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Data mining analysis of mir-638 and key genes interaction in cisplatin resistant triple-negative breast cancer

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ABSTRACT Cisplatin is one of the chemotherapy for the treatment of triple-negative breast cancer (TNBC), but its effectiveness is limited because of the phenomenon of chemoresistance. miR-638 was shown to regulate chemoresistance; however, it has never been validated in the cisplatin-resistant tumor from patients. This present study aimed to identify the key gene regulatory networks of miR-638 and evaluate the potential role of the miR-638 and its targets as potential prognosis biomarkers for cisplatin-resistance triple-negative breast cancer patients. The miR-638 target was obtained from the miRecords database while the mRNA of chemoresistance biomarker candidate was obtained from the GSE18864 of GEO database, which is mRNA of cisplatin-resistance TNBC patients. CCND1 and FZD7 are potential candidates for cisplatin chemoresistance biomarkers in patients with TNBC. Moreover, a Kaplan-Meier survival plot showed that breast cancer patients with low mRNA levels of *FZD7* had significantly worse overall survival than those in higher mRNA expression group. Taken together, miR-638 plays a role in cisplatin resistance mechanism through a mechanism involving its target gene *CCND1* and *FZD7*. Overall, miR-638, *CCND1*, and *FZD7* are candidates for cisplatin biomarker resistance in TNBC.

KEYWORDS miR-638; chemoresistance; triple-negative breast cancer; data mining

1. Introduction

Triple-negative breast cancer (TNBC) occurs in about 20% of cases of breast cancer and is associated with the risk of relapse and poor prognosis (Kuo et al. 2017). Cisplatin is a chemotherapy drug, which is used for the treatment of triple-negative breast cancer, but its effectiveness has not been maximized due to the problem of chemoresistance (Hu et al. 2015). Chemoresistance is a phenomenon when cancer cells become insensitive to chemotherapy and are classified into intrinsic and acquired resistance (Ji et al. 2019). The TNBC is an aggressive subtype that usually evolves chemoresistance (Kim et al. 2018). One of the biomarkers for predicting chemoresistance and prognosis is miRNA (Wei et al. 2019), a small non-coding RNA consisting of 21-22 nucleotides that negatively target mRNA, and thus suppresses the expression of its target genes (Orso et al. 2019).

miR-638 is one of the miRNAs that has been extensively investigated in the development of cancer (Li et al. 2011; Lin et al. 2015; Wei et al. 2017). It acts as either a tumor suppressor gene or oncogene. miR-638 possesses a tumor suppressor gene by inducing apoptosis and inhibiting cell proliferation, invasion, and migration (Shen et al. 2017). In osteosarcoma, miR-638 promotes apoptosis by suppressing cyclin D1, phospholipase D1 (PLD1) and vascular endothelial growth factor (VEGF) (Xue et al. 2019). miR-638 directly targets *HOXA9* and suppresses the expression of Wnt/beta-catenin-regulated oncogenes cyclin D1 and C-MYC (Zheng et al. 2018). On the other hand, miR-638 acts as an oncogene. miR-638 promotes metastasis and prevents cell death in melanoma cells (Bhattacharya et al. 2015). It induces cell proliferation, migration, and invasion in oesophagal squamous cell carcinoma and breast cancer cells by targeting *DACT3*, a key regulator of Wnt/beta-catenin signaling (Ren et al. 2017).

miR-638 also regulates chemoresistance in cancer cells. Increasing expression of miR-638 after chemotherapy in non-small cell lung cancer patients is correlated with better survival (Wang et al. 2015). It also enhances the efficacy of bleomycin and cisplatin in K562 leukemic cells (He et al. 2016). In MDA-MB231 cells, miR-638 regulates cell migration and sensitivity to cisplatin (Tan et al. 2014). Nevertheless, no study has been conducted on the regulation of miR-638 and its regulatory network in cisplatin-resistant TNBC using patient samples.

Over the past few years, bioinformatics has grown and

provided new methods for the prediction of drug-target genes using multiplatform analysis (Wang et al. 2019). Computational approaches have been used to mine and integrate data in public databases to provide researchers with accurate and fast information in the field of biomedicine and drug discovery (Pandika 2018). In this study, several databases were used, including GEO, TargetScan, ONCOMINE, KMPlotter, STRING, and c-Bioportal to identify the interactions between miR-638 and its target genes in patients with cisplatin-resistance TNBC.

