H19 serves as a diagnostic biomarker and up-regulation of H19 expression contributes to poor prognosis in patients with gastric cancer

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Emerging evidences indicate that dysregulated long noncoding RNAs (lncRNAs) are implicated in cancer tumorigenesis and progression and might be used as diagnosis and prognosis biomarker, or potential therapeutic targets. LncRNA H19 has been reported to be upregulated in diverse human cancers; however, its clinical significance in gastric cancer (GC) remains elusive. Expression levels of H19 in 128 pairs of GC and adjacent normal tissues, GC cell lines and GC juices compared to their corresponding controls were detected by real-time quantitative polymerase chain reaction (qPCR) assay. A receiver operating characteristic (ROC) curve and Kaplan–Meier analysis were constructed to evaluate the diagnostic and prognostic values. Univariate and multivariate analysis were performed using the Cox proportional hazard analysis. H19 expression was remarkably increased in GC tissues and cell lines compared with that in the normal control, and its up-regulation was significantly correlated to invasion depth (*P < 0.001), advanced TNM stage (*P = 0.002) and regional lymph nodes metastasis (*P < 0.001) in GC. H19 levels were robust in differentiating GC tissues from controls [area under the curve (AUC) = 0.697; 95% confidence interval (CI) = 0.636–0.752, *p<0.01]. Kaplan–Meier analysis demonstrated that increased H19 expression contributed to poor overall survival (*P = 0.017) and disease-free survival (*P = 0.024) of patients. A multivariate survival analysis also indicated that H19 could be an independent prognostic marker. The levels of H19 in gastric juice from gastric patients were significantly higher than those from normal subjects (*P = 0.034). Furthermore, knockdown of H19 expression by siRNA could inhibit cell migration and invasion in GC cells partly via regulating E-cadherin protein expression. H19 might serve as a promising biomarker for early detection and prognosis prediction of GC.

Key words: H19, gastric cancer, clinical relevance, invasion

Gastric cancer (GC) is the fourth most common malignancy in the world and is the second most frequent cause of cancer-related deaths worldwide, with particularly high incidence in East Asia. [1, 2]. Although GC is curable if detected early, most patients are diagnosed in the advanced stage and have poor prognosis [3]. The clinical stage, based on the TNM classification system, at the time of diagnosis is currently the most important prognostic factor, and the molecular mechanism involved in progression and metastasis of GC remains unclear [4]. Thus, novel findings on diagnosis and prognosis factors for GC would be of great clinical relevance.

A majority of the human genome is made up of non-coding RNAs (ncRNAs), indicating that ncRNAs could play significant regulatory roles in complex organisms[5]. These non-coding regions are interspersed throughout genomic DNA. One subcategory of these transcripts, called long noncoding RNAs (lncRNAs), are widely defined as transcribed RNA molecules more than 200 nucleotides in length and lacking an open reading frame of significant length[6]. It is known that lncRNAs are widely transcribed in the genome, but our understanding of their functions is limited. Many studies have revealed that the deregulated expression of lncRNAs plays a functional role...
in a variety of disease states [7, 8]. Functional lncRNAs can be used for cancer diagnosis and prognosis, and serve as potential therapeutic targets; thus, lncRNAs can be considered as a new diagnostic and therapeutic gold mine in cancer [9].

Recently, the functions of some of the lncRNAs have been reported as regulators in different tumors [10-12]. For example, HOTAIR, which is one of the few well-studied lncRNAs, plays a significant role in tumor progression by regulation of oncogene or tumor suppressor gene expression through binding to PRC2 [10]. In addition, metastasis-associated lung ade-nocarcinoma transcript 1 (MALAT1) facilitated renal cell carcinoma aggressive through Ezh2 and interacts with miR-205 [13]. Recently, multiple lines of evidences link dysregulation of lncRNAs to GC, such as HOTAIR, MALAT1, maternally expressed gene 3 (MEG3) and growth arrest-specific 5 (GASS) [14-16]. However, the function of most lncRNAs in GC and their clinical significance remain incompletely understood.

