# miR-502-5p inhibits the proliferation, migration and invasion of gastric cancer cells by targeting SP1

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**Abstract.** Gastric cancer (GC) is the third most common cause of cancer-associated mortality in China. Aberrant microRNA (miR) expression can occur through multiple biological processes and has been implicated in cancer development. However, to the best of our knowledge, the function of miR-502-5p in GC is currently unclear. In the present study, the expression and function of miR-502-5p in GC was evaluated. Reverse transcription-quantitative (RT-q) PCR was used to measure the expression levels of miR-502-5p in GC tissues, normal adjacent tissues, a normal human gastric epithelial cell line (GES-1) and two GC cell lines. miR-502-5p expression levels were significantly lower in GC tissues and GC cell lines compared with those in adjacent normal tissues and GES-1 cells, respectively. Subsequently, the target genes of miR-502-5p were predicted, and it was demonstrated that the transcription factor SP1 was a direct target. SP1 expression, cell viability, migration and invasion, and SP1 protein levels were examined using RT-qPCR, an MTT assay, Transwell assay and western blotting, respectively. Human GC cells were then transfected with an miR-502-5p mimic to emulate miR-502-5p overexpression, resulting in inhibition of the proliferation, migration and invasion capacities of human GC cells. Compared with the negative control, cells overexpressing miR-502-5p had decreased levels of SP1 mRNA and protein. These data suggest that miR-502-5p serves as a tumor suppressor gene by targeting SP1 to regulate the proliferation, migration and invasion of GC cells.

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## Introduction

Gastric cancer (GC) is the second most commonly diagnosed cancer among men and the third among women, and it was the second leading cause of cancer-associated death worldwide in 2015 (1). Due to the lack of specific early symptoms, the majority of patients are not diagnosed until they have advanced stage GC. The overall prognosis of patients with GC is poor and the 5-year survival rate is <30% (2-4). GC is a heterogeneous disease characterized by different molecular and histological profiles (5), therefore it is important to identify novel sensitive and specific biomarkers for early diagnosis. In addition, a more comprehensive understanding of tumor suppressor genes may provide novel insight into GC therapeutics.

MicroRNAs (miRNAs/miRs) are a conserved group of single-stranded non-coding RNAs that are 17-25 nucleotides long (6). miRNAs directly bind to the 3'-untranslated region of their target mRNA to regulate gene expression after transcription, thereby inhibiting translation or inducing mRNA degradation (7). miRNAs are involved in carcinogenesis, including tumor initiation and disease progression (8,9). In cancer, miRNAs can function as oncogenes or tumor suppressors depending on the function of its target gene (10,11). Recent studies have demonstrated that several miRNAs are involved in tumor occurrence and can function as oncogenes or tumor suppressor genes in GC (12-14). For example, miR-6852 functions as a tumor suppressor by directly targeting forkhead box J1 in gastric cancer (13). In addition, by targeting the B cell lymphoma-2 gene, miR-744 can promote apoptosis in the GC cell line SGC-7901 (14). Therefore, it is important to explore the molecular mechanisms underlying miRNA function in GC to promote the development of targeted therapies.

The purpose of the present study was to investigate the expression levels and function of miR-502-5p and its molecular mechanisms in GC.

## Materials and methods

*Tissue samples, cells and reagents.* Between July 2017 and February 2018, 32 samples of GC and adjacent tissues (5 cm away from tumor tissue) were obtained from patients,

including 19 male and 13 female subjects, and the median age was 57 years (age range, 35-84 years). All patients underwent gastrectomy at the Changhai Hospital of Naval Medical University (Shanghai, China). Tissue samples from the patients with GC were immediately flash frozen in liquid nitrogen following resection at -196˚C. The Changhai Hospital Ethics Committee (Shanghai, China) approved the present study and all patients provided written informed consent.

