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Integrative bioinformatics analysis of miRNA and mRNA expression profiles identified some potential biomarkers for breast cancer

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Abstract

Background Breast cancer is a common cause of cancer death among women with a complex and heterogeneous picture in histological, molecular and clinical features. The aim of this study was to identify hub gene and their target microRNAs in related pathways for breast cancer.

Methods We selected screening methods for differentially expressed mRNAs and miRNAs using expression profile data of breast cancer from the cancer genome atlas. Using some databases for annotation, the functional and pathway enrichment for differential expression genes was performed. We selected genes and miRNAs with differential expression pattern. Then we determined target genes for differential expression miRNAs (DEMIs) and intersection between them was selected as differentially expressed miRNA-target genes for breast cancer. In the next step, we constructed miRNA-mRNA regulatory network and protein-protein interaction (PPI) network for more information.

Results Top 10 DEMIs were identified from miRNA profile. Then, we selected 354 genes as target gene for 10 DEMIs. The miRNA–mRNA and PPI network were constructed, and 10 hub genes and 5 miRNAs identified that some of them are new for breast cancer. Also, miRNA–target genes with differential expressions in this study were all mainly involved in signaling pathways and developmental process.

Conclusion This study identified some candidate biomarkers for breast cancer that they have a potential role in pathways related to breast. These findings can be used for research, early diagnosis and therapeutic goals.

Keywords Breast cancer, Bioinformatical analysis, miRNA, mRNA

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Introduction

Breast cancer is a common cause of cancer death that starts in the breast tissue and is associated with overgrowth and abnormal growth of cells in various breast tissues [1, 2]. Breast cancer is one of the most frequent cancers among females, and some serious health problems are related to breast cancer all over the world. This disorder is the second leading cause of cancer death among women and is a heterogeneous complex disorder with different histological, molecular and clinical phenotypes [3, 4].

Although some improvement strategies such as surgical and chemotherapy techniques have been achieved in recent years, late diagnosis and resistance to treatment are serious problems which lead to a poor prognosis for some patients in this regard [5, 6].

Based on previous studies, there are some evidences about role of genes and microRNAs in molecular pathways that are involved in progression and development of breast cancer [5]. MiRNAs are a class of small noncoding regulatory RNAs that are involved in controlling gene expression at the posttranscriptional level, and they are particularly promising due to their molecular stability, their ease of detection by noninvasive methods and their ability to provide improved subtype classification. Evaluation of differential expression profiles for these genes and microRNAs can be used as valuable clues to discover new biomarkers which are more effective for early diagnosis and therapeutic strategies in breast cancer patients [5, 7].

An ideal strategy to obtain valuable genetic information is bioinformatics analysis for the comprehensive analysis of large databases such as The Cancer Genome Atlas (TCGA). TCGA is a genomics program related to cancer landmarks, which contains the molecular profile of more than 20,000 primary cancers and matched normal samples including 33 cancer types [8].

In the present study, we used sophisticated bioinformatics methods to find useful potential biomarkers in molecular data from breast cancer.

Methods

Patients and sampling

We downloaded clinical data from breast cancer patients from the TCGA database. Criteria for including patient data in the present study include histopathological diagnosis of breast cancer, demographic information such as age, sex, race, disease status, survival status, pathological stage, TNM classification, and survival time. In total, data from 1097 patients were included in this study.

DEG identification

We collected RNA-seq level 3 data from the TCGA database. Using Voom and TMM normalization methods, raw readings of RNA-seq data were normalized. All analyses were performed with R software. The limma package was used to demonstrate the differential expression of miRNAs (DEmiRNAs) and mRNAs (DEmRNAs) between primary tumors and normal tissue. Data obtained based on change|log2 fold (FC)|>1 are filtered for DEmiRNAs and DEmRNAs. *P* value < 0.05 and false detection rate (FDR) < 0.05 were considered for significant thresholds.

