

Downregulation of LINC01140 is associated with adverse features of breast cancer

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Abstract. Breast cancer (BC) is one of the most dangerous malignant diseases among women. A growing amount of evidence has suggested that long non-coding RNAs participate in the development and progression of BC and may potentially serve as therapeutic targets or prognostic markers for the disease. A previous study demonstrated that long intergenic non-protein coding RNA 01140 (LINC01140) was prominently correlated with overall survival in patients with gastric cancer. However, the function of LINC01140 in BC has not yet been elucidated. Therefore, the present study aimed to investigate the roles and molecular mechanisms underlying LINC01140 in BC. LINC01140 expression in 1,085 breast cancer patients and 291 healthy subjects was analyzed from the Gene Expression Profiling Interactive Analysis website. The association between LINC01140 expression and T stages, LINC01140-related biological pathways, and the correlation between LINC01140 expression genes were also analyzed in 825 patients with BC through the cBioPortal database. The present study demonstrated that LINC01140 expression was significantly decreased in the tumor samples compared with normal samples in patients with BC ($P < 0.05$). The present study revealed that LINC01140 expression was significantly decreased in the T4 stage compared with T1, T2 or T3 stage ($P < 0.01$). In addition, high expression levels of LINC01140 predicts longer relapse-free survival probability in patients with BC. It was also observed that LINC01140 participates in a variety of biological pathways, particularly in the epithelial-to-mesenchymal transition. The co-expression relationship

between the LINC01140 and an abundance of genes in samples from the BC study was investigated. These genes, such as *chordin like 1* and *bone morphogenic protein 6*, participate in the development and progression of tumor growth and bone metastasis. Finally, the present study observed the interaction between microRNA (miR)-200b and miR-200c with LINC01140. The results from the present study indicated that higher expression of LINC01140 was beneficial for patients with BC. LINC01140 may be a potential biomarker for the prognosis of patients with BC. The role of LINC01140 in BC needs to be further evaluated.

Introduction

Breast cancer (BC) is one of the most common and dangerous malignant disorders among women. There are ~1.7 million new cases of BC every year, accounting for a quarter of all new cancer cases in women worldwide (1). There is also a higher rate of mortality and morbidity among patients with BC, despite the rapid development of modern diagnostic and therapeutic techniques (2-4). Elucidating the molecular mechanisms underlying BC is essential for discovering new therapeutic targets for BC. Therefore, understanding the regulatory network underlying BC is an essential focus point for future studies. There is an increasing amount of evidence that long non-coding RNAs (lncRNAs) participate in the development and progression of BC and potentially serve as markers of diagnosis or prognosis (4,5).

lncRNAs are defined as RNA transcripts >200 bp in length that lack open reading frames. A number of lncRNAs were preliminary identified by whole-genome sequencing and next generation transcriptome sequencing (6). In previous years, numerous studies have demonstrated that lncRNAs play an important role in the biological process of various diseases, including carcinogenesis and tumor progression, particularly in BC, by means of regulating gene expression at the epigenetic, transcriptional and post-transcriptional levels (6,7).

Long intergenic non-protein coding RNA 01140 (LINC01140) is located on chromosome 1p22.3. At the site of transcription, LINC01140, unlike proteins, could accommodate the transcription of genome-adjacent protein-coding genes in cis and regulate the transcription of distal protein-coding genes in trans (8,9). The association between LINC01140 expression and survival outcome was evaluated in patients with gastric

