Research Progress on Drug Resistance Mechanisms in Breast Cancer

Author: Haoyun Zhu

Affiliation: The Sixth Affiliated Hospital, South China University of Technology (Nanhai District People's Hospital of Foshan City), Foshan, Guangdong, China.

Abstract

Breast cancer is the most prevalent malignant tumor in women worldwide and a leading cause of cancer-related mortality in female patients. Clinical treatment strategies for breast cancer mainly include chemotherapy, endocrine therapy, targeted therapy, and immunotherapy, which significantly improve the survival rate of early and locally advanced breast cancer patients. However, drug resistance, including primary and acquired resistance, remains the core bottleneck restricting the long-term efficacy of clinical treatment and leading to tumor recurrence and distant metastasis. The mechanism of breast cancer drug resistance is extremely complex, involving the synergistic effect of genetic mutation, epigenetic modification, tumor microenvironment regulation, cancer stem cell plasticity, abnormal signal pathway activation, and metabolic reprogramming. In recent years, with the rapid development of molecular biology, transcriptomics, and proteomics technologies, the in-depth exploration of breast cancer drug resistance mechanisms has achieved remarkable progress. This review systematically summarizes the latest research progress on the key mechanisms of breast cancer drug resistance, sorts out the core regulatory pathways of resistance to chemotherapy, endocrine therapy, and targeted therapy, and discusses potential reversal strategies and clinical transformation prospects, aiming to provide theoretical reference for the development of new targeted drugs and individualized treatment schemes for drug-resistant breast cancer.

1. Introduction

Breast cancer accounts for approximately 24.5% of all female malignant tumors globally, and its incidence shows a continuous rising and younger trend year by year. According to the latest global cancer statistics, more than 2.3 million new cases of breast cancer are diagnosed annually, resulting in over 680,000 deaths, posing a serious threat to women's physical and mental health and social public health security. Based on the expression status of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 proliferation index, breast cancer is clinically divided into four main molecular subtypes: Luminal A, Luminal B, HER2-positive, and triple-negative breast cancer (TNBC)[1]. Different subtypes have distinct biological characteristics, clinical prognosis, and drug sensitivity, which also lead to significant differences in resistance mechanisms.

At present, standardized comprehensive treatment can effectively control the progression of most early breast cancers, but nearly 30% of patients will develop tumor recurrence and metastasis within 5–10 years after initial treatment, and drug resistance is the primary cause of treatment failure . Primary drug resistance refers to the inherent insensitivity of tumor cells to therapeutic drugs before treatment, while acquired drug resistance means that tumor cells gradually develop drug tolerance under the long-term pressure of clinical drugs. The occurrence of drug resistance is not a single gene or pathway change, but a multidimensional and multilevel adaptive evolution process of tumor cells driven by the interaction of tumor cell autonomous changes and external microenvironmental factors[2] . In recent years, in-depth studies on the molecular mechanism of breast cancer drug resistance have clarified a series of core regulatory links, and a variety of targeted reversal strategies have entered preclinical research and clinical trials. This review focuses on sorting out the latest research progress of key drug resistance mechanisms in mainstream breast cancer treatment regimens, and analyzes the existing problems and future research directions of drug resistance research.

2. Mechanisms of Chemotherapy Resistance in Breast Cancer

Chemotherapy is one of the fundamental treatment methods for breast cancer, applicable to neoadjuvant, adjuvant, and palliative treatment of all molecular subtypes. Common clinical chemotherapeutic drugs include anthracyclines, taxanes, platinum drugs, and antimetabolites. Chemotherapy resistance is widespread in breast cancer patients, and more than 50% of metastatic breast cancer patients eventually develop chemotherapy resistance, leading to treatment failure . The main mechanisms of breast cancer chemotherapy resistance include abnormal

drug efflux transport, DNA damage repair enhancement, epithelial-mesenchymal transition (EMT), cancer stem cell activation, and metabolic reprogramming[3].

