Pathology - Research and Practice 215 (2019) 152569

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

Original article

Circulating long non-coding RNA *PCGEM1* as a novel biomarker for gastric cancer diagnosis

Hong Jiang[a], Shuai Guo[b], Yan Zhao[b], Yue Wang[b], Hai-yan Piao[c], Yue Wu[d], Jun Zhang[b,*]

[a] *Department of Hepatopancreatobiliary Surgery, Liaoning Province Cancer Hospital & Institute (Cancer Hospital of China Medical University), No. 44 Xiaoheyan Road, Dadong District, Shenyang, 110042 Liaoning, China*

[b] *Gastric Cancer Department, Liaoning Province Cancer Hospital & Institute (Cancer Hospital of China Medical University), No. 44 Xiaoheyan Road, Dadong District, Shenyang, 110042 Liaoning, China*

[c] *Medical Oncology Department of Gastrointestinal Cancer, Liaoning Province Cancer Hospital & Institute (Cancer Hospital of China Medical University), No. 44 Xiaoheyan Road, Dadong District, Shenyang, 110042 Liaoning, China*

[d] *Emergency Department, Sheng Jing Hospital of China Medical University, 36 Sanhao St, Heping District, Shenyang, 110003 Liaoning, China*

ARTICLE INFO

Keywords:
Gastric cancer
Long non-coding RNA
PCGEM1
Diagnosis

ABSTRACT

Aim: Previous studies have confirmed that overexpression of the long non-coding RNA prostate cancer gene expression marker 1 (*PCGEM1*) contributes to the invasion and metastasis of gastric cancer (GC) cells. However, the expression of circulating *PCGEM1* in the plasma of GC patients and its clinical value remain unclear.
Methods: A total of 317 patients with GC and 100 healthy subjects were enrolled in this study. Circulating *PCGEM1* was detected by reverse transcription-polymerase chain reaction. The diagnostic value of plasma *PCGEM1* was evaluated by receiver operating characteristic curves and the area under the curve (AUC) value.
Results: The expression level of *PCGEM1* in the GC group was significantly higher than that in the healthy control subjects. In addition, the *PCGEM1* expression level was associated with tumor differentiation and TNM stage. The AUC value of *PCGEM1* was higher than that of other conventional tumor markers (CEA, CA12-5, CA72-4, AFP, and CA19-9), although the combination of all markers showed the highest predictive value.
Conclusion: Plasma *PCGEM1* may be a potential novel circulating biomarker for GC diagnosis and prognosis.

1. Introduction

Gastric cancer (GC) is one of the most common malignancies of the digestive system; GC is the fourth most common cancer type and the second leading cause of cancer-related deaths in China [1]. Thus, developing strategies for the early diagnosis, and control of the invasion and metastasis of GC is an important research focus, which requires the identification of biomarkers and their underlying molecular mechanisms [2]. Currently, the gold standard of GC diagnosis is gastroscopy along with a pathology examination, which are invasive and uncomfortable procedures [3]. Although humoral biopsy is relatively non-invasive, the traditional serum tumor biomarkers used for GC diagnosis have low sensitivity and specificity [4]. With the development of high-throughput sequencing technology, the levels of circulating RNAs in the serum or plasma have been identified as new non-invasive diagnostic biomarkers for several cancer types [5].

Long non-coding RNA (lncRNA) is a class of non-coding RNAs that are longer than 200 nucleotides with limited protein-coding capacity [6]. LncRNAs can regulate biological processes at multiple levels such as transcriptional, post-transcriptional, and epigenetic regulation [7]. Accumulating evidence has confirmed that lncRNAs play important biological roles in the malignant phenotype of GC [8,9]. In our previous study, we demonstrated that the hypoxia-responsive lncRNA prostate cancer gene expression marker 1 (*PCGEM1*) may play a role in the invasion and metastasis of GC through mediating the epithelial–mesenchymal transition [10]. Under a hypoxic condition, the tumor-derived lncRNAs reshape their surrounding harsh microenvironment, and can also enter the bloodstream to reflect pathological and physiological changes [11,12]. Moreover, other lncRNAs have been shown to be stable in plasma, which is a key requirement of a clinical biomarker [13,14]. Given this background, we hypothesized that GC cells can release the lncRNA *PCGEM1* to be detectable in plasma, which would offer a non-invasive method for GC detection and prognosis prediction.

