Review Article
Breast cancer: molecular mechanisms of underlying resistance and therapeutic approaches

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Abstract: Breast cancer (BC) affects over 250,000 women in the US each year. Drug-resistant cancer cells are responsible for most breast cancer fatalities. Scientists are developing novel chemotherapeutic drugs and targetted therapy combinations to overcome cancer cell resistance. Combining drugs can reduce the chances of a tumor developing resistance to treatment. Clinical research has shown that combination chemotherapy enhances or improves survival, depending on the patient’s response to treatment. Combination therapy is a highly successful supplemental cancer treatment. This review sheds light on intrinsic resistance to BC drugs and the importance of combination therapy for BC treatment. In addition to recurrence and metastasis of BC, the article discussed biomarkers for BC.

Keywords: Breast cancer, intrinsic/acquired resistance, breast cancer recurrence, breast cancer metastasis, breast cancer biomarkers, combination therapies

Introduction
The number of women diagnosed with BC in the US is estimated to be over 250,000 annually [1]. Better treatment choices have helped to reduce BC mortality in developed countries [2]. The advanced stage of BC diagnosis is likely a result of a failure in current BC prevention methods [3], which may have also contributed to an increase in BC incidence [1]. BC is diagnosed in one in eight women aged 85 or older in high-income countries. Preventing breast cancer may be the most cost-effective and socially beneficial strategy [4]. Different subtypes of BC are categorized by their histological appearance and the presence of hormone receptors and growth factors, like ER, PR, and ERBB2. There is a correlation between ER-positive breast cancer and cancer mortality [5-7]. BC is caused by a combination of inherited and non-hereditary risk factors. Various breast cancer-related single nucleotide polymorphisms are frequent in addition to BRCA1 and BRCA2 mutations [8].

Chemoresistance is a key issue in breast cancer treatment. Understanding their chemoresistance mechanisms is challenging. Additional effective treatments are urgently needed to address the drug resistance and improve current therapeutic regimens. The problem can be addressed with innovative agents and carriers of drugs and a combination of treatments. Other emerging medicines, like gene therapy and immune-based therapies, are being evaluated for their ability to overcome drug resistance [9, 10]. This review will discuss the intrinsic drug resistance to breast cancer therapy, breast cancer recurrence, metastasis, predictive biomarkers for breast cancer, and combination therapy to combat breast cancer.

Breast cancer metastasis
The metastatic process ends after a series of sequential steps have been completed [11]. If tumor cells have already invaded the surrounding host tissue, they can spread to lymphatic or blood vessels and other organs and tissues [12]. The cancer cells distribute throughout the body via blood and lymphatic veins. Angiogenesis and proliferation occur when tumor cells are in cell cycle arrest, preventing tumor cells from entering the target organ’s parenchy-
ma [13]. Both apoptosis and immunosuppression must be avoided [14]. If these phases successfully spread cancer, there may be “metastases of metastases” [15]. In its early stages, breast cancer can damage the auxiliary lymph nodes, lungs, bones, brain, liver, and peritoneum. BC that has spread to the bones is a regular occurrence. The metastatic spread of breast cancer tumors to the bones is approximately 67 percent. Breast tumors with luminal B (79%) and luminal A (70%) are more likely to metastasize to the bones, whereas HER2+ and TNBC (basal-like) have 60% and 40% chances, respectively. Breast cancer metastases are often found in the liver, auxiliary lymph nodes, and lungs. In about 37% of instances, advanced BC will spread to the liver and lungs, and 30-50% will spread to the auxiliary lymph nodes. TNBC with HER2+ liver metastases is less common than luminal breast cancer. TNBC has a 35% likelihood of metastasizing to the liver, while HER2+ has a 45% chance. TNBC has a higher risk of angiogenesis and infection of auxiliary lymph nodes than other subtypes. Luminal A and B had a reduced likelihood of metastasis in the lungs (25-30%) than TNBC and HER2+ (45-35%). Metastases to the liver, lungs, or brain can substantially reduce a patient’s survival time. Metastases to other organs affect 12.6 percent of cancer patients. TNBC and HER2+ breast tumors reported more metastases in this metastatic zone (25-30%) than Luminal A and Luminal B (5-15%). Less common metastatic locations include the mammary internal chain lymph nodes (10-40%), contralateral breast (6%), and supraclavicular lymph nodes (1-4%) [16]. Figure 1 displays a slew of distant breast cancer metastases.

The invasion of malignant cells is the first step in the metastasis process. Before tumor cells invade, their attachment to the extracellular matrix must be altered. The cadherin family, which increases cell-to-cell adhesion, has been linked to BC metastasis [17]. E-cadherin, a cell-to-cell adhesion protein, is required to spread metastatic BC cells [18]. E-cadherin downregulation has been linked to the progression and metastasis of BC, which has a poor prognosis [19, 20]. Breast cancer of the lobular type is associated with defective E-cadherin, resulting in its dysfunction [21]. Integrins play a role in tumor cell adhesion to the ECM [34]. The ECM is degraded during the invasion process. This enables invasion of tissue boundaries. ECM degradation is aided by metalloproteinases (MMPs) and the urokinase plasminogen activator system (UPA) [22, 23]. The UPA levels of BC patients are a reliable predictor of the development of distant metastases [24]. Patients with a good prognosis are also included in this group [25]. According to Huang et al., small interfering RNA (siRNA) suppression of UPA reduced invasion and MMP9 production. MMPs promote ECM proteolysis in breast cancer cell lines that invade the ECM’s invadopodia front [26, 27]. Tumor cells must have spread from their original location to other body parts to be considered invasive. Tumor cells can move both individually and in groups [28]. Tumor cells with high differentiation prefer ‘organized migration’ in breast lobular carcinoma [29]. Intercellular adhesion proteins may have structural and functional defects in poorly differentiated cancers that cause cell movement to shift from coordinated to single-cell migration [28]. Intercellular linkages must be established for tumor cells to migrate in groups. Following invasion and intravasation, emboli are discovered in blood and lymphatic arteries [30, 31].

Consider the “seed and soil” approach to understanding how cancer spreads. Tumor cells multiply when they contact suitable “soil” [32]. The tumor microenvironment is thought to influence metastasis [33]. The microenvironment in which metastatic tumor cells survive influences their proliferative ability. A favorable microenvironment is required for tumor growth and progression [34]. The microenvironment, which includes fibroblasts, immune cells, endothelial cells, and the ECM, regulates tumor growth [35].

Furthermore, tumor cells create pre-metastatic niches by producing chemicals that enrich the soil before metastasis [36]. The primary tumor sent signals that induced MMP9 synthesis in lung endothelial cells and macrophages, resulting in tumor invasion into the lungs before metastasis [37]. In the pre-metastatic lymph nodes of patients with early-stage BC, there is a cluster of VEGFR-1-positive hematopoietic progenitor cells [36]. Unlike other cancers, breast cancer prefers bone and lung metastases over other organs (such as the liver and brain) [38]. Metastasizing BC cells prefer the bone marrow and lungs as evidence of tissue
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Chemokines have been found to allow cancer cells to migrate to specific organs.

