Tumor Biol. (2016) 37:3933–3938
DOI 10.1007/s13277-015-4252-y

ORIGINAL ARTICLE

Downregulation of lncRNA-ATB correlates with clinical progression and unfavorable prognosis in pancreatic cancer

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Received: 28 August 2015 / Accepted: 13 October 2015 / Published online: 19 October 2015

Abstract Long noncoding RNAs (lncRNAs) have been shown to play critical roles in the development and progression of diseases. lncRNA activated by transforming growth factor beta (TGF-β) (lncRNA-ATB) was discovered as a prognostic factor in hepatocellular carcinoma, gastric cancer, and colorectal cancer. However, little is known about the role of lncRNA-ATB in pancreatic cancer. This study aimed to assess lncRNA-ATB expression in pancreatic cancer and explore its role in pancreatic cancer pathogenesis. Quantitative real-time polymerase chain reaction was performed to detect lncRNA-ATB expression in 150 pancreatic cancer tissues and five pancreatic cancer cell lines compared to paired adjacent normal tissues and normal human pancreatic ductal epithelial cell line HPDE6c-7. The correlations between lncRNA-ATB expression and clinicopathological characteristics and prognosis were also analyzed. We found that lncRNA-ATB expression was decreased in pancreatic cancer tissues and pancreatic cancer cell lines. Low lncRNA-ATB expression levels were significantly correlated with lymph node metastases (yes vs. no, $P=0.009$), neural invasion (positive vs. negative, $P=0.049$), and clinical stage (early stage vs. advanced stage, $P=0.014$). Moreover, patients with low lncRNA-ATB expression levels exhibited markedly worse overall survival prognoses ($P<0.001$). Multivariate analysis indicated that decreased lncRNA-ATB expression was an independent predictor of poor prognosis in pancreatic cancer patients ($P=0.005$). In conclusion, lncRNA-ATB may play a critical role in pancreatic cancer progression and prognosis and may serve as a potential prognostic biomarker in pancreatic cancer patients.

Keywords Pancreatic cancer · Long noncoding RNA · lncRNA-ATB · Prognosis

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related deaths in men and women, respectively, throughout the world [1]. Although substantial progress has been made in our understanding of pancreatic cancer biology, there are no effective screening tools for detecting asymptomatic premalignant or early malignant tumors [2, 3]. Moreover, pancreatic cancer is often diagnosed at an advanced stage because of its deep location and tardive symptoms. Although advances in patient management have also occurred, the 5-year overall survival rate is still approximately 5 % [3, 4]. Therefore, it is urgent to identify novel potential biomarkers for early diagnosis, accurate prognosis prediction, and the development of new therapeutics.

Long noncoding RNAs (lncRNAs) are a subset of noncoding RNAs >200 nucleotides that do not encode proteins and reside in the nucleus or cytoplasm [5]. Although the function and mechanism of most lncRNAs remain unknown, accumulated evidence suggests that lncRNAs play an important role in the transcriptional, epigenetic, and post-transcriptional regulation of gene expression [5, 6]. Furthermore, the aberrant expression of lncRNAs has been found to correlate with many diseases, including cancer [7, 8]. Using a lncRNA microarray profile, a recent study demonstrated that lncRNA expression in pancreatic cancer was significantly altered between

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pancreatic cancer and paired adjacent normal tissues [9]. Moreover, several studies have shown that lncRNAs are related to pancreatic cancer initiation and progression by regulating cell growth, migration, and invasion [10–14], indicating that lncRNAs play crucial roles in pancreatic cancer. However, research concerning the roles of lncRNA in pancreatic cancer is still in its infancy.

Recently, a report demonstrated that the lncRNA activated by transforming growth factor beta (TGF-β) (lncRNA-ATB) was upregulated in hepatocellular carcinoma and induced epithelial–mesenchymal transition (EMT) and invasion through the TGF-β/miR-200 s/ZEB signaling network [15]. Moreover, subsequent studies have identified that lncRNA-ATB expression correlates with clinical features and prognosis in several types of human cancer, including gastric and colorectal cancers [16, 17]. However, little is known about the pathological role of lncRNA-ATB in pancreatic cancer patients.

