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Research Article

Identifying Gene Signatures Associated with Cancer Stem Cells and Drug Resistance from Triple Negative Breast Cancer Cells after Gene Targeting Treatment

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Abstract

Over 90% of breast cancer death is due to metastatic disease; however, the metastatic behavior of aggressive breast cancer is still not well understood. Accumulating evidence support the idea that initiation, maintenance and metastasis of tumors are through cancer stem cells (or tumor initiating cells). In this study, we focused on the representative MDA-MB-231 cells of the highly aggressive triple negative breast cancer subtype. We obtained and re-analyzed three previously published datasets on MDA-MB-231 cells after treatment targeting the expression ofGATA3, Pin1, or LSD1. Two distinct computational algorithms (dChip and GEO2R) were employed to cross-compare the resulting gene expression profiles. We identified a common gene signature consists of eight genes among the three datasets. Three of the eight genes, i.e., ABCC3, AGR2, and PTGES, were highly correlated with the properties of breast cancer stem cells and drug resistance. Thus, they are predicted as potential genemarkers of breast cancer stem cells and may serve as novel therapeutic targets to combat poor prognostic breast cancers.

Keywords: Genome-wide gene expression; Triple negative breast cancer; MDA-MB-231; Cancer stem cells; Gene signature; Computational analysis

Introduction

One in eight women are diagnosed with breast cancer in the United States, and more than 90% of deaths by breast cancer is attributed to metastatic diseases [1,2]. There are a variety of breast cancer subtypes that vary based on molecular markers such as human epidermal growth factor receptor 2 (HER2), estrogen receptors (ER), and progesterone receptors (PR) [3,4]. The triple-negative breast cancer (TNBC) poses the greatest threat as they are negative for all three of the above markers, making them extremely difficult to target for treatment. In addition, these triple-negative breast cancers are highly aggressive and associated with poor prognosis [5].

Recent studies have strongly supported that metastasis is due to the initiation and maintenance of cancer stem cells in tumors [6,7]. Like normal stem cells, cancer stem cells have the ability to self-renew and differentiate [6-8]. Thus, identifying underlying gene signatures of a representative TNBC cell line such as MDA-MB-231 could indicate markers of those cancer stem cells. These gene signatures then possess potential as therapeutic targets.

Many public databases have accessible datasets for gene expression studies of various cancers. For instance, the NCBI Gene Expression Omnibus (GEO) has 49,161datasets from breast cancer studies (as of August 5, 2014) and is gaining new data at 300% per year. The availability of genome-wide gene expression datasets offers cost-effective secondary opportunities to investigate additional research questions that were not included in the original intended purpose. However, most of the existing approaches for large-scale analyses are heuristic or lacking clear definitions of assumptions for the methods. Furthermore, although many of these studies have addressed the problematic metastatic behavior of breast cancer, they mainly focused on the gene expression changes after targeting a single gene [9-11]. Since breast cancer is known to contain heterogeneous cell population, single gene targeting may not be effective [12,13].

In this study, we applied a systematic approach to conduct a secondary analysis of the public gene expression data and integrate breast cancer genomic studies. We attempt to identify common gene signatures that persist after various treatments via single gene targeting on a representative TNBC cell lineMDA-MB-231. We integrated the results of these treatments that effectively inhibited aggressive cancer behavior and compared the gene signatures among them. A common gene signature persistent across these various treatments could indicate resistance to treatments, which is a characteristic of cancer stem cells. Thus, our study facilitates the reuse of the vast amount of public datasets to answer additional questions, reduce the necessity to generate new data, and improve our understanding of cellular functions and networks under a variety of perturbations with breast cancer cells.

Materials/Methods

Triple-negative breast cancer cells: MDA-MB-231

Three datasets generated from a single cell line(MDA-MB-231 cells) were selected for the following considerations: 1) MDA-MB-231 cell line is a representative of triple-negative cell line and commonly used in studies of metastatic breast cancer and breast cancer stem cells; 2) The MDA-MB-231 cells have also been shown to express many crucial biological and molecular features of basal triple negative

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breast cancer [14]; 3) the common use of MDA-MB-231 cells in research allowed for a more varied pool of treatments for analysis; and 4) the design of the study is to identify common genes after different gene targeting. Since different cancer cells possess their own cellular and molecular properties, there is no evidence that a common gene signature exist after the same gene targeting. In addition, the study using a single cell line ensures the confidence in the interpretation of results and avoids complications from variety different cells.