CXCL12, the chemokine ligand 12 found in breast cancer tissue, is not present in the brain, skin, or skeletal muscle, unlike the CXCR4 receptor and its ligand CXCL12 [41]. Metastatic breast cancer is more likely to spread to CXCL12-producing organs [42]. According to Muller et al., cancer cells can migrate to common sites of metastasis via a connection between CXCR4 and CXCL12 [41]. Tumor vascular growth is also required for metastasis. Angiogenesis is essential for metastasis initiation and progression [43]. It is a distinguishing feature of cancer and a necessary adaptation to the microenvironment for malignancies [44].
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As a result of carcinogenesis, pro-angiogenic and anti-angiogenic components become more evenly distributed \([45, 46]\). The ‘angiogenic switch’ process is influenced by some factors, including genetic changes and mechanical stress \([47, 48]\). Tumor vasculature differs from normal vasculature in form, function, and gene expression. Tumor hypoxia is caused by abnormal blood vessels’ insufficient oxygen delivery to the tumor \([49]\). Tumor cells produce more pro-angiogenic chemicals, leading to abnormal vasculature. As a result, the recursive pattern is repeated indefinitely. Invasive and metastatic mechanisms are activated to avoid the hypoxic environment produced by this cycle \([50]\).

**Breast cancer recurrence**

BC recurrence accounts for up to half of all fatalities \([51]\). Experts in breast cancer recurrence have been working worldwide to identify the causes. Other breast cancer subtypes, such as TNBC and all three estrogen, progesterone, and HER2/ErbB2 receptor-negative breast tumors, have also been studied. According to one study, the recurrence rates of breast cancer subtypes differ \([52, 53]\). In the first five years after diagnosis, recurrence rates for ER-negative breast cancers are higher than those for ER-positive BC. A decade after diagnosis, ER-positive breast tumor recurrence rates gradually increase for the next decade before leveling off at 15 years for both subtypes of BC. BC in situ is more likely to recur in women with low estrogen, progesterone, and testosterone levels than in women with high estrogen, progesterone, and testosterone levels \([54]\).

Lymph node metastases are common in late-stage BC and are associated with poor disease-free survival rates \([55]\). In addition, discovering genetic markers for lymph node metastases may help detect them early and reduce the risk of recurrence \([56]\).

Surgical intervention is an option for patients with advanced BC \([57]\). The type of surgery depends on the stage of the cancer. BC that is detected early is usually treated with radiation therapy and breast-conserving surgery \([58, 59]\). In most cases, additional radiation treatment is not required following a mastectomy \([60]\). Age, ductal carcinoma in situ, and lymph node involvement after mastectomy are risk factors for breast conservation therapy. Patients who choose a surgical approach based on clinical and histologic factors will need more personalized treatments and follow-ups \([61]\). Whether or not a patient had a mastectomy for BC, the chances of recurrence are the same. According to a meta-analysis, radiation therapy lowers the likelihood of recurrence \([62]\). Cancer patients with advanced BC who receive radiation therapy have been shown to have a 50% reduction in recurrence and death rates. This study discovered several additional variables that may influence radiation efficacy. The surgery required is affected by age, cancer grade, estrogen receptor status, and tamoxifen use.

According to a study, recurrence rates after mastectomy and BCS vary by molecular subtype. The 12,592 participants in the study had 57 percent breast conservation and 43 percent mastectomy. TNBC and HER2-positive cancers had lower recurrence rates after breast-conserving therapy. Postmastectomy recurrence, ER, and PR-positive patients performed better than TNBC and HER2. Patients with HER2-overexpression had a higher risk of recurrence after breast-conserving surgery than TNBC patients. The risk of recurrence in HER2-positive mastectomy patients was not higher than in TNBC patients. Thus, focusing on molecular subgroups is critical in treating breast cancer patients \([63]\). Some cancers begin recurring before being identified and mistakenly diagnosed as a single tumor. True local recurrences may never spread to other parts of the body. BC was suggested as a viable option for these studies due to the available clinical data. Oncogenes and wound healing (WOWH) theories may also be linked to cancer recurrence \([64]\). Precancerous lesions, cancer, oncogenesis, wound healing, and cancer recurrence are interconnected. In response to physical, chemical, or biological “wounds”, these oncogenes produce cytokines that cause stem cells to recruit and tissues to remodel (such as chronic inflammation, aging, or reactive oxygen species). All of this leads to the development of malignant tumors.

**Intrinsic/acquired drug resistance and mechanisms of resistance to breast cancer therapy**

Tumors that do not respond to treatment initially are considered intrinsically resistant,
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while those that have relapsed after responding initially are considered acquired resistant. Here we will shed light on the Intrinsic/acquired resistance and mechanisms involved in drug resistance.

Intrinsic/acquired drug resistance

Despite advances in BC treatment [65], chemotherapy helps most people with breast cancer but rarely cures metastatic cancer. Drug resistance is either innate or acquired. Innate and acquired resistance differ based on the classification of clinical resistance. Intrinsic resistance occurs when a patient does not improve after a single treatment attempt, whereas acquired resistance occurs after multiple therapy failures [66]. Anti-cancer cells have many built-in mechanisms for surviving chemotherapy treatment. The efflux pumps cause a reduction in drug concentration in cells [67] and a follow-up [68]. Enzymes such as cytochrome p450 and glutathione transferases that break down biochemically might degrade therapeutic substances [69, 70]. Drug concentrations may be reduced as a result of poor vascularisation [71, 72], ECM interactions, and compounds secreted into the tumor environment [73]. A drug's intrinsic resistance mechanisms play a key role in establishing the initial response to the drug and affecting subsequent outcomes that can lead to acquired resistance (Figure 2A).

Cancer cells’ resistance causes most breast cancer-related fatalities to commonly prescribed treatments. Scientists are working to better understand the genesis of cancer cell resistance and develop novel chemotherapeutic medications or combinations of targeted therapies to improve survival rates. Breast cancer targeted therapy necessitates the expression of specific proteins, such as ER and HER2. Clinical evidence suggests that when there is no ER, endocrine therapy is less likely to be successful [74, 75]. Preclinical research suggests that overexpression of HER2 is essential for trastuzumab response [76]. Targeted therapy depletes the ER and HER2 receptors, which is associated with a worse prognosis [77, 78]. Targeted therapy may not directly affect ER and HER2 expression. The selection of cancer cells under therapeutic stress is a classic example of clonal selection.

Taxanes and anthracycline are the most potent anti-cancer drugs. Anthracycline causes cell death by binding to topoisomerase II, resulting in DNA breakage [79]. Taxanes attach to α-tubulin and stabilize microtubules, causing mitotic arrest and cell death [80]. Topo-II and α-tubulin are involved in the regulation of target proteins. Topo-II expression and location

Figure 2. A. Illustrates the Extrinsic and intrinsic factors such as extracellular matrix proteins, P-gp pump and ABC transporter efflux, and cytochrome P450 and glutathione transferases that are involved in the pathogenesis of cancer. B. Resistance to anticancer drugs can be caused by several mechanisms. As shown in the diagram above, cancer cells can survive and relapse in multiple ways. The mechanism includes MDR1 and MRP genes, miRNAs, CSCs, TME, Hypoxia, Cell cycle checkpoints, Drug uptake, DNA repair, Apoptosis, Drug metabolism, Stress response, and microbiota important mechanisms.
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in the nucleus have influenced anthracycline sensitivity in preclinical mice [81]. Some cell lines’ responses have been linked to Topo-II levels [82]. Topo-II expression fluctuates in tumor tissues, and protein levels do not predict prognosis [83, 84]. Topo-II had an AUC of 0.8641 for breast cancer detection, accurately detecting it in 72.22 percent of patients. Compared to those with high or low Topo II and ERBB2 expression, those with low expression showed a considerably higher survival rate [85]. The response to anthracycline in tumors with high topo-II expression has been contradictory in clinical trials, with some studies indicating a better response and others demonstrating no link [81].

Taxanes influence mitosis and intracellular mobility via interfering with microtubule formation. Several isotypes of α-tubulin have been discovered based on variations in the C-terminus [86]. In breast cancer cell lines, tubulin polymerization occurs more slowly, and the stabilizing effect of taxanes is less efficient [87]. Some clinical studies have revealed that patients with high III-tubulin concentrations may not respond well to taxanes [88]; others have identified no such link [89]. In taxane-resistant breast cancer cells, Let-7c-5p and miR-335 are two significant regulatory variables. CXCL9, CCR7, and SOCS1 are the principal targets of two miRNAs [90].