To test this hypothesis, in the present study, we investigated the potential of the circulating level of the lncRNA *PCGEM1* as a GC biomarker in plasma. First, we examined the expression of *PCGEM1* in GC

Abbreviations: GC, gastric cancer; PCGEM1, prostate cancer gene expression marker 1; qRT-PCR, reverse transcription-polymerase chain reaction

* Correspondence author.
E-mail address: surgeonzhangjun@hotmail.com (J. Zhang).

https://doi.org/10.1016/j.prp.2019.152569
Received 16 April 2019; Received in revised form 15 July 2019; Accepted 26 July 2019

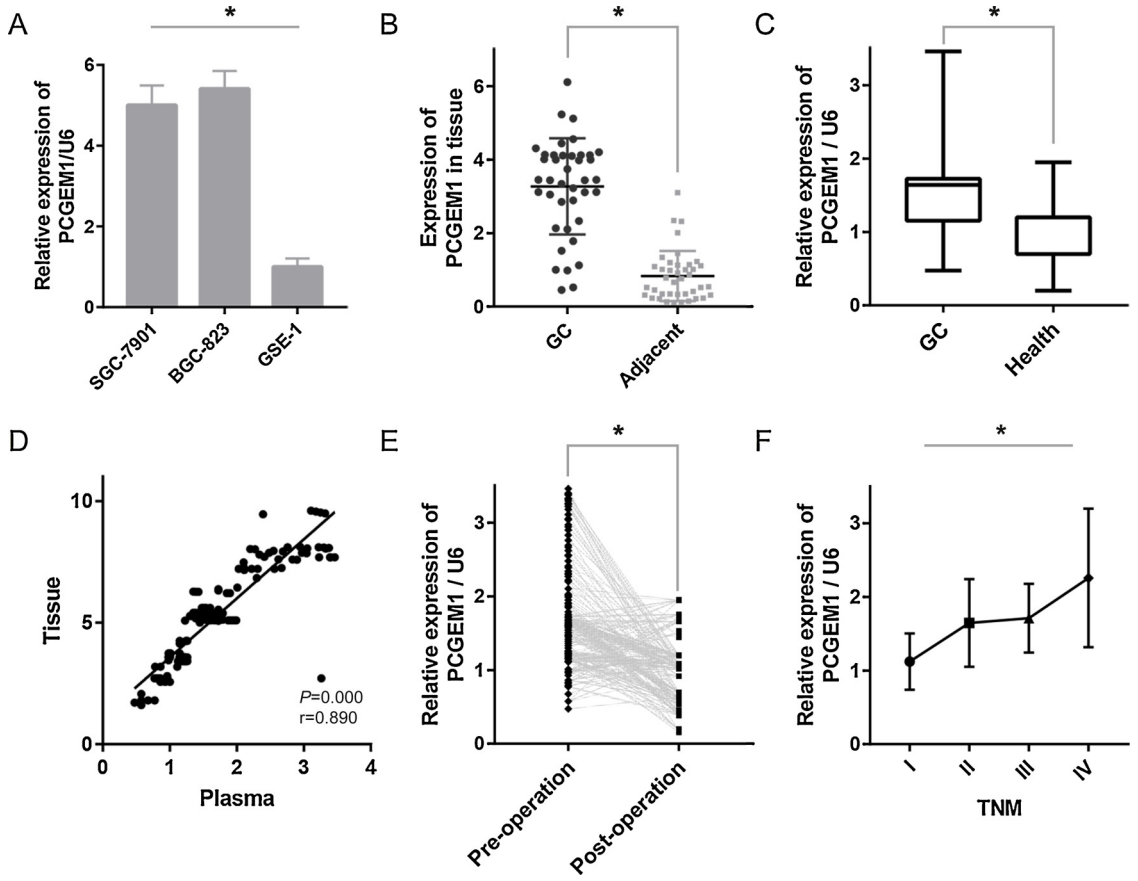

Fig. 1. Expression of *PCGEM1* in human gastric cancer (GC). (A) *PCGEM1* expression in GC cell lines (SGC-7901 and BGC-823) and the human normal gastric epithelial cell line (GSE-1) determined by RT-PCR. (B) *PCGEM1* expression in GC tissues compared to paired adjacent tissues in 40 patients. (C) Differences in plasma *PCGEM1* expression between GC patients and healthy controls. (D) Correlation between *PCGEM1* expression levels in tissues and plasma. (E) Comparison of plasma *PCGEM1* levels in pre- and post-operation samples. (F) Relationship between *PCGEM1* expression in plasma and TNM.

cells and para-cancer tissues, and in the plasma samples of GC patients and healthy controls. We then evaluated the correlation between *PCGEM1* levels and clinicopathological characteristics, and analyzed the diagnostic efficiency of circulating *PCGEM1* in patients with GC.

