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Original Article

The value of LncRNA SNHG5 as a marker for the diagnosis and prognosis of gastric cancer

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Abstract: Objective: To elucidate the value of serum lncRNA SNHG5 as a marker for the diagnosis and prognosis in gastric cancer. Methods: From January 2017 to January 2018, serum samples were collected from 50 cases of gastric cancer patients and 50 cases of benign gastrosia who underwent operations in our hospital, and 50 cases of healthy person. We detected the expression level of serum lncRNA SNHG5 in all research targets and the expression levels of LncRNA SNHG5 in the cancer adjacent tissues and cancer tissues of gastric cancer patients to analyze the relationship between serum LncRNA SNHG5 level and clinicopathological parameters. ROC curve was used to analyze its prognostic value of patients with gastric cancer, while Cox regression model was used to analyze the survival predictors of short-term adverse events. Results: The expression of lncRNA SNHG5 in the serum of gastric cancer was down-regulated, lower than that in the benign gastrosia group and healthy group ($P < 0.05$). The relative expression of lncRNA SNHG5 in cancer tissues was down-regulated compared with that in adjacent tissues ($P < 0.05$). lncRNA SNHG5 was correlated with drinking history and TNM stage ($P < 0.05$). The difference of serum lncRNA SNHG5 15 days and 1 month after operation was significant ($P3 = 0.0001$, $P4 = 0.0135$). The relative expression of serum lncRNA SNHG5 in the death group was noticeably lower than that in the survival group ($P < 0.05$). lncRNA SNHG5 is a survival predictor of short-term adverse events in patients with gastric cancer. Conclusion: The expression of lncRNA SNHG5 in gastric cancer patients before operation and those with poor prognosis decreased. Therefore, it is of high diagnostic value in prognosis prediction and is expected to become a new molecular marker for early diagnosis of gastric cancer.

Keywords: LncRNA SNHG5, gastric cancer, diagnosis, prognosis

Introduction

With fast-paced and bustling city life, coupled with diet changes and build-up stress, an increasing number of people are suffering from gastrointestinal diseases and even gastric cancer. Gastric cancer is a malignant tumor originated from gastric mucosal epithelial lesions [1], which has no obvious early symptoms and is similar to common gastrointestinal diseases. However, the detection rate of early gastric cancer patients in China is only 5-10%, while the rate of missed diagnosis is rather high. Patients will not seek treatment until the advanced stage, which will miss the best time for treatment and result in a poor prognosis [2]. The most commonly used methods are gastroscopy and B-ultrasound, with which the diagnosis is confirmed by biopsy or cytology after sampling. Traditional tumor biomarkers, such as CEA, CA199, AND CA12-5, are usually used to diagnose tumors and evaluate disease progression and prognosis, but their sensitivity and specificity are not satisfactory [3]. Therefore, it is of great significance to find reliable, specific and sensitive markers and targets for gastric cancer.

LncRNA is an RNA sequence transcribed from more than 200 base pairs of non-coding DNA sequences [4, 5]. It can regulate the expression of oncogenes and tumor suppressor genes, participate in many biological processes such as tumor cell proliferation, differentiation and apoptosis. Its role in cancer cannot be underestimated, thus becoming a "new star" in cancer research [6-8]. Studies have indicated that lncRNA is expected to be a new tumor biomarker and therapeutic target, some of which are also related to the poor prognosis of tumors [9].

Small nucleoli RNA gene 5 host (smallnucleolarRNAhostgene5, SNHG5) is a recently discovered abnormal expression of lncRNA in a variety of malignant tumor tissues. Studies have also shown that exogenous lncRNA SNHG5 overexpression affects consistent proliferation and metastasis of cancer cells [10]. However, the value of lncRNA SNHG5 in gastric cancer has not been reported. For this reason, this study explored the clinical value of LncRNA SNHG5 as a marker for the diagnosis and poor prognosis of gastric cancer.

