INTRODUCTION

Gastric cancer (GC) is the most common gastrointestinal cancer; although the incidence rate has declined in recent years, GC is still the second leading cause of cancer, especially in China.1 Globally, in recent decades, its incidence rate has been the fourth highest, and its mortality rate is the third highest among cancers in males.2 Early-stage GCs are difficult to detect because the clinical features are not evident, and patients present with nonspecific symptoms.3 Currently, about 90% of GC is diagnosed at an advanced stage, and the five-year survival rate after surgery is below 30%.4 A study by Sumiyama found that the five-year survival rate of early-stage GC after treatment is greater than 90%.5 This implies that the early detection of GC is critical. However, due to the lack of specific biomarkers, GC is often not diagnosed until it has reached an advanced stage, which significantly affects the patient's prognosis.6 Thus, identifying novel biomarkers for the early detection of GC is critical.

LINC00152 acts as a competing endogenous RNA of HMGA1 to promote the growth of gastric cancer cells

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Funding information
Zhejiang Provincial Natural Science Foundation of China, Grant/Award Number: LY21C060001; K.C. Wong Magna Fund in Ningbo University

Abstract
Background: Long noncoding RNAs (lncRNAs) play important roles in almost every stage of cancer development. Given the competing endogenous RNA (ceRNA) hypothesis for the regulation of gene expression, we investigated the role of LINC00152 as a ceRNA in gastric cancer (GC) cells.

Methods: Gastric cancer cell lines were used in this study. Mimics of miRNAs and siRNA were used to evaluate the interaction between LINC00152 and HMGA1. The quantitative real-time polymerase chain reaction was performed for analyzing gene expression at the transcriptional level. Flow cytometry assay of cell cycle and western blot analysis of related protein expression levels were performed. Online databases such as TCGA and TIMER were used to determine the possibility of HMGA1 and LINC00152 as GC markers and their role in immune infiltration.

Results: Treating GC cell lines with LINC00152 siRNAs downregulated the expression of HMGA1. The cell cycle was arrested in the S phase following a reduction in LINC00152 or HMGA1 expression, whereas the expression of the cell cycle inhibitor P27 increased. In this study, we showed that acting as a ceRNA of HMGA1, LINC00152 has the same function as HMGA1, considering that it could control the cell cycle and promote GC cell proliferation. The TCGA database showed that LINC00152 might be used as a diagnostic marker for GC.

Conclusions: These findings provide mechanistic insights into the role of LINC00152 as a ceRNA to regulate HMGA1 expression in GC cells, where it can promote the proliferation of the GC cells by regulating the expression of the P27.
outcome of GC is closely related to the time of diagnosis. Therefore, determining the specific mechanism of GC to facilitate the screening of a population at high risk might be a feasible and efficient way to improve the current situation.

Many studies on the pathogenesis of GC have demonstrated that the development of GC is the result of combined mutations of multiple genes, like TEAD4-activated MNX1-AS1 to promote the progression of GC cells via the EZH2/BTG2 and the miR-6785-5p/BCL2 axes.\(^6,7\) LncRNAs do not participate in protein synthesis but have a direct biological function in the form of RNA.\(^8,9\) Several studies have linked lncRNAs to the pathophysiological mechanism of various diseases, especially during tumorigenesis.\(^9\) It was recently discovered that RNAs and microRNAs (miRNAs) show mutual influence, i.e., various types of RNAs such as IncRNA and miRNA “talk” to each other using microRNA response elements (MREs) to regulate gene expression, thus forming a competing endogenous RNA (ceRNA) network.\(^10\) As a ceRNA, IncRNA regulates gene expression at various levels by communicating with miRNAs to influence the initiation and progression of cancer and might be used as a biomarker for diagnosis and therapy.\(^11\)

Through the IncRNA microarray analysis of GC tissues, we discovered that the expression of many IncRNAs is altered in GC, with the greatest changes found in LINC00152 and gastric cancer–associated transcript 3 (GACAT3).\(^12,13\) LINC00152 was reported to be associated with cell cycle progression and cell proliferation in various cancers. For example, it promotes the growth and invasion of cells in papillary thyroid carcinoma and regulates the miR-497/BDNF axis;\(^14\) it acts as a ceRNA by sponging miR-193a/b-3p to decrease CCND1 expression and cell proliferation capacity in hepatocellular carcinoma;\(^15\) finally, it promotes tumor growth through the EGFR-mediated PI3K/AKT pathway in GC.\(^16\) However, the role of LINC00152 in GC concerning other signaling pathways still needs further investigation. HMGA1 is a protein closely related to tumor growth, infiltration, and metastasis and is highly expressed in various cancers.\(^17\) We have shown that IncRNA GACAT3 promotes GC cell proliferation as a ceRNA of HMGA1, and its overexpression reduces apoptosis induced by the anticancer chemical compound cucurbitacin B.\(^12\) In this study, we investigated if LINC00152 acts as a ceRNA to regulate HMGA1.

