World Journal of Biomedical Sciences
ISSN: 2960-0189
DOI: 10.61784/wjbs3002

EXPRESSION OF MRPL13 AND ITS PROGNOSTIC SIGNIFICANCE IN BREAST CANCER

ChenWei Li[1#*], Ke Wang[2#], QiuXu Chen[1], Jie Yan[1]
[1]*Clinical Laboratory, The People's Hospital of Yubei District,Chongqing.Yubei, Chongqing 401120, China.*
[2]*Clinical Laboratory, Yongchuan People's Hospital of Chongqing, Chongqing 402160, China.*
Chenwei Li and Ke Wang have contributed equally to this work, they are both first authors.
Corresponding Author: ChenWei Li, Email: 285452208@qq.com

Abstract: Objective: The purpose of this study was to explore the expression of MRPL13 in breast carcinoma and normal breast tissues based on TCGA database, and to explore the influence of MRPL13 on the prognosis of breast carcinoma patients. Methods: Firstly, to analyze the expression of MRPL13 difference in breast carcinoma and normal tissue by TCGA. Secondly, to establish MRPL13 co-expression gene network by using String database and perform on MRPL13 expression spectrum data GO analysis and KEGG analysis by making use of DAVID database. In the end, to analyze the total survival of breast cancer takes advantage of CBioPortal and kaplan-meie Plot. Results: The TCGA database showed that 43% of the 816 samples up-regulated MRPL13 expression in breast cancer tissues. TO obtain interaction pairs of co-expressed MRPL13 genes from the String database. Biological functions main focus on regulating DNA recombination and repair, transcription initiation and binding of transcription factors, and assembly of protein macromolecular complexes, which mainly occurs in the cell membrane system. KEGG pathway analysis was mainly concentrated in cell division cycle and oxidative phosphorylation. The total survival rate (OS) of 1402 breast cancer patients and 814 breast cancer patients respectively via Kaplan-meier Plotter and cBioPortal . Conclusion: Over-expression of MRPL13 in breast cancer tissue predicts poor prognosis and it can regard as one of the prognostic markers of breast cancer patients.
Keywords: Breast cancer; MRPL13; Prognosis; TCGA database

1 INTRODUCTION

Breast cancer is one of the most common malignant tumor among women. Due to the popularity of new treatment strategies and methods, the death rate of breast cancer has gradually declined [1]. But in recent years, the incidence rate and mortality rate of breast cancer had an upward trend in Chinese women [2-3], It poses a huge threat to the physical health of Chinese women. At present, the treatment of breast cancer mainly includes surgery, chemotherapy, radiotherapy, targeted therapy and endocrine therapy. At this stage, the therapeutic effect and prognosis of breast cancer patients are still not optimistic. Therefore, it is particularly important to find target molecules that can be used for early diagnosis, disease assessment, and prognosis prediction. Mitochondrial ribosomal protein L13 (MRPL13) is encoded by nuclear genes and located on chromosome 8 q24.12, assisting in the biosynthesis of mitochondrial proteins. There are reports that MRPL13 mediated oxidative phosphorylation (OXPHOS) deficiency enhances liver cancer cell invasion activity through CLN1 expression, leading to poor prognosis in patients [4]. 12 MRPs were upregulated in breast cancer, which acted as biomarkers in individualized risk prediction and may serve as potential therapeutic targets in breast cancer patients [5].This study conducted the expression profile of breast cancer in the TCGA database by bioinformatics, analyzed the expression and biological function of MRPL13 in breast cancer tissue, predicted its prognostic value in breast cancer, and provided a strong basis for the prognosis of breast cancer.

2 METHODS

2.1 Data Sources and Methods

To obtain the differential expression of MRPL13 in normal and breast cancer tissues, the "Breast Invasive Cancer (TCGA, Cell 2015)" sub library data in the TCGA visualization online database cBioPortal (http://www.cbioportal. org/) was used to select "Putative copy number alterations from GISTIC, mRNA Expression. Select one of the profiles belt: mRNA Expression z-scores (RNA Seq V2 RSEM)" for online data analysis [5].To analyze the expression of MRPL13 and its co expression network and survival of breast cancer data with cBioPortal. Click "OncoPrint", "Plots" and "Survival" in order to obtain the expression of "MRPL13", gene copy number, co expression relationship, and survival information of patients. Then 'Co expression' is used to obtain co expressed genes, and Spearman>0.55 is set to screen them. Using the String database （https://cn.string-db.org/） to obtain the interaction relationship group of these co-expressed genes and construct the co-expression network of MRPL13. and a protein-protein interaction (PPI) network was constructed by Cytoscape 3.6 (https://cytoscape.org/). Finally, analyzed the signaling pathway and function of MRPL13 by utilizing DAVID（http://david.ncifcrf.gov/, elucidating the functions of MRPL13 co expressed genes. Functional enrichment was performed using GO database, and the signaling pathway was analyzed using KEGG database.