Materials and methods

General material

In this study, 100 patients with gastrointestinal diseases treated in our hospital from January 2017 to January 2018 were selected, including 50 patients with benign gastrosia (the benign gastrosia group). Another 50 patients with gastric cancer were confirmed by gastroscopy combined with the pathological examination (the gastric cancer group). Among which, there were 35 cases whose tumor diameter > 5 cm and 15 cases whose tumor diameter ≤ 5 cm. In addition, 50 healthy persons who had a physical examination in our hospital were included as the healthy group. Inclusion criteria: ① Patients who were confirmed with benign gastric disease and gastric cancer; ② Patients who had never accepted anticancer treatment before; ③ All patients received radical radiotherapy; ④ Patients aged above 18 years old; ⑤ All patients signed the informed consent, and the approval was obtained from our hospital ethic committee. Exclusion criteria: ① Patients who were complicated with other malignant tumors; ② Lack of clinical data; ③ Patients who refused to cooperate; ④ Patients with mental disorders. Clinical data such as smoking history, drinking history, tumor size, and TNM stage were collected and recorded in patients with gastric cancer.

Sample collection

For all subjects, 5 mL fasting venous blood was extracted on the day of admission. After being placed at room temperature for 0.5 h, the blood was centrifuged at 1500 r/min. The supernatant was taken 15 min later and stored for later use. Serum samples of gastric cancer patients were collected 3 days, 7 days, 15 days and 1 month after operation in accordance with the above method.

Main instruments and reagents

Sources of main instruments and reagents used are shown in **Tables 1** and **2**.

RNA extraction

The Phenol-chloroform extraction method was adopted to extract serum, adjacent cancer tissues, and total RNA in cancer tissues under Trizol instructions. The RNA was then purified by sodium acetate and ethanol precipitation. The UV absorbance was measured at 260 nm and 280 nm by ultra-micro spectrophotometer. Samples with A260/A280 between 1.9 and 2.1 were qualified. The concentration and purity of RNA were detected. The integrity of RNA was determined by 1% agarose gel electrophoresis.

cDNA inverse transcription

The 1 μg total RNA underwent reverse transcription according to the instructions of the assay kit. The reverse transcription product was used as a template for PCR reaction. The total reaction system was 20 μL. The reaction conditions were pre-denatured at 95 for 5 min, followed by denaturation at 95°C for 15 s, annealing at 55°C for 30 s, and extension at 72°C for 30 s. The cycle was repeated for 40 times.

Real-time and quantitative PCR detection of SNHG5 expression

After the reverse transcription, RT qPCR was conducted according to the kit instructions. β-actin was taken as the internal reference gene for the tissue samples, and the samples were repeated 3 times in each group. The relative expression of the lncRNA SNHG5 was calculated with the $2^{-\Delta\Delta Ct}$ method. $2^{-\Delta\Delta CT} = 2^{-(\Delta CT \text{ Experimental group} - \Delta CT \text{ Control group})}$. ΔCT Experimental group = CT Target gene of the experimental group - CT Reference gene in the experimental group; ΔCT Control group = CT Target gene of the control group - CT Reference gene in the control group.

Observation indexes

(1) The expression levels of serum lncRNA SNHG5, CEA, CA199 and CA12-5 levels in the 3

Table 1. Main instruments and reagents

Instruments and reagents	Name	Company
Instrument	Eppendorf5331PCR instrument	Eppedorf, Germany
	LC480 real-time fluorescence-based quantitative PCR instrument	Roche, Switzerland
	Ultramicrospectrophotometer	Themo, the USA
	SH-318KR high-speed centrifuge	Changzhou Wanhe Instrument Manufacturing Co., Ltd.
Reagents	Trizol reagent	Invitrogen
	Reverse transcription buffer, M-MLV reverse transcriptase, Rnasin Inhibitor	Promega
	2×qPCRmix	Takara, Japan
	TaqMan Small RNA Assays kit	Applied Biosystems
	Primer and reference genes	Shanghai Sangon Biological Engineering Technology & Services Co., Ltd.

