Multidimensional molecular mechanisms of drug resistance in breast cancer: Implications for clinical decision-making and treatment strategies (Review)

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Abstract. Breast cancer has the highest incidence among malignant tumors in women worldwide. Although targeted therapy, chemotherapy, and endocrine therapy have achieved significant efficacy, acquired resistance remains a major challenge affecting patient prognosis. The present review systematically outlines five core mechanisms of resistance to breast cancer treatment, including overexpression of ATP-binding cassette transporters that reduce intracellular drug accumulation; a hypoxic and immunosuppressive tumor microenvironment, together with breast cancer stem cells, that sustains stemness and impairs treatment response; DNA methylation, histone modifications, and non-coding RNAs that mediate epigenetic reprogramming, leading to silencing of tumor suppressors or activation of resistance pathways; compensatory activation of multiple DNA damage repair pathways, including homologous recombination, non-homologous end joining, base excision repair, nucleotide excision repair, and mismatch repair, which compromises the efficacy of chemotherapy and poly (ADP-ribose) polymerase inhibitors; and metabolic reprogramming involving glycolysis, amino acid, nucleotide, and lipid metabolism that supplies tumor cells with energy, reducing equivalents, and biomass for proliferation, while simultaneously promoting immune evasion. Corresponding to these mechanisms, this review also summarizes potential therapeutic strategies, including combined targeted therapy, immunotherapy, and novel drug delivery systems. Therefore, a comprehensive dissection of the multidimensional networks mediating therapy resistance in breast cancer will provide both theoretical foundations and practical pathways for discovering novel biomarkers,

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Abbreviations: TME, tumor microenvironment; BCSCs, breast cancer stem cells; DDR, DNA damage repair; HRR, homologous recombination repair; NHEJ, non-homologous end joining; BER, base excision repair; NER, nucleotide excision repair; MMR, mismatch repair; PARPi, poly(ADP-ribose) polymerase inhibitors; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; HR, hormone receptor; ER, estrogen receptor; SERMs, selective estrogen receptor modulators; SERDs, selective estrogen receptor degraders; AIs, aromatase inhibitors; FDA, U.S. Food and Drug Administration; ESR1, estrogen receptor 1; PI3K, phosphatidylinositol 3-kinase; AKT, protein; ICIs, immune checkpoint inhibitors; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; VEGF, vascular endothelial growth factor; MDR, multidrug resistance; ABCB1, ATP-binding cassette subfamily B member 1; ABCC1, ATP-binding cassette subfamily C member 1; P-gp, P-glycoprotein; ABCG2, ATP-binding cassette subfamily G member 2; GSH, glutathione; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; NF-κB, nuclear factor-κB; HIF-1α, hypoxia-inducible factor-1α; CSCs, cancer stem cells; MDSCs, myeloid-derived suppressor cells; CAFs, cancer-associated fibroblasts; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; lncRNAs, long non-coding RNAs; CAR-T, chimeric antigen receptor T cell; PRMTs, protein arginine methyltransferases; HDAC, histone deacetylase; ncRNAs, non-coding RNAs; circRNAs, circular RNAs; DSB, double-strand break; BRCA1/2, breast cancer susceptibility genes 1/2; Alt-NHEJ, alternative non-homologous end joining; ROS, reactive oxygen species; FEN1, flap endonuclease 1; XPF, xeroderma pigmentosum group F-complementing protein; MLH1, MutL homolog 1; HK2, hexokinase 2; GLS, glutaminase; RAD51, RAD51 recombinase; PALB2, partner and localizer of BRCA2

Key words: breast cancer, drug resistance, tumor, combination therapy, targeted therapy

optimizing precision combination therapies, and ultimately prolonging patient survival.

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1. Introduction

Breast cancer is a malignancy originating from the epithelial cells of the breast and has become one of the most commonly diagnosed cancers worldwide, ranking first among all cancers in women. According to the 2025 Cancer Statistics report, breast cancer is the most common cancer among women, accounting for 32% of all new cancer cases in females, and ranks as the second leading cause of cancer-related mortality in women. The lifetime risk of developing breast cancer for women is 13.1% (approximately one in eight). Since 2012, the incidence rate has been increasing slowly at an annual rate of ~1%, with the fastest rise observed among younger women (1.4% per year) (1). Current clinical management of breast cancer includes surgical resection, radiotherapy, chemotherapy, endocrine therapy, immunotherapy, and targeted therapy. These modalities are applied in combination based on molecular subtype, clinical stage, and individual patient differences (2). Despite advances in modern medicine and the continuous development of targeted and chemotherapeutic regimens, treatment resistance remains a major obstacle, leading to disease progression and reduced survival (3).

The complexity of drug resistance stems largely from the high heterogeneity and adaptability of tumor cells, involving multiple interrelated biological processes such as upregulation of drug efflux pumps, influences of the tumor microenvironment (TME), aberrant epigenetic regulation, enhanced DNA damage repair (DDR) capacity, and cellular metabolic reprogramming. Unlike prior reviews that typically examine resistance mechanisms in isolation, the present review provides a systematically interconnected framework integrating five core axes and directly links each to corresponding therapeutic solutions. Critically, the emerging dual role of the microbiome in resistance modulation is incorporated and an artificial intelligence-driven adaptive therapy model for real-time monitoring and intervention is proposed.

Therefore, a systematic understanding of the core molecular mechanisms and regulatory networks underlying drug resistance in breast cancer will facilitate the identification of novel biomarkers and therapeutic targets. This will provide a theoretical foundation for the design of effective treatment strategies aimed at improving patient prognosis and quality of life.

2. Molecular subtypes of breast cancer and targeted therapies

Breast cancer can be classified into several major molecular subtypes based on gene expression profiles, including Luminal A, Luminal B, human epidermal growth factor receptor 2-positive (HER2)-positive, and triple-negative breast cancer (TNBC) (2). The Luminal A subtype is defined as hormone receptor (HR)-positive [estrogen receptor (ER)-positive and/or progesterone receptor-positive], HER2-negative, and accompanied by a low Ki-67 index. Luminal B shares similarities with Luminal A but exhibits higher Ki-67 expression and may have HER2 overexpression, conferring a relatively poorer prognosis (4). HER2-positive breast cancer is defined by HER2 gene overexpression or amplification, is typically HR-negative, and is associated with high aggressiveness and an unfavorable prognosis (5). TNBC is characterized by the lack of both HR and HER2 expression, often shows high Ki-67 expression, and represents the most aggressive subtype with the worst prognosis (6). As a result of substantial differences in biological behavior, treatment response, and clinical outcomes among subtypes, the development of personalized treatment strategies tailored to specific molecular profiles is required.

HR-positive breast cancer is commonly treated with endocrine therapy, including selective ER modulators (SERMs), selective ER degraders (SERDs), and aromatase inhibitors (AIs). The U.S. Food and Drug Administration (FDA)-approved SERMs include tamoxifen, raloxifene, and toremifene; SERDs include fulvestrant and the oral agent elacestrant; and AIs include anastrozole, exemestane, and letrozole (7). Resistance to long-term endocrine therapy primarily stems from ER 1 (ESR1) mutations and aberrant activation of signaling pathways such as phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) and cyclin-dependent kinases 4 and 6 (CDK4/6), which reduces treatment efficacy (8). Elacestrant, the first oral SERD approved by the FDA, is indicated for postmenopausal women with ER-positive/HER2-negative advanced breast cancer harboring ESR1 mutations who have experienced disease progression on prior endocrine therapy (9). Additionally, targeted agents such as CDK4/6 inhibitors (including palbociclib, ribociclib, and abemaciclib) and PI3K inhibitors (including alpelisib and inavolisib) can precisely inhibit these pathways, significantly prolonging survival in patients with advanced HR-positive breast cancer (10).

HER2-positive breast cancer accounts for 15-30% of all breast cancer cases. Therapeutic agents for this subtype are primarily classified into the following categories: Monoclonal antibodies, including trastuzumab, pertuzumab, and margetuximab, which inhibit tumor cell proliferation by targeting the HER2 receptor; tyrosine kinase inhibitors, including lapatinib, tucatinib, neratinib, and pyrotinib; and antibody-drug conjugates (ADCs), which deliver cytotoxic drugs specifically to tumor sites by coupling tumor antigen-specific antibodies with potent chemotherapeutic agents. Three ADCs have been approved by the FDA: Trastuzumab emtansine, trastuzumab deruxtecan, and sacituzumab govitecan (11,12).

TNBC is frequently treated with cytotoxic chemotherapeutic agents such as doxorubicin, cyclophosphamide, paclitaxel, cisplatin, carboplatin, and capecitabine. However, the efficacy

Table I. Therapeutic agents for various molecular subtypes of breast cancer.

Molecular subtype	Drug category	Representative drugs
HR^+ breast cancer	Selective estrogen receptor modulators	Tamoxifen, raloxifene, and toremifene
	Selective estrogen receptor degraders	Fulvestrant and elacestrant
	Aromatase inhibitors	Anastrozole, exemestane and letrozole
	CDK4/6 inhibitors	Palbociclib, ribociclib and abemaciclib
	PI3K inhibitors	Alpelisib and inavolisib
HER2-positive breast cancer	Tyrosine kinase inhibitors	Lapatinib, tucatinib, neratinib and pyrotinib
	Antibody-drug conjugates	Trastuzumab emtansine, trastuzumab deruxtecan and sacituzumab govitecan
Triple-negative breast cancer	Cytotoxic chemotherapeutic agents	Doxorubicin, cyclophosphamide, paclitaxel, cisplatin, carboplatin and capecitabine
	Poly(ADP-ribose) polymerase inhibitors	Olaparib and talazoparib
	Immune checkpoint inhibitors	Pembrolizumab, atezolizumab, durvalumab and camrelizumab
	Anti-angiogenic drugs	Bevacizumab

of chemotherapy is limited by tumor heterogeneity and drug resistance, and is accompanied by significant toxicity (13). Additionally, patients with breast cancer susceptibility genes 1 and 2 (BRCA1/2; involved in DNA repair) mutations may benefit from poly(ADP-ribose) polymerase inhibitors (PARPi). Olaparib and talazoparib are FDA-approved for breast cancer treatment, while rucaparib and niraparib are approved for ovarian and prostate cancer (14). Immune checkpoint inhibitors (ICIs), such as pembrolizumab, atezolizumab, durvalumab, and camrelizumab, enhance anti-tumor immune responses by blocking the programmed cell death protein 1 and programmed death ligand 1 (PD-1/PD-L1) pathway. Bevacizumab inhibits tumor angiogenesis by targeting vascular endothelial growth factor (VEGF). The combination of ICIs with chemotherapy, PARPi, and ADCs has demonstrated considerable clinical potential (15). In conclusion, elucidating the molecular mechanisms of drug resistance in breast cancer is of paramount scientific and clinical significance, facilitating drug discovery, optimization of therapeutic strategies, overcoming resistance, and improving patient prognosis. The therapeutic drugs for each molecular subtype are detailed in Table I.

3. Aberrant expression of drug efflux proteins

ATP-binding cassette (ABC) transporters are a family of transmembrane proteins that mediate the transport of various molecules, immune recognition, and drug efflux, with their aberrant expression being closely associated with the development of tumor multidrug resistance (MDR) (16). In breast cancer, the overexpression of three major ABC transporters, ABC subfamily C member 1 (ABCC1; also known as multidrug resistance protein 1), P-glycoprotein (P-gp; also known as ABC subfamily B member 1), and ABC subfamily G member 2 (ABCG2; also known as breast cancer resistance protein), mediates chemoresistance by actively pumping out chemotherapeutic drugs, reducing intracellular drug concentrations (17). The drug efflux function of ABCC1 relies on the synergistic effect of glutathione (GSH). Modulators targeting the ABCC1 and GSH axis that inhibit ABCC1 function and facilitate GSH efflux have been suggested as potential therapeutic interventions (18,19). Furthermore, the expression and activity of ABC transporters are regulated by multiple signaling pathways, including PI3K/AKT/mTOR, mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), nuclear factor-κB (NF-κB), and hypoxia-inducible factor (HIF-1α). Activation of these pathways promotes ABC transporter expression and the development of drug-resistant phenotypes, making them potential targets for reversing MDR (20,21).

