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Original Article

A novel circular RNA hsa_circ_0008035 contributes to gastric cancer tumorigenesis through targeting the miR-375/YBX1 axis

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Abstract: Circular RNAs (circRNAs) play an important regulatory role in a variety of human cancers, including gastric cancer. The mechanisms for the circRNAs in gastric cancers are not fully understood. This study aims to uncover the mechanism by which circRNAs regulate gastric cancer tumorigenesis. Among the microarray data, we screened dysregulated circRNAs and identified an up-regulated circRNA, hsa_circ_0008035. Functionally, the hsa_circ_0008035 silencing by the siRNA transfection inhibited the proliferation and invasion of gastric cancer cells. Mechanically, hsa_circ_0008035 acted as a sponge for the miR-375 and absorbed its expression, and miR-375 was found to target YBX1 3'-UTR, constructing a hsa_circ_0008035/miR-375/YBX1 axis. Taken together, these findings are evidence that circRNA hsa_circ_0008035 promotes gastric cancer cell proliferation and invasion by regulating miR-375/YBX1.

Keywords: Gastric cancer, hsa_circ_0008035, miR-375, YBX1

Introduction

Gastric cancer is among the top five most common cancers worldwide and is the third leading cause of cancer-related death worldwide [1, 2]. Despite recent advances in chemotherapy, surgical treatment and molecular targeting therapy, gastric cancer still has a significant rate of morbidity and mortality every year [3, 4]. Challenges for treating gastric cancers not only includes tumor metastasis and recurrence, but also indeterminate and nonspecific therapeutic targets [5]. A better understanding of gastric cancer oncogenesis is critical to advance and improve available therapy markers and targets [6].

Circular RNAs (circRNAs) are a group of transcripts without coding potential that are formed by a closed continuous loop with the covalent union at the 3' and 5' end [7]. Recent research mistakenly characterized circRNAs as by-products or a splicing error of the transcriptome [8]. The function of circRNAs has been investigated using high-throughput sequencing and bioinformatics and identified through molecular verification. These approaches have found that the expression of circRNA circYAP1 is significantly lower gastric cancer tissue, and the overexpression of circYAP1 reduces cell growth and invasion via sponging miR-367-5p to inhibit p27 [7]. Studies have also found that hsa_circ_0000993 inhibits the migration, invasion and proliferation of gastric cancer cells and functions as a miR-214-5p sponge [9]. Finally, Y-box binding protein-1 (YBX1), a member of the cold shock protein family, has been found to regulate the growth and spread of gastric cancers [10]. These results suggest that circular RNA plays an important role in the development and progression of gastric cancers.

A novel circRNA, hsa_circ_0008035, was discovered in the public GEO dataset (www.ncbi.nlm.nih.gov/geo/GSE78092) and found to be generated from the EXT1 gene with spliced

length 670 bp. In present study, results found that hsa_circ_0008035 is overexpressed in gastric cancer tissue and cells and targets the miR-375/YBX1 axis to regulate gastric cancer progression.

Materials and methods

Tissue collection and ethics statement

Paired gastric cancer tissue and adjacent normal tissue was collected from 30 patients who underwent surgical resection without any chemoradiotherapy at the First Affiliated Hospital of Jinan University. Resected tissue were immediately frozen in liquid nitrogen and stored at -80°C for further RNA isolation. All experiments were approved by the Institutional Review Board and all patients provided informed consent in writing prior to participation.

