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ML Models Using Single-Cell Sequencing to Forecast Chemotherapy Resistance in Breast Cancer

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Abstract: One of the most common cancers in the world and a major contributor to cancer-related death in women is breast cancer. Chemotherapy is a common therapeutic approach, especially for aggressive and advanced breast cancer. Chemotherapeutic agent resistance, however, continues to be a major clinical problem that frequently leads to treatment failure, illness recurrence, and a bad prognosis for patients. Therefore, enhancing therapeutic outcomes and increasing precision oncology require an understanding of the ability to forecast chemotherapy resistance. Conventional bulk RNA sequencing techniques yield gene expression patterns that are averaged over substantial cell populations, which may mask significant biological differences within tumours.

This restriction makes it impossible to accurately identify heterogeneous tumour cell groups and uncommon resistant clones that could withstand treatment and cause relapse. Single-cell sequencing technologies, on the other hand, provide high-resolution molecular profiling at the individual cell level. Tumour heterogeneity may be thoroughly examined and malignant cells and the tumour microenvironment, including immunological and stromal components, can be characterised using single-cell RNA sequencing (scRNA-seq). Different resistant subpopulations and dynamic cellular changes that lead to chemotherapy failure can be identified using this method.

A potent computational method for deriving significant insights from intricate scRNA-seq datasets is machine learning (ML). ML models can distinguish between resistant and sensitive tumour states, find predictive biomarkers, and discover therapy-induced transcriptional changes by examining high-dimensional transcriptome profiles. Additionally, these models can reveal clonal evolution trajectories, cell state transitions, and circuit activation patterns linked to drug resistance. The integration of scRNA-seq with ML-based prediction frameworks for predicting chemotherapy resistance in breast cancer is the main focus of this study.

It covers popular machine learning algorithms, feature engineering techniques, preprocessing pipelines, and validation tactics needed to guarantee reliable prediction. The study also identifies important biological processes that contribute to resistance, such as the epithelial–mesenchymal transition (EMT), drug efflux transporter activation, increased DNA repair capability, metabolic reprogramming, and immune microenvironment remodeling. All things considered, the combination of scRNA-seq and ML offers a promising approach for the early detection of resistant tumour clones, directing individualized treatment choices, maximizing chemotherapeutic selection, and enhancing long-term outcomes for patients with breast cancer.

Keywords: Tumour heterogeneity, machine learning, scRNA-seq, single-cell sequencing, breast cancer, chemotherapy resistance, predictive modelling, and biomarker identification.

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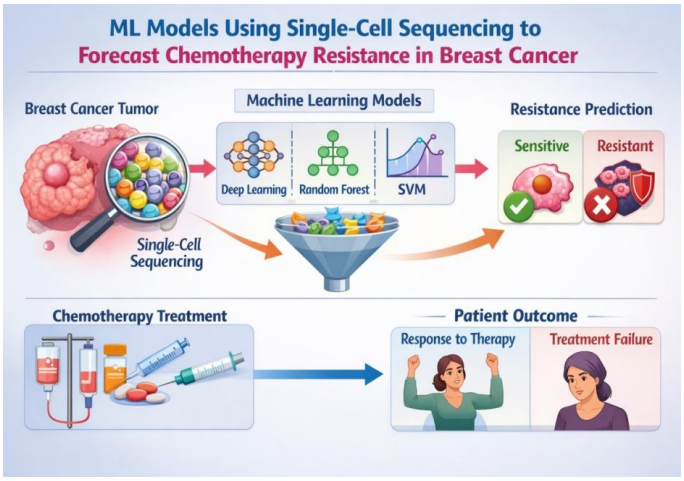
Graphical Abstract:



Research Highlights:

***** Tumour Heterogeneity Uncovered by Single-Cell Transcriptomic Profiling

* Chemoresistance via Predictive Feature Engineering

* Using Supervised Learning to Predict Treatment Results

* Multiomic Single-Cell Data Integration Improves Prediction

* Interpretable AI for the Discovery of Biological Mechanisms

* Modelling Longitudinal Single-Cell Trajectories

1. Introduction

Luminal A, luminal B, HER2-enriched, and triple-negative breast cancer (TNBC) are some of the molecular subtypes that make up the diverse illness known as breast cancer. Each subtype has a unique prognosis, response to chemotherapy, and clinical behaviour. Chemotherapy is still a crucial part of treating breast cancer, especially for aggressive subtypes including HER2-positive tumours and TNBC. Chemotherapy resistance, on the other hand, is a recurring problem that restricts therapeutic efficacy (1-15).

