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Upregulation of Long Non-Coding RNA ENST00000429227.1 Is Correlated with Poor Prognosis in Human Hepatocellular Carcinoma

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Background: Long non-coding RNAs (lncRNAs) have been shown to play an important regulatory role in many tumors. This study was designed to investigate the expression of lncRNA ENST00000429227.1 in hepatocellular carcinoma (HCC) and to determine whether the expression of lncRNA ENST00000429227.1 affects the prognosis of HCC.

Material/Methods: lncRNA ENST00000429227.1 showing differences in expression between M1 and M2 was screened by microarray expression measurements. Quantitative real-time PCR (qRT-PCR) was used to detect the expression of lncRNA ENST00000429227.1 in 161 HCC patients. The chi-square test was used to evaluate the relationship between the expression of ENST00000429227.1 and clinicopathological parameters. A survival curve was drawn and analyzed by Kaplan-Meier method. Cox regression was used for univariate and multivariate analysis to determine whether lncRNA ENST00000429227.1 is an independent factor of the occurrence and prognosis of HCC.

Results: A total of 3703 differentially expressed lncRNAs were obtained, of which 1777 were upregulated and 1926 were downregulated, with multiple change >1.5. The expression of lncRNA ENST00000429227.1 was upregulated in M2 cells. The expression of lncRNA ENST00000429227.1 in HCC tissues was higher than that in adjacent normal tissues ($p<0.05$), which was correlated with pathological parameters such as surgical margin ($p=0.042$), AFP ($p=0.022$) and Barcelona Clinic Liver Cancer (BCLC) stage ($p=0.008$). Survival analysis showed that high expression of lncRNA ENST00000429227.1 was associated with a decrease in overall survival (OS) rate of HCC patients. Cox regression analysis showed that high expression of ENST00000429227.1 may be an independent risk factor affecting the prognosis of HCC patients.

Conclusions: The results suggest that upregulation of ENST00000429227.1 is associated with poor prognosis of HCC patients, and may be a new biomarker for the diagnosis of HCC.

MeSH Keywords: Carcinoma, Hepatocellular • Prognosis • RNA, Long Noncoding

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Background

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in the world, with high morbidity and mortality rates [1] and it is the second leading cause of cancer death [2]. The incidence of HCC in China accounts for almost half of the global incidence of HCC [3]. Statistics show that China accounts for half of the world's new cases of and deaths due to HCC [4]. Early HCC can be treated by liver transplantation, hepatectomy, radiofrequency ablation (RFA), and other surgical methods [5]. Transcatheter arterial chemoembolization (TACE) is suitable for the treatment of intermediate-stage HCC patients, while palliative treatment is more often used for advanced-stage HCC patients [6]. However, early-stage HCC usually show few detectable signs, and it was likely that the appropriate treatment time has been missed during detection and diagnosis. The prognosis of HCC patients with symptoms is very poor, and the overall 3-year survival rate is low [7]. Although progress has been made in the diagnosis and treatment of HCC, the incidence and mortality rates of HCC continue to increase. Therefore, efforts have been made to diagnose HCC in its early stage to improve early diagnosis, treatment, and overall prognosis [8].

Studies have found a new class of non-coding RNA, which is between 200 bp and 100 kbp in length, called long non-coding RNA (lncRNA). Upregulated or downregulated lncRNA expression is involved in many diseases, including cancers [9]. HCC-related lncRNAs play critical roles in the tumorigenesis and development of HCC [10]. Increasing numbers of lncRNAs have become new markers of HCC, which can be used for early diagnosis and prognosis evaluation and as an effective therapeutic target for future clinical application [10,11]. Chen et al. reported that lncRNA BLACAT1 affects the proliferation, migration, and invasion of small cell lung cancer (SCLC) cells, and high expression of lncRNA BLACAT1 is associated with clinicopathologic parameters and prognosis of SCLC patients [12]. Wu et al. reported that high expression of lncRNA MAP3K1-2 could be used as a new independent prognostic marker for gastric cancer [13]. Li et al. suggested that the expression of lncRNA AK021443 increased and the overall survival time decreased in HCC, and it might be an important factor affecting the prognosis of HCC patients [14].

