REVIEW ARTICLE

Molecular and Cellular Expressions in Breast Cancer Responsible for Drug Resistance

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ABSTRACT

Breast cancer continues to be a prevalent and highly lethal cancer affecting women globally. Despite significant advancements in early detection and the development of specific therapeutic approaches, the issue of medication resistance remains a prominent challenge in managing this intricate ailment. The study offers a comprehensive analysis of the mechanisms behind the development of treatment resistance in breast cancer cells. The objective of this study is to provide a comprehensive understanding of the molecular and cellular mechanisms behind the occurrence of therapeutic ineffectiveness. This study elucidates several molecular subtypes of breast cancer and their pharmacological responses. The significance of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) in the development of treatment resistance is emphasized. Additional research on the intricacies of innate and acquired drug resistance mechanisms, including genetic modifications, tumor heterogeneity, and the presence of cancer stem cells, has shed light on the multifaceted nature of drug resistance and its dynamic evolution throughout treatment. Furthermore, this study provides a comprehensive analysis of the impact of microenvironmental variables, including hypoxia, immune evasion, and tumor-stroma connections, on the development of drug resistance. The investigation of the interplay between tumor suppressors and oncogenes in the emergence of drug resistance is now underway, yielding valuable insights into prospective targets for therapeutic intervention. Additionally, this study examines the limitations associated with conventional chemotherapy, endocrine therapies, and targeted medicines, while elucidating the mechanisms underlying treatment resistance and proposing potential strategies to overcome it. Emerging therapies like immunotherapies, epigenetic modulators, and new drug delivery methods are looked at to see if they have the potential to get around mechanisms of resistance and improve patient outcomes. This review aims to give clinicians, researchers, and other healthcare workers a full picture of breast cancer's complex drug resistance mechanisms. By figuring out the molecular complexities and signaling pathways that lead to treatment resistance, we aim to speed up the development of new therapeutic approaches and personalized interventions. This will bring us closer to the long-awaited goal of beating drug resistance and making breast cancer a manageable, treatable condition.

Keywords: Breast cancer, Drug resistance, Molecular complexities, Signaling pathways.

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INTRODUCTION

A little over a quarter of women worldwide are directly touched by breast cancer, making it one of the most common types of cancer in women. Even though most people with breast cancer are 65 years old. Women of any age can get this disease.[1] It is thought that 0.0001% of women under 20 will get breast cancer, 0.0014% of women 20 to 24 years old, 0.0081% of women 25 to 29 years old, and 0.0248% of women 30 to 34 years old. Although breast cancer mostly affects women, about 1% of all cases are found in men. Breast cancer is still one of the top reasons women die worldwide. The disease is linked to how well they fight off cancer treatments.[2]

It is thought that 90% of all treatment failures are due to drug resistance, which can be acquired or built-in. Only 26% of people with metastatic breast cancer in the US will still be alive after 5 years[3]. Drug resistance is thought to be caused by several biological factors, such as changes in genetics, bypass mechanisms, altered effectors in DNA repair, acquired resistance that doesn't depend on a specific route, changes in pH, and increased activity of efflux pumps in cell membranes[4]. The cancer gets bigger, physical hurdles make it harder for drugs to move around and reach the levels needed for lethal concentrations in the areas of interest. A thick extracellular matrix, interstitial hypertension, and hostile conditions like

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low oxygen and high acidity in the tumor microenvironment make it harder for drugs to get into cells or work effectively.[5]