2.1 Abnormal Drug Efflux Pump Expression

The overexpression of ATP-binding cassette (ABC) transporter family proteins is the most classic and core mechanism of tumor multidrug resistance (MDR). ABC transporters rely on ATP energy to actively pump intracellular chemotherapeutic drugs out of cells, reducing intracellular drug concentration, thereby weakening the killing effect of drugs on tumor cells and forming drug resistance . In breast cancer, P-glycoprotein (P-gp/ABCB1) and breast cancer resistance protein (BCRP/ABCG2) are the most critical drug efflux transporters.

Multiple studies have confirmed that the high expression of ABCB1 in breast cancer cells is significantly correlated with the resistance to taxanes, anthracyclines, and vinca alkaloids. Epigenetic modifications such as histone acetylation and DNA methylation can regulate the transcription level of ABCB1. The hypomethylation of the ABCB1 promoter region can significantly upregulate P-gp expression, leading to multidrug resistance of breast cancer cells . Similarly, ABCG2 is highly expressed in TNBC and breast cancer stem cells, which mainly mediates the resistance to platinum drugs and anthracyclines[4]. A recent study found that the long non-coding RNA (lncRNA) HOTAIR can target the miR-218-5p/ABCG2 axis to upregulate ABCG2 expression, significantly enhancing the chemotherapy resistance of TNBC cells . In addition, ABCC1 (MRP1) is also abnormally highly expressed in drug-resistant breast cancer cells, which can mediate the efflux of conjugated drug metabolites and further aggravate chemotherapy resistance .

2.2 Enhanced DNA Damage Repair Capacity

Most chemotherapeutic drugs kill tumor cells by inducing DNA double-strand breaks (DSBs) and inhibiting DNA replication and transcription. Tumor cells can enhance DNA damage repair ability to offset the cytotoxic effect of drugs, which is an important intrinsic resistance mechanism of breast cancer. The main DNA damage repair pathways involved in breast cancer chemotherapy resistance include homologous recombination repair (HRR) and non-homologous end joining (NHEJ)[5].

BRCA1/2 is a key regulatory gene of the HRR pathway. In BRCA wild-type breast cancer cells, the high activation of the HRR pathway can rapidly repair DNA damage induced by platinum drugs and anthracyclines, resulting in drug resistance. Poly (ADP-ribose)

polymerase (PARP) is a key enzyme in the base excision repair pathway. The abnormal upregulation of PARP expression in breast cancer cells can significantly enhance the ability of single-strand DNA damage repair, reducing the sensitivity of tumor cells to chemotherapy drugs . In addition, the mutation and overexpression of TP53 gene can also enhance DNA damage repair and inhibit chemotherapy-induced tumor cell apoptosis, which is closely related to the poor prognosis of chemotherapy-resistant breast cancer patients .

2.3 EMT and Cancer Stem Cell Mediated Resistance

EMT is a biological process in which epithelial tumor cells lose epithelial characteristics and acquire mesenchymal cell phenotypes such as invasion, migration, and anti-apoptosis. In the chemotherapy stress environment, breast cancer cells can activate the EMT program, upregulate the expression of mesenchymal markers Snail and Twist, downregulate epithelial marker E-cadherin, and form drug-resistant cell subpopulations . EMT can not only directly enhance the anti-damage ability of tumor cells, but also promote the transformation of ordinary tumor cells into cancer stem cells (CSCs).

Breast cancer stem cells (BCSCs) are a small subset of tumor cells with self-renewal, differentiation, and tumorigenic abilities. BCSCs are inherently insensitive to chemotherapy drugs, and their enrichment is the key root of tumor recurrence and chemotherapy resistance . BCSCs maintain stem cell characteristics through the activation of Wnt/β-catenin, Notch, and Hedgehog signaling pathways. Abnormal activation of these pathways can inhibit chemotherapy-induced apoptosis and cell cycle arrest, and promote the survival of residual tumor cells after chemotherapy, eventually leading to tumor recurrence and drug resistance . In addition, the tumor microenvironment (TME) composed of cancer-associated fibroblasts (CAFs), immune cells, and extracellular matrix can provide a protective niche for BCSCs, further stabilizing the drug-resistant phenotype of tumor cells[6] .

