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Original Article

High expression of long noncoding RNA AB073614 in colorectal cancer patients and its clinical significance

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Abstract: More and more studies have suggested that long non-coding RNAs (LncRNAs) are involved in different physiological or physiopathologic processes including the development of cancer. Previous studies have suggested long noncoding RNA AB073614 (lncRNA AB073614) is involved in ovarian cancer and glioma, but its role in colorectal cancer (CRC) is still unclear. A study was thus performed to examine the expression of lncRNA AB073614 in CRC patients and its clinical significance. A total of 51 CRC patients were included in the study. Expression of lncRNA AB073614 in tumor tissues and paired adjacent non-tumor tissues were detected by Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR). Logistic regression analysis was also performed. The relative expression of lncRNA AB073614 in the CRC tumor tissues was significantly higher when compared with the paired normal tissues ($P < 0.0001$). The expression of lncRNA AB073614 in the tumor tissues was obviously higher in CRC patients with high grade ($P = 0.003$), larger tumor size (> 5 cm) ($P = 0.008$), distant metastasis ($P = 0.0007$), or poor differentiation ($P = 0.01$). Multivariate logistic regression analysis suggested high expression of lncRNA AB073614 was independently associated with higher possibilities of high grade (OR = 26.08; $P = 0.01$), distant metastasis (OR = 91.14; $P = 0.03$) and poor differentiation (OR = 28.15; $P = 0.006$). The findings above suggest that lncRNA AB073614 may participate in the carcinogenesis and progression of CRC. More researches are needed to validate the role of lncRNA AB073614 in CRC, and to explore the underlying molecular mechanism.

Keywords: Long noncoding RNA, colorectal cancer, LncRNA AB073614, prognostic biomarker

Introduction

Colorectal cancer (CRC) is one of the most common malignant diseases with more than one hundred million newly diagnosed cases every year worldwide [1]. Besides, there are over 600,000 deaths caused by CRC every year, and CRC thus is a huge threat to human health [1, 2]. There were still 134,490 estimated new cases of CRC in the United States, though many preventive projects were applied [3]. In China, there were over 376,000 estimated new CRC cases and about 191,000 deaths caused by CRC [4]. In the past decade, treatments for CRC patients have been improved much, which has led to some improvement in long-term outcomes [5]. However, despite of those advances in the treatment methods of CRC, the prognosis for those patients with advanced stages is still poor with a 5-year survival rate less than 20% [5]. In the past two decades, there are also a large number of progresses in our understanding of the development and progression of CRC, which may help to the development of some effective targeted biologics for CRC patients. However, the improvement in the survival of some CRC patients using those targeted biologics is still limited [6, 7]. Therefore, there is still urgent need for researchers to investigate the pathogenesis of CRC and provide some promising new therapy targets for CRC patients.

Recent studies on epigenetics have helped us get a much better understanding of the carcinogenesis of CRC, which also provide some promising therapy targets for CRC [8]. There are a large number of clinical or experimental studies suggesting the critical roles of epigenetics in the development or the progression of CRC [8-13]. Epigenetics mainly include DNA methylation, histone modifications and noncoding

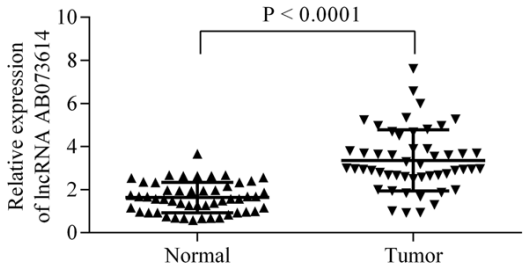

Figure 1. The relative expression of lncRNA AB073614 in the CRC tumor tissues was significantly higher than normal tissue (Relative expression of lncRNA AB073614 was shown using $2^{-\Delta\Delta Ct}$ method).

RNAs, and long non-coding RNAs (lncRNAs) are a newly found epigenetic biomarker [14]. Long non-coding RNAs (lncRNAs) are a large group of RNAs more than 200 nucleotides in length but lack the ability to code proteins [15]. However, lncRNAs have been suggested to have widespread roles in regulating gene expression and other biological functions [16]. Some well-known functions of lncRNAs include chromatin remodeling, regulation of gene transcription, and regulation of micRNAs [17]. Specific alterations of lncRNAs in CRC patients have also been studied, and some useful diagnostic or prognostic biomarkers of CRC have been found, such as lnc34a, lncRNA ASBEL and lncRNA HOTAIR [8, 10, 11, 18, 19]. However, the roles of lncRNAs in both the development and the development of CRC are largely unknown, and more studies are needed to elucidate their critical roles. LncRNA AB073614 is an lncRNA firstly identified in the tissues of primary hepatoblastoma, but its biological function is still unclear [20]. A study in ovarian cancer suggested lncRNA AB073614 was obviously up-regulated in ovarian cancer tissues, and it was a biomarker of poorer prognosis in ovarian cancer patients [21]. Recent studies found that the expression of lncRNA AB073614 was increased in glioma tissues and cell lines, and it also was a poor prognostic biomarker in glioma [22, 23]. However, there is still no study exploring the expression and clinical significance of lncRNA AB073614 in CRC patients, and its role in CRC is still unclear. We thus conducted this study to examine the expression of lncRNA AB073614 in CRC patients and assess its clinical significance by analyzing the relationships of lncRNA AB073614 with clinicopathological characteristics of CRC patients.

