Int J Clin Exp Med 2017;10(8):11984-11990
www.ijcem.com /ISSN:1940-5901/IJCEM0053396

Original Article

Expression of plasma lncRNA BANCR in hepatocellular carcinoma and its diagnostic and prognostic significance

Yunsheng Qin[1], Jun Wu[2], Zhigang Ke[2], Jianghao Xu[2]

[1]Key Laboratory of Combined Multi-Organ Transplantation of Ministry of Health, Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, Zhejiang, China; [2]Department of Surgery, Pujiang County People's Hospital, Pujiang 322200, Zhejiang, China

Received March 21, 2017; Accepted July 6, 2017; Epub August 15, 2017; Published August 30, 2017

Abstract: Purpose: Recent studies have demonstrated that lncRNAs can serve as useful biomarkers for human cancers. The aim of this study was to analyze the diagnostic and prognostic value of plasma lncRNA BANCR in patients with hepatocellular carcinoma (HCC). Methods: Using real-time reverse transcriptase-polymerase chain reaction, we examined BANCR expression in the plasma samples of 110 patients with HCC, 90 patients with benign liver diseases, and 120 healthy volunteers. We also explored the correlation of plasma BANCR levels with clinicopathological factors. At last, we assessed the potential diagnostic and prognostic values of plasma BANCR for HCC. Results: The relative BANCR levels in plasma samples from HCC patients were significantly higher than those obtained from benign liver disease group and healthy controls (both $P < 0.01$). High level of plasma BANCR correlated with large tumor size, poor tumor differentiation, positive venous infiltration, and advanced TNM stage. Increased plasma BANCR expression predicted unfavorable overall survival in HCC independently. Furthermore, ROC curve analysis confirmed plasma BANCR as a useful marker in discriminating HCC from benign liver diseases and healthy controls. Conclusions: These findings suggested that plasma BANCR expression was upregulated in HCC and might act as a novel diagnostic and prognostic biomarker.

Keywords: LncRNA, BANCR, hepatocellular carcinoma, biomarker, prognosis

Introduction

Hepatocellular carcinoma (HCC), accounting for about 80%-90% of all liver cancer cases, is the second leading cause of cancer-related deaths in the world, leading to > 600,000 deaths each year [1]. One of the important reasons for the dismal clinical outcome of HCC patients is lack of effective methods for its early diagnosis. Although alpha-fetoprotein (AFP) has been widely used for the detection and monitoring of HCC, its sensitivity and specificity are insufficient. The false negative rate using AFP level alone may be as high as 45% for early stage HCC and nearly 20% for patients at advanced stage [2]. Thus, novel effective biomarkers for the early diagnosis and prognostic evaluation of HCC are urgently needed.

The long non-coding RNAs (lncRNAs) are transcriptional RNA molecules longer than 200 nucleotides that lack protein-coding potential [3]. Increasing evidence shows that lncRNAs are involved in diverse biological processes, and deregulation of lncRNAs has been found in a wide range of human diseases, including cancer [4]. LncRNAs play a critical role in tumor initiation, progression, and metastasis [5, 6]. In addition, lncRNAs are detectable and stable in serum, plasma, urine and other body fluids, opening a new way for the seeking of tumor markers [7, 8]. For example, plasma lncRNA H19 and serum lncRNA RP11-445H22.4 are useful diagnostic biomarkers for breast cancer [9, 10]. Blood lncRNA HOTAIR and CRNDE-h are prognostic factors for colorectal cancer [11, 12]. High plasma lncRNA MALAT1 expression is associated with distant metastasis in patients with epithelial ovarian cancer and gastric cancer [13, 14]. The levels of lncRNA ABHD11-AS1 in gastric juice from gastric cancer patients were associated with tumor size, tumor stage,

Table 1. The correlations of plasma BANCR and clinical characteristics of HCC patients

