Basic research

Identification of differentially expressed profiles of lncRNAs and mRNAs in ER-negative and HER-2 positive breast cancer

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Abstract

Introduction: Breast cancer is one of the most common malignant tumors in the United States. However, the molecular mechanism involved in the progression of breast cancer has remained unclear. Long non-coding RNAs (lncRNA) have been reported as key regulators in the progression and metastasis of cancer.
Material and methods: In this study, we identified significantly differentially expressed mRNAs and lncRNAs in breast cancer using the GSE70947 dataset. Gene ontology (GO) and KEGG pathway was used to explore the key roles of differentially expressed lncRNAs in breast cancer. The dysregulated lncRNAs and mRNAs expression profiles in HER2-positive and ER-negative breast cancer were also analyzed in this study.
Results: Our results showed that PVT1, LOC145837, FLJ40504 and FLJ45983 were significantly decreased in HER2-positive and ER-negative breast cancers. We also constructed the PVT1, LOC145837, FLJ40504 and FLJ45983 mediated cRNA networks in HER2-positive and ER-negative breast cancers. Moreover, using the Betastasis dataset, we found that high PVT1 expression levels were associated with a lower survival rate in breast cancer patients.
Conclusions: These results elucidate the functions of lncRNAs and provide useful information for exploring therapeutic candidate targets and new molecular biomarkers for ER-negative and HER-2 enriched subtype breast cancer.

Key words: long non-coding RNA, ER-negative, ceRNA networks, HER-2 positive, breast cancer.

Introduction

Breast cancer (BC) is one of the most common malignant tumors, with more than 200,000 newly diagnosed cases in the United States per year [1, 2]. According to Prat *et al.*, the estrogen receptor (ER) was overexpressed in nearly 70% of breast cancer cases [3]. Of note, the molecular subtypes of ER are the main indicator of anti-hormonal therapy for breast cancer [4]. Moreover, ER-negative (ER-) BC exhibited dismal survival rates due to the highly aggressive and metastatic behavior [5, 6]. HER2, also known as HER2/neu and ERBB2, was found to be overexpressed in about 20–30% of early-stage breast cancer cases [7]. A wealth of evidence has shown that HER-2-positive breast cancer is associated

with a more aggressive phenotype and shorter survival time [8]. However, how HER2 and ER dysregulation in breast cancer effect the progression of breast cancer remains unclear [9].

Previous reports had shown that non-coding RNAs (ncRNAs) acted as key regulators in the progression and metastasis of cancer [10, 11]. The best characterized ncRNAs is microRNAs (miRNAs). miRNAs are a class of small ncRNAs and mediate the post-transcriptional regulation of gene expression [12]. Recently, more and more researchers have paid attention to the long non-coding RNAs (lncRNAs). Increasingly reports have shown that lncRNAs can regulate expression of protein-coding genes through transcriptional, post-transcriptional and post-translational regulation [13].

Lately, several reports have also shown that altered expression of lncRNAs also played important roles in regulating breast cancer progression. MALAT1 was up-regulated in multiple human malignancies. In breast cancer, MALAT1 interacted with the estrogen receptor and predicted poor survival. Lin *et al*. also reported that LINK-A lncRNA activates HIF1α signaling to promote breast cancer glycolysis reprogramming and tumorigenesis in triple-negative breast cancer [14]. In 2016, Niknafs *et al*. identified a cohort of breast cancer-associated and estrogen-regulated lncRNAs and demonstrate that DSCAM-AS1 mediates tumorous progression and tamoxifen resistance [15]. However, few studies have focused on the dysregulation of lncRNAs in the HER-2-enriched and ER-negative subtype breast cancer.

In this study, we aimed to identify differentially expressed lncRNAs and mRNAs in breast cancer by analyzing previously published datasets. To understand the biological roles of these differently expressed genes, we performed GO and KEGG analysis to explore the potential roles of dysregulating lncRNAs. We also conducted a bioinformatic analysis to identify the lncRNA-miRNA-mRNA regulatory axis in breast cancer. We hope that our work will be useful to identify candidate therapeutic targets and new molecular biomarkers for HER-2-enriched and ER-negative subtype breast cancer.

Material and methods

Microarray data and data preprocessing

Microarray data were downloaded from the study by Quigley DA, which was referenced in the Gene Expression Omnibus (GEO) database (www.ncbi.nlm.nih.gov/geo/) under accession number GSE70947. In this dataset, expression profiles were obtained from 81 biopsies obtained from 41 patients diagnosed with follicular lymphoma by using Affymetrix HG U133 Plus 2.0 Gene Chip. mRNAs having fold changes ≥ 2 and *p*-values < 0.05 were selected as of significantly differential expression.

LncRNA classification pipeline

To evaluate the lncRNA expressions in microarray data, we applied a pipeline described by Zhang *et al*. [16] to identify the probe sets uniquely mapped to lncRNAs from the Affymetrix array by using the following criteria. For the probe sets with Refseq IDs, we retained those labeled as "NR_" (NR indicates non-coding RNA in the Refseq database). For the probe sets with Ensembl gene IDs, we retained those annotated with "lncRNA", "processed transcripts", "non-coding" or "misc_RNA" in Ensembl annotations. Then, we filtered the probe sets obtained from last step by filtering out pseudogenes, rRNAs, microRNAs, tRNAs, snRNAs and snoRNAs. Finally, we obtained 2448 annotated lncRNA transcripts with corresponding Affymetrix probe IDs.

LncRNAs having fold changes ≥ 2 and *p*-values < 0.05 were selected as of significantly differential expression.

Functional group analysis

GO analysis and KEGG analysis were applied to determine the biological roles of these differentially expressed mRNAs, based on the freely available online MAS system provided by the CapitalBio company (Molecule Annotation System, http://bioinfo.capitalbio.com/mas3/). The *p*-value (hypergeometric *p*-value) denoted the significance of the pathway correlated to the conditions. The recommend *p*-value cut-off is 0.05.

Hierarchical clustering analysis

To generate an overview of lncRNA and mRNA expression profiles between the FL and DLBCL, hierarchical clustering analysis was performed based on the expression value.

PPI network and module analysis

The interaction relationships of the proteins encoded by DEGs were searched by STRING online software [17], and the combined score > 0.4 was used as the cut-off criterion. The PPI network was visualized using Cytoscape software [18]. Then, modules of the PPI network were screened by CFinder software [19], and the parameter k was set to 6.

Statistical analysis

The numerical data were presented as mean ± standard deviation (SD) of at least three determinations. Statistical comparisons between groups

of normalized data were performed using the *t*-test or Mann-Whitney *U*-test according to the test condition. Values of $p < 0.05$ were considered statistically significant with a 95% confidence level.

