HIT000218960 promotes gastric cancer cell proliferation and migration through upregulation of HMGA2 expression

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Abstract. The aim of the present study was to elucidate whether the long non-coding RNA (lncRNA) HIT000218960 could accelerate the proliferative and migratory ability of gastric cancer (GC) cells by regulating high-mobility group AT-hook 2 (HMGA2) gene. The reverse transcription-quantitative polymerase chain reaction was used to determine HIT000218960 and HMGA2 expression levels in GC tissues and cells. The HMGA2 protein level was detected by western blotting. A χ^2 test was used to determine the association between the HIT000218960 expression level and the clinical characteristics of patients with GC. GC cells were transfected with small interfering (si)-negative control, si-HIT000218960 and si-HIT000218960+pcDNA-HMGA2, prior to assessing the cell proliferative and migratory ability using the Cell Counting Kit-8 and Transwell assays, respectively. HIT000218960 and HMGA2 were highly expressed in GC tissues compared with in healthy tissues. In addition, HIT000218960 and HMGA2 were positively correlated in GC tissues. The HIT000218960 expression level was associated with tumor size, Tumor-Node-Metastasis staging and lymph node metastasis in patients with GC. HIT000218960 silencing decreased the proliferative and migratory ability of HGC27 and NCI-N87 cells; however, HMGA2 overexpression partly reversed this inhibitory effect. The results of the present study indicated that HIT000218960 could promote HGC27 and NCI-N87 cell proliferation and migration, which may be mediated by HMGA2.

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Introduction

Gastric cancer (GC) is a malignancy that originates from the glandular epithelial cells of gastric mucosa. It is the second most common cause of cancer-associated mortality in China (1). According to the International Agency for Research on Cancer (https://www.iarc.fr/), GC was the fifth most common type of cancer worldwide in 2012 with 951,000 new cases identified, and represented the third most common causes of cancer-associated mortality, with 723,000 cases. In addition, >70% of new cases of GC occur in developing countries, and ~50% originate from Eastern Asia, mainly China (2). Treatment of GC essentially comprises surgery, chemotherapy and radiotherapy. However, the high rate of GC spreading to local lymph nodes, liver and peritoneal cavity contributes to a poor prognosis and a low 5-year survival rate (<30%) (3,4). Numerous studies suggest that the biological evolution of GC is complex. In China, GC is typically diagnosed at an advanced stage. It is therefore crucial to improve early diagnosis of GC and determine its underlying molecular mechanism in order to increase the 5-year survival rate and improve the quality of life of patients with GC (5,6).

Long non-coding RNA (lncRNA) is an RNA molecule of >200 nucleotides, which is not translated into protein (7). LncRNA was originally considered to be 'noise' in genome transcription. However, an increasing number of lncRNAs have been identified to serve a pivotal role in cancer development (8). A previous study (9) reported that lncRNA acts as a potential therapeutic target, which provides a novel direction for treatment development. Other studies (10,11) have revealed that lncRNAs are associated with stomach cancer development. A previous study identified that GACAT1 expression is correlated with tumor stage, metastasis, differentiation and invasion depth of GC (12). Yang *et al* (13) reported that H19 is overexpressed in GC and correlated with cancer cell proliferation and apoptosis. In addition, H19 interacts with p53 to suppress its activity, which leads to downregulation of the downstream Bax gene, and therefore results in increased cell proliferation and decreased cell apoptosis (13). Colon cancer-associated transcript 1 (CCAT1), which is overexpressed in GC, is associated with tumor size and lymphatic or distant metastasis (13,14). *In vitro* studies indicated that CCAT1 is associated with stomach carcinoma cell migration,

which may result from c-Myc and E-box interaction (15). However, the expression profile and underlying mechanism of lncRNA in GC remain unclear. It is therefore crucial to investigate further the functions and underlying molecular mechanism of lncRNAs in GC.