In the present study, we aimed to investigate lncRNA-ATB expression in pancreatic cancer tissues and cell lines to further explore the clinical significance and biological functions of this lncRNA in pancreatic cancer. Our results revealed that lncRNA-ATB expression levels were decreased in pancreatic cancer tissues and cell lines. Moreover, relatively lower lncRNA-ATB expression levels were significantly associated with the malignant status and poor prognosis of pancreatic cancer patients. The results also suggest that lncRNA-ATB is a potent prognostic biomarker for patients with pancreatic cancer.

Materials and methods

Sample collection

This study was approved by the Ethics Review Board of Xijing Hospital of Fourth Military Medical University. All of the patients provided written informed consent, and samples were anonymized and handled according to accepted ethical and legal standards.

One hundred and fifty pancreatic cancer and paired adjacent normal pancreatic tissues were collected from patients undergoing operations at the Department of Hepatobiliary Surgery at Xijing Hospital. None of the patients had received preoperative chemotherapy, radiotherapy, or targeted therapy. Specimens obtained during surgery were immediately snap-frozen in liquid nitrogen immediately and stored at −130 °C until RNA extraction. Tissue specimen histology was performed by two pathologists. The systematic treatments were performed according to the NCCN guidelines. The clinical staging of the specimens was based on the seventh edition of the AJCC Cancer Staging Manual. All of the patients had complete follow-up information until their deaths, which ranged from 5 to 60 months. The overall survival time was calculated from the date of the initial surgical operation to pancreatic-cancer-related death.

RNA extraction and quantitative real-time PCR

RNA extraction and quality control were completed as described in our previous study [18]. Total RNA (1 μg) was reverse-transcribed into complementary DNA (cDNA) with a sequence-specific primer or an anchored-oligo $(dT)_{18}$ primer and random hexamer primers using the Transcriptor First Strand cDNA Synthesis Kit (Roche, Penzberg, Germany). The sequence-specific primer for lncRNA-ATB was 5′-ACACAGAATAAAATAACAC-3′ [15]. Quantitative real-time PCR (qRT-PCR) was carried out using an iQ5 instrument (Bio-Rad) and FastStart Essential DNA Green Master (Roche) to detect lncRNA-ATB expression. The β-actin level was used as a normalizing control. The following qRT-PCR primers were used: (1) lncRNA-ATB forward, 5′-TCTGGCTGAGGCTGGTTGAC-3′, and reverse, 5′-ATCTCTGGGTGCTGGTGAAGG-3′; and (2) β-actin forward, 5′-CATGTACGTTGCTATCCAGGC-3′, and reverse, 5′-CTCCTTAATGTCACGCACGAT-3′. The qRT-PCR primers were synthesized by Sangon Biotech, Co., Ltd. (Shanghai, China). The qRT-PCR amplification was performed in triplicate reactions under the following reaction conditions: (1) 95 °C for 10 min and (2) 40 cycles of 95 °C for 10 s, 60 °C for 15 s, and 72 °C for 20 s. lncRNA-ATB relative expression was calculated and normalized using the $2^{-\Delta\Delta Ct}$ or the ΔCt ($Ct_{lncRNA\text{-}ATB}$-$Ct_{\beta\text{-}actin}$) method relative to β-actin.

Statistical analysis

All of the statistical analyses were performed using SPSS version 18.0 (SPSS, Chicago, IL, USA) and GraphPad Prism 5.0 (GraphPad software, La Jolla, CA, USA). A P value less than 0.05 was considered statistically significant. Data were presented as the mean with the standard deviation (SD). The paired t test and ANOVA test were respectively applied to test the differential expression of lncRNA-ATB in pancreatic cancer tissues compared with the paired normal tissues, as well as in pancreatic cancer cell lines compared with the normal human pancreatic ductal epithelial cell line HPDE6c-7. The relationship between lncRNA-ATB expression levels and clinicopathological features was examined by chi-square test. Survival curves were plotted using the Kaplan–Meier method and the log-rank test. Univariate and multivariate Cox regression analyses were performed to analyze the survival data.

Results

lncRNA-ATB is downregulated in pancreatic cancer tissues and cell lines

To assess the role of lncRNA-ATB in pancreatic cancer, we performed qRT-PCR to measure lncRNA-ATB expression in 150 paired pancreatic cancer and adjacent normal pancreatic tissues. lncRNA-ATB expression levels were significantly downregulated in pancreatic cancer tissues compared with the paired adjacent normal tissues (**P<0.001, Fig. 1a, b). lncRNA-ATB levels were also determined by qRT-PCR in five pancreatic cancer cell lines and the normal human pancreatic ductal epithelial cell line HPDE6c-7. The results showed that lncRNA-ATB expression was lower in the pancreatic cancer cell lines than in HPDE6C-7 (*P<0.05, Fig. 1c).