Gene chip platform

To ensure the most comprehensive results in comparing across studies, it was important to choose studies that used the same or closely related platform of genome-wide gene expression analysis. Two platforms were selected for their relative common use effectively allowing the greatest variety for treatment selection and reliability of genome-wide expression. The two platforms chosen were Affymetrix Human Genome U133 plus 2.0 (GPL570) and U133A 2.0 (GPL571). Though it would have been ideal to choose only one of these platforms, the advantage of expanding the pool of treatments outweighed the possible loss of data due to the considerable similarities between the two platforms as described by the Affymetrix HG-U133A 2.0/HG-U133 2.0 Plus Technical Note.

Datasets

The selection of datasets was based on the efficacy/reliability of the study and the use of at least three biological replicates.

Dataset 1: GATA3 overexpression study (GSE24249)

GATA3 is one of the most frequently mutated genes in breast cancer [15]; it plays a critical role in luminal cell differentiation during mammary gland development [16,17]. The study by Chu *et al.* overexpressed the GATA3 transcription factor within the MDA-MB-231 cells via transduction with a lentivirus [9]. Overexpressing GATA3 within MDA-MB-231 cells suppressed the expression of various metastasis-related genes such as colony-stimulating factor-1 (CSF-1) via repression of the lysyl oxidase (LOX) expression [9]. LOX is a matrix protein that promotes metastasis by effecting change in cell proliferation, cross-linking of extracellular collagen types, and formation of a metastatic niche [9].

Dataset 2: PIN1 suppression study (GSE26262)

Pin1 is a key regulator downstream of miR-200c that promotes breast cancer stem cells and breast tumorigenicity [18,19]. The study of Girardini *et al.* showed that the influence of Pin1 on mutant p53 dependent promotion of cancer aggressiveness [10]. A study by Soussi and Wiman showed that the relation to human cancer and p53 mutation [20]. In addition, several other studies have suggested the cell migration and metastasis promoting abilities of mutant p53 [21-24]. Studies have shown that Pin1, a prolyl isomerase, promote both Her2/Neu/Ras and Notch1 dependent changes of breast cells [25,26]. Pin1 inhibits the antimetastatic factor p63 via a mutant p53-dependent mechanism and stimulates a mutant p53 transcriptional program to increase aggressiveness [10].

Dataset 3: LSD1 suppression study (GSE30775)

LSD1 is a component of the Mi-2/nucleosome remodeling and deacetylase (NuRD) complex [27]; itis critically involved in the mechanism of de-methylating lysine4 of histone H3 and lysine 9 of histone H3 [28,29]. Studies showed that growth inhibition of breast cancer cells upon pharmacological LSD1 inhibition, e.g., siRNA knockdown of LSD1, promoted expression of proliferation-associated genes like p21, *ERBB2* and *CCNA2* [28]. In aggressive cancer cell lines, the presence of LSD1 was associated with the suppression of proinflammatory cytokine expression such as IL1α, IL1β, IL6, and IL8 as well as the regulation of tumorigenesis [30].

Software for data analysis

Two computational programs with distinct algorithms were used in this study, i.e., DDNA-Chip Analyzer (dChip) [31] and GEO2R [32,33]. dChip is a model-based approach allows probe-level analysis on multiple arrays [31]. By pooling information across multiple arrays, it is possible to assess standard errors for the expression indexes. This approach also allows automatic probe selection in the analysis stage to reduce errors due to cross-hybridizing probes and image contamination. High-level analysis in dChip includes comparative analysis and hierarchical clustering [31]. GEO2R uses linear models and empirical Bayes methods for assessing differential expression in microarray experiments [33]. A significantly differentially expressed gene is defined by the following criteria: 1) gene expression fold change ≥2.0 (for up-regulated genes) or ≤ 0.5(for down-regulated genes); 2) absolute intensity difference value ≥100; and 3) p-value ≤0.05.

Results

Three datasets from genome-wide gene expression studies on MDA-MB-231 cells were selected and downloaded from the NCBI website (Table 1). The dataset GSE24249 contains 3 control samples and 3 experimental samples with GATA3 overexpression [9]. The 6 samples from dataset GSE26262 were included in this analysis containing 3 control samples (siCtl) and 3experimental samples with Pin1 knockdown (siPin1) [10]. The dataset GSE30775 contains 3 control samples and 3 LSD1 knockdown samples (siRNA-LSD1) [28].

To ensure the validity of the results from the computational analysis, the three datasets were processed and analyzed individually by two different computational programs with distinct algorithms, i.e., dChip [31] and GEO2R [32,33]. Thus, the resulting genes should not be biased toward one particular algorithm. A differentially expressed gene is defined as a gene with fold change ≥ 2.0 (for up-regulated genes) or ≤ 0.5(for down-regulated genes); absolute intensity difference value ≥ 100; and p-value ≤ 0.05. The differentially expressed gene profiles resulting from the two algorithms were then cross-compared. A common gene signature consists of eight significant genes (SH2D3A, RBM47, PTGES, AGR2, ABCC3, IFI27, LAMC2, LAPTM5) was identified (Figures 1-2). Further literature

Table 1: Three datasets from genome-wide gene expression studies.