Table 2. Primer and internal reference gene sequence

Primer	Primer sequence
β-actin	Upstream: 5'-GTCCATCCTGGCCTCGCTGT-3'
	Downstream: 5'-GCTGCACCTTCACCGTTCC-3'
SNHG5	Upstream: 5'-TACTGGCTGCGCACTTCG-3'
	Downstream: 5'-CAGTAAAAGGGGAACACCA-3'

groups; (2) The relative expression levels of lncRNA SNHG5 in adjacent tissues and cancer tissues of gastric cancer patients; (3) Correlation analysis between serum lncRNA SNHG5 expression level and clinicopathological data of gastric cancer patients; (4) The relative expression levels of lncRNA SNHG5 in the serum of patients with different prognosis of gastric cancer were observed after 2 years of follow-up. Follow-up: outpatient visits within half a year after surgery, once every two months. Half a year after the operation, patients were followed-up through telephone once every three months about general information, recent symptoms, and whether there was a recurrence. Once the condition changed, the patient was hospitalized for observation and treatment. The follow-up was completed in January 2020.

Statistical methods

SPSS23.0 software was applied in the resent study. Quantitative data were expressed as $\bar{x} \pm sd$. Independent sample T-test was used for comparison between two groups, and variance analysis was used for comparison between multiple groups. The enumeration data were represented by n (%); the comparison between the groups was performed by χ^2 test, and all the experimental data were obtained by three independent replicates. Analysis of factors affecting the prognosis of gastric cancer patients adopted Cox regression model. ROC curve was used to analyze the predictive value of LncRNA-SNHG5 in the diagnosis and prognosis of gastric cancer; survival curve was drawn by Kaplan-Meier method. $P < 0.05$ indicated a statistically significant difference.

Results

Comparison of expression levels of lncRNA SNHG5 in serum

The difference in expression level of serum lncRNA SNHG5 in the 3 groups was noticeable ($P < 0.05$). The pair-based multiple comparison results showed that the expression of lncRNA SNHG5 in gastric cancer serum was lower than that in the benign gastrosia group ($T = 2.998$, $P < 0.05$) and the healthy group ($T = 3.496$, $P < 0.05$). The expression of three serum tumor markers in the three groups and the expression levels of CEA and CA12-5 were statistically different ($P < 0.05$). See **Table 3** and **Figure 1A**, **1B**.

Correlation analysis of serum lncRNA SNHG5 and clinicopathological data in gastric cancer patients

The standard expression quantity of lncRNA SNHG5 in serum was 1.63 (median). The quantity of over 1.63 represented high expression, while ≤ 1.63 represented low expression. The results found no significant difference in the relative expression level of serum lncRNA SNHG5 in patients with different gender, age, smoking history, tumor size, and lymph node metastasis ($P > 0.05$). It was associated with drinking history and TNM stage ($P < 0.05$). See **Table 4**.

Comparison of the relative expression levels of lncRNA SNHG5 in cancer tissues and adjacent tissues

The relative expression levels of lncRNA SNHG5 in the cancer tissues were down-regulated compared with the corresponding adjacent tissues ($P < 0.05$). See **Table 5**.

The relationship of serum lncRNA SNHG5 expression level and prognosis in gastric cancer patients

The results showed that the difference in expression level of serum lncRNA SNHG5 between preoperative and postoperative gastric cancer patients was statistically significant ($P < 0.05$). No significant difference was found between the serum lncRNA SNHG5 before operation and those 3 and 7 days after operation ($P1 = 0.182$, $P2 = 0.129$). The expression of serum lncRNA SNHG5 before operation and 15 days and 1 month after operation was significantly different ($P3 = 0.0001$, $P4 = 0.0135$), respectively. See **Table 5**.