In this study, we utilize a bioinformatics approach with data mining analysis to identify key gene regulatory networks of miR-638 and evaluate the potential role of the miR-638 and its targets as potential prognosis biomarkers for cisplatin-resistance triple-negative breast cancer patients. The target of miR-638 was predicted using miRecords database. Gene expression profile of cisplatin-resistant breast cancer was obtained from GEO datasets. We also performed validation using KM Plot and ONCOMINE and identified genetic alterations among target genes in cBioportal database.

2. Materials and Methods

2.1. Data collection and processing

Microarray data were obtained from GSE18864, which contains twenty-eight women with triple-negative breast cancer stage II or III, which received four cycles of cisplatin. Patient age ranged from 29 to 69 years at diagnosis. Fourteen patients were considered a good response, and fourteen patients were considered as a poor response based on Miller-Payne score (Silver et al. 2010). Data processing was conducted using GEO2R, an online tool for GEO data analysis based on the R programming language (https://www.ncbi.nlm.nih.gov/geo/geo2r/). Differential expression genes (DEGs) between cisplatin sensitive and resistant cells/tissues were screened. Adjusted P value <0.05 and IFCI >1.5 were used to select significant DEGs, as described in a previous study (Zhao et al. 2018).

2.2. miRNA target prediction

The target of miR-638 was predicted using miRecords database (http://c1.accurascience.com/miRecords/) (Xiao et al. 2009). The target genes, predicted from at least four databases, were selected and collected. A Venn diagram was generated to DEGs from GSE18864 and miR-638 target genes from miRecords using Venny 2.1 (https://bioinfogpcnbcsices/tools/venny/indexhtml) (Oliveros 2007) (Oliveros 2007). Interaction between miR-638 and its target genes in target sites was analyzed by TargetScan (http://www.targetscan.org) (Agarwal et al. 2015).

2.3. Analysis of miR-638-target gene regulatory network

miR-638-target gene (*SRGAP1*, *HIC2*, *CCND1*, *SAP30BP*, and *FZD7*) regulatory network was constructed with Cytoscape software (version 3.7.1) by using default parameters (Shannon et al. 2003).

2.4. Kaplan Meier survival analysis

The prognostic value of miR-638 and the target genes (*SRGAP1*, *HIC2*, *CCND1*, *SAP30BP*, and *FZD7*) were evaluated using Kaplan-Meier survival curves (http://kmplot.com) by log-rank test, with p<0.05 was selected as the cut-off value (Gyorffy et al. 2010).

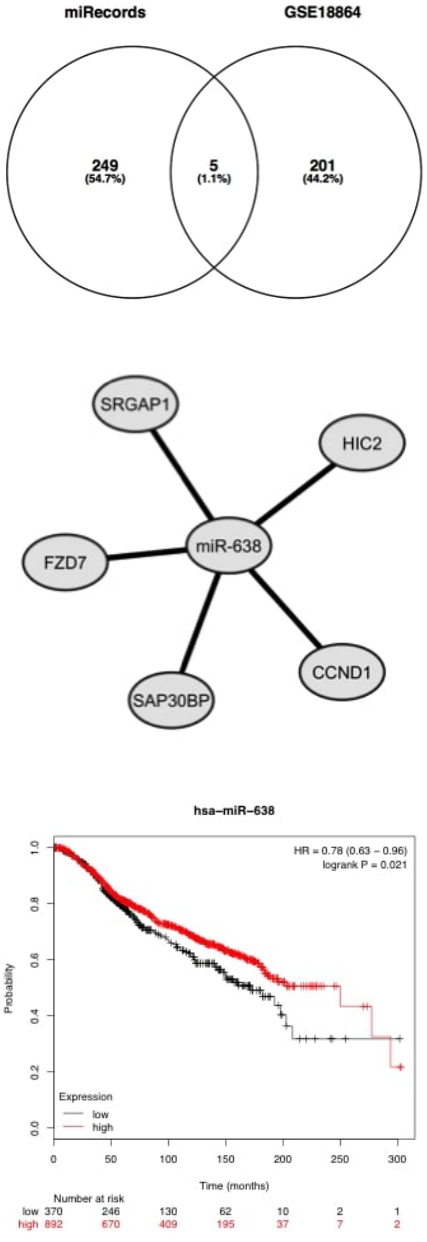

FIGURE 1 (a) Venn diagram of miR-638 target genes analyzed by miRecords and GSE18864; **(b)** miRNA 638-target gene regulatory network in cisplatin-resistant triple negative breast cancer, constructed by Cytoscape; **(c)** Overall survival curve of breast cancer patients related to the expression of miR-638.

