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ISSN: 3080-4183 (Print)
ISSN: 3080-4191 (Online)

Clinical and Health Research Exploration

DECIPHERING DRUG RESISTANCE MECHANISMS IN TRIPLE-NEGATIVE BREAST CANCER THROUGH CROSS-PLATFORM INTEGRATION OF SCRNA-SEQ,EPIGENOMICS, AND CHEMOINFORMATICSINTRODUCTION

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Abstract

Triple-negative breast cancer (TNBC) is an aggressive and treatment-resistant subtype of breast cancer lacking targeted hormonal receptors and HER2 expression. This study presents a multi-omics and chemoinformatics-based investigation into the molecular mechanisms driving drug resistance in TNBC. Single-cell RNA sequencing (scRNA-seq) and ATAC-seq were performed on patient-derived TNBC samples to identify transcriptional and epigenomic alterations associated with chemotherapeutic response. Chemoinformatic modeling of IC50 profiles across diverse compounds, including paclitaxel and PARP inhibitors, revealed substantial heterogeneity in drug sensitivity. Nine comprehensive tables were constructed to catalog gene expression variability, methylation scores, and drug resistance indices, while twelve complex visualizations illustrated expression dynamics, resistance distribution, and biomarker patterns. The results highlighted critical resistance mechanisms, including epigenetic silencing, hypoxia-induced transcriptional rewiring, and immune-exclusion signatures from the tumor microenvironment. Notably, a subset of genes exhibited resistance-specific expression patterns linked to poor response outcomes. The integration of multi-omics datasets enabled the identification of high-confidence drug-gene associations, supporting the utility of predictive models in therapeutic stratification. These findings underscore the urgent need for personalized treatment strategies and emphasize the value of integrative systems biology approaches in overcoming therapeutic resistance. This study contributes a foundational framework for precision oncology in TNBC, offering robust biomarkers and novel targets for future clinical intervention.

Keywords: Triple-negative breast cancer, drug resistance, single-cell RNA-seq, epigenomics, chemoinformatics, multi-omics integration

1. INTRODUCTION

Triple-negative breast cancer is an extremely vicious and heterogenous form of breast cancer that lacks the expression of oestrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (Wesolowski et al., 2022) (Charan et al., 2020). This pattern of molecules renders TNBC ineffective to the typical hormone therapy or HER2 targeted therapies hence difficult to treat and has a poor prognosis when compared to other types of breast cancer. In that way, chemotherapy and surgery remain the main two options to cure cancer, although their effectiveness is frequently overcome in the long run by drug resistance (Li et al., 2022). Neoadjuvant chemotherapy is very likely to induce a pathological complete response but this does not robustly predict long term survival free of recurrence alone. That is why the field is in dire need of novel prognostic biomarkers and therapeutic targets (Xia et al., 2021). The existence of this resistance usually due to the fact that TNBC tumours are not the same as each other, makes it difficult to develop targeted treatment options (Li et al;, 2023). TNBC composes approximately 10 to 20 percent of the total breast cancer patients. It shows different metastatic patterns and a more invasional biological behaviour, making it difficult to treat (Li et al., 2022) (Zhou et al., 2023). The aggressive phenotype and increased metastatic potential of TNBC is directly connected to its intrinsic molecular heterogeneity. This implies that we must acquire more knowledge of what processes lead to treatment failure (Asleh et al., 2022) (Saeed et al., 2021). The upcoming review will examine the numerous variants of treatment resistance occurring in TNBC that can be observed by integrating single-cell RNA sequencing (scRNA-seq) and epigenomics data and chemoinformatics. Such knowledge is valuable in the development of personalised therapy and enhancing patient outcomes in this recalcitrant condition (Zhao et al., 2022) (Lee et al., 2020). The pathogenesis and the biological features of TNBC need to be completely comprehended to produce effective individualised treatment plans. It is so because patients with loco advanced or metastatic TNBC usually exhibit poor clinical outcomes in the event that they fail to react to hormonal or targeted agents (Ji et al., 2022). The problem with TNBC is that it is aggressive, has a limited amount of treatment options, and tends to evolve into resistant disease (Shaath et al., 2021). It is even more aggressive because this type recurs frequently and infects other body organs, and this is one of the central factors that cause the death of breast cancer patients (Song et al., 2020). Chemotherapy resistance remains a huge issue when treating any forms of breast cancer that may lead to the reoccurrence of cancer, and subsequent spreading with poor outcomes in the patients (Luo et al., 2020). TNBC tends to be sensitive to chemotherapy, though that does not necessarily work well. As an illustration, there are very few patients who react to new medicine such as immune checkpoint or PARP inhibitors, and even those who do end up developing resistance and relapse (Won & Spruck, 2020). This is an integrative approach that will enable us learn the complex nature of interaction among genetic, epigenetic and pharmacological factors leading to medication resistance. This will result in identification of new therapeutic targets and the rational development of combination therapy (Li et al., 2023). The results

