD based on at least three independent experiments, **p*<0.05.

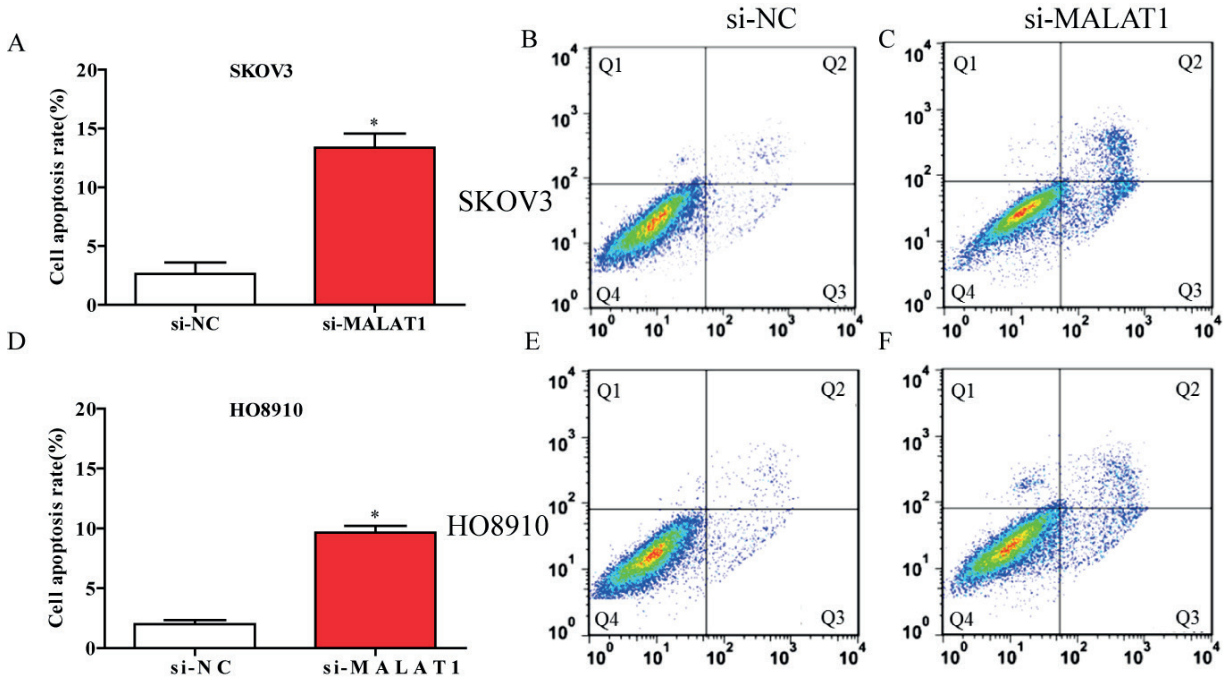

Figure 5. Down-regulation of MALAT1 induced cell apoptosis in ovarian cancer cell lines *A* and *C*. The cell apoptosis rate was detected by Flow cytometry analysis in SKOV3 cells after transfected with si-NC or si- MALAT1. ***B* and *D*.** The cell apoptosis rate was detected by Flow cytometry analysis in HO8910 cells after transfected with si-NC or si- MALAT1. Data are shown as mean ± SD based on at least three independent experiments, **p*<0.05.