High-mobility group AT-hook 2 (HMGA2) is a crucial protein, which is highly expressed during embryonic development and responsible for cell differentiation (16). The gene coding for HMGA2 is located on loci 13-15 of the long arm of chromosome 12 (17). Previous studies have reported that HMGA2 is overexpressed in various types of cancer, including thyroid (17), colon (18), non-small cell lung (19), squamous cell (20) and gastric (21) cancer, and is associated with invasion and metastasis of certain types of malignancy. Furthermore, HMGA2 is an independent factor that can predict the prognosis of certain malignant tumors (20). As a structural transcriptional regulator, HMGA2 is involved in numerous biological processes. For example, HMGA2 mediates glioblastoma cancer stem cell proliferation via forkhead box M1 and plasminogen activator urokinase regulation (22). In addition, HMGA2 serves a role in DNA damage repair (23,24). In addition, previous studies identified that HMGA2 promotes the epithelial-mesenchymal transition (EMT) by targeting Twist family basic helix-loop-helix transcription factor 1 (Twist1), Snail family transcriptional repressor 2 and Wnt/β signaling pathways in tumors (25-28). In summary, HMGA2 serves important roles in the biological evolution of cancer. HIT000218960 is an lncRNA which has not been extensively investigated. A recent study identified that HMGA2 regulates HIT000218960 expression in thyroid carcinoma tissues (29); however, the association between HMGA2 and HIT000218960 in GC remains unclear.

To the best of our knowledge, the present study is the first to investigate the role of HIT000218960 and HMGA2 in GC. The present study clarified the regulatory effects of HIT000218960 and HMGA2 on cell proliferation and migration in gastric tumor, which may provide a novel strategy and potential target for the treatment of GC.

Materials and methods

Tissue samples and clinical characteristics of patients with GC. In total, 60 tumor samples were obtained from patients with GC who were admitted to The First Affiliated Hospital of Zhejiang Chinese Medical University (Hangzhou, China) between March 2016 and March 2017. A total of 25 normal tissues adjacent to cancer were selected as controls. All fresh tissues were quickly frozen in liquid nitrogen. The clinical characteristics of patients with GC were collected, including age, sex, tumor size, Tumor-Node-Metastasis (TNM) staging and lymph node metastasis. The present study was approved by the Ethics Committee of The First Affiliated Hospital of Zhejiang Chinese Medical University. All subjects provided written informed consent.

Cell culture and transfection. The HGC27 and NCI-N87 cell lines (purchased from Shanghai Huiying Biotechnology Co., Ltd., Shanghai, China), which are commonly used as GC cell lines, were selected for the present study (30,31). HGC27 and NCI-N87 cells were cultured in RPMI-1640 (HyClone; GE Healthcare Life Sciences, Logan, UT, USA) containing 10% fetal bovine serum (FBS) (Gibco; Thermo Fisher Scientific, Inc., Waltham, MA, USA) and placed at 37˚C in a humidified incubator containing 5% CO_2. Culture medium was changed after 2 days and replaced according to the cell culture conditions. Cell lines were transfected with small interfering (si)-negative control (NC) (5'-UCCGGCGACCGGGUAACC UTT-3'), si-HIT000218960 (5'-CCUAACCCAGAGCUCUGA UUATT-3') and si-HIT000218960+pcDNA-HMGA2, which were designed and synthesized by GenePharma Biotech Corp., Taipei, Taiwan. A total of 5 μl si-NC, si-HIT000218960 and pcDNA-HMGA2 were dissolved in 250 μl transfection dilution solution, containing LipoHigh transfection reagent (catalog no. E607403; Sangon Biotech Co., Ltd., Shangai China). The mixture was incubated at room temperature for 20 min. The cells were washed three times with PBS prior to transfection and the PBS was then replaced with fresh serum-free culture medium. The cells were incubated with the transfection mixture at 37˚C in a 5% CO_2 incubator and the medium was changed 6 h post-transfection.

