Original Article
LncRNA CERNA2 is an independent predictor for clinical prognosis and is related to tumor development in gastric cancer

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Abstract: Gastric cancer (GC) is the second most common cancer-related mortality worldwide. Mounting evidence has demonstrated that dysregulated long noncoding RNAs (lncRNAs) are involved in the development of GC. LncRNA CERNA2 (competing endogenous lncRNA 2 for microRNA let-7b) was previously found to be upregulated and play an oncogenic role in hepatocellular carcinoma, osteosarcoma and breast cancer. However, the clinical significance and biological functions of CERNA2 in GC remain largely unknown. In this study, we found that CERNA2 expression was significantly increased in GC tissues and cell lines compared to adjacent non-cancerous tissues and normal gastric epithelial cells, respectively. High levels of CERNA2 were correlated with poor clinical parameters and an unfavorable prognosis of GC patients. Moreover, silencing CERNA2 expression effectively inhibited gastric cancer cell growth and induced cell apoptosis in vitro. Collectively, our results demonstrate that the up-regulation of CERNA2 is associated with malignant status and poor prognosis in patients with GC, and silencing CERNA2 expression inhibits gastric cancer cell growth and promotes cell apoptosis, suggesting CERNA2 could possibly be a promising diagnostic and treatment target for GC.

Keywords: GC, lncRNAs, CERNA2, expression, prognosis

Introduction
Gastric cancer (GC) is one of the most aggressive human malignancies and is the second leading cause of cancer-related mortality globally [1]. Many patients are diagnosed with advanced GC and have a poor 5-year survival rate, and over half of GC patients have a carcinoma recurrence after surgical treatment [2]. Much progress has been made in the molecular understanding of GC development in the past decades, including tumor suppressor gene mutations, aberrant gene expression and cancer stem cell activation [3]. However, effective strategies to decrease the incidence and mortality of GC remain lacking. Therefore, a better understanding of the pathogenesis and identification of the molecular alterations is urgent and essential for the development of early diagnostic biomarkers that aid new effective therapies for GC.

Long non-coding RNAs (lncRNAs) are a class of newly found non-coding RNAs longer than 200 nucleotides (nt) [4, 5]. LncRNAs are widely distributed in the human genome that regulates gene expression at the transcriptional and/or post-transcriptional levels [6]. So far, over 3,000 lncRNAs have been identified and well described; they participate in a large range of cellular biological processes, such as proliferation, differentiation, invasion, metastasis, and apoptosis [7, 8]. Recent evidence has indicated that some lncRNAs are dysregulated in various human cancers and play important roles in tumorigenesis and tumor progression [9]. For example, Sun et al. [10] reported that increased expression of HULC (hepatocellular carcinoma up-regulated long non-coding RNA) indicates a poor prognosis and promotes cell metastasis in osteosarcoma. Qiu et al. [11] showed that CDKN2B-AS1 (CDKN2B antisense RNA 1) pre-
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dicts a poor prognosis and increases the invasion and metastasis in serous ovarian cancer. Zhang et al. [12] demonstrated that downregulation of TUG1 (Taurine up-regulated 1) inhibits the proliferation, migration, and invasion and promotes the apoptosis of renal cell carcinoma. Moreover, Ma et al. [13] suggested that MALAT1 (Metastasis associated lung adenocarcinoma transcript 1) plays an important role in glioma progression and prognosis. Thus, IncRNAs may serve as useful tumor biomarkers and therapeutic targets for controlling malignant tumors.

In the present study, we focus on IncRNA CERNA2 (competing endogenous IncRNA 2 for microRNA let-7b), also known as HOST2, a transcript mapped to the human chromosome 10q23.1 location. CERNA2 was previously reported to be upregulated in epithelial ovarian cancer, and the knockdown of CERNA2 contributes to tumor cell growth arrest, invasion, and migration inhibition, and apoptosis induction [14]. Recently, it was reported that inhibition of CERNA2 suppresses the proliferation, migration, and invasion and promotes the apoptosis of osteosarcoma cells [15]. Moreover, CERNA2 expression was found to be higher in breast cancer tissues compared with adjacent normal tissues, and the overexpression of CERNA2 promotes cell migration and invasion in breast cancer [16]. Up to the present, the clinical significance and biological functions of CERNA2 in GC remain largely unclear.

