Analysis of key genes and pathways in breast ductal carcinoma *in situ*

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Abstract. Breast cancer (BC) remains the most common cancer in females. Therefore, the present study aimed to identify key genes involved in the carcinogenesis of BC and to explore their prognostic values by integrating bioinformatics tools. The gene expression profiles of 46 ductal carcinoma *in situ* (DCIS) and three normal breast tissues from the GSE59248 dataset were downloaded. Differentially expressed genes (DEGs) were subsequently identified using the online tool GEO2R and a functional enrichment analysis was performed. In addition, a protein-protein interaction (PPI) network was constructed and the top eight hub genes were identified. The prognostic values of the hub genes were further investigated. A total of 316 DEGs, including 32 upregulated and 284 downregulated genes, were identified. Furthermore, eight hub genes, including lipase E hormone sensitive type, patatin like phospholipase domain containing 2, adiponectin C1Q and collagen domain containing (ADIPOQ), peroxisome proliferator activated receptor γ (PPARG), fatty acid binding protein 4 (FABP4), diacylglycerol O-acyltransferase 2, lipoprotein lipase (LPL) and leptin (LEP), were identified from the PPI network. The downregulated expression of ADIPOQ, PPARG, FABP4, LPL and LEP was significantly associated with poor overall survival in patients with DCIS. Therefore, these genes may serve as potential biomarkers for prognosis prediction. However, further investigation is required to validate the results obtained in the present study.

Introduction

Breast cancer (BC) is the most common cancer and the major cause of cancer-associated mortalities among women worldwide (1). A total of 2,088,849 new cases and

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626.679 mortalities were reported globally for BC in 2018 (2). It was also reported that the 5-year survival rate of patients with BC during 2007-2013 was 90% in the USA. The standard treatment modalities for BC include surgery, radiation, chemotherapy, targeted therapy and hormone therapy (3-5). Ductal carcinoma *in situ* (DCIS) is the earliest stage of BC and refers to a heterogeneous group of precursor lesions (6). Approximately 20-25% of patients with BC are diagnosed with DCIS (7). While not all DCIS cases progress to invasive BC, DCIS is usually excised as its potential for invasion remains difficult to predict (8).

Previous studies have focused on analyzing the molecular differences between DCIS and invasive BC and the potential progression mechanisms (9-12). The upregulation of erb-b2 receptor tyrosine kinase 2 (ERBB2) is considered to be an early step in the progression of DCIS (13,14). Shah *et al* (13) revealed that the downregulation of Rap1Gap, a GTPase-activating protein, promotes the progression of DCIS to invasive ductal carcinoma by activating the extracellular signal-regulated kinase/mitogen-activated protein kinase signaling pathway. In the phosphoinositide 3-kinase signaling pathway alterations have also been reported to be associated with the progression of DCIS (14). Additionally, the upregulation of cyclin D1, MYC proto-oncogene bHLH transcription factor and ERBB2, have previously been observed in DCIS (15). The upregulation of matrix metalloproteinase (MMPs), including MMP2, and downregulation of cadherin 1 are frequently observed in the progression from DCIS to invasive BC via the epithelial-mesenchymal transition (9,16). Previous studies have revealed that certain biomarkers, including the ki67 proliferation marker, the tumor protein p53 tumor suppressor gene and the estrogen receptor, may serve as prognostic predictors in DCIS (17,18). However, further investigation of the molecular features and differences between DCIS and normal breast tissues is required. Therefore, the aim of the present study was to identify key genes involved in DCIS and to explore their prognostic values by integrating bioinformatics tools.

Materials and methods

Gene expression level analysis of DCIS and normal breast tissue samples. The gene expression profiles of 46 DCIS and three normal breast tissues in the GSE59248 dataset (19) were downloaded from the Gene Expression Omnibus

(GEO) (https://www.ncbi.nlm.nih.gov/geo/). This dataset was analyzed using the Agilent-028004 SurePrint G3 Human GE 8x60K Microarray platform (Agilent Technologies, Inc.). The online tool GEO2R (www.ncbi.nlm.nih.gov/geo/geo2r) was subsequently used to identify the differentially expressed genes (DEGs) between DCIS and normal breast tissues using the Benjamini and Hochberg false discovery rate (20). The cut-off criteria for the selection of DEGs were an adjusted $P<0.05$ and a $|\log_2$ fold-change$|>2$.