The relationship between lncRNA-ATB expression and clinicopathological features in pancreatic cancer patients

We next investigated the correlation between lncRNA-ATB expression and pancreatic cancer clinicopathological features. The median expression level was used as the cutoff. Pancreatic cancer tissue specimens were categorized into high and low expression groups. The correlations between the lncRNA-ATB expression level and the clinicopathological features of pancreatic cancer patients are summarized in Table 1. The results showed that lncRNA-ATB expression levels in pancreatic cancer significantly correlated with lymphatic metastasis (yes vs. no, P=0.009), neural invasion (positive vs. negative, P=0.049), and clinical stage (early stage vs. advanced stage, P=0.014). However, lncRNA-ATB expression did not correlate with other clinicopathological characteristics, such as age (P=0.411), gender (P=0.414), tumor size (P=0.412), vessel invasion (P=0.495), distant metastasis (P=0.533), and differentiation (P=0.402). Taken together, these observations indicate that decreased lncRNA-ATB expression might be associated with the development and progression of pancreatic cancer.

lncRNA-ATB downregulation is an unfavorable prognostic factor in pancreatic cancer patients

To assess the prognostic value of lncRNA-ATB expression in pancreatic cancer patients, we examined the association between lncRNA-ATB expression levels and overall survival using Kaplan–Meier analysis with the log-rank test. The results revealed that lncRNA-ATB expression directly correlates with pancreatic cancer patients' overall survival (P<0.001, Fig. 2). In other words, patients with low lncRNA-ATB expression levels displayed lower overall survival rates than patients with high lncRNA-ATB expression levels. We also found that lncRNA-ATB downregulation was an unfavorable prognostic factor in pancreatic cancer patients regardless of lymphatic metastasis, vessel invasion, neural invasion, distant metastasis, or clinical stage. Taken together, multivariate analysis revealed that

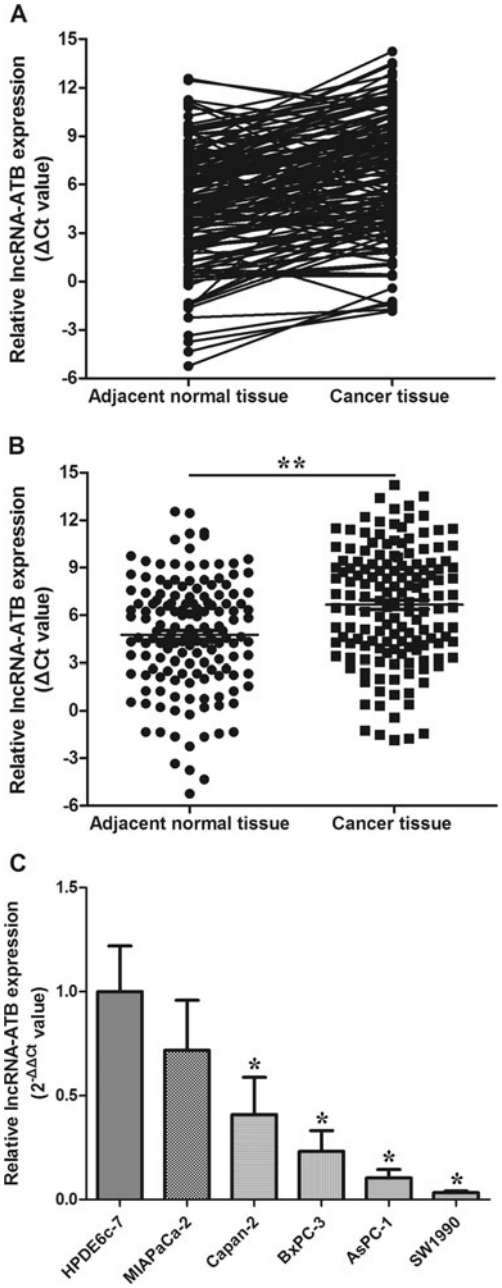

Fig. 1 lncRNA-ATB expression levels in pancreatic cancer by qRT-PCR. **a** Relative lncRNA-ATB expression levels in the cancerous and normal tissues (n=150) for each patient. Higher ΔCt values indicate lower expression. **b** lncRNA-ATB expression is decreased in pancreatic cancer tissues compared with adjacent normal tissues by qRT-PCR (**P<0.001). **c** lncRNA-ATB expression is decreased in five pancreatic cancer cell lines compared with the normal human pancreatic ductal epithelial cell line HPDE6c-7 (*P<0.05)

