Expression and clinical significance of lncRNA BC041954 in ovarian cancer

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Abstract. Ovarian cancer (OC) is a highly lethal disease among all gynecologic malignant tumor types. Accumulating studies have indicated that certain long non-coding RNAs (lncRNAs) serve important roles in the development and progression of OC. In a previous study by our group, lncRNA BC041954 was identified as one of the most upregulated lncRNAs in OC. In the present study, the clinical significance of lncRNA BC041954 in OC was evaluated. The expression of BC041954 was detected in OC and non-tumor tissue (NT) samples using reverse transcription-quantitative PCR. Furthermore, the association between BC041954 and clinicopathological variables was analyzed using the Chi-square test. Survival was determined using Kaplan-Meier analysis. The prognostic significance of BC041954 was evaluated using univariate and multivariate logistic regression analyses. MicroRNA (miRNA)-lncRNA and miRNA-mRNA pairs were used to construct the lncRNA-miRNA-mRNA competing endogenous RNA network with an in-house Perl script. BC041954 expression was increased in 103 OC tissues as compared with that in NT tissues. Upregulated BC041954 expression was significantly associated with the International Federation of Gynecology and Obstetrics stage and distant metastasis. Kaplan-Meier analysis demonstrated that patients with high BC041954 expression had lower overall survival (OS). In the multivariate logistic regression analysis, BC041954 was also identified as an independent poor prognostic factor for OS in patients with OC. The results suggested that overexpression of the lncRNA BC041954 is a poor prognostic indicator in patients with OC.

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Introduction

Ovarian cancer is the second most common cause of gynecological cancer-related mortality among women around the world (1). There were 295,000 new cases and 185,000 deaths reported worldwide in 2018, with increasing trends predicted (1,2). Despite marked efforts in surgery and chemotherapy, clinical outcomes of OC patients remain unfavorable (2). Although numerous studies have indicated that the International Federation of Gynecology and Obstetrics (FIGO) stage and lymph node metastasis are independent prognostic factors for survival of patients with OC, they may not be able to accurately estimate prognosis due to heterogeneities in the patient population. Therefore, it is important to perform experimental and clinical studies to identify novel biomarkers for early diagnosis and prognosis of OC.

Long non-coding RNAs (lncRNA) are molecules consisting of >200 nucleotides that do not encode for proteins (3). Accumulating studies indicated that lncRNAs regulate cancer cellular activities, including proliferation, apoptosis and migration (4). Certain lncRNAs may be potential markers for diagnosing and targets for treating cancer (5,6). To date, the emerging functional roles of lncRNAs in OC remain to be fully elucidated.

A previous microarray analysis performed by our group confirmed a significant number of aberrantly expressed lncRNAs and mRNAs in OC compared to normal ovarian tissues. Among these significantly differentially expressed lncRNAs, BC041954 was the most upregulated lncRNA (7). BC041954 is a novel lncRNA that is located on chromosome 3 near the zinc finger of the cerebellum 4 (ZIC4) gene. The aim of the present study was to investigate the association between BC041954 expression and clinicopathological characteristics and further explore the clinical significance of BC041954 in OC.

Patients and methods

Clinical specimens. The present study included 103 primary tumor samples from patients with OC who underwent surgery at Shengjing Hospital affiliated to China Medical University between September 2006 and September 2015 (Shengjing, China). None of the patients had received any preoperative chemotherapy or radiation treatments. A total of 60 non-tumor tissue specimens (NT), including normal ovarian and fallopian

Table I. Associations between BC041954 expression and clinicopathological characteristics in ovarian cancer.

