Int J Clin Exp Pathol 2015;8(1):779-785
www.ijcep.com /ISSN:1936-2625/IJCEP0003867

Original Article

Long non-coding RNA CCAT2 is up-regulated in gastric cancer and associated with poor prognosis

Chen-Yu Wang*, Long Hua*, Kun-Hou Yao, Jiang-Tao Chen, Jun-Jie Zhang, Jun-Hong Hu

*Department of General Surgery, Huaihe Clinical College of HeNan University, Kaifeng 475000, Henan Province, China. *Equal contributors.*

Received November 15, 2014; Accepted December 24, 2014; Epub January 1, 2015; Published January 15, 2015

Abstract: Introduction: Dysregulation of long non-coding RNAs (lncRNAs) play important roles in tumor progression. The aim of our study was to explore the clinicopathologic and prognostic significance of lncRNA CCAT2 expression in human gastric cancer. Methods: Expression levels of lncRNA CCAT2 in 85 pairs of gastric cancer and adjacent non-tumor tissues were detected by quantitative real-time PCR (qRT-PCR). In order to determine its prognostic value, overall survival and progression-free survival were evaluated using the Kaplan-Meier method, and multivariate analysis was performed using the Cox proportional hazard analysis. Results: Expression levels of lncRNA CCAT2 in gastric cancer tissues were significantly higher than those in adjacent non-tumor tissues. By statistical analyses, high lncRNA CCAT2 expression was observed to be closely correlated with higher incidence of lymph node metastasis and distance metastasis. Moreover, patients with high lncRNA CCAT2 expression had shorter overall survival and progression-free survival compared with the low lncRNA CCAT2 group. Multivariate analyses indicated that high lncRNA CCAT2 expression was an independent poor prognostic factor for gastric cancer patients. Conclusions: Our results suggested that up-regulation of lncRNA CCAT2 was correlated with gastric cancer progression, and lncRNA CCAT2 might be a potential molecular biomarker for predicting the prognosis of patients.

Keywords: Gastric cancer, lncRNA CCAT2, overall survival, progression-free survival, prognosis

Introduction

Gastric cancer is the fourth most common human malignant disease and the second leading cause of cancer-related death worldwide [1]. Despite the significant achievements that have been made in the treatment of early gastric cancer, the long-term survival rate for advanced gastric cancer is still quite low [2]. In China, the 5-year overall survival rate of patients with gastric cancer is lower than 40%, although recent advances in chemotherapy and surgical techniques [3]. This is primarily attributed to the following reasons: lack of diagnostic markers for early detection, weak prognostic value of histological indicators, limited efficiency of current treatment for advanced disease and lack of molecular markers utilized for targeted therapy [4, 5]. Therefore, identification of novel effective molecular markers is of great significance for the improvement of diagnostic and prognostic techniques, and for the development of more efficient therapeutic strategies for patients with gastric cancer.

With the development of whole-genome sequencing technology, it was determined that less than 2% of the mammalian genome is in protein-encoded regions and the remainder is in non-coding RNAs (ncRNAs) [6]. Among them are long non-coding RNAs (lncRNAs), which are more than 200 nucleotides in length and unable to be translated into proteins [7]. Recently, many lncRNAs are known to play important roles in the regulation of gene transcription and translation, cell differentiation, ontogenetic, genetic, and epigenetic and other cellular activities [8-10]. LncRNAs have been considered to be new approaches of tumor biomarkers for early cancer diagnosis and prognosis. They may play roles in the development and progression of cancers similar to those played by oncogenes or tumor suppressor genes. Recent studies have identified a number of lncRNAs with aberrant expression in tumors. For example, Lai et al found that MALAT1 was up-regulated in both hepatocellular carcinoma cell lines and clinical tissue samples. Patients with high expression level of MALAT1 had a sig-

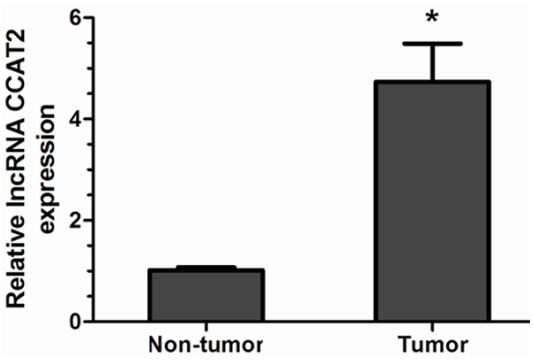

Figure 1. LncRNA CCAT2 expression in 85 pairs of gastric cancer and adjacent non-tumor tissues detected by qRT-PCR. *$P < 0.05$.