Follow-up results of gastric cancer patients with different prognosis

A total of 43 patients with gastric cancer were followed up for 2 years, and the follow-up rate

Table 3. Serum lncRNA SNHG5 expression levels in patients with benign gastrosia and gastric cancer and in healthy physical examination subjects ($\bar{x}$ ± sd)

Group	n	SNHG5	CEA (ng/L)	CA19-9 (U/ml)	CA12-5 (U/ml)
Gastric cancer group	50	1.61±0.57	2.37±1.13	34.6±8.97	43.25±10.03
Benign gastrosia group	50	1.94±0.53	3.96±1.69	33.43±8.45	32.64±6.38
Healthy group	50	2.03±0.63	4.62±1.98	31.26±5.34	29.76±5.96
F		7.315	24.92	2.388	42.82
P		< 0.05	< 0.05	> 0.05	< 0.05

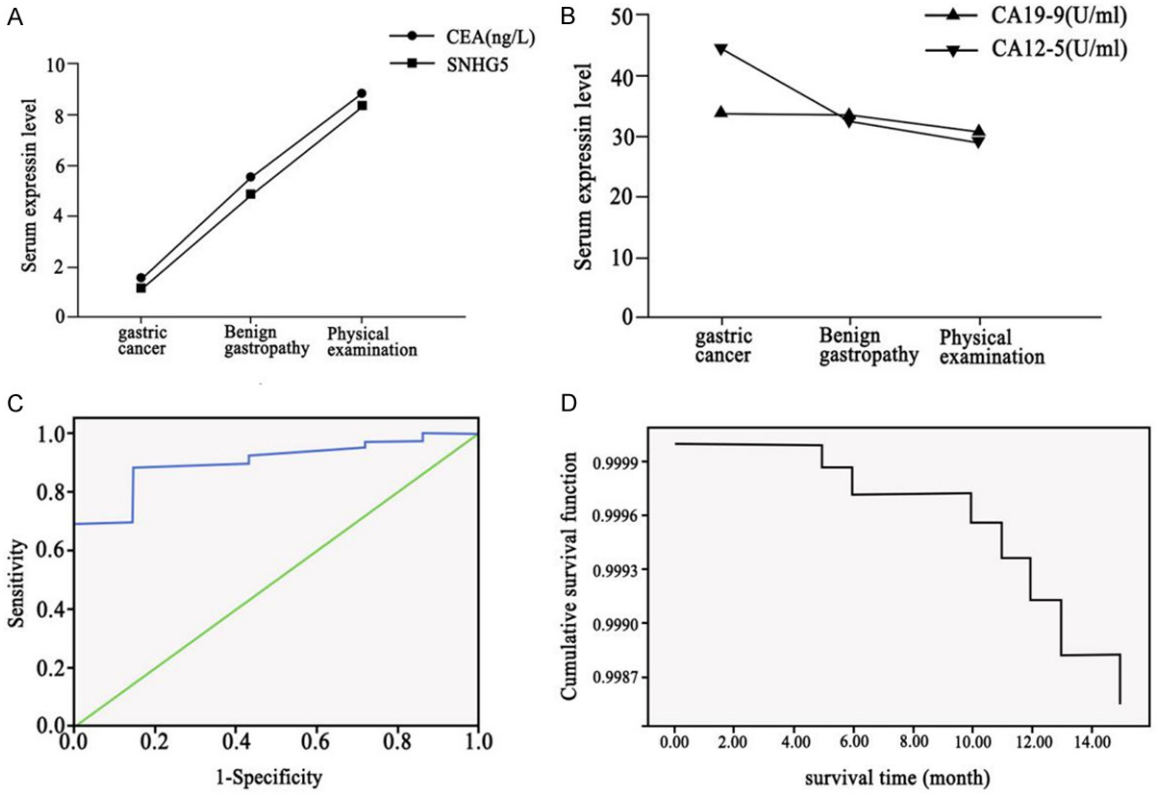

Figure 1. Expression of related serum indicators and its ROC curve. Note: A. Expression of serum SNHG5, CEA in patients with benign gastric disease, gastric cancer and healthy person; B. Expressin of serum CA19-9, CA12-5 in patients with benign gastric disease, gastric cancer and healthy person; C. The value of ROC curve in predicting the prognosis of patients with gastric cancer; D. Survival curve of lncRNA SNHG5.

