European Review for Medical and Pharmacological Sciences 2019; 23: 8852-8860

LncRNA AOC4P affects biological behavior of gastric cancer cells through MAPK signaling pathway

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Abstract. – OBJECTIVE: Long non-coding RNA (lncRNA) is closely related to the occurrence and development of gastric cancer, but the mechanism and clinical significance of lncRNA AOC4P are still unclear. This study aimed to investigate the expression and function of lncRNA AOC4P in gastric cancer.

PATIENTS AND METHODS: Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) was used to detect the expression of lncRNA AOC4P in 80 gastric cancer tissues and adjacent normal tissues. MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide), flow cytometry and transwell assays were used to study the effects of lncRNA AOC4P on the proliferation, apoptosis, migration and invasion of gastric cancer cells. Western blot was used to detect the related protein level of the mitogen-activated protein kinase (MAPK) signal pathway.

RESULTS: The expression of lncRNA AOC4P in gastric cancer tissues was higher than that in adjacent tissues. OS or DFS time were significantly shortened in patients with gastric cancer with high expression of lncRNA AOC4P. Inhibition of lncRNA AOC4P expression can inhibit cell proliferation, migration and invasion, promoting cell apoptosis to some extent. Inhibition of lncRNA AOC4P expression also can result in the decreased expression levels of extracellular-signal-regulated kinase 1 (ERK1), c-Jun N-terminal kinases (JNK) and p38 proteins.

CONCLUSIONS: High expression of lncRNA AOC4P in gastric cancer may be related to the occurrence, development and prognosis of gastric cancer. LncRNA AOC4P is expected to become a new diagnostic marker and therapeutic target for gastric cancer.

Key Words:
LncRNA AOC4P, Gastric cancer, MAPK signaling pathway.

Introduction

Gastric cancer is one of the most malignant tumors in the world today, and the mortality caused by gastric cancer ranks second among various cancer types[1]. Although great progress has been made in the diagnosis and treatment of gastric cancer, its poor prognosis is still a serious problem. Statistics show that more than 70% of patients will eventually die of gastric cancer[2]. If we can find effective early diagnosis and prognostic markers, it will have important clinical value for improving the prognosis of gastric cancer, which may open up new ways for clinical prevention and treatment of gastric cancer. Liquid biopsy is considered to be a promising means of non-invasiveness, but the current positive rates for serum markers such as CEA, CA19-9 and CA72-4 are lower sensitivity[3], so it is urgent to find high specificity new markers for high sensitivity.

Long non-coding RNA (lncRNA) is a type of RNA between 200-100 000 nt, which is mainly located in the nucleus or cytoplasm of the cytoplasm and cannot encode proteins[4]. It has greatly promoted the research progress in the field of non-coding RNA. Recent studies[5-7] have found that lncRNA can participate in many important regulatory processes such as X chromosome silencing, genomic imprinting, chromatin modification, transcriptional activation, nuclear transport; lncRNA also play important roles in biological processes such as apoptosis, cell cycle and invasion[8-10]. Recently, the role of lncRNA in tumors has drawn attention. Zhang et al[11] collected and screened by genome-wide pro-

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filing microarray followed by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) analysis, and identified that lncRNA AOC4P was significantly upregulated in tumor tissues compared with adjacent normal tissues, but its role and mechanism in gastric cancer have not been reported. This study was an in-depth analysis of the differential expression and clinical significance of lncRNA AOC4P in gastric cancer. This work aimed to clarify the role of lncRNA AOC4P in gastric cancer, and provide new targets and new ideas for the development of new drugs for the treatment of gastric cancer.

Patients and Methods

Clinical Information

A total of 80 specimens of gastric cancer patients treated in our hospital from March 2014 to December 2017 were collected. After admission, the standard gastric cancer radical operation was performed. The tumor specimens were taken from the gastric cancer tissues within 30 min of the tumor specimens. All patients did not receive radiotherapy before surgery. This study was approved by the Ethics Committee of Shanxi Provincial People's Hospital. Informed consents were obtained from all participants before the study.

Total RNA Extraction

Tissue RNA was extracted using the TRIzol reagent (Invitrogen, Carlsbad, CA, USA), and the finally obtained RNA was dissolved in RNase-free water and stored at -80°C. The purity was measured by an ultraviolet spectrophotometer, and the integrity of the sample was identified by 1.5% agarose gel electrophoresis.