nificantly increased risk of tumor recurrence [11]. Kogo et al showed that HOTAIR expression levels were higher in colorectal cancer tissues than in corresponding noncancerous tissues and high HOTAIR expression correlated tightly with the presence of liver metastasis [12]. Sun et al found that GAS5 expression was markedly down-regulated in gastric cancer and associated poorer disease-free survival and overall survival of gastric cancer patients. Moreover, ectopic expression of GAS5 was demonstrated to decrease gastric cancer cell proliferation and induce apoptosis in vitro and in vivo [13]. Yang et al revealed that lncRNA H19 were markedly increased in gastric cancer cells and gastric cancer tissues compared with normal controls. Moreover, ectopic expression of H19 increased cell proliferation [14]. However, to our knowledge, the expression pattern and prognostic role of lncRNA CCAT2 expression has not been reported in gastric cancer yet.

In the present study, we investigated the expression level of lncRNA CCAT2 in clinical gastric cancer and adjacent non-tumor tissues, as well as analyzed its association with overall survival and progression-free survival of gastric cancer patients.

Materials and methods

Patients and specimens

Human gastric cancer and adjacent non-tumor tissues were obtained from 85 patients who underwent gastrectomy at the Department of General Surgery, Huaihe Clinical College of HeNan University, between January 2005 and December 2008. All patients did not receive chemotherapy or radiotherapy prior to surgery. After resection, the specimens were immediately frozen in liquid nitrogen and then stored in -80°C until use. The histopathological type and stage of gastric cancer were determined according to the criteria of the World Health Organization classification and the TNM stage set out by the Union for International Cancer Control. Data were retrieved from their operative and pathological reports, and follow-up data were obtained by our clinical database. The written informed consent had been obtained from all the patients, and this study was approved by the Ethical Committee of Huaihe Clinical College of HeNan University.

Quantitative realtime PCR (qRT-PCR)

Total RNA from tissues was extracted using Trizol reagent (Invitrogen). RNA was reversed transcribed into cDNAs using the Primer-Script one step RT-PCR kit (TaKaRa). The cDNA template was amplified by real-time PCR using the SYBR Premix Dimmer Eraser kit (TaKaRa). Glyceraldehyde-3-phos-phate dehydrogenase (GAPDH) was used as an internal control, and lncRNA CCAT2 values were normalized to GAPDH. qRT-PCR reactions were performed by the ABI7900 system (Applied Biosystems). The relative expression fold change of mRNAs was calculated by the $2^{-\Delta\Delta CT}$ method. The PCR primers used were as follows: 5'-CCACATCGCTCAGACACCAT-3' (sense) and 5'-ACCAGGCGCCCAATACG-3' (antisense) for GAPDH; and 5'-CCCTGGTCAAATTGCTTAACCT-3' (sense) and 5'-TTATTCGTCCCTCTGTTTTATGGAT-3' (antisense) for CCAT2.

Statistical analysis

All statistical analyses were performed using SPSS version 18.0 software (IBM). The data were presented as the mean ± SD. The Chi-squared test was used to investigate the significance of lncRNA CCAT2 expression as correlated with clinicopathologic features in gastric cancer. Overall survival and progression-free survival curves were plotted using the Kaplan-Meier method and were evaluated for the statistical significance using a log-rank test. The significance of different variables with respect to survival was analyzed using the univariate and multivariate Cox proportional hazards

Table 1. Association between lncRNA CCAT2 expression and clinicopathological features of human gastric cancer

Clinicopathological features	Total	LncRNA CCAT2 expression		*P*
		Low	High	
Age (years)				0.605
< 60	39	20	19	
≥ 60	46	21	25	
Gender				0.440
Male	41	18	23	
Female	44	23	21	
Tumor size (cm)				0.790
< 5	51	24	27	
≥ 5	34	17	17	
Differentiation				0.345
Well	27	11	16	
Moderate + Poor	58	30	28	
TNM stage				0.157
I + II	43	24	19	
III + IV	42	17	25	
Depth of invasion				0.466
T1 + T2	38	20	18	
T3 + T4	47	21	26	
Lymph node metastasis				0.000
No	49	33	16	
Yes	36	8	28	
Distant metastasis				0.028
No	71	38	33	
Yes	14	3	11	

model. Differences were considered statistically significant when *P* was less than 0.05.