2.2 Statistical Analysis

In the pathway and functional enrichment analysis, P<0.05 was considered statistically significant. Survival analysis was conducted using the Kaplan-Meier online tool (http://www.kmplot.com/), and P<0.05 was considered statistically significant.

3 RESULTS

3.1 The Expression of MRPL13 between Normal Tissue and Breast Cancer

TCGA database showed that in 816 samples, 43% of samples (348 cases) have MRPL13 gene expression up-regulated or amplified, which is consistent with the up-regulated or amplified MRPL13 gene expression and mRNA level in breast cancer samples (Figure 1).

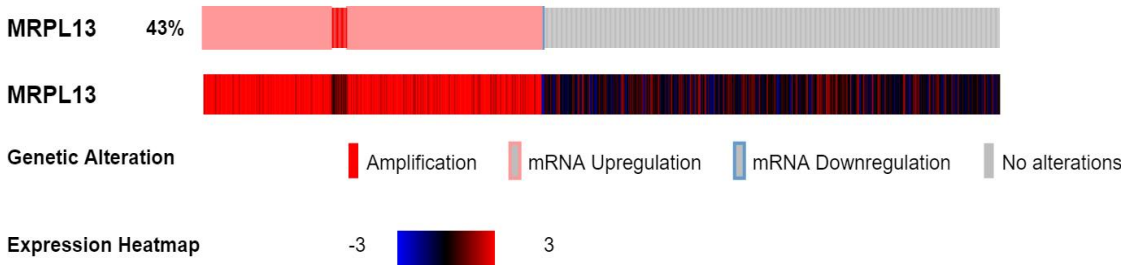

Figure 1 The Expression of MRPL13 Gene in Breast Cancer Tissues

3.2 Screened and Constructed Co-expression Network

In this study, genes with a Spearman correlation coefficient>0.55 were regarded as the moderate level. Next, to get their co-expressed interaction groups were identified though the STRING database. Finally, 100 nodes were obtained in the PPI and the P value of PPI concentration was9.1E-10 (Figure 2). Then, the co-expression network was visualized using Cytoscape 3.6.

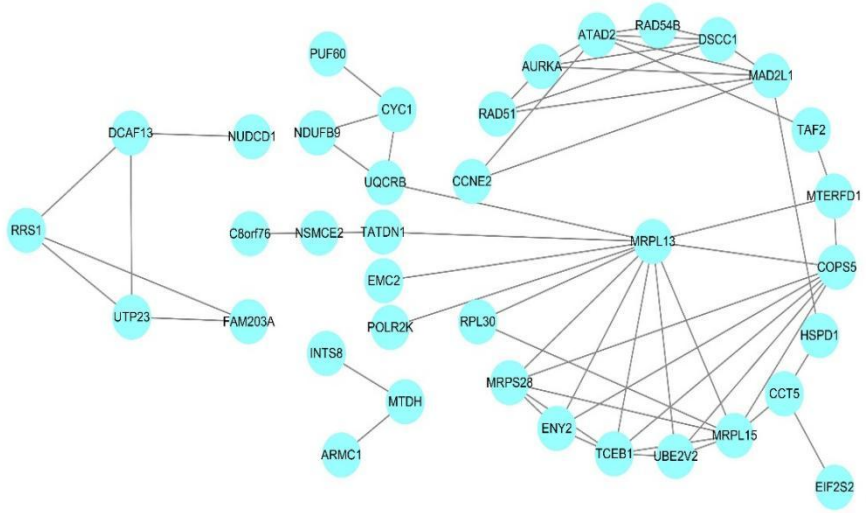

Figure 2 The Co-expression Network of MRPL13 Gene

3.3 The Biological Function and Pathway Analysis of the Co-expressed Network

To further explore the possible role of MRPL13 in breast cancer, the DAVID database was used to identify the functions of the co-expressed network. For the BP, these genes were mainly enriched in regulating cell cycle mitosis, DNA recombination repair, transcription initiation, and assembly of protein macromolecular complexes, The analysis of cellular components and molecular functions revealed that their regulatory processes were mainly concentrated in the mitochondrial inner membrane, mitochondrial ribosomal proteins, nuclear cavity, and cell membrane system, and were

achieved through the binding of transcription factors. KEGG pathway analysis is mainly enriched in cell cycle , oocyte meiosis, and so on. DNA recombination, RNA processing, re double-strand break repair, and so on (Table1). The cellular components (CCs) were significantly located in non-membrane-bounded organelle, ribonucleoprotein complex, mitochondrial membrane, and so on (Table 2). KEGG pathway analysis revealed that the genes were mainly enriched in Cell cycleand Oocyte meiosis. (Table 3).

