

RESEARCH ARTICLE

MicroRNA-148a-3p inhibits cancer progression and is a novel screening biomarker for gastric cancer

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Funding information

The study was funded by Liaoning Natural
Science Fund Plan Guidance Project (2019-
ZD-0739).

Abstract

Purpose: Dysregulation of miR-148a-3p in gastric cancer was reported. However, the diagnostic potential and biological function of miR-148a-3p in gastric cancer progression is not fully studied.

Methods: Bioinformatics analysis and RT-qPCR assay were performed to analyze the expression of miR-148a-3p in gastric cancer tissues and plasma of gastric cancer patients. Receiver operating characteristic curve analysis was performed to analyze the diagnostic value of miR-148a-3p. In vitro proliferation, apoptosis, migration, invasion, sphere formation assay and Western blotting assay were performed to evaluate the biological function of miR-148a-3p in gastric cancer progression.

Results: miR-148a-3p was significantly down-regulated in both gastric cancer patients' tissue and plasma samples. Plasma miR-148a-3p showed promising efficacy for gastric cancer diagnosis. Overexpression of miR-148a-3p could inhibit the proliferative phenotype, metastatic phenotype, and cancer stem-like properties of gastric cancer cells.

Conclusions: miR-148a-3p inhibits cancer progression and is a novel diagnostic biomarker for gastric cancer.

KEYWORDS

biomarker, gastric cancer, microRNA, miR-148a-3p

1 | INTRODUCTION

Gastric cancer is the most common malignant tumor of human digestive system and the second leading cause of cancer-related death.^{1,2} The mortality of gastric cancer has decreased significantly over the last decades worldwide.^{3,4} Advances in clinical diagnosis techniques like gastroscopy have improved the early detection rate of gastric cancer patients.⁵ For patients in the early stage of gastric cancer, surgical resection shows favorable efficacy. However, for patients in the advanced stage, there remain limited treatment options and surgical resection shows unsatisfying efficacy due to the existing local invasion and distant metastasis. Further identification of the key molecules regulating the

progression of gastric cancer could provide novel therapy targets for advanced stage gastric cancer patients.⁶ Considering the invasive nature of gastroscopy, gastric cancer patients would benefit greatly from further development of non-invasive diagnostic techniques like blood biomarkers.⁷⁻¹⁰

microRNAs (miRNAs) are a group of small noncoding RNAs which could regulate the post-transcription expression level of their target genes.^{11,12} Numerous studies have reported the close correlation between the aberrant expression of certain miRNAs and cancer progression.^{13,14} For instance, miR-193a-3p was reported to regulate cisplatin resistance in CD44(+) gastric cancer cells.¹⁵ miR-1224 was reported to inhibit metastasis in intestinal-type gastric cancer by targeting FAK.¹⁶ Cancer stem cells (CSCs) are a specific

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small population of cancer cells. CSCs are considered as tumor-initiating cells as they possess potent self-renewal capabilities and could propagate or differentiate into non-CSCs. Comparing with non-CSCs, CSCs are more resistant to chemotherapy and radiotherapy. Multiple studies have reported that certain miRNAs play critical roles in regulating cancer cell stemness. For instance, miR-221 was reported to promote the tumorigenic capacity of colorectal cancer stem cells by targeting QKI.¹⁷ Inhibition of miR-328-3p was reported to impair cancer stem cell function and metastasis in ovarian cancer.¹⁸

In this study, we analyzed two public gastric cancer miRNAs expression profiles, one plasma miRNAs expression profile (GSE86822) and one tissue miRNAs expression profile (GSE93415). We identified that the expression level of miR-148a-3p was significantly lower in both gastric cancer patients' tissue and plasma samples. Further validation with our own clinical gastric cancer tissue samples and plasma samples showed consistent results with the bioinformatics analysis. We also found promising diagnostic efficacy of plasma miR-148a-3p for gastric cancer. Results of in vitro cellular functional experiments demonstrated that up-regulation of miR-148a-3p could inhibit the proliferative phenotype, metastatic phenotype, and cancer stem-like properties of gastric cancer cells.

2 | MATERIALS AND METHODS

2.1 | Ethics approval and consent to participate

47 gastric cancer tissues paired with para-cancerous tissues and 47 gastric cancer patients' plasma samples paired with 47 healthy participants' plasma samples were used in this study. Clinical cancer tissue and plasma sample collection in this study was approved by the local ethics committee of the Affiliated ShengJing Hospital of the China Medical University. All participants in this study signed a detailed written informed consent form. Tissue and plasma samples were collected and preserved in -80°C freezer (Table 1).