Functional enrichment analyses of the DEGs. Gene Ontology (GO) (http://geneontology.org) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were performed to explore the biological functions of the DEGs. GO functional analysis, which includes biological processes, cellular components and molecular functions, was performed using the Protein Analysis Through Evolutionary Relationships (PANTHER) classification system (16). KEGG pathways enrichment analysis was performed using the Database for Annotation, Visualization and Integrated Discovery (DAVID; version 6.8) (https://david.ncifcrf.gov) (17). The criteria for significance were $P<0.05$ and the number of enriched DEGs in pathways ≥ 5.

Construction of the protein-protein interaction (PPI) network. To further explore the associations between the identified DEGs, a PPI network was constructed using the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database (https://string-db.org) (18) and visualized using Cytoscape software (version 3.6.1) (21). In the PPI network, the nodes and edges represent proteins and their interactions, respectively. The genes in the PPI network with the highest connectivity were considered hub genes. The potential hub genes were screened from the entire PPI network using the cytoHubba plug-in and the maximal clique centrality algorithm (22,23).

Survival analysis of hub genes with the log-rank test. To evaluate the prognostic values of the identified hub genes in patients with DCIS, an overall survival (OS) analysis was carried out using the Kaplan-Meier plotter (https://kmplot.com/analysis/), which is a web-based tool to assess the effect of 54,675 genes on survival in 21 cancer types (24).

Statistical analysis. SPSS software (version 22.0; IBM Corp.) was used to perform the statistical analysis. The data were presented with mean ± SD. The associations between the clinicopathological parameters and hub gene expression were analyzed using the χ^2 test. When the sample size was <40, the Fisher's exact test was applied. $P<0.05$ was considered to indicate a statistically significant difference. The α level was 0.05.

Results

DEGs between DCIS and normal tissue samples. A total of 316 DEGs, including 32 upregulated and 284 downregulated genes, were identified in the GSE59248 dataset. The GSE59248 dataset included the gene expression profiles of 46 DCIS and 3 normal breast tissue samples.

Table I. Functional enrichment analyses of the differentially expressed genes in ductal carcinoma *in situ* using the Protein Analysis Through Evolutionary Relationships classification system. The top eight items with its counting percentage in each category were present.

A, Protein categories

Term	Percentage
Hydrolase	12.60
Signaling molecule	10.20
Enzyme modulator	8.70
Transcription factor	7.80
Transporter	7.80
Nucleic acid binding	7.30
Transferase	6.80
Receptor	6.80

B, Cellular component

Term	Percentage
Cell part	35.50
Organelle	20.30
Membrane	19.50
Macromolecular complex	12.60
Extracellular region	8.70
Cell junction	2.20
Synapse	0.90
Extracellular matrix	0.40

C, Biological process

Term	Percentage
Cellular process	25.80
Metabolic process	16.70
Biological regulation	11.00
Developmental process	10.60
Response to stimulus	9.50
Multicellular organismal process	8.40
Localization	6.10
Cellular component organization or biogenesis	3.90