was 86%. Seven of them died and 43 survived. The relative expression level of lncRNA SNHG5 in the death group was lower than that in the survival group (P < 0.05). See **Table 5**.

The value of ROC curve in predicting the prognosis of gastric cancer patients

The area under the ROC curve of lncRNA SNHG5 was 0.904 (95% CI: 0.81~0.997), the sensitivity was 88.4%, the specificity was 85.7%, and the cutoff value was 1.51 pg/mL, suggesting that lncRNA SNHG5 is of high diagnostic value for prognosis prediction of gastric cancer patients. See **Figure 1C**.

Cox regression analysis of lncRNA SNHG5

LncRNA SNHG5 expression level was determined as the best diagnostic cut-off point through the cut-off value of ROC curve. It was used as the cut-off point for the division of a high-risk group (≥ 1.51 pg/mL) and a low-risk group (< 1.51 pg/mL). Cox proportional hazards survival model was used to further analyze drinking history, TNM stage, and lncRNA

Table 4. Relative expression level of serum lncRNA SNHG5 and its clinical significance in patients with gastric cancer (n)

Clinical features	High expression	Low expression	χ^2	*P*
Gender			0.38	0.536
Male (n = 27)	16	11		
Female (n = 23)	13	10		
Age (years old)			0.645	0.302
≤ 50	11	9		
> 50	13	17		
Drinking history			9.443	0.03
Yes	5	26		
No	11	8		
Smoking history			1.705	0.175
Yes	13	20		
No	10	7		
Tumor size (cm)			0.198	0.454
≤ 5	5	10		
> 5	14	21		
Lymphatic metastasis			0.30	0.403
Yes	10	25		
No	5	10		
TNM stage			4.987	0.026
I-II stage	12	14		
III-IV stage	4	20		

SNHG5. The results showed that lncRNA SNHG5 was a survival predictor for short-term adverse events in gastric cancer patients. See **Table 6** and **Figure 1D**.

Discussion

Gastric cancer is one of the common malignant tumors with no obvious clinical symptoms, which originates from gastric mucosal epithelial lesions. It is of very high incidence, but its early diagnosis rate is rather low. Therefore, once the patient is diagnosed, he/she is already in the middle and advanced stage, resulting in reduced therapeutic effect and increased mortality. With the continuous advancement of scientific knowledge and the development of medical technology, a large number of research data have proved that lncRNA has a great relationship with the occurrence and development of tumors [11, 12]. It is found that LncRNA can play a regulatory role in neuroblastoma, liver cancer, lung cancer and other diseases, but its mechanism is not yet clear [13].

The development of high-throughput screening and sequencing technologies has opened a door for lncRNAs research. More and more lncRNAs are being discovered. Some studies have found that there are binding sites between SNHG5 and miR-26b, and the overexpression of LncRNA SNHG5 in gastric cancer cells can inhibit the expression of miR-26b and primR-26b through other more complex mechanisms. The study on the interaction between the two is expected to become a new research direction in the treatment of gastric cancer [14]. Certain progress has been made in studies of lncRNA and gastric cancer. Studies have found that a variety of lncRNAs, such as lncRNA LINC00675, lncRNA TRERNA1, Lincrna-00152, lncRNA HOTAIR, lncRNA-FENDRR, lncrna-MEG3, etc. are vital in the occurrence, development and prognosis of gastric cancer tumor [15-20], and can be used as potential biological markers. LncRNA SNHG5 is a member of the 5'TOP family. As the spliceosome of host gene exon located at the chromatin genome break point U50, it also has a non-neglectable regulatory role. The results showed that the expressions of LncRNA SNHG5 and human lymphoblast TK6 cells were significantly different under X-ray irradiation in leukemia cells [21], which was speculated to play an important role in gastric cancer.