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

The cDNA was obtained by reverse transcription according to the reverse transcription kit instructions, and Real-Time fluorescence quantitative experiments were performed on the relevant indicators. Human glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as an internal reference, and each experiment was repeated three times. The ratio of the lncRNA AOC4P/GAPDH gene was used as the expression level of lncRNA AOC4P. The sequences of primers used for qRT-PCR of the lncRNA AOC4P are forward 5'-AAAGGAGGTGAGAGGGAATGT-3', reverse 5'-GCTGGGCACTGGGAGATAC-3'.

Cell Culture

The human GC cell lines HGC27, AGS, SGC-7901 and MGC803, and the immortalized human gastric epithelial cell line, GES-1, were purchased from the Chinese Academy of Sciences Committee on Type Culture Collection Cell Bank (Shanghai, China). The cells were cultured in Roswell Park Memorial Institute-1640 (RPMI-1640) complete medium (HyClone, South Logan, UT, USA) and cultured in a 37°C, 5% CO_2 cell culture incubator. The medium was changed every 2 days and passaged when the cells were fused at 80%-90%.

Cell Transfection

The cells were seeded in a 6-well plate for 24 h, and the cells were fused to 70% for transfection. The lncRNA AOC4P interference group (si-lncRNA AOC4P) and the negative transfection group (si-NC) were established. Lipofectamine 2000 was mixed with si-lncRNA AOC4P or si-NC (final concentration 100 nmol/L), added to the cells, incubated for 6 h, then replaced with complete RPMI-1640 for 24 h, and the cells were collected for subsequent experiments.

MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyl Tetrazolium Bromide) Assay for Cell Proliferation

The cells were plated at a density of 5,000 cells/well. The cells were stopped at 24, 48, and 72 h. 4 h before the termination of the culture, MTT solution (5 mg/mL; Sigma-Aldrich, St. Louis, MO, USA) was added, and the culture was continued to remove the medium in the wells. Dimethyl sulfoxide (DMSO) solution (Sigma-Aldrich, St. Louis, MO, USA) was added. The absorbance value (490 nm wavelength) of each well was measured by a microplate reader. The experiment was repeated three times.

Flow Cytometry for Apoptosis

Cells were taken at the logarithmic growth phase and centrifuged for 5 min, then washed twice with Phosphate-Buffered Saline (PBS; Gibco, Grand Island, NY, USA); 100 μL of the cell suspension was added to the flow. In the tube, 10 μL of Annexin-V-FITC (fluorescein isothiocyanate) was added, followed by 10 μL of Propidium Iodide (PI), and incubated for 15 min at room temperature in the dark. The apoptosis rate was detected by flow cytometry and the experiment was repeated 3 times (Partec AG, Arlesheim, Switzerland).

Transwell Assay for Cell Migration and Invasion

After transfection, each group of cells was resuspended in 150 μL of serum-free medium in log phase, and then added to the upper chamber of the transwell chamber. 500 μL of serum-containing complete medium was added to the lower chamber of transwell. The cell culture incubator was routinely cultured at 37°C for 48 h, the upper chamber culture solution was discarded, the upper chamber bottom membrane was removed, the non-penetrating upper chamber cells were removed, the methanol permeabilized cells were fixed for 15 min, and the PBS was washed 3 times. 1% crystal violet stained for 20 min, rinsing 3 times with PBS. The upper chamber bottom membrane was removed, and the cell migration ability was evaluated by light microscopic observation and counting through small pore cells. After diluting the Matrigel gel (BD Biosciences, Franklin Lakes, NJ, USA), 50 μL of each transwell chamber was added and incubated for 3 h at 37°C. In the same transwell method, the transfected cells were resuspended in the serum-free medium, inoculated into the upper chamber of the transwell chamber, and 500 μL of complete medium was added to the lower chamber. The chamber was taken out after 48 hours of routine culture. After unmasked cells were removed, methanol was fixed, stained with 1% crystal violet, photographed under a microscope and observed under a light microscope and counted through small-pore cells to evaluate cell invasion ability.