2.2 | Bioinformatics analysis

Two publicly available miRNA microarray datasets (GSE86822, 5 gastric cancer patients' plasma samples and 3 healthy controls' plasma samples; GSE93415, 20 gastric cancer tissue samples and 20 adjacent healthy gastric mucosa samples) were downloaded from the Gene Expression Omnibus database. Differentially expressed miRNAs were analyzed with the R language package limma. Heatmaps of the identified differentially expressed miRNAs were generated with the R language package pheatmap. The expression level of miR-148a-3p in these two datasets was visualized with GraphPad Prism 7. The expression profile of gastric cancer patients in the TCGA (The Cancer Genome Atlas) database was downloaded with the R language package RCTGA. The expression level of miR-148a-3p in the TCGA database was visualized with GraphPad Prism 7.

2.3 | Cell lines and cell culture

The human gastric cancer cell lines (SGC-7901 and BGC-823) and human normal gastric epithelial cell line (GES-1) were kindly provided by central cell bank of the Huixihu central laboratory of the Affiliated Shengjing Hospital of China Medical University. Cells were cultured in RPMI-1640 medium (Gibco) supplemented with 10% fetal bovine serum (Gibco).

2.4 | Reverse transcription-quantitative polymerase chain reaction (RT-qPCR)

According to the manufacturer's instructions, total RNA from cell lines and ground tissues was isolated with the TRIzol reagent (Invitrogen), and plasma miRNA was isolated with the Plasma miRNA Isolation Kit (Foregene). For miR-148a-3p detection, miRNA 1st Strand cDNA Synthesis Kit (Vazyme) was used to convert total RNA into cDNA. miR-148a-3p expression was measured by qPCR with the SYBR qPCR Master Mix kit (Vazyme). U6 was used as internal control. For CD44, CD47, CD133, and NANOG detection, RT SuperMix for qPCR kit (Vazyme) was used to convert total RNA into cDNA. The corresponding expression level was measured by qPCR with the SYBR qPCR Master Mix KIT (Vazyme). GAPDH was used as internal control. The primer sequences were provided in Table 2.

2.5 | Western blotting assay

Collected cells were treated in RIPA buffer supplemented with protease and phosphatase inhibitor on ice for 15 minutes. Protein concentration

TABLE 1 Clinical characteristics of 47 paired participants

Clinical characteristics	Cancer participants	Normal participants
Gender		
Male	26 (55%)	25 (53%)
Female	21 (45%)	22 (47%)
Age		
≥ 60	34 (72%)	17 (36%)
< 60	13 (28%)	30 (64%)
TNM Stage		
I	7 (15%)	—
II	17 (36%)	—
III	17 (36%)	—
IV	6 (13%)	—
Tumor histological morphology		
Adenocarcinoma	34 (72%)	—
Absolute signet ring cell carcinoma	1 (2%)	—
Mixed carcinoma	12 (26%)	—

TABLE 2 Primer sequences for RT-qPCR

Gene	Primer sequence
Hsa-miR-148a-3p	F: 5'-TCAGTGCCTACAGAACTTTGT-3' R: 5'-GTCACCCTGTTTCTGGCAC-3'
CD44	F: 5'-AGCATCGGATTTGAGACCTG-3' R: 5'-GTTGTTTGTGCACAGAT GG-3'
CD47	F: 5'-CGGCGTGTATACCAATGC-3' R: 5'-TTTGAATGCATTAAGGGGTTCT-3'
CD133	F: 5'-TTCTATGCTGTGCTCTGGGGC-3' R: 5'-TTGTTGGTGCAAGCTCTTCAAGT-3'
NANOG	F: 5'-CACCAGTCCCAAAGGCAAAC-3' R: 5'-GCCTTCTGCGTCACACCATT-3'
U6	F: 5'-CGCTTCGGCAGCACATATAC-3' R: 5'-TTCACGAATTTGCGTGCAT-3'
GAPDH	F: 5'-GGAGCGAGATCCCTCCAAAT-3' R: 5'-GGCTGTTGCATACTTCTCATGG-3'

was measured with the bicinchoninic acid protein assay kit (Beyotime) following the manufacturer's protocol. 40 µg of total protein from each sample was separated on a SDS-PAGE and transferred to a PVDF membrane (Bio-Rad). Membranes were incubated overnight at 4°C with primary antibody against CD44, CD47 (1:1000 and 1:2000; ProteinTech), β-actin (1:8000; ProteinTech). Blots were incubated with horseradish peroxidase-conjugated secondary antibody (1:2000; ProteinTech). Protein bands were visualized using the enhanced BeyoECL Plus kit (Beyotime).

2.6 | Transfection experiments

Synthetic miR-148a-3p mimics, miRNA mimic negative control were purchased from Genepharma Biotechnology (Genepharma). Transfection experiments were performed using the Lipofectamine 3000 reagent (Thermo Fisher Scientific) following the manufacturer's instructions.

