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Long non-coding RNA HOST2 enhances proliferation and metastasis in gastric cancer

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This study investigates the influence of long noncoding RNA HOST2 on the biological functions of gastric cancer cells; including proliferation, migration and invasion. Differentially expressed lncRNAs in gastric cancer (GC) were screened by microarray analysis, and HOST2 expression in GC tissues and cell lines was determined by quantitative real-time PCR (qRT-PCR). GC cell proliferation, migration and invasion were detected by CCK-8, wound healing and transwell assays. Western blot investigated expression of epithelial-mesenchymal transition (EMT) related proteins, and association was established between over-expressed HOST2 and the number of patients with lymph node and distant metastasis. HOST2 expression was also positively related to GC cell invasion ability, and although its expression in the p-shHOST2 group was remarkably decreased, it was significantly higher than in the Mock and NC groups. Compared to the Mock and NC groups, the p-shHOST2 group presented significant decreases in proliferation and wound healing rates, and the reverse result was noted in the p-HOST2 group. In addition, the number of p-shHOST2 group invasive cells was remarkably less than in the Mock and NC group, and the opposite result was achieved in the p-HOST2 group. Moreover, p-HOST2 had more significant EMT, but this was suppressed in the p-shHOST2 group. Finally, HOST2 silencing suppressed GC cell proliferation, migration and invasion; and it could therefore be considered as a novel biomarker and therapeutic target in gastric cancer.

Key words: long noncoding RNA, HOST2, gastric cancer, EMT

Gastric cancer (GC) is aggressive and has the second highest mortality rate of all malignancies, especially in East Asia [1]; and almost half the global gastric patients have been diagnosed in China [2]. Although there has been great progress in GC technological diagnosis, surgical techniques and adjuvant chemotherapy, prognosis remains poor for many patients [3]. Most patients are diagnosed in advanced stages [4], and concurrent tumor metastasis and invasion lead to high mortality [5]. It is therefore essential to find molecular biomarkers as therapeutic targets in GC patients [6].

Long noncoding RNAs (lncRNAs) are part of the family of noncoding RNA's with more than 200 nucleotides (nt). but they do not code proteins [7]. More than 60,000 lncRNA family members have been cataloged in the newest version of LNCipedia, [3] and while these regulate physiological activities such as organism development, they are also involved in diverse disease processes including tumorigenesis [8]. Current research has demonstrated that lncRNAs have significant roles in cancers, with great effect on a variety of cancer processes including tumor initiation, migration and invasion. They act by regulating oncogenic and tumor-suppressing pathways [9], but a number of lncRNAs are de-regulated in GC [10–12]. This research suggests that lncRNA functions makes them novel GC markers [13].

Human ovarian cancer-specific transcript 2 (HOST2) is a relatively new lncRNA with 2.9 kb and five transcripts [14] but it does not possess a notable opening reading frame (ORF) [15]. There is also strong connection between the protein coding genes HOST1,3 and 5 and the biological process of cancer cells including migration, invasion and differentiation [16, 17]. However, preliminary data was only available for HOST2 effect in ovarian cancer [18], and the capacity of HOST2 in GC has not been determined.

Herein, we established connection between HOST2 expression and GC cell progress; including invasion and migration and we then examined the effect of HOST2 expression on GC cell activity *in vitro*. We found the HOST2 expression level is associated with lymph node and distant metastasis, and that

it promoted the invasion and migration ability of GC cells *in vitro*. The combined results suggest that HOST2 is closely connected with GC progression and that HOST2 might have the potential to become a novel biomarker for gastric cancer diagnosis in the future [9].

Patients and methods

Clinical samples. The present study was performed with the approval of the Ethics Committee of Chinese Medicine Hospital. Informed consent was collected from each patient included in this study prior to experiments which were carried out following the relevant regulations and guidelines. Gastric cancer (GC) tumor tissues and adjacent normal tissues were obtained from the same patients (43 males and 29 females) who underwent surgery at Chinese Medicine Hospital. The freshly resected tissues collected from GC patients were immediately frozen in liquid nitrogen and stored until required.

Cell culture. Gastric cancer cell lines NCI-N87, SGC-7901 were acquired from BeNa Culture Collection (Beijing, China), and MKN-7 was donated by Shenyang First People's Hospital. All GC cell lines were routinely grown in Dulbecco's modified Eagle medium (DMEM; Gibco Company, USA) with addition of 10% fetal bovine serum (FBS), 100 U/mL penicillin and 100 µg/mL streptomycin in a 5% CO_2 cell culture incubator.