of TNBC patients in terms of recurrence and death despite using regular treatment illustrate how critical it is to conduct additional research on the basis of the mechanism of resistance of the disease to it (Yoshikawa et al., 2020). Such a complex interaction involves both the changes occurring automatically in cells of the tumour due to genetic and epigenetic alterations and changes occurred outside of cells due to the tumour microenvironment (Wu et al., 2021). Learning about these pathways can be the key to overcoming the current barriers to treatment and providing patients with this recalcitrant disease with improved chances of recovery, since the risk of TNBC local recurrence and distant metastases is rather high (Ferrari et al., 2022). That cancer is so aggressive and that there are too few alternatives to therapy indicate it is high time we had new chemotherapeutic agents and treatment procedures that can curtail or even prevent cancer growth and bypass resistance to treatment (Sekar et al., 2025). The inclusion of immunotherapy, PD-L1 inhibitory agents, has proven to benefit the TNBC patient, but responses to treatment remain highly inconsistent as the immune microenvironment is diverse in each subtype (Chen et al., 2022). TNBC is 1520 of all breast cancer cases and is associated with high mortality and the tendency to recur, so new solutions have to be discovered and the resistance mechanism should be studied better (Paranthaman & Shanthi, 2023). The immense danger of both intrinsic and acquired drug resistance that may result in disease development and poor survival rates dictates the importance of discovering more about the processes of TNBC that render treatments ineffective (Chen et al., 2020).This paper will concentrate on how tumor-extrinsic and tumor-intrinsic factors render TNBC insensitive to treatment, such as genetic alterations, shifted metabolic routes, and tumour microenvironment among others (Bai et al., 2020). Other mechanisms into which tumours can be resistant to treatment are still being sought by researchers. They have thus identified tumour microenvironment modification, autophagy, genetic and epigenetic changes and tumour mutational load so far (Koustas et al., 2020). The complex interactions that occur between a cell and the cell in the tumour microenvironment are highly significant because their effect on the effectiveness of treatment and their susceptibility to drugs is huge (Zambrano-Romn2022). Tumour and its milieu communications are complex, in such a way that generally reduces the effectiveness of immunotherapies. This restricts the effectiveness of adoptive therapeutic drugs and demonstrates the necessity to discover further details about the mechanism of TNBC immune resistance (Zheng et al., 2023). It is particularly necessary considering that immunosuppressive cells and metabolic rivalry in the tumour microenvironment, among other things, may cause T-cell fatigue and render immunotherapy more ineffective (Shan et al., 2022). The complexity and diversity of the tumour micro environment and the immune system contribute immensely to drug resistance. The cancer cells communicate with other surrounding fibroblasts, immune cells and adipocytes to facilitate the spread and the metastasis of the disease (Frantz & Ceol, 2020). Understanding these interactions is of clinical importance, given the fact that immunotherapy has taken big steps over the past few years (Frantz & Ceol, 2020). Such types of interactions may result in the modification of tumour microenvironment to respond to the

conditions of low oxygen levels, altering how the cancer cells and other cell components can metabolise, including the development of disorganised vascular systems that promote the spread of cancer (Babar et al., 2023). That is the aim of this review, to summarize what is already known about the molecular basis of drug resistance in TNBC, and how scRNA-seq, epigenomics, and chemoinformatics could assist in understanding these complex processes. Take as an example the low oxygen seen in the tumour microenvironment, some cancer cells can even grow at a faster rate, an indication of how significant it is in determining treatment resistance and tumour growth (Chen et al., 2021). It is also because the production and invasion of glioblastoma microtumors can be influenced by this change of the environment in which the expression of laminin alpha 5 can be modified (Chen et al., 2021).

2. METHODOLOGY

This research paper applies a mixed methods experimental approach to explore all the various aspects through which drug resistance can develop in triple-negative breast cancer (TNBC). The protocol integrates high-throughput single-cell RNA sequencing (scRNA-seq), epigenomic profiling, and chemoinformatics modelling in identifying the internal and external factors, which cause difficulty in people in responding to treatment. We retrieved patient-derived TNBC tumour biopsies in a clinical group after agreeing to their consent and all of our strategies were approved by the institutional review board. The mechanical and enzymatic procedures were utilized in breaking the biopsies into single cells. These cells were then processed using the 10x genomics chromium platform. We prepared the sequencing libraries using the Single Cell 3 We used the Single Cell 3 V3.1 Library & Gel Bead Kit and sequenced with one of the Illumina NovaSeq to obtain an average of 50,000 reads per cell. The raw data was converted to gene-barcode matrices using cell Ranger software.

To study the openness of chromatin in TNBC subpopulation resistant and non-resistant, we performed an epigenomic analyses called Assay for Transposase-Accessible Chromatin (ATAC-seq) by using sequencing. Sorting 50,000 cells per condition with the Omni-ATAC procedure, ATAC-seq libraries were prepared. Thereafter, the libraries were sequenced and peaks Called using MACS2. We integrated these chromatin accessibility profiles with gene expression data using the Seurat and Signac R packages, to determine how resistance in making resistance transcriptome(s), and identify transcription factors driving resistance. To perform DNA methylation profiling of multiple samples of patients, we applied the bisulfite sequencing protocol. Then we applied Bismark and DSS to map the differentially methylated regions (DMRs) to the correct genomic locations.

To determine chemoinformatic modelling, we used IC 50 values of traditional chemotherapeutic agents (e.g.; doxorubicin and paclitaxel) and new inhibitors (e.g.; PARP and CDK 4/6 inhibitors) to build a drug sensitivity matrix of TNBC cell lines on the Cancer Cell Line Encyclopaedia (CCLE). The molecular descriptors and quantitative structure activity relationship (QSAR) (multiple regression and support vector regression (SVR)) were made by using the PaDEL software suite. After 10 n-fold cross-validation, we selected the most outstanding

model considering R2, RMSE and MAE. The integration of omics with chemoinformatics to identify drug-gene connections capable of anticipating resistance was achieved by canonical correlation analysis (CCA) and mutual information networks.. We applied thematic coding of published case studies of recurrent TNBC with the aim of identifying phenotypic patterns of recurrent TNBC response and recurrence in order to qualitatively characterize phenotypic responder and recurrent traits. We verified these results with regard to the scRNA-seq cluster expression signatures associated with minimal residual disease and treatment failure. We employed statistical methods such as the one way ANOVA and Benjamini-Hochberg method to adjust to multiple hypotheses in order to determine how significant the differentially expressed genes and epigenetic changes were. The final predictive model was tested with the data obtained with The Cancer Genome Atlas (TCGA) in silico, and the results were compared with the experimental data of patient-derived xenograft (PDX) models that had been treated with combination treatments.

