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Association between hsa_circ_0006156 expression and incidence of gastric cancer

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Abstract. – OBJECTIVE: To screen the differentially expressed circular ribonucleic acids (circRNAs) related to gastric cancer and to explore their associations with the clinicopathological features of gastric cancer.

PATIENTS AND METHODS: Cancer tissues of 50 gastric cancer patients undergoing surgical resection in our hospital from April 2015 to December 2018 were collected as an experimental group, while the para-carcinoma tissues were used as the control group. First, the differentially expressed circRNAs were screened by analyzing the circRNA profile in the microarray. Then, the expression of hsa_circ_0006156 in tissues was detected *via* Reverse Transcription-quantitative Polymerase Chain Reaction (RT-qPCR) in both groups. The potential associations of the relative expression level of hsa_circ_0006156 with clinicopathological features and prognosis were analyzed according to the clinical data of gastric cancer patients.

RESULTS: Six significantly downregulated circRNAs in gastric cancer patients were screened out. The results of RT-qPCR showed that the expression level of hsa_circ_0006156 was significantly lower in gastric cancer tissues than that in para-carcinoma tissues ($p<0.05$). Accordingly, 50 gastric cancer patients were divided into hsa_circ_0006156 high expression group and hsa_circ_0006156 low expression group based on the fold change of hsa_circ_0006156 in para-carcinoma tissues than that of gastric cancer tissues (fold change>3). The expression level of hsa_circ_0006156 was not correlated with the age and gender of gastric cancer patients ($p>0.05$) but correlated with the lymph node metastasis ($p<0.05$), nerve invasion ($p<0.05$), and degree of tumor differentiation ($p<0.05$). The expression level of hsa_circ_0006156 was also significantly associated with the progression-free survival (PFS) and overall survival (OS) of patients ($p<0.05$). According to the multivariate analysis of variance, the PFS of gastric cancer patients was associated with nerve invasion, lymph node metastasis, and hsa_circ_0006156 expression (relative risk coefficient=1.742, 2.329, and 3.003). Meanwhile, the OS was associated with lymph node metastasis, nerve invasion, degree of tumor differentiation, and hsa_circ_0006156 expression (relative risk coefficient =1.604, 2.405, 2.114, and 2.004). Moreover, the survival analysis revealed that PFS was markedly prolonged in the hsa_circ_0006156 high expression group compared with that in the hsa_circ_0006156 low expression group.

CONCLUSIONS: The expression of hsa_circ_0006156 substantially declines in gastric cancer tissues, which is related to the differentiation degree, presence, or absence of lymph node metastasis and prognosis of gastric cancer patients. Therefore, hsa_circ_0006156 may clinically serve as a biomarker for the prognostic prediction of gastric cancer patients.

Key Words:
Gastric cancer, Hsa_circ_0006156, Biomarker.

Introduction

Gastric cancer is one of the four major cancers in the world, and its morbidity rate is relatively high[1,2]. The morbidity and mortality rates of gastric cancer both rank first among digestive tract cancers. According to incomplete statistics, the total number of gastric cancer cases is approximately 950,000 in the world, and it increases year by year, accounting for about 7% of the total cancer cases. The incidence of gastric cancer is high in China, and there are about 400,000 new cases of gastric cancer every year, accounting for about 60% of the global total new cases[3,4]. Nowadays, the disease onset of gastric cancer becomes younger with the fast pace of people's life, an increase in pressure, bad eating habits, and environmental factors. There are more and more female patients with gastric cancer currently, which may be relat-

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ed to the estrogen in the body[5]. The positive expressions of estrogen receptors in gastric cancer affect the differentiation degree of gastric cancer cells, leading to poor efficacy and prognosis of gastric cancer[6,7]. The key factors causing gastric cancer involve heredity and the environment. With the advancement of science and technology, the therapeutic effects, such as radiotherapy and surgery, have been greatly improved. Nevertheless, the postoperative 5-year survival rate of gastric cancer patients is still low. Therefore, finding the method for early diagnosis of gastric cancer is a major task to reduce its mortality rate[7,8].