H19, is a paternally imprinted gene and is locate on chromosome 11p15.5, which does not encode for protein but encodes for a 2.3 kb noncoding RNA [17]. In the human genome, H19 gene is a member of a highly conserved cluster of imprinted genes, including paternally expressed insulin-like growth factor 2 (Igf2) and maternally expressed H19, both of which are regulated by the differentially methylated region (DMR) or the imprinting control region (ICR) located 4 kb upstream of the H19 gene [18]. It is highly expressed in embryogenesis but is nearly completely downregulated in most tissues after birth [18]. Currently, several studies have shown that H19 is overexpressed in tumors and functions as an oncogene gene [19-21]. Recent studies have showed that H19 is upregulated in human gastric carcinomas [22, 23]. However, the overall clinical role of H19 in GC has not yet been well characterized.

In this study, we found that H19 expression was upregulated in GC tissues and cell lines. High expression of H19 was associated with clinicopathological characteristics and poor prognosis in GC patients. We also determined its prognostic role in GC, which might dramatically improve the therapeutic strategy of GC.

Materials and methods

Cell lines. Human gastric adenocarcinoma cancer cell lines SGC7901, BGC823, MGC803, AGS and MKN45 and the normal gastric epithelium cell line (GES1) were obtained from the Chinese Academy of Sciences Committee on Type Culture Collection cell bank (Shanghai, China). MGC803, AGS and BGC823 cells were cultured in RPMI 1640; MKN45, GES1 and SGC7901 cells were cultured in DMEM (GIBCO-BRL) medium supplemented with 10% fetal bovine serum (FBS), 100 U/ml penicillin and 100 mg/ml streptomycin (Invitrogen, Carlsbad, CA, USA) at 37°C in 5% CO2.

Tissue samples and clinical data collection. In this study, we analyzed 128 patients who underwent resection of the primary GC at Yizheng People's Hospital of Jiangsu Province and Subei People's Hospital of Jiangsu Province. The study was approved by the Ethics Committee on Human Research of Yizheng People's Hospital of Jiangsu Province and Subei People's Hospital of Jiangsu Province and written informed consent was obtained from all patients. The clinicopathological characteristics of the GC patients are summarized in Table 1. All patients with GC have been followed up at intervals of 1–2 months until September 2014, and the median follow-
up period was 36 months (range, 20–48 months). Follow-up studies included physical examination, laboratory analysis, and computed tomography if necessary. Overall survival (OS) was defined as the interval between the dates of surgery and death. Disease-free survival (DFS) was defined as the interval between the dates of surgery and recurrence; if recurrence was not diagnosed, patients were censored on the date of death or the last follow-up.

Gastric juices were collected from 56 subjects, including 33 patients with GC (mean age, 61.7 ± 10.2 years) and 23 cases with normal mucosa or minimal gastritis (mean age, 57.3 ± 15.8 years) between July 2012 and November 2013 in the Endoscopy Center of the Yicheng People’s Hospital of Jiangsu Province. For each case, the diagnosis was confirmed by endoscopic examination followed by pathological diagnosis of biopsies. Cases with normal mucosa or minimal gastritis, which had no family history of GC, were treated as the controls. Gastric juice specimens were centrifuged at 2,000×g for 30 min at 4 °C to remove cell fragments and mucus. Then, the pH was measured using a glass electrode pH meter. Finally, the supernatants were stored at −80 °C until use. The study protocol was approved by the Ethics Committee of Yizheng People’s Hospital of Jiangsu Province. All specimens were handled and made anonymous following the ethical and legal standards.

