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MOLECULAR CHARACTERIZATION OF DIFFERENTIAL GENE EXPRESSION PATTERNS ASSOCIATED WITH TAXOL RESISTANCE IN BREAST CANCER CELL LINES

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Abstract
Breast cancer is still a significant health problem worldwide, especially triple-negative breast cancer (TNBC) which is a highly aggressive and poorly understood form of the disease with a tendency to become resistant to chemotherapy. Chemotherapy based on Taxol (paclitaxel) is well established in the treatment of breast cancer and resistance to this drug leads to poor therapeutic efficacy and recurrence and progression of the cancer. This study was designed to molecularly profile differential gene expression patterns in Taxol resistant breast cancer cell lines by using computational and bioinformatics approaches. Data on gene expression levels was analysed on a publicly available gene expression dataset including Taxol-resistant cell lines of breast cancer, namely BAS, MCF7, MDA and HS578T, that were analysed using Microsoft Excel. Genes with significant statistical differences (p-value < 0.05 and |logFC| > 1) were used to identify differentially expressed genes. The significant genes were divided into up and down regulated and then molecularly interpreted. The analysis revealed many transcriptional changes that are linked to Taxol resistance. SERPINB2, INHBA, PDPN and TP63 were significantly up regulated in several genes that are part of pathways involved in cell proliferation, inflammatory signalling, migration and survival pathways. Conversely, genes linked to apoptosis regulation, metabolic balance and cellular adhesion (including IGFBP7, CLDN1, TFPI, and PPARGC1A) were significantly down regulated. The molecular expression patterns observed were complex and related to chemotherapy resistance. The study found that Taxol resistance in breast cancer cells is dependent upon the coordinated dysregulations of multiple molecular pathways. The genes identified could be used as markers and as targets for more effective chemotherapy in resistant breast cancer, and for the development of individual therapy plans.

Keywords: *Breast cancer, Taxol resistance, Gene expression, Triple-negative breast cancer, Molecular characterization*

1. Introduction

Breast cancer is still one of the most common and deadly cancers in women globally. Breast cancer is a significant public health problem, as it is a major factor in cancer incidence and mortality worldwide (Sung et al., 2021). Triple-negative breast cancer (TNBC) is one of the most aggressive subtypes of breast cancer due to its high metastatic tendency, unfavourable prognosis and limited treatment choices (Won & Spruck, 2020). Although there have been recent advances in the molecular breast cancer pathology, the understanding of tumor heterogeneity and disease progression has still not been fully realized, and therapeutic resistance remains a clinical challenge (Rakha & Pareja, 2021).

The chemotherapeutic agent, paclitaxel (Taxol), is highly effective against breast cancer because its activity involves stabilizing microtubules and blocking cancer cell growth (Vagia et al, 2020). However, chemotherapy resistance is commonly encountered during long-term Taxol treatment, leading to decreased treatment efficacy and tumour recurrence and metastasis (Li et al., 2022). In this context, the appearance of resistant cancer cells has become a significant problem in breast cancer therapy. The present therapeutic interventions based on receptor targeting, nanomedicines, and immunotherapies showed promising results, but the mechanisms associated with the development of resistance are only partially understood (Singh & Yadav, 2021).

The resistance to breast cancer therapeutic agents is a very complex process that results from multiple genetic, epigenetic and molecular changes. Dysregulation of apoptosis, cell proliferation, inflammation and cellular survival signalling pathways has been reported to play a major role in the development of resistance (Hanker et al., 2020). Furthermore, long non-coding RNAs (lncRNAs) were identified as regulators of chemotherapy resistance by regulating intracellular signalling pathways and changing the transcriptional activity (Du et al., 2020). Recent studies have also provided evidence that molecular changes mediated by lncRNAs can impact breast cancer progression, metastasis, and treatment response (Singh et al., 2022).