### 2 Materials and Methods

#### 2.1 Cell culture

Human gastric cancer cells AGS and BGC-823 were cultured in RPMI 1640 medium (Corning, USA) containing 10% (v/v) fetal bovine serum (PAN, Germany) and 100 U/ml penicillin-streptomycin (Sigma-Aldrich, USA) at 37°C with 5% CO₂.

#### 2.2 miRNA transfection and siRNA knockdown

The mimics of miRNAs Let-7a, miR-103, miR-196, miR-128a, and miR-138 as well as the negative control were synthesized by Shanghai GenePharma (Shanghai, China). The siRNA control, siHMGA1, and siLINC00152 were prepared as described previously,\(^18\) and the miRNA mimics and siRNAs were transfected into the cells using Lipofectamine 2000 and RNAiMAX, respectively, according to the manufacturer’s standard protocols (Invitrogen).

#### 2.3 Quantitative reverse transcription-polymerase chain reaction (qRT-PCR)

RNA was extracted using TRizol (Invitrogen), and the RNA concentration was assessed with Nanodrop 2000 (Thermo Scientific). A total of 500 ng RNA were reverse-transcribed to cDNA with random primer using the GoScript Reverse Transcription System (Promega). For quantification, real-time PCR analysis was performed using the LightCycler 480 SYBR Green I Master kit on a Light Cycler 480 II (Roche). The relative fold changes were calculated by the comparative threshold cycle method, and β-actin (Sigma-Aldrich) staining, and all experiments were performed 3 times.

#### 2.4 Cell proliferation assay

Cell proliferation was measured by cell number counting. Briefly, cells were seeded in 6-well plates at 2 × 10⁵ cells/well and cultured. Cell numbers were counted using a hemocytometer every 24 h after transfection. Apoptotic or dead cells were excluded using 0.2% trypan blue staining, and all experiments were performed 3 times.

#### 2.5 Cell cycle analysis

The cell cycle staining (MultiSciences Biotech Co., Ltd.) was used to analyze the cell cycle by flow cytometry. In brief, siRNA-treated cells were harvested and washed twice with ice-cold phosphate-buffered saline (PBS) and collected according to the previously described method.\(^19\) DNA content was analyzed on a BD FACS Calibur Flow Cytometer (BD Biosciences). Results were analyzed using the cell cycle analysis software ModFit LT (from Verity Software House, Inc.).

#### 2.6 Western Blot

Cells were lysed using a standard RIPA lysis buffer supplemented with 2-mM PMSF, and the extracted proteins were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis (12% SDS-PAGE). Proteins were detected using antibodies against HMGA1 (Active Motif Cat# 3961), P27 (Affinity Biosciences Cat# AF6324), and β-actin (Sigma-Aldrich Cat# A1978).

#### 2.7 Comprehensive analysis

The RNA-Seq data and related clinical information from TCGA were downloaded in GDC API; there are 375 cancer samples and 32 normal samples. All tumor samples are from before treatment. The RNA
expression of HMGA1, LINC00152, and Let-7a was analyzed and compared with stomach adenocarcinoma (STAD) and evaluated the area under the curve (AUC). Using GSEA to analyze the KEGG pathways to investigate possible biological functions of HMGA1, the online database GEPIA (http://gepia.cancer-pku.cn/index.html) was used to check the correlation analysis result between LINC00152/HMGA1 by TCGA and GTEx database. The TIMER (https://cistrome.shinyapps.io/timer/) correlation module was used to perform correlation analysis between HMGA1 and tumor-infiltrating immune cells. The TISIDB (http://cis.hku.hk/TISIDB/index.php) was used to evaluate tumor and immune system interactions in 28 types of TILs across human cancers and the correlation between TILs and STAD. The Human Pathology Atlas project (HPA) (www.proteinatlas.org) provides immunohistochemistry on tissue containing 44 different tissue types. In our study, the HPA was used to analyze protein expression of HMGA1 between normal and stomach cancer tissues.20

2.8 | Statistical analysis

The SPSS software 18.0 was used for statistical analysis. Statistical significance and p values were determined by one-way analysis of variance (ANOVA) and two-sample independent t test, and related values are shown as mean ± SD.