Cell culture

Gastric cancer cells (BGC-823, MGC-803, AGS and SGC-7901) and normal cells (GES-1) were provided from the Cell Resource Center of the Institute of Basic Medical Sciences at the Chinese Academy of Medical Sciences. Cells were maintained in RPMI 1640 (Invitrogen, Shanghai, China) and Dulbecco's modified Eagle's medium (DMEM) supplemented with 100 μg/ml penicillin G and 100 U/ml streptomycin (Invitrogen) and 10% fetal bovine serum (FBS).

siRNA transfection

The siRNA targeting circRNAs and inhibitor targeting miRNA for transfection were prepared by RiboBio (Guangzhou, China) and transfected into MGC-803 and SGC-7901 cells using lipofectamine 3000 (Thermo Fisher Scientific, Rockford, IL, USA). After 48 hours, the cells were harvested and measured for the post-transfection using qRT-PCR. The sequences for the siRNA hsa_circ_0008035 were as follows: siRNA-1, 5'-AGGAGAGAGCAAGGTATGATT-3'; siRNA-2, 5'-AAGGAGAGAGCAAGGTATGAT-3'; siRNA-3, 5'-GAGAGAGCAAGGTATGATTAT-3'.

RNA extraction and qRT-PCR

Total RNA from gastric cancer cells were extracted using TRIzol reagent (Invitrogen) according to the manufacturer's instructions. The isolated RNA (1 μg) was reverse-transcribed into cDNA using the PrimeScript RT reagent kit (Takara, Shanghai, China). qRT-PCR was performed using the StepOneTM Real-Time PCR System and the SYBR® Green Mixture (Takara). Relative data were normalized to GAPDH. The genes primers sequences were as follows: hsa_circ_0008035, forward primer, 5'-CTACCAGCCAAACACCGCT-3', reverse primer, 5'-TCCAGGAATCTGAAGGACCCA-3'.

CCK-8 and colony formation assay

Proliferation ability of gastric cancer cells (MGC-803, SGC-7901) was examined using a Cell Counting Kit-8 (Dojindo Molecular Technologies, Japan). Cells were harvested 48 h after transfection. For the colony formation assay, the transfected cells were cultured in 1640 medium containing 10% FBS in 6-well plate. After 2 weeks, cells were fixed with methanol and stained with 0.1% crystal violet.

Transwell invasion assay

After 24 hours of transfection, the cells (1×10^5 cells/well) were pre-applied with 50 ul Matrigel, harvested and then seeded into the upper Transwell chamber with 200 mL of serum-free medium containing 20% FBS. After 48 hours, the cells through the lower surface were wiped with a cotton swab and fixed with 4% paraformaldehyde and stained with 0.5% crystal violet.

Western blotting

Gastric cancer cells (MGC-803, SGC-7901) were cold under ice and washed with PBS and then harvested with protein extraction reagent buffer (Pierce Chemicals Co, Rockford, IL, USA). Isolated proteins were resolved on SDS polyacrylamide gels (SDS-PAGE, 8-12%) and transferred to PVDF membranes (Millipore, Billerica, MA, USA). The PVDF membranes were blocked with 5% skimmed milk powder and incubated with primary antibodies overnight at 4°C. Secondary anti-rabbit HRP-conjugated antibody was incubated with the members. The blots were treated with ECL Plus reagent (Millipore, USA) and quantified with a multigauge densitometry system (Fujifilm, Tokyo, Japan).

Dual-luciferase reporter assay

A dual-luciferase reporter gene assay kit (Promega) according to the manufacturer's instructions. YBX1 mRNA wild type with potential miR-375 binding sites and mutant without miR-375 binding sites were constructed and amplified and cloned into the psi-CHECK-2 vector. HEK293T cells were co-transfected with luciferase plasmids and miR-375 or control. Dual-Luciferase Reporter Assay System (Promega) was performed based on the Renilla luciferase activity.

Statistical analysis

Student's t-test or one-way ANOVA were used to determine differences between groups. A two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software and graphed using GraphPad Prism software.