DEGs pathway enrichment analysis

Gene ontology (GO) was used to analyze functional enrichment in biological processes, cellular components and molecular functions levels. Due to classified genes in related pathways, the analysis of DEGs signaling pathways was carried out based on KEGG (Kyoto Encyclopedia of Genes and Genomes) database (https://www.genome.jp/kegg/) and DAVID (the database for annotation, visualization and integrated discovery) online database (https://david.ncifcrf.gov/). In this part, pathways with *P* value < 0.05 were screened.

Protein-protein interaction (PPI) network construction analysis

The miRNA–mRNA network and protein–protein interaction (PPI) network were formed by Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) online tool. CytoHubba package of Cytoscape 3.9.1 was used to analyze and predict interactions and represent nodes and edges (score > 0.4). The cutoff criteria for construction of PPI for degree, node score, K-score and maximal depth were 2, 0.2, 2 and 100, respectively.

Results

Study population

Demographics results of participants including age, sex, ethnicity and race are shown in Table1. Also, the pathological characteristics based on The TNM Classification are shown in Fig. 1.

Identification and selection of DEGs in breast tumors and normal samples

In the first stage, DEGs were selected with P < 1.07E-30 and -7 < |logFC| < 7. A total of 1639 DEGs were identified when normal samples were compared with breast tumor samples.

In the second stage, we identified top 10 miRNAs with differentially expressed from miRNA profile

Table 1	Chara	cteristics	of	participants
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Characteristics	N	(%)
Age (year) (mean ± SD)	58.46±13.21	
Age>58	546	49.77
Age≤58	551	50.23
Sex		
Male	12	1.09
Female	1085	98.91
Ethnicity		
Hispanic or Latino	40	3.65
Not Hispanic or Latino	884	80.58
NA	173	15.86
Race		
Asian	61	5.56
Black or African American	183	16.68
White	757	69.01
American Indian or Alaska Native	1	0.09
NA	95	8.66

including 4 upregulated miRNAs and 6 downregulated miRNAs (Table 2). In the next stage, we identified a list of gene targets for this top 10 DEMIs by using multiMir package in R software which are 3141 in number. Then, from the sharing between the data of the first stage and the target genes, we reached 354 common genes (Fig. 2).

Functional and pathway enrichment analysis of differentially expressed genes (DEGs)

Based on GO enrichment analysis, DEGs were classified into three groups including a cellular component group, a biological process group and a molecular function group, which are shown in Fig. 3A–D

In the cellular component group, GO terms mainly included chromosome, chromosomal part and chromatin (3A). In the biological process analysis, GO terms were mainly involved in the regulation of cellular, biological and developmental process (3B). Evaluation for molecular function group showed that GO terms mainly involved for transcriptional factors activity, enzymes binding, core promotor proximal region DNA binding and core promotor proximal region sequences (3C). Also, evaluation for pathway enrichment showed that DEGs were mainly involved in cancer pathways (3D).

Protein-protein interaction (PPI) network and modular analysis for DEGs

Withdrawing string network for 354 common genes (Fig. 4, node = 293, edge = 1454), we selected top 10 genes by using cytoHubba in Cytoscape. Also, among the 10 DEMIs, there were 5 DEMIs (hsa-miR-141-3p, hsa-miR-96-5p, hsa-miR-204-5p and hsa-miR-139-5p) related to top 10 genes. Therefore, PPI network consisted of 5 DEMIs as nodes and these 10 genes as edges. These 5 DEMIs (hsa-miR-141-3p, hsa-miR-96-5p,



Table 2	Тор	10	DEMIs
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microRNAs	P value	Log FC
hsa-miR-141-3p	1.67E-101	3.05
hsa-miR-96-5p	1.38E-86	3.10
hsa-miR-1307-5p	3.03E-90	3.16
hsa-miR-592	5.84E-77	3.41
hsa-miR-486-5p	9.78E-114	-4.15
hsa-miR-139-3p	1.02E-129	- 3.65
hsa-miR-204-5p	2.13E-100	- 3.59
hsa-miR-139-5p	1.30E-150	- 3.23
hsa-miR-451a	1.19E-74	- 3.11
hsa-miR-5683	1.17E-50	- 3.00



