

Knockdown of ST7-AS1 inhibits migration, invasion, cell cycle progression and induces apoptosis of gastric cancer

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Abstract. Role of ST7-AS1 in the malignant progression of gastric cancer (GC) and its molecular mechanisms were investigated. ST7-AS1 level in GC tissues and matched normal tissues was determined by quantitative real-time polymerase chain reaction (qRT-PCR). Its level in GC patients presenting different tumor stages and tumor sizes was determined. Subsequently, ST7-AS1 level in epithelial cells of gastric mucosa and GC cell lines was examined. Cellular behavior of GC cells, including viability, apoptosis, migration, invasion and cell cycle, influenced by ST7-AS1 was evaluated. The interaction between ST7-AS1 and EZH2 was assessed by RNA immunoprecipitation (RIP) assay. The involvement of EZH2 in the progression of GC mediated by ST7-AS1 was identified. ST7-AS1 was upregulated in GC tissues and cell lines. Its level was positively correlated to tumor stage and tumor size of GC. Knockdown of ST7-AS1 attenuated proliferative, migratory and invasive abilities, arrested cell cycle progression and induced apoptosis of GC cells. EZH2 was identified to interact with ST7-AS1, which attenuated the regulatory effects of ST7-AS1 on migratory and invasive abilities of GC cells. Upregulated ST7-AS1 in GC accelerated proliferation, migration and invasion, and inhibited apoptosis, thus aggravating the progression of GC.

Introduction

Gastric cancer (GC) is a malignant tumor originating from the gastric mucosa. It ranks the first in tumor incidence of Chinese population. Regional difference is observed in the incidence of GC. The northwest and eastern coastal areas of China are high incidence regions of GC (1). GC mainly affects people over 50 years, with the male-female ratio of 2:1. Recently, the incidence of GC becomes younger owing to changes in environmental and dietary habits, overloaded working and

increased infection rate of *Helicobacter pylori* (2). GC occurs in any part of the stomach, and more than half of GC cases structurally involve the gastric antrum (3). Based on the pathological classification, the majority of GC belongs to adenocarcinoma. Early-stage symptoms of GC are atypical, manifesting as similar symptoms of gastritis and gastric ulcer, such as upper abdominal discomfort and hernia (4). Unfortunately, detective rate of early-stage GC is low, leading to a poor prognosis of GC patients (5). The overall survival of GC remains at 20%, which is a global health problem (6). Advanced GC has an extreme poor prognosis, with <15% of 5-year survival (7). Development of effective and sensitive hallmarks for GC contributes to improving the clinical outcome of the affected (8).

Long non-coding RNAs (lncRNAs) are transcribed by RNA polymerase II with >200 nucleotides in length. They are a research focus on tumor-targeted therapy (9). lncRNAs are dysregulated in tumors, and mediate oncogenes or tumor-suppressor genes to further influence tumor progression (10). They exert diverse functions in regulating cellular behavior (11). In tumor biology, lncRNAs have been widely explored since they are capable of regulating drug-resistance and malignant phenotypes of tumor cells (12,13). Tumor-related lncRNAs may be promising targets applied in tumor detection (14).

EZH2 encodes a histone lysine N-methyltransferase that is involved in DNA methylation to inhibit transcription of other genes. EZH2 also methylates H3K27me3 (15). The methylation activity of EZH2 promotes heterochromatinization and thus silences downstream genes (16). Mutation or overexpression of EZH2 is associated with multiple types of cancers (17-21). Abnormally activated EZH2 can inhibit expression of tumor-suppressor genes. Therefore, inhibition of EZH2 activity is able to alleviate tumor growth (22).

This study explored the biological function of lncRNA ST7-AS1 in the malignant progression of GC. The potential interaction between ST7-AS1 and EZH2 was investigated, which may provide new directions for developing therapeutic strategies for GC.

Patients and methods

Subjects. GC tissues and matched adjacent normal tissues were surgically harvested from GC patients in The Fourth Affiliated Hospital of China Medical University (Shenyang,

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China) from April 2016 to October 2018. Resected samples were placed into liquid nitrogen until analyses. Enrolled GC patients were pathologically diagnosed and had no medical history of other malignancies. This study was approved by the Ethics Committee of The Fourth Affiliated Hospital of China Medical University and informed consent was received from each subject.

