Constructing mRNA, miRNA, circRNA and lncRNA regulatory network by Analysis of microarray data in breast cancer

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ARTICLE INFO

Edited by Hee-Jeong Im Sampen

ABSTRACT

Background: Luminal tumors are the utmost frequent subtype of breast cancer (BC). Despite luminal BC has relatively good prognosis, in a subset of patients, disease relapse occurs to endocrine therapy; hence, there is a critical need to identify new strategies to promote the early detection and more effective therapies. Noncoding RNAs including microRNAs, long noncoding RNAs, and circular RNAs can interact with and modulate each other via diverse molecular mechanisms and make a complicated regulatory network. ncRNAs participate in diverse biological processes and disorders such as breast tumors. Therefore, understanding their regulatory mechanisms allow to develop new field of research and therapeutic options for BC patients.
Methods: In this study, BC-specific RNA expression profiles including mRNAs, miRNAs, lncRNAs, and circRNAs were retrieved from Gene Expression Omnibus microarray datasets, and differentially expressed (DE) items were obtained. Disease ontology, functional and pathway enrichment analyses were executed. The protein-protein interaction network was constructed, and hub mRNAs were extracted. The prognostic value of hub mRNAs in patients of BC was performed. Subsequently, a ceRNA network was established.
Results: In total, 691 DE genes, 122 DE lncRNAs, 60 DE miRNAs, and 38 DE circRNAs in breast tumor samples were compared with normal samples. Subsequently, 12 hub-genes including FOXO3, RHOA, EZH2, KIT, HSP90B1, NCOA3, RAC1, IGF1, CAV1, CXCR4, CCNB1, and ITGB1 were screened from the network. Kaplan-Meier Plotter results revealed that FOXO3 and RHOA were a suitable prognostic marker for patients with breast cancer. Finally, we determined possible ncRNAs (circ0007535, circ0002727, circ0005240, circ0014130, circ0044927, circ0007001, circ0089153, NORAD, MALAT1, TUG1, ZFAS1, OPI5-AS1, miR183, miR182,

miR101, miR200c, miR200b, miR149, miR342, and miR1207) which could crosstalk with each other to regulate FOXO3 and RHOA through different regulatory patterns.

Conclusion: These data might improve our perception of the breast tumorigenesis and could develop new field of research and therapeutic options for BC patients.

1. Introduction

Female breast cancer remains the most common neoplasm throughout the world and is the fifth leading cause of cancer mortality in women (Bray et al., 2018). Estrogen receptor alpha is expressed in about 70% of breast cancers which are assigned as luminal A or luminal B subtypes BC (Perou et al., 2000). Luminal cancers have a better prognosis than other types of BC and are sensitive to endocrine therapy, however many patients eventually develop resistance (Peng et al., 2017). This situation is attributed to a complex regulatory network of breast cancer. Thus, the discovery and development of new molecular biomarkers and therapeutic targets is imperative in medical research and could potentially improve cancer diagnosis and treatment. During the last decades, advances in high-throughput technologies have made possible the development of new strategies in unraveling puzzles of the complex genetic nature of cancer. Therefore, studies have eventually shifted our conception of noncoding RNAs from worthless transcriptional products to major players that regulate many biological processes (Djebali et al., 2012; Iyer et al., 2015; Weng et al., 2007).

As novel non-coding RNAs (ncRNAs), circRNAs in contrast to linear RNAs are spliced backward from the 5′ to 3′ segment, with covalently closed rings lacking the 5′ cap and 3′ poly(A) tail. Compared to linear RNAs, this structure can be protected, against degradation by the exonucleolytic activity of RNase so their transcripts remain highly conserved and stable (Wang et al., 2016; Suzuki et al., 2006). Recent reports have revealed that aberrant expression of circRNAs is usually associated with diverse pathological conditions, such as neurodegenerative diseases (Piwecka et al., 2017), cardiovascular diseases (Aufiero et al., 2019), and cancers (Vo et al., 2019; Meng et al., 2017) with diagnostic and prognostic value. Although the exact mechanisms of most circRNAs remain unclear, several studies suggest circRNAs are responsible for multiple biological processes via different mechanisms such as gene transcription modulation and interference with RNA splicing (Z. Li et al., 2015; Ashwal-Fluss et al., 2014), gene expression regulation at the RNA level through suppressing miRNAs as competing for endogenous RNA (ceRNA) (Ashwal-Fluss et al., 2014), serving as protein scaffolds (Du et al., 2017) and translation by encoding functional peptides (van Heesch et al., 2019). Previous studies in recent years have demonstrated that the circRNA-miRNA-mRNA regulatory network act as key regulators in breast cancer growth and invasion (Jahani et al., 2020; Xu et al., 2019). For example, circABCB10 was significantly upregulated in BC tissue samples. CircABCB10 substantially promotes BC expansion and dissemination via the sponging of miR-1271 (Xu et al., 2019). However, the functions of circRNAs in BC development and progression are still poorly understood. In addition to circRNAs, long non-coding RNAs as ncRNAs can reduce the miRNA suppression of targeting mRNA and
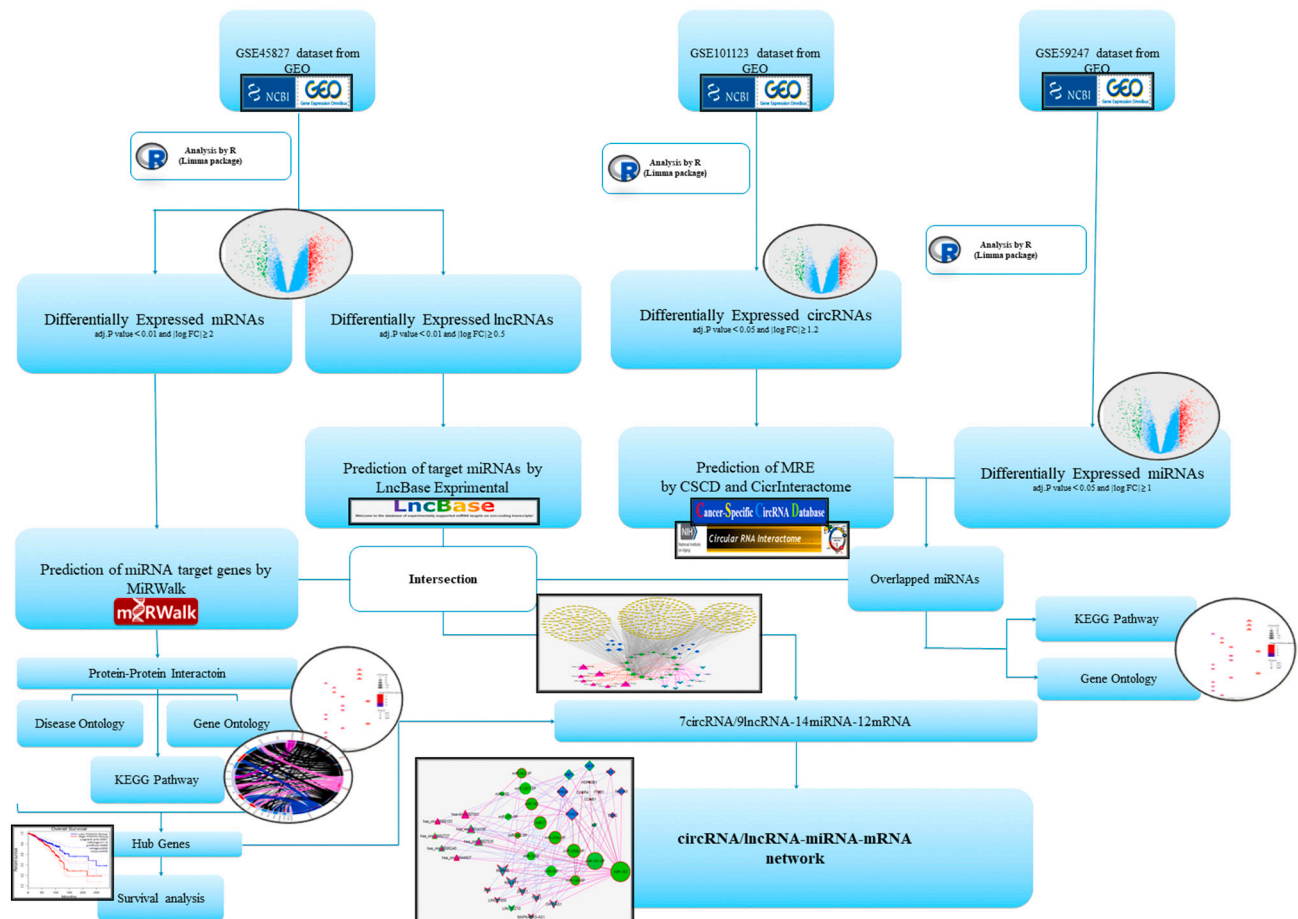

Fig. 1. Flowchart of our in silico assessments.

indirectly regulate the target gene expression level. Plenty of evidence indicates that lncRNAs abnormally express in many cancer types and might be a prominent contributor to tumor progression (Klinge, 2018; Tomar et al., 2020; Bin et al., 2018; Liu et al., 2020). In the current study, we established a breast cancer ceRNA network for both lncRNA-miRNA-mRNA and circRNA-miRNA-mRNA based on bioinformatic prediction methods. In the beginning, we collected significant differentially expressed mRNAs, miRNAs, lncRNAs, and circRNAs according to the analysis of GEO database information. Then, we filtered circRNAs and lncRNAs that could bind to miRNAs and miRNA target genes to design a circRNA/lncRNA/miRNA/mRNA network. Besides, we reconstructed a protein–protein interaction (PPI) network and performed functional and pathway enrichment analyses. Fig. 1 shows the overall flowchart of our in silico assessments.