Characteristics	Patients	BANCR levels (mean ± SEM)	*P* values
Age			
< 60	54	2.79 ± 0.51	
≥ 60	56	2.83 ± 0.49	0.542
Gender			
Male	63	2.66 ± 0.58	
Female	47	2.94 ± 0.47	0.487
Tumor grade			
G1	40	2.29 ± 0.45	
G2+G3	70	3.42 ± 0.59	0.017
AFP (ng/L)			
≥ 400	68	2.99 ± 0.55	
< 400	42	2.61 ± 0.50	0.219
Tumor diameter (cm)			
< 5	65	2.11 ± 0.41	
≥ 5	45	3.56 ± 0.63	0.005
Tumor nodes			
Multi	39	2.87 ± 0.48	
Single	71	2.69 ± 0.42	0.304
Venous infiltration			
Presence	36	3.50 ± 0.44	
Absence	74	2.08 ± 0.39	0.008
TNM stage			
I-II	49	1.97 ± 0.36	
III	61	3.68 ± 0.66	0.002

and blood carcinoembryonic antigen (CEA) levels [15]. However, the use of circulating lncRNA as blood-based, minimally invasive biomarkers in HCC is still relatively less explored.

LncRNA BANCR (BRAF-activated non-coding RNA), 693 bp in length and located in chromosome 9, is a novel identified cancer-related lncRNA. Recent studies have revealed aberrant BANCR expression and its tumor suppressive or oncogenic function in thyroid cancer [16], non-small cell lung cancer [17], bladder cancer [18], melanoma [19, 20], colorectal cancer [21], gastric cancer [22], endometrial cancer [23], esophageal squamous cell carcinoma (ESCC) [24], and HCC [25]. BANCR expression was remarkably increased in HCC tissues, and its up-regulation was correlated with aggressive clinicopathological features and shorter overall survival [25]. More importantly, high plasma BANCR expression and its diagnostic value has been reported in patients with gastric cancer and ESCC [24, 26]. However, it is unclear whether circulating BANCR could serve as a potential biomarker for HCC.

In this study, we firstly detected plasma BANCR expression levels in HCC patients and healthy controls. Then, we investigated the correlations between plasma BANCR levels and clinicopathological features. Lastly, we assessed the potential diagnostic and prognostic values of plasma BANCR for HCC patients.

Materials and methods

Patients and clinical specimens

A total of 110 primary HCC patients who received hepatic resection at The First Affiliated Hospital, School of Medicine, Zhejiang University (Hangzhou, Zhejiang 310003, China) between January 2008 and August 2012 were involved in this study. None of the patients had previously undergone chemotherapy, radiation therapy, or immunotherapy. Peripheral blood (5 ml) were obtained at diagnosis without any treatment. The samples were collected in ethylene diamine tetraacetic acid (EDTA) anti-coagulation tubes, and centrifuged at 2,000 g for 5 min at 4°C, followed by centrifugation at 12,000 g for 5 min at 4°C, to thoroughly remove any cell debris. All blood samples were processed within 6 h after obtained, and the plasma was stored at -80°C until further analysis. Plasma samples from 90 patients with benign liver diseases and 120 healthy volunteers were used as control. The benign liver diseases group contained 75 patients with chronic hepatitis (including 49 with liver cirrhosis and 26 without), 10 patients with fatty liver diseases, and 5 patients with alcoholic liver diseases. The clinical characteristics of HCC patients are shown in **Table 1.** Follow-up data for all HCC patients were acquired. Overall survival was calculated from the date of initial surgical operation to death or last follow-up. This study was approved by the ethics committee of Zhejiang University and informed consent was obtained from each subject.

RNA extraction, reverse transcription, and real-time PCR

Total RNA was extracted from 400 μL of plasma using TRIzol LS reagent (Life Technologies). The quality of RNA samples was assessed by a UV

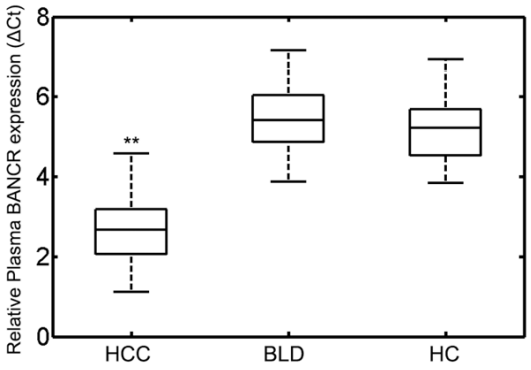

Figure 1. Plasma BANCR levels in hepatocellular carcinoma (HCC) patients were significantly higher than those in benign liver disease (BLD) group and healthy controls (HC). The relative expression of BANCR was determined by qRT-PCR with the ΔCt method. Smaller ΔCt value indicated higher level. **P < 0.01.