Currently, ABC transporter inhibitors have advanced to the third generation. Tariquidar (XR-9576), one of these inhibitors, has entered clinical trials due to its high efficacy and favorable pharmacokinetic properties (22). However, nonspecific targeting and cytotoxicity remain major challenges for the clinical application of ABC inhibitors. To further improve therapeutic specificity and reduce toxicity, strategies have been explored that target upstream signaling pathways regulating ABC transporter expression. For example, the use of PI3K inhibitors (such as alpelisib) or mTOR inhibitors (such as everolimus) can downregulate the expression of P-gp and ABCG2, thereby restoring chemosensitivity in resistant cancer cells (23). Furthermore, novel nanomaterials such as liposomes, polymeric micelles, and mesoporous silica nanoparticles exploit the enhanced permeability and retention effect or targeting ligands to achieve tumor-specific enrichment. These systems can enter cells via endocytosis to bypass efflux pump recognition while co-delivering inhibitors, thereby synergistically increasing the intracellular retention concentration of chemotherapeutic drugs and effectively reversing drug resistance (24,25). Therefore, by downregulating ABC transporter expression using upstream signaling pathway inhibitors and employing nano-based co-delivery systems to bypass efflux pumps, a synergistic dual-level strategy can overcome the off-target toxicity associated with traditional ABC transporter

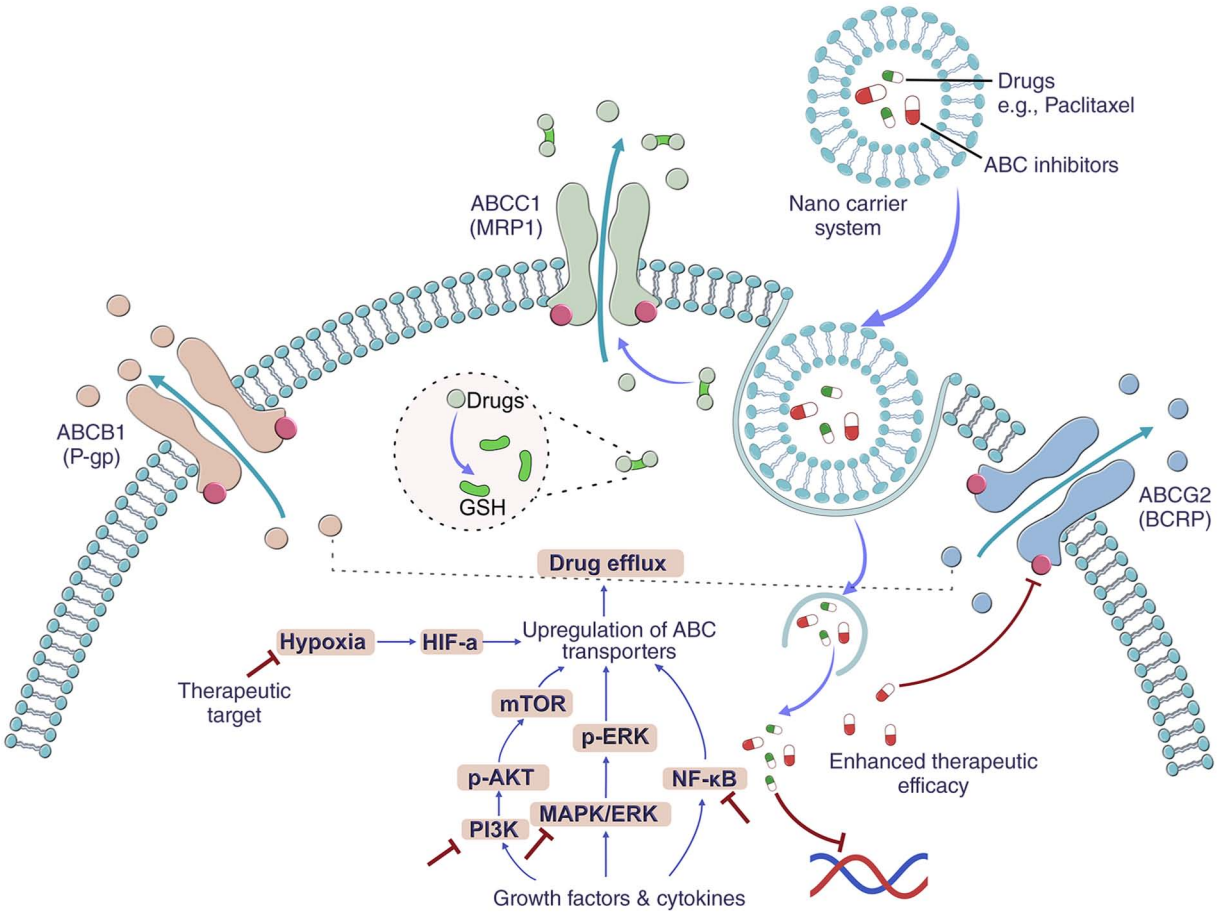

Figure 1. ABC transporter-mediated multidrug resistance in breast cancer. ABCB1 (P-gp), ABCC1 (MRP1), and ABCG2 (BCRP) actively efflux chemotherapeutic drugs, such as paclitaxel, with ABCC1 function assisted by GSH. Hypoxia/HIF-α and growth factor-activated PI3K/AKT/mTOR, MAPK/ERK, and NF-κB pathways upregulate these transporters. Nanocarrier systems co-delivering ABC inhibitors and drugs bypass efflux to enhance intracellular retention and therapeutic efficacy. ABC, ATP binding cassette; ABCB1, ABC subfamily B member 1; P-gp P-glycoprotein; ABCC1, ABC subfamily C member 1; MRP1, multidrug resistance protein 1; ABCG2, ABC subfamily G member 2; BCRP, breast cancer resistance protein; GSH, glutathione; HIF-1α, hypoxia-inducible factor; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; NF-κB, nuclear factor-κB; p-, phosphorylated.

inhibitors, offering a more promising combination treatment approach for patients with advanced chemotherapy-resistant breast cancer (Fig. 1).

4. Tumor microenvironment reprogramming

Hypoxic microenvironment and abnormal angiogenesis. The hypoxic nature of the TME is a critical pathological feature that drives angiogenesis and the development of drug resistance. As tumors proliferate rapidly, the local oxygen partial pressure decreases significantly, leading to the stabilization and activation of HIF-1α (26). As a master regulator of the hypoxic response, HIF-1α promotes the formation of disorganized and dysfunctional tumor vasculature by upregulating pro-angiogenic factors such as VEGF (27). This aberrant vascular network not only impedes effective drug delivery but also supports the survival and stemness of cancer stem cells (CSCs), thereby enhancing chemoresistance (28). Meanwhile, hypoxia facilitates the infiltration of immunosuppressive cells, including myeloid-derived suppressor cells (MDSCs) and regulatory T cells, while impairing the function of cytotoxic T cells, which compromises the response to immunotherapy (29). Moreover, the hypoxia-HIF-α axis reprograms cellular metabolism and induces epigenetic remodeling, further conferring tolerance to chemotherapy and radiotherapy in breast cancer cells (30). It is noteworthy that the expression and activity of HIF-1α are regulated by multiple signaling pathways, including PI3K/AKT/mTOR and MAPK/ERK (31). Therefore, targeting these upstream pathways or directly inhibiting HIF-1α, in combination with anti-angiogenic and immunomodulatory strategies, may represent a promising therapeutic approach to overcome hypoxia-associated treatment resistance (Fig. 2).

Immune microenvironment remodeling. The TME in breast cancer constitutes a complex ecosystem composed of tumor cells, immune cells, cancer-associated fibroblasts (CAFs), and the extracellular matrix (ECM), among other components. Through their interactions, these elements suppress immune responses, thereby promoting tumor progression and conferring drug resistance (32). For instance, the infiltration of immunosuppressive cells, such as CAFs, tumor-associated macrophages, and MDSCs, can secrete inhibitory cytokines that impair the activity of cytotoxic T cells, leading to resistance to immunotherapy (33,34). Furthermore, metabolic

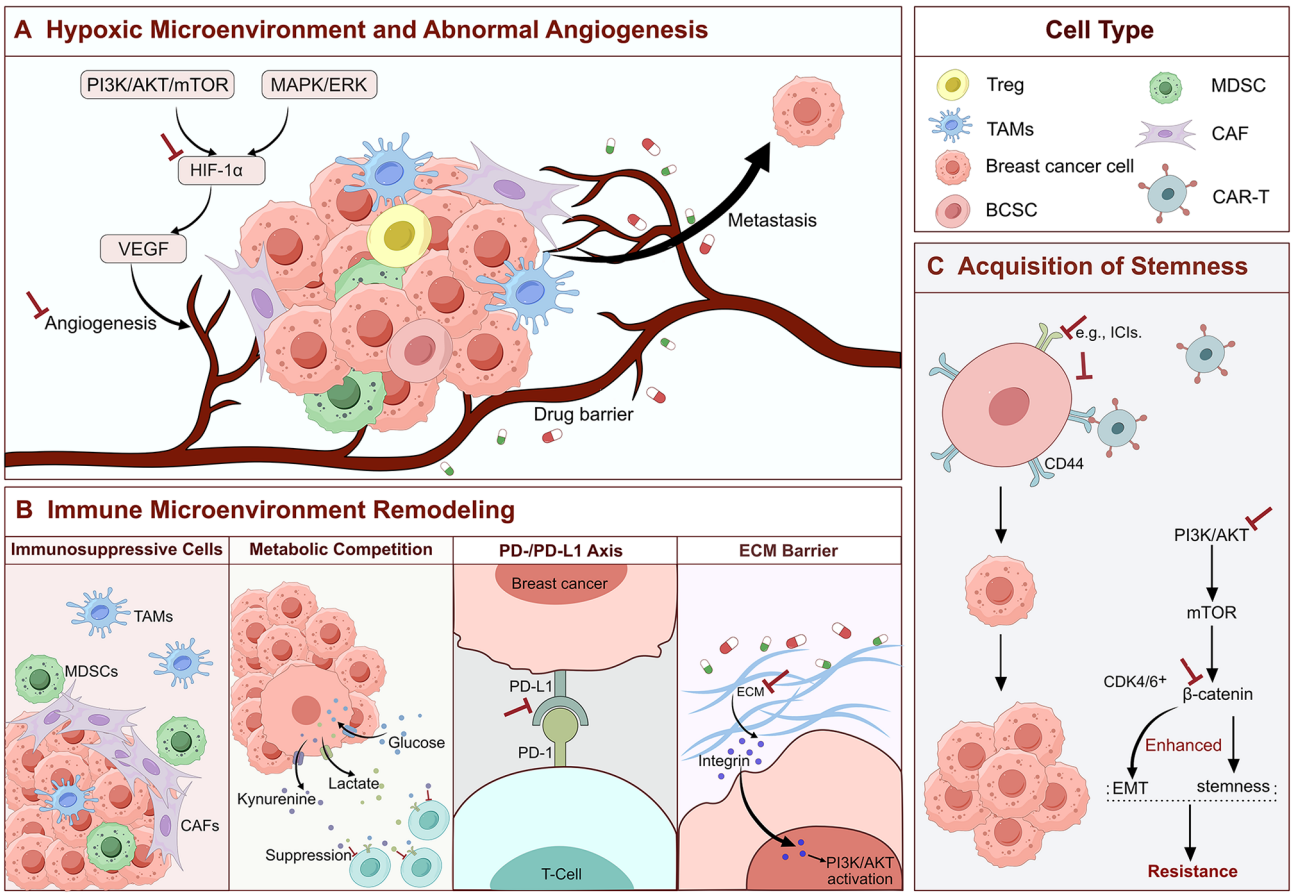

Figure 2. Schematic of tumor microenvironment-mediated drug resistance in breast cancer. (A) Hypoxia-induced HIF-1α/VEGF signaling promotes abnormal angiogenesis and drug barrier formation. (B) Immunosuppressive cells (TAMs, MDSCs, Tregs and CAFs), metabolic competition, PD-1/PD-L1 axis and ECM barrier suppress antitumor immunity. (C) PI3K/AKT/mTOR and Wnt/β-catenin pathways drive BCSC stemness and EMT, conferring therapeutic resistance. HIF-1α, hypoxia-inducible factor; VEGF, vascular endothelial growth factor; TAMs, tumor-associated macrophages; MDSCs, myeloid-derived suppressor cells; Tregs, regulatory T cells; CAFs, cancer-associated fibroblasts; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; ECM, extracellular matrix; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; BCSC, breast cancer stem cell; EMT, epithelial-mesenchymal transition; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; CAR-T, chimeric antigen receptor T cell; ICIs, Immune checkpoint inhibitors; CDK4/6, cyclin-dependent kinases 4 and 6.