Results

Comprehensive analysis of significant differential expression of mRNAs and lncRNAs in breast cancer

To identify significant differential expression of mRNAs and lncRNAs in breast cancer, we analyzed a publicly available gene expression dataset, GSE70947. The GSE70947 database includes 148 paired breast cancer samples. Genes with FC > 2 for both up- or down-regulation and a *p*-value < 0.05 were identified as significantly differentially expressed. Compared to the normal breast tissues, a total of 1,382 lncRNAs displayed differential expression in tumor tissues, including 23 upregulated lncRNAs and 57 downregulated lncRNAs (Figure 1 B). We found 4248 differently expressed mRNAs, of which 2094 were upregulated and 2153 were downregulated (Figure 1 A). Hierarchical clustering showed systematic variations in the expression of lncRNAs and mRNAs in the breast cancer samples.

GO and KEGG analysis of differentially expressed mRNAs

To determine the potential roles of differentially expressed mRNAs, we performed GO and KEGG pathway analysis using mas3.0. GO analysis showed that the dysregulated genes were mainly involved in regulating signal transduction, development, regulation of transcription, oxidation reduction, cell adhesion and the cell cycle (Figure 1 C). Meanwhile, KEGG pathway analysis revealed that dysregulated genes were primarily enriched in pathways associated with the MAPK signaling pathway, insulin signaling pathway, and Jak-STAT signaling pathway (Figure 1 D).

GO and KEGG analysis of differentially expressed lncRNAs

To predict the functions of the differentially expressed lncRNAs, we adopted methods as described by Guttman and Rinn [20] and Shen *et al.* [21]. We first constructed co-expression networks to identify the correlation between differentially expressed mRNAs and lncRNAs by using GSE70947. Next, we performed GO and KEGG pathway analysis for each given lncRNA by using the set of co-expressed mRNAs. In this study, the top 50 related mRNAs of each lncRNA were classified according to GO terms. According to the KEGG pathway analysis, dysregulated lncRNAs were primarily enriched in pathways associated with the insulin signaling pathway, MAPK signaling pathway, PPAR signaling pathway and adipocytokine signaling pathway (Figure 1 F). GO analysis revealed that the dysregulated lncRNAs were enriched in signal transduction, cell adhesion, cell cycle, mitosis, and cell division (Figure 1 E).

Identification of key mRNAs and lncRNAs involved in ER-negative breast cancer

To investigate differences in the expression of mRNAs and lncRNAs between ER-negative and ER-positive breast cancer, we analyzed the GSE70947 database. We found that 162 mRNA transcripts were up-regulated and 812 mRNA transcripts were down-regulated in ER-negative samples compared to the ER-positive samples (Figure 2 A). Of note, we identified 10 dysregulated lncRNAs in ER-negative breast cancer. C21orf81, PVT1, NBPF22P, PP14571, CYP4Z2P, FLJ40504, LOC440335, LOC145837, and FLJ45983 were down-regulated and LOC375196 was up-regulated in ER-negative samples (Figure 2B).

Functional analysis of lncRNA-associated PPI modules in ER-negative breast cancer

We identified a series of dysregulated lncRNAs, including C21orf81, PVT1, NBPF22P, PP14571, CYP4Z2P, FLJ40504, LOC440335, LOC145837, FLJ45983 and LOC375196, in ER-negative breast cancer. Next, we analyzed co-expressed mRNAs of these lncRNAs and examined whether the mRNAs were connected by PPIs.

Based on the information in the STRING database, we first constructed a protein-protein interaction network in the ER-negative breast cancer. The PPI network of the DEGs had 8 nodes comprising ERBB3, KRT8, KRT19, MYB, GATA3, XBP1, FOXA1 and ESR1 (Figure 2 C). Among these genes, ESR1 showed the highest node degree, which was 9.

By analyzing co-expressed mRNAs, we found that these lncRNAs were associated with regulation of transcription, response to estrogen stimulus, tumor necrosis factor-mediated signaling pathway, negative regulation of cell growth, negative regulation of cell adhesion, interspecies interaction between organisms and cell-cell signaling (Figure 3 A).

Identification of key mRNAs and lncRNAs involved in HER2-positive breast cancer

In this study, we also identified differentially expressed mRNAs and lncRNAs between HER2-negative and HER2-positive breast cancer. A total of 373 mRNA transcripts were found to be down-regulated and 137 mRNA transcripts were