2. Materials and methods

2.1. Ethics statement

The study was approved by the Ethics Committee of Liaoning Cancer Hospital & Institute. Informed consent was obtained from all subjects before they participated in the study.

2.2. Patients and samples

Between October 2015 and December 2018, 317 GC patients were enrolled in this study. All patients were diagnosed with GC by two pathologists after undergoing D2 lymph node-dissected gastrectomy. Patients treated with chemotherapy or radiotherapy before blood collection were excluded from the study. Tumors were staged according to the 8th edition of the TNM staging manual of the American Joint Committee on Cancer. In addition, 100 healthy individuals matched for sex and age with the patients were included as the control group.

All blood samples were collected in vacuum blood tubes with ethylenediaminetetraacetic acid anticoagulant before and after surgery and were processed within 1 h after collection. The blood samples were subjected to centrifugation at 5000 rpm for 10 min at 4 °C, and the plasma was stored at −80 °C until analysis.

2.3. Real-time reverse transcription-polymerase chain reaction (qRT-PCR)

Total RNA from the plasma, cells, and tissues was isolated with TRIzol (Invitrogen) cell separation reagent according to the manufacturer's instructions. Promega cDNA core kit (Promega, Madison, WI, USA) was used to generate complementary DNA from 500 ng of total RNA by reverse transcription. SYBR Master Mixture (Takara Bio, Inc., Kusatsu, Japan) was used to perform real-time PCR (LightCycler 480; Roche AG, Basel, Switzerland). Each sample was analyzed three times. U6 was used as the loading control. Fold changes of mRNA expression in different samples were determined by the $2^{-\triangle\triangle CT}$ normalization method. The following primers were used: *PCGEM1* forward 5′-ATGC CGTAACCTGTGTCT-3′ and reverse 5′-TGATGTCATAGTCCTCTTCCA-3′.

2.4. Stability analysis

Ten healthy plasma samples were stored under adverse conditions to evaluate the stability of circulating *PCGEM1* expression and further assess its clinical value as a biomarker. Specifically, the samples were incubated at 4 °C for 0, 6, 12, and 24 h, and were also subjected to three repeated freeze–thaw (4 °C and − 20 °C) cycles.

2.5. Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA), version 22.0. One-way analysis of variance was employed to compare the mean values among groups. The χ^2 test or Fisher's exact test was used to evaluate the correlation between clinicopathological variables and *PCGEM1* levels.

The independent *t*-test was used to compare the *PCGEM1* expression level in GC and healthy control plasma samples. The paired-sample *t*-test was used to compare the *PCGEM1* expression level before and after surgery for the same patient. Spearman correlation was used to analyze the correlations between the *PCGEM1* expression level of the plasma and tissue. The diagnostic value of plasma *PCGEM1* was evaluated by receiver operating characteristic (ROC) curves and the area under the curve (AUC) values. $P < 0.05$ was considered to reflect a statistically significant difference.

3. Results

3.1. PCGEM1 is overexpressed in GC tissues and plasma

We first confirmed that *PCGEM1* was overexpressed in GC cells (BGC-823, SGC-7901) compared to normal human gastric epithelial cells (GSE-1), and in GC tissues compared to paired adjacent non-cancerous tissues (Fig. 1A, 1B), consistent with our previous study [10]. *PCGEM1* was also overexpressed in the plasma of GC patients compared to that of matched healthy controls (Fig. 1C, $P < 0.01$). In addition, the *PCGEM1* expression levels in the plasma and tissue were significantly positively correlated (Fig. 1D, $r = 0.890$, $P < 0.01$), and plasma *PCGEM1* levels were significantly higher in the pre-operative samples than those in the post-operative samples for the same patients (Fig. 1E, $P < 0.01$).

The expression level of *PCGEM1* in plasma was correlated with TNM stage, and increased with greater aggravation of malignancy. However, there was no significant difference in *PCGEM1* expression between samples from patients with stage II and stage III disease (Fig. 1F). Collectively, these results suggested that the plasma *PCGEM1* level can accurately reflect tumor dynamics and tumor progression in GC patients.