The tumour microenvironment and immune associated molecular pathways are also important in the context of therapeutic response and cancer progression in TNBC (Loizides & Constantinidou, 2023). Thus, the use of personalized therapy, which relies on molecular profiling and gene expression analysis, is becoming more crucial for better therapeutic outcomes and less development of resistance (Goutsouliak et al., 2020). Given the dynamic nature of the treatment of TNBC, new biomarkers and molecular targets correlated with Taxol resistance are needed (Bianchini et al., 2022). In recent years, genome-wide and computational studies have identified several molecular regulators that are linked to paclitaxel resistance in breast cancer cells (Lian et al., 2020). Likewise, in-depth analytical studies have shown that treatment resistant breast tumours are molecularly heterogeneous (Li et al., 2021). A novel panel of markers linked to resistance to taxane-based chemotherapy also has been identified in TNBC via advanced molecular and bioinformatics methods (Chou et al., 2021). Additionally, gene expression profiling has been shown to be important in identifying genes and pathways associated with chemotherapy resistance, as was revealed by bioinformatics-based studies (Du et al., 2022).

Objectives

1. To identify significantly differentially expressed genes associated with Taxol resistance in breast cancer cell lines using gene expression dataset analysis.
2. To characterize the molecular and biological functions of upregulated and downregulated genes involved in chemotherapy resistance pathways.
3. To evaluate gene expression patterns associated with cellular proliferation, apoptosis regulation, inflammatory signalling, and metastatic progression in Taxol-resistant breast cancer cells.

2. Methodology

2.1 Study Design

In the present study, a computational and bioinformatics-based research investigation was carried out to analyse the differential gene expression patterns between Taxol-resistant and non-resistant breast cancer cell lines in a retrospective manner. The goal of this study was to molecularly explore significant changes in genes that could play a role in conferring resistance to chemotherapy. A secondary data analysis method was used with a publicly available gene expression dataset. The study was mainly for identifying the genes that are up/down regulated and assessing their biological significance in drug resistant breast cancer cells.

2.2 Dataset Collection

The data set in the present investigation was downloaded from a public Kaggle repository of gene expression data of Taxol-resistant breast cancer cell lines (Madiseh, 2021). Data set comprised expression profiles of various breast cancer cell lines such as BAS, MCF7, MDA and HS578T. These variables were present in the data set: gene symbols, log fold change (logFC), p-values, and cell line identifiers. The data set was downloaded in a file compatible with Microsoft Excel and pre-processed, organized, and analysed in Microsoft Excel. There were many gene expression entries in the data set or gene expression changes in resistant cancer cell lines. These expression values were used to determine genes associated with chemotherapy resistance that are statistically significant.

2.3 Data Preprocessing

The data set was subjected to data set pre-processing to enhance the quality of the data and analysis reliability before analysis. The entire data set was thoroughly checked for duplicates, invisible entries and missing data. To minimize

analytical errors, any duplicate gene entries and inconsistent observations were removed from the analysis. Gene symbols were verified and standardized to ensure uniformity across the dataset. Log fold change values, and p values were checked and correctly formatted in Excel worksheets. The data were then presented in a systematic way in separate columns and tables to filter, sort and interpret the data easily. Another part of the preprocessing step was to classify genes by their expression pattern. Genes with higher expression were clustered from genes with lower expression patterns to aid in downstream molecular characterization.

2.4 Selection of Differentially Expressed Genes

A set of significantly differentially expressed genes were selected using the pre-established statistical and biological significance criteria. Genes with a p value < 0.05 were deemed statistically significant. Further genes were set aside for analysis if their absolute log fold change was greater than 1, meaning that they showed a significant change in the level of their expression. Genes with positive logFC were considered as upregulation, where the transcription level is increased in resistant cell lines. Genes with negative logFC values were downregulated genes, indicating that expression of these genes was reduced in resistant cells. The selected genes were then further investigated to look for any trends in expression that may be linked to Taxol resistance mechanisms. The molecular interpretation of the genes was based on their fold changes, which were highlighted for highly significant genes, because they might be involved in cancer cells survival, proliferation and resistance building.