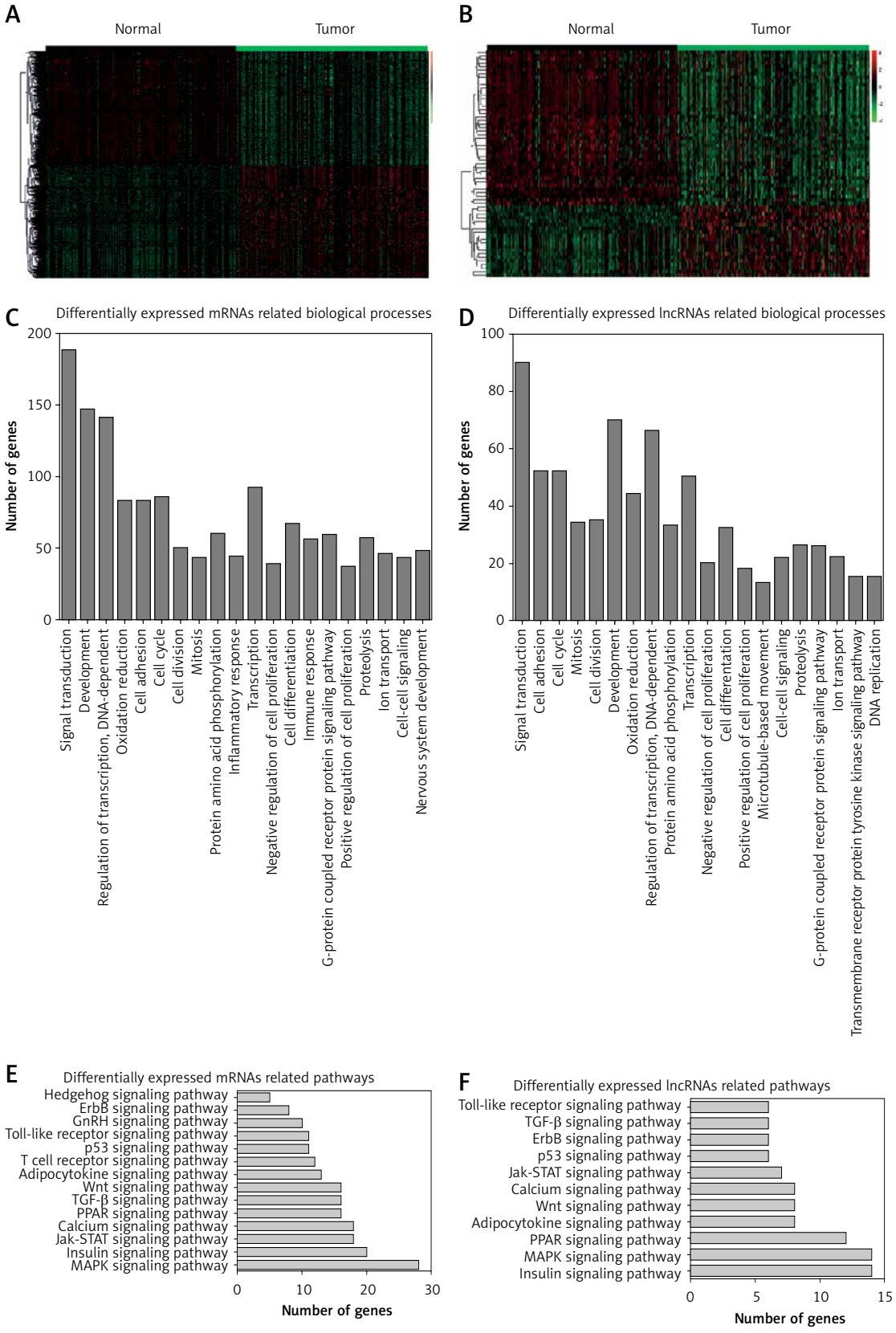

Figure 1. GO and KEGG analysis of differentially expressed mRNAs and lncRNAs in breast cancer. Differentially expressed mRNAs (**A**) and lncRNAs (**B**) in breast cancer patient tumors versus adjacent matched normal tissue obtained from GSE70947 are represented by heatmaps. GO (**C**) and KEGG (**D**) pathway analysis of the dysregulated mRNAs. GO (**E**) and KEGG (**F**) analysis of the dysregulated lncRNAs

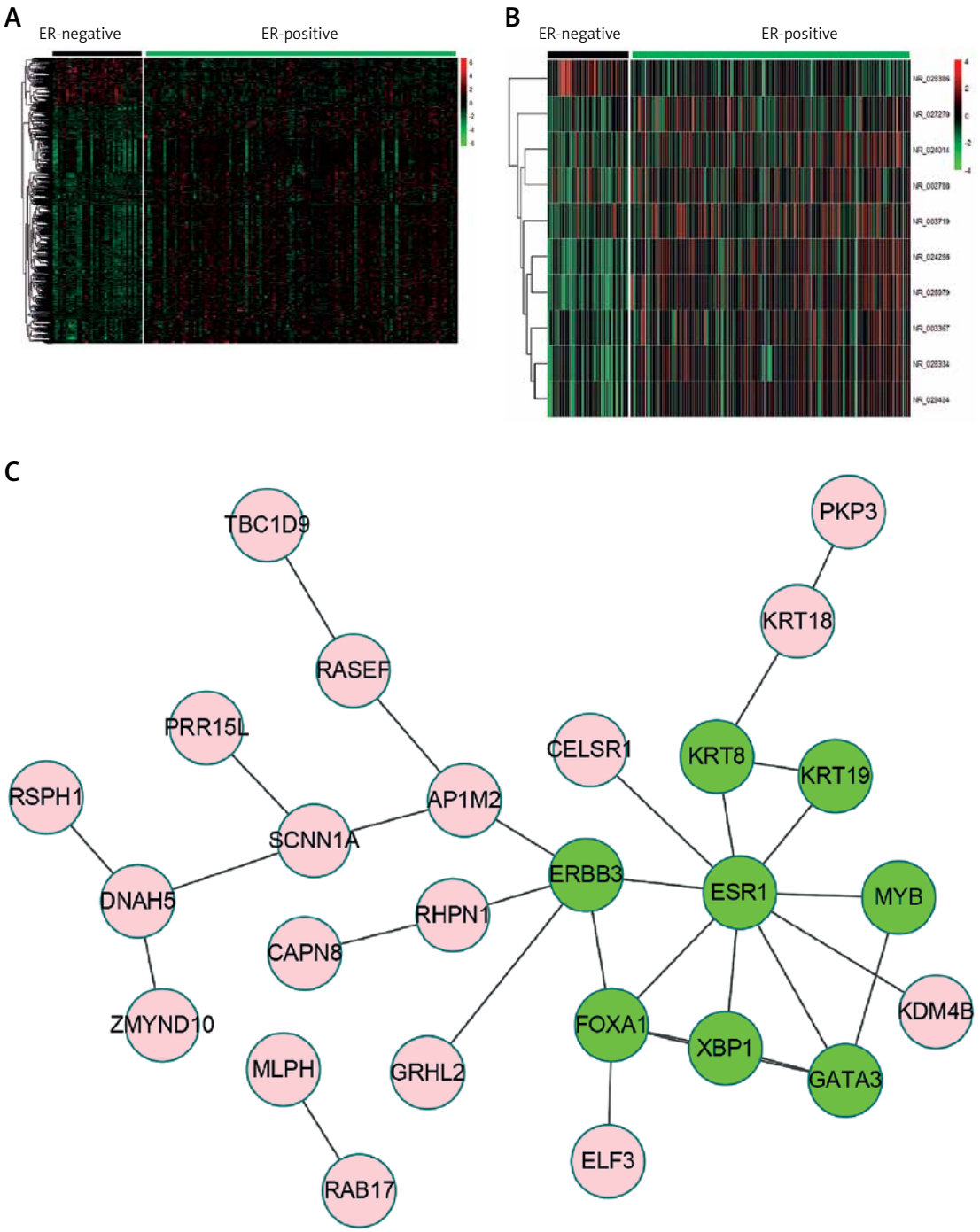

Figure 2. Functional analysis of lncRNA-associated PPI modules in ER-negative breast cancer. Identification of key mRNAs (**A**) and lncRNAs (**B**) in ER-negative breast cancer. **C** – PPI network for the proteins encoded by the DEGs in ER-negative breast cancer

found to be induced in HER2-positive samples compared to the HER2-negative samples (Figure 4 A). Ten lncRNAs – FLJ45983, LOC440335, NEURL3, C9orf122, FLJ40504, LOC145837, PVT1, NCRNA00173, EGOT, and LOC283867 – were down-regulated in HER2-positive samples. Interestingly, we did not find down-regulated lncRNAs in HER2-positive samples (Figure 4 B).