Anthracycline and taxanes must have high intracellular concentrations to be effective. ATP-binding cassette transporters are drug efflux pumps. The role of ABC transporters (ABCA-ABCG) in human chemotherapeutic resistance is unknown [91, 92]. The luminal and biliary canal membranes of the renal tubules and the biliary canalicular cells of the liver aid in detoxification. The luminal membrane of the tubules contains drug efflux pumps [91]. ABCB1 (also known as efflux-related drug resistance in breast cancer) is a multidrug-resistant breast cancer gene that produces P-glycoprotein protein. This protein functions as a mediator. Higher levels of P-gp expression are typically reported in cancer cells that have survived chemotherapy treatment in vitro [93]. P-transmembrane gp sections attach to neutral or positively charged hydrophobic substances, causing the protein to confirm and release the bound drug into the cytoplasm [67]. There is a relationship between taxanes and P-broad gp substrate specificity. A meta-analysis of 31 single-institutional trials demonstrated P-gp expression in almost 40% of breast cancers [94]. Chemotherapy can target a clone of cells with overexpression of P-gp, either directly or by selective selection. However, because P-gp expression varies considerably between studies, using this biomarker to guide treatment selection in solid tumors is problematic. Currently, there is no evidence to support the use of this biomarker to select treatment options for a specific patient’s illness. The MRP1 can transport taxanes, anthracycline, and other hydrophobic substrates [67]. Preclinical research suggests MRP1 is implicated in breast cancer resistance, although early clinical trials have shown that MRP1 does not efficiently identify patients for treatment. Transporter proteins, such as pulmonary resistance-related proteins, are required to deliver drugs into cells [67]. Anthracycline cytoplasmic redistribution could be an effective mechanism for anthracycline resistance.

Mechanisms of breast cancer resistance

Because some breast cancer patients may relapse [95], we need to better understand the resistance mechanisms. The following are examples of breast cancer resistance mechanisms: drugs are degraded by enzyme systems, hormone receptors are influenced, and the cell membrane is involved in drug absorption, transportation, and efflux. In a xenograft model, trastuzumab modulates pro and antiangiogenic effects and normalizes and suppresses human HER2-overexpressing breast cancer vasculature. According to available data, trastuzumab affects cancer cells that are not dependent on VEGF production when injected intravenously [96]. Invivo, a decrease in micro-vessels was observed [97]. Compared to controls, tumor-bearing mice treated with trastuzumab had lower pro-angiogenic factors and higher antiangiogenic factors. The most important mechanisms of trastuzumab resistance in BC are illustrated in Figure 3.

Twist influences the invasion and metastasis of tumors as an epithelial-mesenchymal transition regulator. Many genes, including E-cadherin, use the E-box transcription initiation sequence. They allow non-invasive cells to invade if the function or expression of E-cadherin is reduced or eliminated. Twist, for instance, can be used to identify the E-box on the promoter...
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of E-cadherin and reduce transcription. As a result, cancer cells in the breast will spread more easily. With the use of Twist, cancer cells can become more resistant to chemotherapy [98]. It has been demonstrated that twist-1 upregulation is linked to chemotherapy resistance [99]. It has also been demonstrated that breast cancers with twist overexpression have a reduced ability to utilize the ER protein [100]. Breast cancer mediates resistance to cancer therapy via different mechanisms (Figure 2B).

**MDR1 and MRP gene in conferring resistance to breast cancer therapy**

In cancer, the MDR1 gene plays an important role in determining resistance to therapy. P-gp, GST-, and P53 are MDR1-encoded proteins linked to drug resistance [101]. Some potential molecular pathways were identified using aryl pyrimidine androstane derivatives that inhibit MDR1 in adenocarcinoma cells. There is evidence that the acetylation state of aryl pyrimidine influences their MDR1 inhibitory activity. We may discover new MDR1 inhibitors in the future that can reduce drug resistance and retrain cancer cells to respond to treatment [102]. ATP hydrolysis-dependent effluent transporters, such as MDR, are found in cancer cells [103]; MRP, ABCC subfamily, and breast cancer resistant protein are examples of ABC transporters [104]. In the presence of glycoprotein P-170 and P-150 overexpression, glutathione and DNA repair enzymes are increased, and DNA topoisomerase is reduced, promoting drug efflux.

Tumor cells may become resistant to treatment if MRP affects intracellular drug excretion and redistribution. MRP-mediated resistance is

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**Figure 3.** Both HER2 truncation and epitope masking reduce the amount of trastuzumab that can bind to HER2 in breast cancer. PI3K/Akt activity is also increased, and the Phosphodiesterase 1 (PDK1) gene has been changed. These pathways are being triggered at a considerably higher pace than they were previously. The immune system is also impaired.
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less potent than P-gp-mediated resistance [105, 106]. The BCRP transporter, unlike P-gp and MRP, is a half-size ABC superfamily member. There are many structural and functional similarities between the two. BCRP methotrexate, mitoxantrone, and camptothecin derivatives [107] have a much lower efflux capacity than P-gp and MRP1 [108].

Cryo-vaulted proteins contain LRP, an ABC transporter protein. In addition to preventing nuclear-targeted drugs from entering the nucleus, LRPs can transport anti-tumor medications into vesicles exocytosing from the cell membrane, reducing intracellular drug concentrations.

Role of miRNAs in mediating resistance to breast cancer treatment

According to a new study, miRNAs may regulate the chemosensitivity of BC cells. In the MCF-7 cell line, miR-451 and miR-326 were found to downregulate MDR-1 and MRP-1 expression, resulting in increased doxorubicin sensitivity [109, 110]. A decrease in ERα expression in BC cells can lead to resistance to endocrine therapy [111]. Let-7b/Let-7i, miR-221/222, miR-342-3p, and miR-873 inhibited tamoxifen-resistant breast cancer cells in vitro [112, 113]. Furthermore, miRNA influences ERα post-translational modification, affecting endocrine resistance [113]. MDR reversal may be facilitated by miRNA-129-inhibition of ABCB1 expression [114, 115]. miR-200c increases chemosensitivity by suppressing TUBB3, ZEB1, and ZEB2 in cancer cells [115]. Paclitaxel resistance can be aided by inhibiting the BAK1 [116]. MiR-218, which targets the BRCA1 gene, regulates cisplatin chemosensitivity in BC [116]. Treatment with curcumin had superior ORR and performance to paclitaxel and placebo after 12 weeks. Intravenous curcumin was well-tolerated and had little effect on patient outcomes [117]. Taxanes’ resistance to their effects is regulated by Let-7c-5p and miR-335-5p. Two miRNAs can also direct their activity to specific downstream cells. Taxanes have no effect on the Let-7c-5p/CCR7/SOCS1 axis or the miR-335-5p/CXCL9 axis. Furthermore, the axes miR-335-5p/CXCL9 and let-7c-5p/CCR7/SOCS1/CXCL9 may influence immune cell chemo-resistance [90].

Cancer stem cells and resistance to breast cancer therapy

Chemoresistance in BC is primarily caused by cancer stem cells (CSCs) [118]. ABC transporters over-expressed in CSCs include P-gp, ABCG2, ABCC1, and ABCB5. CSCs can develop drug resistance by increasing anti-apoptotic levels and repairing DNA [119]. ALDH1 over-expression has also been linked to CSC medication resistance [40]. Notch, Hedgehog [120], and Wnt/β-catenin, all involved in stem cell self-renewal and maintenance, may also be involved in CSC drug resistance. Less Let-7 microRNA is expressed in BC stem cells. The let-7 microRNA can assist BC stem cells in specializing and becoming more chemosensitive [121].