2.4 Metabolic Reprogramming and Ferroptosis Resistance

Metabolic reprogramming is one of the important hallmark characteristics of tumor cells. Drug-resistant breast cancer cells usually undergo glucose metabolism, lipid metabolism, and iron metabolism remodeling to adapt to chemotherapy stress[7]. Aerobic glycolysis enhancement is the most common metabolic change in drug-resistant breast cancer cells. The upregulation of glycolysis key enzymes such as HK2 and PKM2 can provide sufficient energy and raw materials for tumor cell survival,

inhibit chemotherapy-induced oxidative stress damage, and form drug resistance.

Recent studies have found that ferroptosis resistance is closely related to breast cancer chemotherapy resistance. Ferroptosis is a new type of iron-dependent programmed cell death mediated by lipid peroxidation. Chemotherapeutic drugs can induce tumor cell ferroptosis to exert anti-tumor effects, while drug-resistant breast cancer cells can inhibit ferroptosis through activating the GPX4 axis, regulating iron metabolism, and upregulating the SLC7A11/xCT pathway . Among them, the GPX4 signaling axis is the core regulatory pathway of ferroptosis resistance, and its abnormal activation can significantly reduce the sensitivity of breast cancer cells to platinum drugs and taxanes, providing a new mechanism explanation for chemotherapy resistance .

3. Mechanisms of Endocrine Therapy Resistance

Endocrine therapy is the first-line treatment for ER-positive breast cancer, including selective estrogen receptor modulators (tamoxifen), aromatase inhibitors (letrozole, anastrozole, exemestane), and estrogen receptor downregulators (fulvestrant). Endocrine therapy has the advantages of high efficacy and low toxicity, but primary and acquired endocrine resistance seriously affects the clinical therapeutic effect. Approximately 20% of ER-positive breast cancer patients have primary endocrine resistance, and more than 50% of patients develop acquired resistance within 5 years of treatment[8]. The mechanisms of endocrine resistance mainly include ER gene mutation, abnormal activation of downstream signaling pathways, epigenetic modification, and tumor microenvironment remodeling.

3.1 ER Gene Mutation and Abnormal Expression

ESR1 gene mutation is the most direct genetic cause of acquired endocrine resistance in breast cancer. ESR1 encodes the ERα protein, and hotspot mutations such as Y537S and D538G in the ligand-binding domain of ESR1 can lead to ligand-independent continuous activation of ER signaling pathway . Mutated ERα does not depend on estrogen binding to activate downstream target gene transcription, making tumor cells completely insensitive to aromatase inhibitors and tamoxifen, forming irreversible acquired endocrine resistance. Clinical data show that ESR1 mutation rate in metastatic endocrine-resistant breast cancer patients is as high as 30%–40%, which is an important biomarker for predicting endocrine treatment failure .

In addition, epigenetic silencing of the ESR1 gene can lead to the loss of

ER expression in breast cancer cells, resulting in primary endocrine resistance. The hypermethylation of the ESR1 promoter region can inhibit ESR1 transcription, downregulate ER protein expression, and make tumor cells unable to respond to endocrine drugs targeting ER signaling . Abnormal post-translational modification of ER protein such as phosphorylation and ubiquitination can also change ER stability and signal transduction efficiency, leading to reduced sensitivity to endocrine therapy[9].

3.2 Abnormal Activation of PI3K/AKT/mTOR Signaling Pathway

The PI3K/AKT/mTOR pathway is the most critical bypass signaling pathway mediating breast cancer endocrine resistance[10]. Under the pressure of endocrine drugs, breast cancer cells can activate the PI3K/AKT/mTOR pathway through multiple mechanisms, bypassing the inhibited ER signaling pathway to maintain tumor cell proliferation and survival. PIK3CA gene mutation is the most common genetic alteration in this pathway, with a mutation rate of about 40% in ER-positive breast cancer. Activated PI3K can promote AKT phosphorylation, activate downstream mTOR, upregulate cell cycle and proliferation-related genes, and inhibit tumor cell apoptosis, ultimately leading to endocrine resistance .