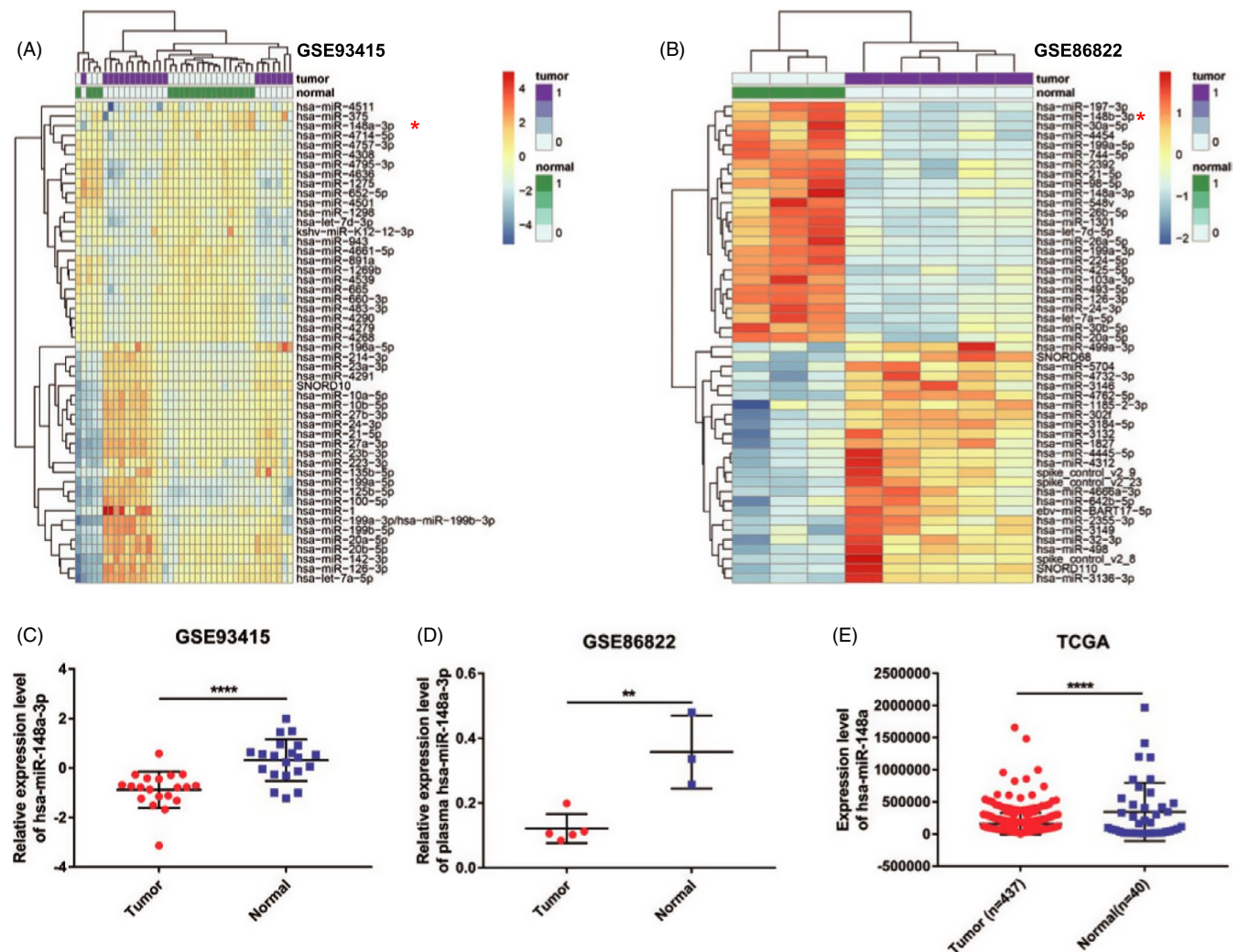


FIGURE 1 miR-148a-3p is down-regulated in gastric cancer tissues and gastric cancer patients' plasma by bioinformatics analysis. A, Heatmap of identified differentially expressed miRNAs in GSE93415. B, Heatmap of identified differentially expressed miRNAs in GSE86822. C, Expression level of miR-148a-3p in GSE93415. D, Expression level of miR-148a-3p in GSE86822. E, Expression level of miR-148a-3p in the TCGA database; $P < .01$ marked** and $P < .0001$ marked****

2.7 | Cell proliferation assay

According to the manufacturers' protocols, the cell proliferation assay was performed with the Cell Counting Kit-8 (Dojindo) and the BeyoClick™ EdU-647 Kit (Beyotime).

2.8 | Flow cytometric apoptosis analysis

For apoptosis analysis, cells were stained with the FITC/Annexin V Apoptosis Detection Kit I (BD Biosciences) and analyzed with the flow cytometry (Thermo Fisher Scientific).

2.9 | In vitro migration assay

For wound healing migration assays, cells were cultured on 6-well plate until it was fully covered with cell monolayer. A wound was made across the cell monolayer using the tip of a 200- μ L pipette.

The wounded cell monolayer was then cultured in RPMI-1640 medium. After 18 hours, closure of the wound was measured.