Cancer cells come in various morphologies and genotypes, resulting in a wide range of malignancies. There is intramura as well as patient-specific heterogeneity in cancer. Heterogeneity is aided by random gene expression and chromosomal rearrangement. It is widely assumed that cancer heterogeneity is caused by intrinsic causes [122, 123]. Additional tumor cell contacts and the paracrine signal are possible [124, 125]. Understanding tumor heterogeneity may result in more effective treatments and decrease drug resistance in breast cancer patients.

Hypoxia-mediated drug resistance to breast cancer therapy

Tumors use glycolysis as their sole source of energy during hypoxia. Hypoxia-induced increases in metabolic enzyme production may render chemotherapy ineffective [126]. Researchers discovered that hypoxia reduced Topo II expression in cancer cells, making them more resistant to chemotherapy [127]. Hypoxia-induced MRP expression influences tumor resistance as well. If the glycolysis process is blocked in anoxic circumstances, drug-resistant cancer cells may become sensitive to chemotherapeutic treatments again [128]. Under hypoxic conditions, HIF-1 forms a heterodimer in both animals and humans. Hypoxic environments can harm HIF-1, which is sensitive to oxygen concentration. As a result, HIF-1 modulates HIF-1 activity. MDR1 refers to the P-coding gp's gene MDR1 in the context of hypoxia. MDR1 has hypoxia response elements.
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(HREs) that bind to and influence P-gp expression [129]. HIF-1 and HIF-2 bind to the HRE on the BCRP gene promoter to initiate BCRP expression and, as a result, produce BCRP1 overexpression [130, 131].

Cancer cells that can move to other body parts are more likely to resist treatment [132, 133]. The proton pump (H+)-vacuolar-ATPase (V-ATPase) can change tissue pH. The V-ATPase transfers H+ into the acidic vacuole lumen and/or into the external environment. This proton pump was discovered to be more common in cancer patients [134, 135].

When breast cancer cells connect and communicate with stromal cells, they may activate paracrine and neighboring signaling pathways. This could contribute to chemotherapy resistance mediated by stromal cells [136]. HS5 stromal cell signaling reduced the amount of MCF7 breast cancer cells [137].

Tumor microenvironment and resistance to breast cancer therapy

The tumor microenvironment comprises interstitial tissues, extracellular matrix, and stromal cells [138]. The biological elements of the microenvironment include TAM, mesenchymal cells, endothelial cells, and CAF [139]. The cathepsin-dependent function of macrophages can shield cancer cells from the harmful effects of chemotherapy [140]. TAMs and their products regulate cancer cell behavior [141, 142]. TAMs can be targeted in conjunction with chemotherapy [143]. When exposed to TM, normal mesenchymal cells are less susceptible to drugs than tumor-resident mesenchymal cells [144]. Research shows mesenchymal stem cells (MSCs) are particularly resistant to paclitaxel [145]. MSCs are also anti-tumors in breast cancer, which is noteworthy [146]. A study revealed an increase in B lymphocytes in draining lymph nodes based on a mouse model of spontaneously metastasized breast cancer lymph nodes. Pathogenic IgG was generated, which activated the HSPA4-binding protein ITGB5 and downstream Src/NF-kB pathways in tumor cells, increasing CXCR4/SDF1-axis-mediated metastasis. There was an increase in serum anti-HSPA4 IgG levels in breast cancer patients with high HSPA4 levels and a poor prognosis in patients with high HSPA4 levels [147].

Drug uptake and resistance to cancer therapy

Developing feasible targeted therapies for breast cancer is difficult due to inherent and/or acquired resistance to chemotherapy. Many signaling pathways and mutations or changes in protein expression have been linked to breast cancer resistance [148]. Evidence suggests that P-gp/MRP1/BCRP, and other members of the drug efflux ABC transporter family, are elevated significantly in resistant breast cancer cells [149]. Further research is required to improve dose-response results and reduce the side effects of de novo and acquired resistance.

Cell cycle checkpoints and resistance to breast cancer therapy

Genomic instability enhances tumor heterogeneity and determines treatment resistance in breast cancer [150]. Cancer cells acquire genetic changes that alter signaling pathways and cellular checkpoints during cancerous transformation. These changes typically prevent genomic instability and uncontrolled cell proliferation. Thus, therapeutic cell cycle targeting has long been considered a viable anticancer treatment. In cancer therapy, selective cell cycle inhibitors have been unable to be used due to poor target specificity and undesirable toxicities. We have identified a therapeutic window that permits us to preferentially target the cell cycle in cancer cells through advances in our understanding of the vulnerabilities of malignant cells, resulting in the development of drugs currently under clinical trials [151]. Activation of the G1/S transition is inhibited by CDK4/6-dependent Rb1 inactivation, resulting in resistance to CDK4/6 inhibition. Understanding the relative contributions of different acquired resistance mechanisms in larger clinical datasets will be easier if we examine paired tumor or liquid biopsies obtained before and after treatment. Through a better understanding of these mechanisms, combination therapies and strategies will almost certainly be developed for preventing or overcoming CDK4/6 inhibitor resistance. In preclinical studies, breast cancer models have shown promise...
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from CDK4/6 inhibitors combined with AKT pathway/mTOR inhibitors [152].

Drug metabolism and breast cancer resistance

The redox balance pathways are implicated in drug resistance to various anticancer treatments. Therefore, redox metabolism may be the key to improving medication responsiveness and combating multidrug resistance. Pharmacological impacts affect the circulating as well as intratumorally metabolome of a patient. A metabolic approach can be used to determine whether breast cancer treatments are effective and safe. Drug-resistant breast cancer cells demonstrate increased glycolysis no matter what type of chemotherapy they receive. Nevertheless, the regulation of this enhanced activity varies between resistant breast cancers. Therefore, drug-induced metabolic profiles vary [153].

In addition, the Warburg effect has been linked to drug resistance, suggesting that cancer cells with a high glycolytic rate are better able to resist anticancer treatment [154]. Higher glycolytic rates may restrict lactate production and acidification of the extracellular space. Overexpressed glycolytic regulators such as PDK1 and LDHA are targets for drug-resistant cancers. SKBR3 breast cancer cells produced more glucose-related genes than sensitive cells, resulting in a worse patient outcome. In addition to glucose transporters and glycolytic enzymes, oxidation routes have also been found [155]. ErbB2-positive breast cancer cells that are resistant to trastuzumab are more susceptible to LDHA-induced glycolysis.

Furthermore, using 2-DG with oxamate to block glycolysis resensitizes cells resistant to trastuzumab [156]. Oxamate and paclitaxel-induced synergistic apoptosis in paclitaxel-resistant breast cancer cells [157]. Each type of cancer uses a different metabolic pathway. Different drugs and drug combinations produce different efficacy and toxicity results in different patients. Malignancies and patients resistant to therapy must be detected early and treated with correct drugs.

DNA repair and resistance to breast cancer therapy

Most cancer patients fail due to treatment resistance. DNA repair capacity (DRC) of tumor cells is associated with chemoradiotherapy, targeted therapy, and immunotherapy resistance. Cisplatin is one common chemotherapy agent that damages DNA. Cisplatin was initially effective but then resistant in a mouse model of human lung cancer [158]. DNA damage repair genes and DRC were more abundant in tumors resistant to cisplatin. By inhibiting the NER pathway, tumor cells were more susceptible to cisplatin [159]. It has been shown that 53BP1, a DDR protein involved in breast preservation, is linked with local recurrence in patients with TNBC treated by breast-conserving surgery and radiotherapy [160]. Doxorubicin (DOX) resistance could also be prevented by inhibiting DNA repair kinases in breast cancer cells [161]. In CDK4/6 inhibitors of palbociclib-resistant breast cancer cells, abnormal DNA repair activity was identified; however, PARP inhibitors, olaparib, and niraparib therapy dramatically reduced palbociclib-resistant cancer cell viability [162]. The PARP inhibitor olaparib significantly increased CD8+ T-cell recruitment and activation by stimulating the cGAS/STING pathway in BRCA1-deficient triple-negative breast cancer [163].