Cell culture and transfection. Epithelial cells of gastric mucosa (GES-1) and GC cell lines (AGS, MG803 and SGC-7901) provided by American Type Culture Collection (ATCC) were cultured in Roswell Park Memorial Institute-1640 (RPMI-1640) containing 10% fetal bovine serum (FBS) (both from HyClone) and 1% penicillin-streptomycin in a 5% CO₂ incubator at 37°C. Prior to transfection, cells were seeded in a 6-well plate with 1x10⁴ cells/well. Serum-free medium (1.5 ml) and 0.5 ml of Lipofectamine™ 2000 (Invitrogen; Thermo Fisher Scientific, Inc.) containing transfection vectors were mixed. At 75-85% confluence, 2.0 ml of transfection mixture was applied in each well. Complete medium was replaced 4-6 h later.

Western blot analysis. Total protein was extracted from cells or tissues using radioimmunoprecipitation assay (RIPA) and loaded for electrophoresis (Beyotime). After transferring on a polyvinylidene fluoride (PVDF) membranes (Millipore), it was blocked in 5% skim milk for 2 h, incubated with primary antibodies at 4°C overnight and secondary antibodies for 2 h. Bands were exposed by electrochemiluminescence (ECL) and analyzed by Image Software (NIH).

RNA extraction and quantitative real-time polymerase chain reaction (qRT-PCR). RNA extraction was performed using TRIzol method (Invitrogen; Thermo Fisher Scientific, Inc.). The extracted RNA was quantified and reverse transcribed into complementary deoxyribose nucleic acid (cDNA), followed by PCR using SYBR-Green method (Takara). QRT-PCR was performed at 94°C for 5 min, and 40 cycles at 94°C for 30 sec, 55°C for 30 sec and 72°C for 90 sec.

Cell counting kit-8 (CCK-8) assay. Cells were seeded in a 96-well plate with 2x10³ cells/well. Absorbance (A) at 450 nm was recorded at the appointed time points using the CCK-8 kit (Dojindo Laboratories) for depicting the viability curve.

Apoptosis determination. Apoptotic rate in GC cells was determined through calculating caspase-3 activity using a relevant commercial kit (Beyotime).

Flow cytometry. Cells were fixed in 75% ethanol at 4°C overnight, and washed with phosphate-buffered saline (PBS) twice. After incubation with RNase A at 37°C for 30 min, cells were dyed with propidium iodide (PI). Cell cycle distribution was finally analyzed by FACSCalibur flow cytometry (BD Biosciences).

RNA immunoprecipitation (RIP). Cells were treated according to the procedures of Millipore Magna RIP™ RNA-Binding Protein Immunoprecipitation Kit (Millipore). Cell lysate was incubated with anti-EZH2 or IgG antibody 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. The magnetic beads were repeatedly washed with RIP washing buffer to remove non-specific adsorption as much as possible. Finally, the extracted RNA was subjected to mRNA level determination using qRT-PCR.

Transwell assay. Fifty microliters of FN (100 µg/ml) was coated in the bottom of Transwell chambers. Cell density was adjusted to 1x10⁶/ml. One hundred microliters of suspension was applied to the upper chamber of Transwell chambers (Millipore) pre-coated with 100 µl of diluted Matrigel (BD Biosciences). Into the lower chamber, 600 µl of medium containing 10% FBS was applied. After 48 h of incubation, invasive cells were fixed in methanol for 30 min and dyed with 0.1% crystal violet for 10 min. Invasive cells were captured and counted in 6 randomly selected fields per sample. Migration assay was similarly performed except for Matrigel pre-coating.

Statistical analysis. Statistical Product and Service Solutions (SPSS) 19.0 software (IBM Corp.) was used for data analyses. Data were expressed as mean ± standard deviation. Intergroup differences were analyzed by the t-test. P<0.05 was considered statistically significant.

Results

Upregulation of ST7-AS1 in GC. Expression pattern of ST7-AS1 in GC tissues was examined. As qRT-PCR revealed, ST7-AS1 was upregulated in GC tissues relative to normal ones (Fig. 1A). Moreover, ST7-AS1 level was higher in GC tissues of >5 cm in size than those ≤5 cm (Fig. 1B). Higher level of ST7-AS1 was observed in GC patients with stage III-IV compared with those with stage I-II (Fig. 1C). It indicated that ST7-AS1 was involved in the progression of GC.