Reverse transcription-quantitative polymerase chain reaction (RT-qPCR). Total RNA was isolated from tissues samples and cancer cells using TRIzol® (Invitrogen; Thermo Fisher Scientific, Inc.). RNA purity and concentration were detected using a Nanodrop 2000c spectrophotometer (Thermo Fisher Scientific, Inc.). The reverse transcription was operated using a PrimeScript™ RT kit (Takara Bio, Inc., Otsu, Japan) according to the manufacturer's protocol. Following reverse transcription, cDNA was diluted with diethy; pyrocarbonate at 1:2 and premixed. Subsequently, 1 μl cDNA, primers, premixed liquid and double-distilled water were mixed into a 20 μl volume in PCR tubes. Following centrifugation at 800 x g for 5 min at 4˚C, PCR amplification was performed under the recommended parameters: 40 cycles of 50˚C for 5 min, 95˚C for 5 min, 95˚C for 5 sec, 60˚C for 15 sec and 72˚C for 15 sec, followed by 94˚C for 15 sec. The fluorescence signals were collected and analyzed. The primer sequences were as follows: HIT000218960 forward, 5-CCACCTACC CATCTGACTTTG-3' and reverse, 5-CCACTATTTCCC ACTGCCTT-3; HMGA2 forward, 5-AGAATCTGGTGC AGGAATGG-3 and reverse, 5-TCGTATTTAGTGTCTCCA GCC-3; and β-actin forward, 5'-CCTCGCCTTTGCCGA TCC-3' and reverse, 5'-GGATCTTCATGAGGTAGTCAG TC-3'. The relative RNA expression levels were analyzed using the $2^{-\Delta\Delta Cq}$ method (32).

Western blotting. Cells were washed with PBS, and lysed using radioimmunoprecipitation assay buffer (Beyotime Institute of Biotechnology, Haimen, China) for 10 min on ice. The BCA method was used for protein quantification. Following centrifugation at 14,000 x g for 15 min at 4˚C, the supernatant was collected. Proteins (30 μg) were separated by SDS-PAGE (12% gel), and transferred onto a polyvinylidene fluoride membrane (EMD Millipore, Billerica, MA, USA). Membranes were washed with Tris-buffered saline containing Tween-20 (TBST), and blocked with 5% skimmed milk with TBST at 25˚C for 1 h. Membranes were then incubated with monoclonal primary antibody at 4˚C overnight. The following primary antibodies were used: Anti-HMGA2 (1:500; catalog no. ab52039; Abcam, Cambridge, UK) and