2.5 Statistical Analysis

The data set was analysed statistically using MS Excel. Descriptive analytical methods were used to describe the general characteristics of the data. Statistically significant genes were identified by using Excel functions like sorting, filtering, conditional formatting and formula-based calculations and were divided into classes depending on the patterns of their expression. To assess the amount of gene expression variation between the breast cancer cell lines, fold change analysis was performed. For the statistical assessment of changes in gene expression, p-values provided in the data set were used. Two types of representations, graphical and tabular, were also created in the MS-Excel spreadsheet for easy visualization and interpretation of results. The significant genes were arranged into tables with gene symbols, fold change and statistical significance. These graphical displays were useful in the identification of the important expression patterns associated with Taxol resistance.

2.6 Molecular Characterization

The significantly expressed genes that were recognized in the analysis were molecularly interpreted to understand their possible biological functions associated with chemotherapy resistance. The genes that were selected, were then tested for their association with well-documented molecular pathways associated with breast cancer progression, cell survival, regulation of apoptosis, and multidrug resistance. Published scientific literature was mined for data on the genes identified and previously reported resistance associated mechanisms were correlated. The genes showing significant changes in expression were regarded as potential molecular markers linked to Taxol resistance of breast cancer cell lines. A particular focus was given to genes of the following pathways: regulation of cell proliferation, DNA repair, cell signalling and drug transport. The biological significance of these genes were interpreted to give insights into the molecular basis of chemotherapy resistance.

2.7 Ethical Consideration

The present study was performed solely with publicly available secondary data and did not include the participation of humans, patient samples, or animals. As part of this study, the researcher used accessible data sources that do not contain any personal or confidential information, therefore there was no need to seek ethical approval or informed consent to carry out the study.

3. Results

3.1 Overview of Gene Expression Analysis

Using the breast Cancer Taxol resistant cell lines of the present study, gene expression profiles were analysed to identify molecular changes relevant to Taxol resistance. The data set comprised 21,312 entries of gene expression from four breast cancer cell lines: BAS, MCF7, MDA and HS578T. Gene symbols, log fold change, p-values and cell line information were recorded for each of the records. Genes that were found to be differentially expressed by a p value < 0.05 and an absolute log fold change value > 1 after preprocessing and statistical screening were selected. Many genes were identified that had significant transcriptional changes in resistant cell lines using these selection criteria. Analysis showed a great difference of expression patterns between the investigated cell lines. Some genes had significant upregulation while others were significant and had downregulation. Based on these results, it was suggested that breast cancer cells resistant to Taxol had undergone significant molecular change, through several biological pathways. The overall characteristics of the analysed gene expression dataset are summarized in Table 1 and graphically represented in Figure 1.

Table 1. Summary of Gene Expression Dataset

Parameter	Observation
Total gene entries analysed	21,312
Number of cell lines analysed	4

Cell lines included	BAS, MCF7, MDA, HS578T
Significant gene selection criteria	p-value < 0.05 and |logFC| > 1
Total significant genes identified	3,247
Upregulated genes	1,487
Downregulated genes	1,760