2. Materials and methods

2.1. Data gathering

Three gene-expression datasets were obtained from the GEO database (https://www.ncbi.nlm.nih.gov/geo/). The GSE45827 (Gruosso et al., 2016) was used to study 130 breast cancer sample mRNAs (41 triple-negative/TN, 30 HER2, 29 Luminal A, and 30 Luminal B) and 11 normal breast tissue samples. The miRNA microarray datasets GSE59247 (Lesurf et al., 2016) included 38 breast cancer samples (4 TN, 9 HER2, 14 Luminal A, and 11 Luminal B) and 10 normal breast tissue samples. The GSE101123 (Xu et al., 2019) with eight breast cancer tissues (4 TN and 4 Luminal A) and three non-tumor breast samples, was used to study circRNA.

2.2. Screening of differentially expressed items

All raw expression data files were subjected to background correction and quantile normalization using RMA (Robust Multi-Array Analysis) from affy Bioconductor package. (Gautier et al., 2004a; Gautier et al., 2004b). The "limma" R package (Wettenhall and Smyth, 2004) was used to identify differentially expressed items between luminal tumor and normal samples. Differentially expressed genes (DEG) were collected with thresholds of adj.P-value < 0.01 and |log 2-fold-change| ≥ 2. The threshold values for differentially expressed miRNAs (DEmiRs) were set to |logFC| > 1 and adj.P-value < 0.05. Based on the cut-off value, adjusted P-values < 0.05 and |log fold change (FC)| > 1.2 were used to select differentially expressed circRNAs (DEcRNAs). Differentially expressed lncRNAs(DELs) were selected according to (|logFC|) >0.5 and the adjusted P-value < 0.01 cutoff criteria between normal and luminal tumor samples. Then, volcano plots were performed using R software ggplot2 package to visualize the results of differential expression analysis.

2.3. Prediction of miRNA binding sites

Putative miRNA response elements (MREs) of differentially expressed circRNAs were assessed using Circular RNA Interactome (CircInteractome) (https://circinteractome.nia.nih.gov/), Cancer-Specific CircRNA (CSCD) (https://gb.whu.edu.cn/CSCD/), and circBank (http://www.circbank.cn/). Only the target miRNAs that overlapped with the differentially expressed miRNAs (DEmiRNAs) were collected from the GEO database and were predicted as possible target microRNAsof the DEcircRNAs.

2.4. Prediction of lncRNAs

In addition to selected differentially expressed lncRNAs based on the GSE45827, the interactions between lncRNA and DEmiRNAs were evaluated by DIANA TOOLs databases (https://diana.e-ce.uth.gr/lncbasev3).

2.5. Prediction of miRNA target genes

The DEmiRNA target genes predictions were retrieved from an online analysis tool called MiRWalk 2.0 (http://mirwalk.umm.uni heidelberg.de), Since the results of MiRWalk 2.0 were derived from different miRNA-target prediction programs (DIANA-microTv4, DIANA-microT-CDS, miRanda, mirBridge, miRDB4, miRmap, miRNAMap, PicTar2, PITA, RNA22v2, RNAhybrid, and Targetscan), their projections were very reliable (Dweep and Gretz, 2015). If there was no interaction between differentially expressed genes (DEGs) obtained from the GEO database and predicted genes in the database, they could be removed after functional enrichment analysis and network centrality analysis.

2.6. Construction of the PPI network

To construct a PPI network among DEGs identified, we used the Search Tool for the Retrieval of Interacting Genes (STRING) database (version 11) (Szklarczyk et al., 2014). The STRING database provides protein–protein interaction based on coexpression experiments, gene fusion, text mining, co-occurrence, and, neighborhood regions as the forecasting methods. DEGs with a joined score >0.9 were selected to create a network using Cytoscape (H. Zhang et al., 2017). Then, the network was processed for module analysis, using Molecular Complex Detection (MCODE) Plugin in Cytoscape software with default parameters as follows: degree cutoff ≥2, node score cutoff ≥2, K-core ≥2, and maximum depth = 100 (Paul et al., 2003; Bader and Hogue, 2003). Cytoscape (v3.8.3) was used to visualize and compute the main characteristics of the PPI network to explore the hub genes, such as average clustering coefficient distribution, closeness centrality, average neighborhood connectivity, node degree distribution, shortest path length distribution, and topological coefficients.

2.7. Functional enrichment of DEGs

To further examine the possible function of mRNAs in the ceRNA network, disease ontology (DO), functional enrichment of gene ontology (GO) including the cellular component (CC), molecular function(MF), and biological process (BP), Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways analyses were conducted using cluster Profiler, and DOSE in R (Tomar et al., 2020). statistical significance was represented by the adjusted P-value (Q-value) < 0.05. Also, assessing miRNAs regulatory roles of DEmiRs was performed with DIANA-miRPath (https://www.microrna.gr/miRPath), an online software.

2.8. Survival analysis of candidate hub genes

The clinical outcomes of hub mRNAs between BC samples and normal tissues were evaluated using the GEPIA (Gene Expression Profiling Interactive Analysis) webserver. It develop new possibility for data exploration of gene functions based on records that have been arranged from TCGA ana GTEx projects (Z. Tang et al., 2017).

2.9. Construction of the ceRNA network

Based on the potential interaction between mRNAs, miRNAs, circRNA, and lncRNAs, the ceRNA network was visualized by Cytoscape software.

3. Results

3.1. Microarray data preprocessing

Following quality assessment and removing inaccurate expression data, 691 DEGs (152 down-regulated and 539 up-regulated) (Fig. 2A); and 122 DElncRNAs (78 down and 44 up-regulated) (Fig. 2B), were identified in breast cancer samples compared to controls in gene chip
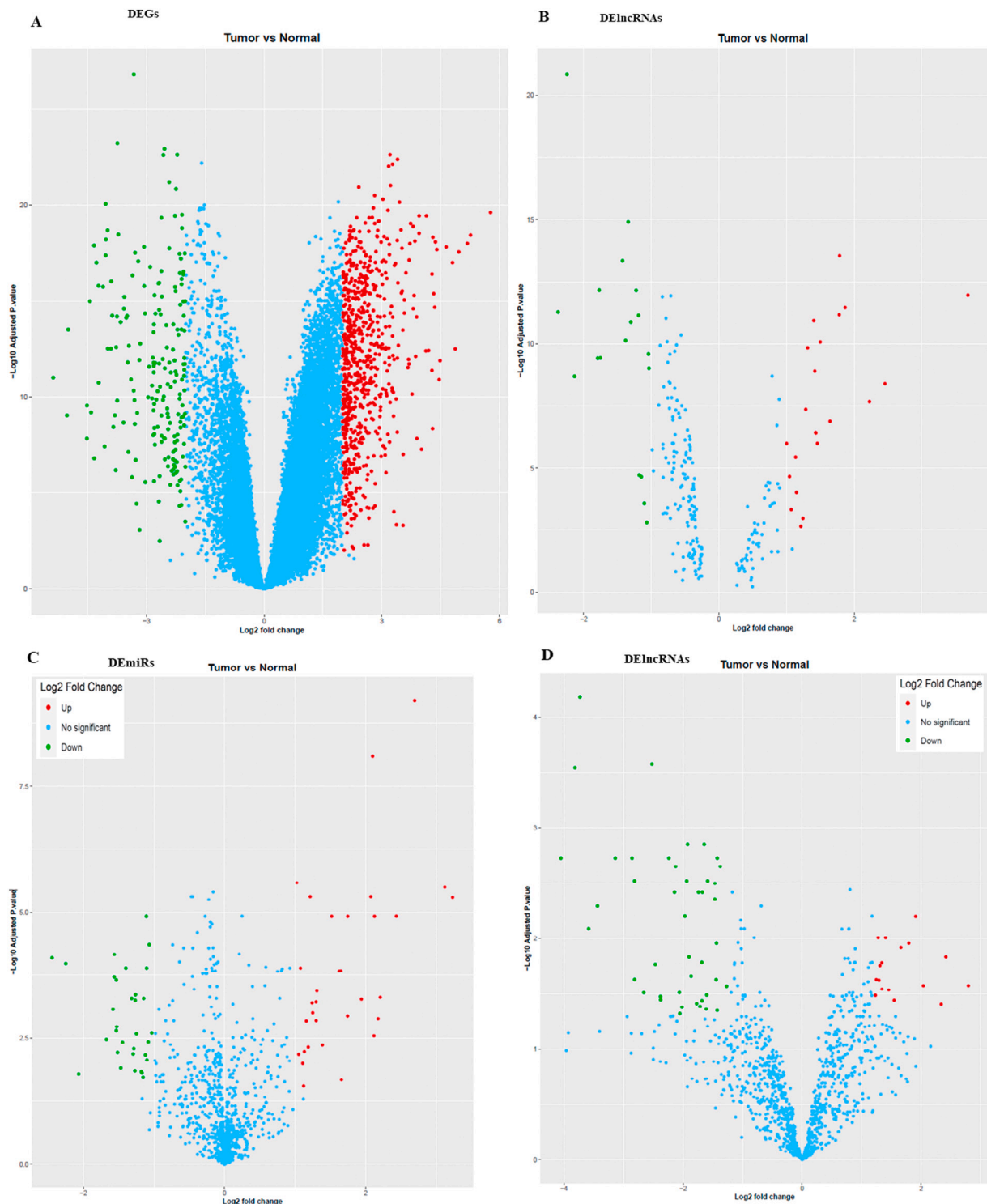
Fig. 2. Volcano plots for differentially expressed items A) DEGs; B) DElncRNAs; C) DEmiRs; D) DEcircRNAs in BC based on GEO datasets. Up-regulated genes are marked with red, while down-regulated genes are marked with green dots. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