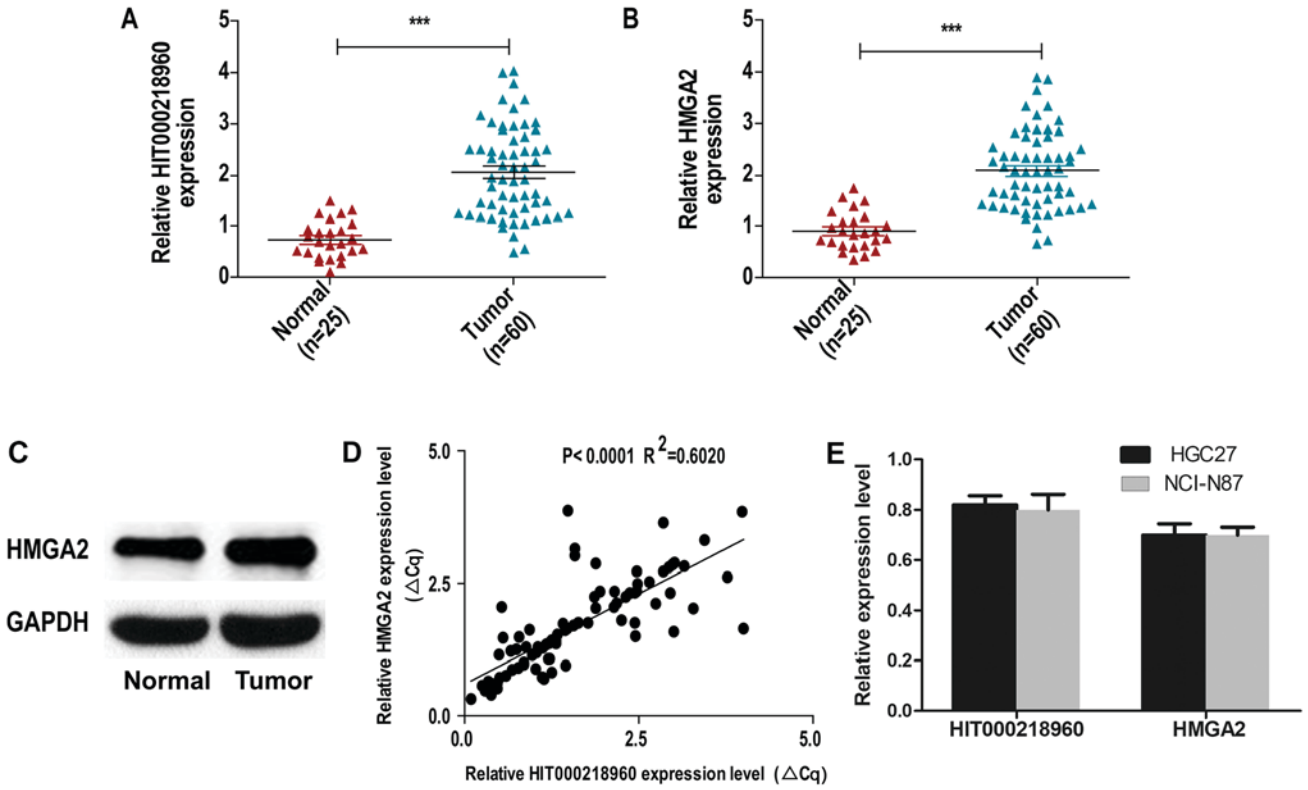

Figure 1. HIT000218960 and HGMA2 are overexpressed in GC tissues. (A) The HIT000218960 expression level is significantly higher in the 60 GC tissues compared with in the 25 normal gastric tissues according to RT-qPCR results. (B) The HMGA2 expression level is significantly higher in the 60 GC tissues compared with in the 25 normal gastric tissues according to RT-qPCR results. (C) Western blotting indicates that the HMGA2 expression level is markedly higher in GC tissues compared with in normal gastric tissues. (D) Positive correlation between HIT000218960 and HMGA2 expression levels. (E) HIT000218960 and HMGA2 expression levels in HGC27 and NCI-N87 cells. ***P<0.001. GC, gastric cancer; HMGA2, high-mobility group AT-hook 2; RT-qPCR, reverse transcription-quantitative polymerase chain reaction.

anti-GAPDH (1:500; catalog no. ab9485; Abcam). Membranes were washed with TBST for 30 min and incubated at 25˚C for 1 h with goat anti-rabbit IgG H&L secondary antibody (1:1,000; catalog no. ab6940; Abcam). Enhanced chemiluminescence reagent (Thermo Fisher Scientific, Inc.) was used to detect the signal on the membrane.

Cell Counting Kit-8 (CCK-8) assay. Cells (2,000 cells/well) were seeded in 96-well plates. CCK-8 reagent (10 μl; Dojindo Molecular Technologies, Inc., Kumamoto, Japan) was added to each well at 4, 24, 48, 72, 96 and 120 h after seeding for 1.5 h. Each group comprised 6 wells and contained a blank control. The absorbance value of each well was determined using a microplate reader at a wavelength of 490 nm.

Migration assay. A Transwell assay was performed to determine the cell migratory ability. HCG2 and NCI-N87 cells ($25x10^4$) were digested, suspended in serum-free RPMI-1640 medium and seeded onto the upper non-Matrigel-coated chamber with a membrane pore size of 8.0-μm (Corning, Inc., Corning, NY, USA). The lower chamber was filled with 500 μl RPMI-1640 medium containing 10% FBS. After 2 h, cells that had invaded the lower chamber were fixed for 20 min with 95% ethanol at room temperature, stained for 20 min with 0.5% crystal violet at room temperature and washed with water. Subsequently, images were captured with a light microscope (magnification, x400) and cells were counted.

Statistical analysis. SPSS software (version 22.0; IBM Corp., Armonk, NY, USA) was used to analyze data. Images were edited with GraphPad Prism 6.0 software (GraphPad Software, Inc., La Jolla, CA, USA). Clinical characteristics were evaluated using a χ^2 test. Student's t-test was applied for comparing data between two groups. Comparison between multiple groups was performed using one-way analysis of variance followed a least significant difference multiple-range post hoc test. Pearson correlation analysis was used to determine the correlation between one dependent variable and single independent variable. P<0.05 was considered to indicate a statistically significant difference.