AGS and MKN45 human GC cells and GES human normal gastric cells were purchased from the American Type Culture Collection. AGS, MKN45 and GES-1 cells were cultured in RPMI-1640 medium (Hyclone; GE Healthcare Life Sciences) containing 10% fetal bovine serum (Hyclone; GE Healthcare Life Sciences), 100 IU/ml penicillin and 100 $\mu$g/ml streptomycin.

*microRNA and cell transfection*. miR-502-5p mimic and miR-502-5p-mimic negative control (NC) was purchased from Shanghai GenePharma Co., Ltd. The microRNA was transfected into GC cells using Lipofectamine 2000 reagent (Thermo Fisher Scientific Inc.) according to the manufacturer's protocol. The time interval between transfection and subsequent experimentation was 48 h.

*RNA and reverse transcription-quantitative (RT-q)PCR*. Total RNA was extracted from the patient tissue samples, and AGS, MKN45 and GES cells using TRIzol® reagent (Invitrogen; Thermo Fisher Scientific Inc.). miR-502-5p expression levels were measured using a TaqMan microRNA assay kit (Takara Bio. Inc.) according to the manufacturer's instructions, using U6 as an internal control. Total RNA was then reverse transcribed into cDNA using a Prime Script RT reagent kit (Takara Bio. Inc.) according to the manufacturer's instructions. SYBR-Green (Takara Bio. Inc.) was used to determine SP1 mRNA expression relative to β-actin. The thermocycling conditions for qPCR were as follows: 95˚C for 5 min followed by 40 cycles of 95˚C for 10 sec, 60˚C for 30 sec. The primers were designed as follows: miR-502-5p forward, 5'-CGGGCATCCTTGCTATCTG-3' and reverse, 5'-CAGCCACAAAAGAGCACAAT-3'; U6 forward, 5'-CTCGCTTCGGCAGCACA-3' and reverse, 5'-AACGCTTCACGAATTTGCGT-3'; SP1 forward, 5'-TGGCAGCAGTACCAATGGC-3' and reverse, 5'-CCAGGTAGTCCTGTCAGAACTT-3'; and β-actin forward, 5'-CCTGGCACCCAGCACAAT-3' and reverse: 5'-GGGCGGGACTCGTCATAC-3'. Each sample was analyzed in triplicate and levels were quantified using the $2^{-\Delta\Delta Cq}$ method (15).

*MTT cell proliferation assay*. AGS and MKN45 cells were transfected with miR-502-5p mimics or NC for 24 h as aforementioned. AGS and MKN45 cells were collected and $5x10^3$ cells per well were seeded into 96-well plates in triplicate. Following 1-4 days in the incubator at 37˚C with an atmosphere of 5% $CO_2$, 10 $\mu$l MTT assay solution was added to each well for 4 h at 37˚C. Next, 100 $\mu$l DMSO was added to each well for 30 min to dissolve the purple formazan, and optical density was measured at 490 nm with a microplate reader (Bio-Rad Laboratories, Inc.).

*Migration and invasion Transwell assays*. In the migration assay, $1x10^5$ cells were plated in 200 $\mu$l serum-free medium in the top Transwell chamber. In the invasive assay, $1x10^5$ cells were plated in 200 $\mu$l serum-free medium in the top Transwell chamber with a Matrigel-coated membrane. The matrigel was pre-coated at 37˚C for 30 min. In both the migration and invasion experiments, 500 $\mu$l medium containing 10% FBS was added into the lower chamber as a chemoattractant. After 24 h, the cells on the top surface of the Transwell chamber were removed using cotton swabs. The cells on the bottom surface were fixed at room temperature with 100% methanol for 30 min, and then stained with 0.05% crystal violet for 30 min at room temperature. Five visual fields were randomly selected to photograph with an Olympus IX51 light microscope (Olympus Corporation; magnification, x20).