Chemotherapy resistance can be divided into two categories: acquired resistance, which occurs when tumour cells change genetically and epigenetically during treatment, and intrinsic resistance, which occurs when tumour cells are naturally resistant to medications. Clinical factors such tumour stage, receptor status, and histopathological grading are used in traditional resistance prediction approaches. Chemotherapy response variability cannot be completely explained by these criteria. By enabling the profiling of individual cells within tumours, single-cell sequencing has transformed the field of oncology (16-27).

Transcriptional diversity, uncommon drug-resistant clones, and dynamic tumour evolution following therapy are all revealed by scRNA-seq. Meaningful patterns can now be extracted from intricate single-cell datasets thanks to the development of machine learning. To forecast treatment response, ML models can use cell population abundance, pathway scores, and gene expression patterns. Thus, using machine learning (ML) on single-cell sequencing data is a potential method for predicting chemotherapy resistance in breast cancer and directing precision medicine strategies (28-53).

2. Background: Chemotherapy Resistance in Breast Cancer:

Chemotherapy, which frequently uses anthracyclines (doxorubicin), taxanes (paclitaxel), cyclophosphamide, and platinum-based medications, is still the principal therapeutic choice for breast cancer. Despite the fact that these drugs can successfully lower the tumour burden, many patients develop inherent or acquired resistance, which results in treatment failure and disease recurrence (54-88). Tumour cells and the tumour microenvironment undergo intricate molecular and cellular changes that lead to chemotherapy resistance. Increased drug efflux through ATP-binding cassette (ABC) transporters, improved DNA repair ability, activation of anti-apoptotic signaling pathways, enrichment of cancer stem-like cells, plasticity driven by the epithelial mesenchymal transition (EMT), changes in the immune microenvironment, and metabolic reprogramming that promotes survival under drug stress are some important mechanisms (Table: 1) (89-101).

Table: 1. Common Chemotherapy Drugs and Resistance Mechanisms in Breast Cancer

Chemotherapy Drug	Drug Class	Mechanism of Action	Common Resistance Mechanisms	Key Genes Involved
Doxorubicin	Anthracycline	DNA intercalation, Topoisomerase II inhibition	Drug efflux, enhanced DNA repair	ABCB1, TOP2A, BRCA1
Paclitaxel	Taxane	Microtubule stabilization	Tubulin mutation, EMT	TUBB3, VIM, SNAI1
Cyclophosphamide	Alkylating agent	DNA cross-linking	Detoxification, DNA repair	ALDH1A1, MGMT
Cisplatin	Platinum agent	DNA cross-linking	Increased repair, apoptosis suppression	ERCC1, TP53
5-Fluorouracil	Antimetabolite	Thymidylate synthase inhibition	Increased thymidylate synthase expression	TYMS

3. Single-Cell Sequencing and Its Role in Resistance Prediction:

Because single-cell sequencing offers high-resolution insights into breast tumour heterogeneity, it is essential for predicting treatment resistance. One popular technique for profiling gene expression patterns at the individual cell level is single-cell RNA sequencing, or scRNA-seq. While single-cell DNA sequencing finds mutations and copy number variations, other technologies like single-cell ATAC-seq evaluate chromatin accessibility (102,103). Multi-omics techniques combine RNA, protein, and epigenetic data, whereas spatial transcriptomics further links gene expression to particular tumour areas. Single-cell techniques can identify uncommon resistant clones, trace clonal evolution under drug selection pressure, monitor therapy-induced transcriptional changes, and assess microenvironment remodeling more effectively than bulk sequencing (**Table:2**) (104-109).