Results

Expression levels of HIT000218960 and HMGA2 in GC tissue samples. A total of 60 GC tissue samples and 25 normal control samples were collected. Expression levels of HIT000218960 and HMGA2 in the two groups were detected using RT-qPCR. The results indicated that HIT000218960 and HMGA2 expression levels were significantly higher in GC samples compared with in control samples (P<0.001; Fig. 1A and B, respectively). In addition, western blotting revealed that HMGA2 protein expression was higher in GC samples compared with in control samples (Fig. 1C). Further analysis indicated a positive correlation between HIT000218960 and HMGA2 expression levels in GC tissues (P<0.001; R^2=0.6020; Fig. 1D). However, there

Table I. Association between HIT000218960 expression level and clinical characteristics of patients with gastric cancer (n=60).

Clinical characteristic	n	HIT000218960 expression level		P-value
		Low (n=30)	High (n=30)	
Age, years				
≤60	31	14	17	0.4383
>60	29	16	13	
Sex				
Male	28	12	16	0.3006
Female	32	18	14	
Tumor size, cm				
≤3	28	20	8	0.0019[a]
>3	32	10	22	
TNM stage				
I-II	31	22	9	0.0019[a]
III-IV	29	8	21	
Lymph node metastasis				
Negative	27	18	9	0.0195[a]
Positive	33	12	21	

[a]P<0.05. TNM, Tumor-Node-Metastasis.