Knockdown of ST7-AS1 suppresses viability, arrests cell cycle and induces apoptosis of GC. Compared with epithelial cells of gastric mucosa, ST7-AS1 was upregulated in GC cells, especially in AGS and SGC-7901 cells (Fig. 2A). Three transfection vectors of sh-ST7-AS1 (sh-ST7-AS1 1#, sh-ST7-AS1 2# and sh-ST7-AS1 3#) were tested for their transfection efficacy. QRT-PCR data revealed pronounced transfection efficacy in the former two vectors (Fig. 2B). In AGS and SGC-7901 cells transfected with sh-ST7-AS1 1# or sh-ST7-AS1 2#, the viability greatly decreased compared with controls (Fig. 2C and D). Apoptotic rate was elevated by transfection of sh-ST7-AS1 1# or sh-ST7-AS1 2# (Fig. 2E). Moreover, cell ratio in G0/G1 phase was enhanced after transfection of sh-ST7-AS1 1# or sh-ST7-AS1 2# in GC cells, indicating arrested cell cycle progression (Fig. 2F).

Knockdown of ST7-AS1 suppressed migratory and invasive abilities of GC. After transfection of sh-ST7-AS1 1# or sh-ST7-AS1 2# in AGS and SGC-7901 cells, Transwell assay illustrated attenuated migratory and invasive abilities relative to controls (Fig. 3).

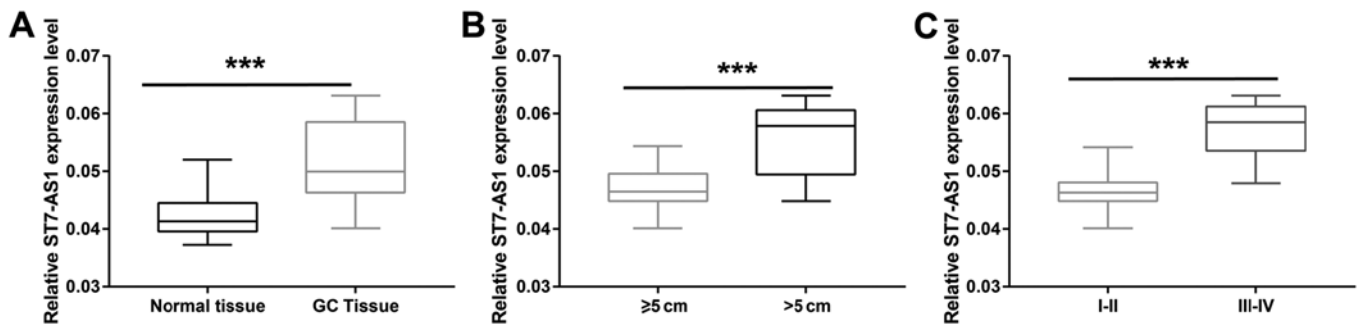


Figure 1. Upregulation of ST7-AS1 in GC. (A) Relative level of ST7-AS1 in GC tissues and matched normal tissues. (B) Relative level of ST7-AS1 in GC tissues >5 cm in size and those ≤5 cm. (C) Relative level of ST7-AS1 in GC patients in stage II-IV and stage I-II. ***P<0.001.