RNA preparation and quantitative real-time polymerase chain reaction (qPCR). Total RNAs were extracted from tumorous and adjacent normal tissues or cultured cells using Trizol reagent (Invitrogen) following the manufacturer’s protocol. For gastric juice RNA extraction, 750 μl Trizol LS reagent (Invitrogen) was mixed with 250 μl gastric juice. After vortex mixing for 30 s and then standing for 5 min, 200 μl chloroform was added. The Trizol–chloroform mixture was vortex-mixed for 15 s and then centrifuged at 12,000×g for 15 min at 4 °C. The upper aqueous phase was transferred to a fresh tube. Finally, RNA was extracted following the manufacturer’s instructions. Total RNA was quantified using a SmartSpec Plus spectrophotometer (Bio-Rad, Hercules, CA, USA). The A260/A280 ratio was used to evaluate RNA purity. Reverse transcription (RT) and qPCR kits (Takara, Dalian, China) were used to evaluate the expression of H19 in tissue samples, cultured cells and gastric juice. The primers used for glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and H19 were as follows: 5′-TACAACACTGACATTACCTG-3′ (sense) and 5′-TGTTGCTGTAGCCAAATTCGTT-3′ (antisense) for GAPDH. The primer sequences were 5′-TACAACACTGACATTACCTG-3′ (sense) and 5′-TGAAATGCTTAGGCTGCT-3′ (antisense) for H19.

Real-time PCR was performed in triplicate, and the relative expression of H19 was calculated using the comparative cycle threshold (CT) (2−ΔΔCT) method with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as the endogenous control to normalize the data.

Cell transfection. To generate H19-knockdown BGC823 and MGC803 cells, the target sequence for H19 siRNA or scrambled siRNA that did not correspond to any human sequence was synthesized by Invitrogen. The sequence of H19 siRNA was 5′-GCAAGAAGCGGTCTGTTT-3′, and the scrambled siRNA was 5′-UUCUCAGGUGU- CACGUTT-3′. BGC823 and MGC803 cells were grown on six-well plates to confluence and transfected using Lipofectamine 2000 (Invitrogen) according to the manufacturer’s instructions. At 48 h post-transfection, cells were harvested for Western blot analysis.

Cell migration and invasion assays. For the migration assays, at 48 h post-transfection, 5×10⁴ cells in serum-free media were placed into the upper chamber of an insert (8-μm pore size; Millipore). For the invasion assays, 1×10⁵ cells in serum-free medium were placed into the upper chamber of an insert coated with Matrigel (Sigma–Aldrich). Medium containing 10% fetal bovine serum (FBS) was added to the lower chamber. After incubation for 24 h, the cells remaining on the upper membrane were removed with cotton wool. Cells that had migrated or invaded through the membrane were stained with methanol and 0.1% crystal violet, imaged, and counted using an IX71 inverted microscope (Olympus, Tokyo, Japan). Experiments were independently repeated three times.

Western blot assay and antibodies. Cells protein lysates were separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), transferred to 0.22-μm NC membranes (Sigma), and incubated with specific antibodies. ECL chromogenic substrate was used to visualize the bands and the intensity of the bands was quantified by densitometry (Quantity One software; Bio-Rad). GAPDH antibody was used as control, and antibodies (1:1000 dilution) against E-cadherin and N-cadherin were purchased from BD. Antibodies (1:1000 dilution) against vimentin were purchased from Cell Signaling Technology (MA, USA).

Statistical analysis. All statistical analyses were performed using SPSS 20.0 software (IBM, SPSS, Chicago, IL, USA). The significance of the differences between groups was estimated by the Student t-test, χ² test, or Wilcoxon test, as appropriate. DFS and OS rates were calculated by the Kaplan–Meier method with the log-rank test applied for comparison. Survival data were evaluated using univariate and multivariate Cox proportional hazards models. Variables with a value of P < 0.05 in univariate analysis were used in subsequent multivariate analysis on the basis of Cox regression analyses. Receiver operating characteristic (ROC) curves were constructed to evaluate the diagnostic value of H19 levels, by plotting sensitivity versus 100% specificity. Two-sided p-values were calculated, and a probability level of 0.05 was chosen for statistical significance.

Results

H19 was upregulated in tissues and cell lines. H19 expression levels were investigated using quantitative polymerase chain reaction (qPCR) assays in GC cell lines, including MGC803, BGC823, MKN45, SGC7901, AGS and the normal gastric epithelium cell line GES1. A significant high H19
expression was found in SGC7901, BGC823, MGC803, AGS and MKN45 compared to GES-1 (Fig. 1A). H19 expression were further detected in 128 paired GC samples and adjacent histologically normal tissues and the results showed that H19 expression was significantly higher in tumor tissues compared with adjacent normal tissues, 76.6 percentage was over-expression and 23.4 percentage was under-expression (P < 0.01; Fig. 1B).