Characteristic	Cases (n)	BC041954 expression		P-value
		High (n=52)	Low (n=51)	
Age (years)				0.279
≤55	43	19	24	
>55	60	33	27	
Histological subtypes				0.737
Serous	62	32	30	
Mucinous	19	7	12	
Endometrioid	9	5	4	
Clear cell	8	5	3	
Others	5	3	2	
FIGO stage				0.018
I+II	35	12	23	
III+IV	68	40	28	
Grade				0.387
G1	44	20	24	
G2 + G3	59	32	27	
Distant metastasis				0.031
Yes	39	25	14	
No	64	27	37	

High BC041954 expression was negatively associated with the FIGO stage and distant metastasis, but not significantly associated with age, histological subtype or grade. FIGO, International Federation of Gynecology and Obstetrics.

tube tissues, were collected from female patients (mean age, 58.27±6.79 years) of the same age receiving hysterectomy for non-malignant conditions (mean age 57.45±8.51 years). There is no significant difference in the age in the two groups. The present study was approved by the Ethics Committee of Shengjing Hospital, China Medical University (Shengjing, China; ethical approval no. 2015PS158K). All cases of OC were histologically diagnosed and classified in accordance with the World Health Organization criteria (8,9). All clinical data were collected by physicians and the investigators who performed the experiments with the samples were blinded to the clinical data. The clinicopathological characteristics of the patients are listed in Table I.

RNA extraction. Tissue samples were collected, immediately snap-frozen in liquid nitrogen and carefully stored at -80˚C until use. TRIzol (Invitrogen; Thermo Fisher Scientific, Inc.) was used to extract total RNA. RNA quantity and quality were evaluated using NanoDrop® 2000 (Thermo Fisher Scientific, Inc.) technology and agarose gel electrophoresis was used to detect the RNA integrity (10).

Reverse transcription-quantitative (RT-q)PCR. According to the manufacturer's protocols, RT of total RNA into complementary DNA was performed using the SuperScript™ III Reverse Transcriptase Kit (Invitrogen; Thermo Fisher Scientific, Inc.). The full temperature protocol was 50˚C for 60 min and 70˚C for 15 min. The ViiA 7 Real-time PCR System (Applied Biosystems; Thermo Fisher Scientific, Inc.) was utilized for RT-qPCR amplification with the Power SYBR Green PCR Master Mix (Applied Biosystems; Thermo Fisher Scientific, Inc.). The thermocycling protocol for qPCR was as follows: Initial denaturation at 95˚C for 10 min, followed by 40 cycles of 95˚C for 10 sec and 60˚C for 60 sec. GAPDH expression was monitored as the endogenous control. The specific primer sequences for the lncRNA BC041954 were as follows: Forward, 5'-TCTGTAGTTCGTTGTTGGTCGTG-3' and reverse, 5'-GCG GTCCTGATTCATTAGCG-3'. The specific primer sequences for GAPDH were as follows: Forward, 5'-GGGAAACTGTGG CGTGAT-3' and reverse, 5'-GAGTGGGTGTCGCTGTTGA-3'. mRNA levels were normalized to GAPDH and fold changes in expression were calculated using the $2^{-\Delta\Delta Cq}$ method (11).

Construction of the lncRNA-micro(mi)RNA-mRNA competing endogenous (ce)RNA network. miRNA response elements are the foundation of the ceRNA hypothesis of RNA transcript crosstalk. Algorithms from Targetscan and miRanda were used to determine putative miRNA-lncRNA interactions. The miRNA-lncRNA and miRNA-mRNA pairs were used to construct the lncRNA-miRNA-mRNA ceRNA network with an in-house Perl script. All interaction information was imported into Cytoscape software version 3.1.1 (http://www.cytoscape.org) to generate the regulatory network (12).

Statistical analysis. lncRNA expression was calculated using fold-change filtering and the independent-samples t-test. The association between BC041954 and clinicopathological

Table II. Univariate and multivariate analyses for overall survival using the Cox regression model.