Results

LncRNA CCAT2 up-regulation in human gastric cancer

LncRNA CCAT2 expression was detected in 85 pairs of gastric cancer and adjacent non-tumor tissues by qRT-PCR. As shown in **Figure 1**, after normalization to GAPDH expression levels, the expression level of lncRNA CCAT2 in gastric cancer tissues was significantly higher than that in adjacent non-tumor tissues. The mean expression level of lncRNA CCAT2 (4.3) was used as a cutoff point to divide all 85 patients into two groups: gastric cancer patients who express lncRNA CCAT2 at levels less than the cutoff value were assigned to the low expression group (n = 41), and those with expression above the cutoff value were assigned to the high expression group (n = 44).

Association between lncRNA CCAT2 expression and clinicopathologic features of gastric cancer

Table 1 summarized the association between lncRNA CCAT2 expression and clinicopathologic features in gastric cancer. LncRNA CCAT2 expression was observed to be closely correlated with higher lymph node metastasis and distance metastasis ($P < 0.05$). However, there were no significant correlations between lncRNA CCAT2 expression and other clinicopathologic features including age, gender, tumor size, differentiation, TNM stage and depth of invasion ($P > 0.05$).

Correlations of lncRNA CCAT2 expression with overall survival and progression free survival of gastric cancer patients

To further investigate the correlation of lncRNA CCAT2 expression with survival of gastric cancer patients, Kaplan-Meier analyses were performed. As shown in **Figure 2A**, the 5-year overall survival of high lncRNA CCAT2 expression group was significantly shorter than that of low lncRNA CCAT2 expression group ($P < 0.05$). Moreover, the 5-year progression-free survival of high lncRNA CCAT2 expression group was significantly shorter than that of low lncRNA CCAT2 expression group ($P < 0.05$) (**Figure 2B**). These data demonstrated that overexpression of lncRNA CCAT2 might be associated with poor survival of gastric patients

Univariate and multivariate determination of prognostic factors in gastric cancer patients

Univariate analyses performed to evaluate the expression of lncRNA CCAT2 and other clinicopathologic features on prognosis of gastric cancer patients. As shown in **Table 2**, it was observed that lncRNA CCAT2 expression, along with lymph node metastasis and distance metastasis, was responsible for efficacy of surgical treatment in gastric cancer patients, by indicating that status of lncRNA CCAT2 expression was significantly correlated with overall survival ($P < 0.05$) and progression-free survival ($P < 0.05$) of gastric cancer patients. Furthermore, multivariate analyses were per-