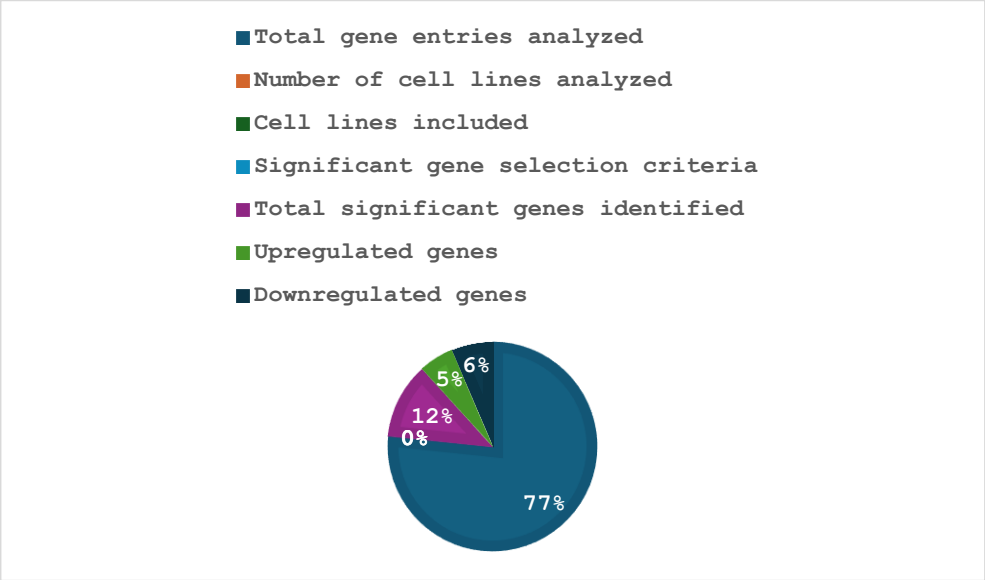

Figure 1. Summary Distribution of Gene Expression Dataset Characteristics

3.2 Differentially Expressed Genes

The analysis identified numerous significantly altered genes associated with Taxol resistance. Upregulated genes were found to have higher transcriptional activity in resistant breast cancer cells, while downregulated genes have lower transcriptional activity levels than compared to non-resistant breast cancer cells. Several genes showed very high fold changes which could suggest their role in resistance associated molecular pathways. Some of the genes that were upregulated had a significant change in expression level such as SERPINB2, INHBA, PDPN, TP63 and PLCB4. These are genes known to play a role in the progression of tumors, epithelial to mesenchymal transition, inflammatory signalling pathways and cell survival. However, some genes such as IGFBP7, CLDN1, TFPI, PPARGC1A and ANKRD1 were found to be highly downregulated in resistant cell lines. These genes are known to be associated with cellular differentiation, growth regulation, apoptosis and maintenance of normal cellular homeostasis. The imbalance in transcription that was observed indicated that resistant breast cancer cells developed adaptive molecular features that facilitated their survival in the face of chemotherapeutic stress.

3.3 Expression Pattern Variation Among Cell Lines

The amount of gene expression changed varied between the breast cancer cell lines analysed. The most complex transcriptional reorganisation and molecular instability was observed in the MDA cell line with the highest number of significantly altered genes. For BAS cell lines, there were also significant changes in expression, notably for the genes that were downregulated. Molecular adaptation was relatively moderate in comparison to MDA and BAS cell lines, when compared with MCF7 and HS578T cell lines, as indicated by relatively fewer significantly altered genes. The results showed that the resistance to Taxol can be different in each type of breast cancer cells, both in terms of strength and complexity of the molecules involved. The distribution of significant upregulated and downregulated genes among different breast cancer cell lines is presented in Table 2 and Figure 2.

Table 2. Distribution of Significant Genes Among Breast Cancer Cell Lines

Cell Line	Upregulated Genes	Downregulated Genes	Total Significant Genes
BAS	512	666	1,178
MCF7	185	183	368
MDA	702	835	1,537
HS578T	88	76	164