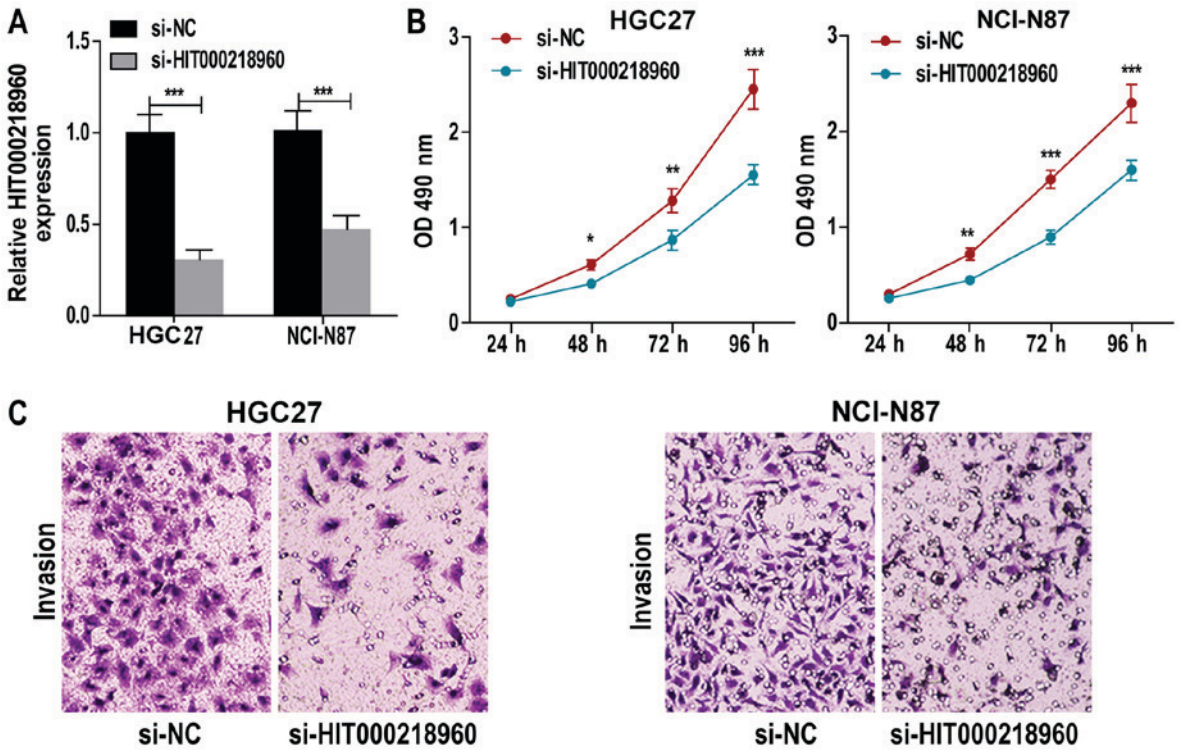

Figure 2. HIT000218960 silencing suppresses GC cell proliferative and migratory ability. (A) Reverse transcription-quantitative polymerase chain reaction results indicated that si-HIT000218960 transfection significantly inhibits the HIT000218960 expression level in GC cell lines. (B) A Cell Counting Kit-8 assay indicated that HGC27 and NCI-N87 cancer cell proliferation is significantly decreased following HIT000218960 silencing. (C) A Transwell assay indicated that the migratory ability of HGC27 and NCI-N87 cell lines decreased following HIT000218960 silencing. Magnification, x400. *P<0.05, **P<0.01, ***P<0.001 vs. si-NC. GC, gastric cancer; NC, negative control; OD, optical density; si, small interfering.

was no difference in HIT000218960 and HMGA2 expression levels between HGC27 and NCI-N87 cell lines (Fig. 1E).

Association between HIT000218960 and clinical characteristics of patients with GC. To clarify the function of