TABLE 1 Analysis of mutual exclusivity among target genes in the MBC study.

Gene A	Gene B	p-Value	Log2 Odds Ratio	Tendency identification
CCND1	SAP30BP	<0.001	2.273	Co-occurrence
SRGAP1	CCND1	0.008	1.76	Co-occurrence
SRGAP1	SAP30BP	0.014	2.052	Co-occurrence
SAP30BP	FZD7	0.105	>3	Co-occurrence
HIC2	SAP30BP	0.2	>3	Co-occurrence
CCND1	FZD7	0.308	>3	Co-occurrence
HIC2	CCND1	0.522	1.179	Co-occurrence
SRGAP1	HIC2	0.83	<-3	Mutual exclusivity
SRGAP1	FZD7	0.911	<-3	Mutual exclusivity
HIC2	FZD7	0.992	<-3	Mutual exclusivity

2.5. Validation of target genes in cisplatin-resistant and sensitive breast cancer cells

Confirmation of the reliability of the target genes in cisplatin sensitive and resistant breast cancer cells was conducted using ONCOMINE (https://www.oncomine.org), a cancer microarray database and web-based data-mining platform (Rhodes et al. 2004). Briefly, the expression level of *SRGAP1*, *HIC2*, *CCND1*, *SAP30BP*, and *FZD7* among cisplatin resistance breast cancer studies were retrieved from ONCOMINE.

2.6. Analysis of genetic alterations among target genes

The genetic alterations of target genes were analyzed from breast cancer studies using cBioPortal (http://www.cbioportal.org) (Cerami et al. 2012; Gao et al. 2013). Screened target genes (*SRGAP1*, *HIC2*, *CCND1*, *SAP30BP*, and *FZD7*) were subjected to genetic alterations analysis in all breast cancer studies. The breast cancer study with the highest genetic alterations was chosen for mutual exclusivity of the screened target genes with p<0.05 was selected as the cutoff value.

SRGAP1

	Predicted consequential pairing of target region (top) and miRNA (bottom)	Site type	Context++ score	Context++ score percentile	Weighted context++ score	Conserved branch length	PCT
Position 523-530 of SRGAP1 3' UTR	5' ...AUUGUCUCCAUGGGACGAUCCCA...	8mer	-0.10	64	-0.08	0.072	N/A
hsa-miR-638	3' UCCGGCGGUGGGCGGGCGCUAGGGA						

HIC2

	Predicted consequential pairing of target region (top) and miRNA (bottom)	Site type	Context++ score	Context++ score percentile	Weighted context++ score	Conserved branch length	PCT
Position 1988-1994 of HIC2 3' UTR	5' ...AGCCCUCCCUGUGGUGAUCCCAG...	7mer-A1	-0.16	77	-0.03	0.048	N/A
hsa-miR-638	3' UCCGGCGGUGGGCGGGCGCUAGGGA						

CCND1

	Predicted consequential pairing of target region (top) and miRNA (bottom)	Site type	Context++ score	Context++ score percentile	Weighted context++ score	Conserved branch length	PCT
Position 2289-2296 of CCND1 3' UTR	5' ...GCAGACACGCGGGCGCGAUCCCA...	8mer	-0.19	84	-0.18	0.031	N/A
hsa-miR-638	3' UCCGGCGGUGGGCGGGCGCUAGGGA						

SAP30BP

	Predicted consequential pairing of target region (top) and miRNA (bottom)	Site type	Context++ score	Context++ score percentile	Weighted context++ score	Conserved branch length	PCT
Position 486-492 of SAP30BP 3' UTR	5' ...CCCAUCUGCCGCCUU-GAUCCCAA...	7mer-A1	-0.27	94	-0.20	0.071	N/A
hsa-miR-638	3' UCCGGCGGUGGGCGGGCGCUAGGGA						

FZD7

	Predicted consequential pairing of target region (top) and miRNA (bottom)	Site type	Context++ score	Context++ score percentile	Weighted context++ score	Conserved branch length	PCT
Position 356-362 of FZD7 3' UTR	5' ...AACGGGGACUGUGAGCGAUCCCC...	7mer-m8	-0.08	57	-0.08	0	N/A
hsa-miR-638	3' UCCGGCGGUGGGCGGGCGCUAGGGA						

FIGURE 2 miR-638-target gene interactions, analyzed by TargetScan.