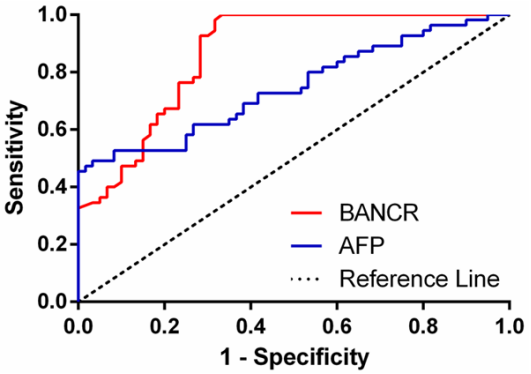

Figure 2. ROC curve analysis of plasma BANCR versus AFP in discriminating HCC from healthy controls. The AUC for plasma BANCR was 0.866 (Cutoff value: 3.17; sensitivity: 92.73%, specificity: 71.67%, PPV: 74.63%, NPV: 89.58). The AUC for AFP was 0.745 (Cutoff value: 210 μg/L; sensitivity: 70.91%, specificity: 58.33%, PPV: 60.94%, NPV: 68.63%).

spectrophotometer (Bio-Rad, Hercules, CA, USA). The OD260/280 ratios for all samples were between 1.8 and 2.0. Complementary DNA was synthesized by using a PrimeScript RT Master Mix Kit (TaKaRa, Dalian, China) in a final volume of 50 μL. Quantitative PCR was performed using ABI Viia7 (Applied Biosystems, Foster City, CA, USA) with SYBR expression assay system (TaKaRa, Dalian, China). GAPDH was chosen as the endogenous control for data normalization because its expression is relatively stable in plasma [27, 28]. The primer sequences used in this study were as follows: BANCR, 5'-ACA GGA CTC CAT GGC AAA CG-3' (forward) and 5'-ATG AAG AAA GCC TGG TGC AGT-3' (reverse); GAPDH, 5'-AGA GGC AGG GAT GAT GTT CTG-3' (forward) and 5'-GAC TCA TGA CCA CAG TCC ATGC-3' (reverse). The relative quantification of BANCR expression was calculated using the ΔCt method, and $\Delta Ct = Ct_{(BANCR)} - Ct_{(GAPDH)}$. A smaller ΔCt value indicates higher expression of BANCR [15, 28].

Statistics

Statistical tests were carried out using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). The differences in BANCR expression were analyzed using a Student's t-test when only 2 groups or one-way analysis of variance (ANOVA) when more than 2 groups were compared. Receiver-operating characteristic (ROC) curve was constructed and the area under the ROC curve (AUC) was calculated to evaluate the diagnostic value of plasma BANCR. Survival curves were constructed with the Kaplan-Meier method and compared by log-rank tests. Cox regression analysis was performed to analyze prognostic significance of each variable. Differences were considered significant when P < 0.05.

Results

Increased plasma levels of BANCR in HCC patients

Plasma BANCR expression was detected in 110 HCC, 90 benign liver disease subjects and 120 healthy controls by using RT-PCR. As shown in **Figure 1**, the relative BANCR levels in plasma samples from HCC patients were significantly higher than those obtained from benign liver disease group and healthy controls (both P < 0.01). No significant difference was observed in the plasma BANCR expression between patients with benign liver diseases and healthy controls.