GSE45827. Then, 60 DEmiRs (31 down-regulated and 29 up-regulated) were determined in gene chip GSE59247 (Fig. 2C). A total of 38 DECs with 17 up-regulated and 41 down-regulated circRNAs were determined in gene chip GSE101123 (Fig. 2D). Subsequently, 20 circRNAs were selected based on adjusted P-value, consisting of 10 down-regulated and 10 up-regulated circular RNAs. All data are presented in the Supplementary file (Tables 1–4).

3.2. Identification of circRNA–miRNA interactions

Evidence suggests that some circular RNAs containing specific miRNA binding sites can reduce miRNA suppression to target mRNA, thus playing an important role in tumorigenesis. We predicted miRNAs that could trap by circRNAs to construct the circRNA-miRNA regulatory network using three online databases, CSCD, CircBank, and CircInteractome. Latter, we selected circRNAs that could intersect with more than

two DEmiRNAs. Therefore, 24 circRNA-miRNA pairs consisting of 7 DEcircRNAs (3upregulated and 4 downregulated) and 14 DEmiRNAs were maintained. The fundamental structure of the 7 circRNAs including MRE (microRNA response element), RBP (RNA binding protein), and ORF (open reading frame) elements are exhibited in Fig. 3. The basic characteristics of the 7 circRNAs are listed in Table 1.

3.3. Indication of lncRNA–miRNA interactions

A total of 203 lncRNA probes were identified in GSE59247 datasets with adjusted P-value < 0.01. Next, 122 lncRNAs probe ID with |logFC| > 0.5 and adjusted P-value < 0.01 were detected among 11 normal and 130 breast tissue samples. Based on the potential interaction between miRNAs and lncRNAs, the interactions between lncRNA and 14 DEmi-RNAs that linked with DEcircRNAs, were detected by DIANA TOOLs databases (https://diana.e-ce.uth.gr/lncbasev3). To improve the reliability of data, two filters (breast tissue selection and high confidence level) were applied. If the predicted miRNAs in the database were not matched with 14 DEmiRNAs, they would be eliminated. Then, lncRNAs that could intersect with more than two DEmiRNAs were selected. Using this technique, 37 lncRNA-miRNA interaction pairs including 9

DElncRNAs and 8 DEmiRNAs were identified. The basic information of the 9 lncRNAs is listed in Table 2.

3.4. PPI network construction and module analysis

To predict the interaction relevance, the STRING database was applied. As a result, 629 nodes and 4252 protein pairs with a combined weight score of >0.4 were found in the network (Supplementary Table 5). All nodes with a combined score of >0.9 were imported into Cytoscape software for visualization. After clustering analysis with MCODE, six modules with a score of >5 were detected (Supplementary Table 6). After centrality analysis, the top 50 nodes with the degree, closeness, and betweenness indices values, higher than the mean value of the whole network, were considered as key nodes. Fig. 4 shows the PPI network of the selected DEGs.

3.5. Functional annotation

Enrichment analysis renders an approach for facilitating the biological interpretation of outcomes from high-throughput datasets (Khatri and Drăghici, 2005). To obtain the biological functions of the 50

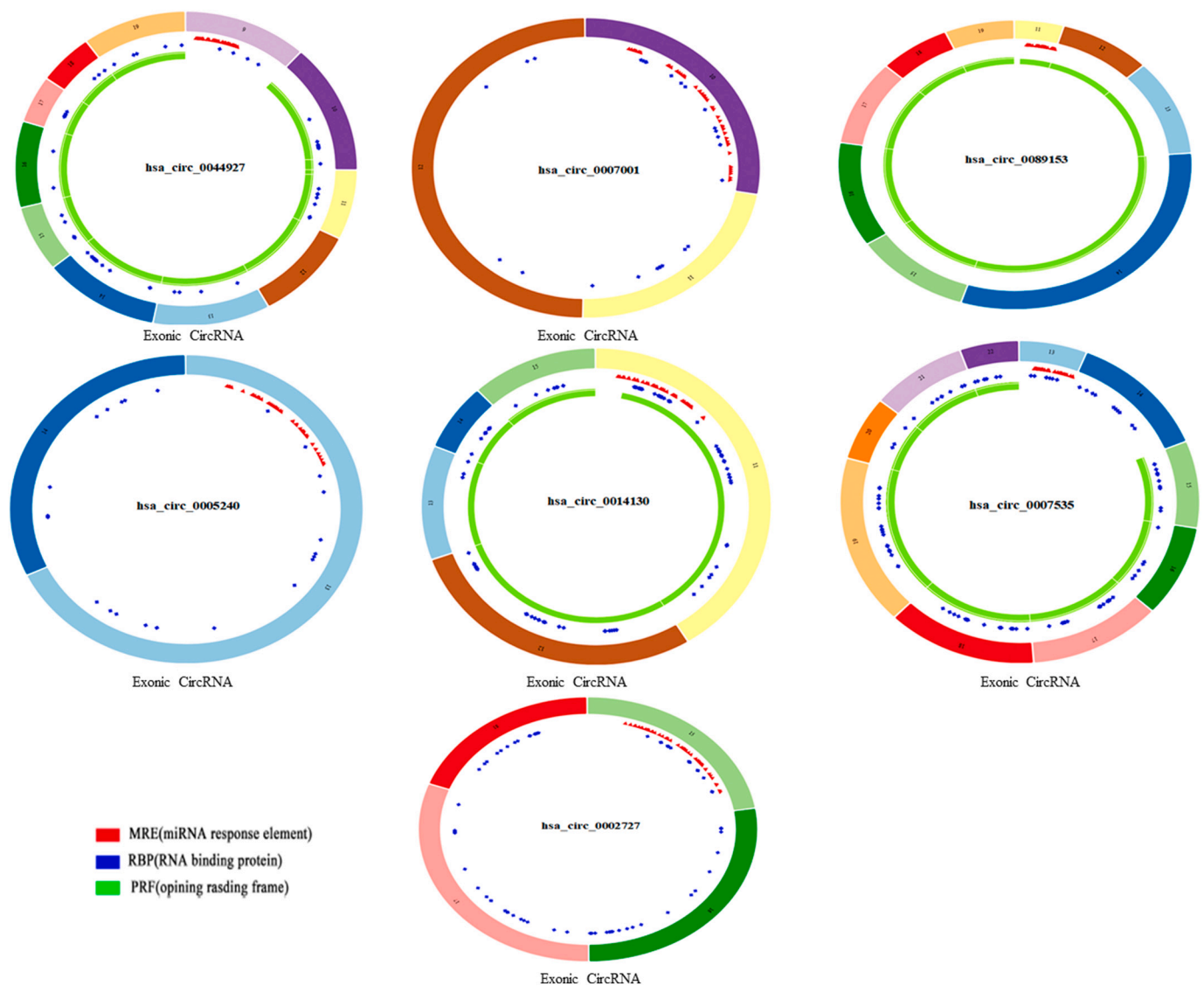**Fig. 3.** Basic structures of 7 circRNAs. This panel displays the image of circRNAs by connecting exons in a circle. The different colors in the outer and inner rings represent different exons. The positions of MRE, RBP, and ORF, MRE are shown in red, blue points to RBP and green shows ORF. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Basic characteristics of these 7 circRNAs.