D, Molecular function

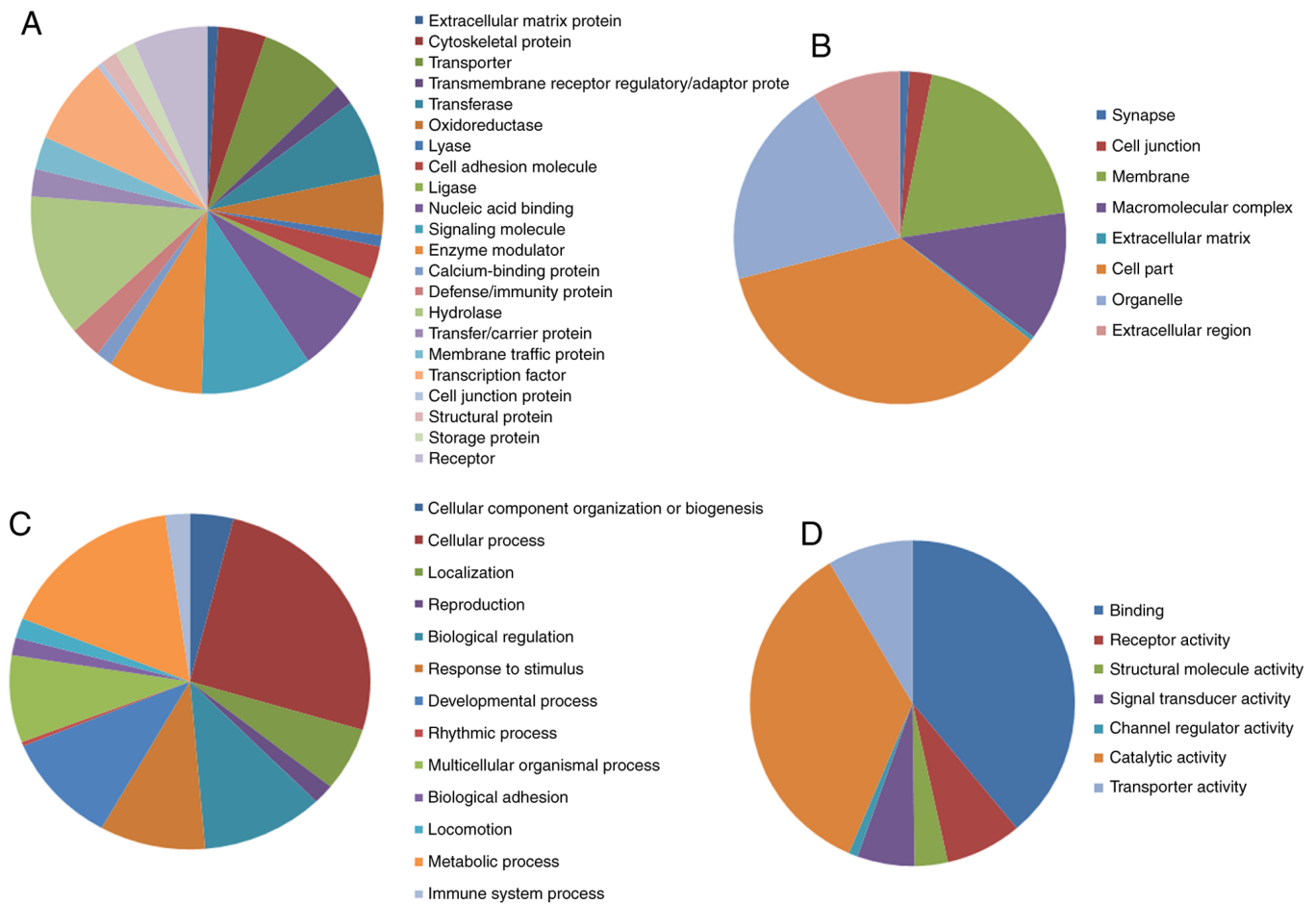| Term	Percentage
Binding	38.90
Catalytic activity	35.10
Transporter activity	8.50
Receptor activity	7.60
Signal transducer activity	5.70
Structural molecule activity	3.30
Channel regulator activity	0.90

Figure 1. Gene Ontology and functional enrichment analyses of the differentially expressed genes in ductal carcinoma *in situ*. (A) Protein categories, (B) cellular component, (C) biological process and (D) molecular function.

Functional enrichment analyses of the DEGs. The analytical results of the PANTHER classification system revealed that the identified DEGs could be classified into 22 protein categories, including signaling molecules, transporters, hydrolases, enzyme modulators and transcription factors (Fig. 1A; Table I). The GO analysis revealed that these DEGs were significantly involved in cellular components such as 'cell part', 'organelle', 'membranes' and 'macromolecular complex' (Fig. 1B; Table I). In terms of biological processes, the DEGs are mainly associated with 'metabolic process', 'cellular process', 'biological regulation', 'developmental process' and 'response to stimulus' (Fig. 1C; Table I). Regarding molecular functions, the DEGs were mainly associated with 'catalytic activity', binding, transporter activity and signal transducer activity (Fig. 1D; Table I). The analysis of KEGG pathways using DAVID indicated that the DEGs are mainly enriched in pathways such as 'PPAR signaling pathway', 'AMPK signaling pathway', 'regulation of lipolysis in adipocytes' and 'glucagon signaling pathway' (Fig. 2).