2.10 | In vitro invasion assay

For invasion assays, a total number of 3×10^4 cells in RPMI-1640 medium were added to the upper chamber of Transwell (24 wells, 8- μ m pore size, Costar) pre-coated with Matrigel (dilution 1:8). The lower chamber of Transwell was filled with RPMI-1640 containing 10% serum. After 18 hours of incubation, invaded cells were fixed with 4% paraformaldehyde, stained with crystal violet (Beyotime), and counted under a microscope (Olympus).

2.11 | Sphere formation assay

For the sphere formation assay, 2000 viable cells per well were planted in 6-well ultra-low attachment flasks (Corning)

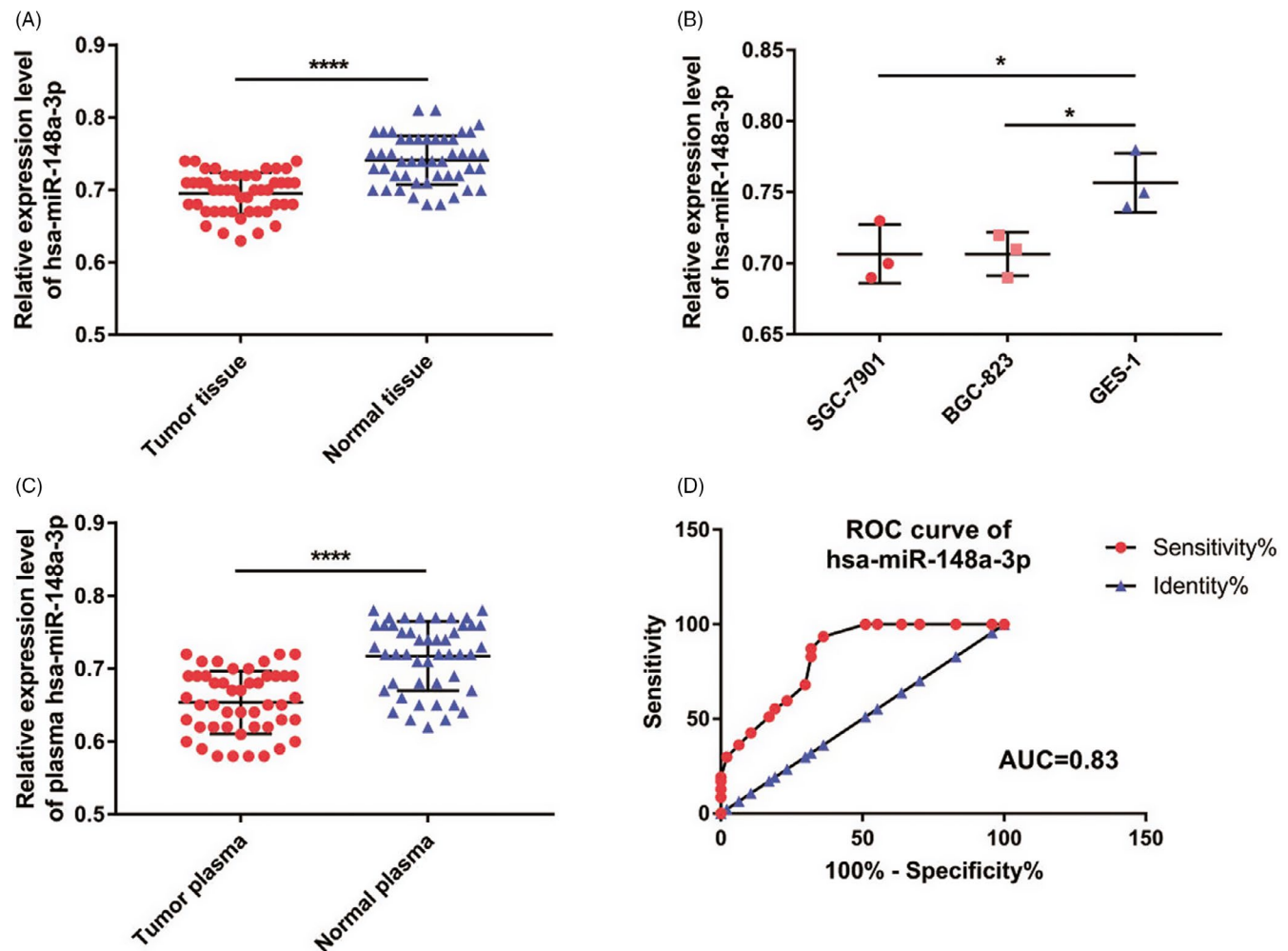


FIGURE 2 miR-148a-3p is down-regulated in gastric cancer tissues and gastric cancer patients' plasma by RT-qPCR analysis. A, Expression level of miR-148a-3p in 47 paired gastric cancer tissues and para-cancerous tissues by RT-qPCR. B, Expression level of miR-148a-3p in SGC-7901, BGC-823 and GES-1 cells by RT-qPCR. C, Expression level of miR-148a-3p in 47 gastric cancer patients' plasma and 47 healthy participants' plasma by RT-qPCR. D, Receiver operating characteristic curve analysis of the diagnostic value of plasma miR-148a-3p for gastric cancer; AUC for area under curve, $P < .05$ marked* and $P < .0001$ marked****