Plasma BANCR correlates with clinicopathological features of HCC

Table 1 displayed the associations between plasma BANCR levels and the clinicopathological features. Increased plasma BANCR expression was significantly associated with poor tumor differentiation (P = 0.017), large tumor size (P = 0.005), vascular invasion (P = 0.008), and advanced TNM stage (P = 0.002). There were no significant correlation between plasma BANCR expression and other clinical features

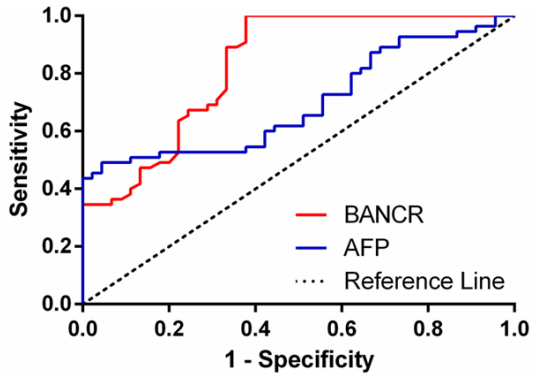

Figure 3. ROC curve analysis of plasma BANCR versus AFP in discriminating HCC from benign liver diseases. The AUC for plasma BANCR was 0.830 (Cutoff value: 3.22; sensitivity: 89.09%, specificity: 66.67%, PPV: 75.81%, NPV: 78.95). The AUC for AFP was 0.696 (Cutoff value: 296 μg/L; sensitivity: 61.82%, specificity: 55.56%, PPV: 62.96%, NPV: 54.35%).

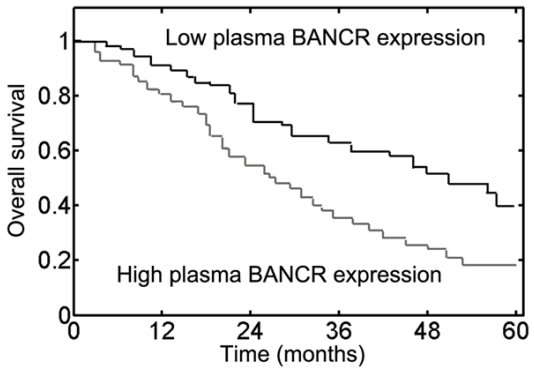

Figure 4. Overall survival curves of HCC patients with high versus low plasma BANCR levels (Cutoff value: ΔCt = 2.1; P < 0.001, log rank test).

such as patient's gender, age, tumor number, and AFP level.

Diagnostic value of plasma BANCR for HCC

ROC curve analysis was performed to detect the diagnostic value of plasma BANCR for HCC. As shown in **Figure 2**, the AUC for plasma BANCR was 0.866 (95% CI: 0.801-0.931; sensitivity: 92.73%, specificity: 71.67%) in discriminating HCC from healthy controls, higher than that for AFP (AUC: 0.745, 95% CI: 0.654-0.836) (P < 0.01). Moreover, plasma BANCR still had a better performance compared with AFP in discriminating HCC from benign liver diseases (**Figure 3**). The AUC for plasma BANCR was 0.830 (95% CI: 0.748-0.911; sensitivity: 89.09%, specificity: 66.67%), higher than that for AFP (AUC: 0.696, 95% CI: 0.593-0.799) (P < 0.01).

Prognostic value of plasma BANCR in HCC

At last, we evaluated the prognostic value of plasma BANCR in HCC. The median value of plasma BANCR was chosen as a cutoff and used to assign the HCC patients to high plasma BANCR group or low plasma BANCR group. Kaplan-Meier analysis with the log-rank test indicated that HCC patients in high plasma BANCR group had a significantly shorter overall survival than those in low plasma BANCR group (P < 0.001; **Figure 4**). Univariate analysis demonstrated that tumor size, tumor differentiation, vascular invasion, and TNM stage could predict patient survival as well (**Table 2**). The multivariate analyses confirmed plasma BANCR (P = 0.011) as an independent prognostic indicator for overall survival of HCC patients in addition to tumor size (P = 0.034), vascular invasion (P = 0.025), and clinical stage (P = 0.006; **Table 2**).