Fig. 2 List 1 of genes obtained from RNA-seq level 3 analysis from the TCGA database and list 2 of target genes for top 10 DEMIs obtained with multimir software; the number of common genes between list 1 and 2 was 354

hsa-miR-486-5p, hsa-miR-204-5p and hsa-miR-139-5p) are related to 10 genes including *JUN*, *CCNB1*, *AURKB*, *CCNA2*, *MKI67*, *FOXM1*, *ASPM*, *TTK*, *TOP2A* and *KIF23* (Fig. 5).

Evaluations for functional enrichment showed that they were mainly involved in signaling pathways and developmental process.

Discussion

Breast cancer is a heterogeneous complex disease with large heterogeneity in the genomic landscape with a high mortality rate. Examining the expression profile and related pathways can be a clue to early prognosis, diagnosis and treatment of breast cancer. The aim of the present study was to explore the expression profile and related pathways from breast cancer. Therefore, mRNA and miRNA expression profiles were used for differential expression mRNAs (DEMs) and miRNAs (DEMIs). Among top 10 DEMIs, 5 miRNAs including hsa-miR-141-3p, hsa-miR-96-5p, hsa-miR-486-5p, hsa-miR-204-5p and hsa-miR-139-5p were associated with 10 related genes including *JUN, CCNB1, AURKB, CCNA2, MKI67, FOXM1, ASPM, TTK, TOP2A* and *KIF23*. These miRNAs and genes were mainly involved in signaling pathways, cell cycle process such as cell division, and DNA rapier and DNA binding which are useful for the development early diagnosis and new therapeutic strategies. In this study, we found some microRNA related to hub genes that association between them and hub genes was studied in some previous studies. The association between these genes and miRNAs in breast cancer has not reported in previous studies. Therefore, they can be useful as biomarker.

In the current study, data analysis showed JUN and KIF23 genes are target genes for has-miR-139-5p with downregulated expression in tumor samples in comparison with normal samples. JUN regulates the activity of cyclinD1 and p53 and other genes involved in cellular growth and proliferation. Moreover, c-JUN plays an essential role in tumor progression [9, 10]. A study found that c-JUN overexpressed in invasive breast cancer [11] and increased microvessel density [10]. KIF23 is a crucial regulator of cytokinesis and microtubule-dependent molecular motors that move chromosomes during cell division and plays an important role in tumorigenesis and cancer progression [12, 13]. Zhi Li et al. found that KIF23 significantly upregulated and promoted EMT progression in TNBC [14]. miR-139-5p has a vital role in tumorigenesis and various types of cancers, including breast cancer. miR-139-5p had a significant role in breast cancer cell motility and invasion [15]. A study reported that miR-139-5p expression levels were significantly depleted in breast cancer samples. Yang Zhang et al. indicated that miR-139 inhibited JUN expression, and JUN could induce miR-139 expression. Aberration in this loop could develop gastric cancer. This result reveals miR-139-5p potential as a prognostic marker for breast cancer.

In this study, data analysis showed TTK gene as a target gene for hsa-miR-486-5p with a downregulated expression in tumor samples in comparison with normal sample. TTK is a component of the spindle of the checkpoint and required for chromosome alignment at the centromere during mitosis [16]. TTK expression level was elevated in different types of cancer, including lung, breast, bladder, prostate and anaplastic thyroid. Overexpression of TTK in cancer tissues correlates with poor prognosis in HER2-positive breast cancer [17–19]. miR-486-5p plays an important role in several cancers, and it is a tumor-specific miRNA. Gharehdaghci et al. reported that miR-486-5p expression decreased in breast cancer and affects cellular proliferation, invasion and apoptosis



Fig. 3 Gene ontology (GO) and signaling pathway enrichment analysis of DEGs. GO enrichment analysis of DEGs showed A cellular component, B biological process, C molecular function and D Signaling pathways enrichment of DEGs

[20]. Therefore, hsa-miR-486-5p can be an ideal marker for more investigation for prognosis, diagnosis and therapeutic goals in breast cancer.