A way to treat cancer is with chemotherapy. In this case, selective and specific chemotherapy drugs are given to the patients. Anticancer drugs with different structures and ways of working often don't work on people who don't respond to chemotherapy. A big problem in treating breast cancer is that some people naturally resist chemotherapy, while others learn to be resistant over time. This clinical resistance, which is similar to an experimental phenomenon called multiple drug resistance (MDR), is probably caused by several different factors and is not all the same.[6] The drug resistance phenotype could be caused by several different molecular processes. The mechanisms involve lowering the amount of anticancer drugs that get into cells by increasing drug efflux and/or reducing drug uptake; drug sequestration; changes in drug targets (for example, topoisomerases) or activation of detoxification systems; increased repair of DNA damage caused by drugs; disruption of cell signaling; changes in factors that control the cell cycle; and stopping apoptosis.[7] ATP-binding Cassette transporters like P-gp, multidrug resistance-associated protein (MRP1), breast cancer resistance protein (BCRP), and lung resistance protein (LRP) become more active at high levels.[8] This leads to more drug release. Another idea for drug resistance is that the caspase cascade could be turned down. Some tumor cell types are resistant to apoptosis, which has been linked to less caspase-3 activity in previous studies. Some cellular mechanisms, like topoisomerase II changes, make many compounds that aren't connected to drugs less effective. Other mechanisms, like topoisomerase II changes that only affect certain targets, make some drugs less effective. But it's important to remember that cancer cells can have different ways of fighting off drugs at any given time, which can lead to more than one cell that can't be killed with a drug. A lot of breast cancer cell lines that are sensitive, naturally immune, or have gained drug resistance have been made and tested to see if they can be used as useful in vitro models of this process. A lot of the biological processes we've talked about here seem to be involved in clinical drug resistance at the same time.[9]

Molecular and Cellular Mechanism Meading to Drug Resistance in Cancer

Cancer treatments that don't work can be caused by several different molecular processes and pathways, and the cancer cells often become resistant to therapy.

Genetic Mutations

Many cancers are caused by changes in genes that turn on oncogenes or turn off tumor suppressor genes. At first, treatment may focus on these changes, but cancer cells can get new mutations that make the treatment useless. This is known as "acquired resistance." Amplification of human epidermal growth factor receptor 2 (HER2) is known to cause breast cancer. Treatments that target HER2, like trastuzumab (Herceptin), work well for breast cancer that is positive for HER2. But because of changes in the HER2 gene, some people with HER2-positive breast cancer may become resistant. Because these mutations can change the structure of the HER2 protein, targeted treatments may not work as well on it.[10] Breast cancer often has changes in the PIK3CA gene, especially in the hormone receptor-positive and HER2-positive forms. These changes can turn on the PI3K/AKT/mTOR signaling system, which makes cells more resistant to hormonal treatments like tamoxifen and aromatase inhibitors and increases their ability to survive.[11] People who have abnormalities in BRCA1 and BRCA2 are more likely to get breast cancer and may not respond well to some treatments. For instance, tumors that have BRCA mutations might not respond as well to hormone treatment but might respond better to PARP inhibitors like olaparib and talazoparib. TP53 is a gene that stops tumors from growing, and changes in this gene are linked to aggressive types of breast cancer.[12] Many treatments, like chemotherapy, radiation therapy, and targeted medicines, can't work on cancer cells that have TP53 mutations. When someone has breast cancer, changes in the ATM gene make them less likely to respond to treatments that damage DNA, like radiation and some chemotherapy drugs.[13] Genes that make fibroblast growth factor receptors (FGFRs) may be changed in some types of breast cancer. These changes can make hormone treatment less effective, but FGFR inhibitors might be able to help. In breast cancer, changes in the ERBB2 gene can make HER2-targeted treatments less effective, along with HER2 being amplified. Changes in the MAP3K1 gene have been linked to breast cancer that is resistant to hormone treatment in women who have estrogen receptor-positive breast cancer. Neurofibromin 1 (NF1) mutations have been linked to breast cancer that doesn't respond to treatments that target HER2.[14]