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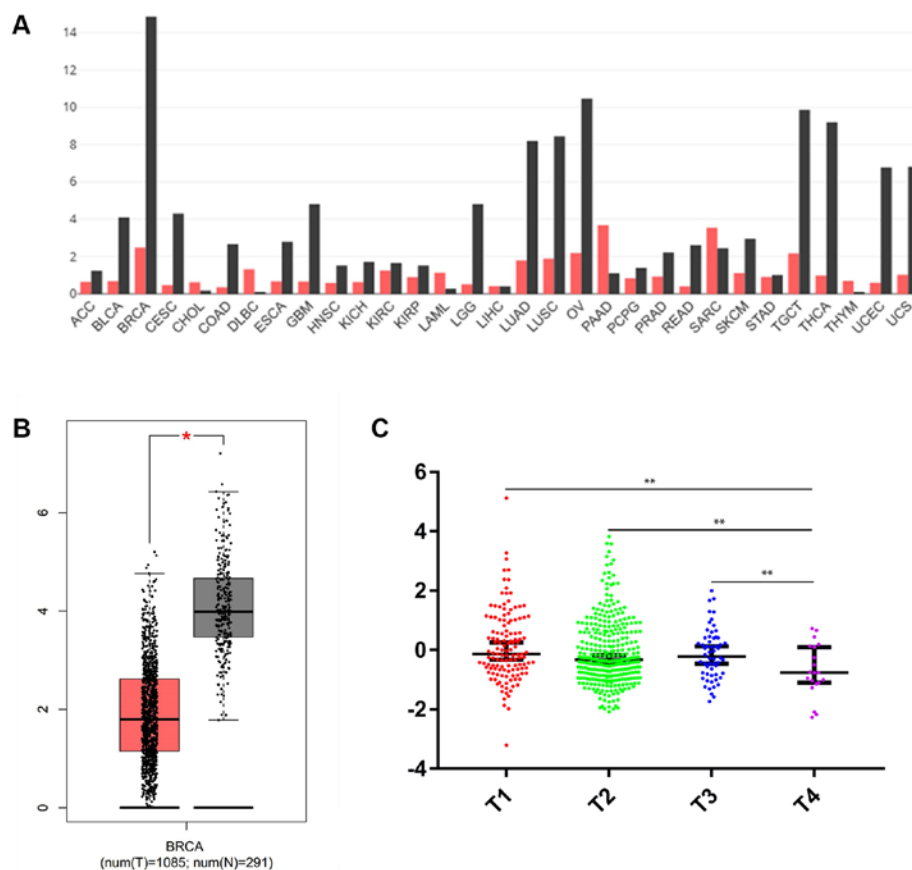


Figure 1. LINC01140 is downregulated in BC tissues. (A) The LINC01140 expression profile across all tumor samples and paired normal tissues. (B) LINC01140 expression was decreased in breast cancer compared with normal tissues. The height of bar represents the median expression level of certain tumor type (red) or normal tissue (black). (C) LINC01140 expression in breast cancer is associated with certain clinical pathological parameters in different stages. The 825 patients with breast cancer were grouped according to their tumor size. LINC01140 expression in each different group of stages is presented as the mean \pm standard error of the mean. A two-tailed Student's t-test was used to calculate statistical significance. * $P < 0.05$ and ** $P < 0.01$. LINC01140, long intergenic non-protein coding RNA 01140.

cancer (GC). The results demonstrated that LINC01140 is significantly associated with overall survival in patients with GC (9). Therefore, it is valuable to investigate the functional roles of LINC01140. To investigate the roles and molecular mechanisms of LINC01140 in BC, LINC01140 expression was analyzed in 1,085 breast cancer patients and 291 healthy subjects using Gene Expression Profiling Interactive Analysis (GEPIA). The association between LINC01140 expression and T stages, LINC01140-related biological pathways, and the correlation between certain LINC01140 expression genes were also analyzed in 825 patients with BC via the cBioPortal database.

Materials and methods

The data on LINC01140 expression from 1,085 patients with BC and 291 healthy tissues were collected from the web resource of Gene Expression Profiling Interactive Analysis (GEPIA) (10). GEPIA is a developed interactive web server for analyzing RNA sequencing expression data from tumors and normal samples. The present study acquired the clinical data for the patients with BC from the open access cBioPortal database (<http://www.cbioportal.org>) (11,12), which provides web resources for analyzing multidimensional cancer genome data, as well as graphical summaries of gene-level data from multiple platforms and survival analyses. The present study used a two-tailed Student's t-test to evaluate statistical

discrepancies between two groups. Survival probability was determined using a Kaplan-Meier plotter (<http://kmplot.com/analysis>) (13). Patients with BC were divided into high LINC01140 or low LINC01140 based on the median value of LINC01140 expression. The association between LINC01140 expression and T stages, LINC01140-related biological pathways, and the correlation between LINC01140 expression genes were analyzed in 825 patients with BC through the cBioPortal database (14). Gene enrichment analyses were performed using FUNRICH software (version 3.0) for the co-expressed genes from the cBioPortal database (15). The microRNA (miRNA/miR)-LINC01140 interactions were analyzed by Ago CLIP-seq Data from starBase (<http://starbase.sysu.edu.cn>) (16).