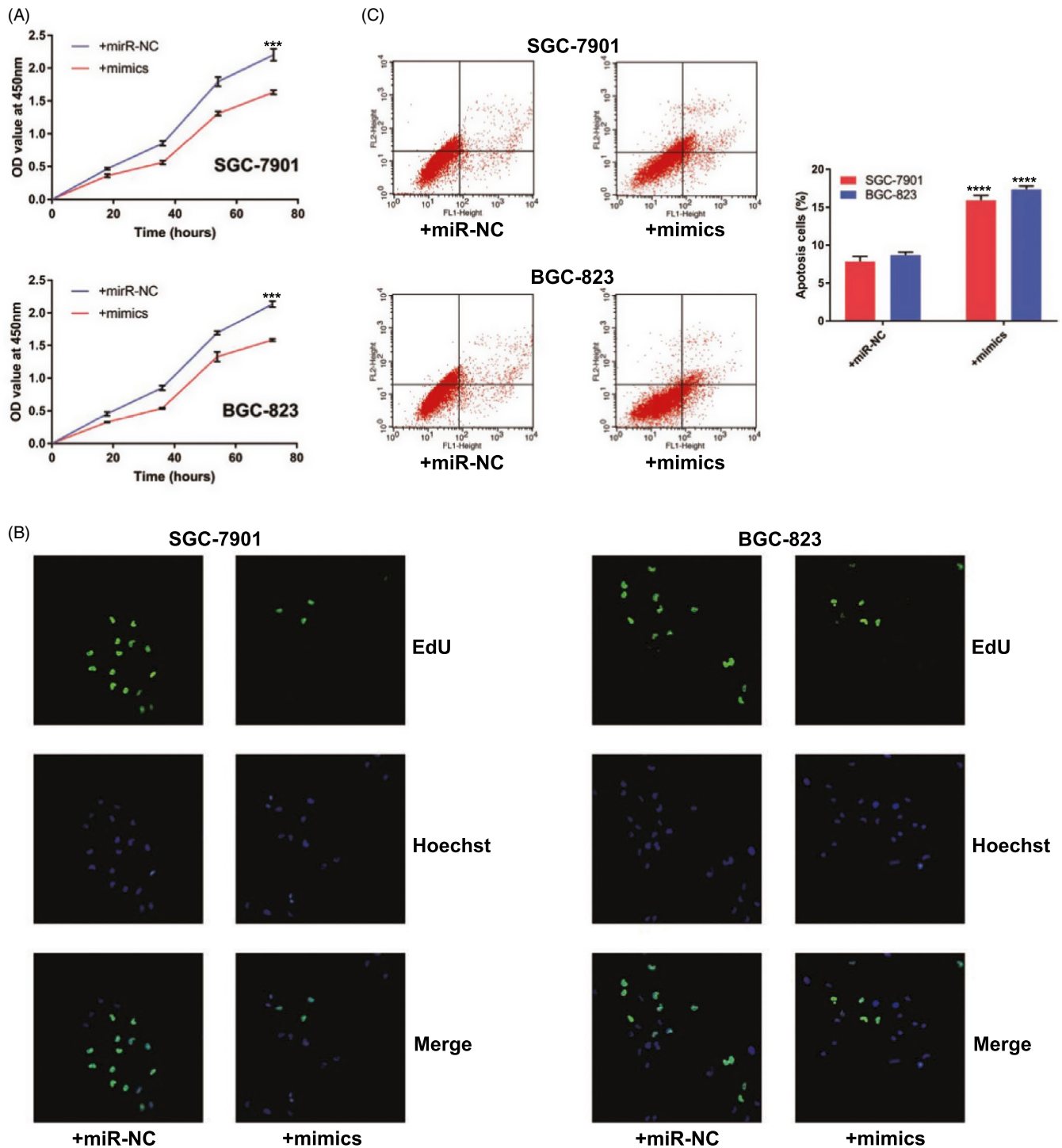


FIGURE 3 miR-148a-3p inhibits proliferation and induces apoptosis in gastric cancer cells. A, CCK-8 assay of SGC-7901 and BGC-823 cells transfected with miR-148a-3p mimics or miR-NC. B, EdU assay of SGC-7901 and BGC-823 cells transfected with miR-148a-3p mimics or miR-NC. C, Apoptosis assay of SGC-7901 and BGC-823 cells transfected with miR-148a-3p mimics or miR-NC; NC for negative control, $P < .001$ marked*** and $P < .0001$ marked****

and cultured in serum-free medium (RPMI-1640/F12; 1:1 mixture) supplemented with EGF (15 ng/mL), B27 (1:50) and bFGF (15 ng/mL). The spheres were imaged after 10 days of culture.