Functional analysis of lncRNA-associated PPI modules in HER2-positive breast cancer

The PPI network of the DEGs in HER2-positive breast cancer had 17 nodes including ERBB3, MUC1, FOXA1, CDH1, MMP3, GATA3 and MYB. FLJ45983, LOC440335, NEURL3, C9orf122, FLJ40504, LOC145837, PVT1, NCRNA00173, EGOT, and LOC283867 were found to be down-regulated in

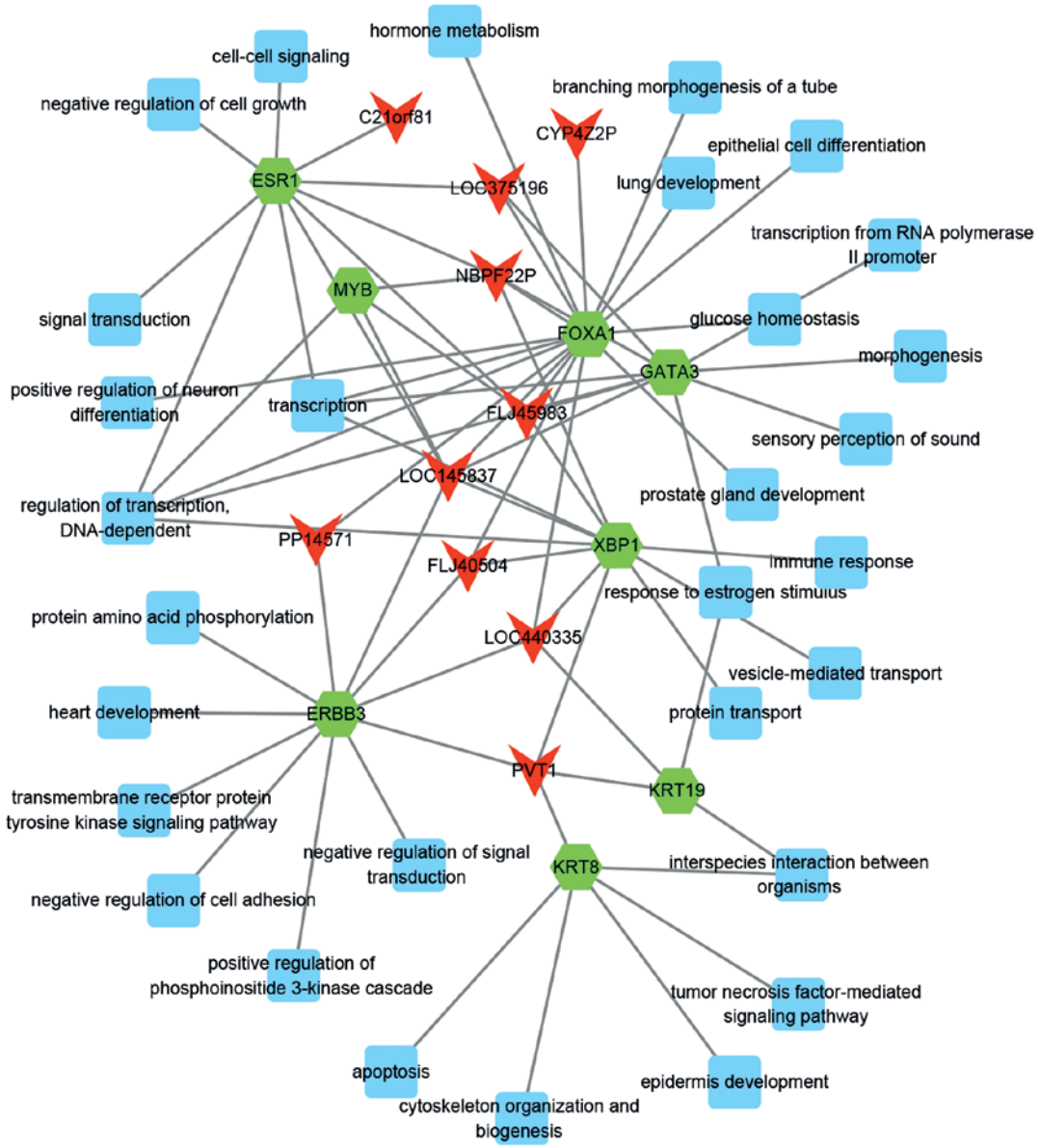

Figure 3. Functional analysis of lncRNA-associated PPI modules in ER-negative breast cancer

HER2-positive breast cancer (Figure 4 C). By analyzing co-expressed mRNAs of each lncRNA, we found that these lncRNAs were associated with collagen catabolism, the estrogen receptor signaling pathway, glucose homeostasis, hormone metabolism, negative regulation of cell adhesion, positive regulation of neuron differentiation, the response to estrogen stimulus and regulation of cell proliferation (Figure 5).

Construction of the PVT1, LOC145837, FLJ40504 and FLJ45983 mediated ceRNA networks in HER2-positive and ER-negative breast cancers

In this study, analysis of the GSE70947 database showed that PVT1, LOC145837, FLJ40504 and FLJ45983 were significantly decreased in HER2-positive (Figure 6 A) and ER-negative breast cancers (Figure 7 A). To explore the molecular mechanisms involved in these lncRNAs regulating breast cancer progression, we constructed lncRNA-miRNA-mRNA ceRNA networks based on our analysis.

First, we constructed a co-expression network based on correlation analysis between the differentially expressed lncRNAs and mRNAs. The lncRNA–mRNA interaction was integrated into the co-expression networks according to the positive regulation and only gene pairs with $|R| > 0.7$ were selected. We next predicted the interactions between differentially expressed lncRNAs and their target miRNAs theoretically by using miRcode