Uncontrolled macrophage polarization is usually associated with disease. M1 and M2 macrophages are distributed in various cancer tissues of humans [15]. Among them, M2 macrophages can promote the development of tumors [16]. Changes in the number of M1 cells and M2 cells may affect the prognosis of HCC patients [17]. Liu et al. found that knocking-out lncRNA CCAT1 promoted macrophage polarization, increased numbers of M2 cells, and enhanced prostate cancer invasion [18].

In our previous studies, we used microarrays to detect differential expression of lncRNAs in M1 (classically activated macrophages) and M2 (alternatively activated macrophages) [19]. In the present study, we selected lncRNA ENST00000429227.1, which is downregulated in M1, to study its effect on HCC prognosis. The expression of ENST00000429227.1 in 161 HCC patients was detected, and the relationship between ENST00000429227.1 expression and clinicopathological parameters and overall survival rate of HCC patients was analyzed. To the best of our knowledge, this is the first study to investigate the relationship between ENST00000429227.1 expression and prognosis in HCC patients.

Material and Methods

lncRNA microarray

U937 cells differentiate into different phenotypes (M1 and M2), and 3 pairs of M1 and M2 cells were subjected to microarray analysis.

Patients and samples

The study included 161 HCC patients at Guangxi Tumor Hospital affiliated with Guangxi Medical University. The HCC tissues and adjacent normal liver tissues were taken from 161 patients who were undergoing first-time surgery without previous chemotherapy or radiotherapy. We froze 161 patients' tissues in liquid nitrogen and stored them at –80°C. HCC diagnosis was based on World Health Organization (WHO) criteria. All patients were followed up by telephone or hospitalization until May 2018. The Ethics Committee of Guangxi Tumor Hospital affiliated with Guangxi Medical University approved the study. We obtained informed consent from all 161 patients. Table 1 lists the clinicopathological parameters of the 161 patients.

Total RNA extraction and quantitative real-time PCR

Total RNA was extracted from the 161 patients' tissues using TRIzol reagent (Invitrogen, Carlsbad, CA, USA). To analyze the expression of ENST00000429227.1, the PtimeScript™ RT reagent kit (Takara Bio, Inc., Dalian, China) was used for reverse transcription of RNA into cDNA, which was then analyzed by quantitative real-time PCR (qRT-PCR) using SYBR Green Master (Rox) (Takara Bio, Co.). The results are expressed as number of transcripts (standardized by β-actin). Primers are listed in Table 2.

Statistical analysis

SPSS (version 22.0) was used to analyze all the data. GraphPad Prism 5 was used to draw graphs. The chi-square test was used to evaluate the relationship between lncRNA

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Table 1. Relationship between expression of ENST00000429227.1 and clinicopathological features of HCC.

Characteristics	Number of patients	ENST00000429227.1		p-Value
		Low expression	High expression	
Sex				
Female	24	7	17	0.278
Male	137	56	82	
Age (years)				
≤55	119	42	77	0.093
>55	42	21	21	
HBV-DNA (cps/ml)				
<5.00*10e2	47	21	26	0.376
≥5.00*10e2	113	42	71	
Surgical margin (cm)				
≥2	20	12	8	0.042
<2	138	50	88	
AFP (ng/l)				
<400	74	36	38	0.022
≥400	87	27	60	
CA153 (U/ml)				
≤31.3	150	57	93	0.733
>31.3	9	4	5	
PA (mg/L)				
≥170	81	34	47	0.457
<170	80	29	51	
Tumor number				
<3	129	52	77	0.538
≥3	32	11	21	
Portal vein tumor thrombus				
No	137	55	82	0.528
Yes	24	8	16	
BCLC stage				
0/A	96	45	51	0.008
B/C	62	16	46	
Embolus				
No	116	50	66	0.097
Yes	45	13	32	
Early recurrence				
No/18 months recurrence	96	41	55	0.258
Contains recurrence within 18 months	65	22	43	

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Table 2. Primers used for quantitative real-time PCR.