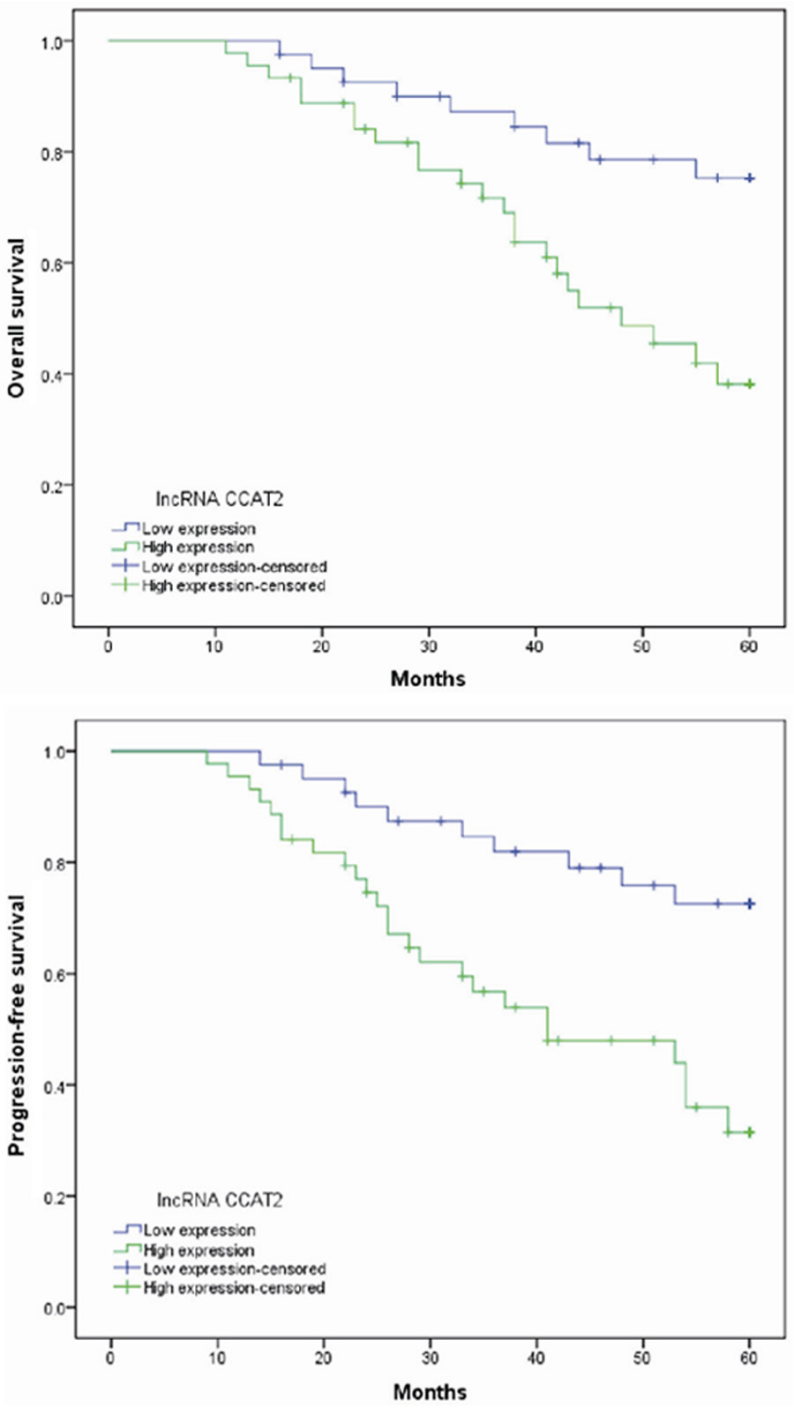

Figure 2. Kaplan-Meier survival curves for gastric cancer patients according to the expression of lncRNA CCAT2. A. Overall survival B. Progression-free survival.

formed to evaluate those clinicopathogic features significant in univariate analyses (lymph node metastasis, distance metastasis and status of lncRNA CCAT2 expression). It was shown that lncRNA CCAT2 expression was an independent molecular biomarker for the predicting of overall survival ($P < 0.05$) and progression-free survival ($P < 0.05$) in gastric cancer (**Table 2**).

Discussion

As different cancer therapies are effective in different subgroups of patients, there is a tremendous need for novel predictive and prognostic markers to improve the outcomes of cancer patients [15]. Gastric cancer is a group of heterogeneous diseases that show various biological and clinical characteristics. Patient management is currently based on easily identifiable clinical and pathological characteristics [16]. In recent years, many molecules have been used for the prediction of the prognosis of gastric cancer patients [17], but their roles in determining the individual risk level of the patient are quite limited. Therefore, further identification of new prognostic markers remains important for the prevention and treatment of gastric cancer.

Previously study showed that almost 50% of transcribed RNA has no protein-coding potential [18]. Early research proposed that lncRNAs may simply represent transcriptional noise [19]. However, in recent years, lncRNAs have been implicated as having oncogenic and tumor suppressor roles and can be used to develop as biomarkers and prognosis factors [20]. So In this study, we focused on lncRNA CCAT2 in gastric cancer.