competition and immunosuppression contribute to therapeutic resistance. Due to metabolic reprogramming, breast cancer cells compete with T cells for nutrients such as glucose, amino acids, and lipids. This process results in the accumulation of metabolites including lactic acid and kynurenine, which suppress T-cell activity. The combined effects of metabolic stress and metabolite-induced immunosuppression significantly enhance immunotherapy resistance in breast cancer (35). Abnormal immune checkpoint activation further promotes tumor evasion. The binding of PD-L1 on tumor cells to PD-1 on T cells inhibits T-cell activation and facilitates immune escape. Clinical studies show that blocking the PD-1/PD-L1 interaction can restore T-cell function (36). ECM-mediated physical barrier also contributes to resistance. Excessive ECM deposition not only impedes drug penetration but also promotes tumor cell survival by activating the PI3K/AKT pathway via integrin signaling. Targeting ECM remodeling can improve drug delivery and restore immune cell infiltration (37). Therefore, developing combination strategies targeting the immunosuppressive microenvironment, such as ICIs combined with metabolic modulators or ECM targeting agents, may provide a novel approach to overcome drug resistance in breast cancer. A comprehensive analysis of the dynamic interaction network among various components within the tumor microenvironment will establish a theoretical foundation for developing more effective therapeutic strategies (Fig. 2).

Acquisition of stemness. Breast CSCs (BCSCs), a subpopulation within tumors endowed with self-renewal and multilineage differentiation potential, are a major driver of chemotherapy and targeted therapy resistance due to their enrichment and expansion (38). The maintenance of BCSC stemness is mediated by aberrant activation of multiple signaling pathways. For example, activation of the PI3K/AKT/mTOR axis enhances BCSC stemness, thereby conferring therapy resistance (39). Activation of the Wnt/β-catenin signaling pathway induces epithelial-mesenchymal transition (EMT) to promote metastasis and confers resistance to endocrine therapy. Notably, studies have shown that inhibiting this pathway, in combination with CDK4/6 inhibitors, can partially reverse this resistance (40,41). The stemness of BCSCs is also regulated by epigenetic mechanisms. For instance, aberrant expression of long non-coding RNAs (lncRNAs) and alterations in DNA

methylation patterns promote the stem cell-like phenotype, thereby reducing treatment efficacy (42). Moreover, inflammatory factors in the TME contribute to stemness maintenance by inhibiting apoptosis, promoting drug efflux protein expression, and enhancing inherent stem-like properties, thereby reinforcing therapy resistance (43). Several therapeutic strategies targeting BCSCs have been developed, including chimeric antigen receptor T-cell (CAR-T) therapy, ICIs, and approaches using BCSCs as drug delivery vehicles. However, these treatments still face challenges such as insufficient targeting specificity, acquired resistance, and safety concerns. Future efforts should focus on in-depth characterization of BCSCs, optimization of treatment strategies, and enhanced clinical validation to improve therapeutic outcomes (44) (Fig. 2).

5. Dysregulation of epigenetics

Aberrant DNA methylation. DNA methylation plays a pivotal role in breast cancer drug resistance. Aberrant DNA methylation patterns can lead to the silencing of tumor suppressor genes or activation of drug resistance-associated genes, thereby altering cellular response to therapy (45). Research has demonstrated a significant correlation between the mRNA expression of drug resistance genes and their DNA methylation status, with variations observed across different molecular subtypes (46). In ER-positive breast cancer, aberrant DNA methylation was shown to be closely associated with resistance to endocrine therapy (47). The DNA methyltransferase inhibitor decitabine has been shown to reverse epigenetic alterations in drug-resistant cells, restoring their sensitivity to chemotherapeutic agents (48). Protein arginine methyltransferases (PRMTs) are fundamental epigenetic enzymes; pharmacological inhibition of PRMTs has been shown to markedly sensitize tumors to diverse anticancer therapies, supporting the potential of combination strategies with conventional agents to circumvent treatment resistance (49). In addition, dysregulation of m6A RNA methylation regulators may contribute to tumor progression. Although their precise role in DNA repair remains incompletely elucidated, preliminary evidence suggests a potential influence on cancer drug resistance (50). DNA methylation-based biomarkers have the potential to identify patients who respond to platinum-based chemotherapy and may offer novel therapeutic targets to combat tumor resistance. However, research in this field continues to face several challenges. The heterogeneity of DNA methylation patterns across distinct breast cancer subtypes, the complexity of the DNA methylation regulatory network, and the limited selectivity of current epigenetic drugs pose significant challenges. The development of liquid biopsy technology has provided new opportunities for the clinical translation of DNA methylation biomarkers by enabling the simultaneous assessment of tumor gene mutations, resistance genes, and DNA methylation status through detection of circulating tumor DNA in blood, thereby offering multidimensional evidence for precision breast cancer therapy (51). Future studies should focus on elucidating the crosstalk between DNA methylation and other epigenetic mechanisms, such as histone modifications, to facilitate the development of more effective combination treatment regimens (Fig. 3).

Histone modifications. Histone modifications refer to various chemical changes, such as methylation, acetylation, phosphorylation, and ubiquitination, that occur on histone proteins. These modifications regulate gene transcription by altering chromatin structure or recruiting modifier proteins, and they play a critical role in epigenetic regulation. Dysregulation of histone modifications is a core epigenetic mechanism underlying acquired drug resistance in breast cancer. In ER-positive breast cancer, aberrant histone H3 modifications, such as H3K27 acetylation, are associated with resistance to endocrine therapy (52). The combination of histone deacetylase inhibitors (HDACi; such as vorinostat) with conventional chemotherapeutic drugs significantly enhances treatment sensitivity in resistant cells (53). Furthermore, following chemotherapy for breast cancer, OTULIN (a deubiquitinating enzyme) stabilizes β-catenin via deubiquitination, activating the Wnt/β-catenin pathway. This activation promotes DDR and metastasis, suggesting that inhibition of this pathway may enhance chemosensitivity (54). The FDA has approved several HDACi, including romidepsin, belinostat, panobinostat, and vorinostat, for clinical use. In addition, small-molecule inhibitors targeting histone acetyltransferases are under clinical investigation (45). In summary, histone modifications drive drug resistance by regulating gene expression, chromatin architecture, and signaling pathway activity. Developing small-molecule inhibitors against specific histone-modifying enzymes, either alone or in combination with other epigenetic drugs, may provide novel therapeutic strategies to overcome drug resistance in breast cancer (Fig. 3).

Non-coding RNA (ncRNA)-mediated regulation. ncRNAs, as crucial players in epigenetic regulation, play key roles in mediating treatment resistance in breast cancer. Diverse ncRNAs, including microRNAs, lncRNAs, and circular RNAs (circRNAs) contribute to resistance by regulating gene expression, modulating the activation of signaling pathways, and remodeling the TME (55,56). For example, in ER-positive breast cancer, ~40% of patients relapse due to acquired tamoxifen resistance, a process involving ncRN-mediated regulation of resistance-related genes (57). HOX transcript antisense intergenic RNA, a well-characterized oncogenic lncRNA, promotes breast cancer metastasis and chemoresistance through epigenetic modifications, regulation of target genes, and activation of signaling pathways (58). Certain lncRNAs enhance chemoresistance by upregulating ABC transporter expression, which reduces intracellular drug accumulation and impairs the efficacy of agents such as gemcitabine (59). Moreover, aberrant expression of circRNAs has been shown to promote tumor cell invasiveness and drug resistance by regulating EMT-related genes (60). Thus, ncRNA expression patterns show promise as biomarkers for predicting the risk of resistance and as potential therapeutic targets. Although antisense oligonucleotide-based interventions have demonstrated efficacy in restoring chemosensitivity, challenges such as a lack of assay standardization and off-target effects have impeded their translation into routine clinical use (61). Future research should focus on elucidating ncRNA-mediated crosstalk within the immune microenvironment, developing highly specific ncRNA antagonists to overcome endocrine resistance through personalized therapeutic approaches, and integrating