2.12 | Statistical analysis

Student's *t* test was performed with the SPSS Statistics 19.0 software. *P*-value of $< .05$ was considered statistically significant. The

screening efficacy of plasma miR-148a-3p was analyzed with the receiver operating characteristic (ROC) curve analysis. ROC curve analysis was performed with GraphPad Prism 7. Area under curve (AUC) > 0.8 was considered as an acceptable screening efficacy. Statistical charts were generated with GraphPad Prism 7.

3 | RESULTS

3.1 | miR-148a-3p is significantly down-regulated in gastric cancer tissues and gastric cancer patients' plasma

We downloaded and analyzed the data from two publicly available GEO microarray data (Figure 1A,B). We found that miR-148a-3p was significantly down-regulated in gastric cancer tissues and gastric cancer patients' plasma (Figure 1C,D). We further analyzed the expression level of miR-148a-3p with the data from the TCGA database. The result showed that miR-148a-3p was significantly down-regulated in gastric cancer tissues (Figure 1E). Finally, we validated the results of bioinformatics analysis with our own cell and clinical samples. The results showed that the expression level of miR-148a-3p was lower in gastric cancer tissues, gastric cancer cell lines, and gastric cancer patients' plasma than para-cancerous tissues, gastric epithelial cell line, and healthy participants' plasma (Figure 2A-C). The result of ROC

analysis indicated an acceptable screening value of plasma miR-148a-3p for gastric cancer with the AUC of 0.83 (Figure 2D).

3.2 | Overexpression of miR-148a-3p inhibits the proliferative and metastatic phenotype of gastric cancer cells

Next, we studied the biological functions of miR-148a-3p in gastric cancer progression. We increased the expression level of miR-148a-3p in SGC-7901 and BGC-823 cells by transfection of miR-148a-3p mimics (Figure S1). In vitro proliferation assays showed that overexpression of miR-148a-3p suppressed the proliferation capabilities of SGC-7901 and BGC-823 cells (Figure 3A,B). In vitro apoptosis assay showed that overexpression of miR-148a-3p induced apoptosis in SGC-7901 and BGC-823 cells (Figure 3C). Furthermore, in vitro migration and invasion assays showed that overexpression of miR-148a-3p suppressed the migration and invasion capabilities of SGC-7901 and BGC-823 cells (Figure 4A,B).

3.3 | Overexpression of miR-148a-3p inhibits the cancer stem-like properties of gastric cancer cells

Finally, we investigated the effect of miR-148a-3p on the cancer stem-like properties of gastric cancer cells. Results of the sphere