Alias	CircRNA ID	Strand	CircRNA type	Position	Gene symbol	Regulation
hsa_circRNA_102348	hsa_circ_0007535	+	Exonic	chr18:33722243-33739978	ELP2	Down
hsa_circRNA_100640	hsa_circ_0002727	−	Exonic	chr10:88230748-88233730	WAPAL	Down
hsa_circRNA_100070	hsa_circ_0005240	−	Exonic	chr1:16464347-16464925	EPHA2	Down
hsa_circRNA_100332	hsa_circ_0014130	+	Exonic	chr1:151206672-151212515	PIP5K1A	Down
hsa_circRNA_102140	hsa_circ_0044927	−	Exonic	chr17:58275620-58292135	USP32	Up
hsa_circRNA_100805	hsa_circ_0007001	−	Exonic	chr11:46515157-46529920	AMBRA1	Up
hsa_circRNA_104940	hsa_circ_0089153	+	Exonic	chr9:134011326-134022971	NUP214	Up

Table 2
Basic characteristics of the 9 lncRNAs which are dominated as important molecules in breast cancer regulatory network.

lncRNA ID	Alias	Strand	lncRNA type	Position	Regulation
FTX	XIST Regulator	−	Intergenic	chrX:73946555-74293574	Up
MALAT1	Metastasis Associated Lung Adenocarcinoma Transcript 1	+	Intergenic	chr11:65496267-65509085	Up
NORAD	Non-Coding RNA Activated By DNA Damage	−	Intergenic	chr20:36045299-36051016	Up
TUG1	Taurine Up-Regulated 1	+	Intergenic	chr22:30969158-30985225	Up
ZFAS1	ZNFX1 Antisense RNA 1	+	Antisense	chr20:49276739-49361131	Up
OIP5-AS1	OIP5 Antisense RNA 1	+	Sense-overlapping	chr15:41283963-41508868	UP
LINC01000	Long Intergenic Non-Protein Coding RNA 1000	+	Intergenic	chr7:128633015-128664182	Up
LINC02210	Long Intergenic Non-Protein Coding RNA 2210	+	Intronic	chr17:45,620,328-45,816,543	Down
MAPKAPK5-AS1	MAPKAPK5 Antisense RNA 1	−	Antisense	chr12:111,839,703-111,843,005	Up
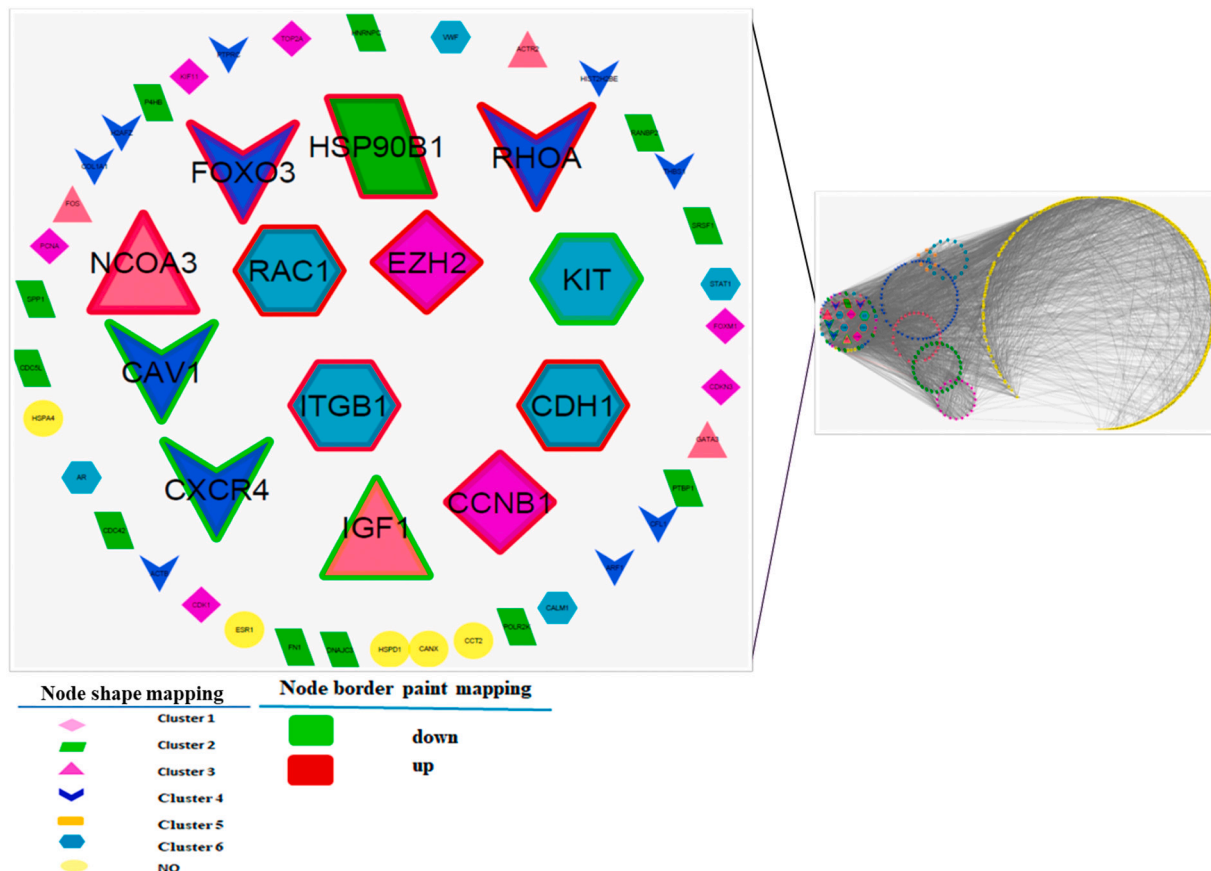
Fig. 4. Protein-protein interaction analysis of differentially expressed genes.Six modules with a score of >5.0 were depicted in the figure in unique shapes and colors. Edges represent interactions between two genes. The significance of protein nodes in the network is presented by a degree where small and large sizes denote low and high values, respectively. The border color indicates the fold change for nodes where upregulated nodes are defined in red and downregulated nodes are defined in green. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

top DEGs, DO functional, GO analyses, and KEGG pathway enrichment was conducted using the cluster Profiler package of R software. The functional characterization of miRNAs was exploited using DIANA-miRPath v3 (Supplementary Table 7). Using disease ontology analysis of 50 top DEGs, revealed that 23 of them were associated with breast carcinoma, hereditary breast, and ovarian cancer, and breast disease (P < 0.05). Gene ontology enrichment in BP terms revealed that these DEGs were mainly involved in response to steroid hormone, regulation of

protein serine/threonine kinase activity, response to ketonea antibiotic, response to oxygen levels, Fc receptor signaling pathway, positive regulation of T cell activation, positive regulation of leukocyte cell-cell adhesion, regulation of DNA metabolic process, leukocyte cell-cell adhesion, cell junction assembly, and positive regulation of cell-cell adhesion. For CC, DEGs were mainly enriched in focal adhesion, cell-substrate adherens junction, and cell-substrate junction. For MF, DEGs were mainly enriched in RNA polymerase II core promoter sequence-specific DNA binding, protease binding, and integrin binding (P < 0.05). In the KEGG pathway analysis, the top enriched pathways included bacterial invasion of epithelial cells, focal adhesion, proteoglycans in cancer, Rap1 signaling pathway, regulation of actin cytoskeleton, PI3K-Akt signaling pathway, tight junction, and ECM-receptor interaction (P < 0.05). The results are demonstrated in Fig. 5A–C. In addition, the cluster Profiler package of R software and DIANA MirPath web server was used to conduct GO analysis and KEGG

pathway analysis for 14 miRNAs, respectively. For BP, 14 DEmiRs were mainly enriched in the regulation of angiogenesis, regulation of endothelial cell migration, and regulation of epithelial cell migration (P < 0.05). Moreover, the top five KEGG analysis pathways included Proteoglycans in cancer, Adherens junction, Cell cycle, FoxO signaling pathway, and Hippo signaling pathway (P < 0.05) (Fig. 5D).