Materials and methods

Clinical CRC samples

A total of 51 CRC patients who underwent surgical resection of primary tumors between January 2015 and December 2015 at the Fifth Affiliated Hospital, Sun Yat-sen University were included in the study. Patients receiving preoperative adjuvant radiotherapy or adjuvant chemotherapy were not included in our study. All tumor tissues and adjacent normal tissues were collected from those 51 patients. All tissues were stored in liquid nitrogen and at -80°C until examination. The present study was approved by the Ethics Committee of the Fifth Affiliated Hospital, Sun Yat-sen University and written consent forms were obtained from all recruited patients. Data on the clinicopathological factors of those included patients, such as age, gender, tumor grade, tumor size, lymphatic metastasis, distant metastasis, differentiation and vascular invasion, were collected.

RNA extraction and quantitative real-time PCR (qRT-PCR)

Expression of lncRNA AB073614 in the tissues was examined by qRT-PCR. To ensure tissue homogeneity, the areas used for examination were selected by a pathologist before extracting total RNA. Total RNA was extracted from tissues using TRIzol reagent following the manufacturer's instructions. Next, a total of 3 μg RNA for each sample was reverse transcribed into cDNA. qRT-PCR was then performed using a Light Cycler 480 System and SYBR Green PCR Master Mix, and GAPDH was used as a normalizing control. The forward and reverse primers for lncRNA AB073614 were 5'-TCTGCTCCTGGGTCTTACAC-3' and 5'-TGCAACCACATGTAACCACA-3', respectively. The forward and reverse primers for GAPDH were 5'-CCCATCACCATCTTCCAGGAG-3' and 5'-GTTGTCATGGATGACCTTGGC-3', respectively. The PCR cycles were programmed as 95°C for 10 min, followed by 40 repeated cycles at 95°C for 10 s, and 60°C for one minute. The relative expression of lncRNA AB073614 was calculated and normalized to GAPDH using the $2^{-\Delta\Delta Ct}$ method.

Statistical analysis

Data were expressed as mean ± standard error (SE) or percentages. Student t-test was used to

Table 1. Difference in the lncRNA AB073614 expression in CRC patients grouped by clinicopathological characteristics

Clinicopathological characteristics	Number of patients	Expression of lncRNA AB073614*	*P*-value
Sex			
Male	28	3.17 ± 0.21	0.32
Female	23	3.57 ± 0.36	
Age (year)			
< 58	26	3.16 ± 0.25	0.33
≥ 58	25	3.55 ± 0.31	
Grade			
I/II	20	2.66 ± 0.32	0.003
III/IV	31	3.80 ± 0.22	
Tumor size			
≤ 5 cm	27	2.87 ± 0.22	0.008
> 5 cm	24	3.89 ± 0.31	
Lymphatic metastasis			
Yes	25	3.64 ± 0.29	0.15
No	26	3.07 ± 0.26	
Distant metastasis			
Yes	12	4.51 ± 0.43	0.0007
No	39	2.99 ± 0.19	
Differentiation			
Poor	33	3.72 ± 0.27	0.01
High	18	2.68 ± 0.17	
Vascular invasion			
Yes	21	3.64 ± 0.38	0.23
No	30	3.15 ± 0.20	

*The relative expression of lncRNA AB073614 was calculated using $2^{-\Delta\Delta Cq}$ method and was shown as mean ± SE.

analyze the difference in the expression of lncRNA AB073614 between tumor tissues and normal tissues. The difference in the lncRNA AB073614 expression in CRC patients between groups by clinicopathological characteristics was also analyzed by Student t-test. Logistic regression analysis was then performed to assess the relationships of lncRNA AB073614 expression with clinicopathological characteristics in CRC patients. SPSS (Version 17.0, Chicago, USA) and GraphPad Prism (Version 6.0, CA, USA) were used for statistical analysis. A *P*-value of < 0.05 was considered statistically significant.