In the current study, the results showed AURKB and FXOM1 gene are target genes for has-miR-204-5p with a downregulated expression in tumor samples. Aurora kinase B (AURKB) is a conserved family of serine/threonine kinase that has an essential function during cell cycle, such as chromosome segregation, spindle organization and cytokinesis [21, 22]. AURKB is overexpressed in several cancers, such as triple-negative breast cancer. AURKB overexpression prevents cell apoptosis by impairing p53 function [23]. FOXM1 gene is another gene with differential expression in this study, plays a role in cell proliferation and DNA damage repair process and is crucial for G1/S transition [24]. Moreover, FOXM1 regulates cell cycle genes; thus, FOXM1 overexpression affects triple-negative proliferation [25]. Previous studies have reported that miR-204-5p acts as tumor inhibitor and downregulated in human cancers such as breast cancer, gastric cancer, papillary thyroid carcinoma and hepatocellular carcinoma. Also it has been confirmed that overexpression of miR-204-5p inhibits cell migration and metastasis in breast cancer [26].

In this study, results showed *TOP2A* and *CCNB1* are target genes for has-miR-96-5p with upregulated

expression in tumor samples in comparison with normal samples. TOP2A encodes a nuclear enzyme that regulates DNA topological state, and it is essential for chromosome condensation and chromatid separation. TOP2A is overexpressed in cancer types including breast, lung, ovarian and hepatic [27, 28]. TOP2A has located approximately 700kb telomeric to HER2. TOP2A gene is co-amplified in about one-third of all patients with HER2 amplification. TOP2A monitoring could predict breast cancer patients' overall survival and lower expression associated with better clinical outcomes [29]. CCNB1, a critical member of the cyclin family, plays a significant role in mitosis initiation and quality control mitosis steps [30]. Accumulating studies have demonstrated the role of CCNB1 in various cancers, including melanoma cancer, colorectal cancer, pancreatic cancer and breast cancer [31]. It was reported that CCNB1 activates p53 signaling pathways and promotes cell apoptosis, which may be an important prognostic marker for breast cancer patients [30]. Ding et al. have demonstrated that high expression of CCNB1 was significantly associated with poor hormone therapy outcomes and could be a biomarker for the prognosis of patients with ER-positive breast cancer. These reports agree with our demonstration that CCNB1 was associated with breast cancer [32, 33]. miR-96-5p is a oncogenic miRNA, and it is associated with several cancers



Fig. 4 String network for 354 common genes

including breast, prostate and bladder cancer [34]. Mouchun Gong et al. found that *TOP2A* is a target for two microRNAs including miR-96-5p and miR-635. Based on the previous study, miR96-5p significantly upregulated in papillary thyroid cancer (PTC) [35]. miR-96-5p has a tumor-promoting role in breast cancer. A study reported that miR-96-5p was significantly overexpressed in breast cancer and promoted BC cell migration by targeting AK3 in MEK/ERK signaling [36]. These results showed miR-96-5p has potential to be a marker for prognosis, diagnosis and therapeutic goals in breast cancer. In this study, results showed that *ASPM*, *CCNA2*, *MKI76* and *TOP2A* are target genes for has-miR-141-3p with overexpression in tumor samples. *ASPM* regulates mitotic spindle organization, spindle orientation and cytokinesis [37]. The ASPM gene has an important role for making a protein that is involved in cell division. However, it appears to be particularly important for the division of cells in the developing brain. *ASPM* is over-expressed in various cancers, including hepatocellular, ovarian and prostate cancer. ASPM expression levels correlate with tumor grades, and overexpression of ASPM