Results

LINC01140 is downregulated in BC tissues and low LINC01140 expression is associated with a worse prognosis in patients with BC. In multiple types of cancer, particularly in BC, the expression of LINC01140 is downregulated (Fig. 1A and B). Compared with the mammary tissues in BC, the expression of LINC01140 is almost 6 times higher in normal mammary tissues. In the present study, LINC01140 expression in 1,085 patients with BC and 291 healthy subjects from RNA sequencing datasets was analyzed through GEPIA. It was revealed that LINC01140 expression was significantly

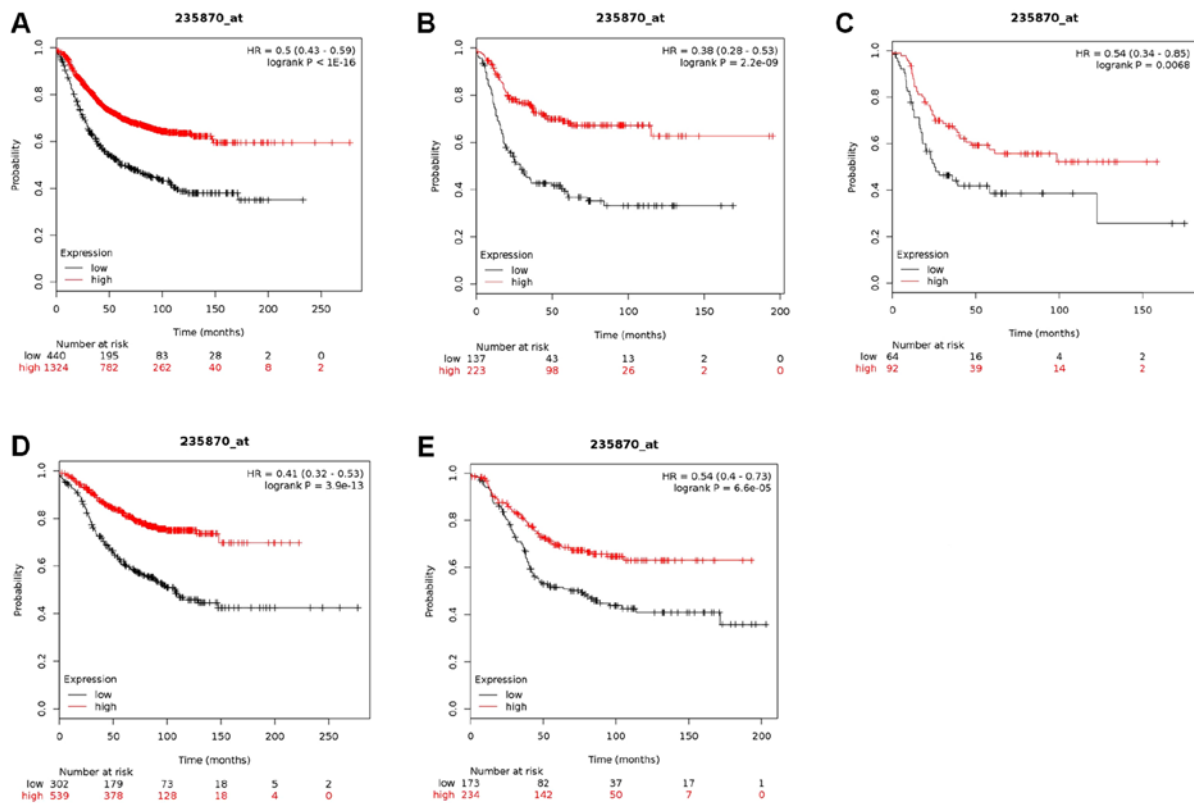


Figure 2. Impact of the LINC01140 (Affymetrix ID: 235870_at) expression on the survival probability and breast cancer. Survival probability determined by Kaplan-Meier plotter. Patients with breast cancer were divided into high expression of LINC01140 (red) or low expression of LINC01140 (black) in the light of the median value of