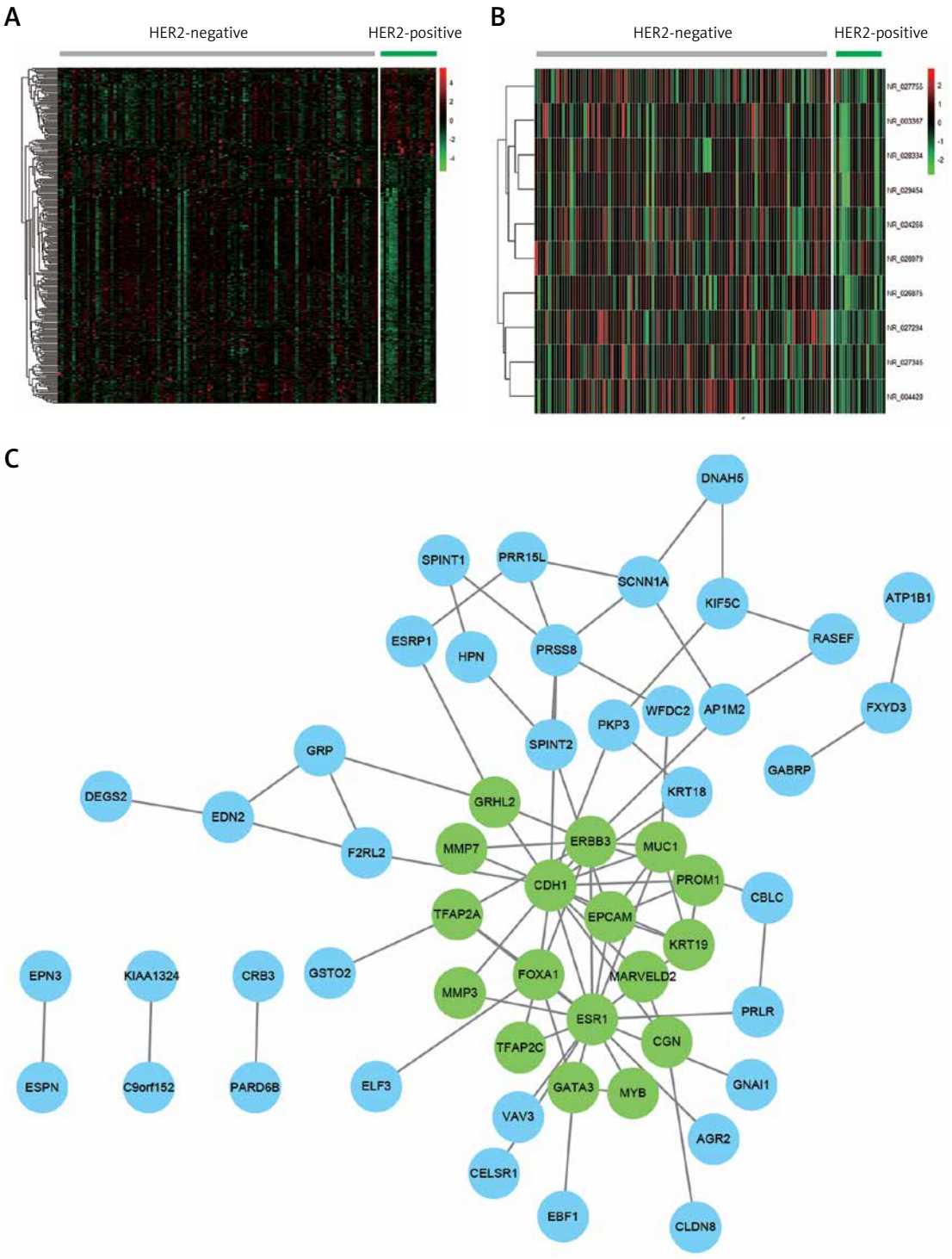

Figure 4. Functional analysis of lncRNA-associated PPI modules in HER2-positive breast cancer. Identification of key mRNAs (**A**) and lncRNAs (**B**) in HER2-positive breast cancer. **C** – PPI network for the proteins encoded by the DEGs in HER2-positive breast cancer

[21]. Finally, TargetScan [22] and StarBase databases were both used to identify miRNAs which suppress mRNAs. The networks were drawn using Cytoscape 3.0.

The ceRNA network in the ER-negative breast cancer tumor group comprised 4 lncRNAs, 32 miRNAs, and 29 mRNAs (Figure 7 B). The ceRNA network in the HER2-positive breast cancer tumor group comprised 4 lncRNAs, 28 miRNAs, and 27 mRNAs (Figure 6 B). Our results showed that PVT1 played the most important roles. The networks were drawn using Cytoscape 3.0.

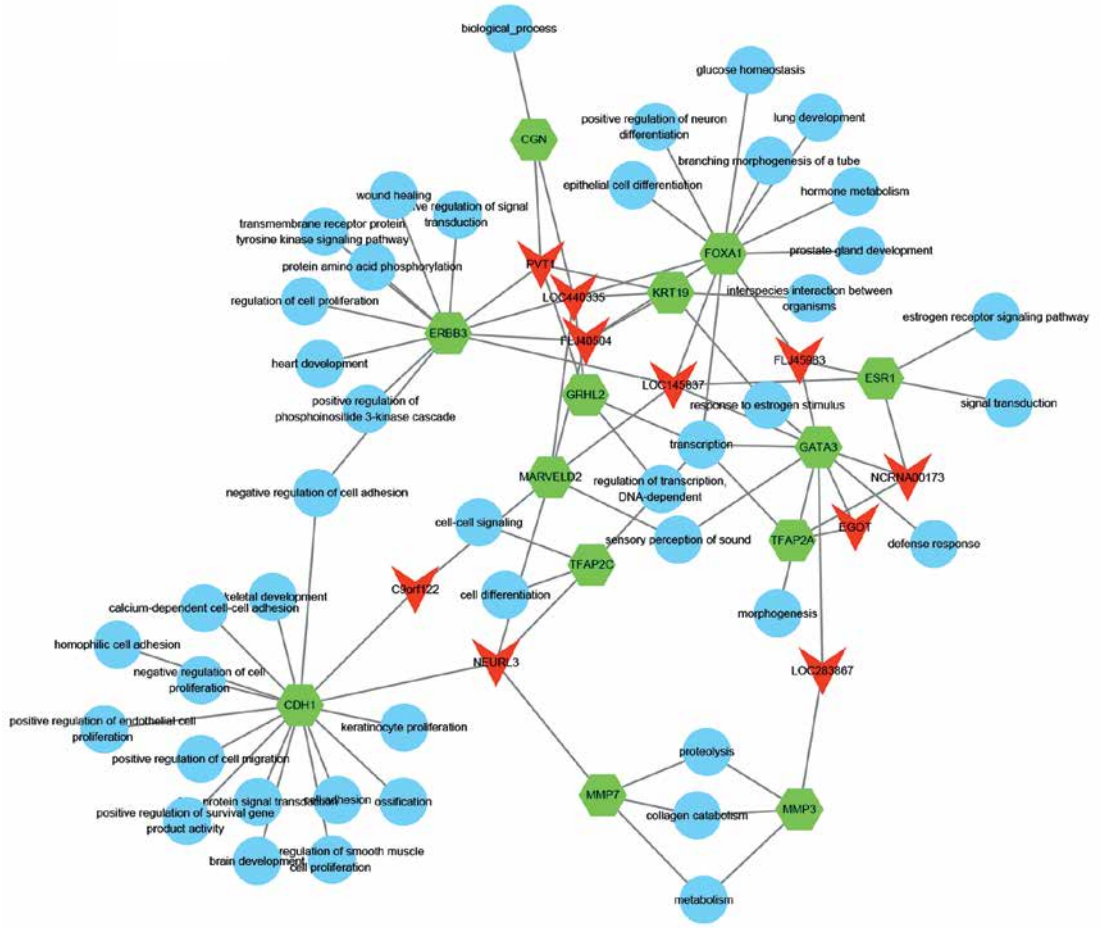

Figure 5. Functional analysis of lncRNA-associated PPI modules in HER2-positive breast cancer