	Univariate analysis			Multivariate analysis		
Variable	Risk ratio	95%CI	P-value	Risk ratio	95%CI	P-value
Age (≤55 years vs. >55 years)	0.987	0.605-1.610	0.959			
Histological subtype [serous vs. (mucinous + endometrioid + clear cell + others)]	1.057	0.640-1.747	0.828			
FIGO stage (I + II vs. III + IV)	0.359	0.199-0.646	0.001	0.371	0.203-0.677	0.001
Grade (G1 vs. G2 + G3)	1.237	0.762-2.008	0.390			
Distant metastasis (yes vs. no)	2.124	1.247-3.616	0.006	1.755	1.061-3.033	0.044
lncRNA BC041954 (high vs. low)	0.522	0.319-0.856	0.010	0.582	0.348-0.975	0.040

FIGO, International Federation of Gynecology and Obstetrics; lncRNA, long non-coding RNA.

variables was evaluated using the Chi-square test. Kaplan-Meier analysis was used to determine the influence of BC041954 on OS. Furthermore, the Cox proportional hazards regression model was used for univariate and multivariate analyses. All experiments were performed in triplicate. P<0.05 was set as the criterion for statistical significance. SPSS software (version 19.0; IBM Corp.) was utilized for statistical analysis.

Results

BC041954 is significantly increased in OC tissues. First, BC041954 expression in OC and NT tissues was detected using RT-qPCR. It was revealed that BC041954 was significantly increased in OC compared to NT tissues (P<0.001; Fig. 1).

Association between BC041954 and clinicopathological parameters in patients with OC. To further explore the clinical significance of BC041954 in OC, the association between lncRNA expression and clinicopathological parameters was evaluated in the 103 patients with OC. According to the median expression level of BC041954 as the cutoff value, patients were divided into two groups: A high BC041954 group and a low BC041954 group. As presented in Table I, high BC041954 expression was negatively associated with the FIGO stage (P=0.018). In addition, higher expression of BC041954 was more frequent in patients with distant metastasis (P=0.031). There was no significant association between BC041954 and any of the other clinicopathological characteristics, including histological subtype and grade.

Influence of BC041954 on the prognosis of patients with OC. The OS of patients with OC was evaluated using Kaplan-Meier analysis. As presented in Fig. 2, OS was significantly lower in patients with high BC041954 expression (P=0.008). Univariate analysis indicated that BC041954 expression (P=0.010), FIGO stage (P=0.001) and distant metastasis (P=0.006) were closely associated with OS of patients with OC. Furthermore, multivariate analysis with the Cox proportional hazards model was performed, according to which the FIGO stage (P=0.001), distant metastasis (P=0.044) and BC041954 expression (P=0.040) were independent prognostic factors in OC (Table II).

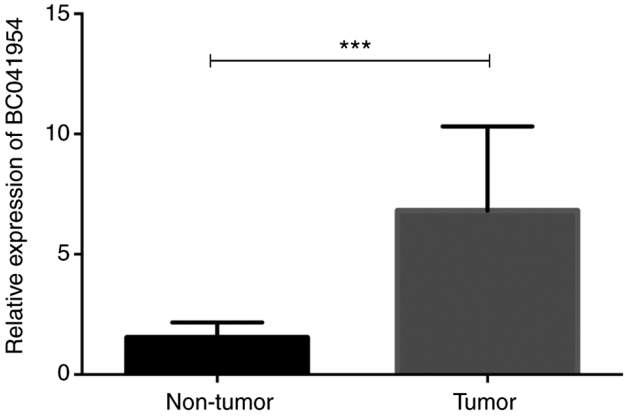

Figure 1. BC041954 expression was assessed using reverse transcription-quantitative PCT. BC041954 was significantly increased in ovarian cancer compared to non-tumor tissues. ***P<0.001.