Discussion

Emerging evidence indicates that lncRNAs play important roles in the biology of human cancers. In terms of HCC, abnormal expression of several lncRNAs and their functions have been reported. For example, the levels of lncRNA SPRY4-IT1 were upregulated in HCC tissues, and its up-regulation was correlated with poor tumor differentiation, large tumor size, and advanced clinical stage [29]. Low lncRNA DGCR5 expression was an independent negative prognostic factor for HCC [30]. Circulating lncRNA HULC and Linc00152 may act as novel diagnostic biomarkers for HCC [31]. Overexpression of lncRNA HOST2 can promote HCC cell proliferation, migration and invasion and inhibit cell apoptosis [32]. Thus, functional lncRNAs may be applied for HCC diagnosis, prognosis, and therapeutics.

There is no optimal biomarker for early diagnosis of HCC at present. Although AFP is widely used in clinic, its sensitivity and specificity are still not satisfactory. Recent study showed that lncRNAs derived from tumor tissues could be secreted into blood [33], and these lncRNAs are detectable and stable in plasma [34]. Circulating lncRNAs are emerging as novel biomarkers for detection and monitoring of several

Table 2. Cox regression analysis of factors associated with 5-year overall survival in HCC patients

Variables	Univariate analysis		Multivariate analysis	
	RR	*P*-value	RR	*P*-value
Age (years) (≥ 60/< 60)	1.008	0.562	–	–
Gender (Male/Female)	0.965	0.647	–	–
Tumor grade (G1/G2+G3)	2.023	0.037	1.254	0.086
AFP (ng/L) (≥ 400/< 400)	1.127	0.098	–	–
Tumor diameter (cm) (≥ 5/< 5)	2.954	0.019	2.425	0.034
Tumor nodes (Multi/Single)	1.212	0.093	–	–
Venous infiltration (Presence/Absence)	5.057	0.003	2.718	0.025
TNM stage (I-II/III)	6.454	< 0.001	5.039	0.006
Plasma BANCR expression (Low/high)	5.966	< 0.001	3.841	0.011

Variables	Univariate analysis			Multivariate analysis			
	Beta	RR	*P*-value	Beta	RR	Reference	*P*-value
Age (years) (≥ 60/< 60)	0.008	1.008	0.562	0.003	1.003	< 60	0.614
Gender (Male/Female)	-0.036	0.965	0.647	-0.022	0.978	Female	0.558
Tumor grade (G1/G2+G3)	0.705	2.023	0.037	0.226	1.254	G1	0.086
AFP (ng/L) (≥ 400/< 400)	0.120	1.127	0.098	0.196	1.217	< 400	0.119
Tumor diameter (cm) (≥ 5/< 5)	1.083	2.954	0.019	0.886	2.425	< 5	0.034
Tumor nodes (Multi/Single)	0.192	1.212	0.093	0.176	1.192	Single	0.133
Venous infiltration (Presence/Absence)	1.621	5.057	0.003	0.999	2.718	Absence	0.025
TNM stage (I-II/III)	1.866	6.454	< 0.001	1.617	5.039	I-II	0.006
Plasma BANCR expression (Low/high, cutoff value: ΔCt = 2.1)	1.791	5.966	< 0.001	1.346	3.841	Low	0.011

types of cancer. In the present study, we found that the levels of plasma BANCR increased significantly in HCC compared with those in benign liver disease group and healthy controls. We also observed a significant association between plasma BANCR expression and aggressive clinicopathological features. Additionally, plasma BANCR could differentiate HCC from benign liver diseases and healthy controls, yielding higher AUC scores than AFP. Patients in high plasma BANCR group had a poorer prognosis than those in low plasma BANCR group. These findings highlight the potential of plasma BANCR as a novel diagnostic and prognostic biomarker for HCC.

Upregulation of plasma BANCR has been reported in patients with ESCC and gastric cancer. Liu et al. showed BANCR overexpression in both tumor tissues and plasma samples from ESCC patients [24]. They also observed a significant correlation between tissue and plasma BANCR levels. Zhang et al. revealed increased plasma BANCR expression and its diagnostic significance in gastric cancer [26]. The potential diagnostic and prognostic values of plasma BANCR in other human malignancies would be an interesting and important topic of future investigations.