3.2. Stability of PCGEM1 expression in plasma

There was no significant change in plasma *PCGEM1* expression after prolonged storage at 4 °C temperature or following repeated freeze-thaw cycles (Fig. 2). These results indicated that the expression of circulating *PCGEM1* remained relatively stable, providing a foundation for its potential use as a reliable plasma biomarker.

3.3. Correlations between clinicopathologic characteristics and PCGEM1 expression

Table 1 shows the relationships between *PCGEM1* expression levels and clinicopathological features. The expression of *PCGEM1* was closely related to tumor differentiation ($P < 0.001$, $\chi^2 = 36.346$) and TNM stage ($P < 0.001$, $\chi^2 = 74.083$). However, *PCGEM1* expression was not related to other clinical characteristics such as age, gender, tumor size, location, Bormann type, and Lauren type. Notably, the *P* value of the association between *PCGEM1* and tumor size was marginally significant at 0.099, which may be worth further study with a larger sample size.

Table 1
PCGEM1 expressions and clinicopathologic characteristics.

Characteristics	PCGEM1		*P*	X^2
	Low	High		
	136(42.9)	181(57.1)		
Age			0.656	0.199
≤60	59(44.4)	74(55.6)		
> 60	77(41.8)	107(58.2)		
Gender			0.184	1.765
Male	85(40.3)	126(59.7)		
Femal	51(48.1)	55(51.9)		
Tumor Size			0.099	2.728
< 5 cm	108(45.6)	129(54.4)		
≥5 cm	28(35.0)	52(65.0)		
Location			0.496	1.402
Up	38(43.7)	49(56.3)		
Middle	11(55.0)	9(45.0)		
Low	87(41.45)	123(58.6)		
Bormann type			0.108	6.066
I	12(70.6)	5(29.4)		
II	58(41.7)	81(58.3)		
III	65(41.4)	92(58.6)		
V	1(25.0)	3(75.0)		
Lauren type			0.272	2.605
Intestinal	96(45.3)	116(54.7)		
Mixed carcinoma	31(41.3)	44(58.7)		
Diffuse	9(30.0)	21(70.0)		
Tumor differentiation			0.000	36.346
Moderate and high	90(60.8)	58(39.2)		
Poor	46(27.2)	123(72.8)		
TNM stage			0.000	74.083
I	52(91.2)	5(8.8)		
II	41(43.6)	53(56.4)		
III	41(25.6)	119(74.4)		
IV	2(33.3)	4(66.7)		

3.4. Diagnostic value of circulating PCGEM1 for GC

The AUC values of the ROC curves for widely used markers in the screening and diagnosis of digestive system malignancies CEA, CA12-5, CA72-4, AFP, and CA19-9 were all lower than that of *PCGEM1* (Fig. 3A–F). The combined AUC value of CEA, CA12-5, CA72-4, AFP,

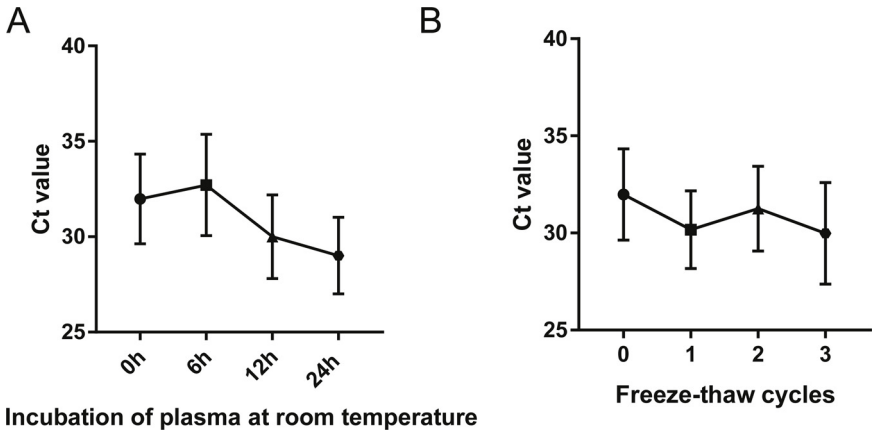

Fig. 2. Stability of circulating *PCGEM1* expression in a harsh environment (A) *PCGEM1* expression after prolonged storage at 4 °C temperature. (B) Expression of *PCGEM1* after three freeze-thaw cycles.