Immuno-checkpoint inhibitors and DDR inhibitors are combined for TNBC or ovarian cancer patients, including Niraparib and pembroliuzumab (NCT02657889). Phase I, multicentre, dose-escalation trials are conducted on AZD1775 (Adavosertib) and MEDI4736 (durvalumab). DNA repair might play an important role in cancer therapy resistance; evaluating DNA repair phenotypes before treatment would be useful [164].

Stress response and breast cancer resistance

Cancer cells live in a dynamic microenvironment that determines their behavior. Therefore, simple models linking cellular stress with cancer progression should be cautiously treated. Crosstalk between cells adds complexity. ROS levels impact oxidative, metabolic, and genotoxic stress. It will be fascinating to determine the level of ROS necessary to produce a particular stress response in the future. We may be able to develop better techniques to target drug-resistant cancer cells if we view drug resistance as a cellular adaptation to severe conditions. Studying cellular responses to immune inhibitors and activators is essential for cancer immunotherapy.
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Several regulatory enzymes and transcription factors (AMPK, HIFα, PGC1α) in the metabolic stress response network can be targeted pharmacologically [165]. In response to MYC-induced metabolic stress, glutaminase and lactate dehydrogenase inhibitors reduce tumor growth by inhibiting the flow of nutrients needed for cancer cell proliferation [166, 167]. Several therapeutic options have been considered for MYC-induced metabolic stress, including manipulating the response pathways involved. A triple-negative breast cancer model showed efficacy with inhibition of IRE1/XBP1, and a hepatocellular carcinoma model showed efficacy with inhibition of ARK5/AMPK [168]. Among the three primary methods under evaluation, pre-clinical/clinical studies have focused on targeting cell contractility, solid stress, and ECM stiffness [169, 170]. As far as treating cancer with the stiffness of the ECM is concerned, it is more effective in solid tumors like breast cancer combined with celecoxib, β-aminopropionitrile, transforming growth factor- and hedgehog signaling inhibitors [171].

A combination of stress-targeted drugs and standard/conventional therapy could develop more effective therapeutic techniques in the future by targeting cellular stress responses. A better understanding of the stress responses of cancer cells is needed to make these drugs effective.

Apoptosis and breast cancer resistance

Planned cell death, or apoptosis, is critical for tissue homeostasis and the removal of abnormal cells [172]. Several therapies may overcome apoptotic resistance. These include downregulation of anti-apoptotic signaling, death-inducing ligands, and caspase gene expression [173]. It has been shown that death receptor ligands such as Fas-L and TRAIL cause apoptosis in breast cancer cells [174]. TRAIL significantly enhances apoptotic cell death and drug sensitivity when administered with chemotherapy drugs. However, chemotherapy alone cannot induce cell death in breast cancer cells [175].

Furthermore, Curcumin reduced primary and metastatic tumor cell proliferation and induced apoptosis, according to a recent study. Metastatic tumor cells, however, exhibited greater resistance to curcumin’s apoptotic action. DR-5 was linked with resistance to apoptosis. DR-5 was significantly upregulated in primary tumor cells following curcumin treatment, compared with metastatic cells [176].

Microbiota and breast cancer resistance

Researchers have identified gut microbiota dysbiosis as a key factor in BC’s development, treatment, and prognosis in recent years. These processes include proliferation and death of host cells, immune system function, chronic inflammation, oncogenic signaling, hormonal changes, and detoxification processes. Colonization of the gut begins during pregnancy and progresses throughout life. There was a difference in the fecal microbiota composition in newly diagnosed postmenopausal BC patients compared to healthy controls. Bacteria that produce β-glucuronidase modulate enterohepatic circulation and estrogen resorption, increasing the risk of hormone-dependent BC. The risk and prognosis of BC are known to be affected by bacterial metabolites, including phytoestrogens, short-chain fatty acids, lithocholic acid, and cadaverine [177]. Inhibition of DNA synthesis occurs with gemcitabine (2’,2’-difluorodeoxycytidine). Gamma proteobacteria, mostly from the Gammaproteobacteria class, can metabolize gemcitabine in its inactive form (2’,2’-difluorodeoxuryridine). This metabolism requires the bacterial enzyme cytidine deaminase, found only in this family of bacteria. Co-administered ciprofloxacin reversed Gemcitabine resistance caused by intratumoral Gamma proteobacteria in a cancer mouse model, indicating that these bacteria are involved in the drug’s failure [178, 179]. A recent study provides evidence for a novel role for local microbiome–immune crosstalk in breast cancer and identifies breast microbial profiles linked to various prognostic clinical variables. This study provides a starting point for further research into how microbial–immune interactions affect breast cancer development and progression. There is also a need for further research on how these microbes mediate resistance to cancer therapies.

Predictive biomarkers for breast cancer

Compared to prognostic biomarkers, predictive biomarkers provide better predictions of patient response. Breast cancer was the first to use treatment efficacy predictors. Although ER
and PR measurements have been used in clinical practice for over 40 years, the benefit of Trastuzumab has only been demonstrated in the last 15 years. ER, or ER-alpha, is the most important breast cancer biomarker. The estrogen receptor (ER) must measure all newly diagnosed breast cancers, and recurrent/metastatic lesions must be measured by the estrogen receptor (ER). While prognostic information is useful in endocrine therapy, predictive biomarkers are the primary clinical application of ER. Endocrine therapy should be initiated or considered if an ER test results positively. Hormones are unnecessary in the absence of an ER. Cancer patients are given Endocrine Therapy (ER) in the early, middle, and late stages of the disease [180, 181]. Because estrogens, particularly estradiol, are required for the growth of some BC, endocrine therapy is used to treat it.

MYC and cyclin D regulate gene regulatory elements associated with estrogens [182]. Because estrogens promote tumor growth by binding to and activating ER, ER levels correlate with antiestrogen efficacy in BC. In patients with advanced BC who tested positive for estrogen receptors, endocrine therapies such as ovariectomy, adrenalectomy, and hypophysectomy resulted in objective regression. Malignancies that lacked an ER receptor had a very poor prognosis [181]. While it is still possible to use ER to identify advanced patients with breast cancer, it is more commonly used to determine which patients require adjuvant treatment such as oophorectomy and tamoxifen or aromatase inhibitors anastrozole or letrozole, or exemestane. In advanced breast cancer patients, endocrine therapies such as tamoxifen predict response and determine which patients require adjuvant tamoxifen treatment. These treatments slow breast cancer progression by targeting the ER protein. These drugs should only be used by patients who have ER-positive cancer. There is no such thing as drug resistance specific to a class [182]. Although ESR1 wild type is a reliable predictor of therapy benefit, ESR1 mutations are linked to endocrine therapy resistance. These mutations are more likely to be discovered if a patient has recurrent/metastatic breast cancer [183, 184]. Most ER ligand-binding domain mutations, such as D538G, Y537S, E380Q, Y537C, or Y537N, cause cancer [183, 185]. These mutations resulted in a lack of sensitivity to aromatase inhibitors and the inability of tamoxifen and fulvestrant to inhibit estrogen receptors in vitro [183, 184]. The Y537S mutation is most likely responsible for ligand-independent activation [185]. The doses of fulvestrant required to inhibit Y537S are higher than for other ER mutants (D538G, Y337C) and wild-type ER (such as Y537S) [185].