Table 1 The Biological P: Rogress of Co-expressed Genes

term	p-value
DNA recombination	5.13E-04
RNA processing	6.14E-04
double-strand break repair	1.37E-03
mitotic cell cycle	1.87E-03
protein complex assembly	1.89E-03
DNA metabolic process	1.91E-03
mitosis	7.57E-03
macromolecular complex assembly	8.54E-03
transcription initiation from RNA polymerase II promoter	2.42E-02

Table 2 The Cellular Components of Co-expressed Genes

term	p-value
non-membrane-bounded organelle	3.95E-03
ribonucleoprotein complex	7.99E-03
mitochondrial membrane	1.10E-02
nuclear chromosome	1.81E-02
cyclin-dependent protein kinase activating kinase holoenzyme complex	2.05E-02
respiratory chain	2.74E-02
endomembrane system	5.00E-02

Table 3 KEGG Pathway Analysis of Co-expressed Genes

term	p-value
Cell cycle	1.81E-03
Oocyte meiosis	1.12E-02

3.4 The Relationship between MRPL13 Gene and Prognosis in Breast Cancer

The online Kaplan Meier Plotter was used to analyze the prognostic relationship between MRPL13 gene expression and four types of breast cancer patients: lumen epithelial type A (Luminal A), lumen epithelial type B (Luminal B), HER-2 overexpression type (HER-2), and basal like type (Basal like) [9]. The results showed that the survival of breast cancer patients with MRPL13 overexpression in the lumen epithelial type A (Luminal A) were significantly decreased, and the survival of other three types of breast cancer patients was not significantly (Figure 3). The TCGA database and cBioPortal were used to analyze the overall survival of breast cancer. Among 814 breast cancer patients, the overexpression of MRPL13 could significantly reduce the survival of breast cancer patients (Figure 4A), P=0.00101. Among 1402 breast cancer patients, the overexpression of MRPL13 was closely related to the decline of overall survival rate (OS) in breast cancer patients (4B), P=0.011, suggesting that patients with up-regulation of MRPL13 might have lower survival and poor prognosis.