*Western blot analysis*. Transfected AGS and MKN45 cells were lysed with RIPA buffer (Cell Signaling Technology, Inc.) containing complete protease inhibitor cocktail (Roche Diagnostics), phosphatase inhibitors (Roche Diagnostics), 5 mM dithiothreitol (DTT, Sigma-Aldrich; Merck KGaA) and 1 mM phenyl methyl sulfonyl fluoride (Sigma-Aldrich; Merck KGaA). The supernatant of the cell lysate was collected and protein concentrations were determined using the bicinchoninic protein assay kit (Thermo Fisher Scientific Inc.) according to the manufacturer's instructions. Then 20 $\mu$g protein was loaded onto a 10% gel, resolved using SDS-PAGE and transferred onto PVDF membranes. Membranes were then blocked with 5% fat-free milk for 2 h at room temperature. Subsequently, membranes were incubated with primary antibodies against SP1 (1:1,000; cat. no. WL02251; Wanleibio Co., Ltd.) and β-actin (1:1,000; cat. no. P30002M; Abmart Pharmaceutical Technology Co., Ltd.) at 4˚C overnight, washed three times with TBST (0.05% Tween-20) and incubated with anti-mouse horseradish peroxidase-conjugated secondary antibody (1:2,000; cat. no. 7054S; Cell Signaling Technology, Inc.) at room temperature for 2 h. Following three washes with TBST, immunoreactive bands were visualized using ECL working fluid (Biochannel, Nanjing, China; http: //www.biochannel.cn/page19.html?product_id=299). This experiment was repeated three times.

*Identification of miR-502-5p target genes*. Target Scan version.7.2 (http: //www.targetscan.org/), miRanda version.2010 (http: //www.microrna.org/microrna/getGeneForm.do) and miRBase version.22.1 (http: //www.mirbase.org/) were used to predict the candidate target genes of miR-502-5p.

*Statistical analysis*. All data are expressed as the mean ± standard deviation, and statistical analyses were performed using SPSS version 17.0 (SPSS, Inc.). Student's paired t-tests were used for comparisons between two groups and one-way ANOVA followed by Tukey's post hoc test was used for multiple comparisons. $P<0.05$ was considered to indicate a statistically significant difference.

## Results

*Expression of miR-502-5p in GC tissues and cells*. Expression levels of miR-502-5p in 32 GC tissues and two GC cell lines were analyzed using RT-qPCR. The expression level of miR-502-5p in GC tissues was significantly lower compared with those in matched normal adjacent tissues ($P<0.05$;

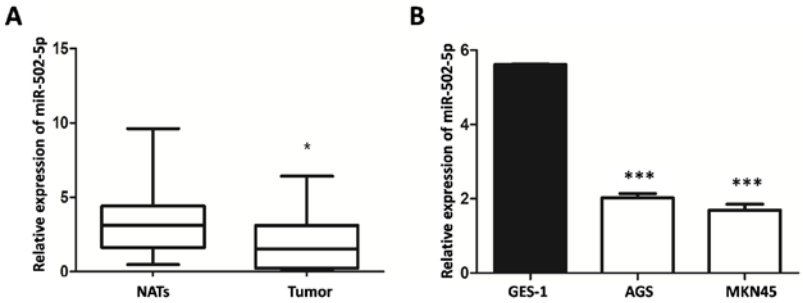


Figure 1. Expression of in miR-502-5p gastric cancer tissues and cells. (A) Expression of miR-502-5p in gastric cancer tissues compared with NATs. *P<0.05 vs. NATs. (B) Expression of miR-502-5p in GC cells compared with GES-1 cells. ***P<0.001 vs. GES-1. NATs, normal adjacent tissues; miR-502-5p, microRNA-502-5p.