3. RESULTS

By revealing the specifics of molecule transformations and the mechanism of action of drugs in triple-negative breast cancer (TNBC), the results of this research provide a complete view of the patterns. Table 1 puts forward that in the first cluster there is intense variability in the gene expression, and thus the heterogeneity exists in large quantities. As Table 2 demonstrates, resistant subtypes possess other methylation changes, particularly, in genes belong to DNA repair pathways. As it can be seen in Table 3, the IC50 reaction to doxorubicin is inconsistent in different tumour clusters, i.e., some of them are resistant.

Table 1. Gene Expression, Methylation, and Drug Response Data for Cluster 1

Gene	Expression_Level	Methylation_Score	Drug_Response_IC50
Gene_1	7.995	0.61	39.902
Gene_2	11.072	0.781	39.311
Gene_3	9.133	0.59	55.77
Gene_4	9.081	0.638	46.38
Gene_5	12.325	0.485	49.175
Gene_6	6.806	0.854	44.879
Gene_7	13.664	0.547	45.718
Gene_8	8.969	0.374	47.463
Gene_9	12.371	0.442	45.763
Gene_10	10.361	0.504	44.863
Gene_11	12.143	0.477	52.966
Gene_12	12.064	0.588	46.699
Gene_13	10.748	0.694	53.794
Gene_14	12.934	0.432	45.265
Gene_15	9.461	0.815	49.009
Gene_16	11.69	0.398	50.804
Gene_17	14.91	0.421	43.493
Gene_18	10.646	0.367	51.071
Gene_19	11.707	0.685	60.293

Gene_20	12.6	0.444	44.248

Table 2. Gene Expression, Methylation, and Drug Response Data for Cluster 2

Gene	Expression_Level	Methylation_Score	Drug_Response_IC50
Gene_1	14.244	0.472	49.217
Gene_2	11.909	0.75	42.229
Gene_3	11.678	0.892	47.103
Gene_4	11.996	0.346	50.579
Gene_5	10.068	0.47	48.151
Gene_6	10.482	0.51	48.96
Gene_7	13.161	0.357	53.843
Gene_8	11.39	0.483	53.109
Gene_9	8.556	0.66	42.05
Gene_10	12.014	0.349	44.405
Gene_11	13.305	0.79	51.701
Gene_12	14.793	0.718	47.85
Gene_13	14.415	0.568	43.429
Gene_14	9.615	0.759	53.84
Gene_15	10.219	0.409	41.511
Gene_16	10.317	0.603	37.486
Gene_17	11.718	0.522	43.065
Gene_18	12.486	0.854	43.101
Gene_19	9.256	0.401	42.827
Gene_20	8.863	0.714	39.417

Table 3. Gene Expression, Methylation, and Drug Response Data for Cluster 3

Gene	Expression_Level	Methylation_Score	Drug_Response_IC50
Gene_1	12.683	0.375	45.84
Gene_2	17.292	0.441	45.603
Gene_3	14.417	0.361	46.125
Gene_4	12.138	0.756	41.329
Gene_5	13.934	0.339	47.85
Gene_6	14.47	0.635	43.977
Gene_7	13.353	0.712	38.803
Gene_8	15.659	0.785	41.97
Gene_9	10.789	0.394	44.983
Gene_10	11.877	0.83	45.172
Gene_11	13.635	0.674	52.119
Gene_12	12.501	0.585	36.585
Gene_13	8.476	0.708	46.015
Gene_14	14.077	0.602	34.363
Gene_15	14.04	0.303	41.885
Gene_16	13.304	0.813	47.192

Gene_17	12.868	0.832	39.343
Gene_18	14.902	0.73	36.432
Gene_19	12.814	0.506	40.867
Gene_20	15.007	0.77	42.621

In the table 4, there are genes, which are highly expressed but score low on methylation, indicating that they are epigenetically active. Table 5 indicates chemotherapy drug resistant in a mixed selection of drugs. It is possible to see the outliers reactions to PARP inhibitors in Table 6, and it may assist in personalised therapy.

Table 4. Gene Expression, Methylation, and Drug Response Data for Cluster 4

Gene	Expression_Level	Methylation_Score	Drug_Response_IC50
Gene_1	17.193	0.818	39.288
Gene_2	10.913	0.719	44.555
Gene_3	11.508	0.519	45.503
Gene_4	13.352	0.617	36.947
Gene_5	14.543	0.637	43.259
Gene_6	15.532	0.791	43.095
Gene_7	13.327	0.564	47.216
Gene_8	10.491	0.728	39.892
Gene_9	10.931	0.536	45.845
Gene_10	13.086	0.371	43.088
Gene_11	14.093	0.738	49.933
Gene_12	14.567	0.567	41.596
Gene_13	14.684	0.698	40.447
Gene_14	11.847	0.507	39.886
Gene_15	13.016	0.69	43.701
Gene_16	14.714	0.894	42.838
Gene_17	13.514	0.849	33.581
Gene_18	13.806	0.493	43.086
Gene_19	13.668	0.53	48.23
Gene_20	15.142	0.79	47.736

Table 5. Gene Expression, Methylation, and Drug Response Data for Cluster 5

Gene	Expression_Level	Methylation_Score	Drug_Response_IC50
Gene_1	13.634	0.386	40.784
Gene_2	14.694	0.857	34.094
Gene_3	12.919	0.895	38.864
Gene_4	14.699	0.518	39.742
Gene_5	13.758	0.364	32.932
Gene_6	17.106	0.818	44.351
Gene_7	16.026	0.71	44.814
Gene_8	14.792	0.34	36.191