Gene	Primer sequence	Length (bp)
ENST00000429227.1	Forward: 5'-AGGAAGCAGTGCCGAATG-3'	868
	Reverse: 5'-AGGTGGAGCTAAATTGAGGG-3'	
β-actin	Forward: 5'-GTCACCAACTGGGACGACAT-3'	208
	Reverse: 5'-GAGGCGTACAGGGA TAGCAC-3'	

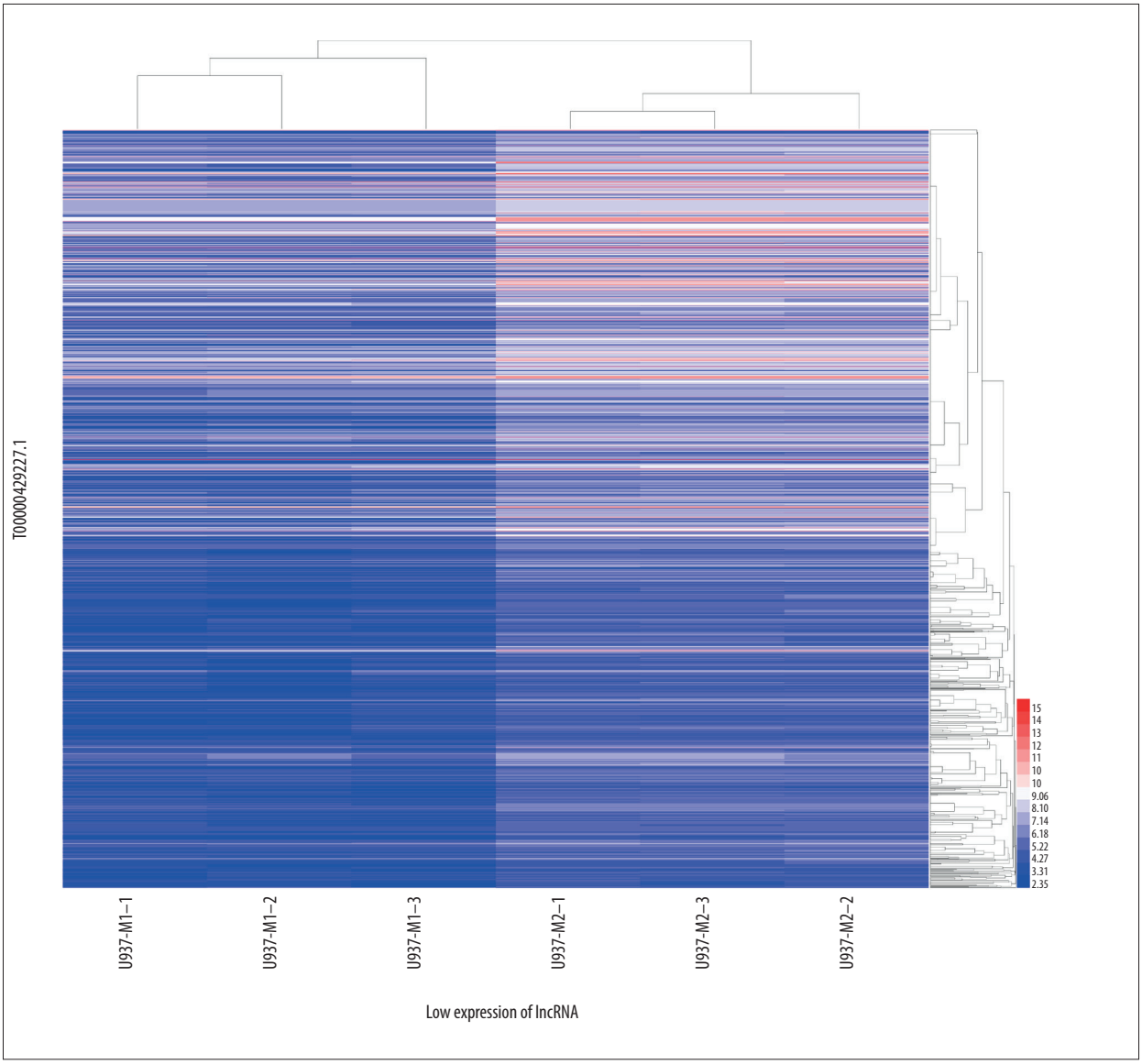

Figure 1. Heat map of the microarray assay represents the downregulated lncRNAs during polarization from M2 to Ml macrophages. Three independent samples of each phenotype for microarray.

ENST00000429227.1 expression and clinicopathological characteristics of HCC patients. Kaplan-Meier method was used to draw the OS rate curve, and the statistical significance was evaluated by logarithmic rank test. Cox regression model is used for univariate and multivariate analysis. P<0.05 indicated a statistically significant difference.