In 1976, circular ribonucleic acids (circRNAs) were first discovered. They were initially considered as the products of gene-splicing errors in the past two decades[9,10]. Later, researchers discovered stable and abundant circRNAs in the eukaryocytes in 2012[11,12], thereby attracting widespread attention. Studies have found that circRNAs can participate in post-transcriptional regulation of cancer genes mainly by sponging miRNAs[13,14]. Hsa_circ_0006156 is lowly expressed in colon cancer. In the present study, the expression of hsa_circ_0006156 was detected in gastric cancer tissues and para-carcinoma tissues, and the association between hsa_circ_0006156 and gastric cancer was explored as well.

Patients and Methods

Tissue Sources and Grouping

The gastric cancer tissues and para-carcinoma normal tissues (at least 5 cm away from the cancer lesion) from 50 gastric cancer patients undergoing surgical resection in our hospital from April 2015 to December 2018 were collected as samples. The clinical data of patients, including gender, age, tumor size, degree of tumor differentiation, lymph node metastasis, and TNM stage, were completely recorded. In this study, the use of all tissue samples was approved by the Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong University. None of the 50 patients underwent pre-operative anti-tumor treatments, such as radiotherapy or chemotherapy.

Tissue Treatment

The fresh tissues obtained in the surgery were immediately frozen in liquid nitrogen and then stored in a refrigerator at -80°C.

Gene Expression Profile Microarray

The gastric cancer tissues in 6 patients and para-carcinoma tissues in 14 patients were subjected to analysis of differentially expressed circRNA by GMINIX (Shanghai, China). The differentially expressed circRNAs were determined using the GG-H microarray (Affymetrix glue grant human transcriptome array, Santa Clara, CA, USA).

Reverse Transcription-Quantitative Polymerase Chain Reaction (RT-qPCR)

The expression of hsa_circ_0006156 in cancer tissues and para-carcinoma tissues was detected *via* RT-qPCR. The total RNA extracted from tissues was taken for PCR amplification. The amplification level of the target gene was verified using 5% agarose gel electrophoresis. The data were quantified and processed using LabWorks 4.0 image acquisition and analysis software. To obtain reliable data, the reaction was repeated 3 times in each group of samples. In this study, the relative levels of the target genes were analyzed using the $2^{-\Delta\Delta Ct}$ method. The primer sequences used in this study were shown in Table I.

Follow-Up and Survival Analysis

All patients were followed up once every 3 months within 6 months after surgery, and then once every 6 months. During the follow-up period, the blood routine and hepatic and renal function examinations were reviewed, and the enhanced magnetic resonance imaging was performed. Tumor progression was determined according to the McDonald criteria, with tumor recurrence or death of any cause as the endpoint of follow-up. The progression-free survival (PFS) is defined as

Table I. Primer sequence.

Primer	Forward/reverse	Primer sequence
Hsa_circ_0006156	F	5'-GGAGGAGCTGGATTTGGGACTGAT-3'
	R	5'-GGTGGAACAATTCCTGTACCTGCACA-3'
β-action	F	5'-CAGAGCCTCGCCTTTGCCGATC-3'
	R	5'-GGCCTCGTCGCCCACATAGG-3'

the duration from the date of surgery to the date of death due to tumor recurrence. The overall survival (OS) is defined as the duration from the date of surgery to the date of death of any cause.

Statistical Analysis

The Statistical Product and Service Solutions (SPSS) 13.0 software (SPSS Inc., Chicago, IL, USA) was used for analysis. The associations of the expression of hsa_circ_0006156 with clinicopathological features, survival rate, and prognosis of gastric patients were analyzed by the *t*-test. Enumeration data were expressed as a percentage (%), and χ^2-test was performed for intergroup comparison. $p<0.05$ suggested the statistically significant difference.

Results

Differentially Expressed CircRNAs in Cancer Tissues and Para-Carcinoma Tissues Screened Using Gene Expression Profile Microarray

The differentially expressed circRNAs in cancer tissues, and para-carcinoma tissues were screened using gene expression profile microarray. A total of 6 circRNAs were significantly downregulated in cancer tissues compared with para-carcinoma tissues (Table II). Hsa_circ_0006156 was the most significantly downregulated, and its expression level in cancer tissues was significantly lower than that in para-carcinoma tissues.