The aim of this study is to identify and characterize the expression pattern and clinical significance of CERNA2 in GC and further explore its biological roles in GC. First, we detected the expression levels of CERNA2 in GC tissues and cell lines by using a real-time PCR assay. Then, we analyzed the association between CERNA2 expression and the clinical parameters of GC patients, to determine if it could be a novel biomarker for poor prognosis. Furthermore, loss-of-function studies of CERNA2 on cell growth and apoptosis in GC were performed using 3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide and Hoechst 33342 staining assays. This study advances our understanding of the roles of CERNA2 as a regulator of GC pathogenesis and facilitates the development of IncRNA-directed diagnostics and therapeutics for GC.

Material and methods

Clinical sample

This study was approved by the Ethics Committees of the First Affiliated Hospital of Bengbu Medical College (Bengbu, China). All clinical investigations were conducted according to the provisions of the Helsinki Declaration. Informed consents were provided by each patient or a legal representative. 67 paired tissue specimens (GC tissues and corresponding non-cancerous tissues) were obtained from patients with GC who had undergone surgery between February 2010 and December 2013 at the First Affiliated Hospital of Bengbu Medical College. No patient received chemotherapy or radiotherapy before surgery. The corresponding non-cancerous tissues were obtained from tissues that were located 5 cm away from the...
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Table 1. Correlations between lncRNA CERNA2 expression and clinicopathological factors in GC patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (n=67, %)</th>
<th>Mean ± SD</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
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<tr>
<td>&lt;60</td>
<td>22 (32.84)</td>
<td>10.19 ± 0.86</td>
<td>0.614</td>
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<tr>
<td>≥ 60</td>
<td>45 (67.16)</td>
<td>10.46 ± 0.90</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
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<tr>
<td>Male</td>
<td>40 (59.70)</td>
<td>10.30 ± 0.94</td>
<td>0.585</td>
</tr>
<tr>
<td>Female</td>
<td>27 (40.30)</td>
<td>10.52 ± 0.81</td>
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</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
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<tr>
<td>Distal-middle</td>
<td>19 (28.36)</td>
<td>10.75 ± 0.74</td>
<td>0.327</td>
</tr>
<tr>
<td>Proximal</td>
<td>48 (71.64)</td>
<td>10.21 ± 0.77</td>
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<tr>
<td>Diameter (cm)</td>
<td></td>
<td></td>
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<tr>
<td>&lt; 5</td>
<td>12 (17.91)</td>
<td>10.53 ± 1.06</td>
<td>0.706</td>
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<tr>
<td>≥ 5</td>
<td>55 (82.09)</td>
<td>10.34 ± 0.93</td>
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<tr>
<td>Histological differentiation</td>
<td></td>
<td></td>
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<tr>
<td>Well-moderate</td>
<td>26 (38.81)</td>
<td>9.05 ± 0.72</td>
<td>0.003</td>
</tr>
<tr>
<td>Poor</td>
<td>41 (61.19)</td>
<td>11.21 ± 1.15</td>
<td></td>
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<tr>
<td>Depth of invasion</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>T1-T2</td>
<td>16 (23.88)</td>
<td>10.17 ± 0.92</td>
<td>0.540</td>
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<tr>
<td>T3-T4</td>
<td>51 (76.12)</td>
<td>10.43 ± 0.89</td>
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<td>Lymph node metastasis</td>
<td></td>
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<tr>
<td>N0</td>
<td>28 (41.79)</td>
<td>9.68 ± 0.87</td>
<td>0.015</td>
</tr>
<tr>
<td>N1-N3</td>
<td>39 (58.21)</td>
<td>10.87 ± 0.99</td>
<td></td>
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<tr>
<td>Distant metastasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>59 (88.06)</td>
<td>10.11 ± 0.83</td>
<td>0.001</td>
</tr>
<tr>
<td>M1</td>
<td>8 (11.94)</td>
<td>12.29 ± 1.40</td>
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<td>TNM stage</td>
<td></td>
<td></td>
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<tr>
<td>I-II</td>
<td>25 (37.31)</td>
<td>9.84 ± 0.91</td>
<td>0.037</td>
</tr>
<tr>
<td>III-IV</td>
<td>42 (62.69)</td>
<td>10.68 ± 0.99</td>
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LncRNA, long noncoding RNA; CERNA2, competing endogenous lncRNA 2 for microRNA let-7b; SD, standard deviation; GC, gastric cancer.