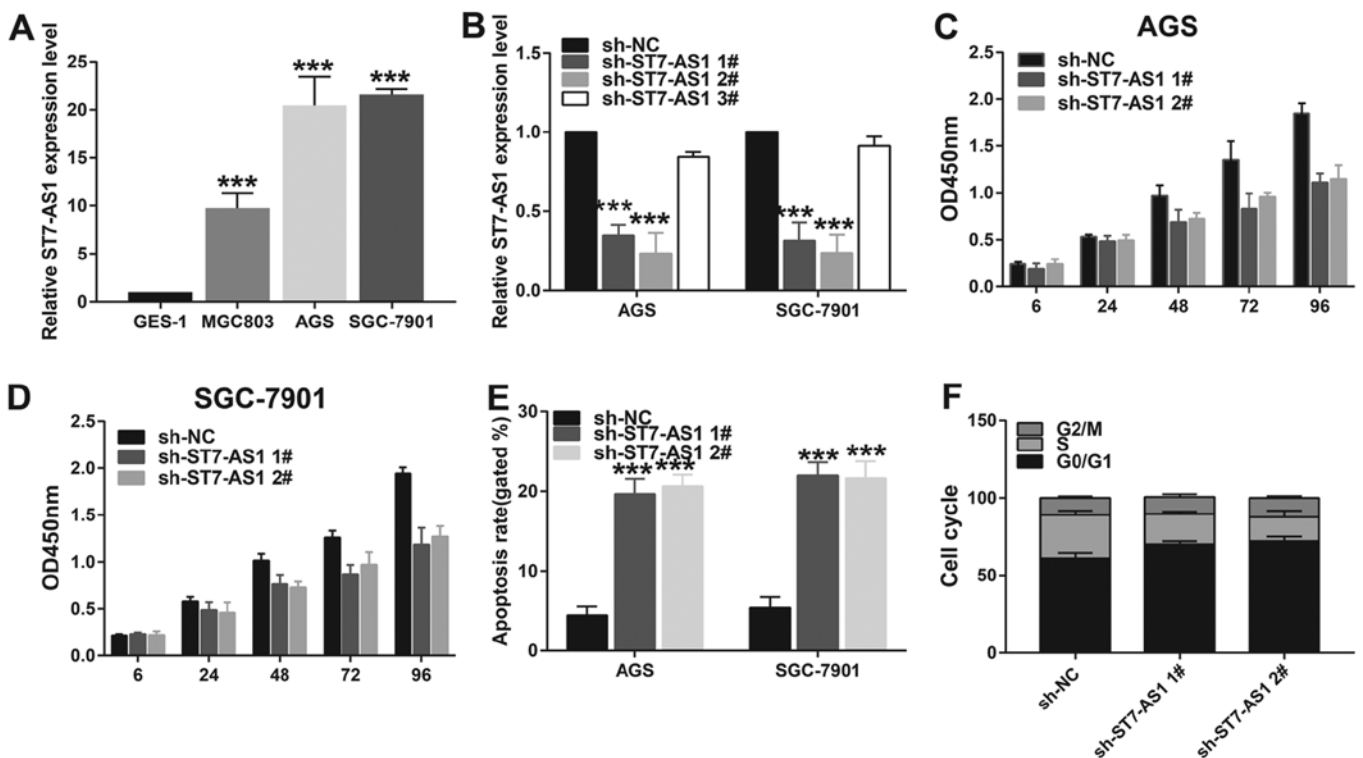


Figure 2. Knockdown of ST7-AS1 suppresses viability, arrests cell cycle and induces apoptosis of GC. (A) Relative level of ST7-AS1 in epithelial cells of gastric mucosa (GES-1) and GC cell lines (AGS, MG803 and SGC-7901). (B) Transfection efficacy of sh-ST7-AS1 1#, sh-ST7-AS1 2# and sh-ST7-AS1 3# in AGS and SGC-7901 cells. (C) CCK-8 showed viability in AGS cells transfected with sh-NC, sh-ST7-AS1 1# or sh-ST7-AS1 2#. (D) CCK-8 showed viability in SGC-7901 cells transfected with sh-NC, sh-ST7-AS1 1# or sh-ST7-AS1 2#. (E) Apoptotic rate in AGS and SGC-7901 cells transfected with sh-NC, sh-ST7-AS1 1# or sh-ST7-AS1 2#. (F) Cell cycle distribution in AGS and SGC-7901 cells transfected with sh-NC, sh-ST7-AS1 1# or sh-ST7-AS1 2#. CCK-8, cell counting kit-8; GC, gastric cancer. ***P<0.001.

ST7-AS1 mediates cellular behavior of GC via interacting with EZH2. To uncover the molecular mechanism of ST7-AS1 in regulating cellular behavior of GC, RIP assay was conducted to assess the potential interaction between ST7-AS1 and EZH2. ST7-AS1 was greatly enriched in anti-EZH2 antibody relative to control IgG, verifying the interaction between ST7-AS1 and EZH2 (Fig. 4A). Transfection of sh-EZH2 markedly downregulated protein level of EZH2, presenting an effective transfection efficacy in GC cells (Fig. 4B). Interestingly, the attenuated migratory and invasive abilities of GC cells transfected with sh-ST7-AS1 1# were further inhibited by co-transfection of sh-EZH2 (Fig. 4C). It is indicated that ST7-AS1 accelerated GC cells to migrate and invade via interacting with EZH2.