Y537S mutation can cause ligand-independent activation. The only other ER mutants, D538G and Y337C, require a lower hormone dose, whereas the wild type requires a much higher dose [186]. Overexpression of HER2 may help tumor growth by deforming cell membranes. A deformed cell loses its attachments to the extracellular matrix and other cells, increasing the possibilities of invasion [187]. Most HER2-positive breast cancers do not spread; only 15-20% do. Cancers that are HER2-positive are more common in ER-negative women than ER-positive cancers. Amplification/overexpression of the HER2 gene is found in 30% of ER-negative tumor samples but only in 12% of ER-positive tumor samples [188]. Breast cancer biomarkers were first proposed, but they are currently only used to predict the efficacy of anti-HER2 therapy after treatment.

In the United States and Europe, trastuzumab, lapatinib, pertuzumab, and trastuzumab emtansine are currently used to treat HER2-positive breast cancer [189]. Based on the evidence, amplification or overexpression of the HER2 gene appears to be required for these treatments. Anti-HER2 therapies are currently only available to those with the HER2 gene mutation. Trastuzumab, an anti-HER2 treatment, is one of the most studied and approved treatments for metastatic breast cancer. Trastuzumab and chemotherapy resulted in pathologically complete remission in more than half of HER2-positive patients, compared to 19-27 percent of those treated with chemotherapy alone [190]. The current evidence suggests that these treatments require HER2 gene amplification or overexpression. Anti-HER2 therapies are now available for patients with HER2 mutations. The most researched and approved treatment for metastatic breast cancer is chemotherapy. In more than half of HER2-positive patients, trastuzumab plus chemotherapy resulted in pathologically com-
complete tumor remission [190]. Due to the benefits of dual anti-HER2 therapy in neoadjuvant and advanced-stage cancer patients, it is important to identify those who will benefit the most. There should be a list of patients who do not require dual anti-HER2 therapy. Patients with these molecular subtypes had a higher chance of achieving a partial response than patients with other molecular subtypes. Trastuzumab-lapatinib achieved pCR in 41 percent of 101 HER2-enriched patients compared to only 5 percent of non-HER2-enriched patients [191]. HER2 levels are directly related to ER, PR, and other hormones. Because HER2 levels are higher in ER-negative tumors, anti-HER2 therapy may be more effective. According to preliminary anti-HER2 therapy studies, patients with HER2-negative tumors had higher partial response rates than those with HER2-positive tumors. Two monoclonal antibodies plus chemotherapy or two monoclonal antibodies alone produced the highest partial response rates in breast cancer patients. Only 63 percent of patients achieved partial responses in triple therapy, while only 20 percent received the treatment. Patients with receptor-negative cancer responded at 29.1 percent, while those with receptor-positive cancer responded at only 5.9 percent. TILs and PIK3CA mutation status should not be used to decide on anti-HER2 therapy [192].

Therapeutic approaches for breast cancer

The risk of BC can be assessed by using risk assessment tools, and individuals identified as high risks may be given risk-reducing medications. Regarding breast cancer treatment, an individual's menopausal status influences the medication they choose. The type of medication they choose varies with the stage of the disease. It may evolve into invasive cancer in 40 percent of individuals with Stage 0 ductal carcinoma in situ [193]. There are a number of options available for BC treatment.

Targeting HER2 pathway

Women with BC who have HER2 as a therapeutic target are in the majority. There is also overexpression of HER2 in certain subsets of patients with other solid tumors, including NSCLC, colon cancer, and biliary tract cancer. HER2 can be targeted in several ways, as discussed below.

Targeting HER2 via trastuzumab

The HER2 receptor is one of four tyrosine kinase (TK) receptors (HER1-4), that control vital cell activities (Figure 4) [194]. HER contains extracellular, transmembrane, and intracellular TTK domains. When these domains interact, signaling pathways for proliferation, apoptosis, invasion, metastasis, angiogenesis, and cell differentiation are activated. Herceptin is a type of antibody to be approved to treat HER2-positive BC. Herceptin is designed to attach to the HER2 extracellular area and decrease cell proliferation in HER2-positive BC models [195]. Inhibition of cell signaling is not completely clear in terms of molecular mechanisms, but data suggest that it is more effective against homodimers of HER2 than heterodimers [196, 197]. In addition to triggering antibody-dependent cytotoxicity, trastuzumab may cause cell apoptosis [198]. Because of the above reasons, preclinical studies indicate a synergistic impact with certain chemotherapy drugs [199, 200]. Trastuzumab was first tested on patients with metastatic BC who had been highly pretreated. The response rates were poor, with only a single example of a complete reaction and 10-15 percent of patients reporting a partial response. Researchers observed that untreated metastatic cancers with HER2-overexpression had higher partial and full responses (26 percent) after single-agent treatment [201]. The inhibition of HER2 only worked in oncogene addiction (gene amplification) cancers. Trastuzumab was also well tolerated but can cause cardiomyopathy in some patients, particularly those who have previously taken doxorubicin or uncontrolled hypertension [202, 203]. Trastuzumab interacts synergistically or additively with alkylating medicines, platinum medications, topoisomerase inhibitors, anthracyclines, and taxanes [199, 200]. In the most important early trial, chemotherapy with doxorubicin and cyclosphosphamide versus chemotherapy plus trastuzumab was compared in HER2+ patients with metastatic disease [203]. FDA approved trastuzumab as a cancer therapy after it significantly increased response rate (50 versus 32%), time to progression (7.4 versus 4.6 months), and overall survival (25 versus 20 months). Importantly, when doxorubicin and
trastuzumab were given together, the trial demonstrated a high prevalence of cardiac dysfunction. The past decade has seen many trastuzumab trials in patients with HER2+ metastatic cancer, which showed that it is more effective when taken in conjunction with other drugs such as vinorelbine and docetaxel, and gemcitabine [204].

As a result of the increased risk of side effects, trastuzumab is usually not given alongside chemotherapy [205, 206]. Studies looking at the combination of chemotherapy and trastuzumab have not shown any benefit in OS. The combination of carboplatin to chemotherapy and trastuzumab was studied in the Breast Cancer International Research Group study 007 [205]. Trastuzumab and paclitaxel with carboplatin or without were randomized for 196 patients. In the triple therapy group, response rates were higher. Although OS was not significantly different, doublet chemotherapy was linked with enhanced toxicity, limiting its clinical significance [206]. An indication of

Figure 4. HER2 is a cancer-causing gene with four membrane tyrosine kinase receptors (HER1-HER4), a molecular switch, and more than ten ligands. Ligand binding causes a conformational change in HER1, HER3, and HER4 that facilitates homo- or heterodimerization with another family member. HER2, which is gene-amplified and/or overexpressed in 20% of breast cancers, lacks a ligand and lies in an open conformation in the membrane. Due to its heterodimerization capability and increased expression, HER2 activates itself by homodimerizing with other ligand-bound HER members. In response to dimerization of the HER receptors, their TKs are activated. This initiates a phosphorylation cascade, which triggers downstream signaling pathways, including Ras/p42/44 MAPK and PI3K/AKT. By modifying and phosphorylating transcription factors and other parts of the transcription and cell-cycle machinery, downstream kinases stimulate the transcriptional and cell-cycle machinery. As a result, tumor cells can be stimulated to proliferate, survive, become angiogenic, and metastatic. Because HER3’s TK is inactive (X), the downstream signaling pathway can only be activated by heterodimerization with other HER members. According to the FDA, the HER2-targeted drugs approved for treating HER2+ breast cancer are trastuzumab, pertuzumab, trastuzumab DMT-1, and lapatinib.
congestive heart failure is the most serious contraindication to HER2-targeted treatments [207]. Trastuzumab and pertuzumab were similarly effective as first-line treatments for HER2-positive metastatic BC patients. After removing patients with de novo illness from the trial, taxanes were found not to affect progression-free survival (PFS) [208].