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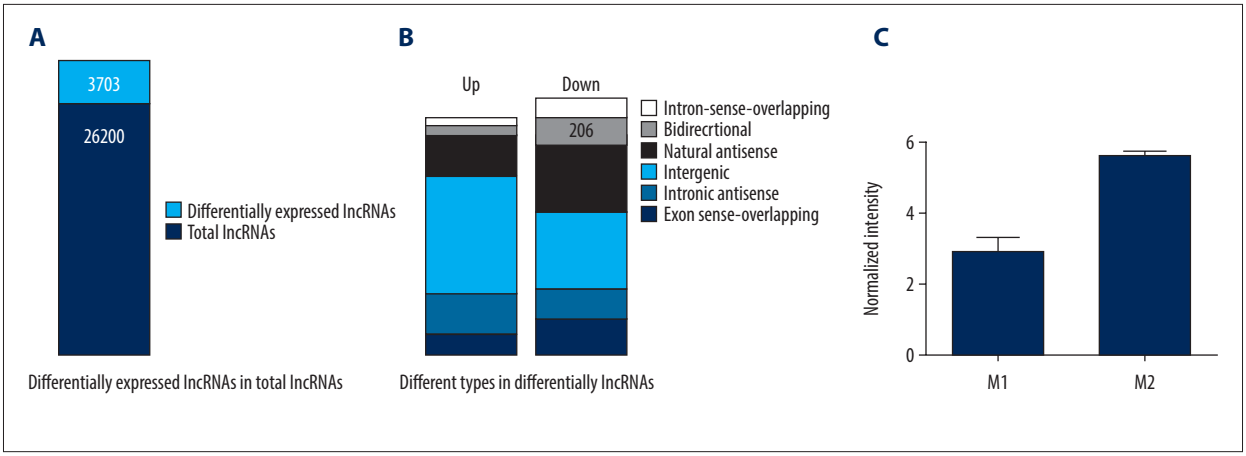

Figure 2. (**A**) Number of differentially expressed lncRNAs. (**B**) Number of different types of lncRNAs. (**C**) The normalized intensity of ENST00000429227.1 between the M1 and M2 cells as determined by microarray analysis.