Table: 2. Comparison of Bulk vs Single-Cell Sequencing in Resistance Studies

Parameter	Bulk RNA Sequencing	Single-Cell RNA Sequencing
Resolution	Average expression across all cells	Expression per individual cell
Tumor heterogeneity detection	Limited	High
Resistant clone identification	Difficult	Highly effective
Microenvironment profiling	Poor	Excellent
Computational complexity	Moderate	High
Cost	Lower	Higher

4. Machine Learning for Chemotherapy Resistance Prediction:

Predictive modelling is made possible by machine learning (ML), a fundamental area of artificial intelligence that finds significant patterns in intricate biological data. ML models are frequently used in breast cancer chemotherapy response analysis to determine the likelihood of drug resistance and to categorise patients as responders or non-responders (110-114). ML can identify resistant cellular signatures and more accurately forecast treatment results when combined with single-cell RNA sequencing (scRNA-seq) datasets. Supervised learning, which needs labelled response data, unsupervised learning, which finds hidden resistant subpopulations, semi-supervised learning, which combines labelled and unlabelled samples, and deep learning models that can handle high-dimensional single-cell transcriptomic profiles are the general categories into which machine learning approaches fall (**Table:3**) (115-119).

Table: 3. Common Machine Learning Models Used in scRNA-seq Chemotherapy Resistance Studies

ML Model	Type	Strengths	Limitations	Application
Logistic Regression	Supervised	Interpretable, fast	Limited for complex patterns	Binary classification
Random Forest	Supervised	Handles non-linearity, robust	Less interpretable	Biomarker selection
Support Vector Machine (SVM)	Supervised	Works well in high dimensions	Needs tuning, slower for large datasets	Response classification
XGBoost	Supervised	High accuracy, feature importance	Risk of overfitting	Resistance prediction
K-means	Unsupervised	Simple clustering	Needs fixed clusters	Subpopulation discovery
Hierarchical Clustering	Unsupervised	Tree structure	Computationally expensive	Cell state analysis
Autoencoders	Deep learning	Dimensionality reduction	Hard interpretation	Latent representation learning
Graph Neural Networks	Deep learning	Models cell interactions	Complex training	Microenvironment prediction

5. Workflow for ML-Based scRNA-seq Chemotherapy Resistance Prediction:

Machine learning (ML) and single-cell RNA sequencing (scRNA-seq) are used in a structured analytical process to predict chemotherapy resistance. First, samples of breast tumours taken both before and after chemotherapy are used to gather scRNA-seq data. To eliminate subpar cells and technical noise, quality control is then carried out (120). After that, the data are scaled and normalized to account for differences in sequencing depth. After feature selection approaches are used to identify highly informative genes, high-dimensional data is simplified using dimensionality reduction methods like PCA or UMAP. Performance metrics such as accuracy and ROC-AUC are then used to train and assess ML models. Lastly, the biomarkers that have been found are analysed for clinical translation and customized treatment planning (**Table:4**) (121-125).

Table: 4. Standard scRNA-seq Preprocessing Steps and Tools

Step	Purpose	Common Methods/Tools
Quality Control	Remove low-quality cells	Seurat, Scanpy
Normalization	Correct sequencing depth bias	Log normalization, CPM
Batch Correction	Remove technical differences	Harmony, ComBat, MNN
Feature Selection	Select highly variable genes	HVG filtering
Dimensionality Reduction	Reduce complexity	PCA, t-SNE, UMAP
Cell Annotation	Identify cell types	SingleR, Cell Marker database
Differential Expression	Detect resistant genes	DESeq2, edgeR, MAST

6. Feature Engineering for Resistance Prediction:

To increase the precision of chemotherapy resistance prediction models utilizing scRNA-seq data, feature engineering is crucial. Gene-level expression of resistance markers like ABCB1 and ALDH1A1, pathway-level activation scores indicating PI3K-AKT signaling or DNA repair activity, and cell population-level metrics like the percentage of resistant subclones are just a few examples of the various biological levels at which features can be derived (126,127). Cell-cell communication metrics obtained from ligand-receptor interaction networks and pseudo time trajectory scores, which depict tumour evolution following treatment, are additional useful aspects. ABCB1 and ABCC1 for drug efflux, ALDH1A1 for stemness, BRCA1 and RAD51 for DNA repair, VIM and SNAI1 for EMT, and BCL2 and MCL1 for apoptosis inhibition are common biomarkers linked to resistance (**Table:5**)(128,129).