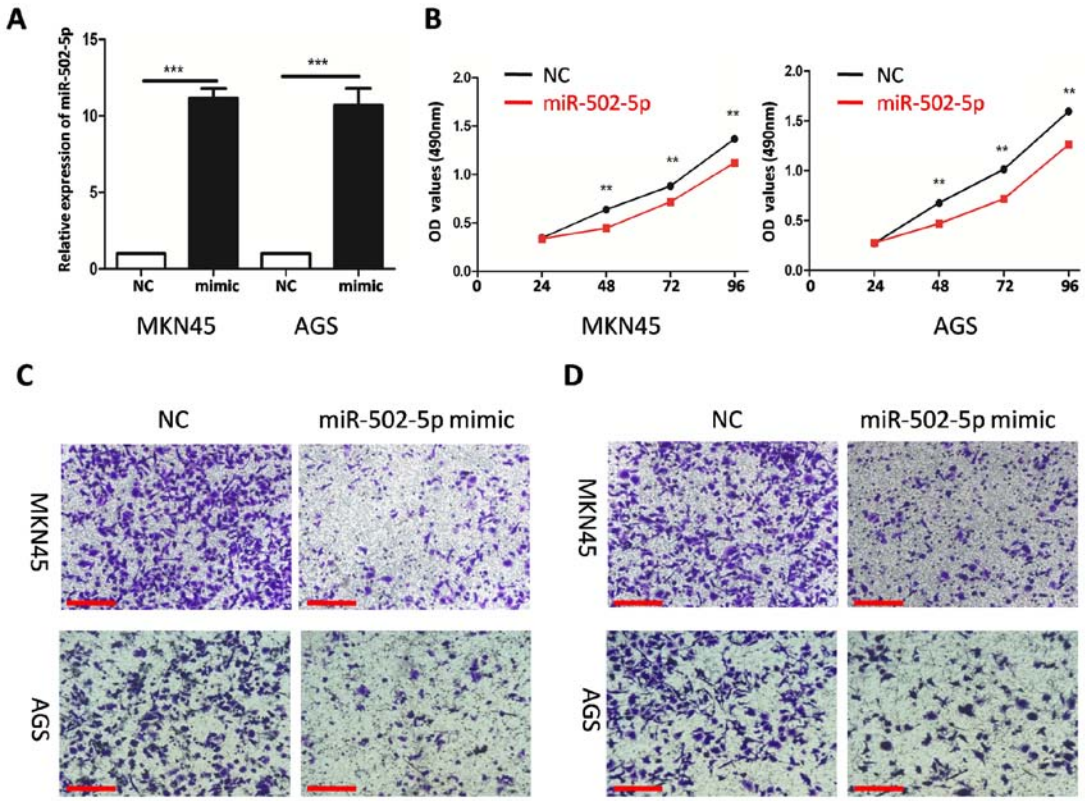


Figure 2. miR-502-5p inhibits the proliferation, migration and invasion of MKN45 and AGS cells. (A) miR-502-5p expression was evaluated in MKN45 and AGS cells transfected with miR-502-5p mimic or NC. ***P<0.001. (B) Effect of miR-502-5p on the proliferation of MKN45 and AGS cells was determined using an MTT assay. **P<0.01 vs. miR-502-5p mimic. Effects of miR-502-5p on the (C) migration and (D) invasion of MKN45 and AGS cells were determined using a Transwell assay. Scale bar=200 $\mu$m. miR, microRNA; NC, negative control; OD, optical density.

Fig. 1A). Compared with normal GES-1 gastric epithelial cells, the two GC cell lines exhibited significantly lower miR-502-5p expression (P<0.001; Fig. 1B).

*miR-502-5p inhibits the proliferation, migration and invasion of GC cells*. To study the effect of miR-502-5p on GC cells, NC or mimics of miR-502-5p were transfected into MKN45 and AGSGC cells. The transfection efficiency of miR-502-5p was evaluated using RT-qPCR. The level of miR-502-5p in MKN45 and AGS cells transfected with miR-502-5p mimics was significantly higher compared with those transfected with NC (both P<0.001; Fig. 2A). Overexpression of miR-502-5p significantly decreased proliferation at all time points compared with the NC group (all P<0.01; Fig. 2B) and reduced the cellular migration and invasion capacities of MKN45 and AGSGC cells (Fig. 2C and D).