CCAT2, a novel long non-coding RNA transcript encompassing the rs6983267 SNP, was highly over-expressed in microsatellite-stable colorec-

Table 2. Univariate and multivariate analysis of overall survival and progression-free survival

Clinicopathological features	Overall survival and			Progression-free survival		
	HR	95% CI	*P*	HR	95% CI	*P*
Univariate analysis						
Age (years) (≥ 60 vs. < 60)	1.461	0.742-2.517	0.306	1.304	0.692-2.304	0.418
Gender (Male vs. Female)	0.924	0.537-1.648	0.351	0.884	0.497-1.526	0.289
Tumor size (≥ 5 cm vs. < 5 cm)	1.391	0.647-2.016	0.273	1.212	0.588-1.946	0.266
Differentiation (Moderate + Poor vs. Well)	1.588	0.515-2.76	0.227	1.794	0.571-3.368	0.297
TNM stage (III + IV vs. I + II)	2.806	0.475-4.476	0.119	2.671	0.418-4.185	0.138
Depth of invasion (T3 + T4 vs. T1 + T2)	2.263	0.697-3.754	0.197	2.374	0.713-3.962	0.244
Lymph node metastasis (Yes vs. No)	3.267	1.218-7.264	0.017	3.152	1.211-6.754	0.009
Distant metastasis (Yes vs. No)	3.872	1.592-8.174	0.008	3.226	1.478-7.361	0.012
LncRNA CCAT2 (High vs. Low)	2.631	1.348-5.672	0.021	2.574	1.201-5.476	0.011
Multivariate analysis						
Lymph node metastasis (Yes vs. No)	3.017	1.018-6.694	0.021	2.944	1.131-6.438	0.015
Distant metastasis (Yes vs. No)	3.615	1.407-7.977	0.013	3.136	1.294-7.066	0.008
LncRNA CCAT2 (High vs. Low)	2.405	1.194-5.417	0.003	2.315	1.097-5.283	0.001

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.

tal cancer and promotes tumor growth, metastasis, and chromosomal instability. They further identify the physical interaction between CCAT2 and TCF7L2 resulting in an enhancement of WNT signaling activity [20]. Redis et al found that lncRNA CCAT2 was up-regulated in breast cancer tissues compare to non-tumor tissues. Additionally, they found that CCAT2 up-regulated cell migration [21]. Qiu et al found that CCAT2 was significantly over-expressed in non-small cell lung cancer tissues and correlated with lymph node metastasis. Silencing CCAT2 by siRNA could inhibit the proliferation and invasion ability of lung cancer cells [22]. However, the status of lncRNA CCAT2 expression in gastric cancer and its prognostic roles are still unclear. Thus, the aim of this study was to investigate the correlations of lncRNA CCAT2 expression with clinicopathologic features and prognosis of gastric cancer patients.

In the present study, we explored the clinical significance of lncRNA CCAT2 in gastric cancer patients. Our results showed that lncRNA CCAT2 expression was significantly higher in gastric cancer compared with that in adjacent non-tumor tissues. In addition, high lncRNA CCAT2 expression was also proved to be associated with lymph node metastasis and distance metastasis, suggesting that up-regulation of lncRNA CCAT2 played an important role in gastric cancer progression. Then, we analyzed the correlation of lncRNA CCAT2 expression with prognosis of gastric cancer patients, and found that patients with high lncRNA CCAT2 expression showed shorter overall survival and progression-free survival than those with low lncRNA CCAT2 expression. More importantly, both the univariate and multivariate survival analyses demonstrated that high lncRNA CCAT2 expression was correlated with shorter overall survival and progression free survival in gastric cancer patients, which proved that lncRNA CCAT2 was an independent prognostic marker for gastric cancer. Our data suggested that lncRNA CCAT2 might be an important modulator involved in gastric cancer development.

In conclusion, our results offer the convincing evidence that lncRNA CCAT2 could play key roles in the progression of gastric cancer and that the increased expression of lncRNA CCAT2 might be independently associated with shorter overall survival and progression-free survival of patients, indicating that lncRNA CCAT2 might be a potential marker for further risk stratification in the treatment of this cancer. However, further studies are needed to elucidate the mechanisms of lncRNA CCAT2 in gastric cancer.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jun-Hong Hu, Department of General Surgery, Huaihe Clinical College of Henan University, 8 Baogonghu North

Road, Kaifeng 475000, Henan Province, China. E-mail: hujunhong73@163.com

References

[1] Siegel R, Naishadham D and Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63: 11-30.

[2] Park do J, Han SU, Hyung WJ, Kim MC, Kim W, Ryu SY, Ryu SW, Song KY, Lee HJ, Cho GS and Kim HH. Long-term outcomes after laparoscopy-assisted gastrectomy for advanced gastric cancer: a large-scale multicenter retrospective study. Surg Endosc 2012; 26: 1548-1553.