Alterations of lncRNAs expression and prognosis in breast cancer

To evaluate the possible prognostic value of PVT1, LOC145837, FLJ40504 and FLJ45983, we analyzed the other dataset which was downloaded from Betastasis (http://www.betastasis.com/). Expression levels of three lncRNA (PVT1, LOC145837, FLJ40504) with survival data were included in this dataset. As shown in Figures 8 A–C, Kaplan-Meier analysis showed that patients with high PVT1 expression levels had decreased overall survival compared to those with low PVT1 levels (p = 0.045). However, we found that the expression levels of LOC145837 and FLJ40504 were not associated with survival status of breast cancer patients.

We also combined PVT1 expression and ER status to stratify the possibility of breast cancer survival. We found that high PVT1 expression levels were also associated with a lower survival rate in both ER-negative and ER-positive patients (Figures 8 D–E). These results suggested that PVT1 may act as an oncogene in breast cancer, which was consistent with previous reports [23].

Discussion

Breast cancer is one of the most common malignant tumors in the United States [24]. However, the molecular mechanism involved in the progression of breast cancer has remained unclear. Recently studies have shown that lncRNAs play key roles in tumorigenesis, cancer progression, and metastasis [1]. Therefore, it was critically important to investigate the potential roles of lncRNAs in breast cancer. In the present study, we analyzed the GSE70947 database and identified 23 upregulated LncRNAs and 57 downregulated LncRNAs in breast cancer compared to normal breast tissues. We also found 4248 differently expressed mRNAs, of which 2094 were upregulated and 2153 were downregulated.

Recently, several reports have shown that some lncRNAs play important roles in regulating breast cancer progression. For example, MALAT1 interacted with the estrogen receptor and was associated with a poor survival rate [22]. Lin *et al.* also reported that LINK-A lncRNA activates HIF1α signaling to promote breast cancer glycolysis reprogramming and tumorigenesis in triple-negative breast cancer [2, 25]. In 2016, Niknafs *et al.*

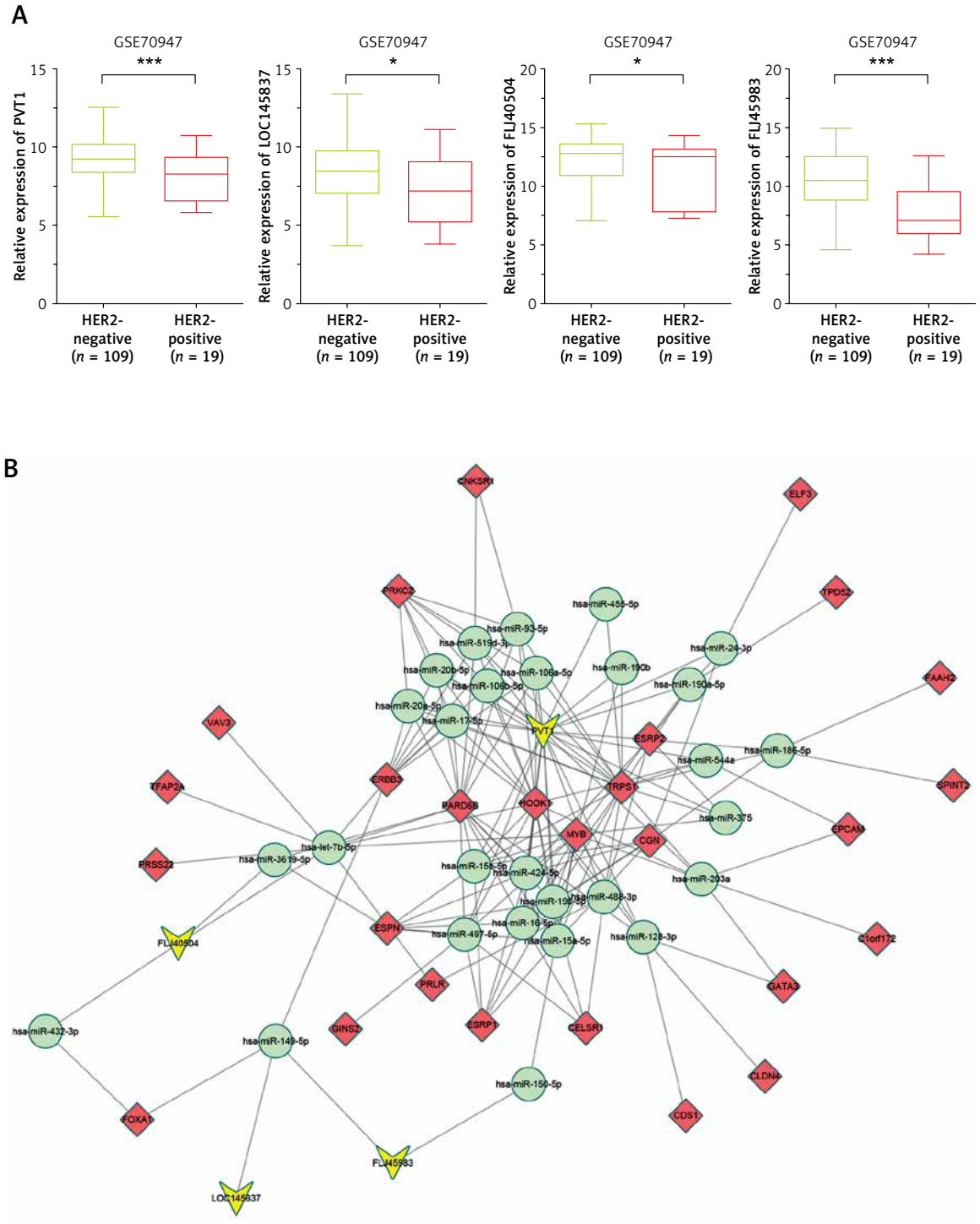

Figure 6. Construction of the PVT1, LOC145837, FLJ40504 and FLJ45983 mediated ceRNA networks in ER-negative breast cancers. **A** – PVT1, LOC145837, FLJ40504 and FLJ45983 expression levels in ER-negative breast cancers compared to ER-positive breast cancers in publicly available gene expression data GSE70947. **B** – PVT1, LOC145837, FLJ40504 and FLJ45983 mediated ceRNA networks in ER-negative breast cancers