NCBI ID	Targeted Gene	Cancer Characteristics	Method of Gene Targeting
GSE24249	*GATA3*	Little to no expression of GATA3 in cancer	Overexpression via transduction with lentivirus
GSE26262	*PIN1*	PIN1 is associated with mutant p53 mechanisms	siRNA-based gene knockdown
GSE30775	*LSD1*	LSD1 is associated with breast cancer cell growth and regulation of tumorigenesis	siRNA-based gene knockdown

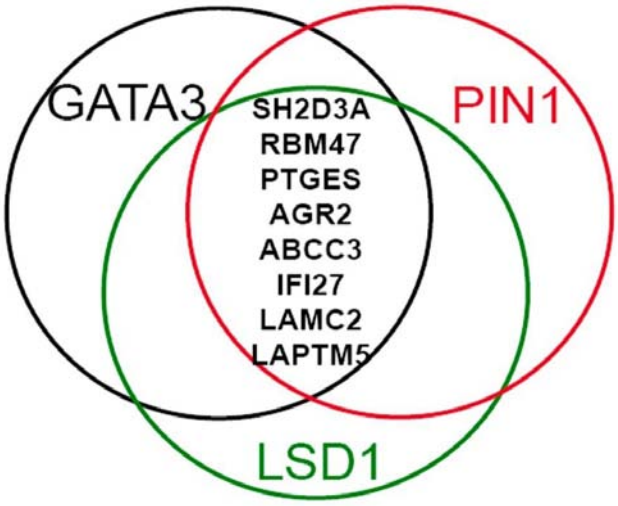

Figure 1: Common genes identified from MDA-MD-231 cells after treatment by gene targeting.
The three treatments with GATA3, PIN1, and LSD1were analyed by dChip and GEO2r and cross-compared, eight genes were identified to be common in MDA-MB-231 cells after gene targeting.

Figure 2: Comparison of the common genes resulting from the two computational algorithms.
The three datasetswere analyzed by dChip (left) and GEO2r (right), respectively. The heatmap shows the fold changesbetween treated and the controlsamples. Green color represents gene up-regulation; Red represents gene down-regulation.

analysis showed that PTGES [34-36], AGR2 [37-40], and ABCC3 [41-44] were genes associated with cancer stem cells and drug resistance. SH2D3A, IFI27, LAMC2, RBM47, and LAPTM5 were identified as genes that play a role in various aspects of tumor growth and pathogenesis [45-47].

Prostaglandin E synthase (PTGES)

PTGES is the gene that codes for glutathione-dependent prostaglandin E synthase and catalyzes the production of prostaglandin E2. A study by Marotta *et al.* suggested that inhibition of the prostaglandin pathway could decrease the number of $CD44^+$ $CD24^-$ stem cell-like cells [48]. Furthermore, triple-negative breast cancers have been shown to contain more $CD44^+$ $CD24^-$ cancer stem/progenitor cells and are associated with poor prognosis [36].

Our analysis showed that PTGES was highly up-regulated as identified by both dChip and GEO2R across all three datasets.

Anterior gradient 2 (AGR2)

AGR2 codes for the anterior gradient protein 2 homolog. A previous study by Smirnov *et al*., have identified this protein to be a marker of circulating tumor cells (CTCs) and cancer stem cells [40]. Recent studies of cancer stem cells have shown its relations with CTCs as a subpopulation of CTCs and a major component in metastasis [49]. In benign non-metastatic rat tumors, overexpressing mammalian AGR2 showed a surge of metastatic potential of those cells in vivo [50].

AGR2 was up-regulated when treated with LSD1 and Pin1 gene knockdown, but down-regulated when treated with GATA3 overexpression.

ATP-Binding cassette, sub-family C, member 3 (ABCC3)

ABCC3 codes for ATP-Binding Cassette, sub-family C, member 3 transporters. The ABCC sub-family contains the nine multiple-drug resistance associated proteins [44]. Expression of these proteins creates a major hindrance in effectively treating cancers due to their role in multiple-drug resistance. ABCC3 was found to be highly up-regulated as identified by both dChip and GEO2r across all three datasets.

Interferon, alpha-inducible protein 27 (IFI27)

IFI27 codes for interferon, alpha-inducible protein 27, which mediates interferon-induced apoptosis and involved in cancers [51,52]. Though these interferons traditionally work within the IFN/STAT1 pathway as a pro-apoptotic tumor suppressor, studies show a possible increase in metastatic ability under certain conditions.