[3] Ye YW, Dong RZ, Zhou Y, Du CY, Wang CM, Fu H and Shi YQ. Prognostic analysis of familial gastric cancer in Chinese population. J Surg Oncol 2011; 104: 76-82.

[4] Roder DM. The epidemiology of gastric cancer. Gastric Cancer 2002; 5 Suppl 1: 5-11.

[5] Yasui W, Oue N, Kuniyasu H, Ito R, Tahara E and Yokozaki H. Molecular diagnosis of gastric cancer: present and future. Gastric Cancer 2001; 4: 113-121

[6] Carninci P, Kasukawa T, Katayama S, Gough J, Frith MC, Maeda N, Oyama R, Ravasi T, Lenhard B, Wells C, Kodzius R, Shimokawa K, Bajic VB, Brenner SE, Batalov S, Forrest AR, Zavolan M, Davis MJ, Wilming LG, Aidinis V, Allen JE, Ambesi-Impiombato A, Apweiler R, Aturaliya RN, Bailey TL, Bansal M, Baxter L, Beisel KW, Bersano T, Bono H, Chalk AM, Chiu KP, Choudhary V, Christoffels A, Clutterbuck DR, Crowe ML, Dalla E, Dalrymple BP, de Bono B, Della Gatta G, di Bernardo D, Down T, Engstrom P, Fagiolini M, Faulkner G, Fletcher CF, Fukushima T, Furuno M, Futaki S, Gariboldi M, Georgii-Hemming P, Gingeras TR, Gojobori T, Green RE, Gustincich S, Harbers M, Hayashi Y, Hensch TK, Hirokawa N, Hill D, Huminiecki L, Iacono M, Ikeo K, Iwama A, Ishikawa T, Jakt M, Kanapin A, Katoh M, Kawasawa Y, Kelso J, Kitamura H, Kitano H, Kollias G, Krishnan SP, Kruger A, Kummerfeld SK, Kurochkin IV, Lareau LF, Lazarevic D, Lipovich L, Liu J, Liuni S, McWilliam S, Madan Babu M, Madera M, Marchionni L, Matsuda H, Matsuzawa S, Miki H, Mignone F, Miyake S, Morris K, Mottagui-Tabar S, Mulder N, Nakano N, Nakauchi H, Ng P, Nilsson R, Nishiguchi S, Nishikawa S, Nori F, Ohara O, Okazaki Y, Orlando V, Pang KC, Pavan WJ, Pavesi G, Pesole G, Petrovsky N, Piazza S, Reed J, Reid JF, Ring BZ, Ringwald M, Rost B, Ruan Y, Salzberg SL, Sandelin A, Schneider C, Schonbach C, Sekiguchi K, Semple CA, Seno S, Sessa L, Sheng Y, Shibata Y, Shimada H, Shimada K, Silva D, Sinclair B, Sperling S, Stupka E, Sugiura K, Sultana R, Takenaka Y, Taki K, Tammoja K, Tan SL, Tang S, Taylor MS, Tegner J, Teichmann SA, Ueda HR, van Nimwegen E, Verardo R, Wei CL, Yagi K, Yamanishi H, Zabarovsky E, Zhu S, Zimmer A, Hide W, Bult C, Grimmond SM, Teasdale RD, Liu ET, Brusic V, Quackenbush J, Wahlestedt C, Mattick JS, Hume DA, Kai C, Sasaki D, Tomaru Y, Fukuda S, Kanamori-Katayama M, Suzuki M, Aoki J, Arakawa T, Iida J, Imamura K, Itoh M, Kato T, Kawaji H, Kawagashira N, Kawashima T, Kojima M, Kondo S, Konno H, Nakano K, Ninomiya N, Nishio T, Okada M, Plessy C, Shibata K, Shiraki T, Suzuki S, Tagami M, Waki K, Watahiki A, Okamura-Oho Y, Suzuki H, Kawai J and Hayashizaki Y. The transcriptional landscape of the mammalian genome. Sci 2005; 309: 1559-1563.

[7] Esteller M. Non-coding RNAs in human disease. Nat Rev Genet 2011; 12: 861-874.

[8] Mercer TR, Dinger ME and Mattick JS. Long non-coding RNAs: insights into functions. Nat Rev Genet 2009; 10: 155-159.