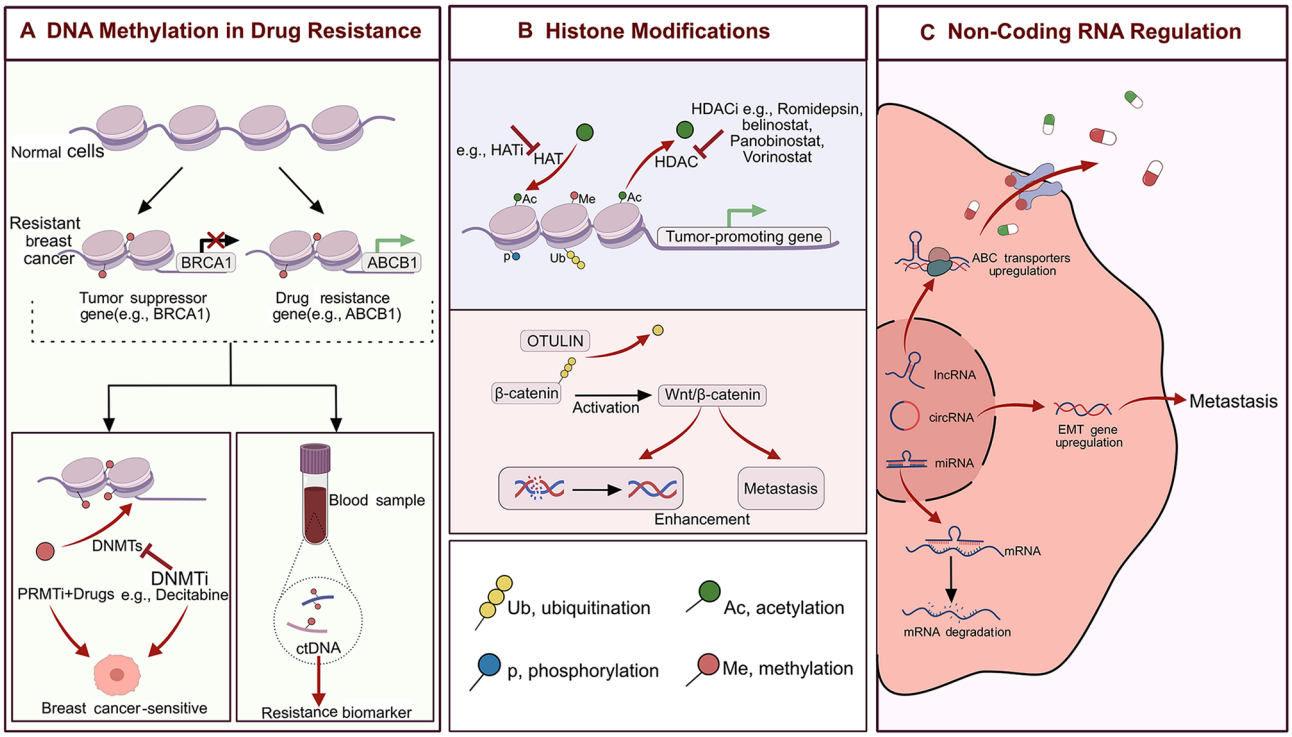

Figure 3. Epigenetic regulation of MDR in breast cancer. (A) DNA methylation by DNMTs silences tumor suppressors, such as BRCA1, and activates resistance genes, such as ABCB1, reversed by DNMTi/PRMTi. (B) Histone modifications (acetylation, phosphorylation, ubiquitination) regulate oncogene expression and Wnt/β-catenin-mediated DNA repair and metastasis. (C) Non-coding RNAs (lncRNAs, circRNAs, miRNAs) modulate ABC transporter expression, EMT and mRNA stability. MDR, multidrug resistance; DNMTs, DNA methyltransferases; BRCA1, breast cancer susceptibility gene 1; ABCB1, ABC subfamily B member 1; DNMTi, DNA methyltransferase inhibitors; PRMTi, protein arginine methyltransferase inhibitors; lncRNAs, long non-coding RNAs; miRNAs, microRNAs; circRNAs, circular RNAs; ABC, ATP binding cassette; EMT, epithelial-mesenchymal transition; HATi, histone acetyltransferase inhibitors; HAT, histone acetyltransferase; HDAC, histone deacetylase; HDACi, histone deacetylase inhibitors.

multi-omics data to accelerate translational applications (62) (Fig. 3).

6. Enhanced DNA damage repair mechanisms

Homologous recombination repair (HRR) restoration. HRR deficiency is closely associated with drug resistance mechanisms in breast cancer, primarily involving restoration of homologous recombination function, alterations in DNA replication fork stability, aberrant epigenetic regulation, and compensatory activation of alternative DNA repair pathways. As core components of the HRR pathway, loss-of-function mutations in BRCA1/2 sensitize tumor cells to PARPi and platinum-based agents. However, clinical observations indicate that restoration of HRR function may lead to acquired resistance (63). Specific mechanisms of resistance include epigenetic regulation-mediated restoration of HRR, exemplified by demethylation of BRCA gene promoters, which restores BRCA protein expression and reactivates the HRR pathway (64) and compensatory upregulation of key DNA repair proteins. For instance, loss of BRCA1/2 induces compensatory activation of RAD51 recombinase (RAD51), which bypasses HRR defects to restore double-strand break (DSB) repair capacity, thereby conferring chemotherapy resistance (65). Loss of 53BP1 partially restores HRR in BRCA-deficient cells by modulating DNA end resection, thereby enabling escape from PARPi-induced synthetic lethality (66,67). Dysfunction of HRR-associated proteins such as partner and localizer of BRCA2 (PALB2), which works together with BRCA1/2 and RAD51 to mediate HRR, may also lead to HRR deficiency and sensitize tumors to PARPi. For example, loss of PALB2 similarly disrupts HRR and increases sensitivity to PARPi. However, certain PALB2 mutations may impair its binding to BRCA1/2, resulting in partially retained HRR function and subsequent drug resistance. Targeting the PALB2 recruitment machinery may thus represent a promising therapeutic strategy for BRCA1-mutated tumors (68-70). Clinical data have demonstrated that combining PARPi with chemotherapeutic agents, such as paclitaxel and gemcitabine, or immunotherapeutic agents, such as pembrolizumab, shows potential in overcoming drug resistance (71). Future precision therapies targeting HRR deficiency are expected to expand the eligible patient population in breast cancer. Further investigation of pathways that crosstalk with the HRR network may reveal novel targets for overcoming PARPi resistance. In clinical practice, molecular profiling of HRR gene alterations could enable early identification of patients at high risk of treatment resistance and guide personalized therapeutic strategies (Fig. 4).

Non-homologous end joining (NHEJ) pathway activation. NHEJ is a primary pathway for repairing DSBs in mammalian cells. Upon the occurrence of DSBs, the Ku70/80 heterodimer is rapidly recruited to the broken ends and binds to them in a sequence-nonspecific manner. This recruitment is followed by the assembly and activation of the DNA-dependent protein kinase catalytic subunit, facilitating synapsis of the broken

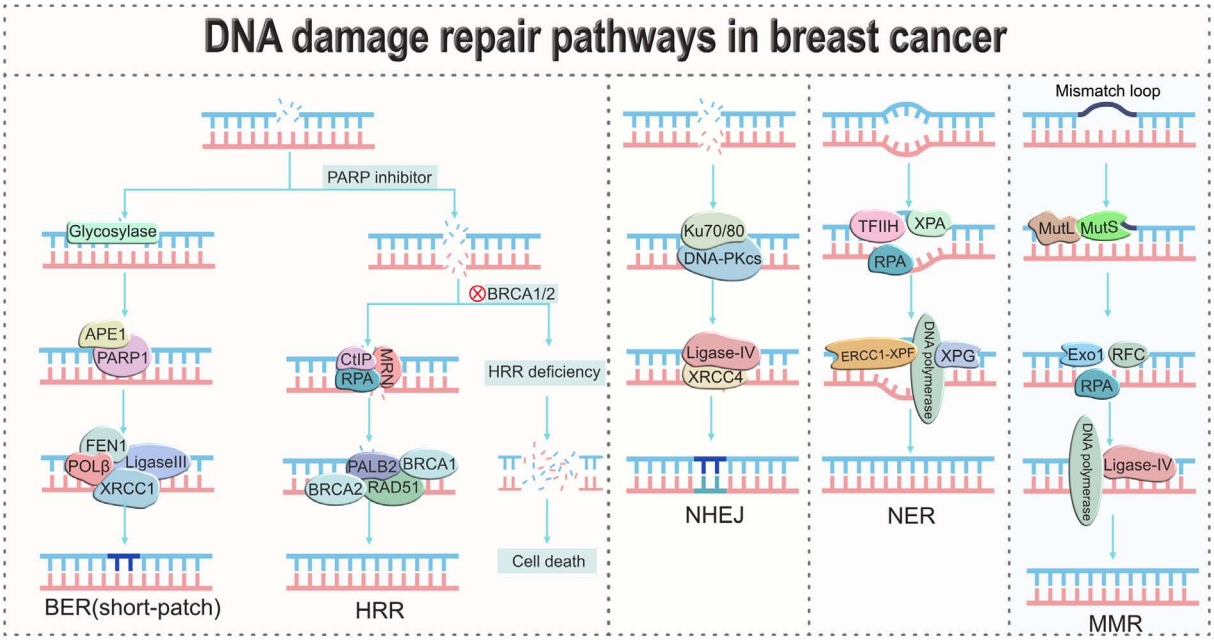

Figure 4. DNA damage repair pathways in breast cancer. The schematic depicts BER, HRR, NHEJ, NER, and MMR mechanisms. PARPi selectively induce cell death via synthetic lethality in BRCA1/2-deficient tumors. Compensatory upregulation of these pathways mediates resistance to chemotherapy and PARPi. BER, base excision repair; HRR, homologous recombination repair; NHEJ, non-homologous end joining; NER, nucleotide excision repair; MMR, mismatch repair; PARP, poly(ADP-ribose) polymerase inhibitors; BRCA1/2, breast cancer susceptibility genes 1/2; APE1, apurinic/apyrimidinic endonuclease 1; CtIP, CtBP-interacting protein; RPA, replication protein A; MRN, MRE11-RAD50-NBS1 complex; HR, homologous recombination; FEN1, flap endonuclease 1; POLβ, DNA polymerase β; LigaseIII, DNA ligase III; XRCC1, X-ray repair cross-complementing 1; PALB2, partner and localizer of BRCA2; BRCA1, breast cancer susceptibility gene 1; BRCA2, breast cancer susceptibility gene 2; RAD51, RAD51 recombinase; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; Ligase-IV, DNA ligase IV; XRCC4, X-ray repair cross-complementing protein 4-like factor; TFIIH, transcription factorIIH; XPA, xeroderma pigmentosum complementation group A protein; ERCC1, excision repair cross-complementation group 1; XPF, xeroderma pigmentosum group F-complementing protein; XPG, xeroderma pigmentosum complementation group G protein; MutL, mismatch repair protein complex; MutS, mismatch recognition protein complex; Exo1, exonuclease 1; RFC, replication factor C.

DNA ends. Subsequently, end-processing factors, including the Artemis nuclease, are engaged to prepare the termini for ligation. Ultimately, the X-ray repair cross-complementing (XRCC) 4-like factor complex, in conjunction with DNA ligase IV, catalyzes the final ligation step to complete the repair process (72-74). The repair process frequently introduces base deletion or insertion mutations, leading to reduced sequence fidelity. In breast cancer, core NHEJ components are frequently upregulated. This elevation is regarded as a compensatory adaptation to genomic instability or impairments in other DSB repair pathways, thereby conferring resistance to radiotherapy and numerous chemotherapeutic agents (75,76). Additionally, the alternative non-homologous end joining (Alt-NHEJ) pathway is mediated by key factors such as DNA ligase III, DNA polymerase θ, and PARP1. Their upregulation is closely associated with tumor progression and drug resistance. When canonical NHEJ is impaired, Alt-NHEJ is activated as a backup pathway to maintain genome integrity, paradoxically promoting drug resistance (77). The aforementioned evidence indicates that NHEJ and its alternative pathways contribute to drug resistance in breast cancer via a multi-molecular interaction network. Targeting key factors in the NHEJ pathway may represent a promising strategy to overcome NHEJ-mediated resistance (Fig. 4).

Base excision repair (BER) pathway activation. The BER pathway serves as a primary cellular defense mechanism against DNA single-base lesions and single-strand breaks, primarily repairing damage caused by both endogenous and exogenous factors such as reactive oxygen species (ROS), alkylating agents, and ionizing radiation (78-80). First, chemotherapy-induced DDR is considered. The BER pathway effectively reverses DNA lesions induced by chemotherapeutic agents such as cisplatin, significantly reducing the cytotoxic efficacy of these drugs against cancer cells (81). Flap endonuclease 1 (FEN1), a key enzyme in BER, is often overexpressed in TNBC and confers resistance to chemotherapeutic agents. Inhibition of FEN1 has been shown to sensitize tumor cells to treatment (82). Second, the influence of genetic variation, such as single-nucleotide polymorphisms in BER-related genes, including XRCC1, may alter BER efficiency and consequently affect treatment response and prognosis in patients with breast cancer (83). Currently, no specific therapeutic agents targeting the BER pathway are available beyond PARPi. Therefore, systematic identification of key biomarkers in the BER pathway, such as the expression level of DNA polymerase β, XRCC1 mutation status, and FEN1 activity, will contribute to the precise screening of patients likely to benefit, and provide a theoretical basis for developing novel targeted strategies (Fig. 4).