LINC01140 expression. (A) Represents the RFS of all patients without distinguishing between breast cancer subtypes. RFS probability in the four subtypes: (B) Basal-like RFS, (C) HER2-positive RFS, (D) Luminal-A RFS and (E) Luminal B RFS. RFS, relapse-free survival; HR, hazard ratio LINC01140, long intergenic non-protein coding RNA 01140.

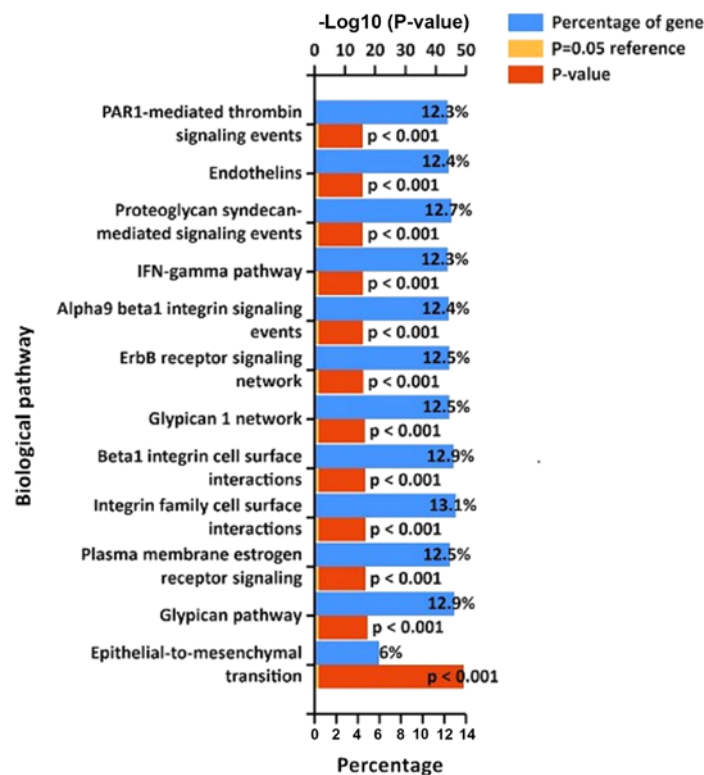


Figure 3. LINC01140 is involved in biological pathways. The biological pathways include PAR1-mediated thrombin signaling events, endothelins, proteoglycan syndecan-mediated signaling events, IFN- γ pathway, $\alpha 9 \beta 1$ integrin signaling events, ErbB receptor signaling network, glypican 1 network, $\beta 1$ integrin cell surface interactions, integrin family cell surface interactions, plasma membrane estrogen receptor signaling, glypican pathway and epithelial-to-mesenchymal transition. IFN, interferon; LINC01140, long intergenic non-protein coding RNA 01140.