LncRNA micro-array analysis. NanoDrop ND-1000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) was preformed to quantify total RNA from GC (n=6) and adjacent normal tissues (n=6), and the integrity of RNA was assessed by standard denaturing agarose gel electrophoresis. Agilent array platform was employed in microarray analysis. Following the producer's instruction, sample preparation and microarray hybridization were employed. Briefly, after rRNA was removed, mRNA was isolated from total RNA (mRNA-ONLY™ Eukaryotic mRNA Isolation Kit, Epicentre). Then, a random priming method was employed to amplify and transcribe each sample into fluorescent cRNA. The marked cRNAs were hybridized onto the Human LncRNA Array v2.0 (8×60 K, Arraystar). Agilent Scanner G2505C was used to scan the arrays after slides were washed.

RNA isolation and qRT-PCR. Extracted RNAs were purified from adjacent normal tissues, tumor tissues and gastric cancer cell lines by Trizol reagent (Invitrogen, Carlsbad, CA, USA) according to the producer's instructions. The HOST2 expressions in gastric cancer tumor tissues and GC cell lines were measured by qRT-PCR using the SYBR-Green method (Takara, Tokyo, Japan) following the producer's protocol, and normalized using GAPDH. The cycling conditions were demonstrated as follows: initial denaturation 95 °C for 30 s, followed by 45 cycles of 95 °C for 5s and 60 °C for 30 s. The connection between the HOST2 expression in the control group and the experimental group was expressed using the $2^{-\Delta\Delta Ct}$ method.

Western blot. Cell protein was extracted with RIPA buffer (Beyotime, Shanghai, China) and quantified using BCA Protein Assay Kit (Beyotime). 30 µg of protein was treated by SDS-PAGE and transferred onto PVDF membranes (Beyotime). 5% non-fat milk was used to block the membrane for 30 minutes at room temperature, following the incubation of the membranes with primary antibodies overnight at 4 °C. Then, HRP conjugated secondary antibody (goat anti-rabbit IgG, 1:2000, Abcam, Cambridge, MA, USA) was appended and incubated for 1 hour at room temperature. Proteins were labeled using BeyoECL Star Kit (Beyotime) and filmed after washing by TBST. Primary antibodies used were as follows: rabbit anti-ZEB1 (1:1500, Abcam), rabbit anti-E-cadherin (1:10000, Abcam), rabbit anti-N-cadherin (1:1500, Abcam), rabbit anti-Vimentin (1:2500, Abcam) and rabbit anti-β-actin (internal control) (1:2500, Abcam).

Transwell assay. Transwell assay detected the migration and invasion of GC cells. These experiments were performed with Transwell chambers of 8 mm pores placed in 24-well plates. (Millipore, USA). 5×10^4 cells were added to the upper Transwell chamber (BD Bioscience, San Jose, CA, USA) for migration assay and 1×10^5 cells were added to the upper Transwell chamber percolated with matrigel (BD Bioscience, San Jose, CA, USA) for invasion assay. In both assays, gastric cancer cells were grown in DMEM without serum in the upper Transwell chamber, and DMEM in the lower Transwell chamber with 10% FBS was added as chemo-attractant. The cells in the upper Transwell chamber were incubated for 24 h at 37 °C. After 24h incubation, the non-migration and non-invasion cells were removed carefully, and 0.5% crystal violet fixed and stained the membranes and a Zeiss (Melville, USA) microscope system was employed for photography. The number of stained cell nuclei in 5 random fields per filter in each group at ×100 magnification was enumerated to evaluate the ability of the migration and invasion of GC cells. Each experiment was conducted three times.

Cell transfection. The GC cells in three cell lines were divided into four groups: mock group, negative control (NC) group, Pcdna3.1-HOST2 (p-HOST2) group and PCMV-shHOST2 (p-shHOST2) group. The Pcdna3.1 and PCMV vectors were prepared from Shanghai GenePharma Co., Ltd. (Shanghai, China). GC cells were digested, counted, and added to a 6-well plate at 2×10^5 per well. The GC cells were briefly transfected with Lipofectamine 2000 according to the producers" instructions (GenePharma, Shanghai, China). The transfected GC cells were bred with 5% CO_2 at 37 °C for 24 to 48 hours, with cell confluency of 50% to 60%. After 4 to 6 hours, the transfection solution was replaced with fresh culture medium. Total HOST2 was extracted after transfection for 48 hours, and QRT-PCR detected HOST2 expression level.