*miR-502-5p targets SP1*. To investigate the molecular mechanism underlying miR-502-5p-mediated inhibition of GC progression, target genes of miR-502-5p were predicted using miRNA prediction software and databases. Target Scan 7.2, miR and a 2010 and miR Base 22.1 predicted that SP1 is a target gene of miR-502-5p. The mRNA level of SP1 decreased significantly in AGS and MKN45 cells transfected with miR-502-5p mimic (P<0.05

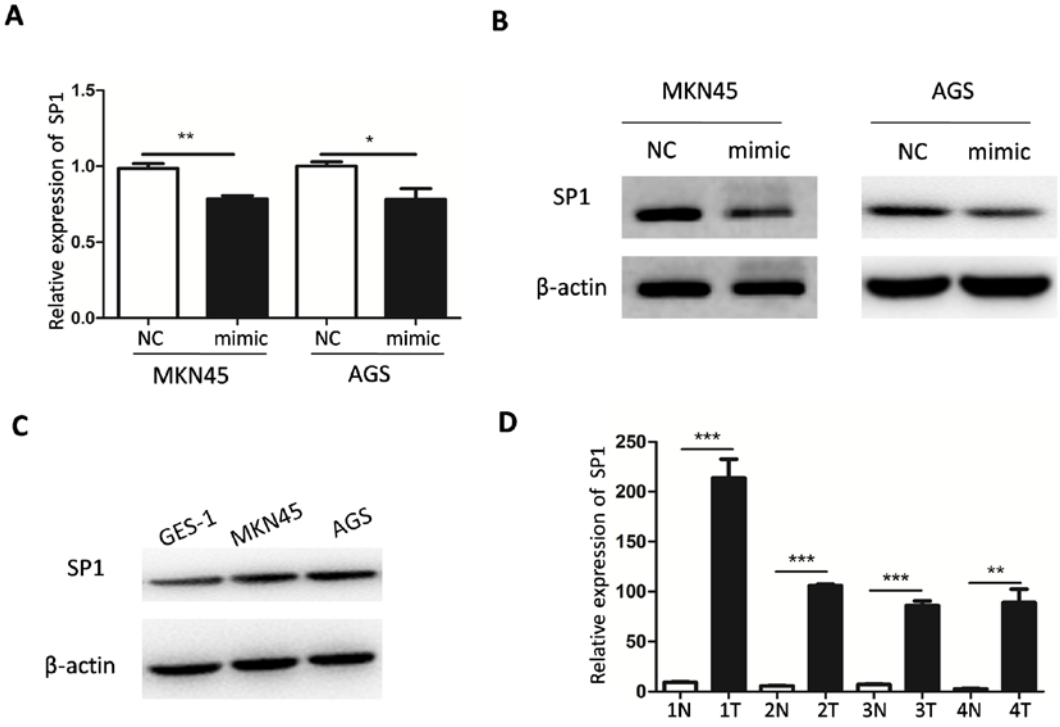


Figure 3. miR-502-5p targets SP1. (A) Expression of SP1 mRNA in AGS and MKN45 cells transfected with miR-502-5p mimic or NC was detected using reverse transcription quantitative-PCR. (B) Expression of SP1 protein in AGS and MKN45 cells transfected with miR-502-5p mimic or NC was analyzed using western blotting. (C) Expression of SP1 protein was evaluated in AGS and MKN45 gastric cancer cell lines and the GES-1 cell line. (D) Expression of SP1 mRNA was evaluated in four gastric cancer tissue samples. $^{*}$P<0.05, $^{**}$P<0.01, $^{***}$P<0.001. miR, microRNA; NC, negative control; T, tumor; N, normal.

and P<0.01, respectively, Fig. 3A). In addition, western blotting demonstrated that the protein level of SP1 was lower in AGS and MKN45 cells transfected with miR-502-5p mimics compared with the controls. SP1 levels were also evaluated in GC cells. Compared with GES cells, the expression of miR-502-5p in AGS and MKN45 cells was lower (Fig. 1B), but the expression of SP1 was higher (Fig. 3C). The mRNA expression level of SP1 in four sets of tumor tissues was significantly higher compared with that in normal paracancerous tissues (Fig. 3D). This suggests that SP1 is targeted by miR-502-5p in GC.