PPI network and hub genes. In the present study, the STRING database was used to construct a PPI network to visualize the protein-protein interactions between the DEGs (Fig. 3). The network consisted of a total of 315 nodes and 474 edges. The local clustering coefficient of the PPI network was 0.374 and the average node degree was 3.01. The top eight
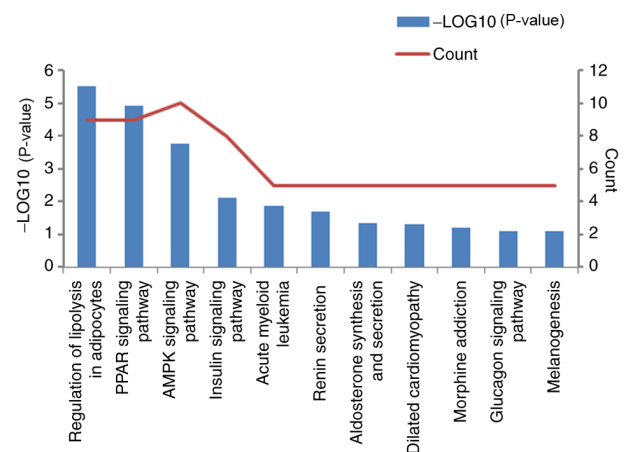

Figure 2. Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis of the differentially expressed genes in ductal carcinoma *in situ*.