Table 1 Relationship between lncRNA-ATB expression and clinicopathological characteristics in pancreatic cancer patients

Characteristics	Number	lncRNA-ATB expression		*P* value
		High (n=75)	Low (n=75)	
Age (year)				
<60	84	45	39	0.411
≥60	66	30	36	
Gender				
Male	76	41	35	0.414
Female	74	34	40	
Tumor size (cm)				
<3	82	44	38	0.412
≥3	68	31	37	
Lymphatic metastasis				
Yes	81	32	49	0.009
No	69	43	26	
Vessel invasion				
Positive	53	24	29	0.495
Negative	97	51	46	
Neural invasion				
Positive	79	33	46	0.049
Negative	71	42	29	
Distant metastasis				
Present	11	4	7	0.533
Absent	139	71	68	
Differentiation				
Well and moderate	92	49	43	0.402
Poor	58	26	32	
Clinical stage				
Early stage (≤IIa)	68	42	26	0.014
Advanced stage (>IIa)	82	33	49	

lncRNA-ATB lncRNA activated by transforming growth factor beta

decreased lncRNA-ATB expression is an independent predictor of poor prognosis for pancreatic cancer patients (P=0.005, Table 2).

Discussion

Pancreatic cancer remains one of the most common and deadly cancers; thus, it is important to identify new molecular targets for the diagnosis, prognosis, and treatment of pancreatic cancer. With the development of genome sequencing technologies, it is well accepted that less than 2 % of the human genome encodes proteins and that the remaining 98 % encodes noncoding RNAs (ncRNAs) [19]. ncRNAs, including lncRNAs and circular RNAs, were initially regarded as transcriptional "noise" or body "dark matter" [20]. In recent years, accumulating studies have suggested that

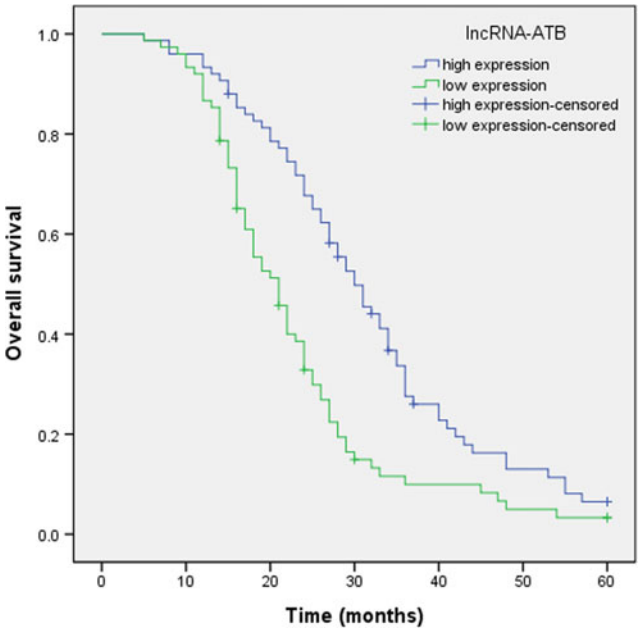

Fig. 2 Decreased lncRNA-ATB expression predicts an unfavorable prognosis. The correlation between lncRNA-ATB expression and overall survival was estimated using Kaplan–Meier analysis and the log-rank test (P<0.001)

lncRNAs play important roles in a variety of diseases, particularly malignant tumors [6, 21].