Western Blot

The total protein in each experimental group was extracted using radioimmunoprecipitation assay (RIPA) cell lysate (Beyotime, Shanghai, China), and the protein concentration was determined by the bicinchoninic acid (BCA) method (Pierce, Waltham, MA, USA). The protein was separated by polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to a polyvinylidene difluoride (PVDF) membrane (Millipore, Billerica, MA, USA), and blocked with 5% skim milk powder in Tris-HCl buffer for 1 h. The primary antibody diluted 1:1500 was incubated overnight at 4°C shaker. The membrane was washed with Tris-Buffered Saline and Tween 20 (TBST; Sigma-Aldrich, St. Louis, MO, USA) for 15 min 3 times, then added with goat anti-rabbit antibody (1:5000), incubated for 1 h at room temperature and washed for 15 min with TBST. After 3 times, an enhanced chemiluminescence reagent (ECL; Thermo Fisher Scientific, Waltham, MA, USA) reagent was added dropwise, and exposed and developed using an infrared fluorescent instrument. The expression level of the target protein was expressed as the internal reference with the expression level of GAPDH.

Statistical Analysis

All statistical analyses were performed using Statistical Product and Service Solutions (SPSS) 17.0 (SPSS, Chicago, IL, USA). Data are expressed as $x \pm s$ and statistical analysis using Student's *t*-test. $p<0.05$ was considered statistically significant.

Results

Expression of LncRNA AOC4P in Gastric Cancer

To explore the expression level of lncRNA AOC4P in gastric cancer, the expression of lncRNA AOC4P in gastric cancer tissues and adjacent normal tissues was detected by RT-PCR. As shown in Figure 1A, the expression level of lncRNA AOC4P was observed to be elevated in tumor tissues compared to normal tissues. In addition, the highly expressed lncRNA AOC4P is associated with the clinical pathological staging of tumors. As shown in Figure 1B, the expression of lncRNA AOC4P in advanced gastric cancer (stage III and IV) is significantly higher than that in early gastric cancer (stage I and II) tissues ($p<0.01$). However, the expression level of lncRNA AOC4P was not markedly correlated with age, sex, tumor location and tissue type ($p>0.05$). The relationship between the expression level of lncRNA AOC4P and OS in gastric cancer patients was analyzed (Figure 1C). The results showed that the expression of lncRNA AOC4P had a significant effect on the overall survival of gastric cancer patients. The overall survival time of patients with high expression of lncRNA AOC4P was remarkably shortened. Further analysis of the effect of lncRNA AOC4P expression on DFS in patients showed that DFS time was significantly shortened in patients with high expression of lncRNA AOC4P (Figure 1D).

Downregulation of LncRNA AOC4P by Small Interfere RNA (siRNA)

To explore the possible biological significance of lncRNA AOC4P in the development of gas-