hub genes were identified from the PPI network using the cyto-Hubba plugin and the maximal clique centrality algorithm. The hub genes were as follows: Lipase E hormone sensitive type (LIPE), patatin-like phospholipase domain-containing 2 (PNPLA2), adiponectin (ADIPOQ), peroxisome proliferator activated receptor γ (PPARG), fatty acid-binding protein 4 (FABP4), diacylglycerol O-acyltransferase 2 (DGAT2),
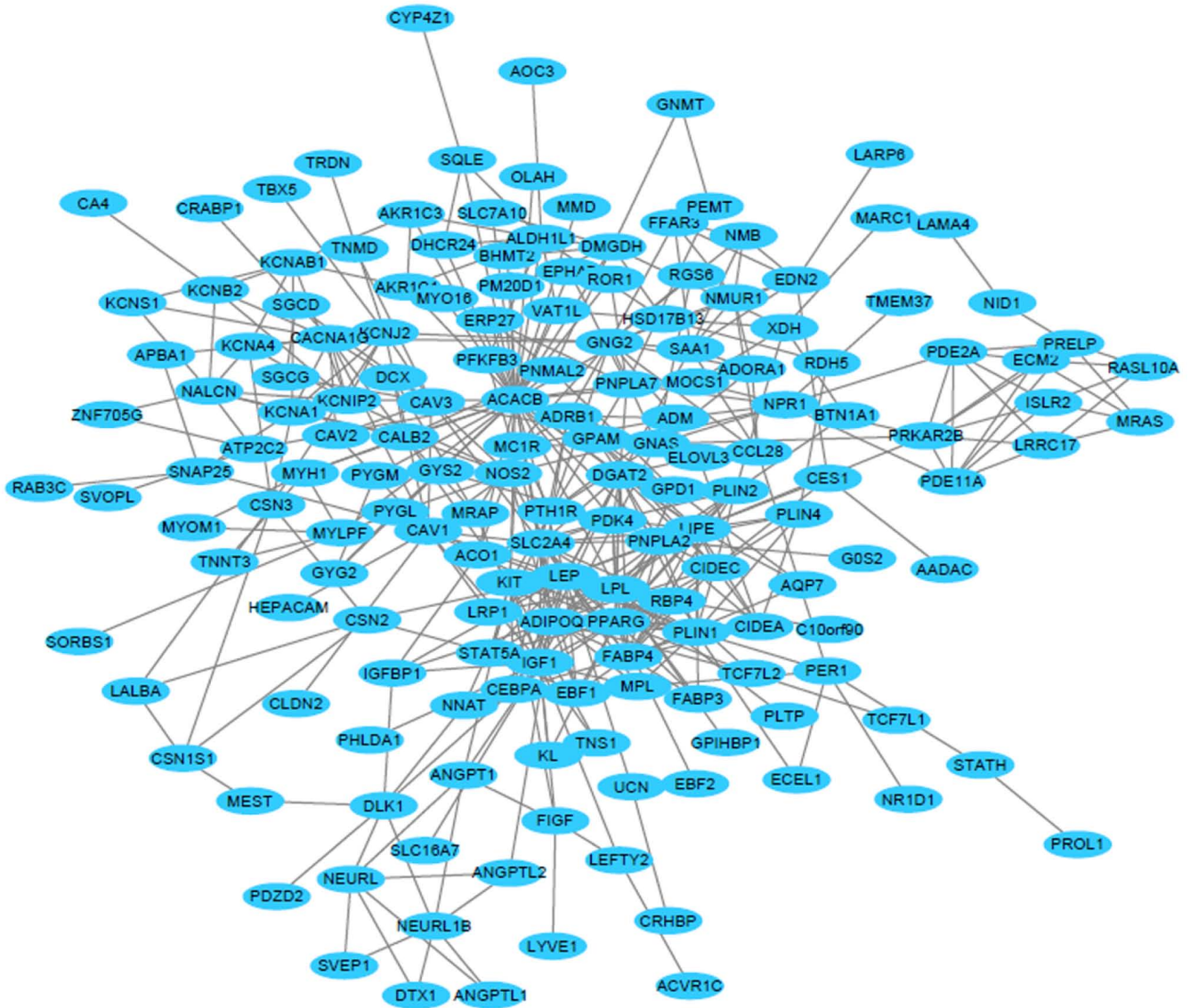
Figure 3. Protein-protein interaction network based on the Search Tool for the Retrieval of Interacting Genes/Proteins and visualized using Cytoscape software.
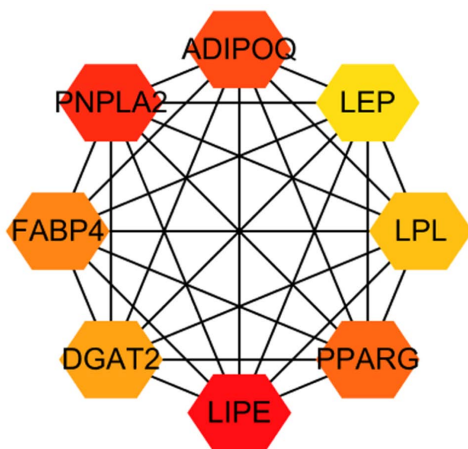