A recent report demonstrated that a small number of lncRNAs were aberrantly expressed in human pancreatic cancer compared with corresponding normal pancreatic tissues. Moreover, lncRNA-BC008363 was significantly lower in pancreatic cancer tissues compared with that in corresponding adjacent normal tissues, suggesting that it could be a novel biomarker for pancreatic cancer prognosis [9]. lncRNA-ENST00000480739 expression levels are remarkably decreased in pancreatic cancer tissues. Research has also shown that lncRNA-ENST00000480739 downregulation contributes to tumor metastasis and progression in pancreatic cancer by regulating HIF-1α [10]. lncRNA H19 is overexpressed in pancreatic cancer compared with adjacent normal tissues and could promote pancreatic cancer metastasis [11]. HOTAIR expression is increased in pancreatic cancer and is associated with more aggressive pancreatic cancers [12]. Additionally, the lncRNA MALAT1 is highly expressed in pancreatic cancer compared with adjacent normal tissues and could facilitate pancreatic cancer cell growth, migration, and invasion and serve as an unfavorable prognostic biomarker in pancreatic cancer patients [13, 14]. Taken together, these studies indicate that lncRNAs may be involved in the progression and prognosis of pancreatic cancer.

lncRNA-ATB (lncRNA-ENST00000493038) was poly(A)-negative and locates on chr14 (q11.2). Originally, lncRNA-ATB expression was shown to be upregulated in hepatocellular carcinomas and associated with poor prognosis

Table 2 Univariate and multivariate Cox regression analyses of overall survival in 150 pancreatic cancer patients

Variable	Univariate analysis (Cox: enter)			Multivariate analysis (Cox: forward conditional)		
	HR	95 % CI	*P*	HR	95 % CI	*P*
Age (year)						
<60 versus ≥60	1.017	0.721–1.435	0.922			
Gender						
Male versus female	1.021	0.726–1.436	0.903			
Tumor size (cm)						
<3 versus ≥3	1.223	0.870–1.721	0.247			
Lymphatic metastasis						
Yes versus no	2.599	1.796–3.761	<0.001	2.144	1.469–3.128	<0.001
Vessel invasion						
Positive versus negative	1.829	1.264–2.647	0.001	2.040	1.394–2.984	<0.001
Neural invasion						
Positive versus negative	1.946	1.369–2.764	<0.001	1.996	1.389–2.868	<0.001
Distant metastasis						
Present versus absent	3.074	1.583–5.967	0.001	2.866	1.459–5.629	0.002
Differentiation						
Well and moderate versus poor	1.068	0.753–1.516	0.711			
Clinical stage						
Early stage (≤ IIa) versus advanced stage (> IIa)	2.595	1.790–3.763	<0.001			
lncRNA-ATB						
High versus low	1.970	1.391–2.790	<0.001	1.675	1.167–2.406	0.005

HR hazard ratio, *95 % CI* 95 % confidence interval, *lncRNA-ATB* lncRNA activated by transforming growth factor beta

[15]. Furthermore, two similar studies by Mimori et al. found that lncRNA-ATB was an independent prognostic marker of gastric cancer and involved in the progression and prognosis of colorectal cancer [16, 17]. Similarly, Shi et al. showed that lncRNA-ATB was remarkably upregulated in trastuzumab-resistant SKBR-3 cells and trastuzumab-resistant tissues in breast cancer patients and that it could facilitate trastuzumab resistance and the invasion–metastasis cascade in breast cancer [22]. However, little is known about the role of lncRNA-ATB in pancreatic cancer patients.

This is the first study to report that lncRNA-ATB is commonly downregulated in pancreatic cancer compared with adjacent normal tissues and in pancreatic cancer cell lines. However, lncRNA-ATB was remarkably upregulated in hepatocellular carcinomas [15]. These findings indicate that lncRNA-ATB might act as an oncogene or tumor suppressor in various tumors. Similarly, miR-200a is commonly downregulated in hepatocellular carcinoma [23], renal cell carcinoma [24], and nasopharyngeal carcinoma [25] but is upregulated in ovarian cancer [26] and endometrial adenocarcinoma [27]. Interestingly, Li et al. had reported that miR-200a was overexpressed in pancreatic cancer [28]. We also found that pancreatic cancer cell line with lower lncRNA-ATB expression had a higher level of miR-200a (data not shown in the paper), which was seem to be consistent with lncRNA-ATB functions as competing endogenous RNA (ceRNA) in hepatocellular cancer [15]. However, further studies need to verify this assumption. Moreover, we further explored the role of lncRNA-ATB in the development and progression of pancreatic cancer. We analyzed the association between lncRNA-ATB expression and clinicopathological features in 150 pancreatic cancer patients. We found that decreased lncRNA-ATB expression positively correlated with lymphatic metastasis, neural invasion, and clinical stage. Thus, overexpressed lncRNA-ATB in pancreatic cancer may inhibit cell invasion and metastasis. Additionally, we also found that lncRNA-ATB expression positively correlated with overall survival in pancreatic cancer patients. Pancreatic cancer patients with downregulated lncRNA-ATB levels had shorter overall survival times, indicating that low lncRNA-ATB expression correlates with malignant status and poor prognosis in pancreatic cancer. According to multivariate analysis, lncRNA-ATB detection may be used as a new biomarker to complement traditional biomarkers to predict

prognosis and improve clinical outcomes for pancreatic cancer patients.