CCK-8 assay. Transfected GC cells were planted in 96-well plate at a density of 1×10^3 cells /well (100 µL). After incubation for 1, 2, 3, 4 and 5 days (culture medium was replaced every 2 days), 10 µL CCK8 solution (5 mg/mL, Sigma-Aldrich, St. Louis, MO, USA) was added to each well. After

4 h incubation, The OD values of each well at 1, 2, 3, 4 and 5 days were measured at 450 nm by microplate reader.

Wound healing assay. GC cells from all groups were collected after 48 h transfection and seeded in a 6-well plate at 2×10^5 cells per well, with approximately 90% confluence. A 200-μL pipette tip was used for four horizontal and four verticals scratches. The widths of several scratches were measured at 0 h and 24 h. The wound healing rate was calculated as follows: [(scratch width at 0 h – scratch width at 24 h)/scratch width at 0 h] × 100%. The assay was conducted 3 times to compare the migration of the cells in three groups.

Statistical analysis. All experiments in this study were repeated three times and GraphPad Prism 6 (San Diego, CA) was used to evaluate data. Data is expressed as average ±SD and analyzed by Student's t-test and Chi-square test as appropriate. The p-value <0.05 was statistically significant.

Results

Differentially expressed lncRNAs in GC and the expression of HOST2 in GC. Differentially expressed lncRNAs in GC with |logFC| >2 and p<0.05 were screened and the top 10 most over-expressed and under-expressed lncRNAs are listed in Figure 1A; showing that HOST2 was highly expressed in GC tumor and under-expressed in normal tissues. Hence, we suspected that the expression of HOST2 correlated with the progress of GC cell proliferation, migration and invasion.

QRT-PCR was employed to detect the HOST2 expression level in GC tumor tissues and adjacent normal tissues. The results revealed that the HOST2 expression in the GC tumor tissues increased significantly compared to adjacent normal tissue (Figure 1B, **p<0.01). The clinical-pathological characteristics of GC patients were analyzed to find relationships with HOST2 expression, and the correlation between the two groups was analyzed by Students t-test as shown in Table 1. There was no visible correlation between HOST2 expression and patient gender, age, tumor size, tumor stage and pathological stages of GC (p>0.05). This shows that HOST2 is highly expressed in the GC tissues; and over-expressed HOST2 and the occurrence and development of GC are considered strongly connected.

Correlation between the HOST2 expression and GC cells migration. Analysis of gastric cancer patient clinical-pathological characteristics revealed visible correlation