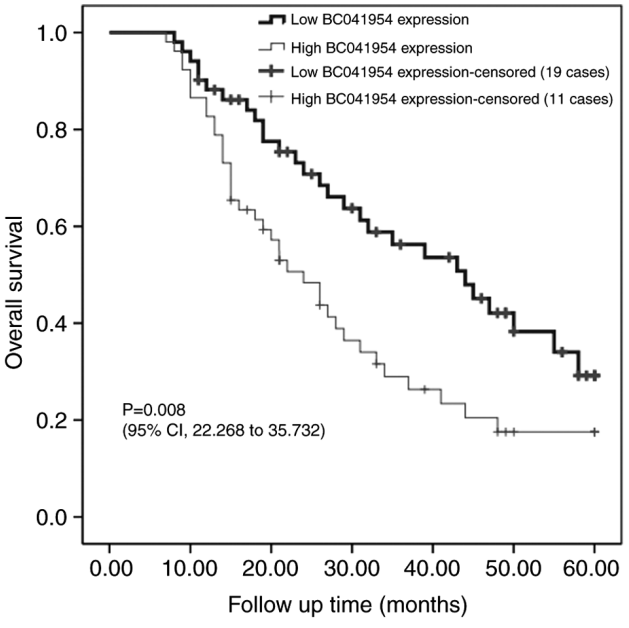

Figure 2. Kaplan-Meier analysis of overall survival in patients with ovarian cancer. The overall survival rate was significantly lower in patients with high BC041954 expression compared to those with low BC041954 expression.