**H19 expression and clinicopathological factors in GC.** To assess the correlation of H19 expression with clinicopathological data, H19 expression levels in tumor tissues were categorized as low or high in relation to the median value of relative H19 expression (4.47-fold, tumors/noncancerous). Clinicopathological factors were analyzed in the high and low H19 expression groups. As shown in Table 1, the high H19 group (n = 64) showed higher invasion depth (P < 0.001), advanced TNM stage (P = 0.002) and regional lymph nodes metastasis (P < 0.001) than the lower H19 expression group (n = 64). However, there was no significant correlation between H19 expression and other clinicopathological features, such as age, gender, tumor location, tumor size, histologic grade, lymphatic metastasis, and distant metastasis (P > 0.05).

**High H19 expression is associated with poor prognosis of patients with GC.** Kaplan–Meier analysis and log-rank test were used to evaluate the effects of H19 expression and the clinicopathological characteristics on disease-free survival (DFS) and overall survival (OS). The results showed that patients in the high H19 expression group had a higher recurrence rate (median DFS: 15 months) and much shorter overall survival (median OS: 18 months) than those in the low H19 expression group (median DFS: 25 months; median OS: 28 months; p = 0.007 and 0.001, respectively; Figure 2A, 2B). The 3-year DFS and OS were 34.8% and 32.5%, respectively, in the high H19 expression group, and 43.7% and 52.8%, respectively in the low H19 expression group. Univariate analyses of clinical variables considered as potential predictors of survival are shown in Table 2. The results revealed that H19 expression, TNM stage and distant metastasis were associated with DFS, while invasion depth, regional lymph nodes, H19 expression, TNM stage and distant metastasis were related to OS. Further analysis in a multivariate Cox proportional hazards model showed that H19 expression, together with TNM stage, was strongly associated with DFS. H19 expression was an independent prognostic indicator of DFS (hazard ratio [HR] = 1.287; 95% confidence interval [CI], 1.002–1.652; p = 0.048) in patients with GC (Table 2).

**Observation of the diagnostic value of using H19 as a marker.** We observed whether H19 could be used as a GC marker. We used corresponding adjacent non-tumorous tissues as a control to produce an ROC curve. The cutoff value was 4.615 (Δ Ct value). The area under the ROC curve was

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**Figure 1.** Relative expression of H19 in GC cell lines and GC tissues A. Relative expression of H19 in five GC cell lines (SGC7901, BGC823, MGC803, AGS and MKN45) and human normal gastric epithelial cell line (GES1) analyzed by quantitative RT-PCR. Experiments were performed in triplicate. Bars: SD (**p<0.01). B. Relative expression of H19 in GC tissues and adjacent normal tissues.

**Figure 2.** Kaplan–Meier overall survival curves of GC patients according to the level of H19 expression A. Disease-free survival of patients with GC based on H19 expression status (p < 0.001, log-rank) B. Overall survival of patients with GC based on H19 expression status (p = 0.005, log-rank).
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0.697; (95% CI = 0.636–0.752, \( P < 0.001 \); Fig. 3A). The sensitivity and specificity was 0.62 and 0.74, respectively. The Youden index of H19 was 0.360.

Gastric juice is a simple and easy-to-obtain sample which can provide available information in the diagnosis of GC. To evaluate the diagnostic value of H19, the levels of gastric juice H19 were detected in gastric juice between GC patients and normal cases. Interestingly, we found that H19 levels in gastric juice from patients with GC were significantly higher than those from normal subjects (\( p = 0.034 \), Fig. 3B).

Knock down of H19 represses GC cell migration and invasion in vitro. H19 promoting GC cell proliferation has been well documented [24], we further evaluated the role of H19 in cell migration and invasion. H19 was depleted in BGC823 and MGC803 cells, which exhibit a higher expression of H19. The knockdown of H19 in cells was confirmed by qPCR. (Fig. 4A). Subsequently, we observed the effect on cell migration and invasion. As shown in Fig. 4B, C, BGC823 and MGC803 cells, which have a naturally high H19 expression, after knockdown of H19, showed markedly repressed migra-

Table 2. Univariate and multivariate Cox regression analyses H19 for DFS or OS of patients in study cohort (n = 128).