Differential expressions of Hsa_circ_0006156 in Cancer Tissues and Para-Carcinoma Tissues Detected Using RT-qPCR

The results of RT-qPCR showed that the expression level of hsa_circ_0006156 was significantly lower in cancer tissues than that in para-carcinoma tissues ($p<0.05$) (Figure 1).

Table II. Differentially expressed circRNAs screened using gene expression profile chip.

Gene	Down-regulation fold	*p*
Hsa_circ_0006156	0.093	$p<0.05$
Hsa_circ_1878921	0.145	$p<0.05$
Hsa_circ_0001666	0.213	$p<0.05$
Hsa_circ_0018909	0.111	$p<0.05$
Hsa_circ_0092145	0.162	$p<0.05$
Hsa_circ_0043277	0.154	$p<0.05$

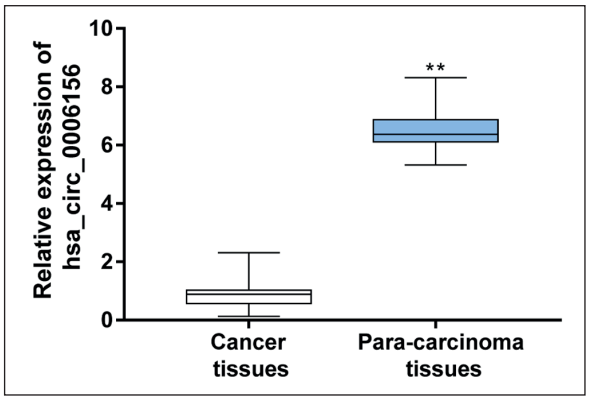

Figure 1. Differential expressions of hsa_circ_0006156 in cancer tissues and para-carcinoma tissues detected using RT-qPCR. $^{**}p<0.01$ compared with para-carcinoma tissues.

Correlations of Hsa_circ_0006156 Expression with Clinicopathological Features of Gastric Cancer

According to the statistical analysis of the clinicopathological features and expression level of hsa_circ_0006156 in patients, the expression level of hsa_circ_0006156 was not correlated with the age and gender of gastric cancer patients ($p>0.05$). Nevertheless, it was correlated with the lymph node metastasis ($p=0.002$), nerve invasion ($p=0.004$), tumor recurrence ($p=0.003$), and death of patients ($p=0.002$). In other words, the level of hsa_circ_0006156 significantly declined in gastric cancer patients with lymph node metastasis, nerve invasion, tumor recurrence, and death (Table III).

Univariate Analysis of Gastric Cancer Patients

The univariate analysis results showed that the PFS and OS of gastric cancer patients were associated with lymph node metastasis, nerve invasion, tumor recurrence, and relative expression of hsa_circ_0006156 ($p<0.05$), but not associated with gender and age of patients ($p>0.05$). Besides, the lymph node metastasis, nerve invasion, degree of tumor differentiation, and hsa_circ_0006156 expression were associated with evidently decreased PFS and OS in gastric cancer patients (Table IV).

Multivariate Analysis of Variance

According to the multivariate analysis of variance, the PFS of gastric cancer patients was associated with nerve invasion, lymph node metastasis, and hsa_circ_0006156 expression (relative risk coefficient =1.742, 2.329, and 3.003). Meanwhile, the OS was associated with lymph node metastasis, nerve invasion, degree of tumor differentiation,

Table III. Association between hsa_circ_0006156 expression and clinicopathological features of gastric cancer.

Feature	Case [n (%)]	Relative expression of hsa_circ_0006156	p
Gender			0.504
Male	28 (56.0%)	0.67±0.71	
Female	22 (44.0%)	0.83±1.23	
Age			0.810
>60	17 (34%)	0.75±0.58	
≤60	33 (66%)	0.76±0.70	
Lymph node metastasis			0.002
Yes	37 (74%)	0.23±0.07	
No	13 (26%)	0.93±0.88	
Nerve invasion			0.004
Yes	43 (86%)	0.18±0.04	
No	7 (14%)	0.84±0.67	
Degree of tumor differentiation			0.001
Low	36 (72%)	0.13±0.02	
High	14 (28%)	0.85±0.41	
Death (until deadline of follow-up)			0.002
Yes	109 (54.5%)	0.33±0.09	
No	91 (45.5%)	0.89±0.68	

and hsa_circ_0006156 expression (relative risk coefficient =1.604, 2.405, 2.114, and 2.004) (Table V).