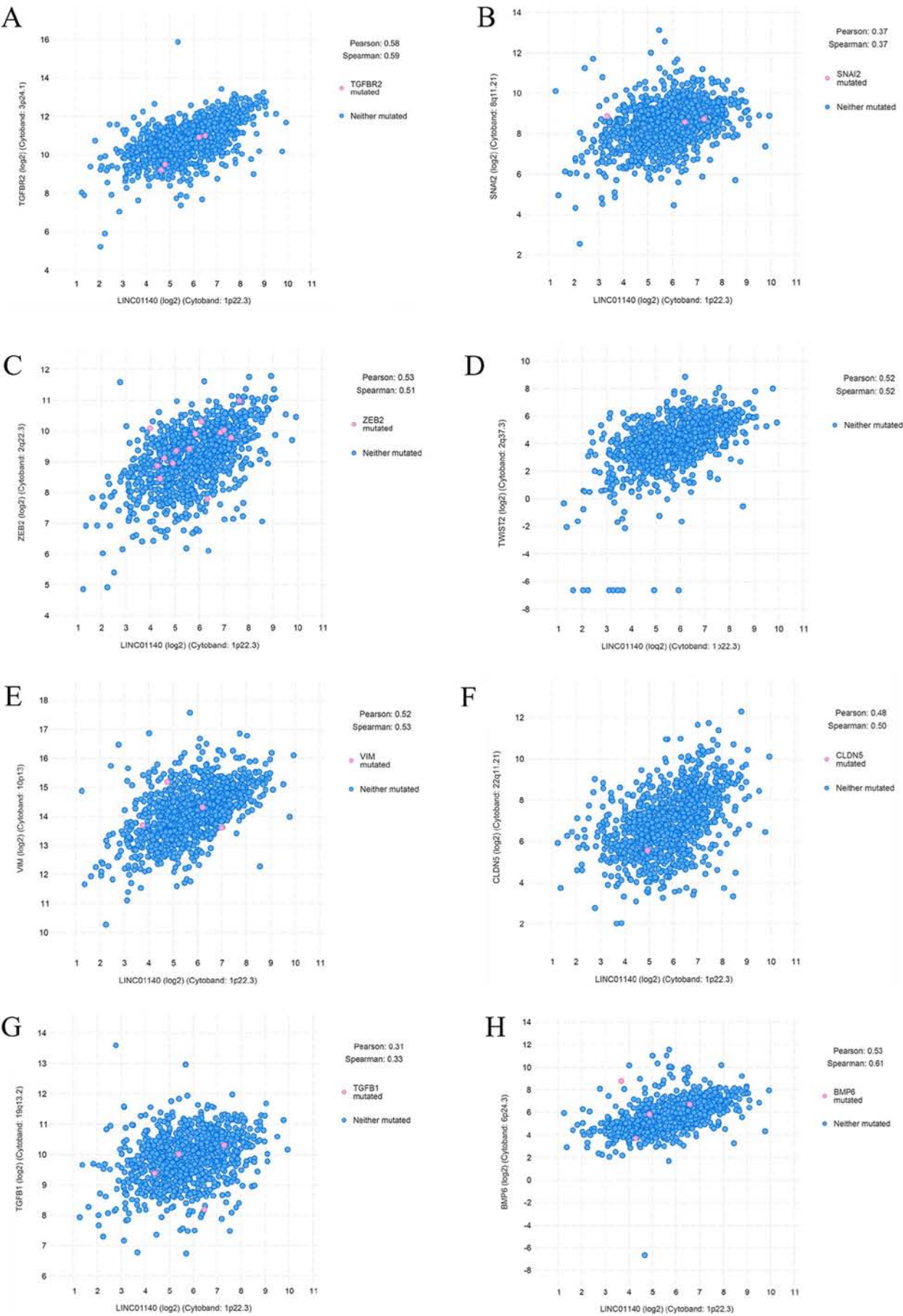


Figure 4. Plot showing the co-expression association between the LINC01140 and the abundance of genes in samples from the breast cancer study. These genes were co-expressed with LINC01140 expression. All the Pearson values are >0.30. (A) TGFBR2, (B) SNAI2, (C) ZEB2, (D) TWIST2, (E) VIM, (F) CLDN5, (G) TGFBI, (H) BMP6.