Table: 5. Key Biomarkers Identified from scRNA-seq Linked to Chemotherapy Resistance

Biomarker Gene	Biological Role	Resistance Mechanism	Breast Cancer Subtype
ABCB1	Drug transporter	Drug efflux	TNBC, HER2+
ALDH1A1	Stemness marker	Cancer stem cell enrichment	TNBC
VIM	Mesenchymal marker	EMT transition	TNBC
BRCA1	DNA repair	Enhanced repair	Luminal, TNBC
BCL2	Anti-apoptotic	Apoptosis suppression	Luminal A/B
PD-L1 (CD274)	Immune checkpoint	Immune evasion	TNBC

7. Deep Learning and Single-Cell Sequencing:

Because deep learning can identify intricate non-linear correlations in huge biological datasets, it has emerged as a potent method for analyzing single-cell RNA sequencing (scRNA-seq) data. Deep learning models can automatically learn hierarchical feature representations from high-dimensional gene expression profiles, in contrast to conventional machine learning. Fully connected neural networks (FNN), convolutional neural networks (CNN), autoencoders like AE and variational autoencoders (VAE), transformer-based attention models, and graph neural networks (GNN) that simulate cell–cell interactions are common architectures used in scRNA-seq resistance prediction (130). Because the data are sparse, noisy, and contain thousands of genes per cell, deep learning is especially useful for scRNA-seq, where precise prediction requires sophisticated representation learning techniques (**Table:6**) (131-140).

Table: 6. Deep Learning Architectures Applied in scRNA-seq Resistance Modeling

Architecture	Function	Strength in scRNA-seq	Example Use Case
Autoencoder	Dimensionality reduction	Handles sparsity	Latent resistant signature
Variational Autoencoder	Generative modeling	Captures cell variability	Clonal evolution modeling
Transformer	Attention-based learning	Captures long-range patterns	Gene interaction modeling
Graph Neural Network	Graph learning	Models cell-cell interactions	Tumor microenvironment resistance

8. Case Study Framework: Predicting Chemotherapy Resistance:

Several clinical and molecular data layers are usually integrated in a case study framework for predicting chemotherapy resistance utilizing scRNA-seq and machine learning. In addition to patient response labels classified as resistant or sensitive, the dataset often includes a scRNA-seq gene expression matrix that represents the transcriptional profiles of thousands of tumours and surrounding cells (141-143). Information on breast cancer subtypes, such as triple-negative breast cancer (TNBC), luminal, or HER2-positive status, as well as specifics of the treatment course, are additional variables. Prediction and validation are further reinforced by clinical outcome markers including overall survival (OS) and progression-free survival (PFS). In a hypothetical study, for instance, 120 patients with breast cancer receiving paclitaxel-based chemotherapy would have tumour biopsies taken both before and after two chemotherapy cycles in order to identify transcriptional changes linked to resistance (**Table:7**) (144).

Table: 7. Example Dataset Structure for ML Modeling

Patient ID	Subtype	Treatment	Pre-treatment Resistant Clone %	ABCB1 Avg Expression	EMT Score	Response Label
P001	TNBC	Paclitaxel	14%	4.6	0.82	Resistant
P002	Luminal B	Doxorubicin	2%	1.2	0.23	Sensitive
P003	HER2+	Paclitaxel+Trastuzumab	9%	3.9	0.71	Resistant
P004	TNBC	Cisplatin	3%	2.0	0.31	Sensitive
P005	Luminal A	Cyclophosphamide	1%	0.9	0.12	Sensitive