In conclusion, our study demonstrates that lncRNA-ATB expression is commonly decreased in pancreatic cancer and significantly correlates with the malignant status in pancreatic cancer patients. Furthermore, lncRNA-ATB downregulation is an independent poor prognostic factor for pancreatic cancer patients. However, further study is needed to reveal the molecular mechanisms of lncRNA-ATB in pancreatic cancer.

Acknowledgments We would like to thank Yan Qiu and Kun Liu (Department of Hepatobiliary Surgery of Xijing Hospital) for collecting the samples and the follow-up information. We thank Xuejun Hu and Zhidong Wang (Fourth Military Medical University) for his help in statistics. We are also grateful for the anonymous reviewers' constructive comments and suggestions. This work was supported by grants from the National Natural Science Foundation of China (No. 81772061) and the Health Public Welfare Industry Special Scientific Research Projects of China (No.201202007).

Conflicts of interest None

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5–29. doi:10.3322/caac.21254.
2. Ryan DP, Hong TS, Bardeesy N. N Engl J Med. 2014;371(22):2140–1. doi:10.1056/NEJMc1412266.
3. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet. 2011;378(9791):607–20. doi:10.1016/S0140-6736(10)62307-0.
4. Hartwig W, Werner J, Jäger D, Debus J, Büchler MW. Improvement of surgical results for pancreatic cancer. Lancet Oncol. 2013;14(11):e476–85. doi:10.1016/S1470-2045(13)70172-4.
5. Ponting CP, Oliver PL, Reik W. Evolution and functions of long noncoding RNAs. Cell. 2009;136(4):629–41. doi:10.1016/j.cell.2009.02.006.
6. Shi X, Sun M, Liu H, Yao Y, Song Y. Long non-coding RNAs: a new frontier in the study of human diseases. Cancer Lett. 2013;339(2):159–66. doi:10.1016/j.canlet.2013.06.013.
7. Xu SP, Zhang JF, Sui SY, Bai NX, Gao S, Zhang GW, et al. Down regulation of the long noncoding RNA EGOT correlates with malignant status and poor prognosis in breast cancer. Tumour Biol. 2015. doi:10.1007/s13277-015-3746-y.
8. Huarte M, Rinn JL. Large non-coding RNAs: missing links in cancer? Hum Mol Genet. 2010;19(R2):R152–61. doi:10.1093/hmg/ddq353.
9. Li J, Liu D, Hua R, Zhang J, Liu W, Huo Y, et al. Long noncoding RNAs expressed in pancreatic ductal adenocarcinoma and lncRNA BC008363 an independent prognostic factor in PDAC. Pancreatology. 2014;14(5):385–90. doi:10.1016/j.pan.2014.07.013.
10. Sun YW, Chen YF, Li J, Huo YM, Liu DJ, Hua R, et al. A novel long non-coding RNA ENST00000480739 suppresses tumour cell invasion by regulating OS-9 and HIF-1α in pancreatic ductal adenocarcinoma. Br J Cancer. 2014;111(11):2131–41. doi:10.1038/bjc.2014.520.
11. Ma C, Nong K, Zhu H, Wang W, Huang X, Yuan Z, et al. H19 promotes pancreatic cancer metastasis by derepressing let-7's suppression on its target HMGA2-mediated EMT. Tumour Biol. 2014;35(9):9163–9. doi:10.1007/s13277-014-2185-5.
12. Kim K, Jutooru I, Chadalapaka G, Johnson G, Frank J, Burghardt R, et al. HOTAIR is a negative prognostic factor and exhibits pro-oncogenic activity in pancreatic cancer. Oncogene. 2013;32(13):1616–25. doi:10.1038/onc.2012.193.