Survival Analysis Results

The patients were followed up for (22.34±2.89) months (1-114 months) on average. It was found that PFS was remarkably prolonged in the hsa_circ_0006156 high expression group compared with that in the hsa_circ_0006156 low expression group (Figure 2).

Discussion

Gastric cancer is a kind of malignant tumor with high morbidity and mortality rates in China. The survival rate of gastric cancer patients in the early stage within 5 years is higher than 80%. However, gastric cancer patients have been mostly diagnosed in the middle or even advanced stage, leading to a poor therapeutic efficacy[15]. Although surgical

Table IV. Univariate analysis of gastric cancer patients.

Variable	Case (n)	PFS%			OS%		
		1-year	3-year	p	1-year	3-year	p
Gender				0.673			0.807
Male	28	56.7	40.5		79.9	43.2	
Female	22	53.1	36.8		65.1	41.8	
Age				0.891			0.750
>60	17	66.9	31.8		76.9	35.1	
≤60	33	56.3	36.8		66.8	39.1	
Lymph node metastasis				0.004			0.004
Yes	37	16.5	10.3		20.5	13.4	
No	13	70.3	54.4		80.7	58.1	
Nerve invasion				0.003			0.002
Yes	43	16.1	8.05		18.1	12.5	
No	7	66.9	44.5		69.3	54.3	
Degree of tumor differentiation				0.003			0.002
Low	36	13.6	7.56		16.4	9.06	
High	14	51.9	27.9		55.8	37.5	
Relative expression of hsa_circ_0006156				0.001			0.001
Low (≤0.55)	119	13.7	5.08		15.4	8.09	
High (>0.55)	81	67.3	33.7		69.1	36.2	

Table V. Multivariate analysis of variance of gastric cancer patients.

Variable	PFS			OS		
	Relative risk	95% CI	p	Relative risk	95% CI	p
Lymph node metastasis (Yes *vs.* No)	1.742	0.742-4.334	0.224	1.604	0.602-4.031	0.313
Nerve invasion (Yes *vs.* No)	2.329	0.541-8.220	0.036	2.405	0.771-9.020	0.219
Degree of tumor differentiation (High *vs.* Low)	3.003	0.034-6.204	0.125	2.114	0.020-4.105	0.034
Relative expression of hsa_circ_0006156 (Low *vs.* High)	2.233	1.003-3.441	0.001	2.004	1.603-5.042	0.001

treatment is helpful for gastric cancer patients, its efficacy is not significant for advanced gastric cancer[16,17]. At present, the early diagnosis and treatment of gastric cancer are the most effective ways to reduce the mortality rate of gastric cancer patients. However, evident clinical features in most of the early gastric cancer patients are lacked. Currently, gastroscopy combined with pathological examination is still the golden standard for diagnosis of gastric cancer[18], but gastroscopy has not been widely popularized yet due also to the influence of the economic level. Moreover, gastroscopy has some disadvantages: for example, a large number of patients with early gastric cancer cannot be diagnosed by gastroscopy due to the poor sensitivity and specificity of tumor markers. Meanwhile, various complications may also be induced by gastroscopy in patients with heart disease[19]. Therefore, the occurrence and development of gastric cancer is a multi-environmental and multi-factor process. Predicting the development and prognosis of gastric cancer and adopting corresponding therapeutic methods through early diagnosis are still challenging problems.