Figure 4. Top eight hub genes screened from the entire protein-protein interaction network. LIPE, lipase E hormone sensitive type; PNPLA2, patatin-like phospholipase domain-containing 2; ADIPOQ, adiponectin; PPARG, peroxisome proliferator activated receptor γ; FABP4, fatty acid-binding protein 4; DGAT2, diacylglycerol O-acyltransferase 2; LPL, lipoprotein lipase; LEP, leptin.

lipoprotein lipase (LPL) and leptin (LEP; Fig. 4). The above mentioned hub genes were downregulated in DCIS compared with normal breast tissue (Fig. 5).

Survival analysis results of the hub genes. The prognostic values of the identified hub genes in patients with DCIS were investigated using the Kaplan-Meier plotter. Only the low expression of ADIPOQ [hazard ratio (HR)=0.75; 95% confidence interval (CI), 0.61-0.94; log-rank P=0.01], PPARG (HR=0.66; 95% CI, 0.53-0.82; log-rank P=0.0013), FABP4 (HR=0.76; 95% CI, 0.61-0.94; log-rank P=0.012), LPL (HR=0.75; 95% CI, 0.61-0.93; log-rank P=0.009) and LEP (HR=0.8; 95% CI, 0.64-0.99; log-rank P=0.037) were significantly associated with poor OS in patients with DCIS (Fig. 5). The associations between the hub gene expression levels and clinicopathological parameters of patients with DCIS are presented in Table II. The expression levels of LIPE, PNPLA2 and DGAT2 did not significantly influence the prognosis of patients with DCIS (Fig. S1).
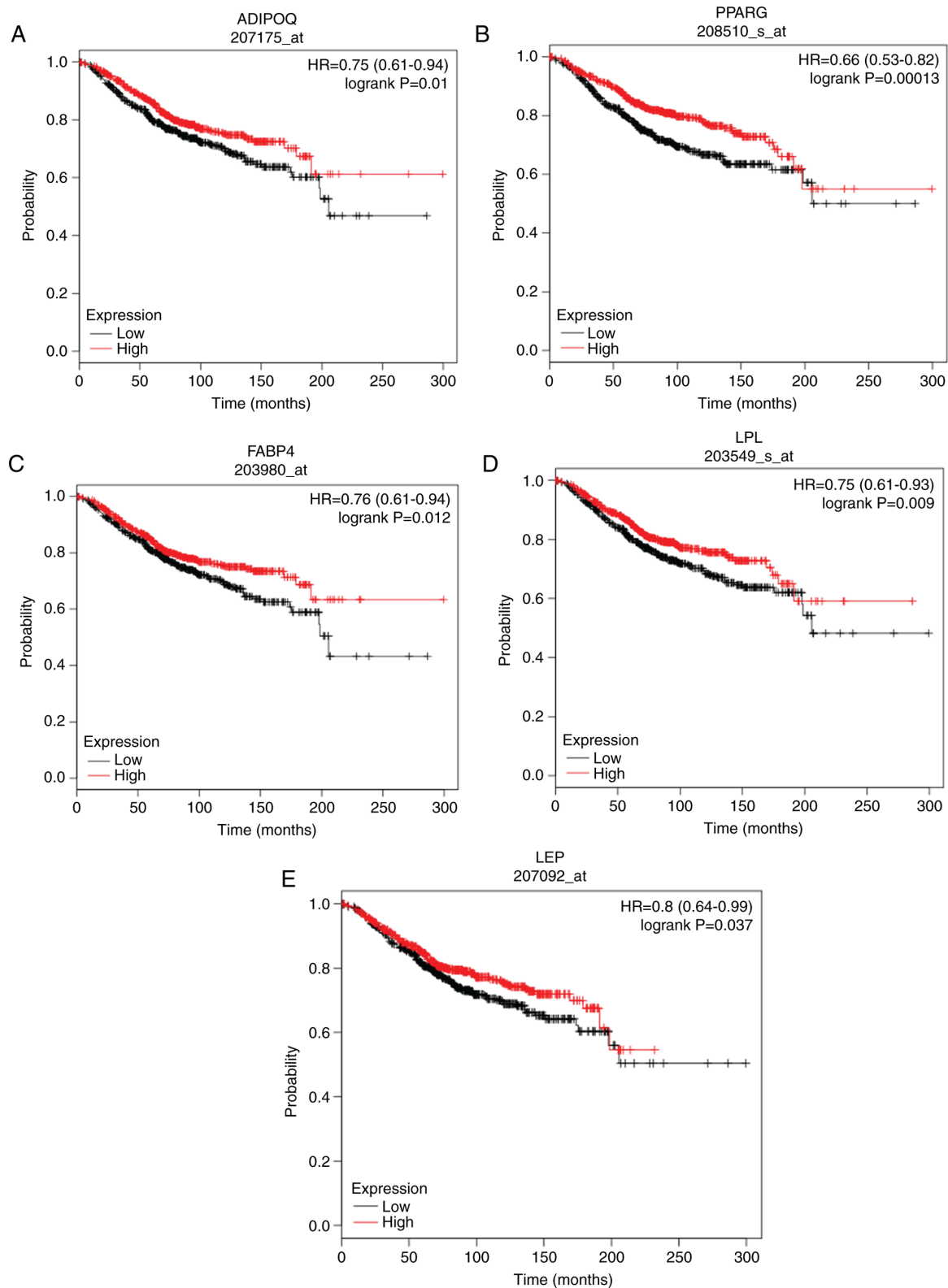
Figure 5. Overall survival analysis of (A) ADIPOQ, (B) PPARG, (C) FABP4, (D) LPL and (E) LEP in ductal carcinoma *in situ* was performed using the Kaplan-Meier plotter. Red and black represent high and low expression, respectively. ADIPOQ, adiponectin; PPARG, peroxisome proliferator activated receptor γ; FABP4, fatty acid-binding protein 4; LPL, lipoprotein lipase; LEP, leptin; HR, hazard ratio.

Discussion

DCIS is a heterogeneous disease and represents the pre-invasive stage of BC (25). Although the majority of patients with DCIS undergo breast excision to remove the lesion, certain patients with DCIS may still develop invasive BC (26). Therefore, it is important to explore the molecular features of DCIS development and to identify potential prognostic biomarkers.

The present study analyzed the gene expression data of 46 DCIS and three normal breast tissues. A total of 316 DEGs

Table II. The correlation analysis of the hub genes' expression levels and the clinicopathological parameters of Ductal Carcinoma in situ of the Breast (data from the GSE59248 dataset).