edge of GC. The paired tissue specimens were observed and evaluated by pathologists. Following excision, the paired tissue specimens were immediately frozen in liquid nitrogen and stored at -80°C until use. Tumor stage evaluation was based on the tumor-node-metastasis (TNM) classification system, and the histopathological evaluation was conducted according to the eighth edition of the AJCC Cancer Staging Manual [17]. The pathological information (gender, age, diameter, location, histological differentiation, depth of invasion, TNM stage, lymph node metastasis, and distant metastasis) was collected.

Real-time PCR

Total RNA was extracted from the tissues and cell lines using RNAiso Plus (Takara, Dalian, China) according to the manufacturer’s instructions. The cDNA (complementary DNA) was synthesized by using a RR036A Takara PrimeScript™ RT Master Mix kit (Takara, Dalian, China), according to manufacturer protocols. The reaction was run under the following conditions: 37°C for 60 min, 85°C for 5 s, and then stored at 4°C. A real-time PCR assay was conducted by using a RR820A SYBR® Premix Ex Taq™ II kit (Takara, Dalian, China) on the Roche LightCycler 480 Real-Time PCR System (Roche Diagnostics, Basel, Switzerland) according to the manufacturer’s instructions. The sequence specific forward and reverse primers for CERNA2 were 5’-CTC-AAATCAATCAGCCT-3’ and 5’-AA-TGTAGCAGAGCC-3’, respectively. The forward and reverse primers sequences for GAPDH mRNA were 5’-CCACCATGCGAAATTC-3’ and 5’-TCTAGCGCGAGCGC-3’, respectively. The reaction conditions were: pre-denaturation at 95°C for 30 s, denaturation at 95°C for 5 s, annealing at 55°C for 30 s, and extension at 72°C for 30 s for a total of 40 cycles. The expression level of CERNA2 was normalized to GAPDH mRNA and was determined by using 2-ΔΔCt method [18].

Cell line and cell culture

Three human GC cell lines (SGC7901, MGC803, and BGC823) and normal gastric epithelium cells (GES-1) were purchased from the Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences (Shanghai, China). Cells were cultured in DMEM (Gibco, NY, USA) and 10% FBS (Gibco, NY, USA) in humidified air containing 5% CO2 at 37°C, supplemented with 100 mg/mL streptomycin sulfate and 100 U/mL penicillin.

CERNA2 siRNA synthesis and cell transfection

The chemically modified siRNA oligo was synthesized by GenePharma Co., Ltd (Shanghai, China). The sense sequence of CERNA2 siRNA was 5’-GACUAAACAAGGUCUAAUTT-3’ and the antisense sequence was 5’-AUUAAGCACCUG-UUAGUCTT-3’. The NC sequence had the
same composition with the siRNA sequence but without obvious homology. The sense sequence of NC siRNA was 5'-UUCUCCGAAC-GUGUCAGCAGUTT-3' and the antisense sequence was 5'-ACGUGACACGUUCGGAGAATT-3'. SGC7901 and BGC823 cells were inoculated in six-well plates with a concentration of 4×10^5 cells/well. Then, GC cells were transiently transfected with either 50 nmol CERNA2 siRNA or NC siRNA by using Lipofectamine 2000 transfection reagent (Invitrogen, Carlsbad, USA) according to the manufacturer’s instructions. After transfection for 48 h, the cells were harvested for a real-time PCR assay to measure the CERNA2 expression in order to evaluate the effect of the CERNA2 siRNA silencing CERNA2.