identified a cohort of breast cancer-associated and estrogen-regulated lncRNAs and demonstrated that DSCAM-AS1 mediates tumor progression and tamoxifen resistance [15]. In this study, to predict the functions of the differentially expressed lncRNAs, we first constructed co-expression networks and we performed GO and KEGG analysis for each given lncRNA by using the set of co-expressed mRNAs. According to the KEGG pathway analysis, dysregulated lncRNAs were primarily enriched in pathways associated with the insulin signaling pathway, MAPK signaling pathway, PPAR signaling pathway and adipocytokine signaling pathway. GO analysis revealed that the

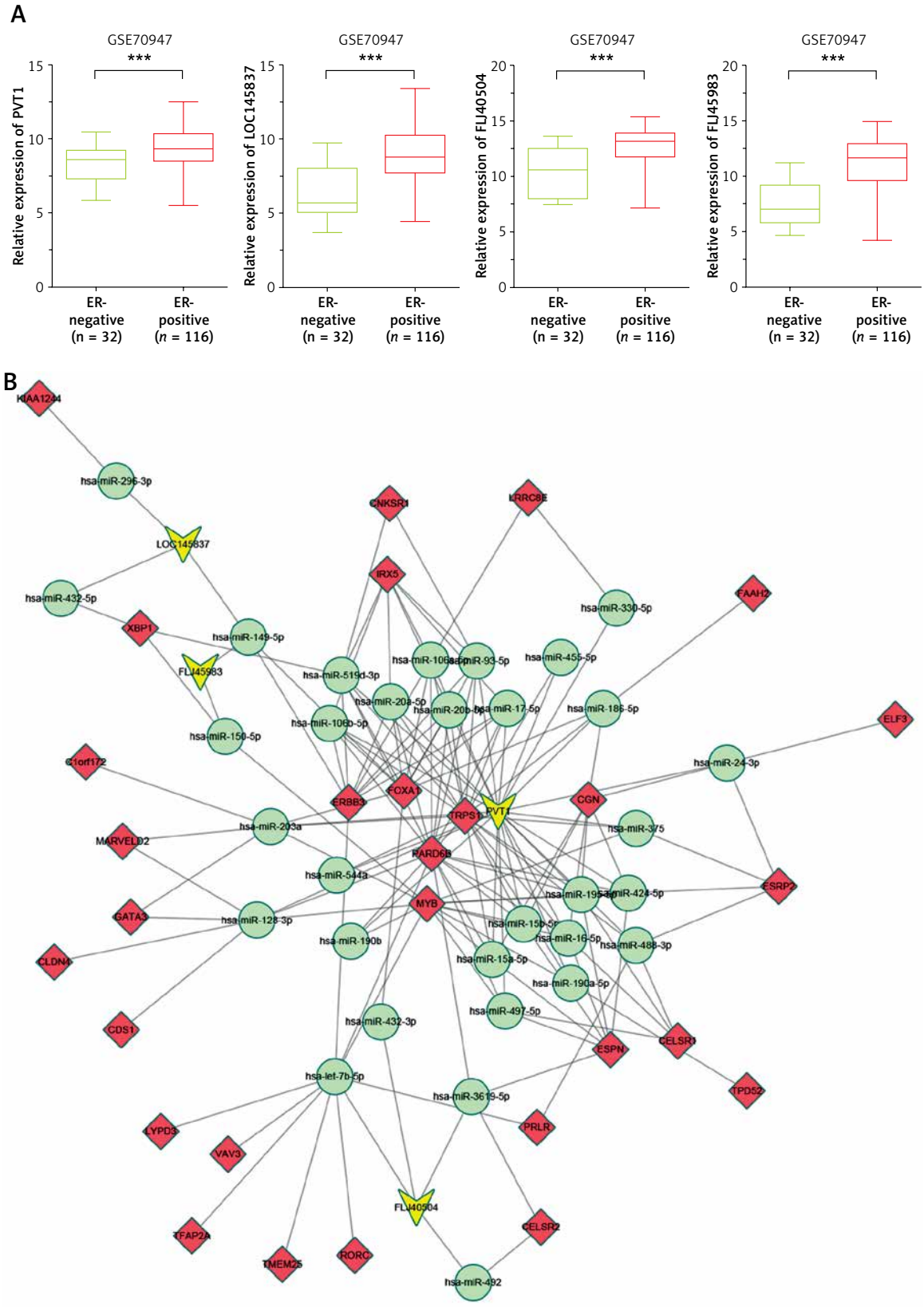

Figure 7. Construction of the PVT1, LOC145837, FLJ40504 and FLJ45983 mediated ceRNA networks in HER2-positive breast cancers. **A** – PVT1, LOC145837, FLJ40504 and FLJ45983 expression levels in HER2-positive breast cancers compared to HER2-negative breast cancers in publicly available gene expression dataset GSE70947. **B** – PVT1, LOC145837, FLJ40504 and FLJ45983 mediated ceRNA networks in HER2-positive breast cancers