Drug Efflux Pumps

Breast cancer resistance is affected by drug efflux pumps, which actively remove treatment drugs and other foreign substances from cancer cells. Since this efflux process lowers the concentration of drugs inside cells, it becomes harder for these drugs to kill cancer cells or stop their growth. One type of membrane transport protein that is known to play a role in breast cancer resistance is P-glycoprotein (P-gp), which is also called ABCB1 or MDR1. In some breast cancer cells, drug efflux pumps like P-glycoprotein are overexpressed. Chemotherapy drugs get into these cells, but P-gp actively pumps them out of the cell, which lowers the cellular drug amounts. This lower drug accumulation makes chemotherapy less efficient. Pharmaceutical efflux pumps like P-glycoprotein are not limited to certain treatment drugs. Numerous drugs can be pumped, including doxorubicin, paclitaxel, and tamoxifen, which are widely used to treat breast cancer. It's called combination resistance when failure to respond to one drug can make you less sensitive to other drugs.[15]

Altered Drug Targets

Cancer cells may not respond as well to targeted treatments if the drug targets become mutated or not expressed correctly. These changes could make some treatments less effective or

mean that new ways of treating the condition need to be found.[16] Hormone receptor-positive breast cancer needs the estrogen receptor to grow. If the ER gene is mutated, it can change its structure or function. This can make hormone treatments like tamoxifen or aromatase inhibitors less effective. One gene that causes some types of breast cancer is HER2 amplification. Trastuzumab (Herceptin) and other HER2-targeted treatments work very well on HER2-positive breast cancer, but some patients can become resistant because of changes in the HER2 receptor or signaling pathways that follow it.[17] PIK3CA gene mutations are common in breast cancers that are positive for hormone receptors and HER2. These changes can turn on the PI3K/AKT/mTOR signaling system, which can make hormone therapies and therapies that target HER2 less effective.[18] Beyond HER2 increase, changes in the ERBB2 gene can also make HER2-targeted breast cancer treatments less effective. Changes in the ESR1 gene, which codes for the estrogen receptor, can make the receptor work even when no ligand is present.[19] It's possible for this to make hormone treatment less effective. Changes in parts of the MAPK signaling system, like mutations in the KRAS or BRAF genes, can make some types of breast cancer resistant to targeted therapies.[20] When the PTEN gene is lost, it can turn on the PI3K/AKT/mTOR signaling pathway. This can make targeted treatments less effective. In hormone receptor-positive breast cancer, drugs called palbociclib and ribociclib are used to stop CDK4/6 from working. If CDK4 or CDK6 changes, these medicines may not work as well.[21] Genes that make FGFRs are changed in some types of breast cancer. These changes can make hormonal treatments less effective, but FGFR inhibitors might be able to help. Most of the time, BRCA mutations make people more sensitive to PARP inhibitors. However, they can sometimes make people resistant to medicines, especially medications that damage DNA.[22]

Tumor Microenvironment (TME)

The environment around the cancer cells comprises many types of cells, parts of the extracellular matrix, and signaling chemicals. The interactions that take place inside the tumor microenvironment (TME) can change how cancer grows and how well it responds to treatment as shown in Figure 1. Solid tumors, like breast cancer, often have areas with low oxygen levels. These areas are known as hypoxic regions. By changing gene expression patterns and helping cancer cells stay alive, hypoxia can make drugs less effective. In addition, it may cause cancer cells to become more invasive.[23] It can weaken the immune system and is marked by immune cells like regulatory T cells (Tregs) and myeloid suppressor cells (MDSCs). These cells can stop the immune system from fighting tumors and make immunotherapies less successful. Cancer-associated fibroblasts (CAFs) are stromal cells in the TME that can release substances that help tumors grow and become resistant to treatment. In addition, they can build a wall that stops drugs from getting into the growth.[24] Changes in the extracellular matrix (ECM) can make it harder for drugs to reach cancer cells and make them more resistant. More of the ECM components, like collagen, can form physical walls that keep drugs from getting to where they're supposed to go. By helping cells stay alive, angiogenesis (the growth of new blood vessels), and tumor development, chronic inflammation in the TME can make drugs less effective. It may be heterogeneous, meaning that different growth parts may have different traits. In the same tumor, this can make different drugs less or more effective. It might help cancer stem cells grow and stay healthy. Cancer stem cells (CSCs) are a type of cell that can divide and start new tumors. CSCs are often harder to treat and play a role in treatment failure and return. It can help new blood vessels grow so that nutrients and oxygen can reach the growth. This process, called angiogenesis, can help tumors grow and give cancer cells a way to get away from treatment. This causes changes in the metabolism of cancer cells, like the "Warburg effect," which makes cancer cells switch to glycolysis even when oxygen is present. This change in metabolism can make some treatments less effective on cancer cells. Exosomes, which are made up of bioactive chemicals, can be released by cancer cells in the TME and affect immune cells and stromal cells nearby. These exosomes may help cells fight drugs by encouraging prosurvival signals and getting around the immune system.[25]