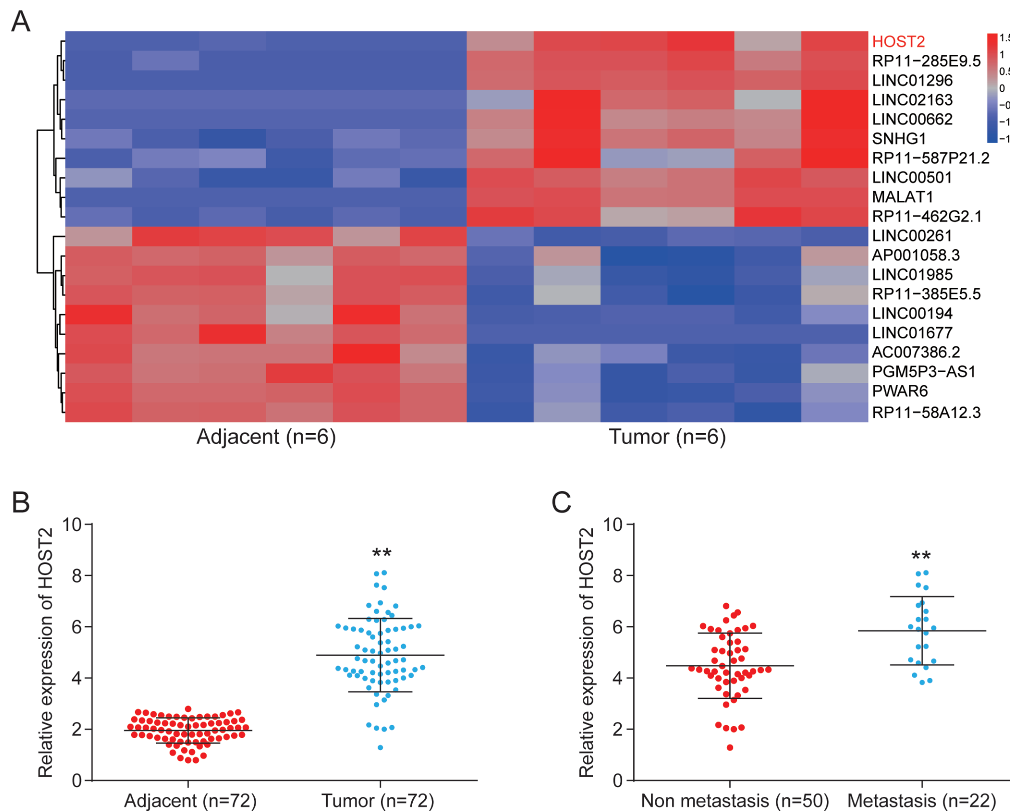

Figure 1. A) Heat map displayed the top 10 up-regulated and down-regulated lncRNAs in GC including HOST2. B) The expression of HOST2 in the adjacent normal tissues and GC tumor tissues (refers to p<0.01 compared with adjacent normal tissues). C) The expressions of HOST2 in the cells that were non-distant metastasis and distant metastasis were detected using RT-qPCR (** refers to p<0.01 compared with the cells without distant metastasis).**

Table 1. Relationship between the relative expression of HOST2 and clinicopathological characteristics of patients with GC including the patients` gender, age, tumor size, tumor stage and pathological stage of GC and whether the patients were lymph node metastasis and distant metastasis.

Clinical parameters	No. of cases	HOST2 expression		χ^2	p-value
		High	Low		
Sex				0.5196,1	0.471
Male	43	20	23		
Female	29	16	13		
Age				1.416,1	0.234
≥60	41	18	23		
<60	31	18	13		
Tumor size				0.5035,1	0.478
≥5 cm	33	15	18		
<5 cm	39	21	18		
Tumor stage				0.9351	0.3336
T1+T2	28	16	12		
T3+T4	44	20	24		
Pathological stage				0.5004,1	0.4793
I+II	26	16	10		
III+IV	46	27	19		
Lymph node metastasis				1.610,1	0.0015
Yes	35	19	16		
No	37	17	20		
Distant metastasis				9.425,1	0.0021
Yes	22	17	5		
No	50	19	31		

The high or low HOST expression is compared with ordinary people. p<0.05 has statistical significant; n=72.

between HOST2 expression and patients with lymph node and distant metastasis, thus showing that the HOST2 expression level was significantly higher in the cells with these metastases (**p<0.01 – Table 1). Therefore, we hypothesized that the over-expression of HOST2 could promote the migration ability of GC cells.

QRT-PCR was employed to analyze the HOST2 expression level in cells with and without distant metastasis in tumor tissue in order to detect the role of HOST2 in GC cell migration. Figure 1C highlights that the expression of HOST2 was significantly higher in the cells with distant metastasis than those with close metastasis (**p<0.01). This phenomenon indicated that the cells with high HOST2 expression had stronger migration capability.

Transwell assay and qRT-PCR detected the migration ability of GC cell lines NCI-N87, SGC-7901 and MKN-7 and the expression of HOST2 (Figures 2A–C, **p<0.01). QRT-PCR then assessed HOST2 expression level in the three GC cell lines in the Transwell lower chamber. The expression of HOST2 was significantly higher in the low than high chamber (**p<0.01). This established that high expression of HOST2 promoted migration capacity in GC cells.