3. Results

3.1. *Identification of miR-638 target genes and miR-638-target gene regulatory network*

A total of 254 and 206 genes were extracted from miRecords and GSE18864, respectively (Figure 1a). A Venn diagram generated five DEGs from miRecords and GSE18864, including *SRGAP1*, *HIC2*, *CCND1*, *SAP30BP*, and *FZD7*. A miR-638 target gene regulatory network was constructed (Figure 1b). Interaction between miR-638 and its target genes in target sites was analyzed by TargetScan (Figure 2).

3.2. *Kaplan Meier survival analysis*

Kaplan Meier plot for overall survival of breast cancer patients showed that patients with the high miR-638 level had significantly worse overall survival than those in the low expression level group (p= 0.021) (Figure 1c). The overall survival was also obtained according to the low and high expression levels of each target gene (Figure 3). The results showed that patients with the high mRNA level of *SRGAP1* (p=0.13), *CCND1* (p=0.18), and *FZD7* (p=0.046) (Figure 3) have better survival than patients with the low mRNA level. Moreover, patients with the high mRNA level of *HIC2* (p=0.81) and *SAP30BP* (p=0.26) have worse survival than those with the low mRNA level.

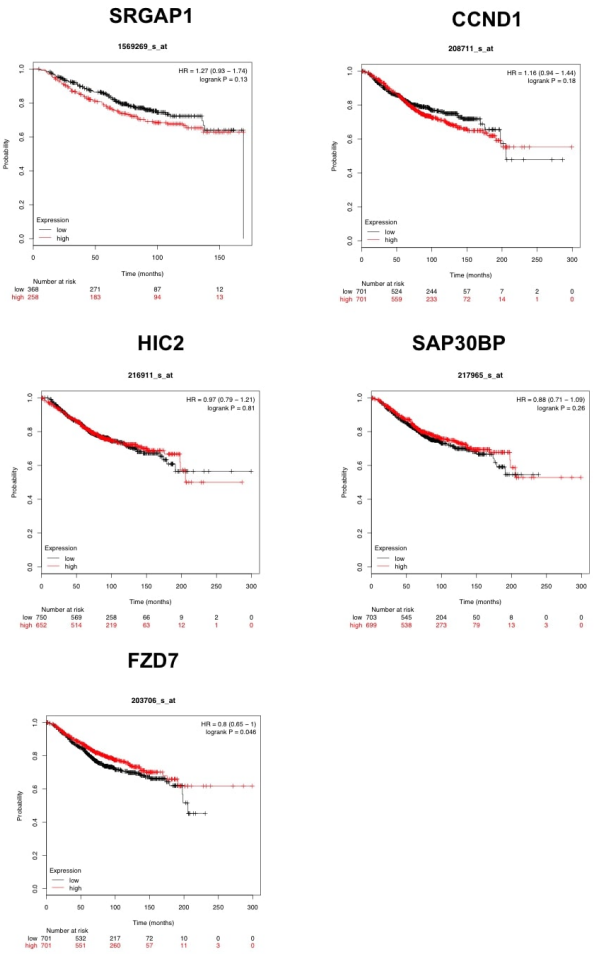

FIGURE 3 Overall survival of *SRGAP1*, *HIC2*, *CCND1*, *SAP30BP*, and *FZD7* across breast cancer samples, analyzed by KMPlotter.