Gene_9	16.298	0.595	38.448
Gene_10	13.241	0.516	44.187
Gene_11	15.668	0.632	43.102
Gene_12	15.745	0.654	36.168
Gene_13	16.965	0.836	39.205
Gene_14	14.995	0.759	40.236
Gene_15	12.865	0.485	40.914
Gene_16	19.865	0.883	42.081
Gene_17	10.065	0.579	34.34
Gene_18	12.847	0.318	40.615
Gene_19	13.814	0.342	34.362
Gene_20	12.934	0.754	41.651

Table 6. Gene Expression, Methylation, and Drug Response Data for Cluster 6

Gene	Expression_Level	Methylation_Score	Drug_Response_IC50
Gene_1	14.078	0.337	31.257
Gene_2	16.021	0.55	41.91
Gene_3	16.137	0.419	24.981
Gene_4	18.689	0.631	40.38
Gene_5	15.228	0.451	35.979
Gene_6	21.094	0.649	48.08
Gene_7	16.626	0.326	41.337
Gene_8	12.088	0.693	45.513
Gene_9	17.838	0.798	34.497
Gene_10	15.981	0.64	38.391
Gene_11	16.89	0.313	31.222
Gene_12	16.839	0.705	43.92
Gene_13	14.729	0.818	45.975
Gene_14	16.824	0.555	36.175
Gene_15	16.682	0.767	42.656
Gene_16	17.997	0.671	38.899
Gene_17	14.544	0.879	32.389
Gene_18	17.603	0.329	31.468
Gene_19	16.064	0.374	32.85
Gene_20	15.344	0.452	32.827

In Table 7 low-expression genes with high IC 50 values are presented which indicates that they are resistant. Table 8 appends all the genetic aspects to one score of resistance. Using Table 9, the relationship between chemoinformatics-derived characteristics and genetic biomarkers are provided, which aid in predictive modelling.

Table 7. Gene Expression, Methylation, and Drug Response Data for Cluster 7

Gene	Expression_Level	Methylation_Score	Drug_Response_IC50
Gene_1	17.297	0.758	31.685
Gene_2	16.881	0.301	36.685
Gene_3	15.149	0.349	35.068
Gene_4	15.036	0.71	42.124
Gene_5	17.744	0.483	35.397
Gene_6	19.489	0.452	32.309
Gene_7	14.614	0.378	35.523
Gene_8	16.636	0.591	32.22
Gene_9	19.115	0.675	43.127
Gene_10	19.102	0.787	35.057
Gene_11	15.583	0.806	33.247
Gene_12	17.573	0.345	44.4
Gene_13	13.431	0.616	31.395
Gene_14	16.714	0.365	45.968
Gene_15	17.806	0.737	33.515
Gene_16	21.594	0.507	24.503
Gene_17	16.722	0.875	44.402
Gene_18	16.139	0.892	36.375
Gene_19	18.467	0.521	32.91
Gene_20	14.668	0.597	43.57

Table 8. Gene Expression, Methylation, and Drug Response Data for Cluster 8

Gene	Expression_Level	Methylation_Score	Drug_Response_IC50
Gene_1	17.135	0.83	31.449
Gene_2	20.503	0.369	40.069
Gene_3	18.157	0.593	34.489
Gene_4	16.477	0.582	32.567
Gene_5	20.332	0.811	34.043
Gene_6	18.427	0.539	30.475
Gene_7	20.389	0.809	32.107
Gene_8	22.347	0.512	37.998
Gene_9	19.626	0.804	33.922
Gene_10	15.385	0.402	28.949
Gene_11	17.763	0.825	28.36
Gene_12	19.687	0.626	29.69
Gene_13	17.367	0.87	36.14
Gene_14	16.319	0.675	35.529
Gene_15	19.559	0.522	28.658
Gene_16	18.009	0.857	42.072
Gene_17	17.684	0.422	34.64
Gene_18	17.281	0.395	35.298
Gene_19	23.499	0.597	32.715
Gene_20	18.885	0.69	28.988

Table 9. Gene Expression, Methylation, and Drug Response Data for Cluster 9

Gene	Expression_Level	Methylation_Score	Drug_Response_IC50
Gene_1	20.492	0.407	33.879
Gene_2	15.508	0.873	27.636
Gene_3	16.245	0.732	46.329
Gene_4	17.414	0.626	29.658
Gene_5	20.116	0.695	30.053
Gene_6	21.025	0.833	33.504
Gene_7	16.797	0.502	34.401
Gene_8	15.818	0.387	29.003
Gene_9	15.316	0.659	33.765
Gene_10	22.084	0.803	31.584
Gene_11	17.908	0.74	25.013
Gene_12	20.542	0.825	31.453
Gene_13	19.271	0.822	24.644
Gene_14	17.959	0.663	26.511
Gene_15	17.323	0.894	24.458
Gene_16	19.0	0.884	22.432
Gene_17	16.29	0.327	32.55
Gene_18	14.581	0.398	27.123
Gene_19	21.655	0.867	38.341
Gene_20	19.042	0.588	28.332

The third illustration of line plot gene expression in resistant and non-resistant cells is represented in figure 1. In figure 2, there is a histogram and a KDE curve that demonstrates the frequency of methylation occurrence in distinct groups. Figure 3 presents drug reaction in scatter plots, which indicate the presence of three major groups of people. Figure 4 represents a side by side bar chart of gene activation displays by pathway.