Clinical parameter	No. of cases (n)	ADIPOQ expression			LEP expression			LPL expression			FABP4 expression			PPARG expression		
		High	Low	P-value	High	Low	P-value	High	Low	P-value	High	Low	P-value	High	Low	P-value
Age																
≤55	19	12	7	0.314	14	5	0.049	12	7	1.00	9	10	0.220	12	7	0.314
>55	27	13	14		12	15		18	9		8	19		13	14	
Tumor size (cm)																
≤3	22	14	8	0.678	14	8	0.242	15	7	0.417	12	10	0.419	12	10	0.419
>3	8	4	4		3	5		4	4		6	2		6	2	
ER																
Positive	15	6	9	0.105	6	9	0.400	7	8	0.210	8	7	1.00	9	6	1.00
Negative	9	7	2		6	3		7	2		5	4		5	4	
PR																
Positive	12	4	8	0.100	4	8	0.220	3	9	0.003	5	7	0.414	8	4	0.680
Negative	12	9	3		8	4		11	1		8	4		6	6	
HER2																
Positive	9	6	3	0.387	5	4	1.00	7	2	0.080	6	3	0.660	6	3	0.660
Negative	12	5	7		6	6		4	8		6	6		6	6	

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

were identified, including 32 upregulated and 284 downregulated genes. The identified DEGs could be classified into 22 protein categories. Moreover, the results of the functional enrichment analysis indicated that the DEGs were mostly associated with cell parts, organelles, metabolic processes, cellular processes, biological regulation, transporter activity and signal transducer activity. A PPI network was constructed and eight hub genes were selected for further investigation. The downregulation of ADIPOQ, PPARG, FABP4, LPL and LEP was significantly associated with poor OS in patients with DCIS.

ADIPOQ encodes an adipocytokine, adiponectin, which is essential for metabolic and hormonal processes (27). A low level of plasma adiponectin has been significantly associated with several types of cancer, including colorectal and prostate cancer (28,29). It was also reported that adiponectin may decrease cancer cell growth by promoting the activity of autophagosomes and decreasing the sequestosome 1/GAP-associated tyrosine phosphoprotein p62 signaling pathway in BC (27). High ADIPOQ expression may serve a protective role in BC (30), consistent with the results obtained in the present study.

PPARG serves an important role in regulating adipocyte differentiation by forming heterodimers with retinoid X receptors (31). Several studies have shown that PPARG serves an anti-inflammatory role and may reduce the risk of breast cancer (32-34). The expression level of PPARG was found to influence the susceptibility to hepatocellular carcinoma (35) and different types of cancer (36). However, the association between PPARG and the risk of BC has not been established (37,38). FABP4 is involved in lipoprotein metabolism (39). A previous study revealed that FABP4 increased cell apoptosis and decreased proliferation (40). FABP4 overexpression has been reported to decrease hepatocellular carcinoma cell growth through the snail family transcriptional repressor 1/p-STAT3 signaling pathway *in vitro* and was associated with tumor size and overall survival in hepatocellular carcinoma (41).

LPL plays a critical role in lipid metabolism (42). Studies have shown that LPL may regulate metabolic pathways to provide additional energy for cancer cells (43,44). Circulating LEP is usually secreted by white adipose tissue and is involved in the regulation of angiogenesis, energy balance, and immune and inflammatory responses (45). Previous studies revealed that LEP altered the cellular response to estrogens in BC and served a role in mammary carcinogenesis (46,47). Furthermore, LEP may promote cell cycle progression by upregulating the levels of cyclin dependent kinase 2 and cyclin D1 (48). However, in the present study, LEP was downregulated in DCIS tissues compared with normal tissues.

The remaining hub genes in the present study, including LIPE, PNPLA2 and DGAT2, were also expressed at low levels in DCIS tissues compared with normal breast tissues. However, these genes were not associated with the prognosis of patients with DCIS. It is worth noting that the GSE59248 dataset used in the present study contained the gene expression profiles of only three normal breast tissues. Therefore, future studies investigating the gene expression profiles from multiple datasets are warranted.

The present study investigated the differences between DCIS and normal breast tissues by integrating comprehensive bioinformatics analyses. The top eight hub genes, namely LIPE, PNPLA2, ADIPOQ, PPARG, FABP4, DGAT2, LPL and LEP, were identified and considered to serve critical roles in the initiation of BC, while only five of the hub genes, ADIPOQ, PPARG, FABP4, LPL and LEP, were further found to be potential biomarkers for predicting the prognosis of patients with DCIS. However, further research is required to validate the results obtained in the present study.

Availability of data and materials

The data that support the findings of this study are available from GEO database, DAVID, STRING and GEPIA database, as is mentioned in the Material and methods.

Author's contributions

MW and ZHM analyzed the data and wrote the manuscript. ZHM supervised the study. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethical approval was not necessary in this study because public datasets were analyzed.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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