In this study, the expression level of serum lncRNA SNHG5 was compared in gastric cancer patients, patients with benign gastrosia and healthy subjects. The results showed that the overall difference was of statistically significant. The expression of lncRNA SNHG5 in gastric cancer serum was down-regulated compared with that in the benign gastrosia group and the healthy group. Meanwhile, the relative expression level of lncRNA SNHG5 in cancer tissues was down-regulated compared with the corresponding expression level in adjacent tissues. Correlation analysis showed that the expression level of lncRNA SNHG5 in the serum of gastric cancer was correlated with drinking history and TNM stage, but not significantly correlated with other clinicopathological features. This indicated that long-term alcohol intake

Table 5. Correlation on the expression levels of lncRNA SNHG5 in the two tissues and prognosis ($\bar{x} \pm sd$)

index	n	SNHG5 (pg/mL)
time		
Before operation	50	1.61±0.57
After operation		
3 days	50	1.45±0.62
7 days	50	1.41±0.73
15 days	50	1.13±0.64
1 month	50	1.98±0.87
F		10.09
P		< 0.0001
Prognosis		
Death	7	0.53±0.15
Survival	43	1.39±0.40
t		4.733
P		< 0.05
tissues		
Adjacent	50	1.79±0.42
Cancer	50	0.87±0.21
t		13.85
P		< 0.01

Note: P1 is the comparison of before operation and 3 days after operation; P2 is the comparison of before operation and 7 days after operation; P3 is the comparison of before operation and 15 days after operation; P4 is the comparison of before operation and 1 month after operation.

Table 6. Cox regression model analysis

Items	B	SE	wald	*P*	Exp (B)	95% CI
Drinking history	-0.14	0.33	0.15	0.602	0.855	1.097~1.789
TNM stage	-0.03	0.29	0.02	0.617	0.970	0.054~13.816
lncRNA SNHG5	1.58	0.39	15.14	0.043	4.890	2.125~14.633

Note: TNM staging (stage I-II = 0, stage III-IV = 1); Drinking history (no = 0, yes = 1); lncRNA SNHG5 (high = 0, low = 1).

may affect the regulation of lncRNA SNHG5 expression, oncogenes, and tumor suppressor genes, and further influence the progression and prognosis of gastric cancer. The relative expression levels of lncRNA SNHG5 in the serum of gastric cancer patients before and after surgery were significantly different as a whole. The expression of serum lncRNA SNHG5 before operation was significantly different compared with that 15 days and 1 month after operation. The relative expression level of serum lncRNA SNHG5 in the death group was lower. The results showed that the low expression level of lncRNA SNHG5 may be an important reason for poor clinical prognosis in gastric cancer patients. The area under ROC curve was 0.904 (95% CI: 0.81~0.997), the sensitivity was 88.4%, and the specificity was 85.7%, indicating that the expression level is of high prognostic value. Further analysis by Cox regression model showed that lncRNA SNHG5 was a predictor of survival for short-term adverse events in gastric cancer patients.

In summary, the serum expression of lncRNA SNHG5 decreased in patients with gastric cancer before operation and those with poor prognosis. LncRNA SNHG5 is of high diagnostic value for gastric cancer. However, the signaling pathway of how it regulates or participates in the progression and prognosis of gastric cancer has not been clear, and the specific mechanism of action remains to be further studied. The next research idea is to explore the regulatory mechanism of lncRNA SNHG5 in gastric cancer, which may improve the value of lncRNA SNHG5 as a biomarker for the diagnosis and prognosis of gastric cancer when combined with other molecular biological tumor markers.

Disclosure of conflict of interest

None.

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