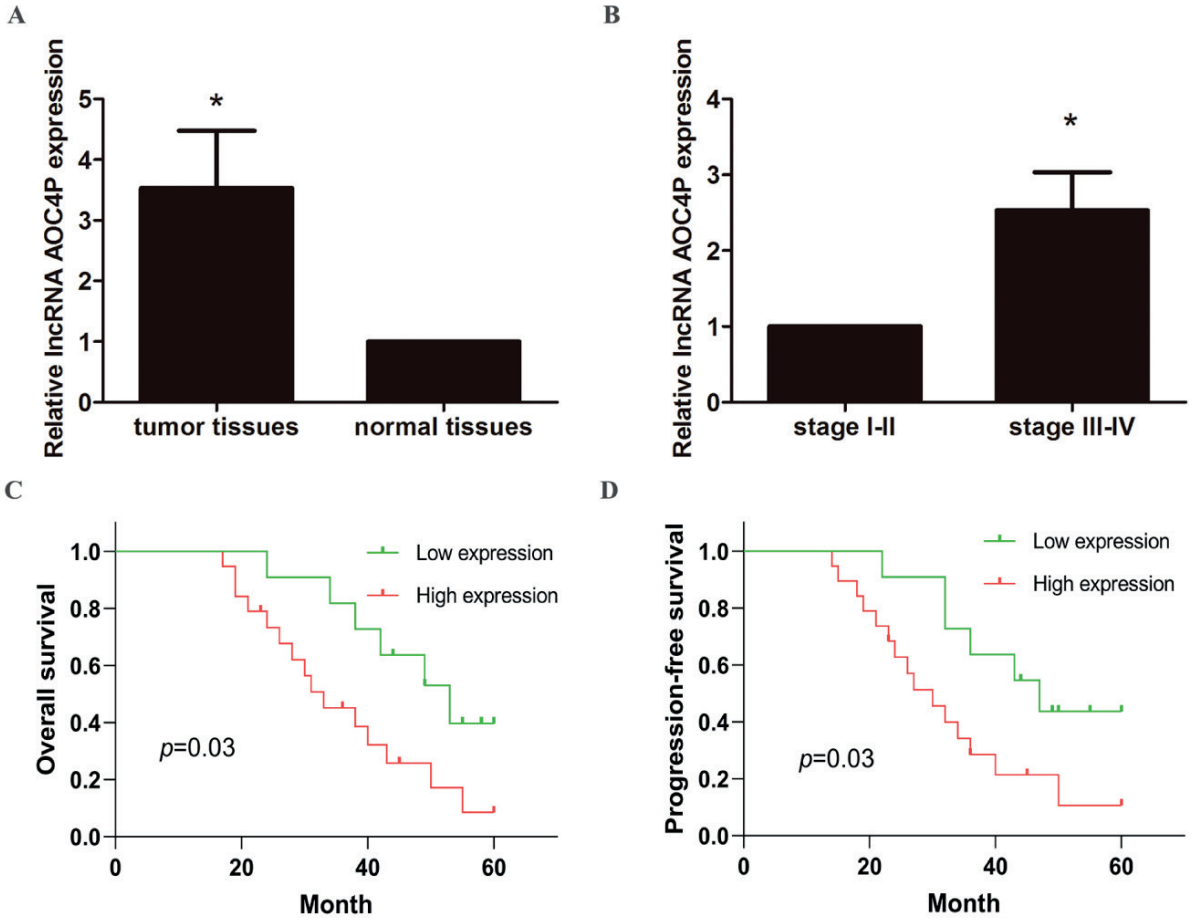

Figure 1. Expression of lncRNA AOC4P in gastric cancer. **A,** The expression of lncRNA AOC4P in gastric cancer tissues and adjacent normal tissues was detected by qPCR. **B,** The expression of lncRNA AOC4P in advanced gastric cancer (stage III and IV) and early gastric cancer (stage I and II) tissues were detected by qPCR. **C,** The relationship between the expression level of lncRNA AOC4P and OS in gastric cancer patients was analyzed. **D,** Further analysis of the effect of lncRNA AOC4P expression on DFS in patients.

tric cancer, this study evaluated the effect of lncRNA AOC4P on gastric cancer cells. First, the expression of lncRNA AOC4P in gastric cancer cell lines (SGC-7901, AGS, MGC803 and HCG-27) and the immortalized human gastric epithelial cell line (GES-1) was measured. The results showed that the expression of lncRNA AOC4P in cancer cell line was markedly higher than that in GES-1 (Figure 2A, $p<0.05$). The lncRNA AOC4P-siRNA was used to inhibit the expression of lncRNA AOC4P. The inhibition efficiency of lncRNA AOC4P was over 70% (Figure 2B, 2C), and there was significant statistical difference compared with the NC group, indicating that the inhibition effect of subsequent experiments was significant and reliable.

Effects of LncRNA AOC4P on Biological Behavior of Gastric Cancer Cells

To determine whether the biological behavior of gastric cancer cells after lncRNA AOC4P expression was changed, the abilities of cell proliferation, apoptosis, migration and invasion in NC and lncRNA AOC4P-siRNA groups were evaluated. Figure 3A, 3B showed that downregulated lncRNA AOC4P can inhibit the proliferation of gastric cancer cells to some extent. Figure 3C, 3D showed that downregulated lncRNA AOC4P can promote the apoptosis of gastric cancer cells to some extent. At the same time, as shown in Figure 3E, the cell migration ability of the lncRNA AOC4P-siRNA group was inhibited to some extent compared with the NC group. As

shown in Figure 3F, the cell invasive ability of the lncRNA AOC4P-siRNA group was inhibited to some extent compared with the NC group. Based on the above results, this experiment confirmed that the down-regulation of lncRNA AOC4P exerts a tumor suppressive effect in gastric cancer cell lines.

Activation of MAPK Signaling Pathway by LncRNA AOC4P

The effect of lncRNA AOC4P on the expression of MAPK pathway protein in gastric cancer cells was detected by Western blot. The results of the experiment showed that after transfection of lncRNA AOC4P-siRNA, the expression levels of ERK1, JNK and p38 proteins were significantly lower than those in the NC group (Figure 4A, 4B). It was shown that inhibition of lncRNA AOC4P can affect the expression of downstream ERK1, JNK and p38 protein levels to regulate the function of the corresponding MAPK signaling pathway.