3.6. Identification of hub genes

In biological networks, hub nodes are crucial proteins, because they are more likely associated with disease pathogenesis. Hence, we selected 12 hub genes based on centrality indices, MCODE results, DO, and functional enrichment analysis including RHOA, EZH2, KIT, FOXO3, HSP90B1, NCOA3, RAC1, IGF1, CAV1, CXCR4, CCNB1, and ITGB1.
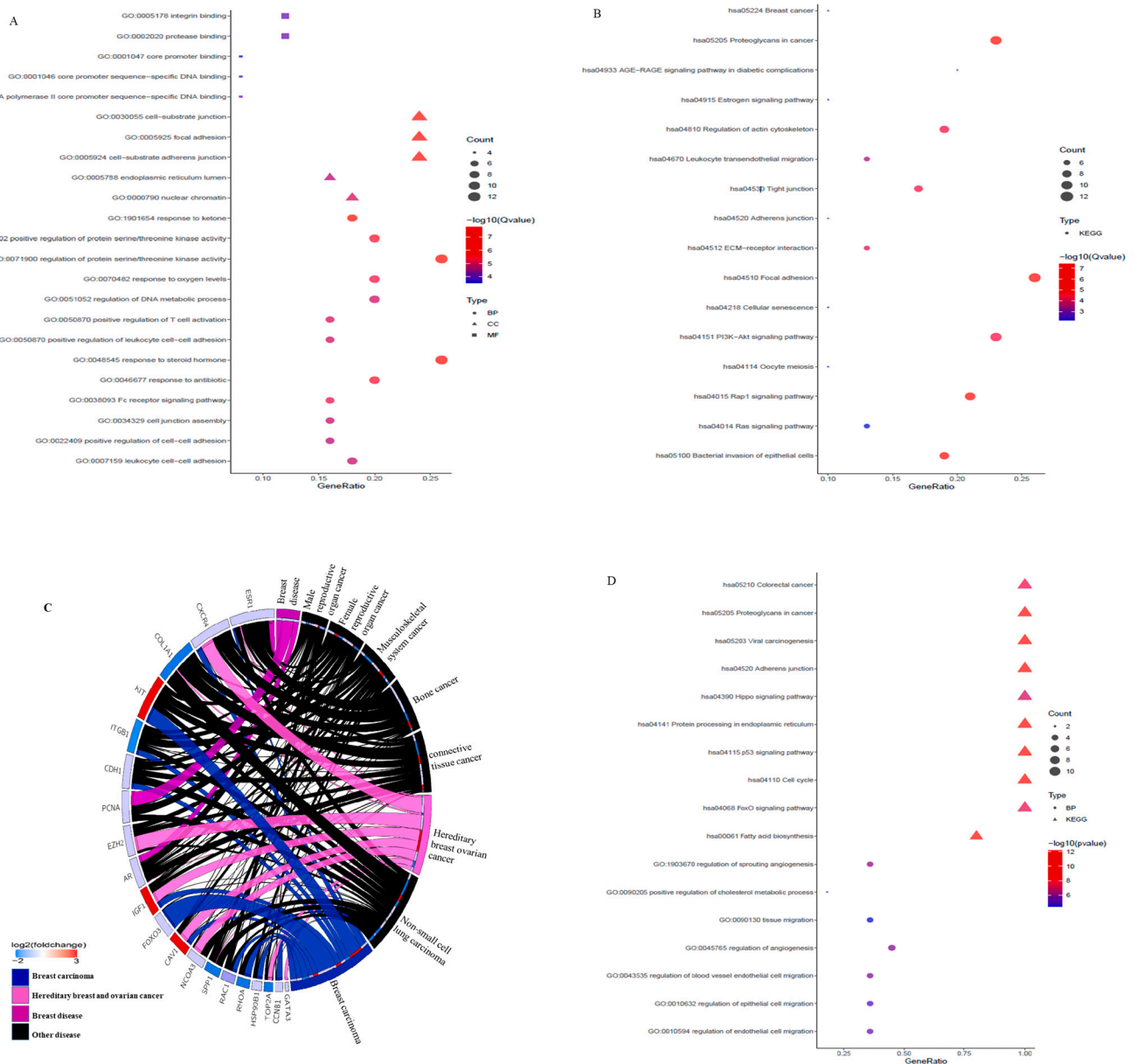
Fig. 5. Functional annotation for DEGs and DEmiRs. (A) Gene Ontology for DEGs; (B) KEGG pathway for DEGs; (C) Disease Ontology for DEGs; (D) KEGG pathway and Gene Ontology for DEmiRs. DO is represented by circular segment. Each ribbon represents a gene. The ribbon color represents the disease ontology for genes and segment color designates the fold change where upregulated and downregulated segments highlighted in red and blue, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.7. Prediction of miRNA target genes

MiRwalk database was searched to determine the interaction between 14 DEmiRs and 691DEGs. If the predicted genes from the database were not considered as hub nodes, they would be removed from our list. Using this approach, 821 miRNA-mRNA interaction pairs were obtained between 14 miRNA and 691 differentially expressed genes. Also, 43 interaction pairs were identified between 14 miRNAs and 12 hub mRNAs.

3.8. The prognostic value of hub mRNAs

The clinical outcomes of key genes were evaluated through survival analysis. GEPIA webserver was applied to determine whether the expression of hub genes were related to the breast cancer patients' overall survival (OS) and disease-free survival (DFS). This analysis indicated that for FOXO3, lower expression is closely related to improved OS (Logrank p = 0.0091; Fig. 6A). Besides, overexpression of RHOA is slightly associated with better DFS in BC patients (Logrank p = 0.015; Fig. 6B). Moreover, higher expression of KIT is associated with slightly higher survival rate in BC patients and this effect was altered over time (Logrank p = 0.016; Fig. 6C). All the other hub genes did not significantly influence the prognosis of patients with breast cancer.

3.9. Construction of a circRNA/lncRNA–miRNA–mRNA network

The circRNA/lncRNA–miRNA–mRNA competitive network was established through merging the circRNA–miRNA, lncRNA–miRNA, and miRNA–mRNA interactions using Cytoscape software (Fig. 7). This network contained 7 circRNAs, 14 miRNAs, 9 lncRNA,12 hub genes, and 378 DEGs, which presented a global outlook into the convoluted links between circRNAs, lncRNAs, miRNAs, and mRNAs in breast tumors.

3.10. Intermodulation of ncRNAs and their targeted gene

Non-coding RNA as main actors in gene regulatory networks, directly or indirectly regulate the function of mRNAs and the disruption of these regulatory networks which are reported in various types of cancer (Gao et al., 2019; Jayapal Manikandan et al., 2008; Qiu et al., 2018). Here, we showed the intermodulation of the distinct regulatory mechanism among various ncRNA and their targeted genes in breast tumors.

Based on the present study, circ_0007535, circ_0014130, and circ_0007001 circRNAs, which could intersect with four miRNAs were selected. circ-0007535 and circ_0014130 were down-regulated, while circ_0007001 was up-regulated in cancer tissues versus normal tissues. In our predicted circRNA-miRNA network, miR-183, miR-188, miR-7,

and miR-630 were recognized as target miRNAs for circ_0007535. There is uncertainty about the action mechanism of miR-183 in cancers. miR-183 has been reported to work as an oncogene or tumor suppressor in a wide range of human cancers (Cao et al., 2020). Several studies suggested that miR-183 acts as an oncogenic factor in human breast cancer thereby promotes cell proliferation and inhibits apoptosis in BC. For example, Yan Cheng et al. found that miR-183 was upregulated in breast tumors, enhances cell proliferation migration, invasion, and inhibits cell apoptosis by targeting PDCD4 (Cheng et al., 2016). Besides, the miR-183/-96/-182 cluster is highly expressed in most breast cancers and promotes cell proliferation and migration (Li et al., 2014). What's more, overexpression of mir-183 and mir-494 serves a critical role in BC metastasis and increases the growth and spread of cancer cells in human BC cell lines (Macedo et al., 2017). In our results, miR-183 was upregulated in breast cancer tissues and based on mirwalk prediction, it can regulate the expression of FOXO3, RHOA, RAC1, CAV1, IGF1, NCOA3, CCNB1, and ITGB1. Along with circ_0007535, we found three possible DEcircRNAs, circ_0002727, circ_0044927, and circ_0089153 can intercommunicate with miR-183 and thereby regulate the expression of above 12 DEGs. Multiple studies show that miR-188 as a potent tumor suppressor, induces apoptosis, and inhibits proliferation in breast cancer cells (Zhu et al., 2020). In our results, there was down-regulation of miR-188 in breast cancer tissues. We identified four probable crosstalk between these miRNAs and circRNAs, including circ_0007535-miR188-FOXO3/RHOA/IGF1, and circ_0002727-miR188-FOXO3/RHOA/IGF1. In the current study, it was found that circ_0014130 may adsorb corresponding miRNA through engaging with miRNA binding sites. It's MREs were detected via online tools including miR-1207, miR-200b, and miR-200c. As a target miRNAs, miR-1207-5p act as an oncogene and stimulates BC cell growth and proliferation by targeting STAT6 (Yan et al., 2017). In triple-negative breast cancer (TNBC), antagomir-1207-5p/chemotherapy combination increases sensitivity to treatment (Hou et al., 2019; Chaudhuri and Misra, 2016). Instead, miR-1207-5p acts as an antioncogene by impairing cell spreading, migration, and invasion in gastric cancer (Chen et al., 2014) and lung cancer (Dang et al., 2016). However, in our results, miR-1207 was down-regulated in luminal cancer tissues versus normal tissues, and further study required to explain the action mechanism of miR-1207 in luminal tumors. In this paper, we predicted miR-1207-5p as a target for circ_0014130 and hsa_circ_0007001 which may present a promising strategy for BC regulation. In addition, miR-200b-3p and miR-200c were associated with the ER status of BC cells and were down-regulated in the basal TNBC compared to ER+/epithelial cancer cell lines (Rhodes et al., 2015). They can repress a program of mesenchymal genes to keep an epithelial state and inhibit metastasis in breast cancer (Rhodes et al., 2015; Zheng et al., 2017; Cochrane et al., 2010). Consequently, triple-
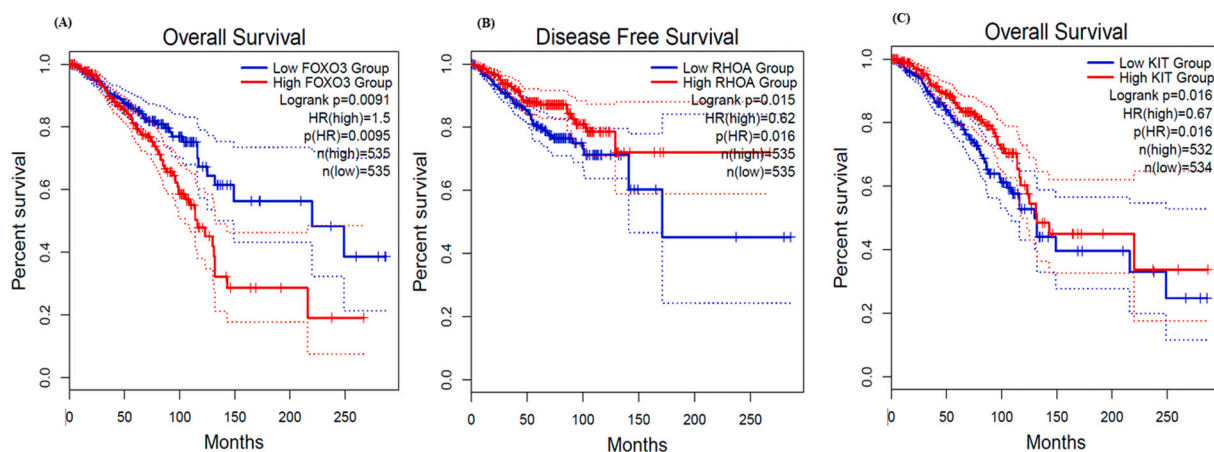