GC cell lines NCI-N87, SGC-7901 and MKN-7 were cultured and divided into four transfected groups; Mock group, NC group, p-HOST2 group and p-shHOST2 group. This enabled further assessment of the correlation between HOST2 expression level and the capability of migration of GC cell lines

The HEK-293T cell line tested 3 shRNA's HOST2 blocking efficiency. qRT-PCR determined that shRNA3 had the best

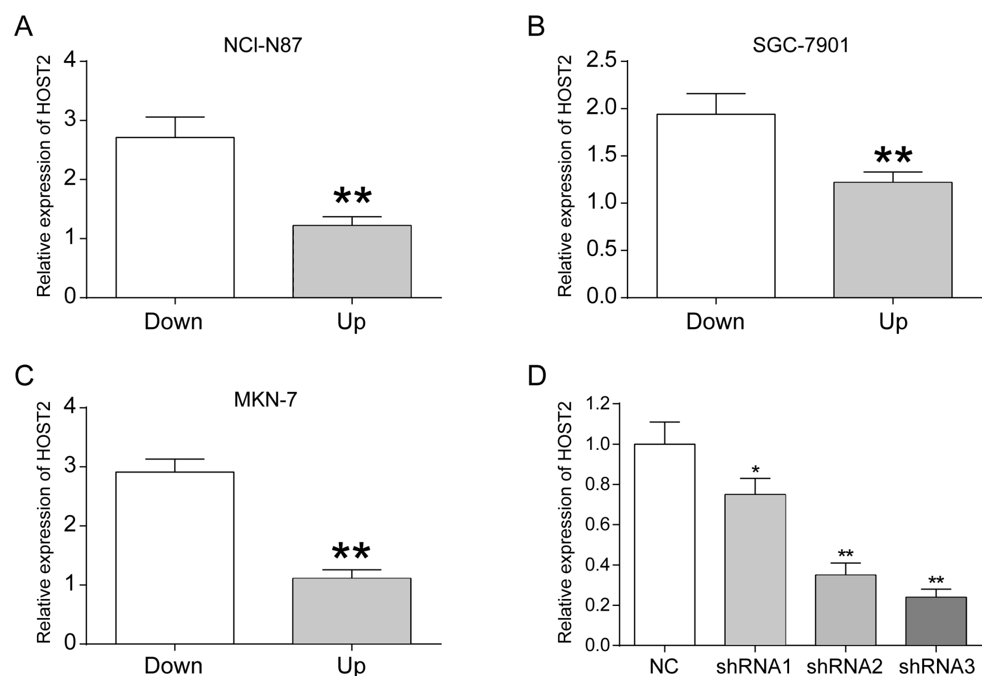

Figure 2. The relative expression of HOST2 of three GC cell lines in the low and high chambers in the Transwell assay measured by RT-qPCR and the expression of HOST2 in the low chamber always was significant high than in the high chamber. A) NCI-N87 cell line, B) SGC-7901 cell line, C) MKN-7 cell line (refers to p<0.01 compared with the cells in the low chamber). D) qRT-PCR detected the blocking efficiency of 3 shRNAs designed for HOST2 in HEK-293T cell line. (* refers to p<0.05, ** refers to p<0.01 compared with NC).**

(Figure 2D, **p<0.01), so shRNA3 was used in following experiments. qRT-PCR then detected the relative expression of HOST2 in the four transfected groups. Figure 3 highlights that the relative expression of HOST2 was significantly higher in the p-HOST2 group than in other groups for all qRT-PCR of GC cell lines (Figures 3A–C, **p<0.01).

Wound healing assay and Transwell invasion assay were employed to detect the HOST2 expression effect on the four groups of three GC cell lines. As shown in Figure 4, the wound healing area of p-HOST2 group was significantly greater than in the Mock group (**p<0.01) and the opposite result was achieved in the p-shHOST2 group for all of three gastric cancer cell lines (**p<0.01). This showed that HOST2 over-expression activated GC cell migration and invasion and HOST2 silencing inhibited them.

Correlation between HOST2 expression and GC cell invasion. Figure 5 shows the number of invasive cells in the Transwell invasion assay. This number was markedly higher in the p-HOST2 group than in the Mock group (**p<0.01), and the opposite for all three GC cell lines (**p<0.01). Over-expressed HOST2 therefore promotes cell invasion in GC cells.

Correlation between HOST2 expression and epithelial-mesenchymal transition (EMT). Herein, we performed Western blot to assess the effect of over-expressing and blocking HOST2 on EMT. The widely studied oncogene ZEB1, epithelial marker E-cadherin, mesenchymal marker N-cadherin and Vimentin were detected in the 3 GC cell lines. Compared with the Mock and NC groups, the p-HOST2 group showed significant decrease of E-cadherin expression and increase in ZEB1, N-cadherin and Vimentin expression, while the p-shHOST2 group gave the reverse result (Figure 6, p<0.01). Hence, HOST2 over-expression could promote the EMT progression of GC cells.