Hyperactivation of nucleotide excision repair (NER). NER is an essential DNA repair mechanism in mammalian cells, dedicated to removing bulky DNA lesions that distort the helical structure, such as UV-induced cyclobutane pyrimidine dimers and DNA damage generated by chemotherapeutic

agents. In breast cancer, aberrantly elevated NER activity efficiently removes cisplatin-induced DNA adducts and impedes damage accumulation, thereby mediating both intrinsic and acquired resistance to this chemotherapeutic agent (84,85). Excision repair cross-complementation (ERCC) group 1, a rate-limiting enzyme in the NER pathway, confers cellular resistance to platinum-based drugs when highly expressed due to enhanced DNA repair capacity (86). Further studies revealed that methylation of the ERCC4 gene promoter results in loss of its encoded product, xeroderma pigmentosum group F-complementing protein (XPF), thereby suppressing NER function and increasing cisplatin sensitivity. Conversely, restoring XPF expression reactivates NER and reduces cisplatin efficacy, suggesting that epigenetic modulation of ERCC4 to target NER activity holds therapeutic potential (87,88). Moreover, under specific contexts, BRCA1 facilitates the clearance of chemotherapy-induced DNA lesions and promotes genomic stability through co-activation of NER (89). However, the functional landscape of NER activity in breast cancer remains incompletely defined. Precise identification of NER deficiencies or hyperactivation is expected to guide the development of NER-targeting agents, thereby increasing chemosensitivity and overcoming drug resistance (Fig. 4).

Mismatch repair (MMR) deficiency. The MMR system maintains genomic stability by recognizing and correcting base-base mismatches during DNA replication. In breast cancer chemoresistance, it mediates context-dependent resistance through bidirectional epigenetic reprogramming. On one hand, loss of MMR function, such as that induced by MutL Homolog 1 (MLH1) or MutS Homolog 2 (MSH2) gene silencing, causes microsatellite instability-high and may initially increase tumor sensitivity to DNA-damaging agents. However, sustained MMR deficiency ultimately promotes genomic instability. For example, in doxorubicin resistance, hypermethylation of the MSH2 promoter compromises MMR function, facilitates the accumulation of acquired mutations, and leads to secondary resistance (90-92). On the other hand, anthracycline-induced hypomethylation of MLH1 or MSH2 promoters can enhance MMR gene expression and repair activity. This enables cancer cells to excessively clear DNA damage, resulting in pan-chemoresistance (93). The MutL complex genes (MLH1, PMS1, PMS2, and MLH3) are core components of the MMR pathway. Defects in these genes disrupt MMR function, preventing ER-positive breast cancers from effectively suppressing CDK4 activity during endocrine therapy, thereby conferring treatment resistance. Consequently, MMR deficiency may serve as a predictive biomarker for response to CDK4/6 inhibitors (94). Furthermore, it has been shown that the HR and MMR pathways are functionally interconnected in DNA repair-deficient tumors and share key protein components. Although the precise mechanisms remain incompletely elucidated, this crosstalk offers novel insights and potential therapeutic targets for precision oncology (95). In summary, co-targeting complementary DNA damage response pathways, such as combining PARPi with MMR targeting strategies, represents a promising therapeutic approach to overcome drug resistance in breast cancer (Fig. 4).

7. Alterations in metabolic reprogramming

Enhanced glycolysis. Metabolic reprogramming in breast cancer cells is characterized by markedly enhanced glycolysis (the Warburg effect), which operates synergistically with the tricarboxylic acid cycle and the hexosamine biosynthesis pathway to supply energy and biosynthetic precursors that promote tumor cell survival, invasion, and maintenance of stemness under chemotherapy-induced stress (96). For instance, Pim-2 proto-oncogene, serine/threonine kinase was shown to bind to and promote phosphorylation of 6-phosphofructo-2-kinase at Ser478, thereby enhancing glycolytic activity and conferring paclitaxel resistance in breast cancer cells (97). Moreover, pyruvate kinase M2 was demonstrated to activate autophagy, supplying tumor cells with energy and metabolic intermediates that bolster survival advantage under drug pressure. Thus, the 'glycolysis-autophagy axis' represents a core mechanism underlying chemoresistance (98). Hexokinase 2 (HK2) also activates the NF-κB pathway, leading to upregulation of PD-L1 expression, which drives immune escape and influences tumor immune infiltration and patient prognosis. These findings suggest that combining PD-L1 blockade with HK2-targeted therapy may offer a novel therapeutic strategy for breast cancer (99). The end product of glycolysis, lactate, contributes to tumor progression by acidifying the tumor microenvironment, suppressing immune responses, and modulating oncogene expression (100). Therefore, developing specific inhibitors targeting key glycolytic enzymes and using them in combination with existing anticancer drugs may overcome therapy resistance by inhibiting tumor glycolytic metabolism and enhancing immune responses, thereby providing a novel strategy for breast cancer treatment (96) (Fig. 5).

Dysregulation of lipid metabolism. Disorders in lipid metabolism contribute to treatment evasion in breast cancer cells by regulating fatty acid synthesis, cholesterol metabolism, and phospholipid remodeling, thereby providing a sustained energy supply and maintaining TME homeostasis (101,102). Key lipid metabolic enzymes are tightly regulated by transcription factors that drive aberrant synthesis and accumulation of fatty acids and cholesterol, thereby enhancing resistance to chemotherapy, endocrine therapy, and targeted therapy. Sterol regulatory element-binding protein 1 promotes fatty acid synthesis via Akt/mTOR activation, thereby increasing cell membrane fluidity and reducing drug influx, leading to doxorubicin resistance (103). Dysregulated cholesterol metabolism enhances chemoresistance by upregulating ABC transporter expression and facilitating lipid raft-mediated signaling (104). The ketone body-producing rate-limiting enzyme 3-hydroxy-3-methylglutaryl-CoA synthase 2 is highly expressed in tamoxifen-resistant breast cancer, and developing inhibitors against it represents a promising strategy for reversing endocrine resistance (105). Notably, lipid metabolic reprogramming also modulates EMT and stemness, remodels the immune microenvironment, and alters chemotherapeutic metabolism, collectively exacerbating drug resistance (106-108). This multi-layered and multi-targeted metabolic network highlights targeting key nodes of lipid metabolism as a potential therapeutic strategy to overcome drug resistance in breast cancer (Fig. 5).

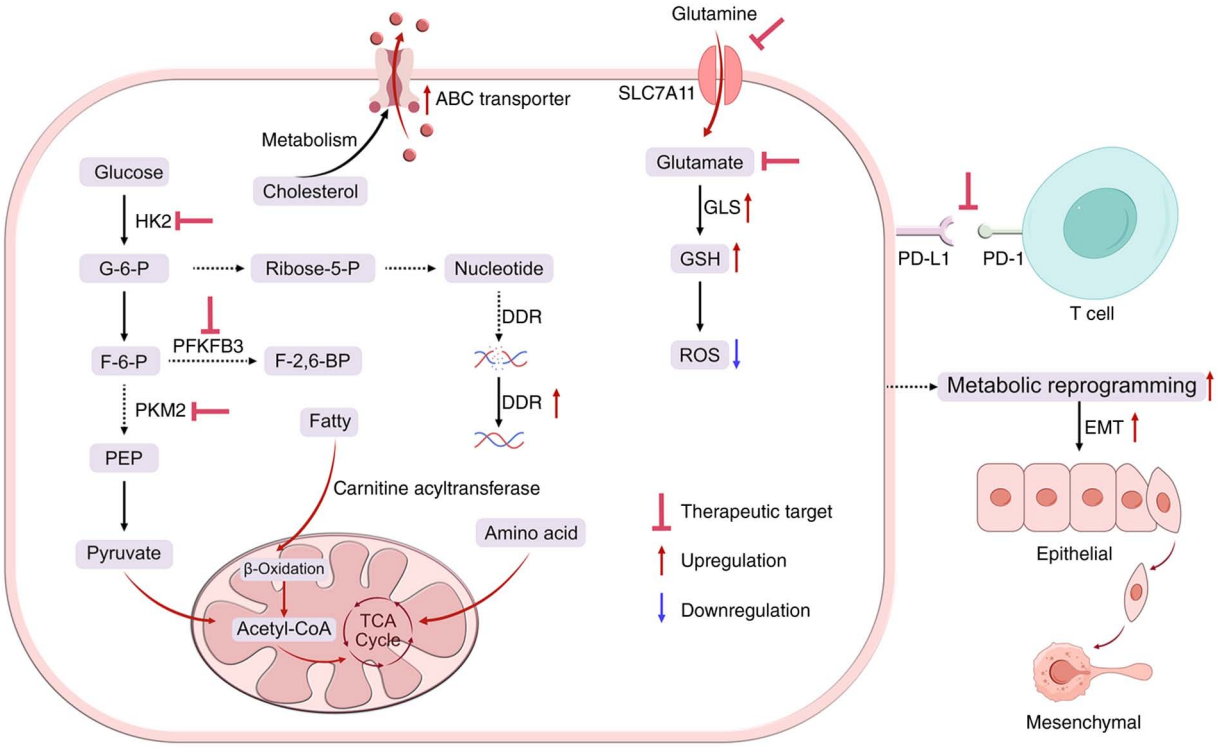

Figure 5. Metabolic reprogramming in breast cancer and its therapeutic targets. Upregulated glycolysis, glutamine metabolism and nucleotide synthesis sustain tumor bioenergetics, redox balance (GSH/ROS) and DDR. Lipid metabolism and the TCA cycle provide additional energetic support. These adaptations drive PD-L1-mediated immune evasion and EMT, promoting drug resistance. GSH, glutathione; ROS, reactive oxygen species; DDR, DNA damage repair; TCA, tricarboxylic acid; PD-L1, programmed death ligand 1; EMT, epithelial-mesenchymal transition; SLC7A11, solute carrier family 7 member 11; ABC, ATP binding cassette; HK2, hexokinase 2; G-6-P, glucose-6-phosphate; F-6-P, fructose-6-phosphate; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; F-2,6-BP, fructose-2,6-bisphosphate; PKM2, pyruvate kinase M2; PEP, phosphoenolpyruvate; Ribose-5-P, ribose-5-phosphate; GLS, glutaminase; PD-1, programmed cell death protein 1.

Aberrant amino acid metabolism. Amino acids serve as essential nutrients for sustaining cellular life. Metabolic reprogramming of amino acids has been demonstrated to significantly promote the proliferation, metastasis, and therapy resistance of breast cancer cells, a process closely associated with dysregulated expression of amino acid transporters and altered activity of key enzymes. Research has revealed that solute carrier family 7 member 5 (SLC7A5), an amino acid transporter, is highly expressed across different breast cancer subtypes, particularly in Luminal B breast cancer, where its elevated expression is associated with poor patient prognosis, suggesting its potential as a therapeutic target in this subtype (109). In TNBC, chemotherapy-induced reactive ROS stress prompts cancer cells to enhance glutamine metabolism by upregulating glutaminase (GLS) and glutamate transporters, leading to massive glutamate efflux. This facilitates GSH synthesis to scavenge ROS and maintain redox homeostasis, thereby driving chemoresistance. Targeting glutamate depletion or inhibiting GLS and the cystine/glutamate transporter SLC7A11 (xCT) disrupts this antioxidant system, resulting in ROS accumulation and resensitization to treatment (110,111). Amino acid metabolism also interfaces with the TME: Tumor cells compete with immune cells, such as T cells, for key amino acids such as tryptophan and arginine, supporting tumor survival and proliferation. Meanwhile, accumulation of the tryptophan metabolite kynurenine suppresses T-cell function and fosters an immunosuppressive TME, ultimately compromising immunotherapy efficacy and indirectly contributing drug resistance in breast cancer (112,113). In summary, targeting amino acid transporters, such as with SLC7A5 inhibitors, in combination with metabolic inhibitors and immunotherapy, along with metabolism-based precision therapy, represents a promising strategy for overcoming drug-resistant breast cancer (Fig. 5).