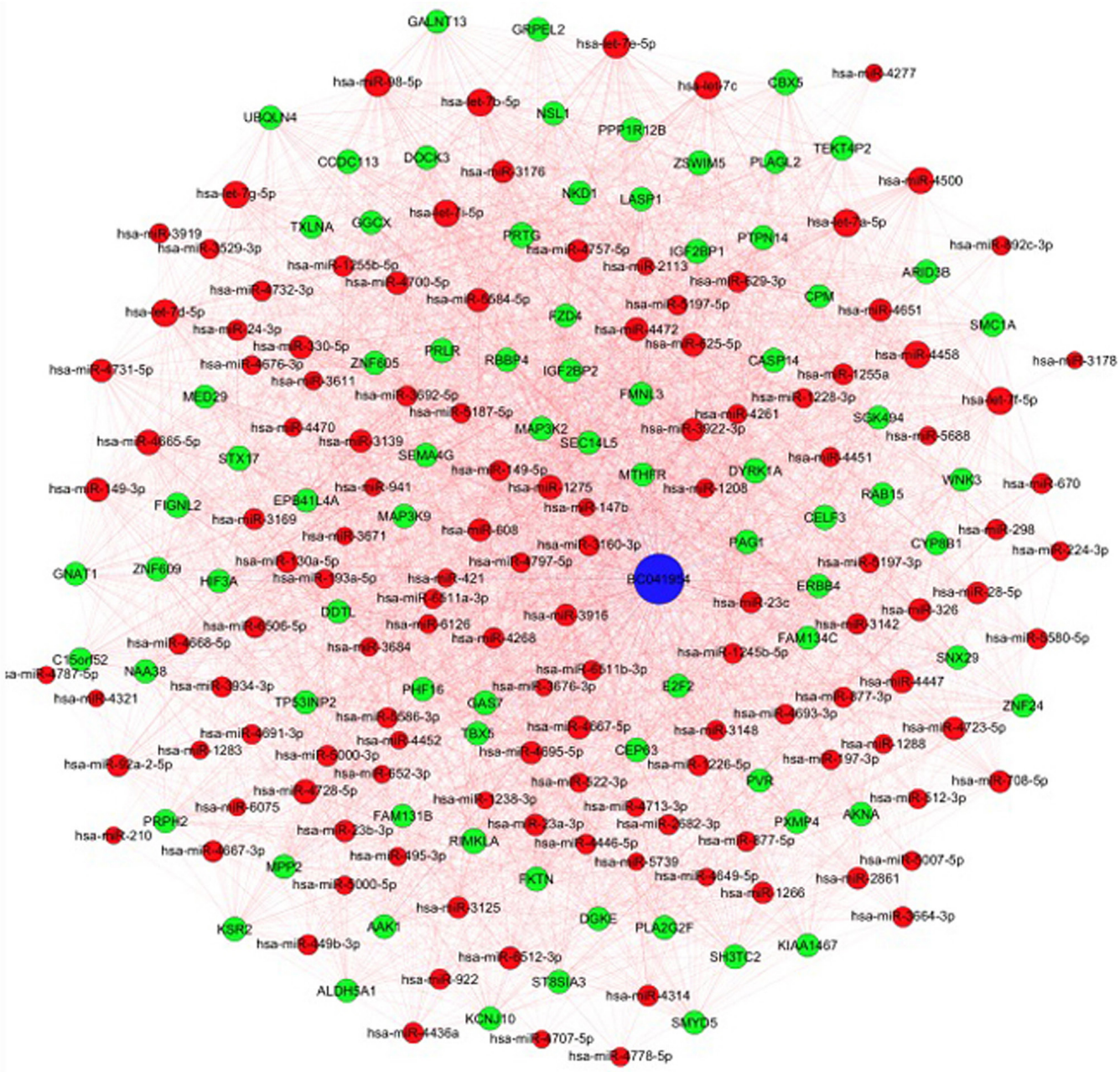

Figure 3. Potential lncRNA/miRNA/mRNA interactions in the competing endogenous RNA network analysis. The potential binding miRNAs of lncRNA BC041954 are depicted. Blue nodes represent lncRNAs including BC041954, red nodes represent miRNAs and green nodes represent mRNAs. lncRNA, long non-coding RNA; miRNA, microRNA.

Functional predictions of the lncRNA/miRNA/mRNA interactions. A ceRNA analysis was performed to provide an overview of the potential lncRNA/miRNA/mRNA interactions (Fig. 3). The potential binding miRNAs of lncRNA BC041954 are depicted. Blue nodes represent lncRNAs including BC041954, red nodes represent miRNAs and green nodes represent mRNAs. These networks were utilized to create functional annotations of the predicted target mRNAs by searching the Gene database. According to the ceRNA theory, lncRNAs may act as natural miRNA sponges to inhibit miRNA function. The expression of lncRNA-miRNA and miRNA-mRNA was negatively correlated. Thus, the ceRNA modulation network of these lncRNAs, miRNAs and mRNAs may provide molecular mechanisms involved in the initiation and progression of OC, providing novel clues for the discovery of clinical diagnostic markers and therapeutic targets. The ceRNA analysis provided an overview of potential BC041954/miRNA/mRNA interactions, indicating that numerous miRNAs interact with BC041954, such as hsa-miR-197-3p, hsa-miR-23b-3p, hsa-miR-149-3p and miR-193a. From the network constructed, 115 miRNAs that potentially interact with BC041954 were identified. BC041954 may serve as a miRNA sponge to inhibit miRNA function. Specifically, miR-193a may directly interact with lncRNA BC041954. Based on the identification of these miRNAs, the miRNA-target interactions database was used to predict mRNA targets. The analysis indicated that miRNAs may interact with receptor protein-tyrosine kinase 4 (ERBB4), γ-glutamyl carboxylase (GGCX), insulin-like

growth factor 2 mRNA-binding protein 2 (IGF2BP2) and growth arrest specific 7 (GAS7) as targets. Furthermore, a previous study confirmed that miR-193a is able to modulate ERBB4 via MAPK/ERK signaling to enhance the progression of OC (13). Thus, it may be speculated that the lncRNA BC041954/miR-193a/ERBB4 interaction has an important role in OC pathogenesis.

Discussion

Numerous differentially expressed lncRNAs have been implicated in tumorigenesis and the progression of various cancer types (6,14). The functional roles of lncRNAs are being increasingly recognized, which has led to a better understanding of the biological processes of different cancer types, such as breast (15), hepatocellular (16), ovarian (1,2,17) and colorectal cancer (18). Various lncRNAs may serve as therapeutic targets as well as biomarkers for early diagnosis and prognosis of human cancers.

It has been reported that lncRNAs have prognostic potential and have critical roles in OC progression (17). Qiu *et al* (19) reported that overexpression of hox transcript antisense intergenic RNA was associated with poor prognosis and facilitated tumor metastasis in patients with OC. Metastasis-associated lung adenocarcinoma transcript 1 was increased in OC tissues and significantly associated with metastasis and tumor size in OC (20). Patients with high colon cancer-associated transcript 2 (CCAT2) had shorter OS and CCAT2 was positively associated with the tumor grade, FIGO stage and metastasis in patients with OC (21). Reduced growth arrest specific 5 (GAS5) was detected in OC tissues and overexpression of GAS5 suppressed aggressive behaviors of OC cells (22). Taken together, lncRNAs may be a novel prognostic factor and a potential therapeutic target for OC.