Discussion

Although LncRNAs were originally considered "transcriptional noise" or background transcription, they have gained attention in numerous biological regulatory functions [19]; deregulated lncRNAs were found to have important effects in many cancers' initiation, proliferation, invasion and metastasis [20].

In recent studies, evidence shows that the newly found lncRNA HOST2 has a close connection with the progress of cancer cells. For example, Gao et al. certified that HOST2 mediated an important network that contributed to epithelial ovarian cancer carcinogenesis (EOC) [14]. Wang et al. then found that the up-expressed HOST2 was observed in both osteosarcoma cell lines and clinical specimens [21].

However, the role of HOST2 in GC cells still remained unclear, so we established that HOST2 expression level in GC

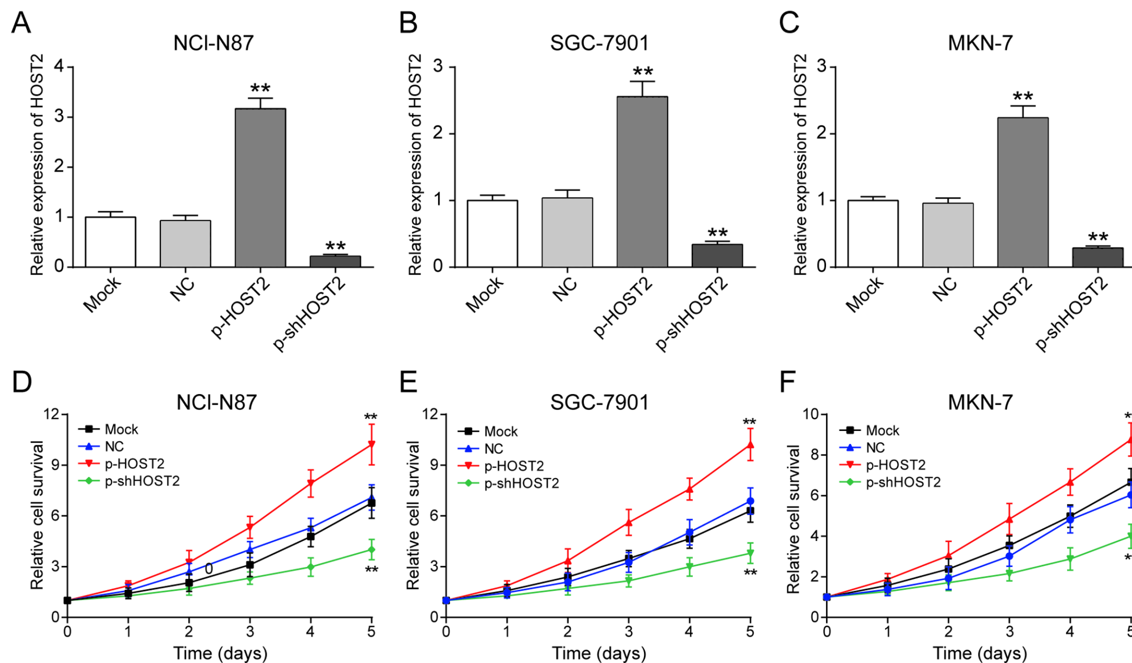

Figure 3. Expression of HOST2 of three GC cell lines in four transfected groups measured by RT-qPCR. HOST2 was markedly highly expressed in p-HOST2 group and lowly expressed in p-shHOST2 group: A) NCI-N87 cell line, B) SGC-7901 cell line, C) MKN-7 cell line (refers to p<0.01 compared with the cells in the NC group). HOST2 enhanced GC cell proliferation while shHOST2 repressed cell proliferation: D) NCI-N87 cell line, E) SGC-7901 cell line, F) MKN-7 cell line (** refers to p<0.01 compared with the cells in the NC group).**