**Cell proliferation analysis**

The cell proliferative ability was analyzed by using a 3-(4, 5-Dimethyl-2-thiazolyl)-2, 5-di-phenyl-2-H-tetrazolium bromide (MTT) assay. Briefly, 4×10^3 SGC7901 and BGC823 cells were seeded into 96-well plates, repeated four times for each condition. Then, GC cells were transiently transfected with either 10 nmol CERNA2 siRNA or NC siRNA by using the Lipofectamine 2000 transfection reagent. The cells were incubated for 1, 2, 3, and 4 days, and twenty microliters of MTT (5 mg/ml; Sigma-Aldrich, St. Louis, MO, USA) was added to each well and incubated in humidified air containing 5% CO_2 at 37°C for 4 h. After that, the supernatants were removed and 180 μL of DMSO (Sigma-Aldrich, St. Louis, MO, USA) was added to each well. The optical density (OD) of each well was measured using a Thermo Scientific Multiskan MCC microplate reader (Thermo Scientific, Waltham, MA, USA) at 480 nm.

**Hoechst 33342 staining assay**

The SGC7901 and BGC823 cells transfected with CERNA2 siRNA or NC siRNA were cultured in 6-well plates. After transfection for 48 h, the cells were fixed with 4% paraformaldehyde for 30 min, and 1 μL of Hoechst 33342 (Sigma-Aldrich, St. Louis, MO, USA) was added to each well. The changes in nuclear morphology were detected by fluorescent microscopy (Eclipse 50i; Nikon, Shinjuku, Tokyo, Japan), and the percentage of cell apoptosis was calculated.

**Statistical analysis**

The data was presented as the mean ± standard deviation (SD) from at least three independent experiments. The statistical analysis was
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Expression of CERNA2 is upregulated in human GC tissues and cell lines

We first examined the CERNA2 expression levels in 67 paired GC tissues and corresponding non-cancerous tissues by real-time PCR assay, and the CERNA2 levels were normalized to GAPDH mRNA expression. The results revealed that CERNA2 expression was significantly up-regulated in the GC tissues compared with the corresponding non-cancerous tissues (Figure 1A, *P<0.05). The expression of CERNA2 was upregulated in 92.54% (62/67) of GC tissues compared with corresponding non-cancerous tissues. The average expression level of CERNA2 in the GC tissues compared with the corresponding non-cancerous tissues was 2.23-fold. To confirm the results of CERNA2 in the GC tissues, we observed its expression levels in three human GC cell lines (SGC7901, MGC803, and BGC823) and in normal gastric epithelium cells (GES-1). As shown in Figure 1B, the levels of CERNA2 in the SGC7901, MGC803, and BGC823 cells were also significantly higher than that in the GES-1 cells (*P<0.05). The data indicate that the up-regulation of CERNA2 may be related to the pathogenesis of GC.

Correlations between CERNA2 expression and clinicopathological factors in GC patients

To identify the clinical relevance of CERNA2 expression in GC patients, the correlation...
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between CERNA2 expression and the clinicopathological parameters such as age, gender, location, diameter, histological differentiation, depth of invasion, lymph node metastasis, distant metastasis, and TNM stage were analyzed. As shown in Table 1, a high level of CERNA2 was significantly correlated with poor histological differentiation \( (P=0.003) \), more lymph node metastasis \( (P=0.015) \), more distant metastasis \( (P=0.001) \), and higher TNM stage \( (P=0.037) \). Taken together, these data suggest that increased CERNA2 expression is associated with poor clinical parameters in GC patients.