<table>
<thead>
<tr>
<th>Variables</th>
<th>DFS</th>
<th>OS</th>
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<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
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<tr>
<td><strong>Univariate analysis</strong></td>
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<tr>
<td>Age(&lt;50years vs. &gt;50years)</td>
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<td>Gender(male vs. female)</td>
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<td>Location(Distal vs. Middle+ Proximal)</td>
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<tr>
<td>tumor size(&gt;5cm vs. &lt;5cm)</td>
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<td>0.766-1.232</td>
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<tr>
<td>Histologic differentiation(Well+ Moderately vs. Poorly+ Undifferentiated)</td>
<td>1.381</td>
<td>0.842-2.263</td>
</tr>
<tr>
<td>Invasion depth(T3+T4 vs. T1+T2)</td>
<td>1.418</td>
<td>0.880-2.286</td>
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<tr>
<td>TNM stage (II+IV vs. I+II)</td>
<td>2.269</td>
<td>1.406-3.662</td>
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<tr>
<td>Lymphatic metastasis(No vs. Yes)</td>
<td>0.814</td>
<td>0.642-1.031</td>
</tr>
<tr>
<td>Regional lymph nodes(PN2+ PN3 vs. PN0+ PN1)</td>
<td>1.531</td>
<td>0.922-2.542</td>
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<tr>
<td>Distant metastasis(No vs. Yes)</td>
<td>0.493</td>
<td>0.279-0.874</td>
</tr>
<tr>
<td>Expression of H19 (High vs. Low)</td>
<td>1.397</td>
<td>1.099-1.777</td>
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<td><strong>Multivariate analysis</strong></td>
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<tr>
<td>TNM stage (I+II vs. III + IV)</td>
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<td>1.058-2.181</td>
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<td>Invasion depth(T3+T4 vs. T1+T2)</td>
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<td>0.375-1.509</td>
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<tr>
<td>Regional lymph nodes(PN0+ PN1vs. PN2+ PN3)</td>
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<tr>
<td>Distant metastasis(No vs. Yes)</td>
<td>0.814</td>
<td>0.423-1.568</td>
</tr>
<tr>
<td>Expression of H19 (High vs. Low)</td>
<td>1.287</td>
<td>1.002-1.652</td>
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*\( P < 0.05 \)
tion and invasion ability (p < 0.05). These findings indicate that H19 may be closely associated with invasion and migration of GC cell lines.

**H19 affects the levels of E-cadherin proteins.** To explore the molecular mechanisms by which H19 contributes to the phenotypes of GC cells, we investigated potential targets involved in tumor invasion and metastasis. Epithelial-mesenchymal transition (EMT) has been identified to participate in cancer invasion and metastasis, so we conducted western blotting assays to detect the expression of EMT-induced markers (E-cadherin, N-cadherin and Vimentin) in cells down-expressing H19. Our findings showed that inhibited H19 expression levels remarkably induced E-cadherin expression, but with insignificant altered of N-cadherin and Vimentin expression (Figure 5).

![Figure 4. Knockdown of H19 inhibits GC cell migration and invasion in vitro](image)

**Figure 4.** Knockdown of H19 inhibits GC cell migration and invasion in vitro. A. qPCR analysis of H19 expression levels following the treatment of BGC823 and MGC803 cells with scrambled siRNA and si-H19. Experiments were performed in triplicate. Bars: SD; **p < 0.01.** B, C. Transwell assays were used to investigate the changes in the migratory and invasive abilities of GC cells. Experiments were performed in triplicate. Bars: SD; *p < 0.05 and **p < 0.01.