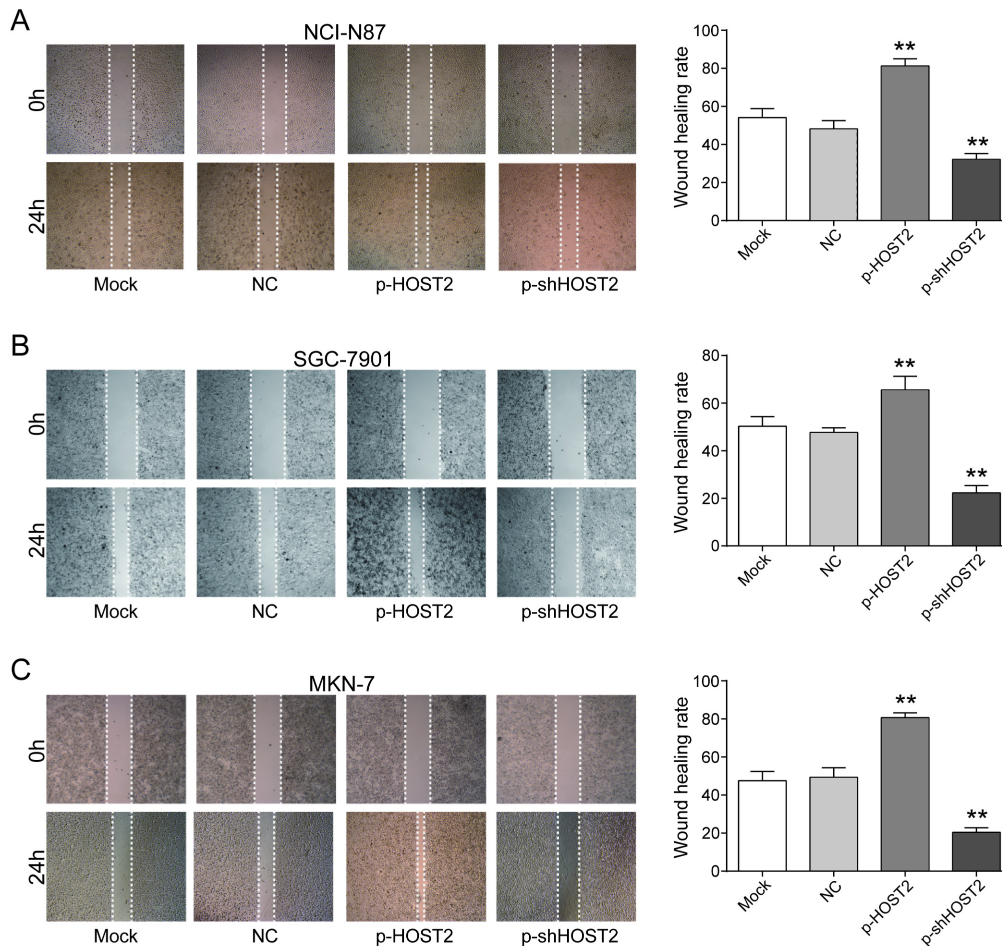

Figure 4. Wound healing area of three GC cell lines in four transfected groups (×40 magnification). The gain-of-function of HOST2 can promote the cell migration of GC cells A) NCI-N87, B) SGC-7901, and C) MKN-7 cell line and the silence of HOST2 would inhibit the migration of GC cells (refers to p<0.01 compared with the cells in the NC group). The picture magnification is ×40.**

tumor tissues was markedly higher than in adjacent normal tissues, and up-regulation of HOST2 enhanced the proliferation of GC cells. Further analysis of these tumor cells revealed that the HOST2 expression level in GC cells with distant metastasis was higher than those without. In addition, highly expressed HOST2 was detected in the patients of lymph node metastasis which is the first transmission in many metastatic tumors; cancer cells are then transported to other organs by blood flow [22].

We then implemented Transwell assay and Wound healing assay to verify the impact of HOST2 on the migration and invasion functions of GC cells. Supporting research had similar results to our study; Lu et al. found that HOST2 inhibited let-7b promotion of breast cancer cells migration and invasion [23] and they then verified that HOST2 promoted cancer cell proliferation, migration and invasion in the SMMC-7721 human hepatocellular carcinoma cell line [15].

In conclusion, we established a strong connection between HOST2 and gastric cancer progress. Over-expressed HOST2 enhanced proliferation, migration and invasion of GC cells, and its silencing significantly inhibited them. This supports HOST2's potential as a novel biomarker and therapeutic target in gastric cancer.

There were, however deficiencies in this study. For example, the upstream and downstream regulatory mechanism for HOST2 remains unclear. We then had to investigate what regulated HOST2 expression, which microRNAs had a targeting relationship with HOST2 [24] and which signaling pathway it regulated in cancer cells [25]. Moreover, no nude mice experiments or experiments *in vivo* were conducted to further verify the study results; therefore, there are some unknown factors that could affect the study results. Encouragingly, future research is expected to elucidate the role of HOST2 in gastric cancer with the advantage of the foundations this study has provided.