Discussion

Gastric cancer is a common malignant tumor of the digestive tract in China. Most of the patients have advanced stages when diagnosed, the proportion of radical resection is less, and the incidence of local recurrence and distant metastasis is high. The treatment effect is poor and has become a serious threat. So far, the relevant mechanisms for the occurrence and development of gastric cancer remain unclear.

In recent years, the prospects for clinical application of lncRNAs have received great attention. LncRNA was originally thought to be the "noise" of genomic transcription, a by-product of RNA polymerase II transcription, and does not have any biological function. More and more studies[12-14] have shown that lncRNA plays an important role in tumorigenesis. With the advancement of high-throughput sequencing technology, the discovery of a large number of lncRNAs has been promoted, but only a few lncRNAs have been

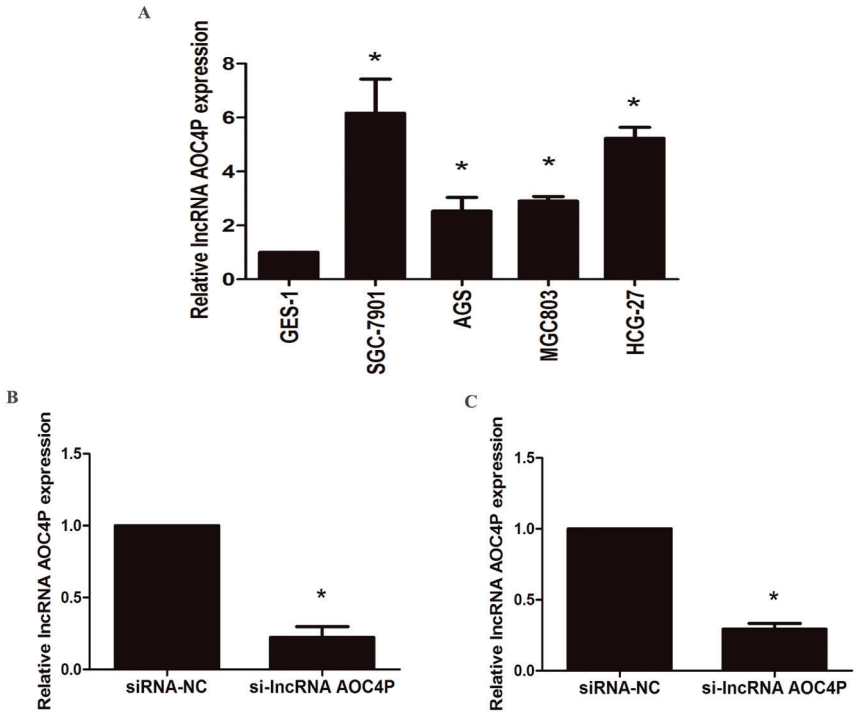

Figure 2. Downregulation of lncRNA AOC4P by small interfere RNA (siRNA). **A,** The expression of lncRNA AOC4P in gastric cancer cell lines (SGC-7901, AGS, MGC803 and HCG-27) and the immortalized human gastric epithelial cell line (GES-1) were measured. **B-C,** The expression level of lncRNA AOC4P-siRNA was used to inhibit the expression of lncRNA AOC4P by qPCR.