RNA-binding motif (RBM47)

The RBMY family has been linked to testicular cancer and recent studies have suspected a connection between the RBMX family and breast cancer tumors. Studies show that breast cancers do express RBM47 and has an explicit relation with CD105, though neither role has been clearly defined [53-55].

Laminin gamma 2 (LAMC2)

Laminins are a family of ECM glycoprotein's and acts as the major component of the noncollagenous basement membranes. This protein is involved in cell migration and tumor invasion. It has been identified as a potential marker for other various types of cancers due to its effects on cell growth, cell cycle, migration, invasion, and EGFR signaling [56]. To the best of our knowledge, no previous study has firmly correlated LAMC2 expression with breast cancer [57-59].

Lysosomal-associated transmembrane protein (LAPTM5)

This protein has been associated with melanoma transformation and also a molecular partner to CD1e [60].

Discussion

In this study, we identified potential therapeutic targets for aggressive breast cancer cells by cross-analyzing the gene expression profiles of MDA-MB-231 cells distinctly targeted with three different genes: 1) GATA3, a key gene in luminal cell differentiation during mammary gland development [16,17]; 2) Pin1, a prolyl isomerase, promotes both Her2/Neu/Ras and Notch1 dependent changes of breast cells [25,26]; 3) LSD1, a subunit of the NuRD complex and targets the metastasis programs in breast cancer [27]. Analysis of the differentially expressed genes in MDA-MB-231 cells before and after the these gene targeting, we identified eight genes common to

the three datasets, of which PTGES, AGR2, and ABCC3 are highly associated with cancer stem cells and drug-resistance, suggesting that they represent potential targets for future anti-cancer drug development. If in fact that metastasis and poor prognosis are due to the maintenance of cancer stem cells in tumors, these genes associated with cancer stem cells can be potential biomarkers for breast cancer.

The effects of the three distinct treatments by single gene targeting were analyzed as three independent studies. Thus, a common gene across all three studies implies that, even under different treatments, the MDA-MB-231 cells utilize a similar mechanism involving cancer stem cells to promote metastasis and drug resistance of tumor cells.

PTGES is an enzyme that catalyzes the production of prostaglandin E2 [35]. It was also known that genetic variation in the prostaglandin pathway affects cancer susceptibility and progression [34]. In addition, inhibition of this prostaglandin pathway led to the decrease of $CD44^+/CD24^-$ stem cell-like cells and those triple-negative breast cancers express a substantial amount of these cells that could be associated with poor prognosis [34]. In this study, PTGES was overexpressed under all three treatments, suggesting that the prostaglandin pathway was promoted to potentially affect the increase of the $CD44^+/CD24^-$ stem cell-like cells. This implies that upon treatment, triple negative breast cancers may initiate a universal survival mechanism involving the prostaglandin pathway and thus makes it a worthwhile marker to investigate as a potential therapeutic target.

ABCC3 is mainly associated with multiple-drug resistance. This gene signature was commonly up-regulated across all three treatments as would be expected from a cancer stem cell that is trying to prolong its survival. Studies have shown that expression of ABC transporters such as ABCC1, ABCC2, ABCC3, and ABCG2 contribute to the drug-resistance of cancer stem cells, and then the relapse of breast cancer [8,61]. Having singled out ABCC3 above the other ABC transporters might be significant insight as to it being the key player in multiple-drug resistance that promotes the survival of cancer stem cells within triple negative breast cancer cells.

AGR2 is a marker for circulating tumor cells whose subpopulation consists of cancer stem cells. Thus, the up-regulation of AGR2 shows the direct result that the objective of this study to identify potential gene signatures associated to metastasis was successful. This gene was up-regulated only in two of the three studies; it was under-expressed in the GATA3 study. It should be considered, however, that the three studies successfully showed an inhibition of aggressive cancer behavior. It could be the case that overexpressing GATA3 specifically interfered with the expression of AGR2, which may have contributed to the favorable results of repressing aggressiveness within the study. Despite this slight inconsistency, the up-regulation of AGR2 in the other two studies still makes it a marker of high interest that should be further studied.

Conclusion

The results of this study identified eight common genes in the MDA-MB-231 cells after different treatment with gene targeting, three of which were directly related to cancer stem cells and drug resistance. There is growing support for cancer stem cells being the major component in metastatic behaviors; thus, these three genes may hold promising potential to be therapeutic targets. Future studies will investigate 1) the therapeutic potential of each one of the three genes; and 2) common gene signature among other cancer cells. In addition, the methods of this study can be applicable to other investigations and reveal even greater insight to the mechanisms behind breast cancer stem cell maintenance.

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