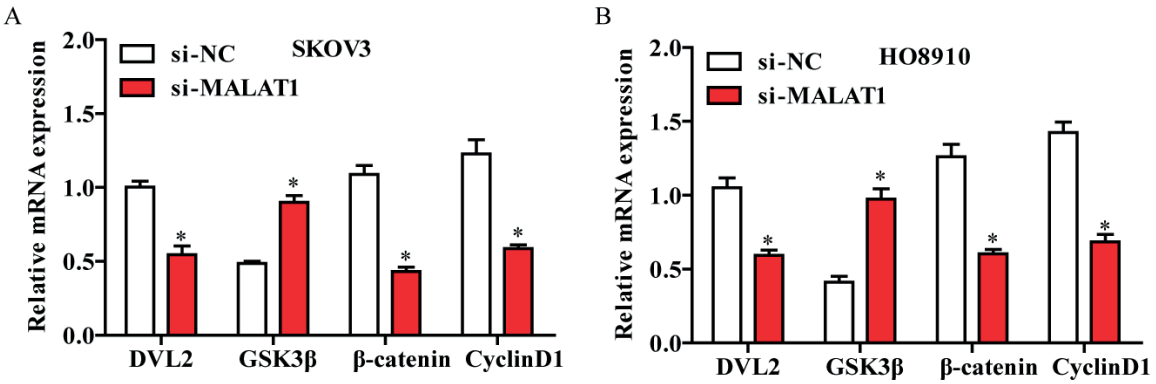

Figure 6. Down-regulation of MALAT1 regulated the Dvl2, GSK-3β, β-catenin and cyclin D1 mRNA expression in ovarian cancer cell lines *A*, The Dvl2, GSK-3β, β-catenin and cyclinD1 mRNA expressions were detected by RT-PCR in SKOV3 cells after transfected with si-NC or si- MALAT1. ***B*,** The Dvl2, GSK-3β, β-catenin and cyclinD1 mRNA expressions were detected by RT-PCR in HO8910 cells after transfected with si-NC or si- MALAT1. Data are shown as mean ± SD based on at least three independent experiments, **p*< 0.05.

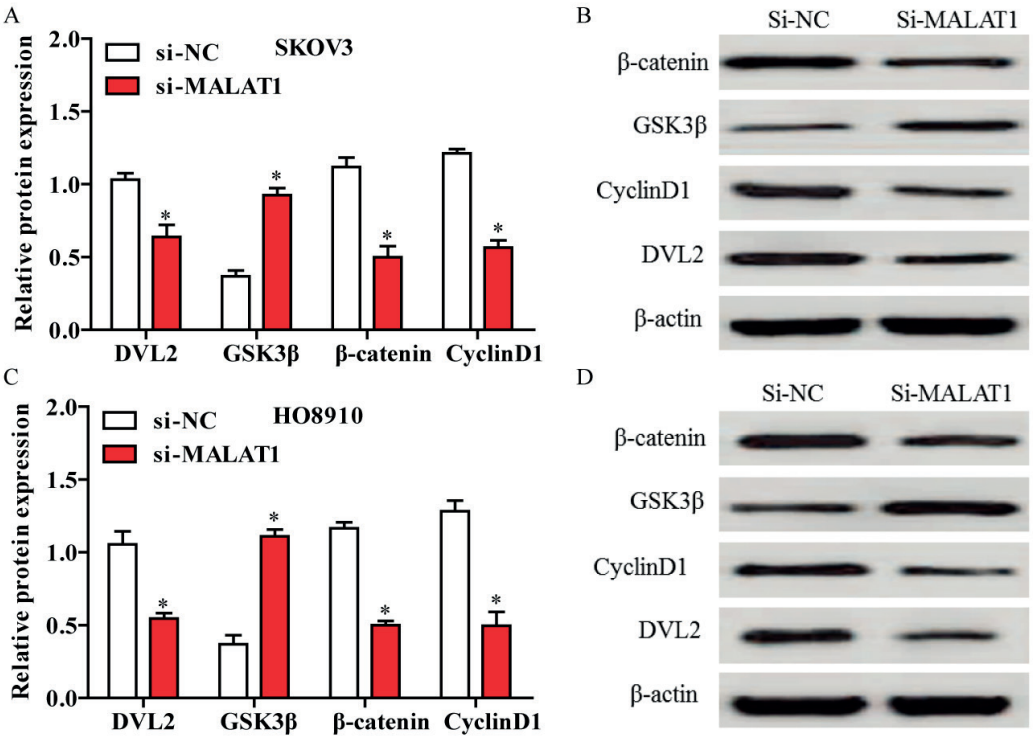

Figure 7. Down-regulation of MALAT1 regulated the Dvl2, GSK-3β, β-catenin and cyclinD1 protein expression in ovarian cancer cell lines *A-B*, The Dvl2, GSK-3β, β-catenin and cyclin D1 protein expressions were detected by Western blot in SKOV3 cells after transfected with si-NC or si- MALAT1. ***C-D*,** The Dvl2, GSK-3β, β-catenin and cyclinD1 mRNA expressions were detected by Western blot in HO8910 cells after transfected with si-NC or si- MALAT1. Data are shown as mean ± SD based on at least three independent experiments, **p*< 0.05.