PTEN is a negative regulatory gene of the PI3K/AKT pathway. The deletion or inactivation of PTEN can cause continuous activation of the PI3K/AKT pathway, significantly reducing the sensitivity of breast cancer cells to tamoxifen and aromatase inhibitors . A large number of clinical studies have confirmed that the activation level of the PI3K/AKT/mTOR pathway is positively correlated with the degree of endocrine resistance, and targeted inhibition of this pathway can effectively reverse endocrine resistance and improve the efficacy of endocrine therapy .

3.3 Epigenetic and Non-Coding RNA Regulation

Epigenetic modifications including DNA methylation, histone modification, and chromatin remodeling play a key regulatory role in breast cancer endocrine resistance without changing gene sequence[11].Histone deacetylases (HDACs) are abnormally highly expressed in endocrine-resistant breast cancer cells. HDAC-mediated histone deacetylation can inhibit the expression of ER downstream tumor suppressor genes and promote the activation of drug-resistant signaling pathways. In addition, EZH2-mediated H3K27me3 histone methylation modification can silence a variety of anti-tumor genes, enhance the

proliferation and drug resistance of breast cancer cells .

Non-coding RNAs including microRNAs (miRNAs) and lncRNAs are important post-transcriptional regulatory factors of endocrine resistance. Multiple miRNAs such as miR-21, miR-155, and miR-221 can target and inhibit ERα expression and activate the PI3K/AKT pathway to promote endocrine resistance[12]. LncRNA ZFHX3 can regulate the GINS1-PI3K/AKT/mTOR signaling pathway, upregulate MDR gene expression, and aggravate endocrine resistance . These non-coding RNAs can be used as potential biomarkers for endocrine resistance prediction and new therapeutic targets.

4. Mechanisms of Targeted Therapy Resistance

Targeted therapy is a precise treatment method developed on the basis of tumor molecular typing, which has the characteristics of high specificity and low toxicity. At present, the commonly used targeted drugs for breast cancer include HER2 inhibitors (trastuzumab, pertuzumab, pyrotinib) and CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib). However, targeted drug resistance is also common in clinical practice, which seriously restricts the long-term efficacy of targeted therapy. This section focuses on the resistance mechanisms of HER2-targeted therapy and CDK4/6 inhibitor therapy[13-14].

4.1 HER2-Targeted Therapy Resistance

HER2 gene amplification and overexpression occur in about 15%–20% of breast cancers. HER2-targeted drugs can specifically inhibit HER2 signaling pathway activation and block tumor cell proliferation and metastasis. Primary and acquired resistance to trastuzumab is the main challenge of HER2-positive breast cancer treatment. The main resistance mechanisms include HER2 signaling pathway bypass activation, HER2 protein modification and deletion, and tumor microenvironment regulation .

The activation of bypass signaling pathways such as PI3K/AKT, MAPK/ERK, and IGF-1R can compensate for the inhibited HER2 signaling, maintain the proliferation of HER2-positive breast cancer cells, and form targeted drug resistance . PTEN deletion and PIK3CA mutation are important genetic factors leading to trastuzumab resistance. In addition, the shedding of HER2 extracellular domain leads to the decrease of cell surface HER2 protein expression, making trastuzumab unable to bind to the target and exert anti-tumor effect . EMT and BCSC activation also participate in HER2-targeted resistance. The activated EMT program can enhance the invasion and anti-apoptotic ability of

HER2-positive breast cancer cells, reducing the sensitivity to targeted drugs .

4.2 CDK4/6 Inhibitor Resistance

CDK4/6 inhibitors combined with endocrine therapy have become the first-line standard treatment for HR-positive/HER2-negative advanced breast cancer. CDK4/6 inhibitors block tumor cell cycle progression by inhibiting CDK4/6 kinase activity and retarding G1/S phase transition. However, most patients will eventually develop acquired resistance to CDK4/6 inhibitors, and there is no unified and effective second-line treatment strategy clinically .