Fig. 6. The overall survival time of two hub-genes. (A) OS based on the FOXO3 expression level; (B) DFS based on the RHOA expression level; (C) OS based on the KIT expression level.
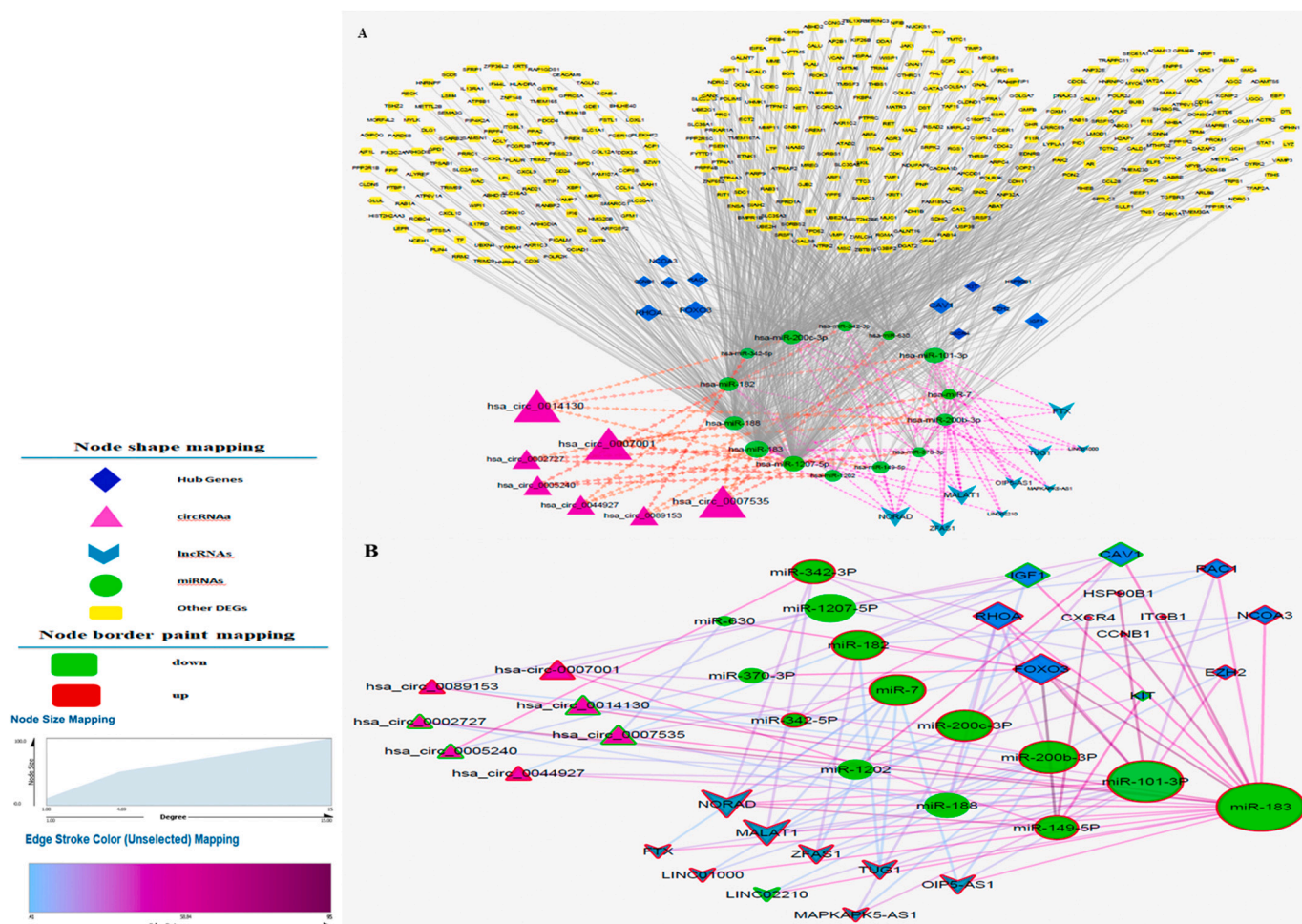
Fig. 7. A) A network of circRNA/lncRNA–miRNA–mRNA. B) A predicted network which shows the interactions between circRNA/lncRNA–miRNA–hub-genes.

negative breast cancer cells could benefit from the restoration of these microRNAs. Based on our assessment, there are links between circ_0007001 and miR-200b-3p in breast tumors, thus, inhibition of circ_0007001 by RNA interference (RNAi) may be an interesting target for TNBC treatment.

In this study, also a second regulatory network, interactions between differentially expressed lncRNAs, miRNAs, and mRNAs were determined. In our in silico assessments, among 9 selected DElncRNAs, five including NORAD, MALAT1, TUG1, ZFAS1, OIP5-AS1 could intersect with more than three DEmiRNAs like miR-183, miR-182, miR-7, miR149, miR-200b, miR,200c, miR-101, and miR-342. All of the above five LncRNAs were upregulated and could function as oncogenic ncRNAs contributing to the progression and invasivasion of breast tumors through modulating downstream pathways. Therefore, it is imperative to explore the molecular pathways implicated in BC drug resistance or tumor metastasis to refine therapeutic outcomes. Increased expression of lncRNA-NORAD in breast cancer tissues facilitates proliferation and invasion of breast cancer cells and is associated with poor prognosis. The study by Ke Zhou et al. showed that lncRNA NORAD was overexpressed in breast cancerous tissues and stimulated BC cell progression by regulating the TGF-β pathway (Zhou et al., 2019). We showed that NORAD could promote the occurrence and development of breast tumors by adsorbing miR-183, miR-182, miR-7, miR149, miR,200c, miR-101, and miR-342 as a sponge to regulate the expression of 12 hubs DEmRNAs including FOXO3, RHOA, EZH2, KIT, HSP90B1, NCOA3, RAC1, IGF1, CAV1, CXCR4, CCNB1, and ITGB1. Another lncRNA, taurine upregulated 1 gene (TUG1) is a lncRNA associated with diverse types of cancer such as breast tumors. The expression and action

mechanism of TUG1 in breast carcinoma is a quite arguable subject. The study by Teng Li. demonstrated that the TUG1 expression was enhanced in breast cancer tissues and highly invasive BC cell lines and was related to clinical and pathologic tumor characteristics including tumor size, distant metastasis, and TNM staging (T. Li et al., 2017). Whereas other studies reported downregulation of TUG1 in triple-negative BC and that its expression increases cisplatin sensitivity in TNBC cells (Tang et al., 2018). Based on our results, TUG1 could regulate the expression of 12 hubs DEmRNAs including FOXO3, RHOA, EZH2, KIT, HSP90B1, NCOA3, RAC1, IGF1, CAV1, CXCR4, CCNB1, and ITGB1by trapping miR-183, miR-182, miR-7, and miR-101. In most studies, Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALAT1) is commonly overexpressed and acts as a poor prognosticator lncRNAs in some types of cancers, including breast tumors (Amodio et al., 2018; Jadaliha et al., 2016). The action mechanism of MALAT1 on breast cancer cell proliferation is disputable, as reported that MALAT1 can act as metastasis promoter (Wang et al., 2018) and cell proliferation suppressor (Kim et al., 2018). The controversial evidence in the role of MALAT1 in tumorigenesis from distinct studies may be based on the specific tumor subtypes or different cell types (Wu et al., 2019; Arun and Spector, 2019). Likewise, MALAT1 might regulate the above mentioned hub DEGs by trapping miR-183, miR-342, miR-7,miR-200b, miR-200c, and miR-101. The study by Haibing Xiao et al., revealed that MALAT1 can modulate ZEB2 expression via trapping miR-200 s as a competing endogenous RNA and serve as a possible therapeutic target in clear cell kidney carcinoma (Xiao et al., 2015). Similarly, MALAT1 promotes melanoma expansion by inhibiting the expression and function of miR-183 and ITGB1 signal activation (Sun et al., 2017). Furthermore, the

repressive function of miR-101 on the autophagy and growth of colorectal cancer cells was abrogated by MALAT1 (Si et al., 2019). Consequently, NORAD, TUG1, and MALAT1 may be desirable biomarkers for breast cancer diagnosis and therapeutic targets in breast cancer management. It is noteworthy that these ncRNAs could interact with other 378 DEGs in the network and construct a complex regulatory RNA network. This study listed many ncRNAs, which might bind to miRNAs to regulate breast cancer progression. All potential circRNA–miRNA–mRNA and lncRNA–miRNA–mRNA crosstalks in breast cancer are summarized in Table 3.