Alterations in nucleotide metabolism. Nucleotides function as the fundamental building blocks for DNA/RNA synthesis and participate in cellular energy metabolism, signaling transduction, and proliferation regulation. In breast cancer, upregulation of rate-limiting enzymes in the *de novo* nucleotide synthesis pathway promotes excessive purine and pyrimidine accumulation, which activates downstream signaling cascades, enhances tumor stemness and metastatic potential, and facilitates DDR, ultimately leading to chemoresistance (114,115). For instance, elevated expression of the purine metabolic enzyme phosphoribosylaminoimidazole succinocarboxamide synthetase enhances ERα activity through the cyclic adenosine monophosphate-protein kinase A-mTOR signaling axis, resulting in tamoxifen resistance in breast cancer (116). Furthermore, nucleotide metabolic reprogramming contributes to therapy resistance by modulating the TME. Tumor cells consume nucleotide precursors and release immunosuppressive metabolites, leading to T-cell dysfunction through nutrient competition and subsequent immune escape (117,118). Therefore, targeting nucleotide metabolism in combination with conventional therapies may offer a novel multi-target strategy to overcome drug

resistance in breast cancer by synergizing metabolic intervention with immune modulation (Fig. 5).

8. Conclusions and future perspectives

Breast cancer is one of the most common malignancies in women. Standard treatment regimens include chemotherapy, as well as endocrine and targeted therapies; however, acquired drug resistance significantly shortens patient survival and remains a major clinical challenge. Drug resistance in breast cancer arises from a multifactorial, interconnected network encompassing ABC transporter-mediated drug efflux, hypoxic and immunosuppressive TME remodeling, aberrant epigenetic reprogramming via DNA methylation, histone modifications and ncRNAs, compensatory activation of DDR pathways including HRR and NHEJ, and adaptive metabolic rewiring involving glycolysis, lipid, amino acid, and nucleotide metabolism. These mechanisms are co-regulated by key signaling axes such as PI3K/AKT/mTOR, Wnt/β-catenin, and HIF-1α. Correspondingly, effective therapeutic solutions include combination regimens integrating targeted inhibitors, such as PI3K/mTOR inhibitors and HDACi, immune-based modalities such as CAR-T, CAR-natural killer cells, bispecific T-cell engagers, oncolytic viruses, and ADCs, alongside stimuli-responsive nanocarriers and proteolysis-targeting chimeras that enhance delivery precision and reduce off-target toxicity.

Additionally, it is worth noting that the microbiome can regulate estrogen metabolism and host immune responses, directly promoting breast cancer development and the emergence of chemotherapy resistance. Conversely, certain probiotic *Lactobacillus* species can enhance antitumor immunity, thereby playing a bidirectional regulatory role in disease progression and treatment (119). This duality is well exemplified by previous studies. Pro-tumorigenic effects were observed in the findings of Ma *et al* (120), who reported that enterotoxigenic *Bacteroides fragilis* activates nucleotide-binding oligomerization domain-containing 1-Notch receptor 1 signaling via *Bacteroides fragilis* toxin-1, enriching BCSCs and driving chemoresistance; similarly, Fu *et al* (121) showed that intratumoral bacteria remodel the cytoskeleton of circulating tumor cells, facilitating metastatic colonization (121). Conversely, anti-tumorigenic effects were demonstrated by Wu *et al* (122), who found that flaxseed lignans, converted by the gut microbiota into enterolactone, downregulate CD38 and enrich Akkermansia, synergizing with PD-1/PD-L1 inhibitors to suppress tumor growth (122). Therefore, through the integration of prospective interventional trials with multi-omics and artificial intelligence, the clinical value of gut and breast microbiota as predictive biomarkers for therapeutic response and as druggable targets for reversing drug resistance in breast cancer can be systematically validated.

In summary, future efforts should focus on developing switch-controlled immunotherapies and local prodrug strategies to improve treatment safety, constructing smart-responsive nanocarriers and exosome-based platforms to overcome drug delivery challenges, and adopting staged combination regimens along with microenvironmental synergistic modulation to reduce drug toxicity. Artificial intelligence should assist in designing highly potent, low-toxicity candidate molecules, recommending personalized regimens based on dynamic changes in drug resistance, and forming a closed-loop feedback with intelligent delivery systems to establish a precision framework that transitions from real-time monitoring to adaptive therapy. Ultimately, this would transform breast cancer resistance into a long-term controllable paradigm characterized by predictability, real-time monitoring, and timely intervention, thereby delaying or even reversing resistance.

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Authors' contributions

WX, MS and YZ conceived the review and wrote the original draft. SK designed the scope and structure of the review. SX and YW performed structured literature searches. MS and YZ critically synthesized and interpreted the findings. MS and WX revised major sections of the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors decalre that they have no competing interests.

References

1. Siegel RL, Kratzer TB, Giaquinto AN, Sung H and Jemal A: Cancer statistics, 2025. CA Cancer J Clin 75: 10-45, 2025.
2. Xiong X, Zheng LW, Ding Y, Chen YF, Cai YW, Wang LP, Huang L, Liu CC, Shao ZM and Yu KD: Breast cancer: Pathogenesis and treatments. Signal Transduct Target Ther 10: 49, 2025.
3. Guiu S, Michiels S, André F, Cortes J, Denkert C, Di Leo A, Hennessy BT, Sorlie T, Sotiriou C, Turner N, *et al*: Molecular subclasses of breast cancer: How do we define them? The IMPAKT 2012 working group statement. Ann Oncol 23: 2997-3006, 2012.

4. Dai X, Xiang L, Li T and Bai Z: Cancer hallmarks, biomarkers and breast cancer molecular subtypes. J Cancer 7: 1281-1294, 2016.
5. Fedele P, Sanna V, Santoro AN, Iaia ML and Fancellu A: Tailoring antiHer2 treatment strategies in breast cancer and beyond. Curr Probl Cancer 46: 100892, 2022.
6. Yin L, Duan JJ, Bian XW and Yu SC: Triple-negative breast cancer molecular subtyping and treatment progress. Breast Cancer Res 22: 61, 2020.
7. Roskoski R Jr: Targeted and cytotoxic inhibitors used in the treatment of breast cancer. Pharmacol Res 210: 107534, 2024.
8. Khan A, Sisodiya S, Aftab M, Tanwar P, Hussain S and Gupta V: Mechanisms and therapeutic strategies for endocrine resistance in breast cancer: A comprehensive review and meta-analysis. Cancers (Basel) 17: 1653, 2025.
9. Hoy SM: Elacestrant: First approval. Drugs 83: 555-561, 2023.
10. Ziyeh S, Wong L and Basho RK: Advances in endocrine therapy for hormone receptor-positive advanced breast cancer. Curr Oncol Rep 25: 689-698, 2023.
11. Stanowicka-Grada M and Senkus E: Anti-HER2 drugs for the treatment of advanced HER2 positive breast cancer. Curr Treat Options Oncol 24: 1633-1650, 2023.
12. Randall M, Akers R and Rao R: A review of current and future antibody drug conjugates in breast cancer. Curr Treat Options Oncol 25: 1506-1516, 2024.
13. Bhise K, Gavande NS and Iyer AK: Leveraging hypoxia in triple-negative breast cancer as a promising treatment strategy. Drug Discov Today 28: 103761, 2023.
14. Li Y, Liu CF and Rao GW: A review on poly (ADP-ribose) polymerase (PARP) inhibitors and synthetic methodologies. Curr Med Chem 28: 1565-1584, 2021.
15. Wu S, Ge A, Deng X, Liu L and Wang Y: Evolving immunotherapeutic solutions for triple-negative breast carcinoma. Cancer Treat Rev 130: 102817, 2024.
16. Muriithi W, Macharia LW, Heming CP, Echevarria JL, Nyachieo A, Filho PN and Neto VM: ABC transporters and the hallmarks of cancer: Roles in cancer aggressiveness beyond multidrug resistance. Cancer Biol Med 17: 253-269, 2020.
17. Stefan K, Schmitt SM and Wiese M: 9-Deazapurines as broad-spectrum inhibitors of the ABC transport proteins P-glycoprotein, multidrug resistance-associated protein 1, and breast cancer resistance protein. J Med Chem 60: 8758-8780, 2017.
18. Hanssen KM, Wheatley MS, Yu DMT, Conseil G, Norris MD, Haber M, Cole SPC and Fletcher JI: GSH facilitates the binding and inhibitory activity of novel multidrug resistance protein 1 (MRP1) modulators. FEBS J 289: 3854-3875, 2022.
19. Nasr R, Lorendeau D, Khonkarn R, Dury L, Pérès B, Boumendjel A, Cortay JC, Falson P, Chaptal V and Baubichon-Cortay H: Molecular analysis of the massive GSH transport mechanism mediated by the human multidrug resistant protein 1/ABCC1. Sci Rep 10: 7616, 2020.
20. Anish Ruban S, Raj FJ and Thangaraj P: Phytochemical intervention in BCRP-driven cancer drug resistance: A comprehensive review. Biochim Biophys Acta Rev Cancer 1880: 189349, 2025.
21. Dong J, Yuan L, Hu C, Cheng X and Qin JJ: Strategies to overcome cancer multidrug resistance (MDR) through targeting P-glycoprotein (ABCB1): An updated review. Pharmacol Ther 249: 108488, 2023.
22. Mohammad IS, He W and Yin L: Understanding of human ATP binding cassette superfamily and novel multidrug resistance modulators to overcome MDR. Biomed Pharmacother 100: 335-348, 2018.
23. Alves CL and Ditzel HJ: Drugging the PI3K/AKT/mTOR pathway in ER+ breast cancer. Int J Mol Sci 24: 4522, 2023.
24. Shah D, Ajazuddin and Bhattacharya S: Role of natural P-gp inhibitor in the effective delivery for chemotherapeutic agents. J Cancer Res Clin Oncol 149: 367-391, 2023.
25. Zhu S, Sun C, Cai Z, Li Y, Liu W, Luan Y and Wang C: Effective therapy of advanced breast cancer through synergistic anticancer by paclitaxel and P-glycoprotein inhibitor. Mater Today Bio 26: 101029, 2024.
26. de Heer EC, Jalving M and Harris AL: HIFs, angiogenesis, and metabolism: Elusive enemies in breast cancer. J Clin Invest 130: 5074-5087, 2020.
27. Shi S, Ou X, Liu C, Wen H and Ke J: Research progress of HIF-1a on immunotherapy outcomes in immune vascular microenvironment. Front Immunol 16: 1549276, 2025.
28. De Francesco EM, Maggiolini M and Musti AM: Crosstalk between Notch, HIF-1α and GPER in breast cancer EMT. Int J Mol Sci 19: 2011, 2018.
29. Zhang G, Tao X, Ji B and Gong J: Hypoxia-driven M2-polarized macrophages facilitate cancer aggressiveness and temozolomide resistance in glioblastoma. Oxid Med Cell Longev 2022: 1614336, 2022.
30. Capatina AL, Malcolm JR, Stenning J, Moore RL, Bridge KS, Brackenbury WJ and Holding AN: Hypoxia-induced epigenetic regulation of breast cancer progression and the tumour microenvironment. Front Cell Dev Biol 12: 1421629, 2024.
31. Rashid M, Zadeh LR, Baradaran B, Molavi O, Ghesmati Z, Sabzichi M and Ramezani F: Up-down regulation of HIF-1α in cancer progression. Gene 798: 145796, 2021.
32. Dominguez-Cejudo MA, Gil-Torralvo A, Cejuela M, Molina-Pinelo S and Salvador Bofill J: Targeting the tumor microenvironment in breast cancer: Prognostic and predictive significance and therapeutic opportunities. Int J Mol Sci 24: 16771, 2023.
33. Akinsipe T, Mohamedelhassan R, Akinpelu A, Pondugula SR, Mistriotis P, Avila LA and Suryawanshi A: Cellular interactions in tumor microenvironment during breast cancer progression: New frontiers and implications for novel therapeutics. Front Immunol 15: 1302587, 2024.
34. Kundu M, Butti R, Panda VK, Malhotra D, Das S, Mitra T, Kapse P, Gosavi SW and Kundu GC: Modulation of the tumor microenvironment and mechanism of immunotherapy-based drug resistance in breast cancer. Mol Cancer 23: 92, 2024.
35. Zou J, Mai C, Lin Z, Zhou J and Lai G: Targeting metabolism of breast cancer and its implications in T cell immunotherapy. Front Immunol 15: 1381970, 2024.
36. Kaufman B, Abu-Ahmad M, Radinsky O, Gharra E, Manko T, Bhattacharya B, Gologan D, Erlichman N, Meshel T, Nuta Y, *et al*: N-glycosylation of PD-L1 modulates the efficacy of immune checkpoint blockades targeting PD-L1 and PD-1. Mol Cancer 24: 140, 2025.
37. Liang D, Liu L, Zhao Y, Luo Z, He Y, Li Y, Tang S, Tang J and Chen N: Targeting extracellular matrix through phytochemicals: A promising approach of multi-step actions on the treatment and prevention of cancer. Front Pharmacol 14: 1186712, 2023.
38. Bhavnagari H, Raval A and Shah F: Deciphering potential role of Hippo signaling pathway in breast cancer: A comprehensive review. Curr Pharm Des 29: 3505-3518, 2023.
39. Zhang C, Xu S, Yin C, Hu S and Liu P: The role of the mTOR pathway in breast cancer stem cells (BCSCs): Mechanisms and therapeutic potentials. Stem Cell Res Ther 16: 156, 2025.
40. Sakunrangsit N and Ketchart W: Plumbagin inhibits cancer stem-like cells, angiogenesis and suppresses cell proliferation and invasion by targeting Wnt/β-catenin pathway in endocrine resistant breast cancer. Pharmacol Res 150: 104517, 2019.
41. Ham A, Cho MH, Won HS, Jo J and Lee KE: β-catenin blockers enhance the effect of CDK4/6 inhibitors on stemness and proliferation suppression in endocrine-resistant breast cancer cells. Oncol Rep 48: 130, 2022.
42. Luo F, Zhang M, Sun B, Xu C, Yang Y, Zhang Y, Li S, Chen G, Chen C, Li Y and Feng H: LINC00115 promotes chemoresistant breast cancer stem-like cell stemness and metastasis through SETDB1/PLK3/HIF1α signaling. Mol Cancer 23: 60, 2024.
43. Liu Y, Sun X, Wei C, Guo S, Song C, Zhang J and Bai J: Targeted drug nanodelivery and immunotherapy for combating tumor resistance. Comb Chem High Throughput Screen 28: 561-581, 2025.
44. Zhang Z, Li T, Li Y, Wang XI, Liu H, Shen X, Xu A, Xia T and Xu BO: Cancer stem cell specificity as new targets in breast tumor treatment. Oncol Res 33: 811-819, 2025.
45. Wang N, Ma T and Yu B: Targeting epigenetic regulators to overcome drug resistance in cancers. Signal Transduct Target Ther 8: 69, 2023.
46. Torabian P, Yousefi H, Fallah A, Moradi Z, Naderi T, Delavar MR, Ertas YN, Zarrabi A and Aref AR: Cancer stem cell-mediated drug resistance: A comprehensive gene expression profile analysis in breast cancer. Pathol Res Pract 246: 154482, 2023.
47. Dimitrakopoulos FI, Kottorou A and Tzezou A: Endocrine resistance and epigenetic reprogramming in estrogen receptor positive breast cancer. Cancer Lett 517: 55-65, 2021.
48. Buocikova V, Longhin EM, Pilalis E, Mastrokalou C, Miklikova S, Cihova M, Poturnayova A, Mackova K, Babelova A, Trnkova L, *et al*: Decitabine potentiates efficacy of doxorubicin in a preclinical trastuzumab-resistant HER2-positive breast cancer models. Biomed Pharmacother 147: 112662, 2022.
49. Zhu Y, Xia T, Chen DQ, Xiong X, Shi L, Zuo Y, Xiao H and Liu L: Promising role of protein arginine methyltransferases in overcoming anti-cancer drug resistance. Drug Resist Updat 72: 101016, 2024.