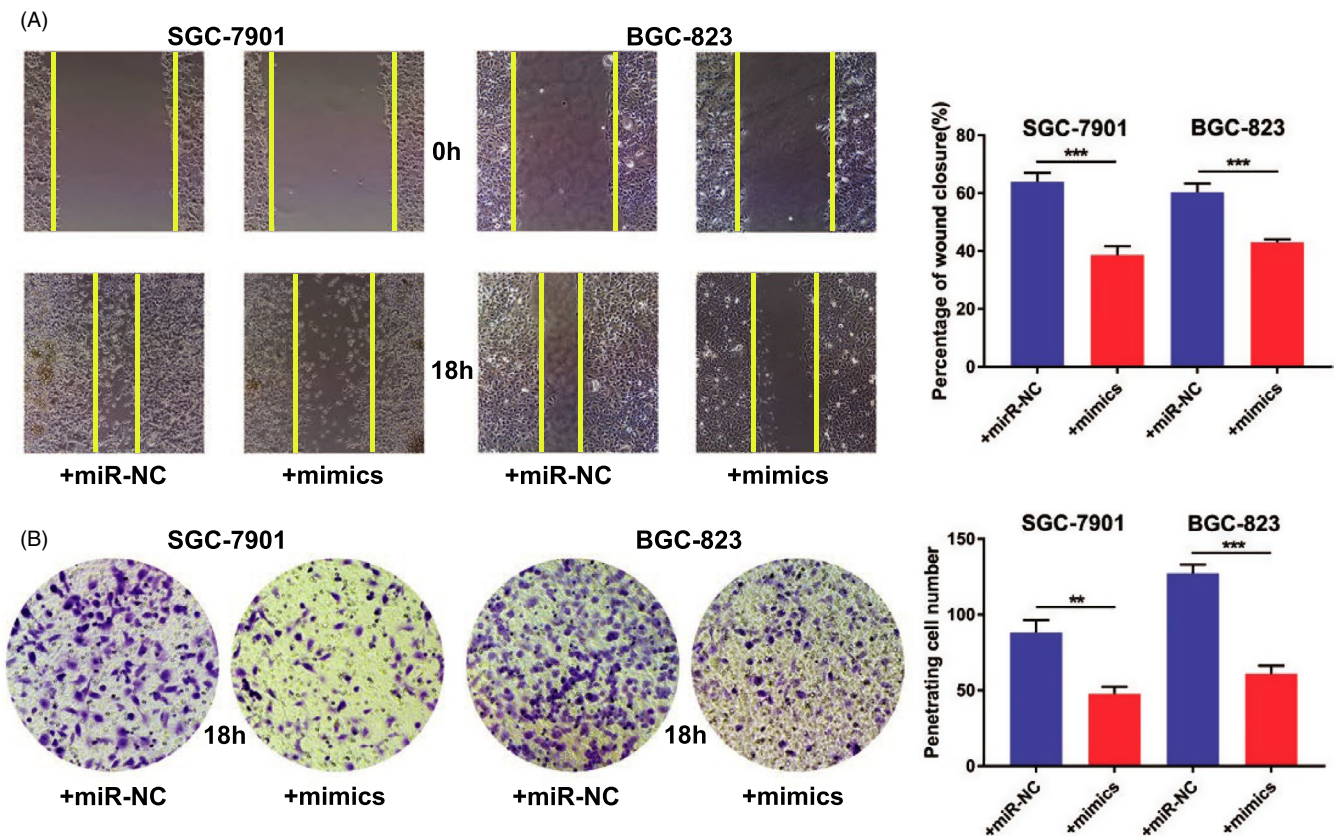


FIGURE 4 miR-148a-3p inhibits migration and invasion in gastric cancer cells. A, Migration assay of SGC-7901 and BGC-823 cells transfected with miR-148a-3p mimics or miR-NC. B, Invasion assay of SGC-7901 and BGC-823 cells transfected with miR-148a-3p mimics or miR-NC; NC for negative control, $P < .01$ marked** and $P < .001$ marked***