Association between CERNA2 expression and the prognosis of GC patients

GC patients \( (n=67) \) were classified into the low CERNA2 expression group \( (n=36) \) and the high CERNA2 expression group \( (n=31) \) according to the mean ratio of CERNA2 expression (Figure 2A). To explore the prognostic value of CERNA2 expression in GC patients, we measured the association between the expression of CERNA2 and GC patients’ survival by using Kaplan-Meier method and log-rank test. In 67 GC patients with prognosis information, we found that CERNA2 expression was significantly associated with the overall survival of GC patients, as patients in the high CERNA2 expression group had poorer overall survival than those in the low CERNA2 expression group (Figure 2B, \( P<0.001 \)). As shown in Table 2, four prognostic factors were identified by univariate Cox regression analysis, including lymph node metastasis \( (N0 \text{ vs. } N1-N3) \), distant metastasis \( (M0 \text{ vs. } M1) \), TNM stage \( (I+II \text{ vs. } III+IV) \), and CERNA2 expression \( (\text{low vs. high}) \). Other clinicopathological characteristics, such as age, gender, location, diameter, histological differentiation, and depth of invasion, were not statistically significant prognosis factors. Furthermore, multivariate Cox regression analysis showed that CERNA2 expression \( (P=0.024) \), lymph node metastasis \( (P=0.041) \), and TNM stage \( (P=0.013) \) were independent prognostic markers for patients with GC. These data indicate that CERNA2 expression is an independent predictor for overall survival in patients with GC.

CERNA2 silencing impairs the growth of GC cells in vitro

As CERNA2 was remarkably overexpressed in GC tissues and cell lines and CERNA2 upregulation indicated a poor prognosis in patients with GC, we next explored its biological functions in GC cells. To understand whether CERNA2 is involved in the growth of GC cells, we transiently transfected CERNA2 siRNA or NC siRNA into SGC7901 and BGC823 cells to knockdown CERNA2 expression. Forty-eight hours after transfection, we compared with cells treated with NC siRNA, and CERNA2 expression was significantly decreased in the SGC7901 and BGC823 cells after being treated with CERNA2 siRNA (Figure 3, \( P<0.05 \)). Then, CERNA2 siRNA or NC siRNA was transfected into GC cells, and an MTT assay was performed to determine cell proliferative ability. The growth curves showed that CERNA2 siRNA treated SGC7901 cells had a decreased growth ratio to NC siRNA transfected cells over a four day period (Figure 4A, \( P<0.05 \)). Similarly, CERNA2 silencing significantly suppressed cell growth in BGC823 cells.
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(Figure 4B, P<0.05). These results suggest that CERNA2 inhibition dramatically suppresses GC cells growth.

Knockdown of CERNA2 promotes the apoptosis of GC cells in vitro

To determine whether apoptosis was a contributing factor to cell growth inhibition, we performed a Hoechst 33342 staining assay analysis of CERNA2 siRNA or NC siRNA transfected SGC7901 and BGC823 cells. The results showed that the number of cells with condensed and fragmented nuclei indicating the fraction of early apoptotic cells was significantly different in CERNA2 siRNA treated cells compared with NC siRNA transfected cells. Compared with the NC siRNA group, the percentage of early apoptotic cells was significantly increased in the CERNA2 siRNA group (Figure 5, P<0.05). These results demonstrate that CERNA2 suppression dramatically promotes GC cells apoptosis.

Discussion

As the discovery of the roles of HOTAIR (HOX transcript antisense RNA) lifts IncRNAs to new levels, a large number of studies have demonstrated the functions of IncRNAs in diverse biological processes, such as the development and immunity of a wide range of diseases, including human cancer [19]. Unsurprisingly, accumulating studies have illustrated that IncRNAs are dysregulated in GC and closely related to tumorigenesis and progression [20]. Growing evidence highlights the important roles of IncRNAs acting as biomarkers for the early diagnosis of GC, as indicators of GC prognosis, or even as therapeutic targets in GC.