50. Qu L, Liu SJ, Zhang L, Liu JF, Zhou YJ, Zeng PH, Jing QC and Yin WJ: The role of m6A-mediated DNA damage repair in tumor development and chemoradiotherapy resistance. Cancer Control 31: 10732748241247170, 2024.
51. Tavares NT, Gumauskaite S, Lobo J, Jerónimo C and Henrique R: DNA methylation biomarkers for prediction of response to platinum-based chemotherapy: Where do we stand? Cancers (Basel) 14: 2918, 2022.
52. Gemma C, Lai CF, Singh AK, Belfiore A, Portman N, Milioli HZ, Periyasamy M, Raafat S, Nicholls AJ, Davies CM, *et al*: Induction of the TEAD coactivator VGLL1 by estrogen receptor-targeted therapy drives resistance in breast cancer. Cancer Res 84: 4283-4297, 2024.
53. Vijayaraghavalu S and Labhasetwar V: Nanogel-mediated delivery of a cocktail of epigenetic drugs plus doxorubicin overcomes drug resistance in breast cancer cells. Drug Deliv Transl Res 8: 1289-1299, 2018.
54. Wang W, Li M, Ponnusamy S, Chi Y, Xue J, Fahmy B, Fan M, Miranda-Carboni GA, Narayanan R, Wu J and Wu ZH: ABL1-dependent OTULIN phosphorylation promotes genotoxic Wnt/β-catenin activation to enhance drug resistance in breast cancers. Nat Commun 11: 3965, 2020.
55. Kang Y: Landscape of NcRNAs involved in drug resistance of breast cancer. Clin Transl Oncol 25: 1869-1892, 2023.
56. Shaikh M and Doshi G: Unraveling non-coding RNAs in breast cancer: Mechanistic insights and therapeutic potential. Med Oncol 42: 37, 2024.
57. Moradi F, Mohajerani F and Sadeghizadeh M: CCAT2 knockdown inhibits cell growth, and migration and promotes apoptosis through regulating the hsa-mir-145-5p/AKT3/mTOR axis in tamoxifen-resistant MCF7 cells. Life Sci 311: 121183, 2022.
58. Raju GSR, Pavitra E, Bandaru SS, Varaprasad GL, Nagaraju GP, Malla RR, Huh YS and Han YK: HOTAIR: A potential metastatic, drug-resistant and prognostic regulator of breast cancer. Mol Cancer 22: 65, 2023.
59. Ying Z, Wenjing S, Jing B, Songbin F and Kexian D: Advances in long non-coding RNA regulating drug resistance of cancer. Gene 887: 147726, 2023.
60. Yang S and Li D: The role of circRNA in breast cancer drug resistance. PeerJ 12: e18733, 2024.
61. Yan Y and Zhang J: Mechanisms of tamoxifen resistance: Insight from long non-coding RNAs. Front Oncol 14: 1458588, 2024.
62. Uppaluri KR, Challa HJ, Gaur A, Jain R, Krishna Vardhani K, Geddam A, Natya K, Aswini K, Palasamudram K and K SM: Unlocking the potential of non-coding RNAs in cancer research and therapy. Transl Oncol 35: 101730, 2023.
63. Tang H, Chen J, Jiang K, He J, Tang F, Li D and Wu Y: Unraveling the resistance: Challenges and advances in PARP inhibitor therapy for BRCA1/2 breast cancer. Anticancer Agents Med Chem 26: 268-277, 2026.
64. Wang C, Han X, Kong S, Zhang S, Ning H and Wu F: Deciphering the mechanisms of PARP inhibitor resistance in prostate cancer: Implications for precision medicine. Biomed Pharmacother 185: 117955, 2025.
65. Wiegmans AP, Ward A, Ivanova E, Duijf PHG, Adams MN, Najib IM, Van Oosterhout R, Sadowski MC, Kelly G, Morrical SW, *et al*: Genome instability and pressure on non-homologous end joining drives chemotherapy resistance via a DNA repair crisis switch in triple negative breast cancer. NAR Cancer 3: zcab022, 2021.
66. Sun Y, Patterson-Fortin J, Han S, Li Z, Nowicka Z, Hirohashi Y, Kilgas S, Yi JK, Spektor A, Fendler W, *et al*: 53BP1 loss elicits cGAS-STING-dependent antitumor immunity in ovarian and pancreatic cancer. Nat Commun 15: 6676, 2024.
67. Ma L, Chen W, Yang M, Ha S, Xiong S, Zhu J, Xiang H and Luo G: Discovery and proof of concept of potent dual Polθ/PARP inhibitors for efficient treatment of homologous recombination-deficient tumors. J Med Chem 67: 3606-3625, 2024.
68. Guacci A, Cordella A, Rocco T, Giurato G, Nassa G, Rizzo F, Carlomagno C, Pepe S, Tarallo R and Weisz A: Identification of a novel truncating mutation in PALB2 gene by a multigene sequencing panel for mutational screening of breast cancer risk-associated and related genes. J Clin Lab Anal 32: e22418, 2018.
69. Foo TK, Tischkowitz M, Simhadri S, Boshari T, Zayed N, Burke KA, Berman SH, Blecua P, Riaz N, Huo Y, *et al*: Compromised BRCA1-PALB2 interaction is associated with breast cancer risk. Oncogene 36: 4161-4170, 2017.
70. Foo TK and Xia B: BRCA1-dependent and independent recruitment of PALB2-BRCA2-RAD51 in the DNA damage response and cancer. Cancer Res 82: 3191-3197, 2022.
71. Dilmac S and Ozpolat B: Mechanisms of PARP-inhibitor-resistance in BRCA-mutated breast cancer and new therapeutic approaches. Cancers (Basel) 15: 3642, 2023.
72. Kefala Stavridi A, Appleby R, Liang S, Blundell TL and Chaplin AK: Druggable binding sites in the multicomponent assemblies that characterise DNA double-strand-break repair through non-homologous end joining. Essays Biochem 64: 791-806, 2020.
73. Brouwer I, Sitters G, Candelli A, Heerema SJ, Heller I, de Melo AJ, Zhang H, Normanno D, Modesti M, Peterman EJ and Wuite GJ: Sliding sleeves of XRCC4-XLF bridge DNA and connect fragments of broken DNA. Nature 535: 566-569, 2016.
74. Yang K, Guo R and Xu D: Non-homologous end joining: Advances and frontiers. Acta Biochim Biophys Sin (Shanghai) 48: 632-640, 2016.
75. Dong W, Zhang H, Zhuang Z and Jiang Y: PIPKIγ promotes non-homologous end joining through LIG4 to enhance radiotherapy resistance in triple-negative breast cancer. Cell Death Dis 16: 578, 2025.
76. Du J, Chen F, Yu J, Jiang L and Zhou M: The PI3K/mTOR inhibitor ompalisib suppresses nonhomologous end joining and sensitizes cancer cells to radio- and chemotherapy. Mol Cancer Res 19: 1889-1899, 2021.
77. Caracciolo D, Riillo C, Di Martino MT, Tagliaferri P and Tassone P: Alternative non-homologous end-joining: Error-prone DNA repair as cancer's achilles' heel. Cancers (Basel) 13: 1392, 2021.
78. Elsakrmy N, Zhang-Akiyama QM and Ramotar D: The base excision repair pathway in the nematode caenorhabditis elegans. Front Cell Dev Biol 8: 598860, 2020.
79. Antoniali G, Malfatti MC and Tell G: Unveiling the non-repair face of the Base excision repair pathway in RNA processing: A missing link between DNA repair and gene expression? DNA Repair (Amst) 56: 65-74, 2017.
80. Madders ECET and Parsons JL: Base excision repair in chromatin and the requirement for chromatin remodelling. Adv Exp Med Biol 1241: 59-75, 2020.
81. Caffrey PJ and Delaney S: Chromatin and other obstacles to base excision repair: Potential roles in carcinogenesis. Mutagenesis 35: 39-50, 2020.
82. Xin X, Wen T, Gong LB, Deng MM, Hou KZ, Xu L, Shi S, Qu XJ, Liu YP, Che XF and Teng YE: Inhibition of FEN1 increases arsenic trioxide-induced ROS accumulation and cell death: Novel therapeutic potential for triple negative breast cancer. Front Oncol 10: 425, 2020.
83. Chen HW, Kuo WH, Lu YS, Chen IC, Hu FC, Wang MY, Zahid M, Rogan EG, Cheng AL and Lin CH: Interaction of base excision repair gene polymorphism and estrogen-DNA adducts in breast cancer risk among East Asian women. Breast Cancer Res Treat 208: 283-292, 2024.
84. Li F, Sun H, Ren J, Zhang B, Hu X, Fang C, Lee J, Gu H and Ling D: A nuclease-mimetic platinum nanozyme induces concurrent DNA platination and oxidative cleavage to overcome cancer drug resistance. Nat Commun 13: 7361, 2022.
85. Borszéková Pulzová L, Ward TA and Chovanec M: XPA: DNA repair protein of significant clinical importance. Int J Mol Sci 21: 2182, 2020.
86. Szatkowska M and Zdrada-Nowak J: Genetic polymorphisms in base excision repair (BER) and nucleotide excision repair (NER) pathways as potential biomarkers for gynecological cancers: A comprehensive literature review. Cancers (Basel) 17: 2170, 2025.
87. Rajkumar-Calkins AS, Szalat R, Dreze M, Khan I, Frazier Z, Reznichenkov E, Schnorenberg MR, Tsai YF, Nguyen H, Kochupurakkal B, *et al*: Functional profiling of nucleotide excision repair in breast cancer. DNA Repair (Amst) 82: 102697, 2019.
88. Manandhar M, Boulware KS and Wood RD: The ERCC1 and ERCC4 (XPF) genes and gene products. Gene 569: 153-161, 2015.
89. Pietrasik S, Zajac G, Morawiec J, Soszynski M, Fila M and Blasiak J: Interplay between BRCA1 and GADD45A and its potential for nucleotide excision repair in breast cancer pathogenesis. Int J Mol Sci 21: 870, 2020.
90. Sun L, Fan G, Zhang Z, Chang D, Zhang X, Zhang T, Geng J, Zhang X, Lin M, Hu C, *et al*: Phosphorylation of SIRT7 by ATM causes DNA mismatch repair downregulation and adaptive mutability during chemotherapy. Cell Rep 44: 115269, 2025.
91. Eso Y, Shimizu T, Takeda H, Takai A and Marusawa H: Microsatellite instability and immune checkpoint inhibitors: Toward precision medicine against gastrointestinal and hepatobiliary cancers. J Gastroenterol 55: 15-26, 2020.