Results

LncRNA AB073614 expression in CRC tissues

The relative expression of lncRNA AB073614 was examined in 51 paired CRC tumor tissues and normal tissues. As show in the **Figure 1**, the relative expression of lncRNA AB073614 in the CRC tumor tissues was significantly higher than normal tissues (P < 0.0001; **Figure 1**).

Difference in lncRNA AB073614 expression between groups by clinicopathological characteristics

The expression of lncRNA AB073614 in tumor tissues was obviously higher in CRC patients with high grade compared with those with low grade (3.80 ± 0.22 vs. 2.66 ± 0.32, P = 0.003) (**Table 1**; **Figure 2A**). CRC patients with larger tumor size (> 5 cm) also had increased expression of lncRNA AB073614 in the tumor tissues (P = 0.008) (**Figure 2B**). The expression of lncRNA AB073614 in the tumor tissues was obviously higher in CRC patients with distant metastasis (P = 0.0007) (**Figure 2C**) or poor differentiation (P = 0.01) (**Table 1**; **Figure 2D**).

Correlations of lncRNA AB073614 with clinicopathological characteristics

To investigate the correlations between lncRNA AB073614 expression and clinicopathological factors in CRC patients, logistic regression analysis was further performed. As presented in **Table 2**, univariate logistic regression analysis suggested that high expression of lncRNA AB073614 was associated with high grade (OR = 8.39; P = 0.002), lymphatic metastasis (OR = 3.36; P = 0.03), distant metastasis (OR = 19.64; P = 0.007) and poor differentiation (OR = 18.40; P = 0.001) (**Table 2**). In the multivariate logistic regression analysis, high expression of lncRNA AB073614 was independently associated with higher possibilities of high grade (OR = 26.08; P = 0.01), distant metastasis (OR = 91.14; P = 0.03) and poor differentiation (OR = 28.15; P = 0.006) (**Table 2**).

Discussion

The critical roles of lncRNAs in CRC have been reported by more and more studies [8, 10, 11, 24-29]. Previous studies have suggested lncRNA AB073614 is involved in ovarian cancer and glioma, but its role in CRC is still unclear [21, 22]. We thus carried out this study to evaluate its role in CRC patients. To our knowledge, it's the first study on the roles of lncRNA AB073614 in CRC patients. The findings of the present study suggested that the relative expression of lncRNA AB073614 in the CRC tumor tissues was significantly higher when

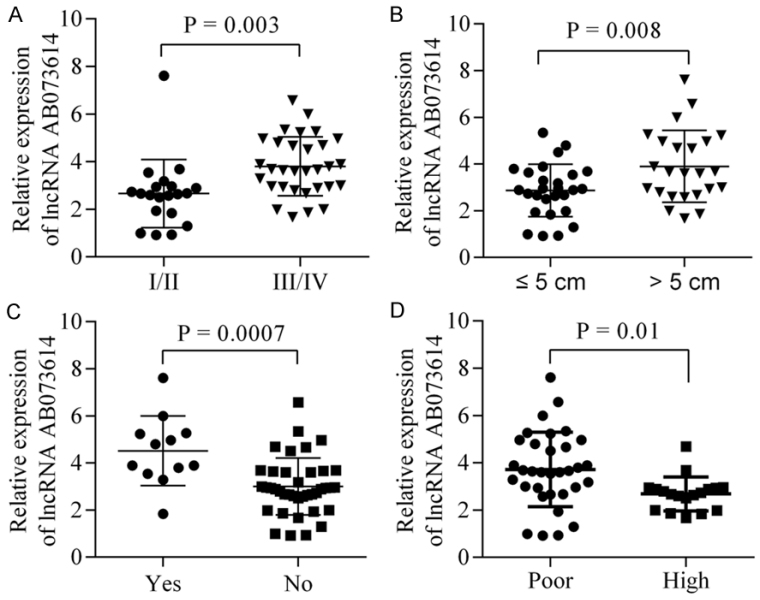

Figure 2. Difference in lncRNA AB073614 expression between groups by clinicopathological characteristics. Higher expression of in lncRNA AB073614 in CRC patients with high grade (A), larger tumor size (> 5 cm) (B), distant metastasis (C), and poor differentiation (D).

compared with the paired normal tissues (P < 0.0001). Besides, high expression of lncRNA AB073614 was obviously associated with some clinicopathological characteristics of CRC patients, such as high tumor grade (P = 0.003), larger tumor size (> 5 cm) (P = 0.008), distant metastasis (P = 0.0007), and poor differentiation (P = 0.01). The findings above indicate that lncRNA AB073614 have an important role in CRC and may participate in the carcinogenesis and progression of CRC.