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4. Discussion

Non-coding RNA regulatory networks as bridges between DNA and protein play significant roles in specific biological processes. Although nearly 40 years have elapsed since circular RNAs were first discovered, they were initially neglected as functionless byproducts of errors in the normal splicing process (Hsu and Coca-Prados, 1979; Sanger et al., 1976). Nonetheless, in the past few years, continuous achievements in sequencing technology and new bioinformatics algorithms leading to the enigma of circRNAs have gradually been unveiled that these molecules serve a significant role in pathogenesis and progression in a broad spectrum of human diseases, in particular in cancer (Haddad and Lorenzen, 2019; Yang et al., 2018; Li et al., 2018; Chen et al., 2019). Furthermore, circRNAs show valuable opportunity as diagnostic and prognostic biomarkers, due to high levels of evolutionary conservation and abundance, stability, and tissue- specificity (Zuo et al., 2020; Jeck et al., 2013). For instance, the plasma level of circ_0001785 in breast cancer patients compared to healthy donors is upregulated and acts as a diagnostic biomarker for BC detection (Yin et al., 2018). Based on the evidence, circRNAs have great therapeutic potentials. Thus, the application of RNA interference (RNAi) for oncogenic circRNAs and induction of tumor-suppressive circRNAs expression for tumor suppressive

Table 3
All potential circRNA–miRNA–mRNA and lncRNA–miRNA–mRNA axes in breast cancer.

DEcircRNA	DElncRNA	DEmiRNA	DEG
circ-0007535	NORAD	miR-183	RHOA
circ-0044927	MALAT1		IGF1
circ-0089153	OIP5-AS1		CCNB1
circ-0002727	TUG1		ITGB1
	FTX		RAC1
	LINC01000		FOXO3
	LINC02210		CAV1
circ-0014130	NORAD	miR-101	RHOA
circ-0044927	MALAT1		EZH2
	OIP5-AS1		RAC1
	TUG1		HSP90B1
	ZFAS1		FOXO3
	FTX		
	LINC02210		
	MAPKAPK5-AS1		
circ-0007001	NORAD	miR-149	FOXO3
			CXCR4
			KIT
circ-0044927	NORAD	miR-182	IGF1
	TUG1		FOXO3
	ZFAS1		CAV1
			NCOA3
circ-0014130	MALAT1	miR-200b	RHOA
circ-0007001	OIP5-AS1		EZH2
	ZFAS1		
	LINC01000		
	LINC02210		
	MAPKAPK5-AS1		
circ-0014130	NORAD	miR-200c	RHOA
	MALAT1		FOXO3
	LINC01000		CAV1
	MAPKAPK5-AS1		NCOA3

circRNAs in cancer cells or tissue could have anticancer effects (Zhang et al., 2020; Li et al., 2020; Wan et al., 2020). Additionally, lncRNAs would serve as promising biomarkers for clinical diagnosis and prognosis (Sun et al., 2013; Baratieh et al., 2017; Hashad et al., 2016; Elsayed et al., 2018). Research has indicated that circular RNAs share similar features and biological functions with lncRNAs. For example, they regulate mRNA expression by adsorbing miRNAs like miRNA sponges (Peng et al., 2017; Hansen et al., 2013), serve as protein scaffolds (Du et al., 2017; Rinn and Chang, 2012), remained stable in extreme conditions over a relatively long time (Cheetham et al., 2013; Jeck and Sharpless, 2014), and are associated with a variety of diseases (J. Li et al., 2015; Anastasiadou et al., 2018). Numerous studies that simultaneously investigate these regulatory networks are required to further discover the complexity of the networking between different types of non-coding RNAs to find new opportunities for the therapeutic management of breast cancer.

In this study, based on the potential interaction between mRNAs, miRNAs, circRNAs, and lncRNAs, we constructed a ceRNA regulatory network. First, breast cancer-specific RNAs, including mRNAs, miRNAs, lncRNAs, and circRNAs were filtered and differentially expressed items were obtained. Next, we identified seven circRNAs could interact with more than two of DEmiRNAs (hsa_circ_0007535, hsa_circ_0002727, hsa_circ_0005240, hsa_circ_0014130, hsa_circ_0044927, hsa_-circ_0007001, hsa_circ_0089153). As reported previously, some circRNAs can regulate the expression of the target genes by competitive binding with miRNA response elements to inhibit their expression (Zhong et al., 2018). Thus, we predicted MREs in seven circRNAs mentioned through CSCD, CircInteractome, and CircBank online tools. Every seven circRNAs were found out as ceRNA to regulate the expression of 14 miRNA that overlapped with DEmiRs including miR-183, miR-101,miR-200b, miR-1202, miR-1207, miR-200c, miR-7, miR-342, miR-182, miR-188, miR-149, miR-370, miR-630. To determine whether these DEmiRNAs are linked with DElncRNAs, we predicted their interactions via the LncBasev3 online tool. At last, nine lncRNAs including MALAT1, NORAD, TUG1, ZFAS1, FTX, OIP5-AS1, LINC01000, LINC02210, MAPKAPK5 -AS1 were detected. Many studies have revealed that dysregulation of circRNAs is significantly correlated with pathogenesis and prognosis in BC and can be regarded as a new diagnostic biomarker. For instance, hsa_circ_0001982 was upregulated in BC tissue and cell lines and increases cell migration by decoying miR-143 (Y.-Y. Tang et al., 2017). In addition, plasma hsa_circ_0001785 level was related with histological grade, TNM stage, and distant metastasis and act as a breast cancer biomarker for the detection and progression tracking (Yin et al., 2018). Meanwhile, several lncRNAs are abnormally overexpressed in various types of BC cells like HOTAIR (Wu et al., 2014), linc-ROR (Fan et al., 2015), and BCAR4 (Xing et al., 2014) and they foster BC invasion and metastasis. In contrast, some evidence showed that lncRNAs can suppress breast tumor growth via inhibitory effects such as MALAT1 (Xu et al., 2015), NKILA (Su et al., 2015), and ANCR (Z. Li et al., 2017).

As part of this study, to better explain the action mechanism of nRNAs in gene expression regulation by targeting miRNA, we constructed a PPI network. Following centrality analysis, we determined the top 50 nodes based on degree, closeness, and betweenness indices. It was necessary to prune the fifty identified genes to make the study more reliable and to achieve this goal, enrichment analyses were performed. The functional enrichment and pathway analyses elucidated these genes were related to many significant tumor-associated pathways. Additionally, we obtained 23 breast tumor-associated genes depend on disease ontology. In the final analysis, 12 hub genes were picked out based on centrality indices, modularity analysis, DO, and functional enrichment analyses including FOXO3, RHOA, EZH2, KIT, HSP90B1, NCOA3, RAC1, IGF1, CAV1, CXCR4, CCNB1, and ITGB1.

Among these hub-genes, FOXO3 shows considerable impacts on OS between the BC and normal tissue groups. Moreover, high expression of RHOA is slightly associated with a higher rate of disease-free survival in BC patients.