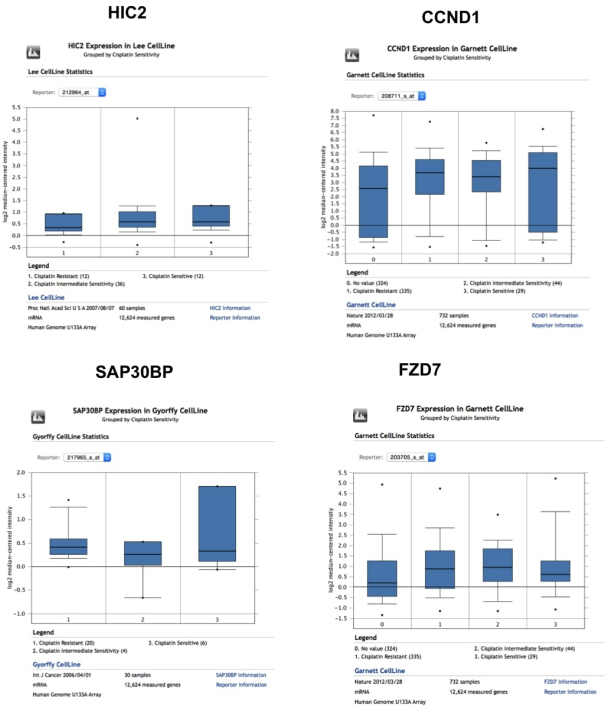

FIGURE 4 Expression of *HIC2*, *CCND1*, *SAP30BP*, and *FZD7* across cisplatin-resistant breast cancer samples, analyzed by ONCOMINE.

3.3. *Validation of target genes in cisplatin-resistant and sensitive breast cancer cells*

ONCOMINE was used to confirm the reliability of the target genes in cisplatin sensitivity (Figure 4). A study using cell lines showed the downregulation of *HIC2* in cisplatin-resistance breast cancer cells (Lee et al. 2007). Another study showed a similar level of *CCND1* among cisplatin-resistant and cisplatin-sensitive breast cancer cells (Garnett et al. 2012). A study showed the downregulation of *SAP30BP* cisplatin-resistance breast cancer cells (Gyorffy et al. 2006). Moreover, a study using cell lines showed a similar expression level of *FZD7* among cisplatin-sensitive and cisplatin-resistance breast cancer cells (Garnett et al. 2012). No study was found in ONCOMINE related to *SRGAP1* and cisplatin resistance in breast cancer.

3.4. *Analysis of genetic alterations among target genes*

Five target genes (*SRGAP1*, *HIC2*, *CCND1*, *SAP30BP*, and *FZD7*) were analyzed using cBioportal to explore their genomic alterations across breast cancer studies. A study, namely the MBC Project (Lefebvre et al. 2016), showed the highest genetic alterations among breast cancer studies and was selected for further analysis (Figure 5a). Genetic alterations for each target genes were found from 0.6% (*FZD7*), 1.1% (*HIC2*), 11% (*SRGAP1*), 13% (*SAP30BP*) and 35% (*CCND1*) (Figure 5b). Moreover, most gene alterations belonged to amplification (Figure