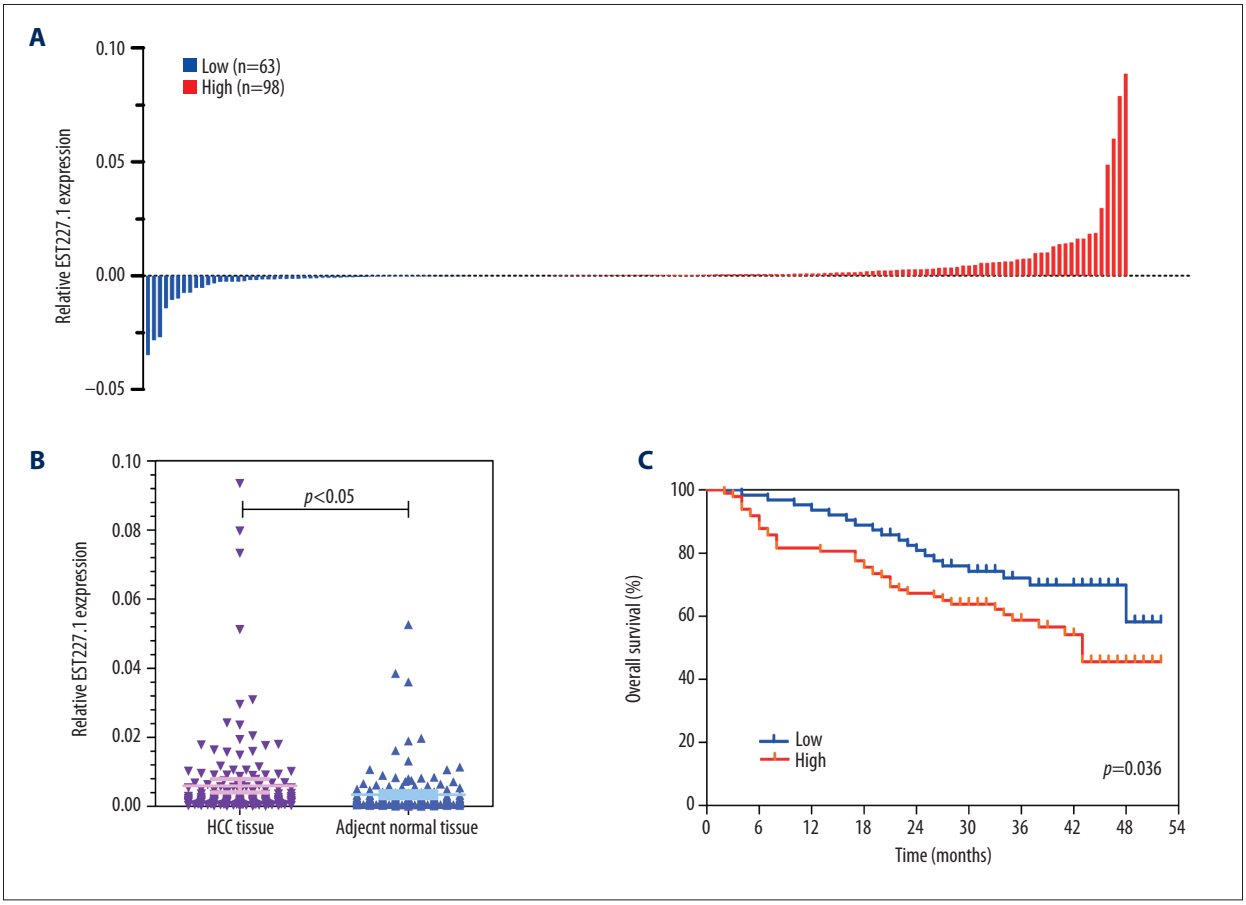

Figure 3. Expression of ENST00000429227.1 in 161 pairs of HCC and adjacent normal tissues. (**A**) HCC patients were ranked according to difference between ENST00000429227.1 expression in cancer and adjacent normal tissues, and were divided into a high ENST00000429227.1 expression group and a low ENST00000429227.1 expression group. Each experiment was performed in triplicate. (**B**) Relative expression levels of ENST00000429227.1 in HCC tissues and adjacent normal tissues. A total of 161 pairs of HCC and adjacent normal tissues were used to measure the relative expression levels of ENST00000429227.1. Differences were assessed by paired *t* test. (**C**) Kaplan-Meier analysis of ENST00000429227.1 expression in HCC patients and mapping survival curves (P<0.05).

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Table 3. Univariate analysis of overall survival in 161 patients with HCC.

Variable	Univariate analysis		P-value
	HR	95% CI	
Sex	1.306	0.622–2.744	0.481
Female			
Male			
Age (years)	0.454	0.231–0.893	0.022
≤55			
>55			
HBV-DNA (cps/ml)	1.320	0.748–2.329	0.337
<5.00*10e2			
≥5.00*10e2			
Surgical margin (cm)	1.321	0.600–2.908	0.489
≥2			
<2			
AFP (ng/l)	2.357	1.374–4.042	0.002
<400			
≥400			
CA153 (U/ml)	2.311	1.051–5.079	0.037
≤31.3			
>31.3			
PA (mg/L)	1.696	1.023–2.810	0.040
≥170			
<170			
Tumor number	2.026	1.171–3.506	0.012
<3			
≥3			
Portal vein tumor thrombus	1.840	1.015–3.335	0.045
No			
Yes			
BCLC stage	1.929	1.166–3.193	0.011
0/A			
B/C			
Embolus	2.194	1.328–3.626	0.002
No			
Yes			
Early recurrence	6.408	3.691–11.125	0.000
No/18 months recurrence			
Contains recurrence within 18 months			
ENST00000429227.1 expression	1.751	1.027–2.986	0.039

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Table 4. Multivariate Cox regression analysis of overall survival rate in 161 patients with HCC.

Variable	HR	95%CI	P-value
CA153(U/ml)			
≤31.3	5.812	2.260–14.942	0.000
>31.3			
Portal vein tumor thrombus			
No	0.360	0.148–0.872	0.024
Yes			
Embolus			
No	3.180	1.465–6.904	0.003
Yes			
Early recurrence			
No/18 months recurrence	8.919	4.537–17.532	0.000
Contains recurrence within 18 months			
ENST00000429227.1 expression	2.032	1.134–3.642	0.017

Results

lncRNA microarray analysis

A total of 26 200 lncRNAs were obtained from the 2 phenotypes (M1 and M2) of U937 cells, of which 3703 were differentially expressed during differentiation from M2 to M1 (Figure 1). Among them, 1777 lncRNAs were upregulated and 1926 were downregulated ($p<0.05$; multiple change >1.5) (Figure 2A). Six different types of lncRNAs were found in the 3703 lncRNAs, including bidirectional, exon overlap, intergenic, intron overlap, intron antisense, and natural antisense (Figure 2B). lncRNA ENST00000429227.1 was bidirectional (multiple change >2, $p<0.05$) and was expressed at low levels in M1 phenotype and at high levels in M2 phenotype (Figure 2C).