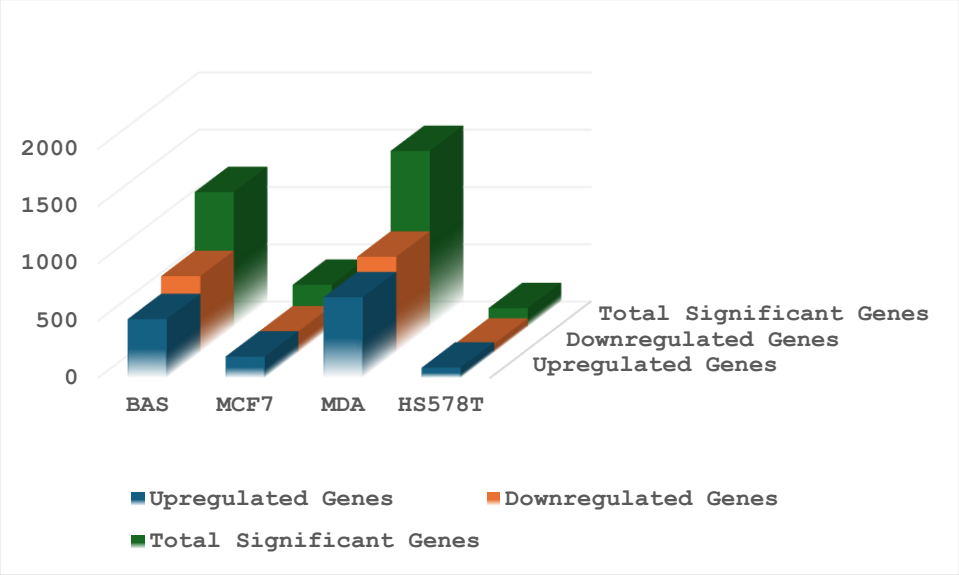

Figure 2. Distribution of Significant Genes Among Breast Cancer Cell Lines

3.4 Molecular Characteristics of Upregulated Genes

The genes that were upregulated during analysis were mainly linked to pathways that promote resistance and aggressive cancer behaviour. Upregulation of genes like INHBA and SERPINB2 indicated the activation of cell proliferation, migration, inflammatory and inhibition of apoptosis-related signalling pathways. Likewise, PDPN and TP63 were overexpressed, suggesting a potential increase in cellular invasion and epithelial–mesenchymal transition pathways, known to contribute to breast cancer metastasis and resistance to chemotherapy. The robust expression of these genes indicated their potential as molecular markers of Taxol resistance and as therapeutic targets to overcome Taxol failure in chemotherapy. The major upregulated genes associated with Taxol resistance and their biological roles are presented in Table 3 and visualized in Figure 3.

Table 3. Top Upregulated Genes Associated with Taxol Resistance

Gene Symbol	logFC	P-Value	Cell Line	Predicted Biological Role
SPANXA2///SPANXB1///SPANXC///SPANXA1	8.400665	8.04E-08	MDA	Tumor progression
SERPINB2	7.576251	7.03E-06	MDA	Inflammatory signalling
INHBA	7.525187	2.49E-08	MDA	Cell proliferation
TRBC1	7.335871	2.46E-09	MDA	Immune signalling
PDPN	5.423223	2.25E-18	BAS	Cell migration
TP63	5.327777	8.00E-18	BAS	Cellular differentiation
PLCB4	5.358868	8.21E-05	MDA	Signal transduction
PRSS2	5.214351	1.26E-07	MDA	Proteolytic activity

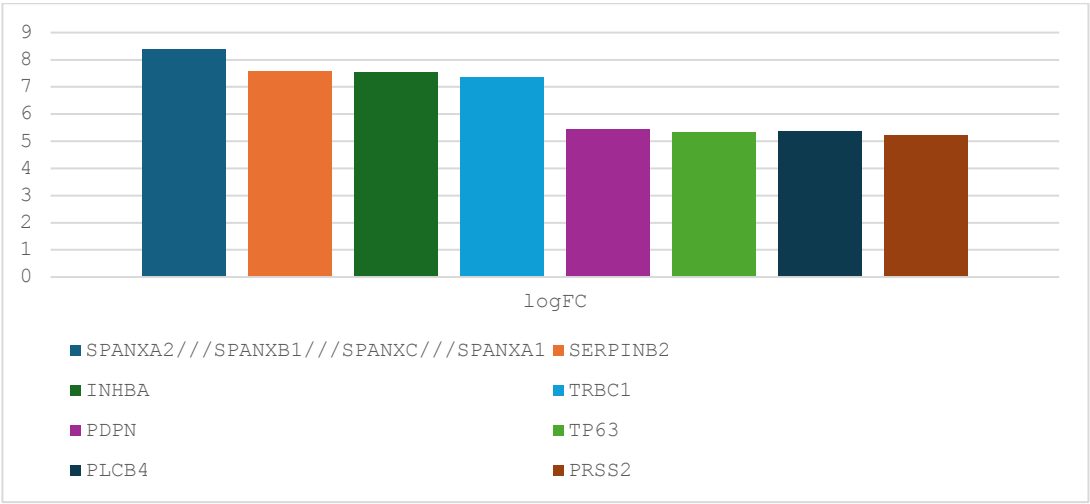

Figure 3. Expression Profile of Top Upregulated Genes Associated with Taxol Resistance