Results

hsa_circ_0008035 is overexpressed in the gastric cancer tissue and cells

To investigate dysregulated circRNAs in gastric cancer, we searched the public database Gene Expression Omnibus database (GEO, GSE78092) and analyzed the data using the GEO2R tools. Within the top 250 differently expressed circRNAs, we selected five up-regulated and five down-regulated circRNAs. These are presented as the heatmap in **Figure 1A**. Following verification using RT-PCR, results showed that the five circRNAs (hsa_circ_0005529, hsa_circ_0061274, hsa_circ_0008035, hsa_circ_0032821 and hsa_circ_0061265) were significantly increased (**Figure 1B**). While, the five circRNAs (hsa_circ_0005927, hsa_circ_0040039, hsa_circ_0092341, hsa_circ_0068610 and hsa_circ_0000026) were significantly reduced (**Figure 1C**). Hsa_circ_0008035 was selected as the target further experiments and its level in gastric cancer cells was retested (**Figure 1D**). In the clinical gastric cancer tissue, hsa_circ_0008035 expression was significantly overexpressed (**Figure 1E**, **1F**). These findings suggest that hsa_circ_0008035 is overexpressed in gastric cancer tissue and cells.

Hsa_circ_0008035 knockdown represses the proliferation and metastasis of gastric cancer cells

Loss-of-function experiments were performed using siRNA targeting hsa_circ_0008035 for gastric cancer cells (MGC-803, SGC-7901) to detect the malignant tumor phenotype (**Figure 2A**). Clone formation assay a reduced number of clones in the hsa_circ_0008035 knockdown transfection group (**Figure 2B**). CCK-8 assay was carried out to investigate the inhibition of hsa_circ_0008035 knockdown on cell proliferation (**Figure 2C**). Transwell assay was carried out and found that hsa_circ_0008035 knockdown inhibited the invasion of gastric cancer cells compared to the control group (**Figure 2D**). These results suggest that hsa_circ_0008035 knockdown represses the proliferation and metastasis of gastric cancer cells.

Hsa_circ_0008035 targets miR-375 as a miRNA sponge

Research shows that circRNAs can target miRNAs by acting as miRNA sponges, and binding with the RNA binding protein (RBP) to exert their function [11, 12]. Results from this study found that miR-375 had complementary binding sites with the hsa_circ_0008035 (**Figure 3A**). The luciferase activity demonstrated the interaction between the molecular binding of hsa_circ_0008035 and miR-375 (**Figure 3B**). In the gastric cancer tissue, the level of miR-375 was significantly reduced (**Figure 3C**) and the same result was found in the gastric cancer cells (**Figure 3D**). Results also found that miR-375 was highly expressed in the hsa_circ_0008035 knockdown transfection in the SGC-7901 cells, suggesting a negative correlation between hsa_circ_0008035 and miR-375 (**Figure 3E**). The results suggest that hsa_circ_0008035 serves as a miRNA sponge for miR-375.

YBX1 serves as the functional protein of hsa_circ_0008035/miR-375

Further experiments aimed to investigate the downstream target of hsa_circ_0008035 and miR-375. Results indicated that YBX1 mRNA 3'-UTR had complementary sites with miR-375 (**Figure 4A**). The luciferase activity showed the molecular binding between YBX1 mRNA and miR-375 (**Figure 4B**). The expression of YBX1 in gastric cancers (stomach adenocarcinoma) is higher than normal tissue according to the GEPIA database (http://gepia.cancer-pku.cn/index) (**Figure 4C**). Western blot analysis revealed that miR-375 silencing activated the expression of YBX1 (**Figure 4D**). RT-PCR illustrated that YBX1 mRNA expression was increased in