HER2-targeted therapy offered improved responses, longer PFS, longer TTP, and longer OS when combined with chemotherapy in the first-line setting. In this study, HER2-targeted therapy combined with chemotherapy was linked to improved MBC treatment results as a first-line treatment.

Targeting HER2 via lapatinib

A tyrosine kinase inhibitor small molecule called lapatinib targets EGFR1 and human HER2. After oral treatment, lapatinib has a half-life of 24 hours, with peak plasma levels occurring within 4 hours and steady-state levels establishing 6-7 days later [209]. For HER2-positive MBC resistant to anthracyclines, taxanes, or trastuzumab-based regimens, lapatinib and capecitabine are authorized as second-line combination therapy [209]. When used in conjunction with chemotherapy, lapatinib is also effective as first-line therapy, though it may not be as effective as trastuzumab-based therapy [210, 211]. Lapatinib has been studied as a first-line treatment in two phase III studies, one of which compared lapatinib to a placebo. Paclitaxel plus lapatinib or placebo were administered to participants who had never received chemotherapy for metastatic illness [210]. The MA.31 trial compared paclitaxel 80 mg/m² three times a week with lapatinib or trastuzumab as first-line anti-HER2 therapy, followed by anti-HER2 monotherapy [211]. According to the existing evidence, trastuzumab-based regimens are still regarded standard of therapy in this situation.

Targeting HER2 via neratinib

Upon administration, neratinib binds to and inhibits the phosphorylation of EGFR, HER2, HER4, AKT, and MEK in HER2-overexpressing BC cell lines [212]. The orally administered drug, neratinib, inhibits several EGFR family members by interfering with their respective catalytic domains. Four hundred and seventy-nine women with HER2-positive recurring and/or metastatic BC were randomized evenly between neratinib-paclitaxel and trastuzumab-paclitaxel in the NEOFERT-T study [213]. Using neratinib-paclitaxel as a first-line treatment for metastatic HER2-positive BC has been found to delay the onset of and reduce the incidence of central nervous system side effects. Diarrhea (30.4 percent) and neutropenia were the most common adverse effects (12.9 percent).

Targeting HER2 via toralizumab

The dimerization of HER2 with HER1, HER3, and HER4 results in the strongest mitogenic stimulus, activating PI3K and MAPK and therefore promoting cell survival and growth [214]. HER2 dimerization with other HER receptors is prevented by toralizumab, a potent inhibitor of double HER2 signaling [215]. Although epratuzumab and trastuzumab bind different epitopes of HER2, the antibodies are more effective when used together than if used alone since they block signals from multiple epitopes [215]. Phase II studies demonstrated that epratuzumab, whether given alone or combined with trastuzumab or other cytotoxic drugs, was generally well tolerated; they also suggested combining epratuzumab and trastuzumab boosted efficacy for early and advanced HER2-positive BC [216]. The CLEOPATRA study showed that epratuzumab, trastuzumab, and docetaxel were more effective than placebo, trastuzumab, and docetaxel [217].

The CLEOPATRA study found that epratuzumab increased PFS in all biomarker subgroups, including ER-negative and ER-positive women [218]. Patients with PIK3CA alpha or low HER2 protein levels had a considerably better prognosis than those with high HER2 protein levels (P 0.05). Patients with malignancies that expressed wild-type PIK3CA had a higher median survival rate than those with mutant Pik3CA in both the control and epratuzumab groups. Patients with MBC who got lapatinib with capecitabine but not T-DM1 had a worse prognosis. New biomarkers have the potential to refine and optimize therapy for specific patient subgroups in the future.

Targeting the hedgehog signaling pathway in breast cancer

There are various strategies for inhibiting the Hh pathway, including antibodies that target Hh ligands, SMO inhibition, and GLI [219, 220].
Breast cancer resistance and therapeutic approaches

Cyclopamine has limited clinical effectiveness due to its low potency and poor solubility [221]. SMO inhibitors such as sonidegib [222] and taladegib [223, 224] are FDA-approved to treat advanced cell carcinoma. Other SMO inhibitors, including saridegib [225], taladegib [223], and glasdegib [226], are also being tested. In basal cell carcinomas, SMO mutations can cause secondary resistance [227]. Due to its unique method of action compared to other SMO antagonists, SMO antagonist itraconazole appears to preserve Hh inhibition even in mutants resistant to drug-resistant SMOs [228].

The GLI1 protein is activated by pathways other than the canonical ones in several cancers, including breast cancer. Direct activation of the GLI1 protein is one mechanism of resistance to SMO inhibitors. GLI might be treated effectively by targeting it with drugs like PI3K inhibitors and other chemotherapy agents [229]. In preclinical studies, GANT61 is the most effective antagonist. However, no clinical data demonstrate the efficacy of GANT58 [219, 230]. Vismodegib and GANT61 reduced tumor growth in another xenograft model using TUBO cells [231]. With GANT61, the degree of tumor regression and the duration of tumor remission were significantly longer than with vismodegib, an SMO inhibitor. In 80 percent of mice, GANT61 produced complete tumor regression and remission, and these animals remained tumor-free for 30 weeks [231]. In GLI1 overexpressing breast cancer cell lines, GANT61 significantly reduced cell proliferation, motility, and invasion [232]. This research provides significant preclinical evidence that GANT61 could be used in clinical trials in BC patients.

In xenograft mouse models derived from human patients, SMO inhibitor treatment increased the susceptibility of tumors to docetaxel chemotherapy [223]. The result was the phase I “3 + 3” trial of sonidegib combined with docetaxel for metastatic TNBC. Patients with metastatic TNBC benefited clinically from combination therapy in 3/10 cases (3/10 at recommended doses in phase 2), one of whom had a complete response [234]. No dose-limiting toxicities were observed in the clinical trial with vismodegib and standard neoadjuvant chemotherapy, cyclophosphamide, and epirubicin. Patients are being included in ongoing clinical trials to see the treatment's influence on the pathological complete response rate in patients with locally advanced TNBC.

Targeting notch signaling pathway in breast cancer

A study using ER+ BC lines identified Notch activation as a mechanism of resistance to endocrine therapy, and the potential use of genetic or pharmacologic treatments to inhibit Notch1 or Notch4 reversed it. The first Notch inhibitor was a GSI, which inhibited the final cleavage of NotchIC and inhibited Notch target gene activation. When combined with tamoxifen, the GSI significantly reduced the growth of ER+ T47D cells and led to extensive cell death in T47D-A18 xenograft tumors [235]. In mice, cells taken from tumors treated with RO49-29097 GSI reduced tumor-initiating capacity and ALDH activity 90 days after implantation [236]. Compared to LY-411,575, MRK-003, and Z-Leu-Leu-Nle-CHO GSIs, Z-Leu-Leu-Nle-CHO or MRK003 GSIs led to significant reductions in mammosphere formation, whereas LY-411,575 had a non-significant reduction [237]. In vitro and in vivo, MRK-003 has provoked apoptosis in mammosphere-derived stem-like cells, suggesting a possible method of targeting BCSCs using a GSI [237, 238].