LncRNAs have been suggested to have important roles in the carcinogenesis of malignant diseases [13-15, 30]. Some published studies have proven that abnormal expressions of some lncRNAs are strongly associated with CRC development and progression [31-35]. Therefore, the roles of lncRNAs in CRC are gaining more and more attentions. Studies on CRC-associated lncRNAs have helped us get a much better understanding of the carcinogenesis of CRC, which also provide some promising therapy targets for CRC [8, 36]. Previous study in ovarian cancer showed that lncRNA AB073614 was abnormally expressed in the tumor tissues of ovarian cancer [21]. Another study also found elevated expression of lncRNA AB073614 in glioma tissues and cell lines [22]. Knockdown of lncRNA AB073614 could inhibit the proliferation and migration of glioma cells, suggesting the tumor promoting role of lncRNA AB073614 in the development of glioma [22]. This study suggested an obviously higher expression of lncRNA AB073614 in the tumor tissues of CRC patients. In addition, high expression of lncRNA AB073614 was obviously associated with some clinicopathological characteristics of CRC patients, such as high tumor grade, larger tumor size, distant metastasis, and poor differentiation in CRC patients, which further added the evidence for lncRNA AB073614 as a tumor promoting factor in the pathogenesis of cancer. Those findings also suggest the potential of lncRNA AB073614 as a therapeutic target in the treatment of malignant diseases. However, the roles of lncRNA AB073614 in other types of cancer have not been studied, which needed to be explored in future researches. In addition, Cheng et al. suggested that lncRNA AB073614 could promote the tumorigenesis of ovarian cancer by targeting ERK1/2 and AKT-mediated signaling pathway [21]. However, the molecular mechanism underlying the roles of lncRNA AB073614 in CRC has not been elucidated and further studies are needed to provide possible explanations.

Previous study proved that the survival time of ovarian cancer patients with high expression of lncRNA AB073614 was obviously lower than those patients with low expression (P = 0.0025), suggesting the significance of lncRNA AB073614 as an useful prognostic biomarker in ovarian cancer [21]. Another study found that high lncRNA AB073614 expression level was also an unfavorable prognostic factor in patients with glioma [23]. Several lncRNAs have been reported to be associated with the prognosis of CRC patients, such as lncRNA HOTAIR, lncRNA H19 and lncRNA Loc554202 [19, 25, 26, 31]. However, no study has been performed to evaluate the role of lncRNA AB073614 as a prognostic biomarker for CRC

Table 2. Logistic regression analysis of the associations between lncRNA AB073614 expression and clinicopathological characteristics in CRC

Variables	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Sex (Female vs Male)	1.26	0.42-3.80	0.68	0.87	0.13-5.98	0.89
Age (< 58 years)	1.09	0.36-3.29	0.87	0.61	0.07-5.16	0.65
Grade (III/IV vs I/II)	8.39	2.22-31.7	0.002	26.08	2.06-329.84	0.01
Tumor size (> 5 cm)	2.83	0.90-8.83	0.07	1.09	0.10-11.98	0.94
Lymphatic metastasis	3.36	1.06-10.59	0.03	0.68	0.07-6.28	0.73
Distant metastasis	19.64	2.29-168.48	0.007	91.14	1.27-6524.2	0.03
Poor differentiation	18.40	3.54-95.50	0.001	28.15	2.64-300.25	0.006
Vascular invasion	2.44	0.77-7.65	0.13	0.57	0.05-7.06	0.66

OR, odds ratio; 95% CI, 95% confidence interval; CRC, colorectal cancer.

patients, which can be investigated in future studies.

The present study didn't find obvious correlations of lncRNA AB073614 level with tumor size, lymphatic metastasis and vascular invasion in the multivariate logistic regression analysis (**Table 2**). This might be attributed to the relatively small sample size of recruited CRC patients, which was a limitation in our study. In addition, owing to the relatively small sample size of recruited CRC patients, we didn't perform subgroup analysis by sites of CRC. Therefore, future studies with larger sample size of CRC patients are required to validate the findings in our study.

The findings from the current study suggests that lncRNA AB073614 is highly expressed of in the tumor tissues of CRC, and it is obviously associated with clinicopathological characteristics of CRC patients, which suggests that lncRNA AB073614 may participate in the carcinogenesis and progression of CRC and may be a potential and novel therapeutic target for CRC. However, more studies are still needed to validate the role of lncRNA AB073614 in CRC, and to explore the underlying molecular mechanism. Some studies on the role of lncRNA AB073614 as a prognostic biomarker in CRC patients are also needed.

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Disclosure of conflict of interest

None.

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