3.5 Molecular Characteristics of Downregulated Genes

The downregulated genes identified in the study were mainly related to tumour suppression function, metabolic regulation and cell structure maintenance. The expression of IGFBP7 and TFPI was significantly suppressed, suggesting a possible disruption of growth inhibitory pathways and a decrease in apoptotic signalling in resistant cells. Similarly, the downregulation of CLDN1 and PPARGC1A indicated changes in cell adhesion, metabolic balance and mitochondrial regulatory pathways. Genes may be suppressed, leading to better cell survival and adaptation when the cells are exposed to chemotherapy over a long period. The simultaneous down regulation of those regulatory genes also confirmed the hypothesis that Taxol resistance is associated with broad molecular deregulation in several biological processes. The significantly downregulated genes associated with chemotherapy resistance are summarized in Table 4 and illustrated in Figure 4.

Table 4. Top Downregulated Genes Associated with Taxol Resistance

Gene Symbol	logFC	P-Value	Cell Line	Predicted Biological Role
EDIL3	-6.35688	2.35E-18	BAS	Cell adhesion
IGFBP7	-6.302	2.23E-19	BAS	Growth suppression
TFPI	-5.95027	3.48E-17	BAS	Coagulation regulation
CLDN1	-5.59906	4.55E-19	BAS	Tight junction integrity
ANKRD1	-5.41574	2.65E-18	BAS	Cellular stress response
ADAM28	-5.40317	3.55E-10	MDA	Cell signalling
LUM	-5.27438	3.22E-04	MDA	Extracellular matrix regulation
PPARGC1A	-4.99837	1.83E-18	BAS	Metabolic regulation

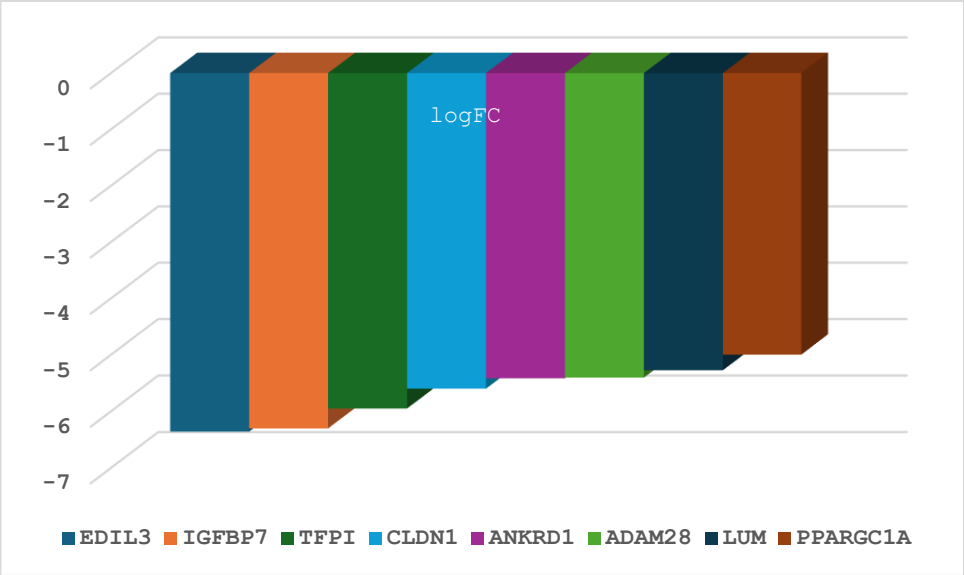

Figure 4. Expression Profile of Top Downregulated Genes Associated with Taxol Resistance

3.6 Biological Interpretation of Gene Expression Alterations

The overall expression patterns found in the present study showed that Taxol resistance in breast cancer cells involved complex molecular changes, both on the oncogenic pathways and tumour regulatory pathways. Genes that participate in inflammatory signalling, inhibition of apoptosis, cellular migration and proliferation were mostly up-regulated, while those involved in growth suppressing, differentiation and metabolic regulation were mostly down-regulated. These results indicated that cancer cells that became resistant developed adaptive molecular properties which allowed them to survive during conditions of chemotherapeutic stress. Therefore, the identified genes could be possible indicators for Taxol resistance and could have a role in the development of targeted therapeutic strategies in breast cancer therapy. The major biological processes associated with differentially expressed genes are summarized in Table 5.