3 | RESULTS

3.1 | LINC00152 and HMGA1 are suppressed by the same miRNAs

The entire mRNA sequence of LINC00152 and the 3′-UTR sequence of HMGA1 were obtained from the NCBI database (National Center for Biotechnology Information, https://www.ncbi.nlm.nih.gov/). We used the software microT (http://diana.imis.athena-innovation.gr/DianaTools/), miRcode (http://www.mircode.org/mircode/) and TargetScan (http://www.targetscan.org/) to predict the binding sites of the miRNAs in LINC00152 and the HMGA1 3′-UTR. Two miRNAs, let-7a and miR-15, were found to have binding sites in both genes (Figure 1A). To verify the regulatory effects of the two miRNAs, mimics of let-7a and miR-15 were transfected into human GC cells AGS and BGC-823 (Figure 1B, C). Both miRNA mimics decreased the expression of LINC00152 and HMGA1 in BGC-823 cells two-fold (Figure 1B), while a greater reduction in the expression of

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**FIGURE 1** LINC00152 and HMGA1 are suppressed by the same miRNAs. (A) Common miRNAs that have putative binding sites in the LINC00152 and HMGA1 3′-UTR sequences are presented based on the analysis performed using microT, mirCode, and TargetScan. (B and C). Both LINC00152 and HMGA1 gene expression was inhibited by the common miRNAs. In vitro synthesized miRNA mimics of miR-7a and miR-15 were applied to human gastric cancer cells AGS and BGC-823. LINC00152 and HMGA1 expression levels were determined by qRT-PCR. Data represent the mean ± S.D. (n = 3). ***p < 0.001
**FIGURE 2**  HMGA1 and LINC00152 are reciprocally regulated. (A and B). To further verify that LINC00152 was used as the ceRNA of HMGA1, the relative expression of LINC00152 and HMGA1 in two GC cell lines (A) AGS, (B) BGC-823) was measured by qRT-PCR 48 h after siRNA transfection. Data represent the mean ± S.D. (n = 3). **p < 0.01; ***p < 0.001

**FIGURE 3**  HMGA1 and LINC00152 promote cell proliferation in GC cells. (A) Cell growth was determined by cell number after knockdown of LINC00152 and HMGA1 in AGS cell. (B) Analysis of the effects of LINC00152 and HMGA1 knockdown on the cell cycle by flow cytometry 48 h after siRNA transfection in AGS cell. Data represent the mean ± S.D. (n = 3). (C and D) GSEA indicates that high expression of HMGA1 is associated with the DNA replication (C) and cell cycle (D) in the TCGA database. **p < 0.01; ***p < 0.001
these two genes was observed in the AGS cells (Figure 1B), indicating that both genes are regulated by these two miRNAs.

3.2 | LINC00152 and HMGA1 are reciprocally regulated

The ceRNA hypothesis suggests that various types of RNA transcripts compete to bind to a common miRNA site, thereby affecting the level of free miRNAs and achieving mutual regulation. The results mentioned above showed that LINC00152 and HMGA1 share the same miRNA binding sites, and the inhibition of their expression by the same miRNAs is consistent with the ceRNA hypothesis. To further determine whether LINC00152 is a ceRNA of HMGA1, we reduced the expression of HMGA1 and LINC00152 by specific siRNAs. The expression of LINC00152 was significantly inhibited in HMGA1 knockdown AGS (Figure 2A) and BGC-824 (Figure 2B) cells. HMGA1 expression decreased when LINC00152 expression was inhibited (Figure 2). Thus, our results indicated that LINC00152 acts as the ceRNA of HMGA1, and the two genes mutually regulate each other.