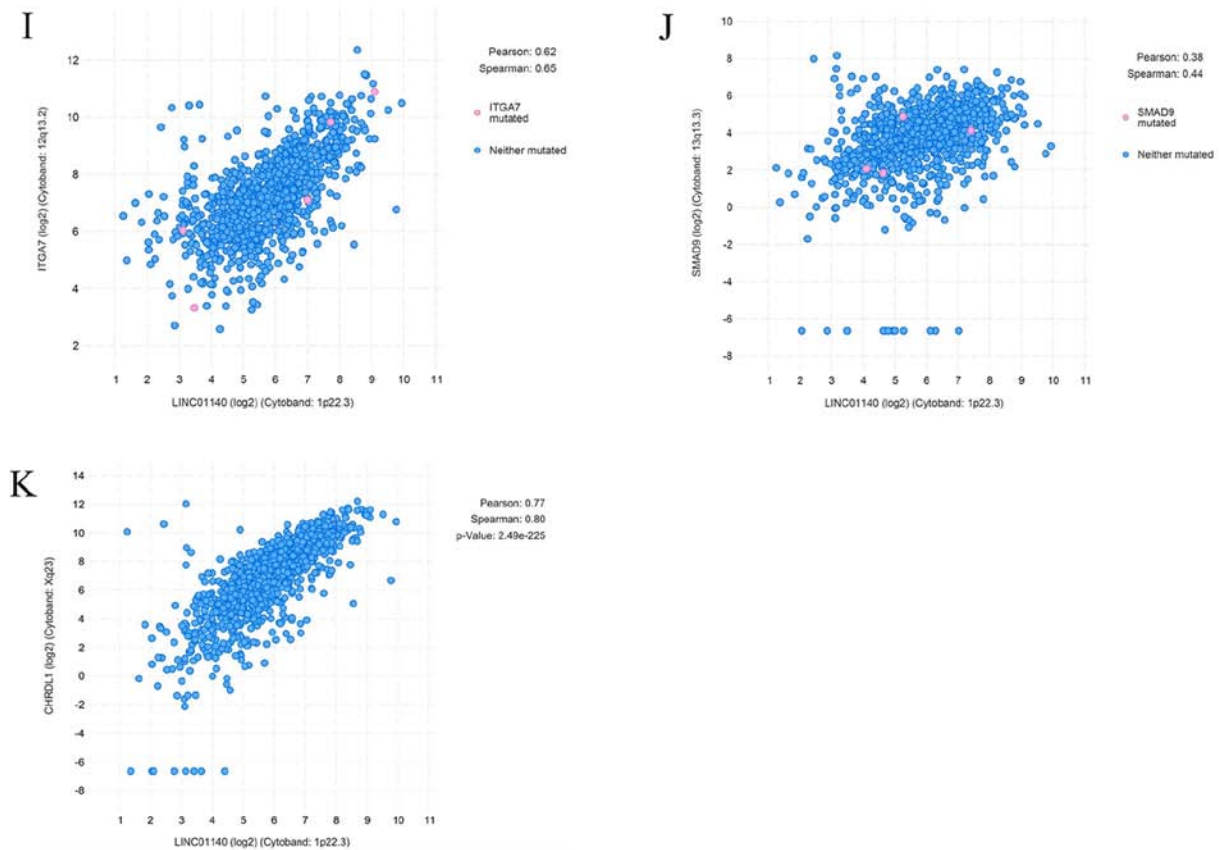


Figure 4. Continued. Plot showing the co-expression association between the LINC01140 and the abundance of genes in samples from the breast cancer study. These genes were co-expressed with LINC01140 expression. All the Pearson values are >0.30 . (I) *ITGA7*, (J) *SMAD9*, (K) *CHRDL1*. LINC01140, long intergenic non-protein coding RNA 01140; *TGFBR2*, transforming growth factor β receptor 2; *SNAI2*, snail family transcriptional repressor 2; *ZEB2*, zinc finger E-box binding homeobox 1; *TWIST2*, twist family bHLH transcription factor 2; *VIM*, vimentin; *CLDN5*, claudin 5; *TGFB1*, transforming growth factor β 1; *BMP6*, bone morphogenic protein 6; *ITGA7*, integrin subunit α 7; *SMAD9*, SMAD family member 9; *CHRDL1*, chordin like 1.

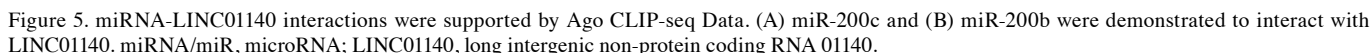
decreased in BC tissues compared with normal tissues ($P < 0.05$; Fig. 1B). The impact of the LINC01140 expression on RFS probability and BC was analyzed using a Kaplan-Meier plotter. The results revealed that in general, high LINC01140 expression predicts longer RFS probability in all patients with BC, including those with Basal-like, HER2-positive and Luminal-A and Luminal-B subtypes. While, low LINC01140 expression levels were associated with shorter RFS survival probability of patients with BC (Fig. 2), which is consistent with the fact that LINC01140 expression was decreased in BC compared with normal tissues.