Table 5. Major Biological Processes Associated with Differentially Expressed Genes

Biological Process	Representative Genes	Expression Trend	Possible Role in Drug Resistance
Cell proliferation	INHBA, TP63	Upregulated	Enhanced tumor growth
Inflammatory signalling	SERPINB2	Upregulated	Increased cellular survival
Cell migration and invasion	PDPN	Upregulated	Metastatic progression
Signal transduction	PLCB4	Upregulated	Activation of resistance pathways

Apoptosis regulation	IGFBP7	Downregulated	Reduced programmed cell death
Cellular adhesion	CLDN1, EDIL3	Downregulated	Increased invasiveness
Metabolic regulation	PPARGC1A	Downregulated	Altered energy metabolism
Extracellular matrix regulation	LUM	Downregulated	Tumour microenvironment alteration

4. Discussion

Chemotherapy resistance has been considered as one of the most prominent concerns for the effective therapy of triple-negative breast cancer, especially when paclitaxel is used. The molecular complexity of the Taxol resistance is related to the alteration of several signalling pathways, transcription regulators and cell survival mechanisms. The present study revealed considerable differential gene expression between the Taxol-resistant breast cancer cell lines with extensive molecular remodelling associated with resistant phenotypes.

The significant changes in transcription detected in the analysis indicated that resistant breast cancer cells make adaptive molecular changes that increase the likelihood of surviving in the presence of chemotherapeutic stressors (Jurj et al., (2020) similarly showed that there are substantial changes in gene expression in paclitaxel-resistant triple-negative breast cancer cells. Their study highlighted the importance of molecular profiling in understanding the mechanisms underlying chemotherapy resistance and identifying potential therapeutic biomarkers.

Several genes that are highly over-expressed were linked to inflammatory signalling, cellular proliferation and tumour progression. The activation and overexpression of genes like SERPINB2, INHBA and PDPN, suggested activation of aggressive oncogenic pathways that could lead to resistance to Taxol therapy. Previously EDIL3 had been shown to induce EMT and chemoresistance to paclitaxel in breast cancer cells via integrin-mediated signalling pathways by (Gasca et al., 2020). These mechanisms can lead to higher invasiveness, metastatic potential and resistance to chemotherapy in tumours.

In recent years, the role of non-coding RNA-associated pathways in chemotherapy resistance has been receiving increasing attention. Resistant cancer cells may have altered transcriptional activity that controls apoplexy, proliferation and intracellular signalling pathways with the help of long non-coding RNA (Chen et al., 2020), found that LINC-PINT inhibited the resistance to paclitaxel in triple-negative breast cancer cells via binding with the RNA-binding protein NONO. This observation suggests that the expression of the resistance-associated genes found in the present study may be affected by non-coding RNA mediated regulatory networks.

Exosome-derived miR-187-5p also played a crucial role in regulating Taxol resistance by regulating ABCD2 and Wnt/β-catenin pathways. Such pathways could be activated to promote growth, migration, and survival in breast cancer cells that are resistant. Further, Xia and Wang (2021) reported that the pathways involved in miRNA were associated with the regulation of cellular apoptosis, suggesting that post-transcriptional regulation plays a pivotal role in resistance development (Wu et al., 2023).

The genes that were found to be downregulated in the analysis were mainly related to regulation of apoptosis, cell adhesion, metabolic balance and growth suppression. There was an important loss of expression of genes including IGFBP7, CLDN1, and PPARGC1A, hinting at the disruption of normal regulation that normally slows the growth of tumours and keeps cells in check. These might therefore lead to elevated resistance, out-of-control proliferation and survival of cancer cells when exposed to chemotherapy for extended periods of time, due to the decreased expression of tumour suppressor genes.