[9] Hu W, Alvarez-Dominguez JR and Lodish HF. Regulation of mammalian cell differentiation by long non-coding RNAs. EMBO Rep 2012; 13: 971-983.

[10] Kaikkonen MU, Lam MT and Glass CK. Non-coding RNAs as regulators of gene expression and epigenetics. Cardiovasc Res 2011; 90: 430-440.

[11] Lai MC, Yang Z, Zhou L, Zhu QQ, Xie HY, Zhang F, Wu LM, Chen LM and Zheng SS. Long non-coding RNA MALAT-1 overexpression predicts tumor recurrence of hepatocellular carcinoma after liver transplantation. Med Oncol 2012; 29: 1810-1816.

[12] Kogo R, Shimamura T, Mimori K, Kawahara K, Imoto S, Sudo T, Tanaka F, Shibata K, Suzuki A, Komune S, Miyano S and Mori M. Long Noncoding RNA HOTAIR Regulates Polycomb-Dependent Chromatin Modification and Is Associated with Poor Prognosis in Colorectal Cancers. Cancer Res 2011; 71: 6320-6326.

[13] Sun M, Jin FY, Xia R, Kong R, Li JH, Xu TP, Liu YW, Zhang EB, Liu XH and De W. Decreased expression of long noncoding RNA GAS5 indicates a poor prognosis and promotes cell proliferation in gastric cancer. BMC Cancer 2014; 14: 319.

[14] Yang F, Bi J, Xue X, Zheng L, Zhi K, Hua J and Fang G. Up-regulated long non-coding RNA H19 contributes to proliferation of gastric cancer cells. FEBS J 2012; 279: 3159-3165.

[15] Weber WA. Assessing tumor response to therapy. J Nucl Med 2009; 50 Suppl 1: 1S-10S.

[16] Shah MA and Ajani JA. Gastric cancer--an enigmatic and heterogeneous disease. JAMA 2010; 303: 1753-1754.

[17] Crew KD and Neugut AI. Epidemiology of gastric cancer. World J Gastroenterol 2006; 12: 354-362.

[18] Eddy SR. Non-coding RNA genes and the modern RNA world. Nat Rev Genet 2001; 2: 919-929.

[19] Rinn JL and Chang HY. Genome regulation by long noncoding RNAs. Annu Rev Biochem 2012; 81: 145-166.

[20] Spizzo R, Almeida MI, Colombatti A and Calin GA. Long non-coding RNAs and cancer: a new frontier of translational research? Oncogene 2012; 31: 4577-4587.

[21] Ling H, Spizzo R, Atlasi Y, Nicoloso M, Shimizu M, Redis RS, Nishida N, Gafa R, Song J, Guo Z, Ivan C, Barbarotto E, De Vries I, Zhang X, Ferracin M, Churchman M, van Galen JF, Beverloo BH, Shariati M, Haderk F, Estecio MR, Garcia-Manero G, Patijn GA, Gotley DC, Bhardwaj V, Shureiqi I, Sen S, Multani AS, Welsh J, Yamamoto K, Taniguchi I, Song MA, Gallinger S, Casey G, Thibodeau SN, Le Marchand L, Tiirikainen M, Mani SA, Zhang W, Davuluri RV, Mimori K, Mori M, Sieuwerts AM, Martens JW, Tomlinson I, Negrini M, Berindan-Neagoe I, Foekens JA, Hamilton SR, Lanza G, Kopetz S, Fodde R and Calin GA. CCAT2, a novel noncoding RNA mapping to 8q24, underlies metastatic progression and chromosomal instability in colon cancer. Genome Res 2013; 23: 1446-1461.

[22] Redis RS, Sieuwerts AM, Look MP, Tudoran O, Ivan C, Spizzo R, Zhang X, de Weerd V, Shimizu M, Ling H, Buiga R, Pop V, Irimie A, Fodde R, Bedrosian I, Martens JW, Foekens JA, Berindan-Neagoe I and Calin GA. CCAT2, a novel long non-coding RNA in breast cancer: expression study and clinical correlations. Oncotarget 2013; 4: 1748-1762.

[23] Qiu M, Xu Y, Yang X, Wang J, Hu J, Xu L and Yin R. CCAT2 is a lung adenocarcinoma-specific long non-coding RNA and promotes invasion of non-small cell lung cancer. Tumor Biology 2014; 1-6.