A previous study by our group profiled differentially expressed lncRNAs and mRNAs in OC vs. normal tissues and detected 2,870 dysregulated lncRNAs. There were 2,658 differentially expressed mRNAs in OC (1,014 were upregulated and 1,644 were downregulated compared with those in NT). BC041954 was selected from the obviously upregulated lncRNA for further validation using RT-qPCR in 25 OC and 15 NT samples and the results confirmed the alterations of the lncRNA expression in OC (7). However, the role of BC041954 in OC has remained elusive. BC041954, located on chromosome 3 near the ZIC4 gene, is a novel lncRNA that was identified by microarray analysis. In the present study, the relative expression of BC041954 OC was detected in patients using RT-qPCR to estimate the clinical significance of BC041954 in OC. First, it was confirmed that BC041954 expression was markedly increased in OC tissues compared with that in NTs. Furthermore, it was indicated that abnormal BC041954 expression may be associated with OC progression. Elevated BC041954 was closely associated with the FIGO stage and distant metastasis. In addition, patients with high BC041954 expression had significantly shorter OS, as determined using Kaplan-Meier analysis. Multivariate analysis demonstrated that the FIGO stage, distant metastasis and BC041954 expression were independent prognostic factors for patients with OC. These results reveal that BC041954 is a potential predictor of OC progression. The ceRNA analysis provided an overview of potential lncRNA/miRNA/mRNA interactions, indicating that numerous miRNAs interact with BC041954. Among these miRNAs, miR-193a was identified to directly interact with BC041954. It was previously reported that miR-193a silencing contributes to a dynamic process of cell growth suppression and migratory/invasive abilities of OC cells (13).

Based on the present results, an miRNA-target interactions database was used to predict miRNA targets. The miRNAs may interact with ERBB4, GGCX, IGF2BP2 and GAS7 as targets, most of which are cancer-associated genes, including ERBB4 (23), IGF2BP2 (24) and GAS7 (25), which have important roles in tumor cell apoptosis, proliferation and metastasis.

Accumulating evidence has indicated that ErbB family members are overexpressed and mutated in OC, and further that ErbB family members are considered important therapeutic targets. The ErbB receptor family (including ERBB4) and its downstream pathways have been reported to be involved in the regulation of epithelial-mesenchymal transition, migration and tumor invasion (26). It has been indicated that the ERBB4 rs1836724 polymorphism is associated with OS of patients with OC (27). miR-193a is able to modulate ERBB4 via the MAPK/ERK signaling pathway to increase the oncogenic properties of OC (13). The present results suggested that ERBB4 may also directly interact with BC041954. Based on the present results, in conjunction with those of previous studies, it may be hypothesized that the BC041954/miR-193a/ERBB4 interaction has an important role in the pathogenesis of OC. Therefore, further functional analyses of BC041954 as a biomarker for tumor diagnosis and prognosis in OC are required. The present study indicated that targeting the lncRNA BC041954 may provide benefits for treating OC.

In conclusion, the present study indicated for the first time that upregulation of lncRNA BC041954 is a frequent event in OC and BC041954 may be a novel biomarker for predicting poor prognosis in patients with OC. However, the molecular mechanisms by which BC041954 is upregulated in OC requires to be further investigated.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YML contributed to the study design, writing of the manuscript and adjustment of the experimental design. YRG collected and analyzed the data. MYZ performed the experiments and

analyzed the data. YW generated the lncRNA/miRNA/mRNA regulatory network and associated data analysis. All authors read and approved the final manuscript. YML and YRG confirm the authenticity of all the raw data.

Ethics approval and consent to participate

This study was approved by our Ethics Committee in Shengjing Hospital, China Medical University (Shengjing, China). Written informed consent was obtained from the patient at the time of recruitment.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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