92. Ponnusamy L, Mahalingaiah PKS, Chang YW and Singh KP: Reversal of epigenetic aberrations associated with the acquisition of doxorubicin resistance restores drug sensitivity in breast cancer cells. Eur J Pharm Sci 123: 56-69, 2018.
93. Dasgupta H, Islam S, Alam N, Roy A, Roychoudhury S and Panda CK: Hypomethylation of mismatch repair genes MLH1 and MSH2 is associated with chemotolerance of breast carcinoma: Clinical significance. J Surg Oncol 119: 88-100, 2019.
94. Haricharan S, Punturi N, Singh P, Holloway KR, Anurag M, Schmelz J, Schmidt C, Lei JT, Suman V, Hunt K, *et al*: Loss of MutL disrupts CHK2-dependent cell-cycle control through CDK4/6 to promote intrinsic endocrine therapy resistance in primary breast cancer. Cancer Discov 7: 1168-1183, 2017.
95. Incorvaia L, Bazan Russo TD, Gristina V, Perez A, Brando C, Mujacic C, Di Giovanni E, Bono M, Contino S, Ferrante Bannera C, *et al*: The intersection of homologous recombination (HR) and mismatch repair (MMR) pathways in DNA repair-defective tumors. NPJ Precis Oncol 8: 190, 2024.
96. Niu Z, He J, Wang S, Xue B, Zhang H, Hou R, Xu Z, Sun J, He F and Pei X: Targeting glycolysis for treatment of breast cancer resistance: Current progress and future prospects. Int J Biol Sci 21: 2589-2605, 2025.
97. Lu C, Qiao P, Sun Y, Ren C and Yu Z: Positive regulation of PFKFB3 by PIM2 promotes glycolysis and paclitaxel resistance in breast cancer. Clin Transl Med 11: e400, 2021.
98. Jiang CF, Xie YX, Qian YC, Wang M, Liu LZ, Shu YQ, Bai XM and Jiang BH: TBX15/miR-152/KIF2C pathway regulates breast cancer doxorubicin resistance via promoting PKM2 ubiquitination. Cancer Cell Int 21: 542, 2021.
99. Lin J, Fang W, Xiang Z, Wang Q, Cheng H, Chen S, Fang J, Liu J, Wang Q, Lu Z and Ma L: Glycolytic enzyme HK2 promotes PD-L1 expression and breast cancer cell immune evasion. Front Immunol 14: 1189953, 2023.
100. Paul S, Ghosh S and Kumar S: Tumor glycolysis, an essential sweet tooth of tumor cells. Semin Cancer Biol 86: 1216-1230, 2022.
101. Fu W, Sun A and Dai H: Lipid metabolism involved in progression and drug resistance of breast cancer. Genes Dis 12: 101376, 2024.
102. Bian X, Liu R, Meng Y, Xing D, Xu D and Lu Z: Lipid metabolism and cancer. J Exp Med 218: e20201606, 2021.
103. Liang LC, Zhao L, Yu B, Hu HX, He XH and Zhang YM: Caffeic acid phenethyl ester reverses doxorubicin resistance in breast cancer cells via lipid metabolism regulation at least partly by suppressing the Akt/mTOR/SREBP1 pathway. Kaohsiung J Med Sci 39: 605-615, 2023.
104. Li J, Guo Y, Zhang W, Xia M, Liu G, Sun Y, Liu C and Zhong J: Cholesterol metabolism: A strategy for overcoming drug resistance in tumors. Biochem Pharmacol 238: 116974, 2025.
105. Hwang S, Park S, Kim JH, Bang SB, Kim HJ, Ka NL, Ko Y, Kim SS, Lim GY, Lee S, *et al*: Targeting HMG-CoA synthase 2 suppresses tamoxifen-resistant breast cancer growth by augmenting mitochondrial oxidative stress-mediated cell death. Life Sci 328: 121827, 2023.
106. Vishwa R, BharathwajChetty B, Girisa S, Aswani BS, Alqahtani MS, Abbas M, Hegde M and Kunnumakkara AB: Lipid metabolism and its implications in tumor cell plasticity and drug resistance: What we learned thus far? Cancer Metastasis Rev 43: 293-319, 2024.
107. Wan M, Pan S, Shan B, Diao H, Jin H, Wang Z, Wang W, Han S, Liu W, He J, *et al*: Lipid metabolic reprograming: The unsung hero in breast cancer progression and tumor microenvironment. Mol Cancer 24: 61, 2025.
108. Huang X, Liu B and Shen S: Lipid metabolism in breast cancer: From basic research to clinical application. Cancers (Basel) 17: 650, 2025.
109. Liu Y, Zong X, Altea-Manzano P and Fu J: Amino acid metabolism in breast cancer: Pathogenic drivers and therapeutic opportunities. Protein Cell 16: 506-531, 2025.
110. Yu C, Wang N, Chen X, Jiang Y, Luan Y, Qin W and He W: A photodynamic-mediated glutamine metabolic intervention nanodrug for triple negative breast cancer therapy. Mater Today Bio 19: 100577, 2023.
111. Choi H, Gupta M, Sengupta A, Furth EE, Hensley C, Weljie AM, Lee H, Lu YT, Pantel A, Mankoff D and Zhou R: Disruption of redox balance in glutaminolytic triple negative breast cancer by inhibition of glutaminase and glutamate export. Neoplasia 61: 101136, 2025.
112. Yang L, Chu Z, Liu M, Zou Q, Li J, Liu Q, Wang Y, Wang T, Xiang J and Wang B: Amino acid metabolism in immune cells: Essential regulators of the effector functions, and promising opportunities to enhance cancer immunotherapy. J Hematol Oncol 16: 59, 2023.
113. Yoo HC and Han JM: Amino acid metabolism in cancer drug resistance. Cells 11: 140, 2022.
114. Shi DD, Savani MR, Abdullah KG and McBrayer SK: Emerging roles of nucleotide metabolism in cancer. Trends Cancer 9: 624-635, 2023.
115. Lv Y, Wang X, Li X, Xu G, Bai Y, Wu J, Piao Y, Shi Y, Xiang R and Wang L: Nucleotide de novo synthesis increases breast cancer stemness and metastasis via cGMP-PKG-MAPK signaling pathway. PLoS Biol 18: e3000872, 2020.
116. Hany D, Vafeiadou V and Picard D: CRISPR-Cas9 screen reveals a role of purine synthesis for estrogen receptor α activity and tamoxifen resistance of breast cancer cells. Sci Adv 9: eadd3685, 2023.
117. Suleiman H, Emerson A, Wilson PM, Mulligan KA, Ladner RD and LaBonte MJ: Harnessing nucleotide metabolism and immunity in cancer: A tumour microenvironment perspective. FEBS J 292: 2155-2172, 2025.
118. Madsen HB, Peeters MJ, Straten PT and Desler C: Nucleotide metabolism in the regulation of tumor microenvironment and immune cell function. Curr Opin Biotechnol 84: 103008, 2023.
119. Viswanathan S, Parida S, Lingipilli BT, Krishnan R, Podipireddy DR and Muniraj N: Role of gut microbiota in breast cancer and drug resistance. Pathogens 12: 468, 2023.
120. Ma W, Zhang L, Chen W, Chang Z, Tu J, Qin Y, Yao Y, Dong M, Ding J, Li S, *et al*: Microbiota enterotoxigenic *Bacteroides fragilis*-secreted BFT-1 promotes breast cancer cell stemness and chemoresistance through its functional receptor NOD1. Protein Cell 15: 419-440, 2024.
121. Fu A, Yao B, Dong T, Chen Y, Yao J, Liu Y, Li H, Bai H, Liu X, Zhang Y, *et al*: Tumor-resident intracellular microbiota promotes metastatic colonization in breast cancer. Cell 185: 1356-1372. e26, 2022.
122. Wu H, Liu J, Zhang XH, Jin S, Li P, Liu H, Zhao L, Wang J, Zhao S, Tian HD, *et al*: The combination of flaxseed lignans and PD-1/PD-L1 inhibitor inhibits breast cancer growth via modulating gut microbiome and host immunity. Drug Resist Updat 80: 101222, 2025.