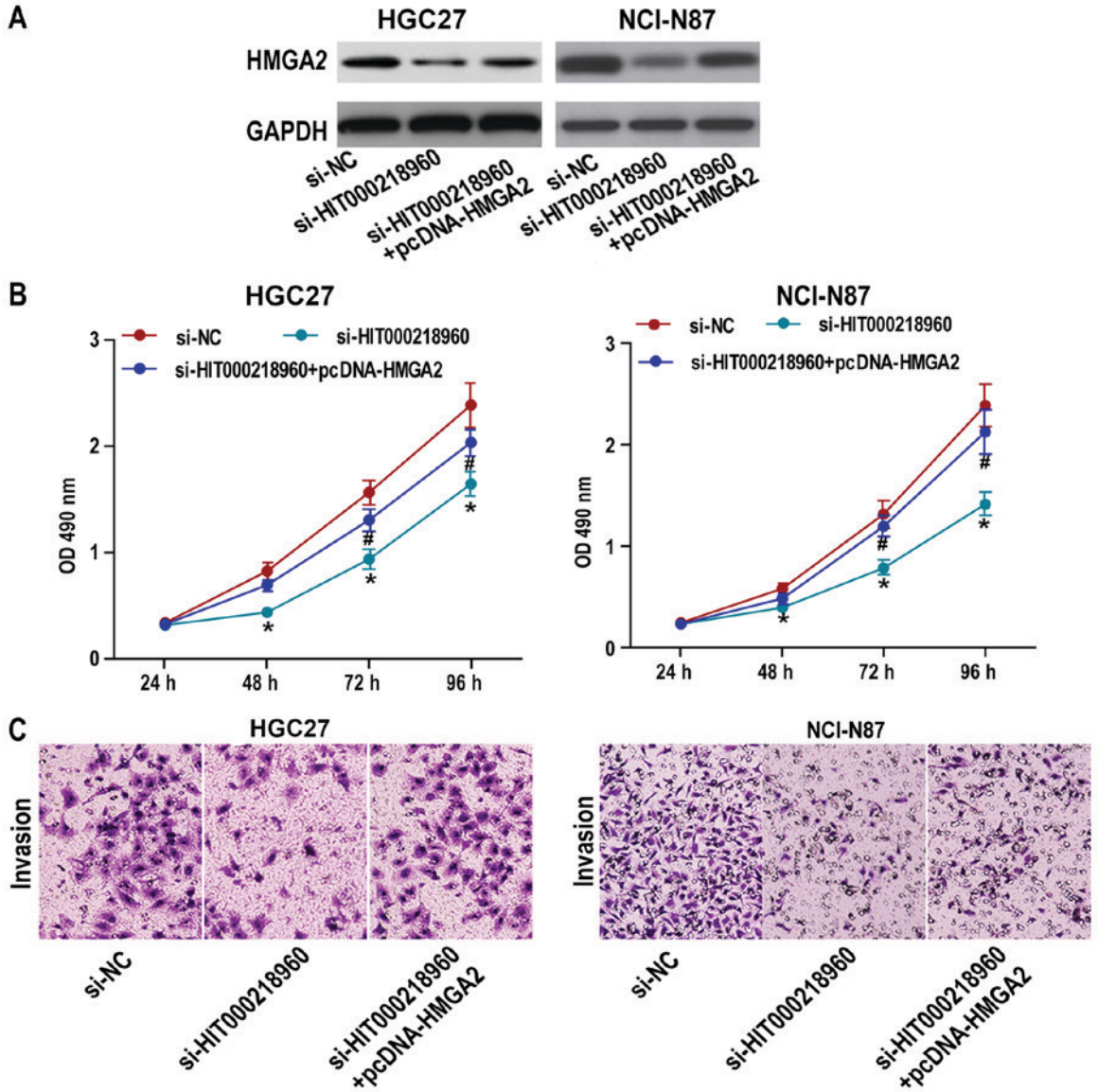

Figure 3. HMGA2 regulates the effect of HIT000218960 on GC cell proliferation and migration. (A) HIT000218960 silencing markedly decreased the HMGA2 protein level in HGC27 and NCI-N87 cell lines, and transfection with pcDNA-HMGA2 increased the expression of HMGA2. (B) A Cell Counting Kit-8 assay indicated that HMGA2 overexpression reverses the si-HIT000218960-induced decrease in proliferation in HGC27 and NCI-N87 cell lines. (C) A Transwell assay indicated that HMGA2 overexpression reverses the si-HIT000218960-induced decrease in the migratory capacity of HGC27 and NCI-N87 cells. Magnification, x400. *P<0.05 vs. si-NC; #P<0.05 vs. si-HIT000218960. GC, gastric cancer; HMGA2, high-mobility group AT-hook 2; NC, negative control; OD, optical density; si, small interfering.

HIT000218960 in GC tissue, the association between the clinical characteristics and HIT000218960 expression levels of the 60 patients with GC was analyzed. Patients were divided into lower-expression and higher-expression groups according to the median level of HIT000218960. Patients with an expression level ≥2.1 were placed in the higher-expression group and patients with an expression level <2.1 were placed in the lower-expression group, and each group consisted of 30 patients (Table I). Analysis using a χ^2 test indicated that the tumor size of patients in the higher-expression group was significantly larger compared with those in the lower-expression group (P=0.0019). In addition, compared with the lower-expression group, the rate of advanced TNM staging (P=0.0008) and the incidence of lymph node metastasis (P=0.0195) were higher in the higher-expression group (P=0.0008 and P=0.0195, respectively). These data suggested that the level of HIT000218960 expression was associated with tumor size, TNM stage and lymph node metastasis in patients with GC.

HIT000218960 silencing inhibits HGC27 and NCI-N87 cell proliferation and migration. RT-qPCR analysis indicated that si-HIT000218960 transfection significantly decreased HIT000218960 expression levels in HGC27 and NCI-N87 cell lines (P<0.001; Fig. 2A). CCK-8 assay demonstrated that HGC27 and NCI-N87 cell proliferation was significantly decreased following si-HIT000218960 transfection compared with si-NC (P<0.001; Fig. 2B). The results of the Transwell assay indicated that HIT000218960 silencing decreased HGC27 and NCI-N87 cell migratory ability (Fig. 2C). These results suggested that decreasing HIT000218960 expression decreased GC cell proliferative and migratory ability.

HMGA2 mediates the regulatory effect of HIT000218960 on GC cell proliferation and migration. Western blotting indicated that HIT000218960 knockdown induced HMGA2 downregulation in HGC27 and NCI-N87 cells, whereas pcDNA-HMGA2 reversed this phenomenon (Fig. 3A). In order to further clarify the association between HIT000218960 and HMGA2, HGC27 and NCI-N87 cells were transfected with si-NC, si-HIT000218960 or si-HIT000218960+pcDNA-HMGA2. A CCK-8 assay revealed that HMGA2 overexpression reversed the si-HIT000218960-induced decrease in cell proliferation (Fig. 3B) and migration (Fig. 3C) of HGC27 and NCI-N87 cell lines. These results suggested that HIT000218960 may promote the proliferative and migratory ability of HGC27 and NCI-N87 cells through HMGA2 upregulation.