Epigenetic Changes

In epigenetics, changes that are passed down through genes are made to DNA and proteins called histones that control gene expression. These changes don't affect the DNA code itself. Unwanted epigenetic changes can turn on or off certain genes that are involved in the growth of breast cancer and how it responds to treatment. Adding a methyl group to cytosine bases in DNA, usually in CpG dinucleotides, is what DNA methylation is all about. Breast cancer often has DNA methylation patterns that aren't working right, which can silence genes that help fight tumors.[26] A process called promoter hypermethylation has been linked to the growth of breast cancer in genes like BRCA1, p16INK4a, and RASSF1A. Histones are proteins that keep DNA in the cell nucleus neat and in order.[27] Changes that happen after histones are translated, like acetylation, methylation, and phosphorylation, can affect the organization of chromatin and gene expression. Changes in the modifications that histones go through can make genes that control the cell cycle and fix DNA not work right in breast cancer. MicroRNAs, or miRNAs, are small noncoding RNAs that control gene expression by choosing messenger RNAs (mRNAs) to be broken down or stopped from translating. When miRNAs are not working properly, they can greatly affect how oncogenes and tumor suppressor genes are expressed. Changes in miRNA expression levels have been linked to breast cancer spreading and getting worse. Chromatin remodeling complexes can change how transcription factors and RNA polymerase can reach DNA, which can change gene expression. Breast cancer has been linked to changes in chromatin remodeling genes like ARID1A, which may have an effect on the epigenetic environment. Long noncoding RNAs (lncRNAs) can control gene translation by working with chromatin-modifying

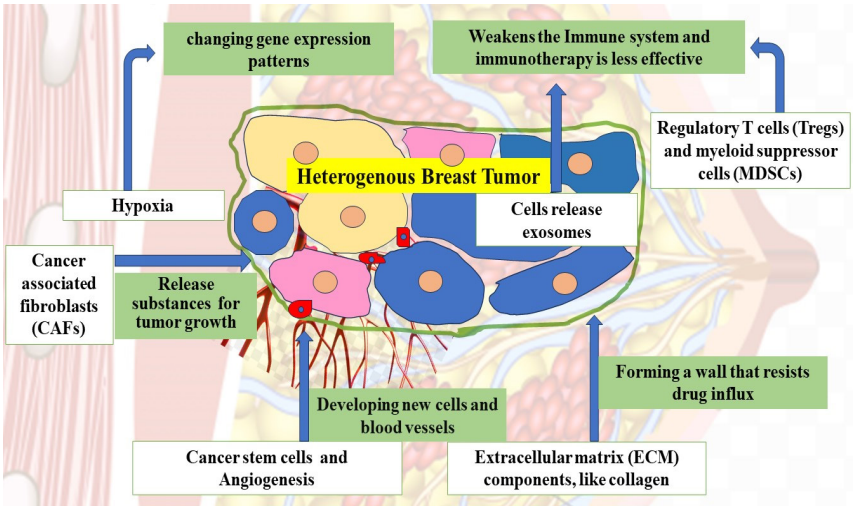

Figure 1: The interactions in the breast tumor microenvironment

complexes. In breast cancer, lncRNAs that aren't expressed properly may mess up the epigenetic control of genes that help the cancer grow, invade, and spread.[28] The epithelial-mesenchymal transition (EMT) is the process by which cells that are normally epithelial become mesenchymal and can invade more deeply. Changes in epigenetics can cause EMT in breast cancer cells, which can help them spread and become resistant to treatment.[29]