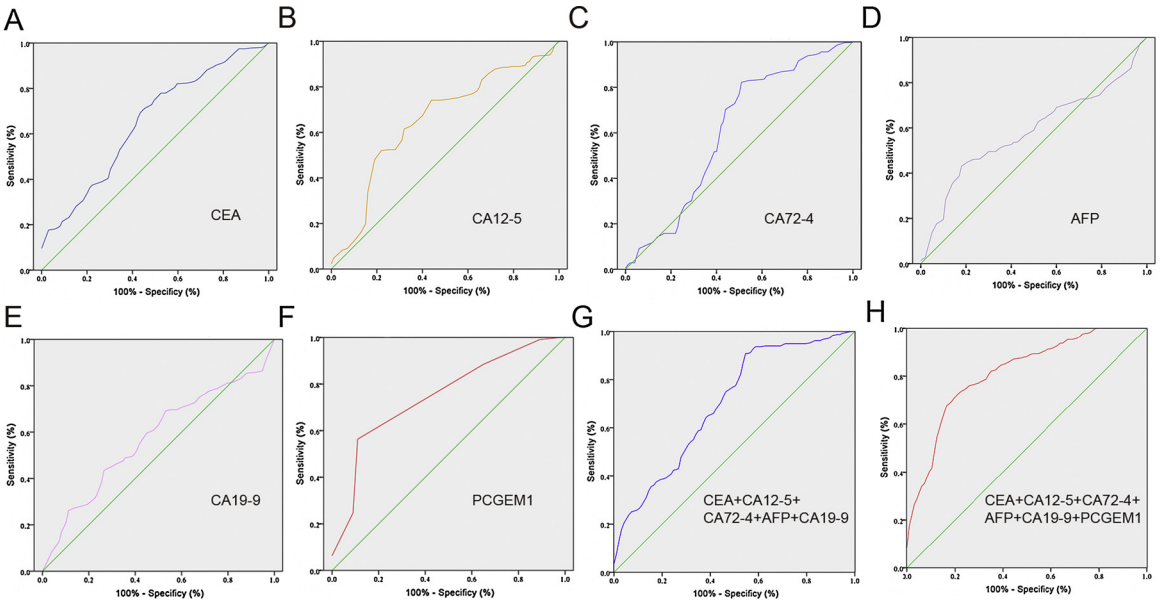

Fig. 3. Receiver operating characteristic (ROC) curves of biomarkers. (A) ROC curve of CEA, area under the curve (AUC) = 0.661. (B) ROC curve of CA12-5, AUC = 0.657. (C) ROC curve of CA72-4, AUC = 0.621. (D) ROC curve of AFP, AUC = 0.594. (E) ROC curve of CA19-9, AUC = 0.572. (F) ROC curve of plasma *PCGEM1,* AUC = 0.750. (G) ROC curve of combined CEA, CA12-5, CA72-4, AFP, and CA19-9; AUC = 0.699. (H) ROC curve of combined CEA, CA12-5, CA72-4, AFP, CA19-9, and PCGEM1; AUC = 0.815.

and CA19-9 (Fig. 3G) was higher than the individual markers but was still lower than that of *PCGEM1*. Thus, *PCGEM1* is superior to these biomarkers for GC diagnosis. In addition, we evaluated the value of CEA, CA12-5, CA72-4, AFP, CA19-9, and PCGEM1 in jointly diagnosing GC, revealing a higher AUC value than that of any biomarker alone (Fig. 3H). The sensitivity and specificity of *PCGEM1* were 72.9% and 88.9%, respectively, when choosing 1.705 as the optimal cut-off value. Collectively, these data suggested that circulating *PCGEM1* is a potential biomarker for GC diagnosis.

4. Discussion

GC is a common malignant tumor of the digestive system with a complex etiology. Owing to the low rate of early diagnosis, most GC patients are diagnosed at an advanced stage in China. Although the traditional treatment strategy has improved, the 5-year survival rate is still not optimistic [15]. Therefore, there is a critical need to improve the early diagnosis of GC, and finding a suitable plasma molecular biomarker is an effective method.

Based on the vital role of lncRNAs in tumor biology, some circulating lncRNAs have been proposed as potential biomarkers for cancer. H19 was the first lncRNA reported to be overexpressed in the plasma of GC patients, with a sensitivity and specificity of 74% and 58%, respectively, for GC diagnosis. Moreover, the expression level of H19 is sharply reduced after surgery [16]. Subsequently, the expression level of LINC00152 was found to be significantly higher in the tissues, plasma, and gastric juice of GC patients [17,18], with sensitivity and specificity of 48.1% and 85.2%, respectively [18]. In addition, the lncRNAs AA174084 and UCA1 (carcinoma-associated 1) are overexpressed in the gastric juice, but their expression levels in plasma are still unclear [19,20]. The plasma expression level of the lncRNA FER1L4 (Fer-1-Like Protein 4) is associated with surgery, but does not show any diagnostic and prognostic value [21].