In this study, the differentially expressed circRNAs in cancer tissues, and para-carcinoma tissues were screened. A total of 6 significantly downregulated circRNAs were identified in cancer tissues compared with para-carcinoma tissues. Hsa_circ_0006156 was the most significantly downregulated one, and its expression level in cancer tissues was significantly lower than that in para-carcinoma tissues. The results of RT-qPCR showed that the expression level of hsa_circ_0006156 was significantly lower in cancer tissues than that in para-carcinoma tissues ($p<0.05$). According to the statistical analysis of the clinicopathological features and expression level of hsa_circ_0006156 in patients, the expression level of hsa_circ_0006156 was not correlated with the age and gender of gastric cancer patients ($p>0.05$). The univariate analysis results showed that the PFS and OS of gastric cancer patients were associated with lymph node metastasis, nerve invasion, tumor recurrence, and relative expression of hsa_circ_0006156 ($p<0.05$), but not associated with gender and age of patients ($p>0.05$). Besides, the lymph node metastasis, nerve invasion, degree of tumor differentiation, and hsa_circ_0006156 expression were associated with evidently decreased PFS and OS. In addition, according to the multivariate analysis of variance, the PFS of patients was associated with nerve invasion, lymph node metastasis, and hsa_circ_0006156 expression (relative risk coefficient = 1.742, 2.329, and 3.003). In addition, OS was associated with lymph node metastasis, nerve invasion, degree of tumor differentiation, and hsa_circ_0006156 expression (relative risk coefficient=1.604, 2.405, 2.114, and 2.004). Finally, the patients were followed up for (22.34±2.89) months (1-114 months) on average. It is found that PFS was remarkably prolonged in the hsa_circ_0006156 high expression group compared with that in the hsa_circ_0006156 low expression group. The above findings demonstrated that hsa_circ_0006156 may be involved in the occurrence and development of gastric cancer.

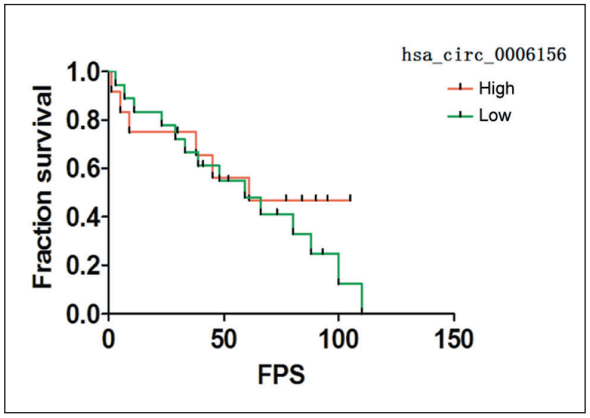

Figure 2. Survival curve of gastric cancer patients.

With the development of molecular research, increasingly more ncRNAs have been well concerned, and circRNAs, as the downstream of ncRNAs, have been paid more and more attention by many researchers due to the special structure and source[20]. There are three types of circRNAs, including the first type totally derived from exon, the second one totally derived from intron, and the third one derived from exon + intron[21]. CircRNAs are widely present in the incidence and development of tumors, indicating that they have great potential in the diagnosis, prognosis, and targeted therapy for tumors. However, the research on circRNAs is still in its infancy, and some scholars have analyzed the protein-coding genes of miRNA-circRNA in tumor diseases[22,23]. Thus, it is found that hsa_circ_0001649 is lowly expressed, but hsa_circ_0005075 is highly expressed in liver cancer tissues. The expression of hsa_circ_100855 is upregulated, and hsa_circ_104912 is downregulated in laryngeal cancer tissues[24]. In gastric cancer, 68 differentially expressed circRNAs have been found, and hsa_circ_0006156, as a novel circRNA, has been proven to be lowly expressed in gastric cancer tissues. Its plasma level is also different in gastric cancer patients before and after surgery. Furthermore, it has been found that the low expression of hsa_circ_0006156 has an evident association with distant metastasis and TNM stage[25,26]. Different circRNAs in the same family of hsa_circ_0006156 also have a similar expression in gastric cancer tissues. The expression of hsa_circ_0001649 evidently declines in gastric cancer tissues but rises in para-carcinoma tissues. Its serum level significantly rises in gastric cancer patients after surgery[27]. Experiments have demonstrated that the expression of hsa_circ_0001666 in gastric cancer tissues was significantly lower than that in the corresponding para-carcinoma normal tissues, which was similar to hsa_circ_0006156. Therefore, hsa_circ_0001666 may become a potential marker in the clinical treatment of gastric cancer.

Conclusions

In summary, we first confirmed that the expression of hsa_circ_0006156 significantly declines in gastric cancer tissues, which is related to the differentiation degree, presence or absence of lymph node metastasis and prognosis of gastric cancer patients. Therefore, hsa_circ_0006156 may clinically serve as a biomarker for the prognostic prediction of gastric cancer patients.

Conflict of Interests

The authors declare that they have no conflict of interest.

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