9. Model Training and Validation:

To create trustworthy machine learning models for predicting chemotherapy resistance from scRNA-seq data, model training and validation are essential. Models are often assessed using k-fold cross-validation, independent test sets, and external cohort validation using various clinical datasets to reduce overfitting and guarantee generalizability. Stratified splitting guarantees balanced representation of breast cancer subtypes like TNBC, luminal, and HER2-positive patients, while bootstrapping approaches increase resilience by regularly resampling training data (145). Several evaluation metrics are used to evaluate model performance. While precision and recall gauge forecast reliability for resistant cases, accuracy offers total correctness. Recall and precision are balanced by the F1-score. PR-AUC is particularly useful when datasets are unbalanced with less resistant samples, while ROC-AUC assesses classification power across thresholds (**Table:8**) (146).

Table: 8. Example Model Performance Comparison

Model	Accuracy	Precision	Recall	F1-score	ROC-AUC
Logistic Regression	0.78	0.74	0.71	0.72	0.81
Random Forest	0.84	0.82	0.79	0.80	0.87
SVM	0.83	0.80	0.78	0.79	0.86
XGBoost	0.88	0.86	0.84	0.85	0.91
Deep Neural Network	0.90	0.88	0.87	0.87	0.93

10. Identifying Resistant Subpopulations Using Unsupervised Learning:

Without the need for predetermined response labels, unsupervised learning is crucial for finding chemotherapy-resistant subpopulations in breast cancer. While dimensionality reduction technologies like t-SNE and UMAP allow the visualization of separate cellular groupings, algorithms like Louvain and Leiden clustering are used in scRNA-seq research to cluster tumour and microenvironment cells based on transcriptional similarities (147). Genes connected to drug survival mechanisms, such as high expression of ABC drug transporters, stemness-associated markers like SOX2 and NANOG, EMT-related genes like VIM and ZEB1, and anti-apoptotic regulators like BCL2, are frequently concentrated in resistant clusters. Furthermore, tumour evolution under chemotherapy pressure is modelled by pseudo time trajectory inference techniques like Monocle and Slingshot, which frequently identify resistant clones as terminal branches with distinct transcriptional signatures and adaptive pathways (**Table:9**) (148).

Table: 9. Cell Cluster Interpretation in Breast Cancer scRNA-seq

Cluster ID	Dominant Cell Type	Marker Genes	Role in Resistance
C1	Proliferating tumor cells	MKI67, PCNA	Drug-sensitive population
C2	EMT tumor cells	VIM, ZEB1	High resistance
C3	Cancer stem-like cells	ALDH1A1, SOX2	Recurrence risk
C4	Immune cells (T cells)	CD3D, CD8A	Immune response
C5	Macrophages (TAMs)	CD68, IL10	Immunosuppression

11. Tumor Microenvironment and Resistance:

By promoting tumour survival and immune evasion, the tumour microenvironment (TME) is a key factor in the development of treatment resistance in breast cancer. By detecting several immunological and stromal cell types, including as cytotoxic T cells, regulatory T cells, macrophages, fibroblasts, and endothelial cells, single-cell sequencing allows for thorough profiling of the TME. Tumor-associated macrophages (TAMs), which stimulate immunosuppressive signalling and accelerate tumour growth, are frequently linked to resistance (149). Additionally, cancer-associated fibroblasts (CAFs) limit medication penetration by secreting cytokines and altering the extracellular matrix, while reduced cytotoxic T-cell activity lowers anti-tumor immunity. Immune checkpoint-mediated escape is made easier by elevated PD-L1 expression, which permits resistant tumour clones to endure treatment (**Table:10**) (150).