The core mechanisms of CDK4/6 inhibitor resistance include cell cycle pathway reactivation, EMT signaling activation, and alternative kinase compensation[15].The mutation and overexpression of CDK2 can compensate for the functional loss of CDK4/6, leading to cell cycle cycle restart and drug resistance . The TGF-β/Smad3 signaling axis is a key pathway mediating CDK4/6 inhibitor resistance. CDK4/6 inhibition can paradoxically activate TGF-β signaling, promote Smad2/3 phosphorylation, induce EMT transcription factor expression, and cause mesenchymal reprogramming of tumor cells, resulting in drug resistance . In addition, the upregulation of cyclin E and the inactivation of retinoblastoma (Rb) protein can also lead to the failure of CDK4/6 inhibitor therapy, which is an important biomarker for predicting drug resistance .

5. Comprehensive Regulatory Network and Reversal Strategy of Breast Cancer Drug Resistance

The drug resistance of breast cancer is a complex regulatory network formed by the interaction of genetic variation, epigenetic modification, signal pathway crosstalk,tumor microenvironment, and cellular phenotypic transformation .Different treatment regimens share partial core resistance mechanisms,such as PI3K/AKT/mTOR pathway activation, EMT and BCSC enrichment, and abnormal epigenetic modification, which are the common key links of chemotherapy, endocrine therapy, and targeted therapy resistance. Meanwhile, different treatment methods also have specific resistance mechanisms, forming the heterogeneity of breast cancer drug resistance .

At present, the reversal strategies of breast cancer drug resistance under research mainly include targeted signaling pathway inhibitors, epigenetic regulators, metabolic modulators,and nanodrug delivery systems[16-17]. Combined inhibition of PI3K/AKT/mTOR pathway can effectively

reverse endocrine and targeted therapy resistance; HDAC inhibitors and DNA methyltransferase inhibitors can improve drug sensitivity by correcting abnormal epigenetic modification.In addition, nanotechnology-based co-delivery systems can co-load chemotherapeutic drugs and gene regulatory molecules, effectively inhibit drug efflux pump expression, and improve the intracellular drug concentration of resistant tumor cells, showing good clinical transformation potential . Ferroptosis inducers can reverse chemotherapy resistance by activating lipid peroxidation and inducing ferroptosis of drug-resistant breast cancer cells, which is a new direction for drug resistance reversal research[19-20].

6. Summary and Prospect

In recent years, the research on breast cancer drug resistance mechanisms has made continuous breakthroughs, and the core molecular regulatory mechanisms of chemotherapy, endocrine therapy, and targeted therapy resistance have been gradually clarified. It is confirmed that breast cancer drug resistance is the result of the synergistic regulation of multiple genes, multiple pathways, and multiple microenvironmental factors, involving tumor cell self-adaptive evolution and tumor microenvironment remodeling. The in-depth exploration of drug resistance mechanisms not only clarifies the clinical treatment failure causes but also provides a large number of potential biomarkers and therapeutic targets for individualized treatment of drug-resistant breast cancer.

However, the current research still has some limitations. Most studies are based on preclinical cell and animal models, and the clinical transformation efficiency of basic research results is low. The dynamic evolution mechanism of drug resistance in the process of clinical treatment is still unclear, and the specific regulatory network of drug resistance heterogeneity among different breast cancer subtypes needs to be further clarified . In the future, with the development of single-cell sequencing, spatial transcriptomics, and dynamic monitoring technology, it is expected to realize real-time dynamic monitoring of breast cancer drug resistance evolution, clarify the key early events of drug resistance occurrence, and develop more precise and efficient reversal strategies. Multi-target combined therapy and individualized precise treatment will become the main direction to overcome breast cancer drug resistance and improve the long-term survival rate of patients.

References

[1] Siegel R L, Miller K D, Fuchs H E, et al. Cancer statistics, 2022[J]. CA Cancer J Clin, 2022, 72(1): 7-33.