Repair Mechanisms

DNA repair systems are very important because they fix broken DNA and keep the genome's integrity. Cancer cells can get better at fixing DNA, which makes them less vulnerable to treatments that damage DNA, like radiation and some chemotherapies. Dysregulation of these repair processes can have big effects on how the disease starts, how it spreads, and how well it responds to treatment in breast cancer, as well as in other types of cancer. A very accurate way to fix DNA errors called homologous recombination (HR) is needed to fix double-strand breaks (DSBs) in DNA.[30] People who have changes in genes that play a role in HR, like BRCA1 and BRCA2, are more likely to get breast cancer. These changes can make it harder for HR repair to work and cause DNA damage to build up, which makes cells more likely to become genomically unstable and cancerous. Non-homologous end joining (NHEJ) is a way to fix DNA that can go wrong. It joins broken DNA ends together. When fixing DSBs, HR is usually a more accurate method, but NHEJ can add or remove small pieces that could lead to changes. Breast cancer cells may have genetic instability because of problems with NHEJ repair. Base excision repair (BER) fixes DNA bases that are broken or don't match up correctly. Changes or mutations in BER genes, like XRCC1 or APEX1, may impact the ability to fix DNA, which can lead to genetic instability in breast cancer. Nucleotide excision repair (NER) fixes large DNA damage, like that caused by UV light or chemicals that can cause cancer. NER defects can make people more likely to get breast cancer, especially those who have genetic diseases like xeroderma pigmentosum. Fixing mistakes that happen during DNA replication is what mismatch repair (MMR) does. This stops the buildup of misaligned base pairs. Microsatellite instability and a higher chance of some types of breast cancer can happen when MMR levels are low. This can happen because of changes in genes like MLH1 or MSH2. Cross-links and interstrand cross-links in DNA are fixed by the Fanconi anemia (FA) pathway. Hereditary breast cancer is linked to changes in FA genes like BRCA2 and FANCD1. These changes can make it harder to fix DNA damage. Single-strand DNA breaks can be fixed by several processes, one of which is the poly (ADP-ribose) polymerase (PARP) pathway. Inhibiting PARP enzymes in breast cancers with BRCA mutations can cause synthetic lethality, which makes them a specific treatment for this subtype. The DNA damage response (DDR) system comprises a group of signaling and repair proteins that turn on cell cycle checkpoints and repair mechanisms when DNA is damaged. When DDR parts are not working properly, it can cause genetic instability and cancer growth.[31]

Immune Evasion

An environment created by breast cancer weakens the immune system. They involve immune-suppressing cells like regulatory T cells (Tregs) and MDSCs. These cells stop lethal T cells and natural killer (NK) cells from killing cancer cells.[32] Tissue-specific immune checkpoint molecules, like PD-1 and PD-L1, are very important for controlling immune reactions. Some chemicals in breast cancer cells can be turned up, and they work with immune cell receptors to stop immune cells from doing their job. The immune system can't find and fight cancer cells because of this interaction. Different types of tumor proteins can be expressed by breast cancer cells. In other words, not all cancer cells in a tumor may show proteins that the immune system can recognize. Some immune cells may attack some cancer cells but not others, which keeps the tumor alive. Certain molecules in the major histocompatibility complex (MHC) are

crucial for immune cells to recognize antigens. Some breast cancer cells can lower the expression of MHC, which makes it hard for the immune system to find and fight them. Over time, immune editing can happen in breast cancer cells. This is a process by which the cells change to deal with immune pressure. This could be a change in the genes that help the cancer cells hide from the immune system. Immunosuppressive cytokines, like TGF-β and IL-10, can be released by breast cancer cells. These cytokines stop immune cells from working and make the tumor immunosuppressive. Long-term contact with cancer cells can wear down the immune system, making immune cells less able to fight tumor proteins and less effective. The immune reaction against breast cancer is less effective because of this depletion.[33]