Table: 10.TME Components and Their Role in Chemotherapy Resistance

TME Component	Major Markers	Function	Contribution to Resistance
TAMs	CD68, IL10	Immune suppression	Enhances survival signaling
CAFs	ACTA2, COL1A1	ECM remodeling	Drug penetration reduction
T-cells	CD8A, GZMB	Tumor killing	Exhaustion reduces response
Endothelial cells	PECAM1	Angiogenesis	Supports tumor growth
Regulatory T-cells	FOXP3	Immune tolerance	Blocks immune-mediated killing

12. Drug Resistance Prediction Through Multi-Omics Integration:

While scRNA-seq offers useful transcriptome data, genetic changes and epigenetic regulation also have a significant impact on chemotherapy resistance in breast cancer. Predictive accuracy and biological interpretation are enhanced when scRNA-seq is integrated with complementing single-cell multi-omics datasets. Whereas scDNA-seq finds mutations and copy number variants (CNVs) causing clonal growth, scATAC-seq shows chromatin accessibility patterns associated with resistant transcriptional programs (151). Metabolomics records metabolic changes that promote medication survival, while proteomics techniques like CyTOF quantify functional protein-level drug targets. Multi-view learning, which treats each omics layer independently, early fusion embedding models that combine features at the input level, late fusion models that merge predictions from independent classifiers, and graph-based fusion networks that capture interactions across omics modalities and cell populations are common machine learning frameworks for multi-omics resistance prediction (**Table:11**) (152).

Table: 11. Single-Cell Multi-Omics Data Types for Resistance Modeling

Data Type	Output	Resistance Insight	Example Tool
scRNA-seq	Gene expression	Cell state identification	Seurat
scATAC-seq	Chromatin accessibility	Epigenetic resistance	ArchR
scDNA-seq	Mutations/CNVs	Clonal evolution	CopyKAT
Spatial transcriptomics	Spatial gene expression	Local resistance niches	10x Visium
Proteomics	Protein levels	Drug target expression	CyTOF

13. Challenges in ML Modeling of Single-Cell Data:

Combining scRNA-seq with machine learning for chemotherapy resistance prediction poses a number of technical and clinical difficulties, despite its great potential. Data sparsity is a significant problem since scRNA-seq datasets have dropout events, which result in incomplete gene expression profiles that could mislead machine learning models. Additionally, batch effects reduce the generalizability of the model by introducing undesired variability because of variations in sequencing platforms, sample preparation procedures, or hospital-specific workflows (153). Interpretability is another drawback because deep learning techniques frequently operate as "black-box" models, making it challenging to defend predictions for clinical decision-making. Large-scale training datasets are expensive and time-consuming to gather, because chemotherapy resistance outcomes necessitate long-term clinical follow-up, survival tracking, and treatment response evaluation, which limits the availability of labelled datasets (**Table:12**) (154).

Table: 12. Challenges and Possible Solutions in scRNA-seq ML Resistance Prediction

Challenge	Description	Impact	Possible Solution
Dropout noise	Missing expression values	False biomarker detection	Imputation methods
Batch effects	Technical variability	Reduced generalization	Harmony, MNN
Small sample size	Few patients labeled	Overfitting risk	Transfer learning
Model interpretability	Black-box models	Low clinical adoption	SHAP, LIME
Cost	Expensive sequencing	Reduced dataset size	Targeted sequencing

14. Clinical Applications and Personalized Treatment:

Single-cell RNA sequencing (scRNA-seq) data-trained machine learning models have substantial clinical relevance for enhancing breast cancer treatment results. By identifying resistant subclones and unfavourable tumour microenvironment signals prior to the start of therapy, these models can facilitate the early identification of individuals who may develop chemotherapy resistance. By directing the choice of substitute medications and creating potent combination therapies that target several resistance mechanisms, these forecasts assist individualized treatment planning. In addition to tracking clonal evolution and the emergence of resistant populations, ML-based monitoring of scRNA-seq profiles during treatment enables prompt therapy modification. Furthermore, single-cell immune profiling helps stratify patients for combined chemotherapy and immunotherapy strategies. Model outputs can be converted into predicted risk scores in clinical decision support systems, which help oncologists choose the best course of action by estimating the likelihood of chemotherapy failure (**Table:13**).