PCGEM1 is located at chromosome 2q32.3 and its carcinogenic effects were initially demonstrated in aggressive prostate cancer, as a prostate-associated gene and regulated by androgen [22,23]. Zhang et al. [24] confirmed that myocyte enhancer factor 2 (MEF2) can bind to the promoter of *PCGEM1,* which is activated to induce cell proliferation by decreasing the expression level of the microRNA miR-148a. Similarly, P54/nrb can also up-regulate the expression of *PCGEM1*, which was associated with castration resistance in prostate cancer [25]. Moreover, *PCGEM1* can exacerbate the invasion and metastasis of ovarian cancer by regulating RhoA [26] or STAT3 [27] pathways. *PCGEM1* is also a malignant biomarker of endometrial cancer [27] and glioma [28]. In our previous study [10], we found that *PCGEM1* was overexpressed in 40 GC and paired adjacent tissues, and was associated with invasion and metastasis. This finding motivated us to further evaluate the expression level of *PCGEM1* in plasma and investigate its diagnostic value for GC.

Consistent with these previous results, RT-PCR showed that the plasma *PCGEM1* expression level in GC patients was significantly higher than that in the healthy controls. Moreover, the expression level of *PCGEM1* in plasma was correlated with that in the tissues, and was associated with TNM stage. Furthermore, the overexpression of *PCGEM1* in plasma was significantly reduced after surgery, suggesting a direct correlation between tumor tissue and circulating *PCGEM1* expression. Thus, circulating *PCGEM1* appears to show high specificity in GC diagnosis.

Stable expression is a prerequisite for the clinical application of *PCGEM1* as a diagnostic marker. We confirmed that neither prolonged exposure to 4 °C temperature nor repeated freezing and thawing influenced the expression of *PCGEM1*. In addition to its strong ability to diagnose GC (AUC = 0.750), the sensitivity and specificity of *PCGEM1* for diagnosis was higher than that of H19 [16], one of the most well-known oncogenes and diagnostic biomarkers in GC.

Although we verified the diagnostic value of *PCGEM1* in GC, the present study has some limitations. First, it remains to be determined whether *PCGEM1* enters the bloodstream by direct secretion or if it is encapsulated in vesicles. Second, the prognostic value of *PCGEM1* should also be validated in a larger sample.

Along with continuous advances in transcriptome research and technology, the discovery of circulating lncRNAs has opened up exciting prospects for diagnostics and prognostics, and has further provided new insight into the basic mechanisms of oncogenesis. Nevertheless, research into circulating lncRNAs is still a relatively young field with much more to be explored. To further develop lncRNA-based circulating biomarkers for clinical application, several challenges must first be overcome. First, the accuracy of the measurement of

circulating lncRNAs is a difficult problem due to the low abundance of these nucleic acids in body fluids, low stability of single-stranded nucleotides, and the lack of consensus regarding data normalization. Second, non-uniform sample choice, handling and processing, and blood cell contamination during sample preparation limit accurate and consistent measurements. Third, the form of lncRNAs in the blood circulation remains unclear; thus, further research is needed to verify whether lncRNAs exist in body fluids similar to cytokines, or whether they are enveloped and transported by vesicles such as exosomes. Further comprehensive understanding of the factors that influence the measurement of lncRNAs will help to establish a generally accepted procedure for sample collection, storage, and processing, as well as quantification. Despite these challenges, gaining further understanding of the origin and function of lncRNAs is expected to realize the ultimate goal of their application to the diagnosis and treatment of cancer.

Author contributions

Jiang H performed the majority of experiments and analyzed the data and drafted the manuscript; Zhang J designed the research; Piao HY, Wu Y assisted in writing the manuscript; Guo S, Wang Y collected and analyzed the data; Zhao Y provided critical revision of the manuscript for important intellectual content.

Supported by

Liaoning S&T Project (20180550971, 20170520447).

Ethics statement

The study was approved by Ethics Committee, Liaoning Cancer Hospital &Institute (NO. 20181226).

Declaration of Competing Interest

The authors declare that there are no conflicts of interest related to this study.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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