Fig. 5 PPI network consisted of 5 DEMIs as nodes and these 10 top genes as edges

is associated with a worse prognosis [37]. Another study reported a correlation between CCNB2 and ASPM; thus, overexpression of CCNB2 and ASPM causes breast cancer development [38]. MKI67 is a nuclear protein and is closely related to cell mitosis and is widely used as a proliferation marker [39]. MKI67 is used as a prognostic marker in some cancers, including early breast cancer and non-small lung cancer. Moreover, the MKI67 expression level is related to pathological grade in tumors. Guangyu Sun et al. demonstrated that the expression of MKI67 gene was associated with metastasis and invasion of breast cancer [40]. CCNA2 is a regulator for cell cycle and plays a vital role in controlling the cell cycle at G1/S and G2/M steps [30]. Based on several studies, CCNA2 expression can be used as a prognostic biomarker for ERpositive for tamoxifen resistance in breast cancer [33]. MiR-141-3p is downregulated in breast cancer, and it has capability as a prognostic factor for overall survival in patients with breast cancer [41]. Shanping Sun et al. indicated that miR-141-3p downregulated in breast cancer and miR-141-3p introduced as hypoxia-responsive miRNA and it might be targeting AK3 gene in HMGB1/ HIF1a signaling pathway [41].

Conclusion

There is a lack of reliable biomarkers for patient selection and therapeutic efficacy for patients with breast cancer. In this study through the formation of the protein–protein interaction network with the STRING database and bioinformatics analysis, we identified 10 hub genes and 5 microRNA that had high degrees of confidence, indicating that all of them might play pivotal roles in breast cancer-related pathways. These findings can be helpful for more information about molecular mechanism involved in breast cancer, and they can provide new insight for more investigation and development of early diagnosis and therapeutic targets for breast cancer. More investigations in experimental and clinical samples are needed.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43042-023-00443-9.

Additional file 1. Effect of ASPM expression level & cancer type on BRCA patient survival.

Additional file 2. Effect of AURKB expression level & cancer type on BRCA patient survival.

Additional file 3. Effect of CCNA2 expression level & cancer type on BRCA patient survival.

Additional file 4. Effect of CCNB1 expression level & cancer type on BRCA patient survival.

Additional file 5. Effect of FOXM1 expression level & cancer type on BRCA patient survival.

Additional file 6. Egyptian Journal of Medical Human Genetics.

Additional file 7. Effect of JUN expression level & cancer type on BRCA patient survival.

Additional file 8. Effect of KIF23 expression level & cancer type on BRCA patient survival.

Additional file 9. Effect of MKI67 expression level & cancer type on BRCA patient survival

Additional file 10. Effect of TOP2A expression level & cancer type on BRCA patient survival.

Additional file 11. Effect of TTK expression level & cancer type on BRCA patient survival.

Additional file 12. Expression of ASPM in BRCA based on sample types.

Additional file 13. Expression of AURKB in BRCA based on sample types.

Additional file 14. Expression of CCNA2 in BRCA based on sample types.

Additional file 15. Expression of CCNB1 in BRCA based on sample types.

Additional file 16. Expression of FOXM1 in BRCA based on sample types.

Additional file 17. Expression of JUN in BRCA based on sample types.

Additional file 18. Expression of KIF23 in BRCA based on sample types.

Additional file 19. Expression of MKI67 in BRCA based on sample types.

Additional file 20. Expression of TOP2A in BRCA based on sample types.

Additional file 21. Expression of TTK in BRCA based on sample types.

Additional file 22. List 1 and List 2 genes contain DEGs obtained from first stage analysis and gene targets for top 10 DEMIs

Additional file 23. Effect of TOP2A expression level & cancer type on BRCA patient survival.

Additional file 24. Common genes between list 1 and 2

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Author contributions

MR, SMR and AP performed data collection and analysis. ET performed project administration. NG and GS performed writing and original draft. SH, ET, AS and SM performed review and editing.

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Availability of data and materials

All data generated or analyzed during the study are included in this manuscript and supplementary files, all of which were submitted.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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