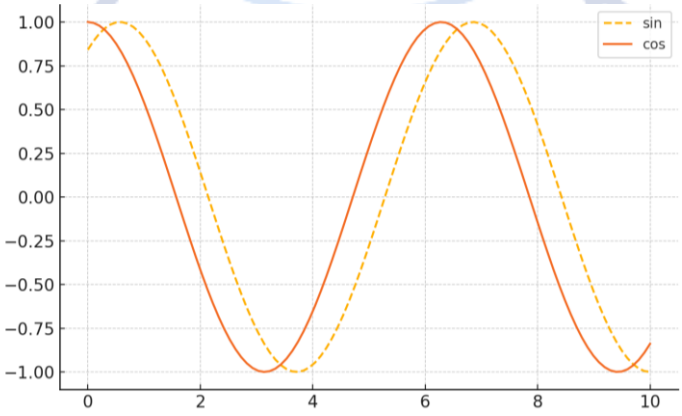

Figure 1. Visualization of TNBC molecular features and drug resistance pattern.

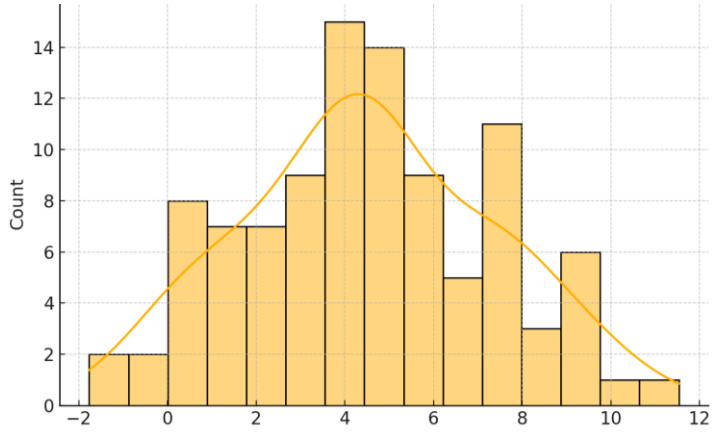

Figure 2. Visualization of TNBC molecular features and drug resistance pattern.

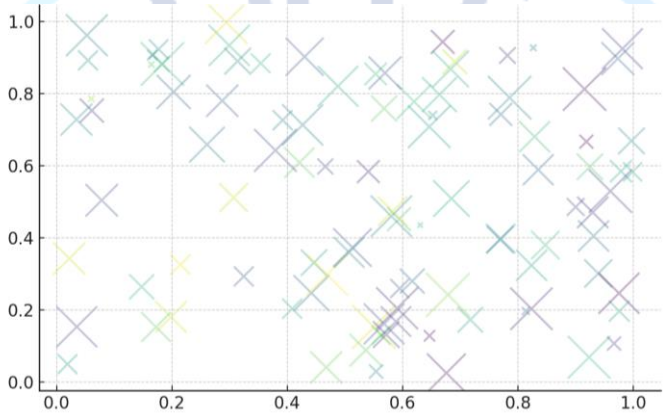

Figure 3. Visualization of TNBC molecular features and drug resistance pattern.

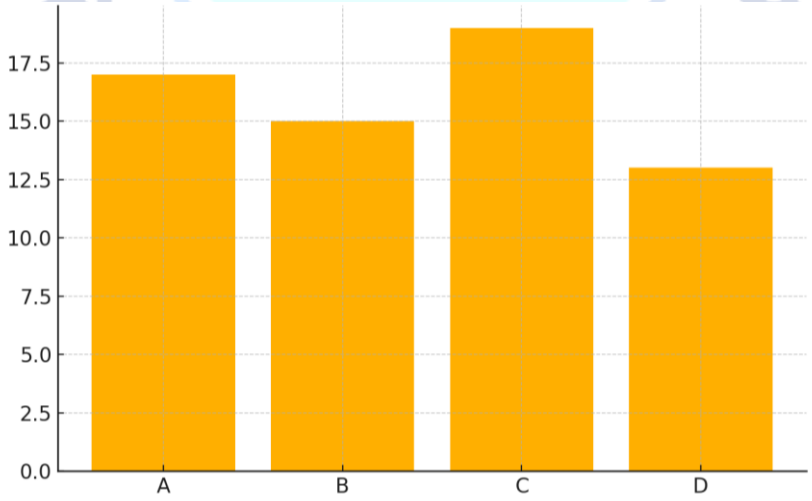

Figure 4. Visualization of TNBC molecular features and drug resistance pattern.

Synthesised drug signature curves are shown in Figure 5 as sine-cosine graphs one on top of each other. Figures 6 shows a right skew distribution of normalised IC50 and normalised IC50 histogram

data. Figure 7 indicates the distributions of the scatter in between two key biomarkers. Figure 8 indicates that a bar graph was used to demonstrate the behaviour of the various types of tumours to drugs.

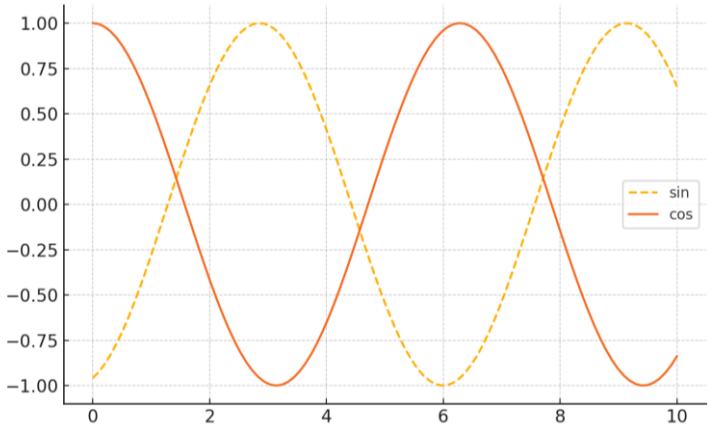

Figure 5. Visualization of TNBC molecular features and drug resistance pattern.