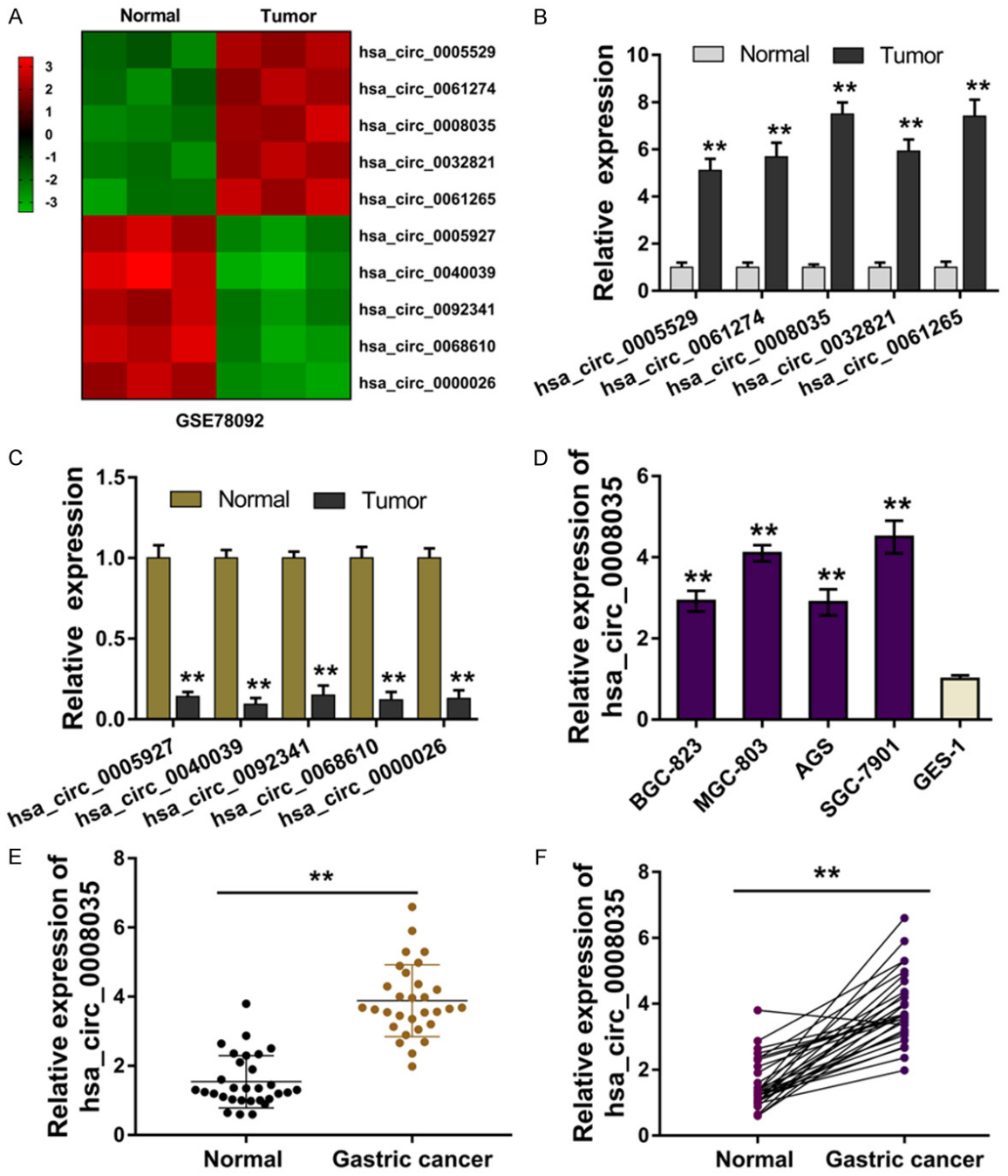

Figure 1. hsa_circ_0008035 is overexpressed in the gastric cancer tissue and cells. A. The heatmap showed the dysregulated circRNAs derived from Gene Expression Omnibus database (GEO, GSE78092) and analyzed the data using the GEO2R tools. B. RT-PCR showed the five increased circRNAs, including hsa_circ_0005529, hsa_circ_0061274, hsa_circ_0008035, hsa_circ_0032821 and hsa_circ_0061265. C. RT-PCR showed the five reduced circRNAs, including hsa_circ_0005927, hsa_circ_0040039, hsa_circ_0092341, hsa_circ_0068610 and hsa_circ_0000026. D. Hsa_circ_0008035 was tested in the gastric cancer cells. E, F. Hsa_circ_0008035 expression was significantly over-expressed in the clinical gastric cancer tissue. **p-value less than 0.01.

the miR-375 silencing group, which was recovered by hsa_circ_0008035 siRNA (**Figure 4E**). These results suggest that YBX1 serves as the functional protein of hsa_circ_0008035/miR-375.