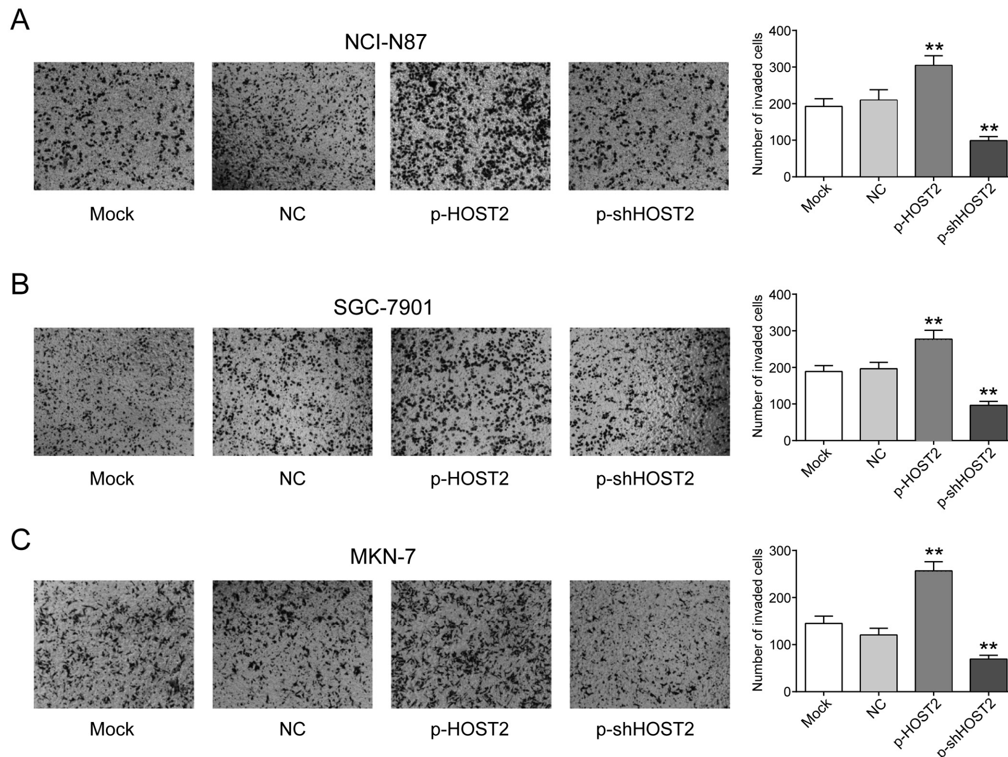

Figure 5. Transwell invasion assay of three GC cell lines in four transfected groups (×100 magnification). The gain-of-function of HOST2 can promote the cell invasion of GC cells and the silence of HOST2 would inhibit the invasion of GC cells: A) NCI-N87, B) SGC-7901, and C) MKN-7 cell line (refers to p<0.01 compared with the cells in the NC group).**

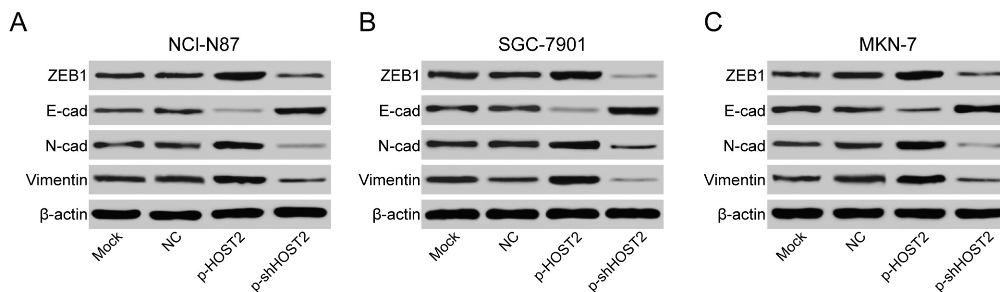

Figure 6. Western blot detected the expression of ZEB1, E-cadherin, N-cadherin and Vimentin in four transfected groups. HOST2 could promote EMT and the silence of HOST2 could suppress EMT in A) NCI-N87, B) SGC-7901, and C) MKN-7 cell line (refers to p<0.01 compared with the cells in the NC group).**

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