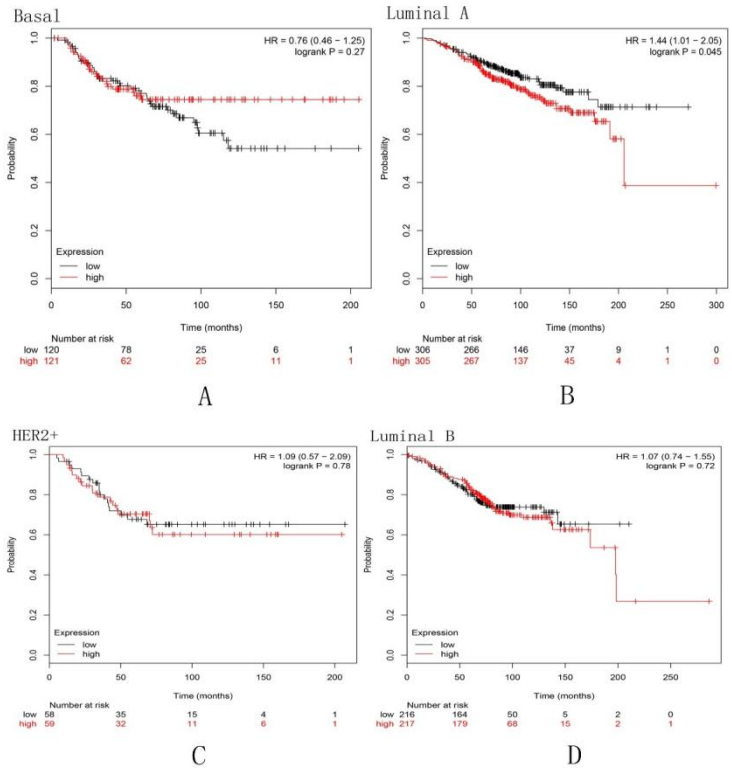

Figure 3 Kaplan-Meier Survival Analysis of MTERF3 mRNA Expression Level

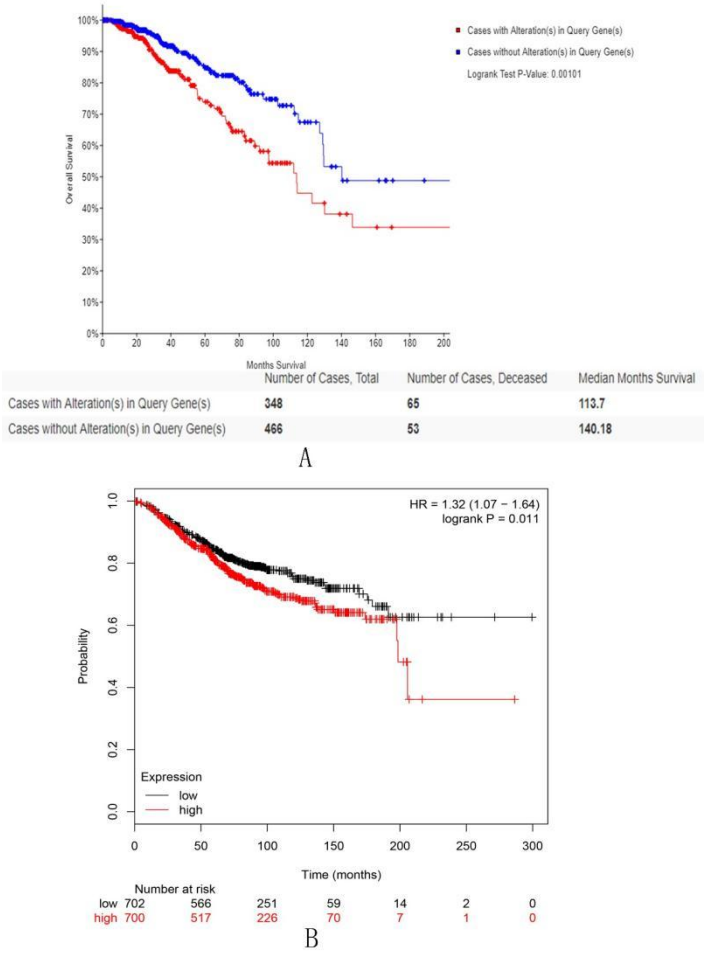

Figure 4 The Relationship between MRPL13 Expression and Total Survival in Breast Cancer Patients

4 DISCUSSION

In recent years, the survival of breast cancer patients has been greatly improved, but there are still some patients with poor prognosis, and the incidence rate has increased year by year [10]. Therefore, it is necessary to research the molecular mechanism of breast cancer occurrence and development, and find the new therapeutic targets and potential molecular markers for prognosis in breast cancer. The TCGA online database cBioPortal was used to obtain that MRPL13 expression was changed in the 43% of 816 breast cancer samples, which preliminarily confirmed that there was a certain correlation between the expression of MRPL13 and breast cancer occurrence and development.

Further establishing the MRPL13 co-expression gene network, and analyzing the biological functions and signal pathway enrichment by building a co-expression network of DCAF13 and conducting bioinformatics analysis.These genes were mainly enriched in DNA recombination repair, transcription initiation and immediate transcription factor and protein macromolecular complexes. We further analyzed the expression of MRPL13 on the survival of breast cancer patients, the results showed MRPL13 overexpression reduced the survival of breast cancer patients with luminal epithelial type A (Luminal A), but had no significant impact on the survival period of the other three types of breast cancer, and its reason need further study.

At present, these research suggests that mitochondria play an important role in regulating the pathway of cancer cell death and main regulatory factor in cell death [11-12]. Mitochondrial defects can lead the occurrence and development of tumors [13-14]. The human mitochondrial ribosome is composed of 82 mitochondrial ribosomal proteins, all encoded by nuclear DNA and introduced into mitochondria [15]. Mitochondrial ribosomal protein (MRP) consists of small subunit 28S and large subunit 39S, small subunit (MRPS) consists of 30 mitotic ribosomal proteins (MRPS), and large subunit (MRPL) consists of 52 MRPS [16]. The differential and altered expression of MRP genes is closely related to the importance of OXPHOS damage in cancer development [17]. The decreased expression of MRPL13 was a key factor in OXPHOS deficiency [4], which may be due to enhance the invasiveness of liver cancer cells by lactate released from adjacent glycolytic tumor cells during cancer development. In this study, the bioinformatics of breast cancer expression from TCGA databases were used to analyze the expression and biological function of MRPL13 in breast cancer tissue, and found that high expression of MPRL13 can significantly reduce the survival of breast cancer patients, but its detailed mechanism needs further study.