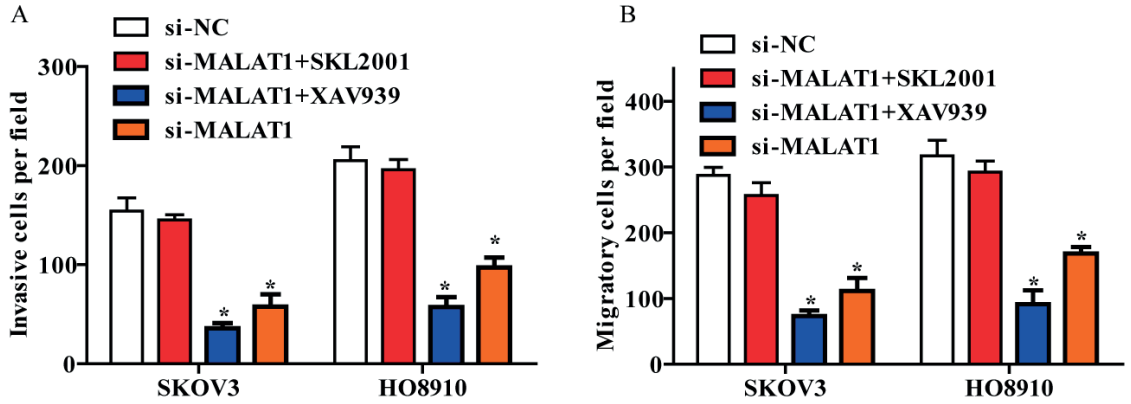

Figure 8. Blockade or activation of Wnt/β-catenin signaling pathway in ovarian cancer cell lines after transfected with si-MALAT1 affected cell invasion and migration *A*, Invasion activities were measured by transwell in SKOV3 and HO8910 cells after transfected with si-MALAT1 and with the blockade or activation of Wnt/β-catenin signaling pathway. ***B*,** Migration activities were measured by transwell in SKOV3 and HO8910 cells after transfected with si- MALAT1 and with the blockade or activation of Wnt/β-catenin signaling pathway. Data are shown as mean ± SD based on at least three independent experiments, *$p<0.05$.

time, several studies[29,30] have shown that the Wnt/β-catenin signaling pathway plays an important role in the occurrence and development of ovarian cancer. Wnt is a kind of cell growth factor, can promote Frz proteins expression and activate Dvl protein in cells to induce intracellular signal transduction and make GSK-3β phosphorylation and inhibit its activity[31]. β-catenin protein binds to e-cadherin to increase the adhesion between cells. In the cytoplasm, the β-catenin is transferred to the nucleus, which further activates the transcription of the downstream cyclin D1 and other target genes to increase the cell proliferation and migration ability. These target genes are involved in regulating the occurrence, development and metastasis in tumors. Researches have shown[32] that β-catenin was high expressed in patients with lung cancer and associated with the malignancy and invasion ability. In this work, down-regulation of MALAT1 may inhibit the activation of the Wnt/ beta-catenin signaling pathway to inhibit the invasion and migration in ovarian cancer cells.

Conclusions

The current research demonstrated that MALAT1 was overexpressed in ovarian cancer and associated with poor prognosis. Down-regulation of MALAT1 inhibited cell proliferation, invasion and migration, arrested cell cycle progression in S-phase and induced cell apoptosis by restraining the activation of Wnt/β-catenin signaling pathway in ovarian cancer cells.

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Conflict of Interest

The Authors declare that they have no conflict of interest.

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