FOXO3, a member of the Forkhead box O (FoxO) transcription factor family, is important mediator of many different bioprocess like cell cycle progression, apoptosis, survival, and DNA damage. FOXO3, also known as FOXO3a, play a role a tumor suppressor in variety of human cancers and has a protective role in ER+ breast tumors. Many evidences have revealed that FOXO3a serves as a prognostic biomarker in multiple cancers, especially in Luminal-like BC. While tamoxifen therapy is still a good choice for ER+ breast cancer patients, in many cases, acquired resistance to anti-hormone therapy is inevitable (Bullock, 2016; Taylor et al., 2015). In tamoxifen-resistant BC, upregulation of growth factor signaling pathways, activation of phosphatidylinositol 3-kinase (PI3-K)/Akt, including PTEN down-regulation, make the growth of resistant cells easier. FOXO3a works downstream of PI3K/AKT pathway and is inactivated by overactivation of the PI3K/Akt pathway in the most of breast tumors (Pellegrino et al., 2019; X. Zhang et al., 2017). Meanwhile, dysregulation of the PI3K/AKT signaling pathway is one of the most frequent oncogenic aberrations in TNBC (Taylor et al., 2015). Noteworthy, FOXO3a may be an attractive therapeutic target, especially cells like TNBC and also in tamoxifen resistance breast tumors. Several miRNA binding sites in 3′UTRs of FOXO3a can greatly increase the level of regulation (Taylor et al., 2015; Liu et al., 2018). Many miRNAs regulate the FOXO3 expression in several physiological and pathological processes. For instance, MicroRNA-155 can regulate cell survival, growth, and chemosensitivity by targeting FOXO3a in breast cancer and overexpression of miR-155 represses this gene (Kong et al., 2010). In our constructed ce-network by microarray analysis, we show that FOXO3 is up-regulated in breast cancer tissues and it's expression can modulate via 9 miRNAs including miR-183, miR-342,miR-370,miR-101, miR-182, miR-149, and miR-200c. Moreover, we demonstrated that circ_0007535, circ_0014130, circ_0007001, circ_0002727, circ_0005240, circ_0044927, and circ_0089153 might regulate expression of FOXO3 via targeting these miRNAs. In parallel, lncRNAs NORAD, MALAT1, TUG1, ZFAS1, and OPI5-AS1 by adsorbing miR-183, miR-182, miR149, miR,200c, miR-101, and miR-342 through sponge mechanism, regulate expression of FOXO3. So far, no relevant study has reported this axis aforementioned to target FOXO3 in breast cancer. However, Jie Lin et al. showed that miR-149 plays a critical role in pyroptosis during cardiac I/R injury by silencing FOXO3 and thus, may offer a novel therapeutic opportunity (Lin et al., 2019). As mentioned earlier, FOXO3a may be a critical therapeutic target in hormone-independent breast cancers. Therefore, these ncRNAs can play anti-oncogenic roles in BC by creating miRNA sponge constructs for miR-183,miR-101, miR-149, miR-182, miR-342, and miR-200c, and thereby promoting tumor-suppressive function of FOXO3 [79]. Therefore, FoxO3a reactivation via overexpression of the circRNAs and/or lncRNAs, and down-regulation of miRNAs which were up-regulated in cancer(miR-183,miR-342, miR-101, miR-182, miR-149, and miR-200c), seems to be a promising tool in the development of a novel treatment strategy for cells like TNBC and also in tamoxifen resistance breast tumors. RHOA and RAC1, are another important hub genes in our ce-network . Rho GTPases belong to the Ras superfamily and are classified into eight subfamilies (Rho, Rac, Cdc42, RhoD/RhoF, RhoH, RhoU/RhoV, Rnd, and RhoBTB). The RHO GTPase family play central roles in diverse biological processes, including cell morphology phenotypes, cytoskeletal rearrangements, cell polarity, cell cycle progression, and cell migration, by regulating actin cytoskeletal dynamics and cell adhesion (Nam et al., 2019; Jung et al., 2020). RhoA and Rac1 have been described as oncogenes due to their overexpression within malignant tumors such as breast cancer, and their associations to metastasis, migration, invasion, cell cycle progression, drug resistance, and diverse clinical outcomes (Jung et al., 2020; Yadav et al., 2020). Hence, targeting RHOA1and RAC1 represents a right approach for suppressing cancer cell proliferation (Pillé et al., 2005; del Mar and Dharmawardhane, 2018). Our results showed that RHOA and RAC1were up-regulated in breast cancer tissues. Parallelly, microarray analysis revealed that circ_0089153, circ_0007001, circ_0044927, NORAD,

MALAT1, TUG1, ZFAS, OPI5-AS1 were up-regulated in breast cancer tissues, and might serve as oncogenic ncRNAs by competitive binding with miRNAs(miR-342, miR-101, miR-200b, and miR-200c) to inhibit their expression and therefore increase the expression of RHOA and RAC1 genes. In addition, miR-1207, which is down-regulated in breast cancer tissues, is a negative regulator of RAC1, thus overexpression of miR-1207 may lead to significant tumor regression. Therefore might be anticipated that application of precise RNA interference (RNAi) to oncogenic circRNAs and lncRNAs or targeted delivery of miRNAs to reduce the mRNA levels of oncogenes could develop an effective means for inhibiting tumor growth and aggression.

5. Conclusion

Here, regulatory networks were designed for both lncRNA-miRNA-mRNA and circRNA-miRNA-mRNA and highlighted the importance of cooperation between circRNAs with lncRNAs which could regulate the same miRNAs and could generate a complicated regulatory RNA network. Likewise here, circ0007535/ circ0002727/circ0044927/ circ0089153-miR183 and NORAD/MALAT1/TUG1/OPI5.AS1/ZFAS1-miR183; circ0014130/circ0044927-miR101 and NORAD/MALAT1/ TUG1/OPI5.AS1/ZFAS1-miR101; circ0014130-miR200c and NORAD/ MALAT-miR-200c; circ0005240-miR342 and NORAD/MALAT-miR342; circ0044927-miR182 and NORAD/TUG1/ZFAS1-miR182; circ0007001-miR149 and NORAD-miR149, might target FOXO3 to control BC progress. As well, circ0007535/circ0002727/circ0044927/ circ0089153-miR183 and NORAD/MALAT1/TUG1/ZFAS1/ OPI5.AS1-miR183; circ0014130/circ0044927-miR101 and NORAD/ MALAT1/ TUG1/OPI5.AS1/ ZFAS1-miR101; circ0014130-miR200c and NORAD/ MALAT-miR-200c; circ0005240-miR342 and NORAD/MALAT-miR342; circ0007001/ circ0014130-miR200b and MALAT1/ OPI5. AS1/ZFAS1-miR200b might target RHOA to control BC progress (Fig. 8).

The current study provides a new perspective into the possible molecular mechanisms among various RNA crosstalks underlying the carcinogenesis and progression in luminal breast tumors and especially endocrine-resistant breast cancer patients. The aim of this study was to revive researchers' enthusiasm in studying the potential role of ncRNAs as novel prognostic biomarkers and to make new treatment decisions for breast cancer patients. Improving our understanding of the nature of ceRNA crosstalk makes new opportunities to establish ceRNA-based therapeutic purposes. However, these findings need further experimental validation and confirmation in the future.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

CRediT authorship contribution statement

Bita Hassani and Hassan Mollanoori contributed to the data collection and interpretation.

Yazdan Asgari, Farkhondeh Pouresmaeili and Soudeh Ghafouri-Fard designed the study, drafted and revised the manuscript.

Declaration of competing interest

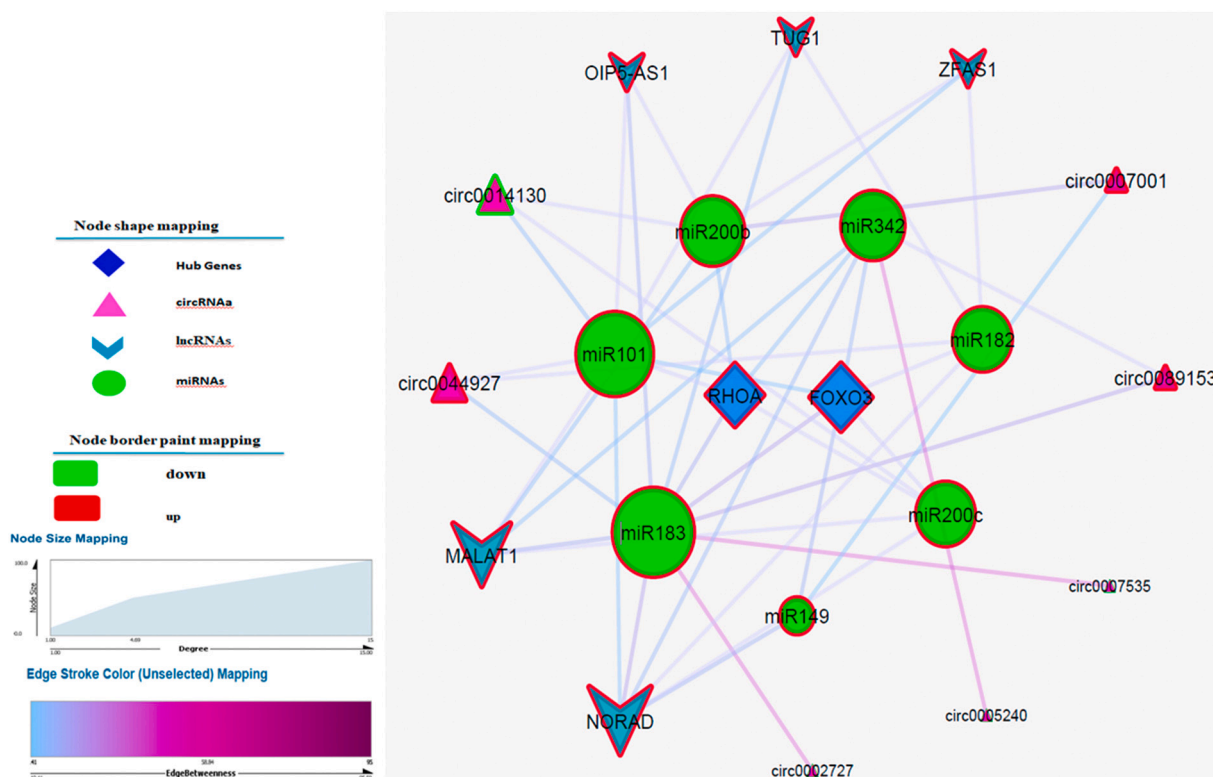All authors have contributed significantly and that all authors are in

Fig. 8. Predicted network for CircRNA/lncRNA-miRNA-FOXO3/RHOA gene communications.

agreement with the content of the manuscript. The authors declare that they have no competing interests.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Additional file 1: Supplementary file. Significant genes. Table 1. Significant miRNAs. Table 2. Significant circRNAs. Table 3. Significant lncRNAs. Table 4. String Result. Table 5. Centrality Results. Table 6. Functional annotation Result. Table 7. Supplementary data to this article can be found online at https://doi.org/10.1016/j.genrep.2022.101510.

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