Generally, lncRNAs involved in regulation of cancer cells phenotypes by regulating target gene expression by different mechanisms, including chromatin modification, genomic imprinting, RNA decay and sponging miRNAs [35, 36]. BANCR regulated the proliferation and migration of malignant melanoma and lung cancer cells via MAPK pathway [20, 37]. BANCR contributed to colorectal cancer migration by inducing epithelial-mesenchymal transition (EMT) [21]. NF-kappaB1 and miR-9 were involved in the role of BANCR in gastric cancer cell growth and apoptosis [22]. Zhou et al. found that BANCR downregulation inhibited HCC cell proliferation and invasion and suppressed EMT [25]. Future studies are encouraged to identify novel downstream genes or pathways of BANCR and further clarify the mechanisms how BANCR exerts the oncogenic function in HCC.

We are aware of some limitations in our work. First, it was a retrospective study, and the sample size was relatively small. Second, the plasma expression of only one lncRNA (BANCR) was examined in our study. Several other lncRNAs, such as HULC and Linc00152, were also expressed abnormally in the plasma of HCC patients and may act as biomarkers [31].

Genome-wide microarray analysis might be an ideal way to identify circulating lncRNAs with diagnostic ability, and a plasma-based biomarker panel including several lncRNAs would help to improve the sensitivity and specificity.

Conclusions

In summary, our study showed that lncRNA BANCR was significantly up-regulated in plasma samples of HCC patients, and high BANCR levels were correlated with aggressive clinicopathological features and poor overall survival. In addition, plasma BANCR expression achieved a fine diagnostic accuracy in discriminating HCC from benign liver diseases and healthy controls. Our results suggest that plasma BANCR may act as a novel diagnostic and prognostic biomarker for HCC.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yunsheng Qin, Key Laboratory of Combined Multi-Organ Transplantation of Ministry of Health, Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, Zhejiang, China. E-mail: 1202059@zju.edu.cn

References

[1] El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011; 365: 1118-1127.

[2] Ertle JM, Heider D, Wichert M, Keller B, Kueper R, Hilgard P, Gerken G and Schlaak JF. A combination of alpha-fetoprotein and des-gamma-carboxy prothrombin is superior in detection of hepatocellular carcinoma. Digestion 2013; 87: 121-131.

[3] Shi X, Sun M, Liu H, Yao Y and Song Y. Long non-coding RNAs: a new frontier in the study of human diseases. Cancer Lett 2013; 339: 159-166.

[4] Zhang Y, Xu Y, Feng L, Li F, Sun Z, Wu T, Shi X, Li J and Li X. Comprehensive characterization of lncRNA-mRNA related ceRNA network across 12 major cancers. Oncotarget 2016; 7: 64148-64167.

[5] Han P, Li JW, Zhang BM, Lv JC, Li YM, Gu XY, Yu ZW, Jia YH, Bai XF, Li L, Liu YL and Cui BB. The lncRNA CRNDE promotes colorectal cancer cell proliferation and chemoresistance via miR-181a-5p-mediated regulation of Wnt/beta-catenin signaling. Mol Cancer 2017; 16: 9.

[6] Li Z, Hou P, Fan D, Dong M, Ma M, Li H, Yao R, Li Y, Wang G, Geng P, Mihretab A, Liu D, Zhang Y, Huang B and Lu J. The degradation of EZH2 mediated by lncRNA ANCR attenuated the invasion and metastasis of breast cancer. Cell Death Differ 2017; 24: 59-71.

[7] Tong YK and Lo YM. Diagnostic developments involving cell-free (circulating) nucleic acids. Clin Chim Acta 2006; 363: 187-196.

[8] Su YJ, Yu J, Huang YQ and Yang J. Circulating long noncoding RNA as a potential target for prostate cancer. Int J Mol Sci 2015; 16: 13322-13338.

[9] Zhang K, Luo Z, Zhang Y, Zhang L, Wu L, Liu L, Yang J, Song X and Liu J. Circulating lncRNA H19 in plasma as a novel biomarker for breast cancer. Cancer Biomark 2016; 17: 187-194.

[10] Xu N, Chen F, Wang F, Lu X, Wang X, Lv M and Lu C. Clinical significance of high expression of circulating serum lncRNA RP11-445H22.4 in breast cancer patients: a Chinese population-based study. Tumour Biol 2015; 36: 7659-7665.