## Discussion

In GC, miRNAs are considered as novel potential diagnostic biomarkers, prognostic factors and therapeutic targets (16). Abnormal expression of miRNAs in GC has previously been reported (13,14). However, the specific role and subsequent underlying molecular mechanisms of miR-502-5p in GC remain unclear. To the best of our knowledge, the present study is the first to report the expression, biological function and molecular mechanism of miR-502-5p in GC. The level of miR-502-5p was downregulated in GC tissues and cell lines, and, in functional analyses, miR-502-5p significantly decreased the proliferative, migratory and invasive properties of GC cells.

Aberrant expression of miR-502-5p is associated with tumorigenesis and is a tumor suppressor in hepatocellular carcinoma, breast and colon cancer (17-19). In hepatocellular carcinoma cells, miR-502-5p significantly inhibits proliferation *in vitro* and tumor growth *in vivo* by targeting phophatidylinositor-4, 5-bisphosphate 3-kinase catalytic subunit ɣ (17). It has been reported that miR-502-5p expression in MCF-7 and MDA-MB-231 cells is low, and miR-502-5p can promote apoptosis and inhibit the proliferation of breast cancer cells *in vitro* by binding to the tumor necrosis factor receptor-associated factor 2 (TRAF2) gene in breast cancer (18). Another study indicated that miR-502 can inhibit autophagy, proliferation and cell cycle progression in colon cancer cells *in vitro*. Furthermore, miR-502 can inhibit colon cancer progression in mouse tumor xenografts models *in vivo* (19). These previous studies suggest that miR-502 may be implicated in tumor progression.

SP1 is a ubiquitous transcription regulator in human cells that regulates proliferation, apoptosis and embryonic development (20). SP1 also promotes the invasion and metastasis of tumor cells by regulating cell adhesion protein matrix metalloproteinase, urokinase-type plasminogen activator and micro-vessel density in tumors (21). SP1 is abnormally expressed in gastric cancer cells and participates in the proliferation and apoptosis of these cells (22); however, the relationship between SP1 and tumor metastasis is complex. For example, in certain tumors, such as glioma (23) and colon cancer (24), the effect of SP1 on tumor metastasis can be reduced by inhibiting the expression of SP1 in tumor cells. However, in GC (25) and lung adenocarcinoma (26), inhibiting the expression of SP1 can promote the metastasis and invasion ability of tumor cells.

The present study investigated the molecular mechanisms underlying miR-502-5p function in GC. First, bioinformatics was used to predict the potential target genes of miR-502-5p, which identified SP1 as a candidate. Then, mRNA expression levels of SP1 were measured in four GC tissue sets. It was determined that SP1 mRNA levels were significantly higher

compared with those in normal adjacent tissues. In addition, RT-qPCR and western blotting demonstrated that overexpression of miR-502-5p decreased the expression levels of SP1 mRNA and protein in GC cells, respectively. These results suggest that SP1 is a downstream target gene of miR-502-5p.

In conclusion, the present study demonstrated that miR-502-5p is a novel tumor suppressor, as overexpression of miR-502-5p inhibited the proliferation, migration and invasion of GC cells. Thus, downregulation of miR-502-5p may be necessary for GC carcinogenesis via SP1 regulation. The present findings may improve our understanding of the molecular pathogenesis of GC and highlight the potential of miR-502-5p as a target for antitumor therapy. However, the present study also has some limitations. For example, the effect of miR-502-5p on the biological behavior of GC cells at the cellular level was only investigated *in vitro*. In the future, further studies should be conducted to demonstrate the effect ofmiR-502-5p on the biological behavior of GC *in vivo*.

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**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Authors' contributions**

XP and MW designed the study. WL and CG performed the data analysis. CG sorted out the experimental data. XP, LZ and XZ performed the data analyses and wrote the manuscript. LZ taught the experimental protocols. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

The Changhai Hospital Ethics Committee (Shanghai, China) approved the present study (approval no. CHEC2016-157). All patients who agreed to participate in the study provided written informed consent.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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