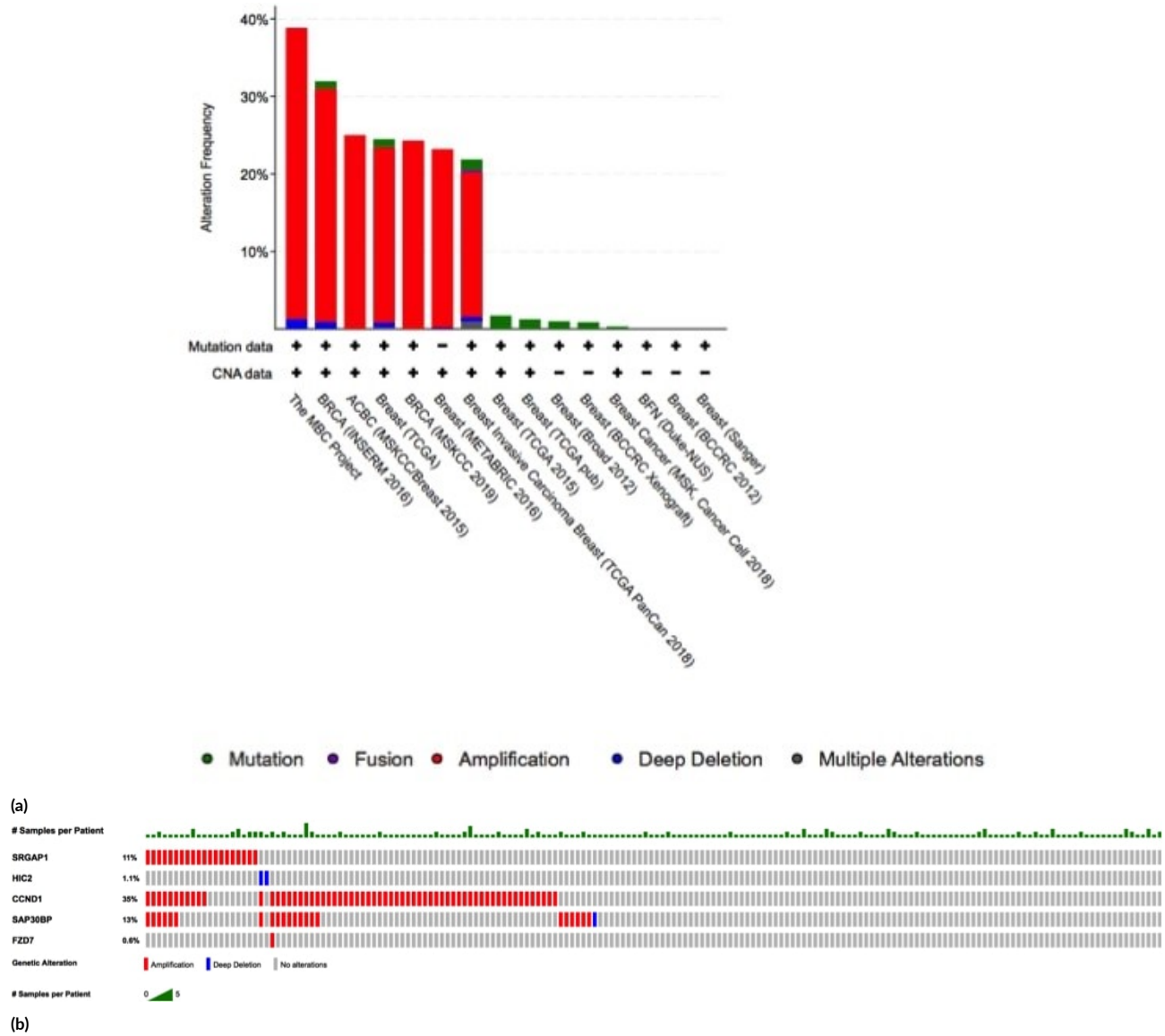

FIGURE 5 Summary of alterations for hub genes in breast cancer patients **(a)** Based on breast cancer study; **(b)** Genetic alterations of *SRGAP1*, *HIC2*, *CCND1*, *SAP30BP*, and *FZD7* based on a study by Lefebvre et al. (2016).

5b). Additional mutual exclusivity showed that only three gene pairs (*CCND1-SAP30BP, SRGAP1-CCND1,* and *SRGAP1-SAP30BP*) exhibited significant co-occurrence ($p < 0.05$) in breast cancer study by the MBC Project (Table 1).

4. Discussion

This present study aimed to identify the key gene regulatory networks of miR-638 and evaluate the potential role of the miR-638 and its targets as potential prognosis biomarkers for cisplatin-resistant TNBC patients. Understanding the relevance of miRNA and its mRNA target is very important to elucidate the mechanism of gene transcription and cellular pathophysiology. In addition, understanding the mechanism of resistance is very important for diagnosis and treatment in TNBC patients because this sub-type is hard to treat.

In this present study, five genes were identified from miRecords and GSE18864. Based on Kaplan Meier overall survival (Figure 3) and validation of target genes in cisplatin-resistant and sensitive breast cancer cells with ONCOMINE (Figure 4), two potential biomarkers were identified, which are *CCND1* and *FZD7*. Genetic alterations analysis among samples from the MBC Project (Lefebvre et al. 2016) showed genetic alterations of *CCND1* and *FZD7* in 35% and 0.6% of samples, respectively (Figure 5). Thus, *CCDN1* and *FZD7* are the potential key genes in cisplatin-resistant TNBC.