Discussion

GC is a common malignancy worldwide, especially in China (23). Recently, identification of novel therapeutic hallmarks of GC have been widely conducted (24). GC is characterized by infinitely excessive proliferation and growth of tumor cells (25). Oncogene activation and tumor-suppressor gene inactivation are the main causes of tumorigenesis (26). Traditional treatments for GC include surgery, chemotherapy and radiotherapy. These therapeutic strategies destroy normal tissues and cells while destroying tumor tissues (27). In addition, the development of chemotherapy-resistance markedly limits the therapeutic efficacy of GC (28). Hence, it is urgent to search for effective targets for GC treatment.

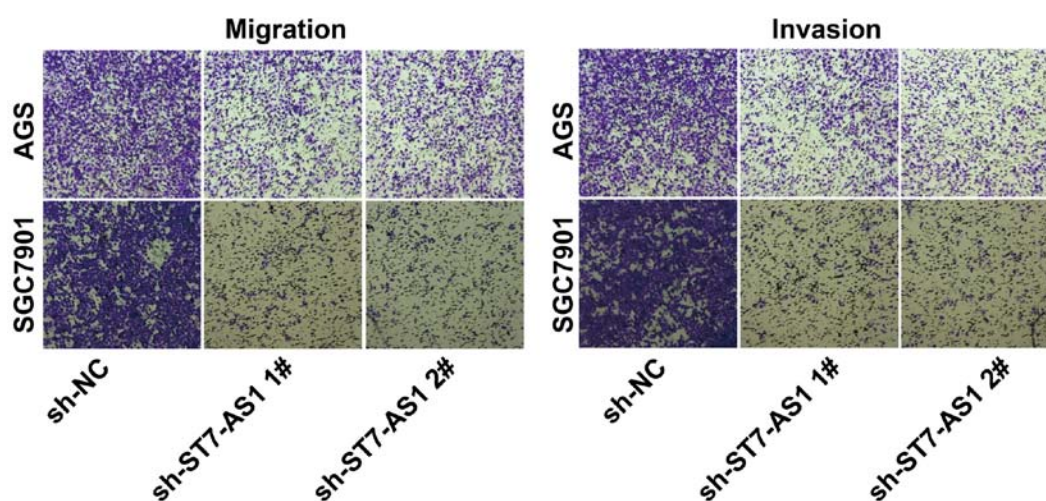


Figure 3. Knockdown of ST7-AS1 suppressed migratory and invasive abilities of GC. Transwell assay showed migration (left) and invasion (right) in AGS and SGC-7901 cells transfected with sh-NC, sh-ST7-AS1 1# or sh-ST7-AS1 2#. GC, gastric cancer; AGS, GC cell lines.