Metabolic Adaptation

To stay alive and grow during treatments, cancer cells can change the way their metabolism works because they are metabolically flexible. In the presence of oxygen, cancer cells often choose glycolysis over other types of energy production (Warburg effect). They can make energy quickly now that their metabolism has changed, which helps them grow and stay alive. When cancer cells are exposed to chemotherapy or targeted therapies, they may change how they make energy by either increasing glycolysis even more or moving to other energy sources like fatty acid oxidation or glutaminolysis. Breast cancer cells can change how they take in nutrients to deal with stress caused by drugs. They can eat more of certain nutrients, like glucose or amino acids, which are necessary for them to keep growing and reproducing.[34] Cancer cells can turn on survival pathways like the PI3K/Akt/mTOR system to avoid cell death caused by drugs. These processes help cells stay alive by making it easier for them to take in and use nutrients and stop apoptosis. Upregulating hypoxia-inducible factors (HIFs) can cause metabolic changes that help cancer cells stay alive and fight treatment.

MicroRNA Dysregulation

MicroRNAs, or miRNAs, are small molecules of non-coding RNA that control gene translation after transcription. They can change many biological processes, such as those that control how cancer grows and how well medicines work. MiRNAs that are out of whack can directly target genes that are involved in drug reaction pathways. For instance, miRNAs can target genes that make drug transporters, drug-metabolizing enzymes, or drug targets themselves, which can change how well a drug works. Some miRNAs can target genes that are involved in apoptosis, which means "programmed cell death." If these miRNAs are not working properly, they may help cancer cells stay alive and fight the killing effects of chemotherapy drugs. Cancer cells become less sensitive to treatment when undergoing epithelial-mesenchymal transition (EMT). This is because they lose their epithelial properties and gain mesenchymal properties. When miRNAs are not working properly, they can help EMT happen and make breast cancer cells less likely to die from drugs. By going after genes involved in DNA repair processes, miRNAs can change how DNA damage is dealt with. When miRNAs are not working properly, cancer cells may be able to fix their DNA better, which makes them less vulnerable to chemotherapy drugs that damage DNA. Some miRNAs can control the production of drug efflux pumps, like P-glycoprotein. When these pumps are overexpressed, drug amounts inside cells can drop, which makes chemotherapy less effective[35.]

CONCLUSION

The review provides a critical analysis of the constraints associated with conventional chemotherapy, endocrine treatments, and targeted medicines. The overview offers an explanation of the mechanisms underlying the development of resistance to these therapies, so establishing a foundation for the critical reassessment of current therapeutic strategies. Significantly, ongoing research pertaining to novel therapeutic approaches such as immunotherapies, epigenetic modulators, and revolutionary drug delivery techniques presents a promising prospect. These innovative approaches have favorable prospects for overcoming current resistance mechanisms and substantially enhancing patient outcomes.

The study highlights the significant feature of identifying prospective therapeutic targets by examining the interplay between tumor suppressors and oncogenes. The process of unraveling these complex networks provides opportunities for novel therapeutic approaches and has the ability to disrupt the mechanisms that contribute to the development of drug resistance. This methodology not only offers significant data for continued scholarly investigation but also holds the potential to convert scientific breakthroughs into actual clinical advantages for individuals in need.

In essence, this review provides a stimulating analysis of the obstacles and possibilities within the realm of breast cancer therapy. Through a comprehensive examination of the molecular, cellular, and microenvironmental complexities linked to the phenomenon of drug resistance, the summary presents a strategic plan for directing future research endeavors. It is evident that a comprehensive strategy encompassing targeted medicines and novel treatment modalities is important in order to surmount medication resistance and enhance the well-being of individuals diagnosed with breast cancer.

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