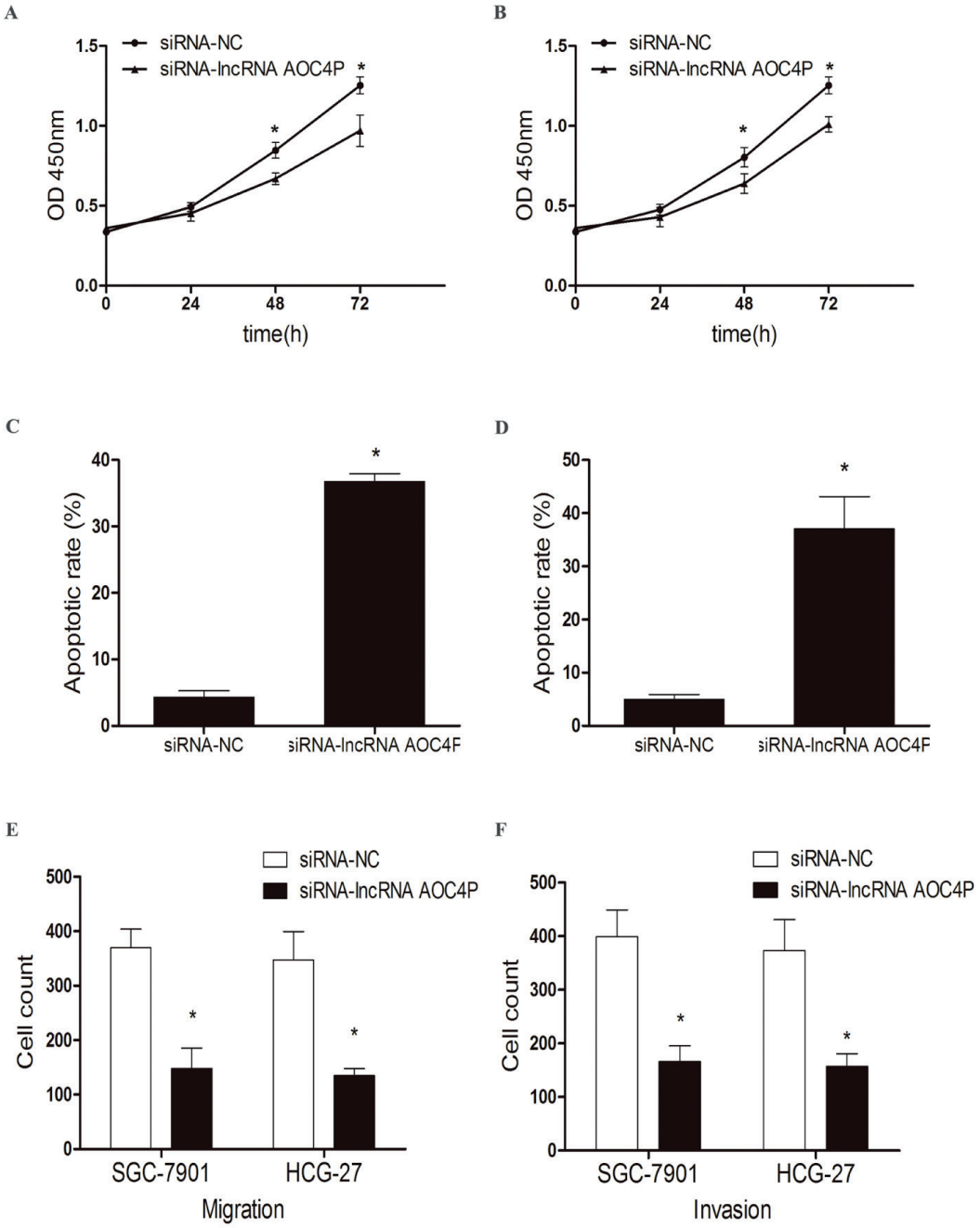

Figure 3. Effects of lncRNA AOC4P on biological behavior of gastric cancer cells. **A-B,** the changes in cell proliferation in NC and lncRNA AOC4P-siRNA groups were evaluated by MTT assay. **C-D,** Cell apoptosis in NC and lncRNA AOC4P-siRNA groups were detected by Flow cytometry. **E-F,** Cell migration and invasion in NC and lncRNA AOC4P-siRNA groups were investigated by transwell assay.

studied in gastric cancer, including SNHG14, HOTAIR, and H19. For example, high expression of SNHG14 is closely related to lymph node metastasis and clinical stage, suggesting a poor prognosis for patients[15,16]. Through this work, we have discovered a new lncRNA-AOC4P involved in the development of gastric cancer.

In this study, it was gradually demonstrated that lncRNA AOC4P is highly expressed in gastric cancer tissues and cell lines, and inhibition of lncRNA AOC4P can inhibit the proliferation and promote the apoptosis of gastric cancer cells *in vitro*, which can inhibit the migration and invasion behavior of gastric cancer cells to some extent. These findings

indicate that lncRNA AOC4P plays a significant tumorigenic role in gastric cancer.

Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) family members function in a cell context-specific and cell type-specific manner to integrate signals that affect proliferation, differentiation, survival and migration. Consistent with the importance of these events in tumorigenesis, JNK and p38 MAPK signaling is associated with cancers in humans[17-19]. Here, we found that inhibition of lncRNA AOC4P can regulate the expression of downstream ERK1, JNK and p38 proteins and regulate the function of the corresponding MAPK signaling pathway. Our results provide reliable evidence for the functional study of lncRNA AOC4P in human gastric cancer.