On the whole,the over-expression of MRPL13 suggests that the prognosis of breast cancer patients are poor, and it can be used as an important biomarker for patient prognosis. This study is based on TCGA databases and bioinformatics methods to analyze the relationship between the expression of MRPL13 and the prognosis of breast cancer patients. The study will further verify the expression of MRPL13 in breast cancer by immunohistochemistry, polymerase chain reaction and Western-blot to further explore its function and mechanism.

5 CONCLUSIONS

MRPL13 was significantly over-expressed in breast cancer than in normal tissue. Patients with up-regulation of MRPL13 might have lower survival and poor prognosis. It is possible to find the biomarker to evaluate patient prognosis. This finding provides a new target mechanism and cell research of breast cancer.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

FUNDING

This study was supported by Chongqing Natural Science Foundation(Grant: No.cstc2021jcyj-msxmX0851).

REFERENCES

[1] Zhong X, He Z, Fan Y, et al. Multi-omics analysis of MRPL-13 as a tumor-promoting marker from pan-cancer to lung adenocarcinoma. Aging (Albany NY), 2023, 15(19): 10640-10680.
[2] Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin, 2016, 66(2): 115-132.
[3] Chen D, Nemazanyy I, Peulen O, et al. Elp3-mediated codon-dependent translation promotes mTORC2 activation and regulates macrophage polarization. EMBO J, 2022, 41(18): e109353.
[4] Lee YK, Lim JJ, Jeoun UW, et al. Lactate-mediated mitoribosomal defects impair mitochondrial oxidative phosphorylation and promote hepatoma cell invasiveness. J Biol Chem, 2017, 292(49): 20208-20217.
[5] Lin X, Guo L, Lin X, et al. Expression and prognosis analysis of mitochondrial ribosomal protein family in breast cancer. Sci Rep, 2022, 12(1): 10658.
[6] Hillier LD, Lennon G, Becker M, et al. Generation and analysis of 280,000 human expressed sequence tags. Genome Res, 1996, 6(9): 807-828.
[7] Brown A, Rathore S, Kimanius D, et al. Structures of the human mitochondrial ribosome in native states of assembly. Nat Struct Mol Biol, 2017, 24(10): 866-869.
[8] Lee YK, Lim JJ, Jeoun UW, et al. Lactate-mediated mitoribosomal defects impair mitochondrial oxidative phosphorylation and promote hepatoma cell invasiveness. J Biol Chem, 2017, 292(49): 20208-20217.

[9] Gyorffy B, Lanczky A, Eklund AC, et al.An online survival analysis tool to rapidly assess the effect of 22, 277 genes on breast cancer prognosis using microarray data of 1809 patients. Breast Cancer Res Treatment, 2010, 123(3): 725-731.
[10] Miller KD, Siegel PL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin, 2016, 66(4): 271-289.
[11] Tao Z, Suo H, Zhang L, et al. MRPL13 is a Prognostic Cancer Biomarker and Correlates with Immune Infiltrates in Breast Cancer. Onco Targets Ther, 2020, 13:12255-12268.
[12] Lopez J, Tait SW. Mitochondrial apoptosis: killing cancer using the enemy within. Br J Cancer, 2015, 112(6): 957-962.
[13] Lee YK, Youn HG, Wang HJ, et al. Decreased mitochondrial OGG1 expression is linked to mitochondrial defects and delayed hepatoma cell growth. Mol Cells, 2013, 35(6): 489-497.
[14] Liu Y, Sun H, Li X, et al. Identification of a Three-RNA Binding Proteins (RBPs) Signature Predicting Prognosis for Breast Cancer. Front Oncol, 2021, 11:663556.
[15] Ye H, Zhang N. Identification of the Upregulation of MRPL13 as a Novel Prognostic Marker Associated with Overall Survival Time and Immunotherapy Response in Breast Cancer. Comput Math Methods Med, 2021, 2021: 1498924.
[16] Greber BJ, Ban N. Structure and Function of the Mitochondrial Ribosome. Annu Rev Biochem, 2016, 85: 103-132.
[17] Gopisetty G, Thangarajan R. Mammalian mitochondrial ribosomal small subunit (MRPS) genes: A putative role in human disease. Gene, 2016, 589(1): 27-35.