13. Jiao F, Hu H, Yuan C, Wang L, Jiang W, Jin Z, et al. Elevated expression level of long noncoding RNA MALAT-1 facilitates cell growth, migration and invasion in pancreatic cancer. Oncol Rep. 2014;32(6):2485–92. doi:10.3892/or.2014.3518.
14. Pang EJ, Yang R, Fu XB, Liu YF. Overexpression of long non-coding RNA MALAT1 is correlated with clinical progression and unfavorable prognosis in pancreatic cancer. Tumour Biol. 2015;36(4):2403–7. doi:10.1007/s13277-014-2850-8.
15. Yuan JH, Yang F, Wang F, Ma JZ, Guo YJ, Tao QF, et al. A long noncoding RNA activated by TGF-β promotes the invasion-metastasis cascade in hepatocellular carcinoma. Cancer Cell. 2014;25(5):666–81. doi:10.1016/j.ccr.2014.03.010.
16. Saito T, Kurashige J, Nambara S, Komatsu H, Hirata H, Ueda M, et al. A long non-coding RNA activated by transforming growth factor-β is an independent prognostic marker of gastric cancer. Ann Surg Oncol. 2015. doi:10.1245/s10434-015-4554-8.
17. Iguchi T, Uchi R, Nambara S, Saito T, Komatsu H, Hirata H, et al. A long noncoding RNA, lncRNA-ATB, is involved in the progression and prognosis of colorectal cancer. Anticancer Res. 2015;35(3):1385–8.
18. Qu S, Song W, Yang X, Wang J, Zhang R, Zhang Z, et al. Microarray expression profile of circular RNAs in human pancreatic ductal adenocarcinoma. Genomics Data. 2015;5:385–7.
19. Esteller M. Non-coding RNAs in human disease. Nat Rev Genet. 2011;12(12):861–74. doi:10.1038/nrg3074.
20. Qu S, Yang X, Li X, Wang J, Gao Y, Shang R, et al. Circular RNA: a new star of noncoding RNAs. Cancer Lett. 2015;365(2):141–8. doi:10.1016/j.canlet.2015.06.003.
21. Kung JT, Colognori D, Lee JT. Long noncoding RNAs: past, present, and future. Genetics. 2013;193(3):651–69. doi:10.1534/genetics.112.146704.
22. Shi SJ, Wang LJ, Yu B, Li YH, Jin Y, Bai XZ. LncRNA-ATB promotes trastuzumab resistance and invasion-metastasis cascade in breast cancer. Oncotarget. 2015;6(13):11652–63.
23. Yang X, Wang J, Qu S, Zhang H, Ruan B, Gao Y, et al. MicroRNA-200a suppresses metastatic potential of side population cells in human hepatocellular carcinoma by decreasing ZEB2. Oncotarget. 2015;6(10):7918–29.
24. Lu R, Ji Z, Li X, Qin J, Cui G, Chen J, et al. Tumor suppressive microRNA-200a inhibits renal cell carcinoma development by directly targeting TGFB2. Tumour Biol. 2015 Mar 27. doi:10.1007/s13277-015-3355-9.
25. Xia H, Ng SS, Jiang S, Cheung WK, Sze J, Bian XW, et al. miR-200a-mediated down regulation of ZEB2 and CTNNB1 differentially inhibits nasopharyngeal carcinoma cell growth, migration and invasion. Biochem Biophys Res Commun. 2010;391(1):535–41. doi:10.1016/j.bbrc.2009.11.093.
26. Liu N, Zhong L, Zeng J, Zhang X, Yang Q, Liao D, et al. Up regulation of microRNA-200a associates with tumor proliferation, CSCs phenotype and chemosensitivity in ovarian cancer. Neoplasma. 2015;62(4):550–9. doi:10.4149/neo_2015_066.
27. Snowdon J, Zhang X, Childs T, Tron VA, Feilotter H. The microRNA-200 family is upregulated in endometrial carcinoma. PLoS One. 2011;6(8):e22828. doi:10.1371/journal.pone.0022828.
28. Li A, Omura N, Hong SM, Vincent A, Walter K, Griffith M, et al. Pancreatic cancers epigenetically silence SIP1 and hypomethylate and overexpress miR-200a/200b in association with elevated circulating miR-200a and miR-200b levels. Cancer Res. 2010;70(13):5226–37.