Discussion

GC is a common gastrointestinal cancer in China, which leads to high mortality and low 5-year survival rates. The treatment of GC is essentially based on conventional surgery; however, there is currently a lack of research on the mechanisms of occurrence and development of GC, compared with other gastrointestinal malignancies. It has been reported that lncRNAs are involved in numerous biological processes, and that dysregulation of RNA expression is associated with various types of disease, including cancer. Subsequently, studies have identified the underlying mechanisms of lncRNA in cancer. For example, the antisense non-coding RNA in the INK4 locus and HOX transcript antisense RNA can determine chromatin localization by recruiting chromatin-modifying complexes and can regulate histone modifications (33,34). To the best of our knowledge, only a few studies on HIT000218960 have been performed. A recent study reported that HIT000218960 is highly expressed in thyroid carcinoma tissues, and that HIT000218960 inhibition induces a decrease in the papillary thyroid carcinoma cell proliferative, migratory ability and invasive capacity (29). They also reported for the first time that HMGA2 regulates HIT00021896 expression. However, the effect of HIT000218960 in GC has not been yet reported. Further investigation on the mechanism of action of HIT000218960 in GC is therefore required. The aim of the present study was to investigate the effect of HIT000218960 in GC. The results demonstrated for the first time that HIT000218960 expression level was significantly higher in GC tissues compared with normal tissues, and that HIT000218960 knockdown inhibited HGC27 and NCI-N87 cell proliferative and migratory ability.

A previous study reported that HMGA2 overexpression is closely associated with the occurrence and development of GC. Motoyama *et al* (33) observed that HMGA2 expression level in cancerous tissue was high in 110 patients with gastric cancer and was positively correlated with infiltration depth and lymph node metastasis. In addition, follow-up analysis revealed that patients with a high HMGA2 expression level had a shorter survival time compared with that of healthy subjects. This was consistent with the results from the present study, where HMGA2 expression was higher in GC tissues compared with in normal tissues. In addition, HIT000218960 expression level was positively correlated with HMGA2 expression level in GC tissues. HMGA2, which is a non-histone protein present in the nucleus, can change chromosome structure and regulate the expression of various target genes (15). HMGA2 is now considered to be a oncogene (27). However, the underlying molecular mechanism of HMGA2 in tumors is not fully understood and may be associated with activation or translocation of certain oncogenes. Motoyama *et al* (33) reported that in the transforming growth factor β signaling pathway, Smad upregulates its downstream target genes, including Snail, Twist1 and Snail family transcriptional repressor 2 through HMGA2 and functions as an epithelial (E-)cadherin transcription inhibitor. This results in downregulation of E-cadherin expression and loss of intercellular polarity, which induces EMT. Currently, the association between HMGA2 and the clinical characteristics of patients is being investigated to determine whether HMGA2 can be used to distinguish benign from malignant tumors. For example, a high HMGA2 expression level is associated with N staging, 2-year metastasis and poor prognosis in patients with nasopharyngeal carcinoma (35,36). In the present study, the expression levels of HIT000218960 and HMGA2 were associated with the clinical characteristics of patients with GC. These results suggested that HIT000218960 may serve a tumorigenic role by upregulating HMGA2 expression.

In conclusion, the results of the present study indicated that HIT000218960 and HMGA2 were significantly overexpressed in GC tissues and HGC27 an NCI-N87 cell lines. HIT000218960 and HMGA2 expression levels were positively correlated in GC tissues, and the HIT000218960 expression level in patients with GC was associated with tumor size, TNM stage and lymph node metastasis. In addition, HIT000218960 promoted the HGC27 and NCI-N87 cell proliferative and migratory capacity by upregulating HMGA2 expression.

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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

LS and SR designed the study and performed the experiments. JY, PW and MS collected the data. JY and PW analyzed the data. LS and SR 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 First Affiliated Hospital of Zhejiang Chinese Medical University

(Hangzhou, China). All subjects and/or guardians provided written informed consent.

Patients consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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