[11] Svoboda M, Slyskova J, Schneiderova M, Makovicky P, Bielik L, Levy M, Lipska L, Hemmelova B, Kala Z, Protivankova M, Vycital O, Liska V, Schwarzova L, Vodickova L and Vodicka P. HOTAIR long non-coding RNA is a negative prognostic factor not only in primary tumors, but also in the blood of colorectal cancer patients. Carcinogenesis 2014; 35: 1510-1515.

[12] Liu T, Zhang X, Gao S, Jing F, Yang Y, Du L, Zheng G, Li P, Li C and Wang C. Exosomal long noncoding RNA CRNDE-h as a novel serum-based biomarker for diagnosis and prognosis of colorectal cancer. Oncotarget 2016; 7: 85551-85563.

[13] Xia H, Chen Q, Chen Y, Ge X, Leng W, Tang Q, Ren M, Chen L, Yuan D, Zhang Y, Liu M, Gong Q and Bi F. The lncRNA MALAT1 is a novel biomarker for gastric cancer metastasis. Oncotarget 2016; 7: 56209-56218.

[14] Chen Q, Su Y, He X, Zhao W, Wu C, Zhang W, Si X, Dong B, Zhao L, Gao Y, Yang X, Chen J, Lu J, Qiao X and Zhang Y. Plasma long non-coding RNA MALAT1 is associated with distant metastasis in patients with epithelial ovarian cancer. Oncol Lett 2016; 12: 1361-1366.

[15] Yang Y, Shao Y, Zhu M, Li Q, Yang F, Lu X, Xu C, Xiao B, Sun Y and Guo J. Using gastric juice lncRNA-ABHD11-AS1 as a novel type of biomarker in the screening of gastric cancer. Tumour Biol 2016; 37: 1183-1188.

[16] Liao T, Qu N, Shi RL, Guo K, Ma B, Cao YM, Xiang J, Lu ZW, Zhu YX, Li DS and Ji QH. BRAF-activated LncRNA functions as a tumor suppressor in papillary thyroid cancer. Oncotarget 2017; 8: 238-247.

[17] Sun M, Liu XH, Wang KM, Nie FQ, Kong R, Yang JS, Xia R, Xu TP, Jin FY, Liu ZJ, Chen JF, Zhang EB, De W and Wang ZX. Downregulation of BRAF activated non-coding RNA is associated with poor prognosis for non-small cell lung cancer and promotes metastasis by affecting epithelial-mesenchymal transition. Mol Cancer 2014; 13: 68.

[18] He A, Liu Y, Chen Z, Li J, Chen M, Liu L, Liao X, Lv Z, Zhan Y, Zhuang C, Lin J, Huang W and Mei H. Over-expression of long noncoding RNA BANCR inhibits malignant phenotypes of human bladder cancer. J Exp Clin Cancer Res 2016; 35: 125.

[19] Flockhart RJ, Webster DE, Qu K, Mascarenhas N, Kovalski J, Kretz M and Khavari PA. BRAFV600E remodels the melanocyte transcriptome and induces BANCR to regulate melanoma cell migration. Genome Res 2012; 22: 1006-1014.

[20] Li R, Zhang L, Jia L, Duan Y, Li Y, Bao L and Sha N. Long non-coding RNA BANCR promotes proliferation in malignant melanoma by regulating MAPK pathway activation. PLoS One 2014; 9: e100893.

[21] Guo Q, Zhao Y, Chen J, Hu J, Wang S, Zhang D and Sun Y. BRAF-activated long non-coding RNA contributes to colorectal cancer migration by inducing epithelial-mesenchymal transition. Oncol Lett 2014; 8: 869-875.

[22] Zhang ZX, Liu ZQ, Jiang B, Lu XY, Ning XF, Yuan CT and Wang AL. BRAF activated non-coding RNA (BANCR) promoting gastric cancer cells proliferation via regulation of NF-kappaB1. Biochem Biophys Res Commun 2015; 465: 225-231.