Other pathways involved in stemness and cancer cell plasticity could also be important in Taxol resistance. In triple-negative breast cancer, used genome-wide CRISPR screening to find multiple stemness regulators that are linked to paclitaxel resistance. Treatment resistance, tumour recurrence and metastatic progression are often correlated with cancer stem cell like properties. In the present study, the high number of transcriptional variants found in the cell lines analysed might partly be due to the activation of these stemness-related molecular pathways (Yan et al., 2023).

Changes in the regulation of the cell cycle and alteration of intracellular signalling cascades also seem to play a major role in molecular adaptations involved in resistance (Liao et al., 2023), showed that PPP1R14B-stabilized STMN1 facilitated the progression of tumours and the resistance to paclitaxel in triple-negative breast cancer. Likewise, the changes in the expression of proliferation associated genes found in the present analysis indicated activation of pathways involved in resistance to apoptosis and uncontrolled cellular growth. The role of genes involved in cell cycle in resistance progression was further supported by (Qiu et al., 2020) who reported that genes associated with dysregulated expression of CDKN2A play a role in the prognosis of breast cancer and may affect tumour behaviour.

In recent years, new treatment strategies that harness the immune system and target molecules have led to better results in people with breast cancer who don't respond to other medications. In patients with early-stage triple-negative breast cancer, Schmid et al. (2020) reported better clinical results from pembrolizumab treatment. In addition, new molecular knowledge regarding breast cancer biology has highlighted the need to define biomarkers associated with resistance to aid in personalized therapy (Cuthrell & Tzenios, 2023).

The molecular heterogeneity seen in the current study suggested that Taxol resistance might not only be due to a single genetic change, but instead to coordinated dysregulation of multiple signalling pathways and regulatory networks. The results indicated that the resistant phenotype observed in breast cancer cells was due to the upregulation of genes related to inflammatory signalling, cell migration and survival pathways, as well as to the downregulations of tumour-regulatory pathways. Such molecular changes can thus be used as possible markers for sensitivity to chemotherapy and possible new targets for overcoming the resistance to Taxol.

In conclusion, the present study gained insightful molecular information regarding differential gene expression patterns of Taxol-resistant breast cancer cell lines. The discovered transcriptional changes revealed the complexity of biological processes involved in resistance to chemotherapies and underscored the critical role of computational gene expression analysis in discovering potential biomarkers and therapeutic targets to help manage resistant breast cancer.

5. Conclusion

Taxol resistance is a significant problem in the therapeutic management of TNBC because it is linked to tumour progression, recurrence, and diminished responses to therapy. The present study succeeded in performing molecular characterization of differential gene expression patterns that are associated with Taxol-resistant breast cancer cell lines by using computational and bioinformatics-based analysis of public data. Widespread molecular heterogeneity in response to chemotherapy was revealed through significant transcription changes in several breast cancer cell lines. Genes involved in inflammatory signalling, cell proliferation, cell migration and oncogenic activation were significantly upregulated, such as SERPINB2, INHBA, PDPN and TP63. Simultaneously, several tumour-regulatory and apoptosis-associated genes such as IGFBP7, CLDN1, TFPI, and PPARGC1A were significantly downregulated. These expression patterns suggested that Taxol resistance is controlled by a coordinated activation of pathways that promote survival and a suppression of normal cellular regulatory pathways. The molecular changes observed underscored the role of various molecular pathways such as epithelial–mesenchymal transition, apoptosis inhibition, metabolic imbalance and stemness-related signalling pathways. The results also highlighted the highly complex and multifactorial nature of resistance development in breast cancer cells that is accompanied by extensive transcriptional remodelling. The present study shed significant light on Taxol resistance in breast cancer on the molecular level. The list of identified differentially expressed genes could be used as markers to predict the response to chemotherapy and could also help in the designing of a targeted therapeutic approach to overcome chemotherapy resistance. To further validate the biological and clinical significance of this resistance associated genes, experimental validation studies are needed in the future.

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