3.3 | HMGA1 and LINC00152 promote cell proliferation in GC cells

HMGA1 has been reported to be highly expressed in GC and can promote tumor cell growth. We next tested whether LINC00152 had similar functions as HMGA1 in GC cells. Using specific siRNAs to reduce the expression of HMGA1 and LINC00152, we found that cell proliferation was significantly inhibited in AGS cell (Figure 3A). Moreover, the proportion of cells arrested in the S phase nearly doubled in HMGA1 knockdown (45.76%) and LINC00152 knockdown (40.84% and 37.34%) cells, compared to the proportion of arrested cells in the control group (24.09%) (Figure 3B). Furthermore, GSEA in the TCGA database indicated that a high expression of HMGA1 was associated with DNA replication (N = 1.8, nominal p-value = 0.001, FDR q-value = 0.047) and cell cycle (N = 1.8, nominal p-value = 0.012, FDR q-value = 0.045) (Figure 3C, D). These results revealed that the downregulation of both HMGA1 and LINC00152 can inhibit cell proliferation by affecting cell cycle progression.

3.4 | HMGA1 and LINC00152 regulate key cell cycle–related genes

To further elucidate the mechanism of how LINC00152 and HMGA1 block the proliferation of GC cells, we measured the expression levels of the cell cycle–related protein P27 at both the RNA and protein levels. The mRNA expression of P27 increased two-fold in the LINC00152 (Figure 4A) and HMGA1 knockdown groups, and the P27 protein level also increased (Figure 4B), compared to the levels in the control group. The protein expression of HMGA1 decreased 1.5-fold in the LINC00152 siRNA-treated cells, and the P27 protein level increased consistently in the HMGA1 siRNA-treated cells (Figure 4C). These results further indicated the mutual regulation of these two genes and that they regulate the cell cycle by altering the expression of P27.

3.5 | HMGA1 and LINC00152 are closely associated with GC

The TCGA database was used to investigate the expression of HMGA1, LINC00152, and Let-7a in GC. As shown by scatter plots, a significantly decreased Let-7a expression was observed in cancer tissues compared to that in normal tissues (p < 0.05), HMGA1 and LINC00152 were significantly decreased as well (p < 0.05, Figure 5A).
LINC00152 were highly expressed in cancer tissues (Figure 5A–C). These clinical results from the database were consistent with the results of our cell experiments, suggesting that Let-7a, HMGA1, and LINC00152 affect GC by forming a ceRNA network. Additionally, a positive correlation between HMGA1 and LINC00152 in stomach tumors was detected from the GEPIA database (Figure 5D).

Immunohistochemistry (IHC) staining indicated that HMGA1 protein expression was higher in tumor tissues than in nontumor tissues from the HPA (Figure 6A). After integrating the clinicopathological parameters and gene expression profiles to analyze the potential ability of HMGA1 and LINC00152, the AUC indices for the HMGA1 and LINC00152 were found to be 0.795 and 0.848 (Figure 6B, C). These results suggested that HMGA1 and LINC00152 might be used as diagnostic markers of STAD.

3.6 | HMGA1 influences immune infiltration and is associated with tumor-infiltrating lymphocytes

Tumor progression is associated with the suppression of antitumor immunity.22 As HMGA1 can promote cell proliferation during cancer development, we used the TIMER database to analyze the impact of HMGA1 in immune infiltration, after determining the multiple types of copy number alterations (CNAs) of HMGA1 that were significantly correlated with the infiltration levels of several immune cells in STAD, both in HMGA1 deletion and amplification (Figure 7A and Table S1). We next performed correlation analysis between HMGA1 and immune infiltration level for STAD. HMGA1 expression showed a significant negative correlation with the levels of B cells, CD8 + T cells, CD4 + T cells, macrophages, neutrophils, and dendritic cells (p < 0.001, Figure 7B), leading to a general decrease in immune infiltration.

Additionally, we further assessed the possible correlations between 28 types of tumor-infiltrating lymphocytes (TILs) through the TISIDB database. The results showed significant correlations between HMGA1 and the 28 types of TILs found in human cancers (Figure 8A). HMGA1 showed significantly negative correlations with the abundance of eosinophil (rho = -0.404, p < 0.001), Tem CD4 (rho = 0.485, p < 0.001), Mast (rho = -0.352, p < 0.001), and Act B (rho = -0.312, p < 0.001) (Figure 8B–E). These results indicated that HMGA1 has the potential to regulate immune infiltration in GC.