For example, Sox2ot (SOX2 overlapping transcript) overexpression serves as a poor prognostic biomarker and increases cell growth and motility in GC [21]. SPRY4-IT1 (SPRY4 intronic transcript 1) predicts poor patient prognosis and promotes tumorigenesis in GC [22]. Downregulated MEG3 (Maternally expressed 3) is associated with metastatic GC and inhibits gastric carcinogenesis [23]. In addition, SNHG6 (small nucleolar RNA host gene 6) is associated with a poor prognosis of GC and facilitates cell proliferation and epithelial-mesenchymal transition [24].

As a novel gene, CERNA2 is a member of IncRNAs with 2.9 kb in length contains multiple copies of retroviral-related sequences in the absence of an obvious open reading frame. Gao et al, reported that CERNA2 promotes tumor cell proliferation, migration, and invasion in epithelial ovarian cancer [14]. Recently, Liu et al, demonstrated that CERNA2 promotes cell proliferation, migration and invasion and inhibits cell apoptosis in the human hepatocellular...
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carcinoma cell line SMMC-7721 [25]. Lu et al. showed that CERNA2 increases cell motility, migration and invasion in breast cancer [16]. This common characteristic has therefore strengthened the clinical application value of CERNA2. Therefore, we hypothesized that CERNA2 expression was also increased in GC tissues and the up-regulation of CERNA2 could predict the prognosis of patients with GC. To test this hypothesis, paired tissue specimens (GC tissues and corresponding non-cancerous tissues) from 67 GC patients were collected, and CERNA2 expression was detected in GC tissues and cell lines by using a real-time PCR assay. Our study first found the expressions of CERNA2 were obviously increased in GC tissues and cell lines compared with adjacent non-cancerous tissues and normal gastric epithelial cells. This result was similar with CERNA2 expression in epithelial ovarian cancer and breast cancer.

The clinical significance of CERNA2 has been reported in osteosarcoma and breast cancer. In patients with osteosarcoma, CERNA2 expression was not associated with age, gender, or histopathologic subtype [15]. In patients with breast cancer, CERNA2 expression was associated with lymph node metastasis as well as clinical stage, and not correlated with age, tumor type or tumor size [16]. We then used the mean expression level of CERNA2 as a cutoff to divide the 67 patients into the high CERNA2 expression group (n=31) and the low CERNA2 expression group (n=36). The Pearson's chi-squared test was used to examine the correlation between the expression of CERNA2 and the clinicopathological characteristics. In GC, we presented evidence showing that patients in the high CERNA2 expression group showed poor histological differentiation, more lymph node metastasis, more distant metastasis, and higher TNM stages than those in the low CERNA2 expression group. Importantly, high CERNA2 expression was correlated with poor overall survival and could be an independent prognostic factor in patients with GC. These findings indicate that CERNA2 plays a direct role in the regulation of GC progression and may be used as a novel biomarker for GC prognosis.

To further investigate the biological roles of CERNA2 in GC, we explored the effects of CERNA2 on the proliferation and apoptosis of GC cells by applying a loss-of-function approach. SGC7901 and BGC823 cells with higher CERNA2 expression were chosen to investigate the effects of CERNA2 inhibition on GC cells phenotype. The result showed that RNAi-mediated suppression of CERNA2 in SGC7901 and BGC823 cells led to a significant cell growth arrest and the promotion of apoptosis. The data was similar with CERNA2 effects in epithelial ovarian cancer, osteosarcoma, and breast cancer. These findings indicate that CERNA2 promotes cell proliferation and inhibits cell apoptosis in GC.

In conclusion, our results provide the first evidence that CERNA2 is highly expressed in GC tissues and cell lines, and the enhanced expression of CERNA2 is correlated with poor clinical parameters and unfavorable prognosis of patients with GC. Knockdown of CERNA2 suppresses cell proliferation and induces cell apoptosis in GC. These data suggest an important role of CERNA2 in the molecular etiology of GC and facilitate the development of lncRNA-directed prognosis and therapeutics against this cancer.

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Disclosure of conflict of interest

None.

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