Expression of LINC01140 is associated with T stages of patients with BC. The 825 patients with BC were divided into T1, T2, T3 and T4 stages according to tumor size. The detailed demographic of the patients with BC is presented in Table SI. It was revealed that LINC01140 expression was significantly decreased in T4 stage in the patients with BC when compared with T1, T2 or T3 stages ($P < 0.01$; Fig. 1C). Above all, it was demonstrated that higher LINC01140 expression was beneficial for patients with BC.

Potential biological pathways or processes that LINC01140 may be involved in. The present study also demonstrated that LINC01140 may be involved in a series of biological pathways, such as PAR1-mediated thrombin signaling events,

endothelins, proteoglycan syndecan-mediated signaling events, interferon- γ pathway, α 9 β 1 integrin signaling events, ErbB receptor signaling network, glypican 1 network, β 1 integrin cell surface interactions, integrin family cell surface interactions, plasma membrane estrogen receptor signaling, glypican pathway and particularly in the EMT (Fig. 3).

Results in Fig. 4 showed the correlation of each gene expression with LINC01140 expression, including *transforming growth factor β receptor 2* (*TGFBR2*; Pearson $r = 0.58$), *snail family transcriptional repressor 2* (*SNAI2*; Pearson $r = 0.37$), *zinc finger E-box binding homeobox 1* (*ZEB2*; Pearson $r = 0.53$), *twist family bHLH transcription factor 2* (*TWIST2*; Pearson $r = 0.52$), *vimentin* (*VIM*; Pearson $r = 0.52$), *claudin 5* (*CLDN5*; Pearson $r = 0.48$), *transforming growth factor β 1* (*TGFB1*; Pearson $r = 0.31$), *bone morphogenic protein 6* (*BMP6*; Pearson $r = 0.53$), *integrin subunit α 7* (*ITGA7*; Pearson $r = 0.62$), *SMAD family member 9* (*SMAD9*; Pearson $r = 0.38$) and *chordin like 1* (*CHRDL1*; Pearson $r = 0.77$). These genes were co-expressed with LINC01140 expression. The miRNA-LINC01140 interactions supported the Ago CLIP-seq Data. It was observed that miR-200c and miR-200b interacted with LINC01140 (Fig. 5). The competing endogenous RNA interaction network of LINC01140 in humans was also obtained through Ago CLIP-seq Data. LINC01140 and *PITX2* share miRNA families, such as miR-200c and miR-200b (Table I).



LINC01140 is located in chromosome 1p22.3 and is involved in regulating the transcription of genomic neighboring protein coding genes and long distance protein-coding genes in cis or in trans, respectively. A previous study evaluated the association between LINC01140 expression and survival outcome in patients with GC (9). A significant correlation between LINC01140 and overall survival was observed in patients with GC. Therefore, LINC01140 was combined to form a single prognostic signature in GC.

CHRD1 is a bone morphogenetic protein (BMP) inhibitor and is involved in modulating the activity of the BMP signaling pathway. The CHRD1 protein could competitively bind to BMPs and antagonize their function by the means of secreting into the extracellular space (19). BMPs were first identified for inducing ectopic bone formation and play an important role in morphogenesis during the development period. They are multifunctional growth factors that belong to the superfamily of transforming growth factor- β (TGF- β) (20). Cyr-Depauw *et al* (21) demonstrated that under decreased ShcA signaling conditions, *CHRD1* expression is upregulated in a large amount of breast cancer cells following TGF-stimulation. The authors also observed that CHRD1 plays a role as an inhibitor of BMP4-induced migration and invasion by the way of *in vitro* experiments. Furthermore, *CHRD1* expression is a favorable prognostic factor for patients with BC. Another study revealed a significant downregulation of *CHRD1* expression in GC tissues, which was associated with a low survival rate. A close association between low *CHRD1* expression and metastasis was observed through the clinical and pathological parameter. Furthermore, the authors revealed that downregulation of *CHRD1* promoted the proliferation and migration of tumor cells through the BMP receptor II. In addition, the authors confirmed that *CHRD1* is a tumor suppressor gene that inhibits tumor growth and metastasis (22).