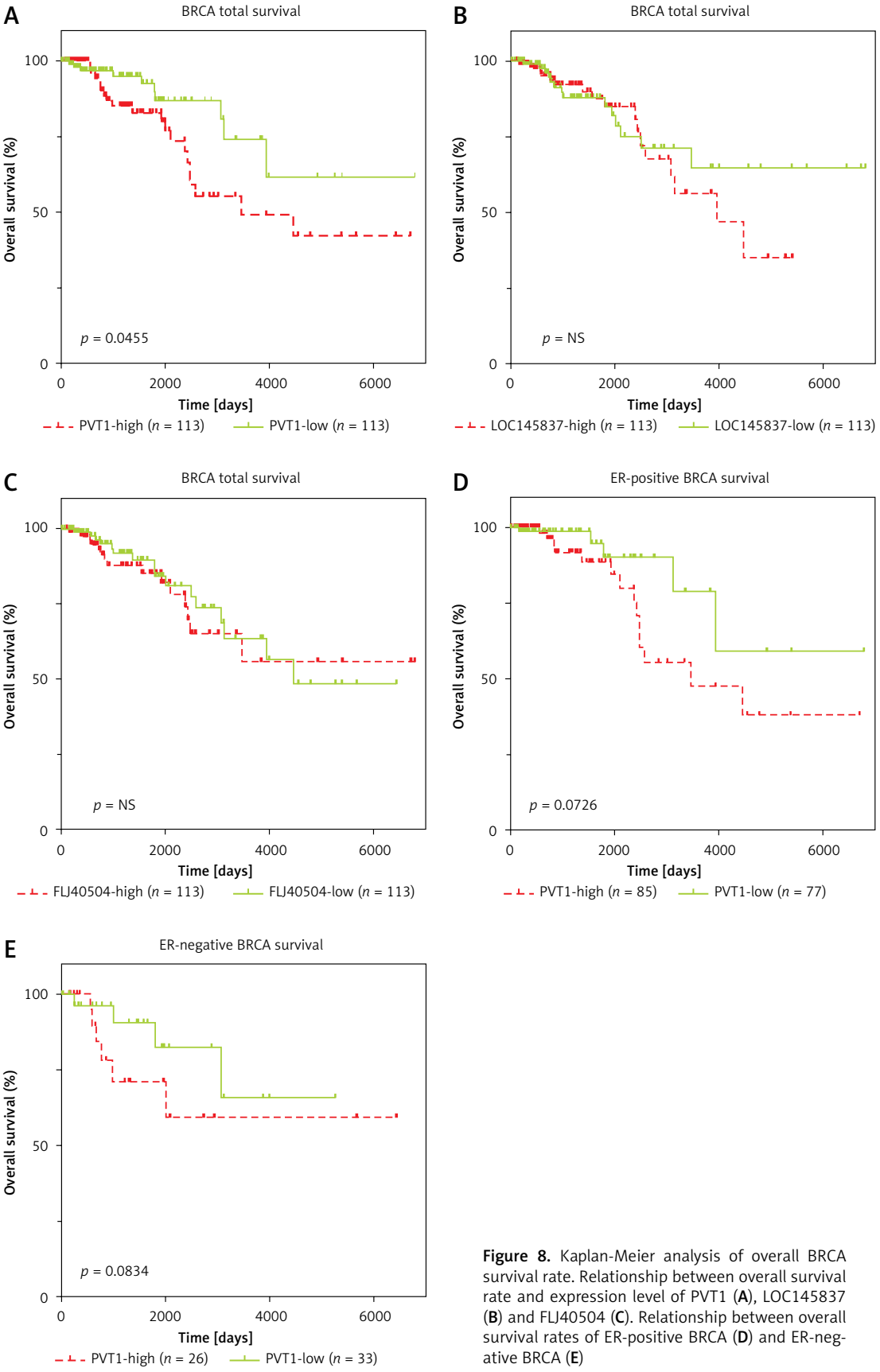

Figure 8. Kaplan-Meier analysis of overall BRCA survival rate. Relationship between overall survival rate and expression level of PVT1 (**A**), LOC145837 (**B**) and FLJ40504 (**C**). Relationship between overall survival rates of ER-positive BRCA (**D**) and ER-negative BRCA (**E**)

dysregulated lncRNAs were enriched in signal transduction, cell adhesion, cell cycle, mitosis, and cell division.

The estrogen receptor (ER) was overexpressed in nearly 70% of breast cancer cases [15]. The molecular subtypes of ER have been the main indicator of anti-hormonal therapy for breast cancer [26]. Moreover, ER-negative (ER-) BC exhibited dismal survival rates due to the highly aggressive and metastatic behavior. However, how ER leads to uncontrolled cell proliferation of breast cancer is yet to be fully understood [27, 28]. Moreover, few studies have focused on the dysregulation of lncRNAs in the ER-negative subtype breast cancer. In this study, by analyzing GSE70947, we found that C21orf81, PVT1, NBPF22P, PP14571, CYP4Z2P, FLJ40504, LOC440335, LOC145837, FLJ45983 were down-regulated and LOC375196 was up-regulated in ER-negative samples. Functional analysis of lncRNA-associated PPI modules in ER-negative breast cancer showed that these lncRNAs were associated with regulation of transcription, the response to estrogen stimulus, the tumor necrosis factor-mediated signaling pathway, negative regulation of cell growth, negative regulation of cell adhesion, interspecies interaction between organisms and cell-cell signaling.

Previous studies had shown that HER-2-positive breast cancer was more aggressive and had a shorter survival time [29]. In this study, by analyzing GSE70947, we found that FLJ45983, LOC440335, NEURL3, C9orf122, FLJ40504, LOC145837, PVT1, NCRNA00173, EGOT, and LOC283867 were down-regulated in HER2-positive samples. Functional analysis of lncRNA-associated PPI modules in HER2-positive breast cancer showed that these lncRNAs were associated with collagen catabolism, the estrogen receptor signaling pathway, glucose homeostasis, hormone metabolism, negative regulation of cell adhesion, positive regulation of neuron differentiation, the response to estrogen stimulus and regulation of cell proliferation.

Of note, analysis of the GSE70947 database showed that PVT1, LOC145837, FLJ40504 and FLJ45983 were significantly decreased in HER2-positive and ER-negative breast cancers. To explore the molecular mechanisms involved in these lncRNAs regulating HER2-positive and ER-negative breast cancer progression, we constructed lncRNA-miRNA-mRNA ceRNA networks based on our analysis. Our results showed that PVT1 played the most important roles. PVT1 was reported as an oncogene in different kinds of cancer, including non-small cell lung cancer [30] and breast cancer. However, whether PVT1 could act as a biomarker for breast cancer remains unknown. Here, we analyzed the Betastasis dataset and found that high PVT1 expression levels were associated with a lower survival rate in breast cancer patients.

Conclusions

We identified the significantly differentially expressed mRNAs and lncRNAs in breast cancer by using GSE70947. GO and KEGG pathway analysis showed that differentially expressed lncRNAs played key roles in regulating signal transduction, cell adhesion, the cell cycle, the insulin signaling pathway and the MAPK signaling pathway. The dysregulated lncRNA and mRNA expression profiles in HER2-positive and ER-negative breast cancer were also analyzed in this study. We also constructed the PVT1, LOC145837, FLJ40504 and FLJ45983 mediated ceRNA networks in HER2-positive and ER-negative breast cancers. Moreover, using the Betastasis dataset, we found that high PVT1 expression levels were associated with a lower survival rate in breast cancer patients. These results elucidate the functions of lncRNAs and provide useful information for exploring candidate therapeutic targets and new molecular biomarkers for ER-negative and HER-2 enriched subtype breast cancer.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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