Table: 13. Clinical Use Case Outcomes of ML-Based Resistance Prediction

Clinical Use Case	ML Contribution	Expected Outcome
Pre-treatment screening	Detect resistant clones	Personalized therapy selection
Treatment monitoring	Track resistant evolution	Adaptive drug switching
Drug combination design	Identify pathways	Reduced relapse
Prognosis prediction	Survival modeling	Improved risk stratification
Immunotherapy planning	Immune profiling	Better immunotherapy response

15. Future Trends:

Future developments in machine learning and scRNA-seq-based chemotherapy resistance prediction are anticipated to revolutionize precision oncology. Combining scRNA-seq ML processes with large language model (LLM)-driven biological reasoning could enhance resistance mechanism interpretation and automate biomarker development. Rapid tumour evolution monitoring during chemotherapy could be made possible by real-time sequencing in clinical oncology, supporting flexible treatment approaches (155-156). Federated learning techniques will become more significant since they enable multi-center model training while protecting patient privacy and data security. By learning intricate gene expression connections, transformer-based deep learning models trained on extensive single-cell atlases will improve prediction accuracy. Furthermore, localized microenvironment influences will be shown by mapping resistance niches within tumour locations using spatial single-cell machine learning models. Future research is anticipated to be dominated by graph neural networks and transformers because of their powerful capacity to simulate gene regulatory networks, cellular interactions, and communication patterns in the tumour microenvironment (157-166).

16. Conclusion:

One of the biggest challenges to the successful treatment of breast cancer is chemotherapy resistance, which frequently results in treatment failure, tumour recurrence, and lower survival rates. Many individuals still have intrinsic resistance or progressively develop acquired resistance throughout treatment, despite significant advancements in targeted treatments and chemotherapy regimens. This clinical problem emphasizes the critical need for sophisticated predictive techniques that can detect resistance early and direct tailored treatment approaches.

In cancer research, single-cell sequencing has become a ground-breaking technique that allows for the examination of tumours at a previously unheard-of level of detail. Single-cell RNA sequencing (scRNA-seq) offers detailed insights into intra-tumoral heterogeneity, enabling the identification of uncommon resistant subclones that may survive chemotherapy and subsequently dominate tumour regrowth, in contrast to bulk sequencing techniques that average gene expression signals across millions of cells. Furthermore, scRNA-seq allows for thorough assessment of the tumour microenvironment, which includes fibroblasts, immune cells, and stromal elements that have a major impact on medication response. Finding mechanisms of resistance, such as cancer stemness, epithelial–mesenchymal transition (EMT), immune evasion, metabolic reprogramming, and increased DNA repair capacity, requires a thorough understanding of the cellular level.

An effective analytical paradigm for deciphering complicated scRNA-seq datasets is machine learning. ML models are able to predict chemotherapy resistance and classify patients according to anticipated response outcomes by identifying significant patterns in high-dimensional gene expression profiles. By identifying important biomarkers and categorizing resistant vs sensitive instances, supervised machine learning techniques like Random Forest, Support Vector Machines (SVM), and XGBoost have shown good prediction performance. Furthermore, by capturing intricate non-linear correlations, gene regulatory linkages, and cell–cell communication patterns inside tumours, deep learning architectures—such as autoencoders, transformers, and graph neural networks—offer sophisticated modelling capabilities. Gene-level expression, pathway activation scores, resistant clone proportions, and pseudo time trajectory development are examples of feature engineering techniques that improve model accuracy and biological interpretability.

Before these methods can be completely applied in standard clinical practice, there are still a number of obstacles to overcome. Because of dropout effects, scRNA-seq data are frequently sparse and noisy, and model generalizability is diminished by batch effects across sequencing platforms. Furthermore, model training is constrained by the scarcity of large labelled patient cohorts, and problems with deep learning interpretability may erode therapeutic trust. Improved preprocessing pipelines, strong validation with external cohorts, and the use of explainable AI techniques are all necessary to overcome these obstacles. Clinical translation is anticipated to be accelerated by future developments including multi-omics integration, spatial transcriptomics, federated learning for privacy-preserving collaboration, and interpretable machine learning frameworks. All things considered, ML-driven scRNA-seq forecasting models have great potential for precision oncology since they can detect resistance early, optimize chemotherapy choices, lower the likelihood of relapse, and ultimately improve the prognosis of patients with breast cancer.

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