Discussion

Long noncoding RNA (lncRNAs) and circular RNAs (circRNAs) are important factors in human cancer research [13-15]. Both lncRNAs

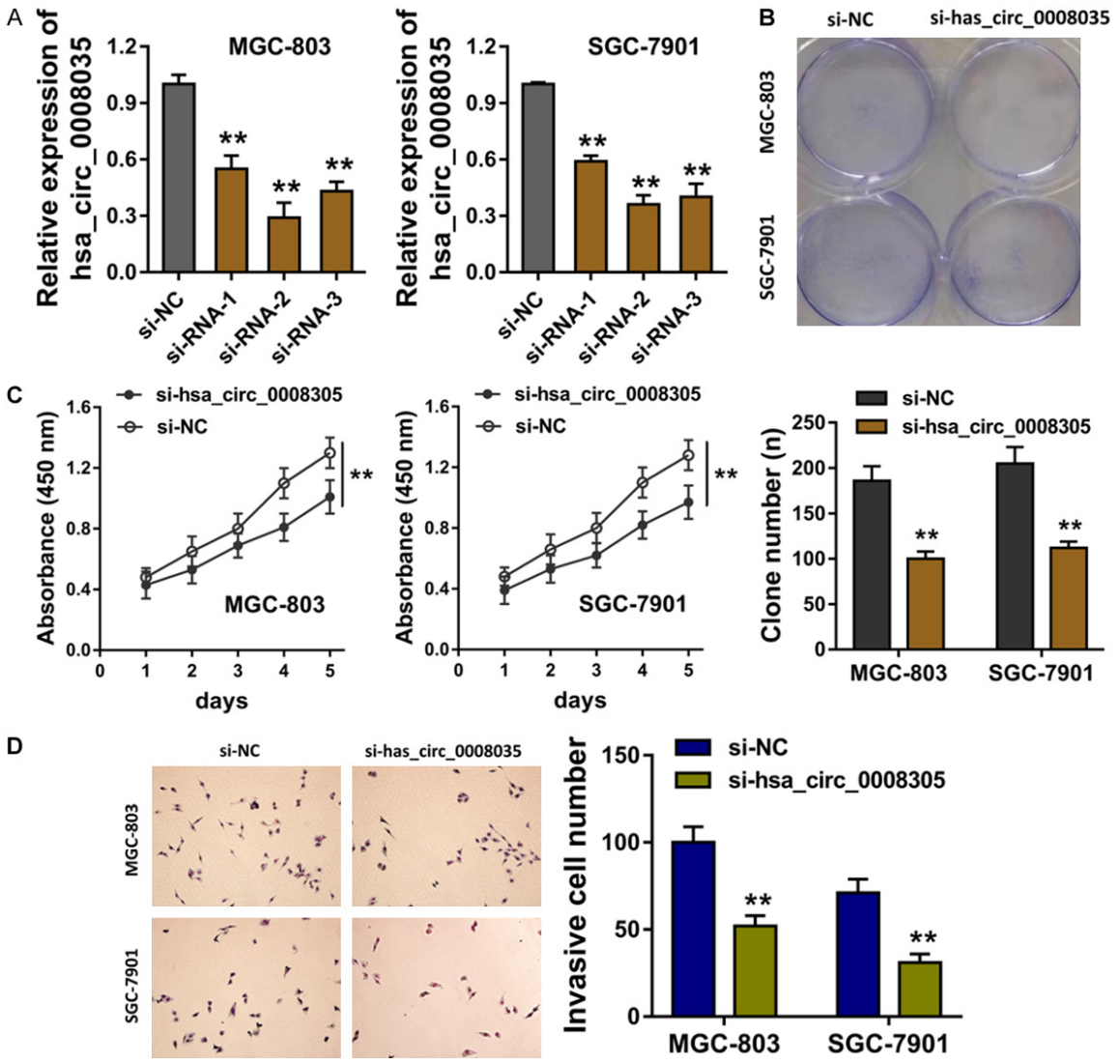

Figure 2. Hsa_circ_0008035 knockdown represses the proliferation and metastasis of gastric cancer cells. A. Loss-of-function experiments were performed using siRNA targeting the hsa_circ_0008035 for gastric cancer cells (MGC-803, SGC-7901). B. Clone formation assay demonstrated the clone number in the hsa_circ_0008035 knockdown transfection group and the control transfection. C. CCK-8 assay showed the inhibition of hsa_circ_0008035 knockdown on the proliferation ability. D. Transwell assay demonstrated the hsa_circ_0008035 knockdown for the invasion of gastric cancer cells comparing to the control transfection. **p-value less than 0.01.

and circRNAs lack the ability to encode proteins and circRNAs are characterized by the covalent conjunction and lack of the 3' and 5' end. In the gastric cancer, circRNAs have been found to exert an oncogenic or anti-oncogenic role in tumorigenesis [16, 17].

In the present study, dysregulated circRNA (hsa_circ_0008035 was identified in gastric cancer tissue and found to be significantly up-regulated. Five overexpressed circRNAs were identified, including hsa_circ_0005529, hsa_circ_0061274, hsa_circ_0008035, hsa_circ_0032-821 and hsa_circ_0061265. Another five under-expressed circRNAs were also identified, including hsa_circ_0005927, hsa_circ_0040-039, hsa_circ_0092341, hsa_circ_0068610 and hsa_circ_0000026.

Functional cellular experiments indicated that hsa_circ_0008035 silencing inhibited the gastric cancer cell proliferation and invasion. CircRNAs can target miRNAs by acting as a miRNA sponge and binding with the RNA binding protein (RBP) to exert their function. Mechanical investigation indicated that hsa_circ_0008035