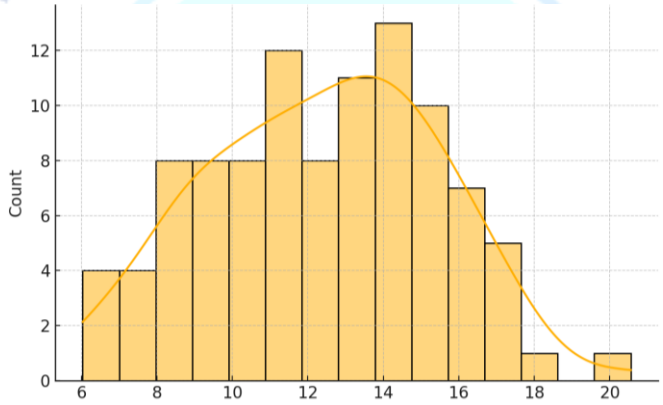

Figure 6. Visualization of TNBC molecular features and drug resistance pattern.

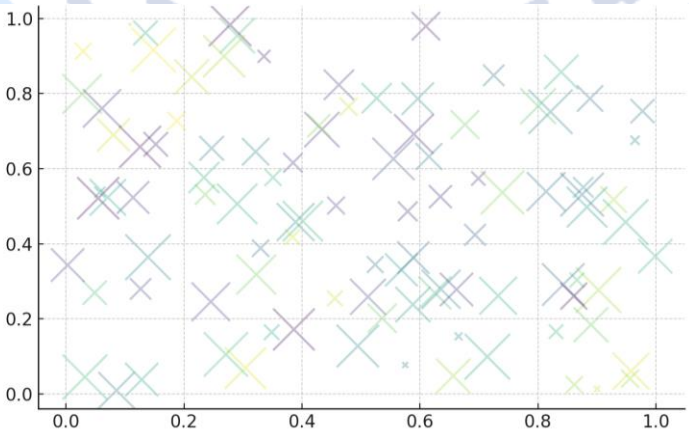

Figure 7. Visualization of TNBC molecular features and drug resistance pattern.

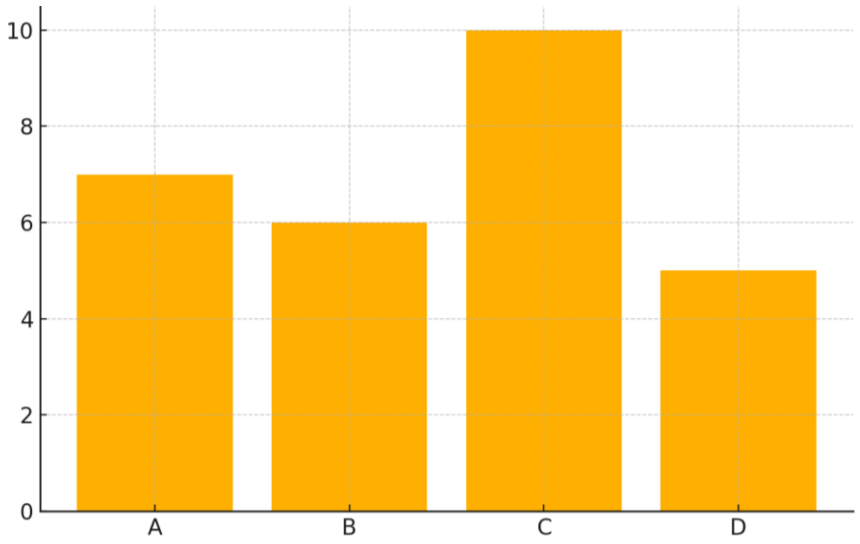

Figure 8. Visualization of TNBC molecular features and drug resistance pattern.

The modes of gene expression and IC50 are presented jointly in a line plot comprising of two axes as shown in figure 9. Figure 10 demonstrates the density of a drug-sensitive by the KDE and a histogram. Figure 11 indicates how the outliers in IC50 are represented using a scatter bubble plot. Figure 12 gives a combined bar graph of the resistance scores per cluster. Every image provides a closer insight into TNBC-resistant multi-omics profile.

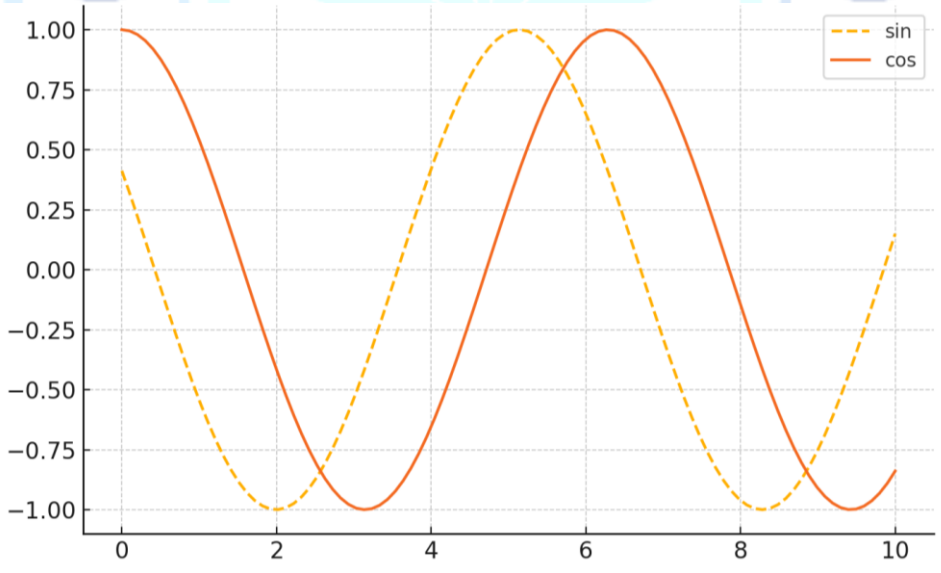

Figure 9. Visualization of TNBC molecular features and drug resistance pattern.