The two biomarker candidates, *CCND1* and *FZD7*, are extensively studied for its regulation in cancer development. *CCND1* encodes cyclin D1, which plays a role in cell cycle progression in the G1-S phase transition (Seiler et al. 2014). Cyclin D1 plays a role in the process of cell proliferation and growth regulation, DNA repair, cell

migration, and a prognostic and predictive marker in different types of cancer (Ramos-Garcia et al. 2017). Cyclin D1 is frequently overexpressed in human cancers, including breast cancer (Maia et al. 2016), cervical cancer (Xu et al. 2016), and non-small cell lung cancer (Baykara et al. 2017). Cytoplasmic level of cyclin D1 is used for a biomarker of early diagnosis in breast cancer (Ullah Shah et al. 2015), as well as for biomarkers of invasiveness in endometrial, breast, prostate and colon cancer (Fuste et al. 2016). However, high expression of Cyclin D1 has a positive correlation with the beneficial effect of chemotherapy in metastatic bladder cancer (Seiler et al. 2014).

Genetic alterations study with cBioportal revealed alterations of *CCND1* in 35% of patient samples, with amplification as the highest alterations. Previous studies demonstrated that amplification in *CCND1* is an early event in the development of a breast cancer stem cells (Burandt et al. 2016), and mutations in *CCND1* is associated with increased risk of breast cancer (Soleimani et al. 2017). A previous study demonstrated that overexpression of *CCND1* has occurred through amplification, translocation, or post-transcriptional regulation (Xu and Lin 2018). *CCND1* gene amplification is a molecular key alteration in breast cancer and was suggested to predict resistance to endocrine therapy (Kilker et al. 2004). Taken together, gene amplification of *CCND1* possibly plays an essential role in cisplatin-resistant TNBC. This mechanism needs to be explored further.

The results of this present study revealed that *CCND1* is downregulated in cisplatin-resistant TNBC. A previous study demonstrated that targeting *CCND1* with miR-503 leads to the induction of G0/G1 cell cycle arrest and reduction of cell proliferation in breast cancer (Long et al. 2015). Another study showed that downregulation of cyclin D1 inhibits proliferation and colony formation in SKOV3 ovarian cancer the cells (Yang et al. 2017). In addition, inhibition of proliferation in human ovarian cancer cells by cisplatin is correlated with inhibition of *CCND1* expression (Dai et al. 2016). miR-638 targets *CCND1* and thus inactivates PI3K/Akt pathway-regulated cell growth in Sertoli cells (Hu et al. 2017). Therefore, further studies on the role of *CCND1* in TNBC resistance mechanism to cisplatin are needed.

FZD7 encodes frizzled homolog 7 (Yang et al. 2011) and plays an important role as a membrane receptor in Wnt/β-catenin signaling in cancer cells (Xie et al. 2018). Wnt signaling is activated in TNBC (King et al. 2012). The expression of FZD7 is upregulated in patients with breast cancer compared to normal tissues (Jia et al. 2018). In addition, inhibition of *FZD7* with interfering RNA (King et al. 2012; Yang et al. 2011) or monoclonal antibody (Zarei et al. 2018) could reduce cell proliferation in TNBC. Recently, *FZD7* is targeted by miR-638, leading to inhibition of Wnt signaling in glioma progression (Chen and Duan 2018). Therefore, it is necessary to further investigate the role of *FZD7* in the mechanism of cisplatin resistance in TNBC. Further, in vitro and in vivo studies need to be done on the mechanism of miR-638 regulating cisplatin resistance in TNBC, as well as how miR-638 regulates its target gene.

5. Conclusions

Our study provides an integrated data mining analysis of the cisplatin resistance association between miR-638 with the overall survival of breast cancer patients. miR-638 plays a role in cisplatin resistance mechanism through a mechanism involving its target genes *CCND1* and *FZD7*. This present study also identifies miR-638 and its target genes (*CCND1* and *FZD7*) as a key gene and the potential biomarker of cisplatin resistance in TNBC. However, further *in vitro* and *in vivo* validation is needed to develop the target gene as a biomarker.

Authors' contributions

AH—conception and design of the study, acquisition, analysis and interpretation of data, drafting and revising the article and final approval of the version to be published, HP—acquisition and analysis of data, drafting the article and final approval of the version to be published. All authors read and approved the final version of the manuscript.

Competing interests

The authors declare no competing interest.

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