Conclusions

We examined the expression of lncRNA AOC4P in gastric cancer tissues and observed

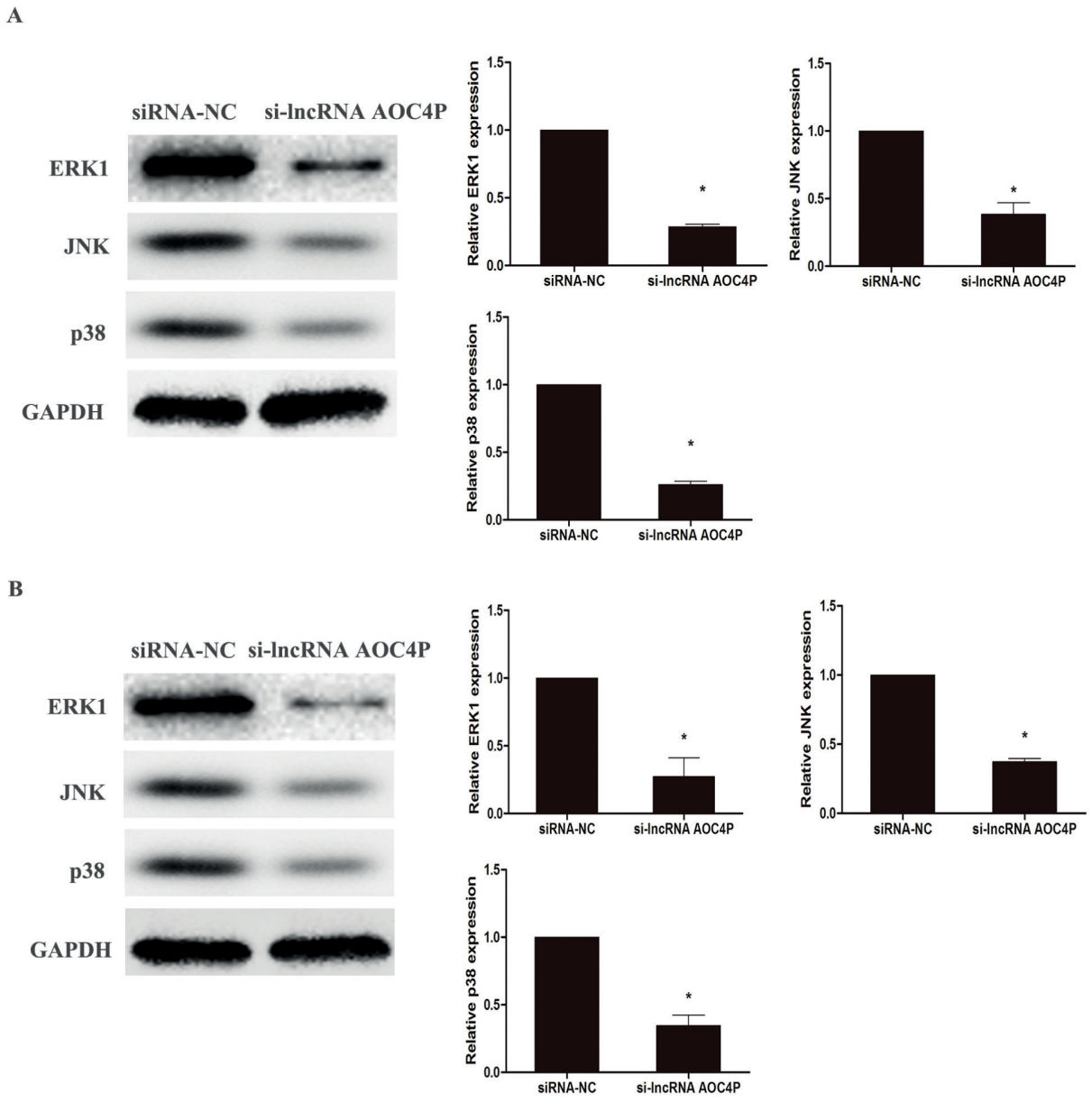

Figure 4. Activation of MAPK signaling pathway by lncRNA AOC4P. **A-B,** The effect of lncRNA AOC4P on the expression of MAPK pathway protein in gastric cancer cells was detected by Western blot.

that lncRNA AOC4P is closely related to the occurrence and development of gastric cancer, and can be used as a reliable indicator for prognosis. It is expected to provide a new target for the treatment of gastric cancer.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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