Using monoclonal antibodies, one can directly target Notch receptors and ligands. Monoclonal antibodies suppress interactions between Notch receptors and their ligands. Using this strategy, one can selectively target Notch signaling in tumors while avoiding the unintended side effects of GSIs. Based on clinical studies of TNBC, OMP-59R5 has shown stable disease efficacy against Notch2 and Notch3 receptors [239]. MCF-7 and MDA-MB-231 cells responded dramatically to an antibody targeting EGF repeats within Notch1’s ligand-binding domain. The key point is that it specifically targets BCSCs by modulating stem cell gene expression and inducing apoptosis [240].

Researchers have worked to develop strategies to inhibit transcription by targeting Notch receptors. A class of agents called “stapled peptides” can block MAML1 interaction with NotchIC to prevent transcription [241]. Hydrocarbon-stapled peptides generated from MAML1’s dominant-negative variant SAHM1 bind to the Notch1-CSL transcriptional complex in T-cell
acutelymphoblastic leukemia and block Notch1 target gene expression [241]. There have been investigations to determine whether not only MAML1 but also CSL can be targeted to inhibit Notch signaling [242]. Inhibiting CSL expression or activity was another directly targeted strategy that decreased breast cancer cell proliferation and growth [243, 244]. Targeting the Notch pathway's downstream signaling components and its transcriptional partners could provide a more focused and potentially more effective strategy for treating Notch-driven breast cancer.

Targeting Wnt signaling in breast cancer

The past few decades have seen hundreds of inhibitors developed. These inhibitors inhibit Porcupine, Fzds, DVLs, TNKS 1/2, and TCF/Catenin and co-activators. Since Porcupine inhibitors such as LGK974, have Wnt-targeting and anticancer activity, they have recently received considerable attention [245-247]. Historically, blocking Wnt signaling by targeting Fzds has been a mainstay strategy. Niclosamide is an FDA-approved antihelminth. It may have tested for its ability to inhibit Fzd1 and may hold the most promise of any Fzd inhibitor [248]. One of the potential drugs for BC and other solid tumors is OMP-18R5, a monoclonal antibody that targets multiple Fzds. Indium 111 and Yttrium 90 are also used as radioactive labels on three antibodies against Fzd10. One of these antibodies is suited for radiotherapy of metastatic synovial sarcoma [249, 250].

The FDA approves Lincomycin as an ingredient in poultry feed for killing BCSCs [251]. Further studies have shown that it blocks the phosphorylation of LRP by Wnt [252]. Monomethyl auristatin E (MMAE) inhibits tubulin, thus killing LGR5-positive cancer cells selectively [253]. A small-molecule inhibitor called Sulindac is among the most promising Dvl inhibitors in development. Sulindac is an anticancer drug that is FDA-approved and has been shown to inhibit not only cyclooxygenase 1/2 (COX1/2) but also cyclooxygenase 3 (CYP3A), a metabolic enzyme that is involved in the formation of cancer [254]. The hypothesized mechanism of Sulindac's actions is that it inhibits the activity of cyclooxygenase 1/2 (COX1/2) as well as Dvl in its PDZ domain [255-257].

Inhibition and degradation of β-Catenin are undeniably effective approaches to inhibiting the canonical Wnt signaling. To date, only two drugs have been identified that are directly targeting β-Catenin [258] and NRX-252262 [259]. These compounds also enhance the destruction of β-Catenin by activating CK1α, which is a small molecule that targets β-Catenin [260-262], GSK3β [263], and Axin [264]. With hexachlorophene, Siah-1-induced degradation of β-Catenin can also be triggered without requiring a destruction complex. Several small-molecule inhibitors are currently being developed to block TNKS1/2’s important role in Axin breakdown mediated by Axin. 2X-121 is the most promising candidate for treating BC and ovarian cancer [265]. The phase I clinical trial for PRI-724, an anti-β-Catenin/CBP drug, is underway for advanced solid tumors. It disrupts the connection between β-Catenin and BCL9 or CBP [266]. TBL1-related protein (TBLR1) and β-Catenin then collaborate to push TLE and HDAC1 out of the way, enhancing Wnt target gene expression [266]. There is a phase I clinical trial for BC2059 [266], a β-Catenin/TBL1 disruptor, to treat desmoid tumors [267].

The findings showed apicularen A and bafilomycin A1 as a potent Wnt signaling inhibitor related to vacuolar H+ adenosine triphosphatase (V-ATPase) [268]. Even though KY02111’s direct targets are not SM04690, it has entered a phase II clinical trial for knee osteoarthritis [269], and SM04690 remains unclear [270].

Conclusion

Cancer cells that are resistant to traditional treatments cause the majority of breast cancer fatalities. Scientists are developing new chemotherapeutic drugs or targeted therapy combinations to improve BC treatment. Endocrine therapy’s effectiveness percentage is reduced when there is no ER expression. Topo-II properly identified 72.22 percent of breast cancer patients. Those with low Topo-II and CERBB2 expression survived longer than those with high or low expression. Chemotherapy can directly or indirectly target P-gp-overexpressing cells. Anacyclines, taxanes, and vinca alkaloids are examples of P-broad gp substrates. This biomarker’s used in determining a patient’s treatment options.

EGFR positivity is found in less than 1% of luminal A breast cancers. Lymph node metastases are strongly linked to poor survival rates in late-stage breast cancer, regardless of type. These
individuals require more personalized therapy and follow-up measures based on clinical and histological characteristics. The recurrence rate following mastectomy and BCS varies according to the molecular subtype of breast cancer. After breast-conserving surgery, TNBC patients showed lower recurrence rates than HER2+ patients. Some cancers may begin to recur before they are diagnosed, resulting in misdiagnosing a single tumor. Oncogenes may play a role in cancer recurrence. “Metastases of metastases” may arise if cancer spreads through these phases.

The ECM is disrupted during the invasion, facilitating tissue border penetration. MMPs in breast cancer cells stimulate proteolysis on the invasion front of the ECM. Protease-dependent mesenchymal mobility and amoeboid migration are used by tumor cells to disseminate. According to research, bone and lung metastases outperform liver and brain metastases. Cancer cells can migrate to certain organs by using a protein known as a chemokine. Metastasis cannot begin without angiogenesis. Tumor hypoxia occurs when the blood supply to a tumor is insufficient. When Twist recognizes the E-box on E-cadherin promoters, transcription is reduced. Twist has the potential to make cancer cells more resistant to chemotherapy. Twist-overexpressed breast tumors are unable to use ER protein.

MDR1 inhibitors can reduce drug resistance and reprogram cancer cells to react to the therapy. If MRP hinders drug excretion and redistribution, tumor cells may become resistant to treatment. Drug resistance mediated by MRP is weaker than P-global drug resistance.

Nonspecific biodistribution of chemotherapy agents, dose-limiting toxicity, and drug resistance are some of the drawbacks of current cancer treatment methods. As a result, the development of new cancer therapies like liposomal drug delivery systems has accelerated.

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Disclosure of conflict of interest

None.

Abbreviations

BC, Breast Cancer; ER, Estrogen Receptor; PR, Progesterone Receptor; ERBB2, Erb-b2 Receptor Tyrosine Kinase 2; HER2, Human Epidermal Growth Factor Receptor 2; Topo-2, Topoisomerase II; AUC, Area Under Curve; MRP1, Multidrug Resistance-associated Protein 1; TNBC, Triple Negative Breast Cancer; VEGFR1, Vascular Endothelial Growth Factor Receptor 1; NER, Nucleotide Excision Repair; BER, Base Excision Repair; NHEJ, Non-homologues End Joining; BAK1, Bcl-2 Antagonist Killer 1; ABCG2, ATP-Binding Cassette Transporter G-2; ABC1, ATP-binding cassette sub-family C-1; ABCB5, ATP-binding cassette sub-family B-5; HIF-1, hypoxia-inducible factor-1; DLMC, Doxorubicin-liposome-microbubble-complex; US, Ultrasound.

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