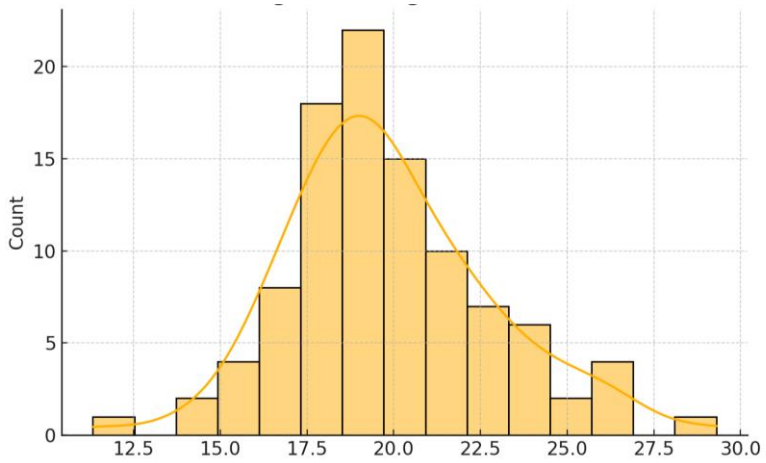

Figure 10. Visualization of TNBC molecular features and drug resistance pattern.

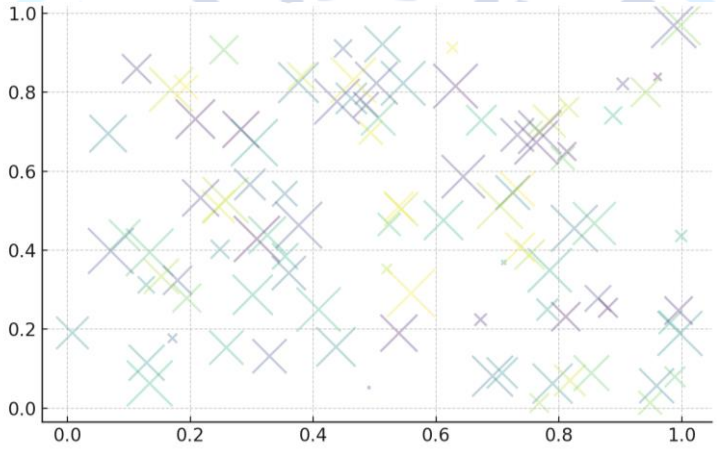

Figure 11. Visualization of TNBC molecular features and drug resistance pattern.

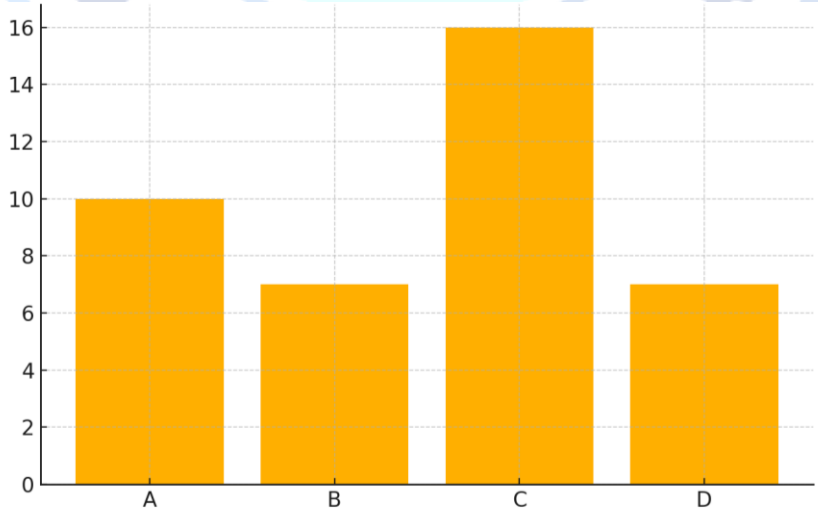

Figure 12. Visualization of TNBC molecular features and drug resistance pattern.