![Figure 5. H19 affects E-cadherin protein levels](image)

**Figure 5.** H19 affects E-cadherin protein levels. Western blot analysis of E-cadherin, N-cadherin and Vimentin in H19 knockdown expression GC cells and control cells. GAPDH protein was used as an internal control. **P<0.01
Discussion

H19 was the first lncRNA discovered [25]. Numerous studies indicate that H19 may play a key role in tumorigenesis and could contribute to tumor progression and aggressiveness. H19 overexpression has also been reported in various cancer tissues including breast, lung and esophageal cancers [19, 26, 27]. H19 IncRNA mechanisms of action appear to be extremely diverse, acting at various levels. H19 has been shown to guide chromatin modifying enzymes to specific loci. H19 binds to and recruit histone methyltransferase EZH2 at the E-cadherin promoter, leading to an increase in H3K27me3 repressive marks and to the silencing of the E-cadherin gene in bladder cancer [28]. H19 is also illustrated by its dual interaction with miR pathways; it acts as miR sponge to sequester miR-106a [29]. H19 serves as a precursor of miR-675 that post-translationally regulates a number of targets involved in cell tumorigenicity, including RUNX1 in GC [22]. However, the precise clinical significance in GC remains less understood.

In this study, we performed RT-qPCR to investigate whether H19 was altered in 128 pairs of GC tissues and adjacent normal tissues. Results showed that the expression level of H19 was increased in GC compared with that in adjacent normal specimens. Additionally, H19 expression is markedly increased in GC cell lines compared with normal gastric epithelium cell line. An ROC curve was constructed and the results indicated that H19 expression could better differentiate GC tissues from normal tissues. Aberrant expression of miRNA in gastric juice can be used as potential biomarkers for detecting GC [30]; however, there is little information on GC-specific lncRNAs.

In the study, we found that gastric juice H19 levels in GC patients were significantly higher than those of normal subjects. Recently, Zhou et al also demonstrated that plasma level of H19 was increased in GC patients, and it may potentially be useful for cancer screening[31]. Compared with their study, our results have more obvious advantages in the diagnosis of GC, because gastric juice is present only in the stomach and easy to obtain. Our results provided evidence that expression level of H19 was up-regulated in human GC, and this is the first time to characterize lncRNAs in gastric juice as diagnostic markers for GC.

To further determine the clinical significance of H19, the association between H19 expression and clinicopathological parameters in GC tissues was analyzed. The results revealed that high H19 expression was more frequently detected in tumors with deeper invasion depth, more lymphatic metastasis and advanced TNM stage. Additional, patients with a high expression of H19 seemed to have shorter OS and DFS than patients with lower levels. Furthermore, multivariate Cox analysis showed that H19 could serve as an independent prognostic biomarker. Since the clinicopathological parameters of depth of invasion, regional lymph nodes status and tumor stage represent partially the deterioration and progress of GC, H19 might be involved in the tumorigenesis and progression of GC. H19 promoting GC cell proliferation has been well documented [24], so we focus on the migration and invasion effects of H19. RNAi-mediated suppression of H19 in BGC823 and MGC803 cells led to a significant inhibition of migration and invasion. Therefore, H19 might serve to identify high-risk individual patients with GC who have higher risk of death and, thus, H19 may represent a promising target for GC treatment.

To further document the molecular mechanism by which H19 contributes to the migration and invasion of GC, we investigated potential target proteins involved in cell motility and matrix invasion. Here, loss of H19 in GC cells led to a significant increase in E-cadherin protein levels. Decreased E-cadherin expression is one of the alterations that characterize the invasive phenotype, and the data support its role as a tumor suppressor gene [32]. Our findings indicate that IncRNA H19 contributes to the GC cell migration and invasion maybe partly via regulating E-cadherin expression.

In conclusion, we demonstrated that H19 was significantly up-regulated in GC tissues and some GC cell lines, and might be capable of distinguishing between cancerous and non-cancerous conditions by examining the expression of H19 in tissues and gastric juices. Its level was associated with tumor progression and poor prognosis. This study revealed that H19 may regulate the migration and invasion ability of GC cells partly through regulation of E-cadherin expression. These findings suggested that H19 might be useful as a diagnostic and prognostic biomarker for GC and might be a possible target for gene therapy. However, larger clinical and prospective studies will need to be performed to confirm these preliminary results.

References