[23] Wang D, Wang D, Wang N, Long Z and Ren X. Long non-coding RNA BANCR promotes endometrial cancer cell proliferation and invasion by regulating MMP2 and MMP1 via ERK/MAPK signaling pathway. Cell Physiol Biochem 2016; 40: 644-656.

[24] Liu Z, Yang T, Xu Z and Cao X. Upregulation of the long non-coding RNA BANCR correlates with tumor progression and poor prognosis in esophageal squamous cell carcinoma. Biomed Pharmacother 2016; 82: 406-412.

[25] Zhou T and Gao Y. Increased expression of LncRNA BANCR and its prognostic significance in human hepatocellular carcinoma. World J Surg Oncol 2016; 14: 8.

[26] Zhang K, Shi H, Xi H, Wu X, Cui J, Gao Y, Liang W, Hu C, Liu Y, Li J, Wang N, Wei B and Chen L. Genome-wide lncRNA microarray profiling identifies novel circulating lncRNAs for detection of gastric cancer. Theranostics 2017; 7: 213-227.

[27] Tong YS, Wang XW, Zhou XL, Liu ZH, Yang TX, Shi WH, Xie HW, Lv J, Wu QQ and Cao XF. Identification of the long non-coding RNA POU3F3 in plasma as a novel biomarker for diagnosis of esophageal squamous cell carcinoma. Mol Cancer 2015; 14: 3.

[28] Han L, Ma P, Liu SM and Zhou X. Circulating long noncoding RNA GAS5 as a potential biomarker in breast cancer for assessing the surgical effects. Tumour Biol 2016; 37: 6847-6854.

[29] Jing W, Gao S, Zhu M, Luo P, Jing X, Chai H and Tu J. Potential diagnostic value of lncRNA SPRY4-IT1 in hepatocellular carcinoma. Oncol Rep 2016; 36: 1085-1092.

[30] Huang R, Wang X, Zhang W, Zhangyuan G, Jin K, Yu W, Xie Y, Xu X, Wang H and Sun B. Downregulation of LncRNA DGCR5 correlates with poor prognosis in hepatocellular carcinoma. Cell Physiol Biochem 2016; 40: 707-715.

[31] Li J, Wang X, Tang J, Jiang R, Zhang W, Ji J and Sun B. HULC and Linc00152 act as novel biomarkers in predicting diagnosis of hepatocellular carcinoma. Cell Physiol Biochem 2015; 37: 687-696.

[32] Liu RT, Cao JL, Yan CQ, Wang Y, An CJ and Lv HT. Effects of LncRNA-HOST2 on cell proliferation, migration, invasion and apoptosis of human hepatocellular carcinoma cell line SMMC-7721. Biosci Rep 2017; 37.

[33] Ren S, Wang F, Shen J, Sun Y, Xu W, Lu J, Wei M, Xu C, Wu C, Zhang Z, Gao X, Liu Z, Hou J, Huang J and Sun Y. Long non-coding RNA metastasis associated in lung adenocarcinoma transcript 1 derived miniRNA as a novel plasma-based biomarker for diagnosing prostate cancer. Eur J Cancer 2013; 49: 2949-2959.

[34] Arita T, Ichikawa D, Konishi H, Komatsu S, Shiozaki A, Shoda K, Kawaguchi T, Hirajima S, Nagata H, Kubota T, Fujiwara H, Okamoto K and Otsuji E. Circulating long non-coding RNAs in plasma of patients with gastric cancer. Anticancer Res 2013; 33: 3185-3193.

[35] Cheetham SW, Gruhl F, Mattick JS and Dinger ME. Long noncoding RNAs and the genetics of cancer. Br J Cancer 2013; 108: 2419-2425.

[36] Lalevee S and Feil R. Long noncoding RNAs in human disease: emerging mechanisms and therapeutic strategies. Epigenomics 2015; 7: 877-879.

[37] Jiang W, Zhang D, Xu B, Wu Z, Liu S, Zhang L, Tian Y, Han X and Tian D. Long non-coding RNA BANCR promotes proliferation and migration of lung carcinoma via MAPK pathways. Biomed Pharmacother 2015; 69: 90-95.