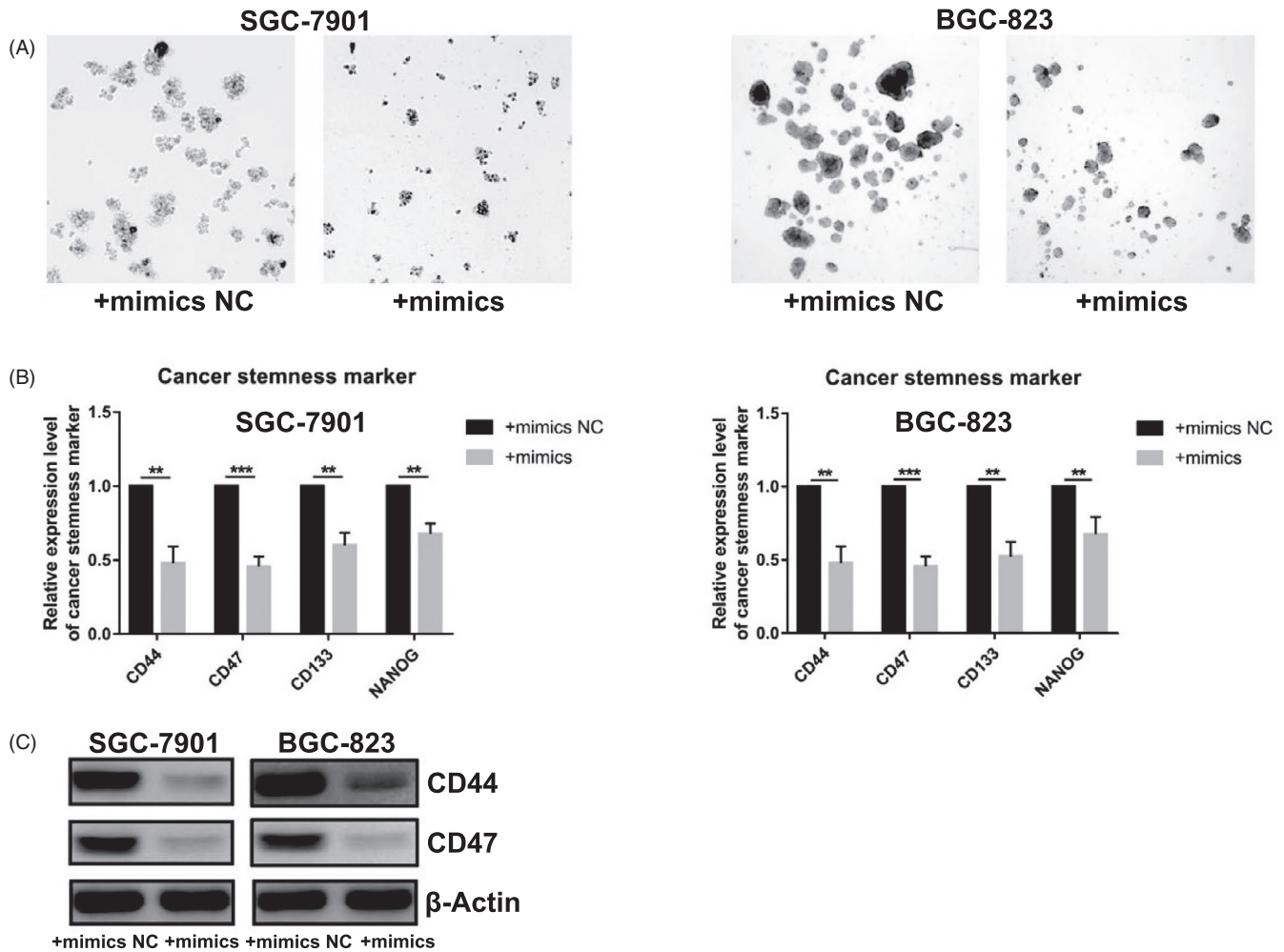


FIGURE 5 miR-148a-3p inhibits cancer stem-like properties of gastric cancer cells. A, Sphere formation assay of SGC-7901 and BGC-823 cells transfected with miR-148a-3p mimics or miR-NC. B, Expression level of cancer stemness marker in SGC-7901 and BGC-823 cells transfected with miR-148a-3p mimics or miR-NC by RT-qPCR. C, Expression level of cancer stemness marker in SGC-7901 and BGC-823 cells transfected with miR-148a-3p mimics or miR-NC by Western blotting; NC for negative control, $P < .01$ marked** and $P < .001$ marked***

formation assay indicated that overexpression of miR-148a-3p inhibited the sphere formation capabilities of SGC-7901 and BGC-823 cells (Figure 5A). Results of the Western blotting assay and RT-qPCR assay showed that overexpression of miR-148a-3p down-regulated the expression level of stemness-related regulator (CD44, CD47, CD133, and NANOG) in these two cell lines (Figure 5B,C). These results suggested that overexpression of miR-148a-3p could inhibit the cancer stem-like properties of gastric cancer cells.

4 | DISCUSSION

In this study, we analyzed one tissue miRNAs expression profile and one plasma miRNAs expression profile of gastric cancer patients. miR-148a-3p was the only commonly differentially expressed miRNA in these two expression profiles. Several studies have reported the tumor-suppressing functions of miR-148a-3p

in other cancer types. For instance, miR-148a-3p was reported to repress proliferation and EMT in bladder cancer by regulating ERBB3/AKT2/c-myc and DNMT1.¹⁹ miR-148a-3p could suppress ovarian cancer progression primarily by targeting c-Met or suppress proliferation and invasion of esophageal cancer by targeting DNMT1.^{20,21} Long noncoding RNA SNHG4/miR-148a-3p/c-Met axis was reported to promote cervical cancer progression.²² In ovarian cancer, LINC00339/miR-148a-3p/ROCK1 axis was reported to promote cell proliferation, migration, and invasion.²³ One published article has mentioned that dysregulation of miR-148a-3p, miR-193b-3p, miR-1179, NCAPG, and KNL1 may contribute to the progression of gastric cancer.²⁴ However, the biological function and screening potential of miR-148a-3p in gastric cancer progression has not been reported. Therefore, we investigated that whether miR-148a-3p could function as a potent tumor-suppressing microRNA and a novel screening biomarker for gastric cancer.

Validation with our own clinical samples showed consistent results with the bioinformatics analysis. These results suggested that miR-148a-3p may possess a potential screening value for gastric cancer patients. Currently, the standard early diagnosis procedure for gastric cancer patients is gastroscopy followed by pathology examination. However, the acceptance of this diagnosis procedure for gastric cancer early detection was unsatisfying due to its invasive and uncomfortable characteristics. Utilization of novel blood biomarker for cancer early detection could overcome the aforementioned shortcomings of gastroscopy. Therefore, we further studied the screening value of plasma miR-148a-3p for gastric cancer patients. The result of ROC analysis showed an area under curve of 0.832 suggesting a promising screening value of plasma miR-148a-3p for gastric cancer. A combination of miR-148a-3p and several other oncogenetic miRNAs may possess a higher screening efficiency. This speculation requires further validation in future studies. Results of in vitro cellular functional experiments demonstrated that overexpression of miR-148a-3p could inhibit the proliferative phenotype, metastatic phenotype, and cancer stem-like properties of gastric cancer cells. These results suggested a potent tumor-suppressing function of miR-148a-3p in gastric cancer cells. The underlying molecular mechanism of miR-148a-3p in gastric cancer cells was not studied in this study which will be addressed in our future studies.

In conclusion, in this study we identified and validated miR-148a-3p as a novel tumor suppressor and screening biomarker for gastric cancer.

CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

AUTHOR CONTRIBUTIONS

Chenhui Bao performed the majority of experiments and analyzed the data and drafted the manuscript; Lin Guo provided critical revision of the manuscript for important intellectual content.

ETHICS STATEMENT

The study was reviewed and approved by the Faculty of Science Ethics Committee at ShengJing Affiliated Hospital of China Medical University.

INFORMED CONSENT

Informed consent was obtained from patients before surgery at the ShengJing Hospital of China Medical University.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Bao C, Guo L. MicroRNA-148a-3p inhibits cancer progression and is a novel screening biomarker for gastric cancer. *J Clin Lab Anal*. 2020;34:e23454. <https://doi.org/10.1002/jcla.23454>