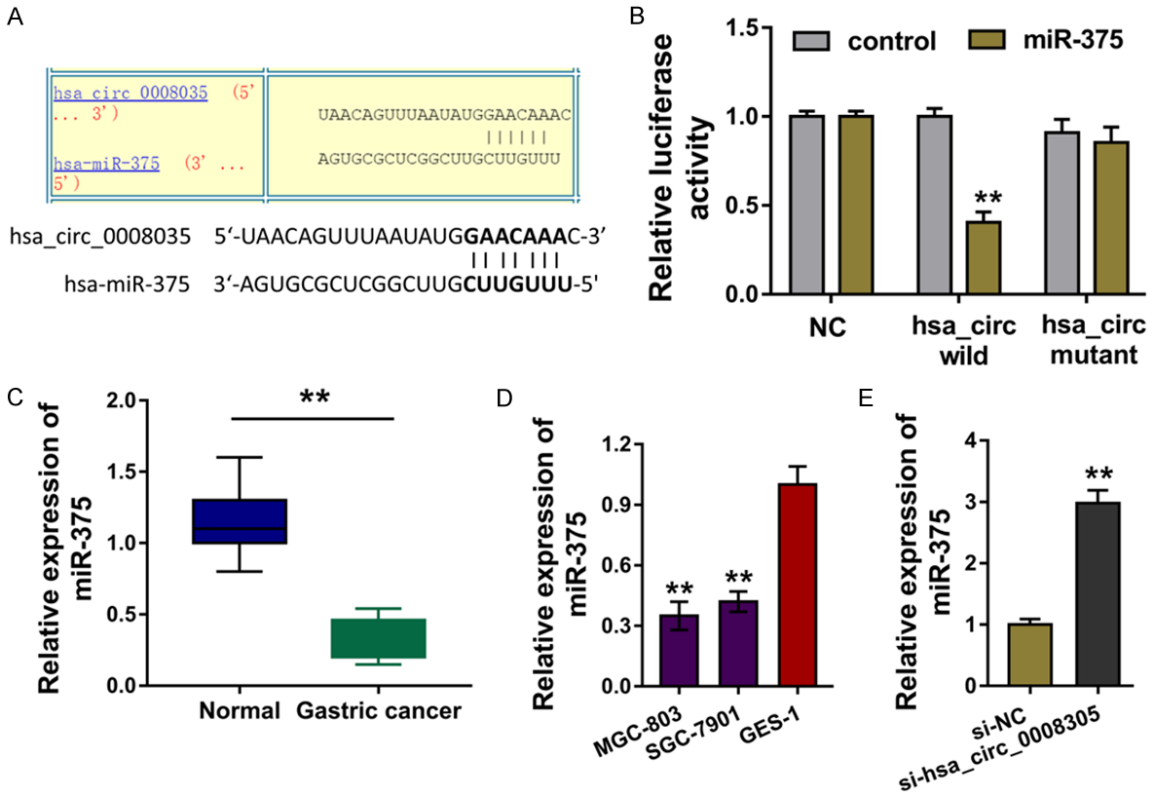

Figure 3. Hsa_circ_0008035 targets miR-375 as a miRNA sponge. A. miR-375 had the complementary sites with the hsa_circ_0008035. B. The luciferase activity on behalf of the molecular binding of hsa_circ_0008035 and miR-375 was tested. C. miR-375 level in the gastric cancer tissue was tested using RT-PCR. D. miR-375 level in the gastric cancer cells. E. miR-375 level was decreased in the gastric cancer SGC-7901 cells transfected with hsa_circ_0008035 siRNA and control. ***p*-value less than 0.01.

targets miR-375 as a miRNA sponge, which was confirmed using luciferase reporter assay. MicroRNA-375 has been found to act as a tumor suppressor for gastric cancer. For example, miR-375 has been found to directly target the 3'-UTR of RON mRNA and its overexpression inhibited mRNA and protein expression of RON [18]. Further, miR-375 was found to be downregulated in gastric cancer due to promoter methylation and histone deacetylation of miR-375 and ectopic expression of miR-375 inhibited tumor growth in vitro and in vivo via targeting YAP1, TEAD4 and CTGF [19].

Further exploration indicates that the YBX1 protein acts as a target of miR-375, forming the hsa_circ_0008035/miR-375/YBX1 axis. The expression of YBX1 in gastric cancer (stomach adenocarcinoma) is higher than normal tissue based on the GEPIA database [20] (http://gepia.cancer-pku.cn/index). In gastric cancer cells, RNA pull-down mass spectrometry analysis revealed that YBX1 interacts with HOXC-AS3, suggesting that YBX1 participates in HOXC-AS3-mediated gene transcription regulation in the tumorigenesis of gastric cancer [21].

The role of circRNAs in human cancers has been established in previous studies [22-24]. For example, circRNA, hsa_circ_0001461, also termed circFAT1(e2), is significantly downregulated in gastric cancer tissue and cell lines and was found to be correlated with survival rate of patient with gastric cancer. CircFAT1(e2) acts as a sponge of miR-548g and directly interact with Y-box binding protein-1 (YBX1) inhibiting its function [25]. Further, circRNA_001569 regulates the expression of miR-145, which targets NR4A2 to regulate its expression in gastric cancer cells [26]. All these studies suggest that circRNAs target the miRNA as a miRNA sponge, and bind to its target and modulate the cellular function.