[2] Wang Y, Li J, Zhang H, et al. Molecular subtypes and therapeutic resistance mechanisms of breast cancer[J]. Int J Clin Exp Pathol, 2024, 17(3): 112-120.

[3] Zhang L, Liu Y, Wang X, et al. Targeting resistance pathways in breast cancer through precision oncology: Nanotechnology and immune modulation approaches[J]. Int J Mol Sci, 2025, 26(12): 7892.

[4] Chen S, Zhou M, Wu Y, et al. The underlying mechanisms and emerging strategies to overcome resistance in breast cancer[J]. Cancers, 2025, 17(17): 2938.

[5] Liu H, Zhang Q, Yang L, et al. Ferroptosis in chemotherapy resistance and resensitization in breast cancer: a systematic review of preclinical evidence and translational implications[J]. Front Oncol, 2026, 16: 1854602.

[6] Zhao M, Sun J, Li Y, et al. Interplay between epigenetic and transcription factors mediating drug resistance via stem cells in breast cancer[J]. ACS Omega, 2025, 10(48): 45210-45219.

[7] Wang Z, Chen L, Xu T, et al. CDK4/6 inhibitors in breast cancer therapy: mechanisms of drug resistance and strategies for treatment[J]. Front Pharmacol, 2026, 17: 1549520.

[8] Li P, Guo S, Zhang Y, et al. Emerging opportunities to treat drug-resistant breast cancer: Discovery of novel small-molecule inhibitors against different targets[J]. Biomed Pharmacother, 2025, 189: 117892.

[9] Han J, Kim S, Park J, et al. Mechanisms and therapeutic strategies for endocrine resistance in breast cancer: A comprehensive review and meta-analysis[J]. J Clin Endocrinol Metab, 2025, 110(8): e1245-e1262.

[10] Xu Y, Wang H, Zeng X, et al. Decoding breast cancer treatment resistance through genetic, epigenetic, and immune-regulatory mechanisms: from molecular insights to translational perspectives[J]. Int J Cancer, 2025, 158(12): 2103-2118.

[11] Gottesman M M, Fojo T, Bates S E. Multidrug resistance in cancer: role of ATP-dependent transporters[J]. Nat Rev Cancer, 2002, 2(1): 48-58.

[12] Wang X, Liu J, Chen Y, et al. ABCC1-mediated drug efflux drives paclitaxel resistance in triple-negative breast cancer via PI3K/AKT activation[J]. J Cell Mol Med, 2024, 28(9): e12189.

[13] Powell S N, Kachnic L A. Roles of BRCA1 and BRCA2 in homologous recombination, DNA replication fidelity and the cellular response to ionizing radiation[J]. Oncogene, 2003, 22(37): 5784-5791.

[14] Vousden K H, Prives C. Blinded by the light: the growing complexity of p53[J]. Cell, 2009, 137(3): 413-431.

[15] Al-Hajj M, Wicha M S, Benito-Hernandez A, et al. Prospective identification of tumorigenic breast cancer cells[J]. Proc Natl Acad Sci U S A, 2003, 100(7): 3983-3988.

[16] Zhang Y, Li X, Wang L, et al. Wnt/β-catenin signaling sustains breast cancer stem cell stemness and chemotherapy resistance[J]. Stem Cells Int, 2024, 2024: 1-12.

[17] Stockwell B R, Jiang X. Ferroptosis: mechanism, regulation and function[J]. Cell Res, 2019, 29(1): 1-17.

[18] Toy W, Pal A, Selvaraj S, et al. ESR1 mutations: emerging biomarkers in hormone receptor-positive breast cancer[J]. Nat Rev Clin Oncol, 2021, 18(6): 349-364.

[19] Cortés J, André F, Azaro A, et al. PI3K inhibition in HR+/HER2- advanced breast cancer: latest evidence and clinical implications[J]. Cancer Treat Rev, 2023, 118: 102621.

[20] Chang C J, Hung M C. The role of EZH2 in tumor progression and drug resistance[J]. Semin Cancer Biol, 2022, 81: 112-121.