4 | DISCUSSION

LncRNA was considered a junk gene until the ceRNA hypothesis was proposed, which suggests that lncRNA, cirRNA, and miRNA can interact with other mRNAs through the ceRNA mechanism to regulate cellular functions.10,23 Moreover, the dysregulation of lncRNAs may disrupt cellular functions and lead to diseases, including cancer.23 For example, Inc-ATB was found to promote tumor progression by interacting with miR-141-3p/TGF-β2 in a ceRNA-mediated manner,
and high expression of LNC-ATB indicates a poor prognosis in GC patients. In this study, we found that HMGA1 shares common miRNA binding sites (let-7a and miR-15) with LINC00152, and that the HMGA1 and LINC00152 expression are mutually regulated.

We used the TCGA data to verify our hypothesis that the expression of miRNA Let-7a in gastric cancer tissue was downregulated, and the expression of HMGA1 and LINC00152 was upregulated, which showed that our previous hypothesis, i.e., HMGA1-Let-7a-LINC00152 is a ceRNA, was correct. Moreover, the expression of RNA and protein indicated the value of HMGA1 and LINC00152 as diagnostic markers.

HMGA1 is a transcriptional regulatory molecule involved in tumorigenesis, affecting the normal growth and differentiation of cells, gene transcription and regulation, cell cycle progression, and DNA replication and repair in various ways. Normally, the expression level of HMGA1 is very low, but HMGA1 is a cancer-promoting gene that is overexpressed in many malignant tumors. Previous studies have found that HMGA1 is overexpressed in GC cells and promotes their proliferation. In this study, we also found that HMGA1 promoted GC cell proliferation and that the cell cycle was arrested in the S phase when HMGA1 expression was inhibited. The main function of P27 is to control the cell cycle by inhibiting the progression of cells from the G1 phase to the S phase after binding to cyclin/Cdk2. Thus, we selected P27 to elucidate the role of HMGA1 and LINC00152 in cell cycle and proliferation. As a ceRNA of HMGA1, LINC00152 has a similar function in GC cell proliferation. Furthermore, we found that the cell cycle inhibitor P27 was upregulated in AGS cells after the downregulation of HMGA1/LINC00152, thereby blocking cell growth. The results indicated that low levels of HMGA1 and LINC00152 arrest cell cycle progression and inhibit GC cell proliferation, suggesting that LINC00152 promotes tumor growth and can form a ceRNA network with HMGA1 to regulate the proliferation of GC cells.

In the tumor microenvironment, immune cells are crucial elements and significantly influence tumor progression. Our study used the TIMER and TISIDB databases to reveal the connections between the expression of HMGA1 and immune infiltration levels in STAD. We found that HMGA1 has a strong negative correlation with macrophages and CD4+ T cells. Macrophages can perform phagocytosis of immune cells. Changes in the levels of immune infiltration indicated that the ability of macrophages was affected by the expression of HMGA1. Furthermore, we found that the expression of HMGA1 also had a very strong negative correlation with the abundance of TILs, particularly eosinophil, Tem_CD4, Mast, and Act_B cells. Thus, combining the results of the biosynthesis analysis and the cell experiments, we hypothesized that HMGA1 might...
promote the proliferation of GC cells, possibly by reducing the infiltration level of immune cells and the content of TILs. Additionally, we found that LINC00152 has the same function as HMGA1 in GC cells, and LINC00152 might also promote GC proliferation by affecting immune cells.

5 | CONCLUSION

In summary, our findings provided mechanistic insights into the role of LINC00152 as a ceRNA to regulate HMGA1 expression in GC cells. LINC00152 thus promotes the proliferation of GC cells.
by regulating the expression of the cell cycle inhibitor P27. The immune-related bioinformatics results showed that HMGAI and LINCO00152 play a role in the cell cycle and proliferation of GC cells, perhaps by reducing the infiltration of immune cells and the content of TILs. Moreover, the bioinformatics results indicated that HMGAI and LINCO00152 might be used as diagnostic markers of GC.

ACKNOWLEDGEMENTS
This work was supported by the Zhejiang Provincial Natural Science Foundation of China [grant number LY21C060001] and the K.C. Wong Magna Fund in Ningbo University.

DATA AVAILABILITY STATEMENT
All data included in this study are available upon request by contact with the corresponding author.

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SUPPORTING INFORMATION
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How to cite this article: Chen J, Zheng Q, Liu F, Jin H, Wu X, Xi Y. LINCO00152 acts as a competing endogenous RNA of HMGAI to promote the growth of gastric cancer cells. J Clin Lab Anal. 2022;36:e24192. doi: 10.1002/jcla.24192