Taken together, this study identified the role of hsa_circ_0008035 in gastric cancer cells via

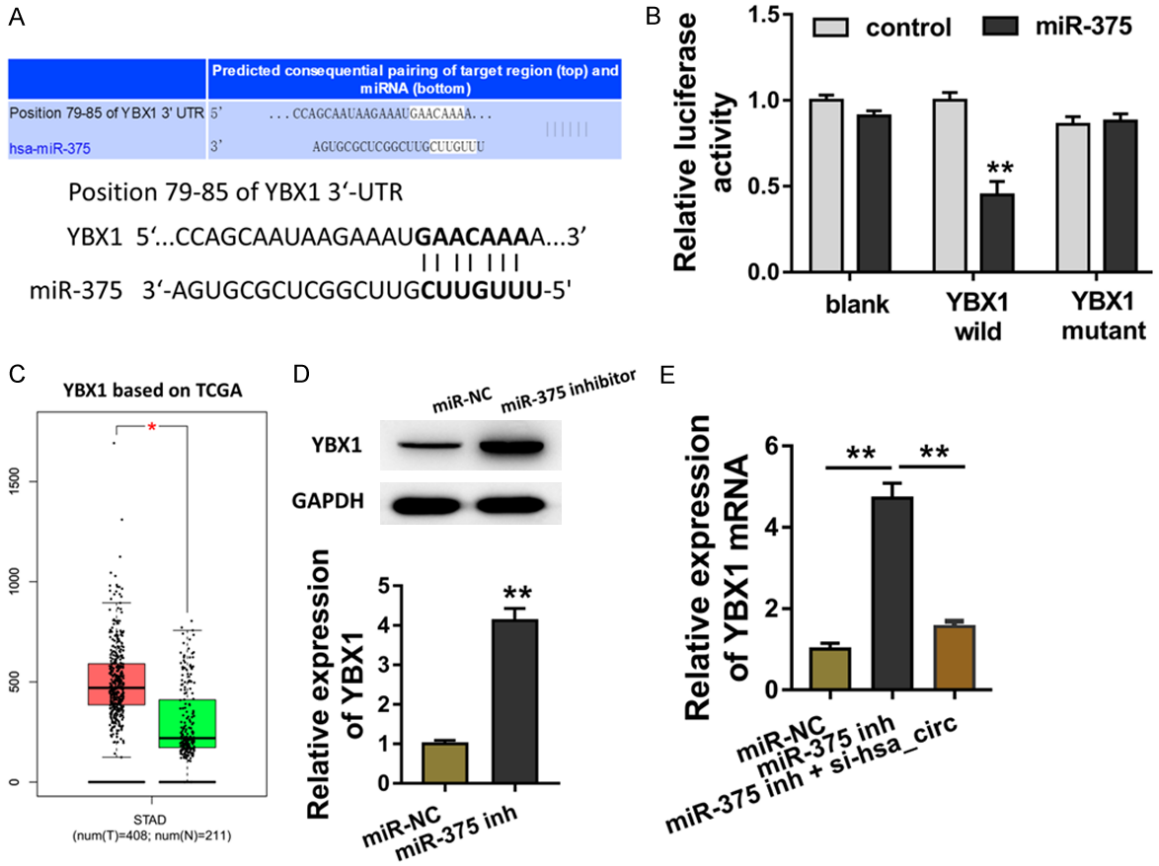

Figure 4. YBX1 serves as the functional protein of hsa_circ_0008035/miR-375. A. YBX1 mRNA 3'-UTR had the complementary sites with miR-375. B. The luciferase activity for the molecular binding of YBX1 mRNA and miR-375. C. The expression of YBX1 in the gastric cancer (stomach adenocarcinoma) based on the GEPIA database (http://gepia.cancer-pku.cn/index). D. Western blot analysis revealed the YBX1 protein expression after the miR-375 silencing. E. RT-PCR illustrated the YBX1 mRNA expression in the miR-375 silencing and hsa_circ_0008035 siRNA. ****p*-value less than 0.01.

sponging miR-375 to initiate YBX1 potential. This research characterized the regulation of hsa_circ_0008035/miR-375/YBX1 axis and its role in gastric cancer.

Disclosure of conflict of interest

None.

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