Table I. The ceRNA interaction network of LINC01140 in humans.

ceRNA Gene ID	ceRNA name	ceRNA type	Gene ID	Gene name	Gene type	HitMitRnum	P-value	FDR	Pan-cancer
ENSG00000267272	LINC01140	LincRNA	ENSG00000164093	<i>PITX2</i>	Protein coding	4	2.103x10 ⁻⁴	1.051x10 ⁻³	18
ENSG00000267272	LINC01140	LincRNA	ENSG00000085433	<i>WDR47</i>	Protein coding	5	2.801x10 ⁻⁴	1.051x10 ⁻³	26
ENSG00000267272	LINC01140	LincRNA	ENSG00000176401	<i>EID28</i>	Protein coding	4	4.767x10 ⁻⁴	1.051x10 ⁻³	17
ENSG00000267272	LINC01140	LincRNA	ENSG00000172260	<i>NEGR1</i>	Protein coding	5	5.257x10 ⁻⁴	1.051x10 ⁻³	21
ENSG00000267272	LINC01140	LincRNA	ENSG00000164609	<i>SLU7</i>	Protein coding	5	6.490x10 ⁻⁴	1.051x10 ⁻³	15

LINC01140 and *PITX2* share miRNA families, especially, such as miR-200c and miR-200b. This table presents the ceRNA networks from thousands of interactions of miRNA-targets supported by CLIP-seq data. The results could be examined by P-value and FDR. The ceRNA gene selected was LINC01140. The cut-off for common miRNA family numbers was 2. The cut-off for the P-value was <0.01. The cut-off for FDR was set at 0.01. Explore the ceRNA networks with Pan-Cancer analysis: 5. miR/miRNA, microRNA; ceRNA, competing endogenous RNA; FDR, False Discovery Rate; LINC01140, long intergenic non-protein coding RNA 01140.

BMP6 is closely associated with tumor differentiation and bone metastasis (23). Hamdy *et al* (24) revealed that *BMP6* expression in primary malignant cancer was closely associated with bone metastasis. The result implied that BMP6 may be partly responsible for osteoblastic changes in prostate cancer secondary metastases. Taking previous studies into consideration, it can be confirmed that patients with ER+ BC are more likely to develop bone metastasis. These results confirmed that BMP6 plays a vital role in the development of ER+ BC bone metastasis (23-25).

Further analyses observed that miR-200b and miR-200c interacted with LINC01140. The miR-200 family consists of five members in humans. One cluster comprised of miR-200b, miR-200a and miR-429 on the chromosome one, while another cluster included two members, miR-200c and miR-141, which were located on chromosome 12. During tumorigenesis and development, the miR-200 family could regulate cell viability, cell division, cell cycle progression, differentiation, apoptosis, self-renewal, reversal of chemotherapy resistance and EMT (26). Abnormal expression of the miR-200 family is associated with the occurrence and development of BC (27,28). A study by Yang *et al* (29) demonstrated that the miR200 family is actively associated with the EMT through targeting and inhibiting the expression of genes, such as *ZEB1*, *ZEB2*, β -catenin/Wnt signaling, while a number of transcription factors, including Snail, Slug, ZEB-1, ZEB-2 and Twist1, are associated with tumor invasion and metastasis. Therefore, LINC01140 may interact with miR-200 according to the prediction results of the database.

In conclusion, LINC01140 expression was observed to be lower in individuals with BC. In general, its expression was associated with the probability of RFS. High LINC01140 predicts longer RFS probability of patients with BC. LINC01140 plays an important role in the development and progression of BC. Further studies are required in order to elucidate the underlying molecular mechanisms. The present study provides the foundations for investigating the underlying molecular mechanism of LINC01140 in the development and progression of BC.

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Availability of data and materials

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

Authors' contributions

YC and XC participated in the conception and design of the study. DL and LL analyzed and interpreted the data. DL and LL drafted the manuscript, and YC and XC edited it critically. All authors gave final approval of the version to be published.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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