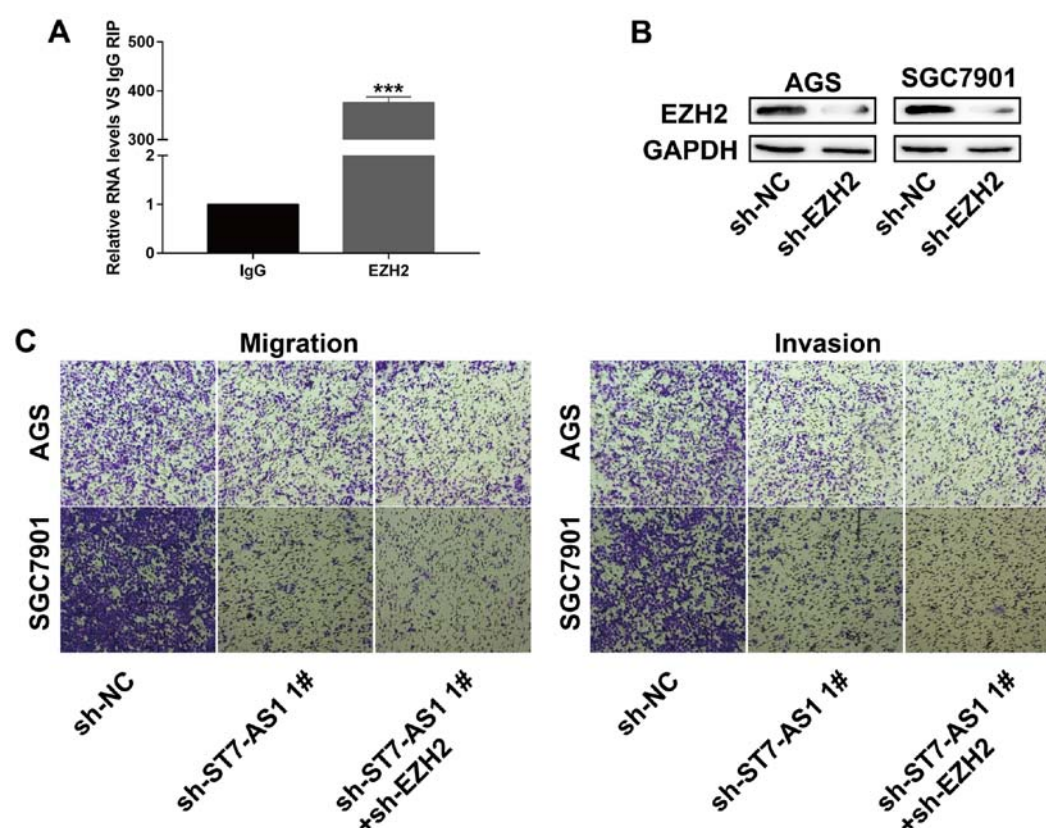


Figure 4. ST7-AS1 mediated cellular behavior of GC via interacting with EZH2. (A) RIP assay of the enrichment of ST7-AS1 in anti-IgG and anti-EZH2. (B) Transfection efficacy of sh-EZH2 in AGS and SGC-7901 cells. (C) Transwell assay of migration and invasion in AGS and SGC-7901 cells transfected with sh-NC, sh-ST7-AS1 1# or sh-ST7-AS1 1#+sh-EZH2. GC, gastric cancer; AGS, GC cell lines; RIP, RNA immunoprecipitation. *** $P < 0.001$.

lncRNAs barely encode proteins, but mediate gene expression at multiple levels (29,30). Increasing evidence has proven the role of lncRNAs in tumor progression (31). They are capable of mediating epigenetic regulation and cellular behavior (32). lncRNA ST7-AS1 is a newly discovered one located on 7q31.2 (33). In this study, ST7-AS1 was upregulated in GC tissues and cell lines. ST7-AS1 level was higher in GC patients with worse tumor stage and larger tumor size, indicating its carcinogenic role in GC. Moreover, knockdown

of ST7-AS1 attenuated proliferative, migratory and invasive abilities, arrested cell cycle and induced apoptosis of GC cells.

Epigenetic modifications are involved in gene expressions of tumor-related molecules. Polycomb repressive complex 2 (PRC2) regulates transcription of target genes mainly by trimethylation of H3K27me3 (34). Multiple studies have shown that EZH2 is the methylation enzyme subunit of PRC2. Overexpression or mutation of EZH2 can induce

tumorigenesis and promote tumor progression (35). EZH2 is able to mediate multiple pathological processes in cells, such as cell cycle, cell senescence, and cell differentiation (36).

The present study confirmed the interaction between ST7-AS1 and EZH2 through RIP assay. Subsequently, we speculated whether EZH2 was involved in the malignant progression of GC regulated by ST7-AS1. Notably, the decreased migratory and invasive abilities in GC cells with ST7-AS1 knockdown were further attenuated by EZH2 knockdown. Collectively, ST7-AS1 mediated malignant phenotypes of GC cells via interacting with EZH2.

In conclusion, upregulated ST7-AS1 in GC accelerated proliferative, migratory and invasive abilities, and inhibited apoptosis, thus aggravating the progression of GC. lncRNA ST7-AS1 could be utilized as a promising target for improving clinical outcomes of GC patients.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

SC and FM designed the study and performed the experiments, SC and YW collected the data, FM and PL analyzed the data, SC and FM prepared the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of The Fourth Affiliated Hospital of China Medical University (Shenyang, China). Signed informed consents were obtained from the patients and/or guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare they have no competing interests.

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