ENST00000429227.1 is upregulated in human HCC

We examined the expression of ENST00000429227.1 by qRT-PCR in 161 patients. ENST00000429227.1 was more significantly upregulated in HCC than that in adjacent normal tissues ($p<0.05$). (Figure 3B). The results suggest that the high expression of ENST00000429227.1 is involved in the pathogenesis of HCC.

Relationship between lncRNA 227.1 expression and clinicopathological parameters of HCC patients

We ranked 161 patients according to the difference in relative expression of ENST00000429227.1 in HCC tissues and adjacent normal tissues (Figure 3A). To explore the relationship between ENST00000429227.1 expression and the clinicopathological characteristics of HCC patients, we assigned the patients with a positive difference to the high expression group, and those with a negative difference were assigned to the low expression group. Statistical analysis showed that ENST00000429227.1 expression was related to incision margin ($p=0.042$), AFP ($p=0.022$), BCLC stage ($p=0.008$), but not related to sex, age, number of tumors, portal vein cancer thrombus, prealbumin, CA153, early recurrence, embolus, or other parameters (all $p>0.05$) (Table 1).

Correlation between lncRNA ENST00000429227.1 expression and the prognosis of HCC patients

Kaplan-Meier analysis and logarithmic rank test were used to assess whether lncRNA ENST00000429227.1 was associated with the prognosis of HCC patients. The results showed that the overall survival rate in the high expression group was lower than that in the low expression group ($p=0.036$, Figure 3C). Univariate analysis showed that age, number of tumors, portal vein thrombus, BCLC stage, prealbumin, CA153, early recurrence, embolus, and ENST00000429227.1 expression were significantly correlated with the survival rate ($p<0.05$, Table 3). Multivariate Cox regression analysis showed that portal vein cancer thrombus, CA153, early recurrence, embolus, and ENST00000429227.1 expression were independent predictive factors of the overall survival rate of HCC patients ($p<0.05$, Table 4).

Discussion

HCC is one of the commonest cancers in the world, with a steadily increasing mortality rate [20], and a new method with high sensitivity and specificity is needed for early diagnosis and early detection of metastasis. Abnormal expression

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of lncRNAs can cause many human diseases and cancers [21]. Abnormal expression of lncRNAs in various cancers indicate that lncRNAs may act as a potential tumor suppressor or oncogene [22,23], suggesting that cancer-related lncRNAs can be used as biomarkers for the diagnosis or prediction of cancers, which provides a new therapeutic strategy [22,24]. Quagliata et al. reported that the high expression of lncRNA HOTTIP was associated with shorter overall survival time in HCC patients and can used as a biomarker for predicting HCC [25]. Tu et al. reported that the low expression of GAS5 was related with poor prognosis of HCC patients [26]. Yang et al. reported that HOTAIR is an independent factor prediction of HCC recurrence in patients receiving liver transplantation, and that no recurrence or shortened survival time were observed in HCC patients with high HOTAIR expression [27].

To sum up, lncRNA ENST00000429227.1 was differentially expressed in 3 pairs of M1 and M2 macrophages (P=0.002), while lncRNA ENST00000429227.1 was differentially expressed in 161 HCC tissues and adjacent normal tissues and it was upregulated in HCC tissues. The high expression of lncRNA ENST00000429227.1 is related to the incision margin, AFP and BCLC stage. Kaplan-Meier analysis showed poor survival of HCC patients with lncRNA ENST00000429227.1 upregulation, and multivariate Cox analysis showed that high expression of lncRNA ENST00000429227.1 was an independent predictor of HCC prognosis.

Conclusions

All these results indicate that lncRNA ENST00000429227.1 is involved in the occurrence and prognosis of HCC. In the future, lncRNA ENST00000429227.1 may be used as a new biomarker of hepatocellular carcinoma and a potential target for HCC treatment. However, the mechanism by which upregulation of lncRNA ENST00000429227.1 occurs in HCC needs further study.

Conflict of interest

None.

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