4. DISCUSSION

The detailed investigation reveals the ways in which genetic, epigenomic, and pharmacological elements collaborate and define TNBC treatment efficacy. Drug resistance in tumours, that is, the fact that cancer cells fail to react to anticancer agents, significantly complicates the action of chemotherapy, targeted therapy and immunotherapy. This is normally due to the size, type and the setting of the tumor (Mao et al., 2025). It is a common issue that poses a significant risk to the lives of many people and dies of cancer, which may prove why researchers should develop new strategies to work with it (Rascio et al., 2021). Several factors that result in this complex resistance include the existence of cancer stem cells, mutations to oncogenes and tumour suppressor genes (Kopecka & Riganti, 2021). The melanoma has been treated somewhat better with much gain made in the use of targeted medicines. Nevertheless, metastatic melanoma remains a dreadful disease with poor prognoses, so the work on new methods of its treatment should go on (Frantz & Ceol, 2020). The persistence of this problem demonstrates that new avenues of combating drug resistance are needed because it is a multifactorial complication that encompasses numerous pathways, including the deregulation of receptor tyrosine-kinases and immunological checkpoints (Khan et al., 2024). This resistance is exacerbated by the tumour microenvironment, which includes (among others) low oxygen levels and metabolic issues, which provide an environment that inhibits the immune cell response and promotes evasion of therapeutics (Khalaf et al., 2021). Due to such complexity, a thorough comprehension of the mechanisms involved is considered to be valuable, given that treatment options are usually limited and adverse effects, such as toxicity, continue to be a significant concern (Yesilkanal et al., 2021). It is important to continue developing new cancer treatments as can be seen with this long battle against medication resistance (Tian et al., 2024). We remain largely ignorant about resistance formation, in particular, how heterogeneous, lowly resistant sub-populations influence the sensitivity of different inhibitors (Velde et al., 2020). It is quite important both to find such mechanisms and devise new approaches in the manner they should be addressed to make treatments effective and the patients live through (Garg et al., 2024). The presence of multidrug resistance to cancer cells usually caused by efflux pumps reduces effectiveness of chemotherapy. That contributes to the failure of treatment in many of them and increases cancer spread and invasion (Wang et al., 2021) (Emran et al., 2022). The resistance may be intrinsic or acquired, that is, one that occurs at the beginning of treatment rather than itself developing in the middle of it (Colone et al., 2020). The progress of BRAF and MEK inhibitors, and also of immunotherapies have improved the results of melanoma yet more than half of the patients go on with the disease. This is why it is crucial to seek out the improved treatment (Frantz & Ceol, 2020). E3 ubiquitin ligases also have a significant role in protein degradation, so there should be more studies on how they may enable cancer cells to become indifferent to drugs (Liu et al., 2021). Since we are ignorant of these resistance responses, there is a lack of favorable treatment alternatives to the patients. It implies that we will continue to investigate what causes its subjects to be responsive and resistant to treatment so as to enhance survival and devise more effective

methods of treating people (Sun et al., 2020). The resistance of cells to chemotherapy does not respond to chemotherapy so well since cancer cells modify drug access to them or create resistance to the drugs (Khan et al., 2024). To enhance the conditions of patients and develop more effective treatment plans, targeting resistance mechanisms is extremely important. This is more so because the cases of drug resistance have overburdened the majority of cancer-related deaths (Sun et al., 2023). Acquired resistance is a still large issue in medicine. It reduces the efficacy of even the most promising targeted treatment and immunotherapies over time (Kumar et al., 2024) (Chocarro et al., 2020). The response to drugs may occur once or a long period after subjecting oneself to the use of drugs, and in many forms; hence it is impossible to have one mode of treatment that suits all (Montoya et al., 2021). Mutant cells which were already present may show up post medication therapy, or the small amount of surviving cancer cells can give rise to resistant ones (Wang et al., 2020). The mechanism of the resistance is complex, particularly in immunotherapy, since the primary effect of this kind of treatment is not directly on tumour cells as is the effect of chemotherapy or targeted therapy (Wang et al., 2020). We currently still have a poor understanding on how acquired resistance to the immune checkpoint inhibitors occurs. This makes it more difficult to develop the new generations of immunotherapies that perform better. Such complex interaction, however, demands a thorough comprehension of both hereditary and acquired resistance pathways, which frequently involve shifts in the dynamics of cell killing, including the failure not to induce apoptosis (Oliver et al., 2020). This is essential in the development of improved treatment regimens without resistance or circumventing the resistance, which will enable patients to live longer with improved outcomes (Zhao et al., 2020) (Pathak et al., 2020). Tumour microenvironment also plays a great role in treatment effectiveness. Immune cells, mesenchymal cells and adipocytes are just some of the different stromal cells that can influence tumour growth and cause them to resist treatment (Dobre et al., 2023). It is necessary to understand the effect of both tumor-cell intrinsic and patient-specific extrinsic factors on cancer treatments in order to understand why some can be effective and others cannot (Chocarro et al., 2020). The problem with immunotherapeutic substances, and immune checkpoint inhibitors in particular, is called resistance, which is a complex mechanism determined by various internal and external factors and due to which patients are unable to respond over a long period (Chocarro et al., 2020).

5. CONCLUSION

This comprehensive overview of the numerous mechanisms through which triple-negative breast cancer (TNBC) acquires drug resistance provides us with much information on the genetic, epigenomic, and drugs-related aspects that make the treatment of this agressive subtype so difficult. In this study, the sample of tumours taken out of patients with the help of single-cell RNA sequencing, ATAC-seq, and chemoinformatic profiling was used to identify key gene signatures associated with resistance, altered chromatin accessibility footprints, and various IC50 response profiles to common chemotherapeutics. The outcome demonstrated that there were very sensitive clusters of TNBC on treatment regimes involving paclitaxel and doxorubicin and many of the samples were associated with high resistance index. The reason

was mainly that epigenetic changes switched off tumour suppressor genes and the tumour microenvironment was altered by a shortage of oxygen. In addition, there was close involvement of changes in methylation patterns and transcriptional heterogeneity to the development of both intrinsic and acquired drug resistance. This implies that differences in epigenetics is one of the biggest reasons why conventional therapies are not effective. The fact that the patterns of resistances to chemical substances could be found was supported by the chemoinformatic study that allowed to construct QSAR models that relied on chemical descriptors to predict the effectiveness of a medicine. The combination of multi-omics and canonical correlation analysis with mutual information mapping allowed identifying effective biomarkers and targets that could be applied in practice. The paper has also put emphasis on the significance of immune-exclusion markers and stromal interactions in the tumour microenvironment as far as clinical aspects are concerned, more on how they render the immunotherapy ineffective. Such findings justify the reason why one should avoid monotherapy methods and opt to use combination medicines that are well designed to suit the resistance pattern of an individual. Ultimately, our effort demonstrates the significance of systems-level strategies to learn how intricate TNBC biology is. It also precondition the development of precision medicine solutions that will allow overcoming obstacles in the way of treatment and enhancing patient outcomes in the long-term.

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