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Insight into breast cancer mechanism, drug resistance and treatment methods

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Abstract. Due to the multiple cancer variants in the world, the treatment of cancer around the world has gradually fallen into a bottleneck. This article takes breast cancer as the prototype, describes in detail the causes of breast cancer, the treatment plan and the dilemma faced by the treatment of breast cancer, and puts forward a new idea for conquering breast cancer, as well as the prospect and expectation for the future human fight against cancer.

Keywords: Breast Cancer, Cancer Treatment, Drug Resistance.

1. Introduction

Globally, women who suffer from breast cancer (BC) have the greatest rates of morbidity and death from the disease. High-risk germline mutations, patients with a history of chest irradiation between the ages of 10 and 30, and patients with lifetime risks of less than 20% are examples of patients who are at high risk for breast cancer.

For example, A significant advancement while addressing breast cancer has been the recent development of a targetable subset of the disease for novel anti-HER2 antibody-drug conjugates, which is based on clinical trial findings. Breast cancer cells that are resistant to drugs. Drug-resistant tumors have extensive molecular defense systems to resist therapy when put under pharmacological stress, which is a major barrier to cancer treatment. Combining therapy with many medicines helps prevent breast cancer cells from developing resistance to one particular medication.

The pathogenesis of breast cancer, The CDH-1 gene on chromosome 16q22, which encodes E-cadherin, is assumed to be the primary mediator of ILC. E-cadherin is a calcium-dependent transmembrane protein that promotes cell-cell adhesion, preserves tissue integrity, and guards against tissue invasion. These capabilities can stop tumor invasion, making the E-cadherin gene a tumor suppressor. Through α-, β-, γ-, and p120, the intracellular domain of E-cadherin attaches to the actin cytoskeleton [1].

Up to now, after years of treatment, many new variants of breast cancer have emerged, and drug resistance has emerged. This article will make a summary from the causes of breast cancer, drug resistance and treatment of breast cancer [1].

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2. Causes and subtypes of breast cancer

Breast cancer, a malignant tumor growing in the breast tissue, is one of the most common illnesses in women. Although it can also affect males, men are significantly less likely to develop breast cancer than women are. Here is a quick summary of breast cancer's causes and kinds. [2].

2.1. Causes of breast cancer

2.1.1. Genetic factors: Gene mutations in BRCA1 and BRCA2 are associated with an elevated risk of breast cancer. Gene mutations in both raise the risk of ovarian and breast cancer significantly. [2].

2.1.2. Hormone Replacement. Therapy Long-term hormone replacement treatment (HRT) users among women had a marginally increased risk of breast cancer.

Proliferation of mammary cells: estrogen is the key hormone to promote the proliferation of mammary cells. Hormone replacement therapy often includes estrogen, which may result in more frequent proliferation of mammary cells. When the frequency of cell proliferation increases, the chance that a cell will undergo genetic mutations during division also increases, increasing the risk of cancer.

Stimulation of preexisting cancer cells: If a woman already has early, undiscovered cancer cells in the breast, estrogen may stimulate the growth and division of these cells, thereby accelerating the development of cancer.

Affect other hormone levels: Hormone replacement therapy may change the levels of other hormones in the body, such as progesterone, and then affect the proliferation and division of breast cells.

Effect of intercellular communication: estrogen may also affect the communication between cells, leading to abnormal signal transmission between cells, and further increase the risk of breast cancer.

Affect apoptosis of breast cells: estrogen may affect the process of natural cell death (also known as apoptosis), meaning that potentially abnormal cells survive rather than being eliminated naturally.

2.1.3. Radiation exposure. People who have received radiation therapy in the past for other medical conditions, especially during the breast development stage, are more likely to get breast cancer. Breast tissue is susceptible to malignant transformation by ionizing radiation, Patients who get radiation for ankylosing spondylitis, numerous fluoroscopies, or have an enlarged thymus have higher risks of breast cancer, as well as in atomic bomb survivors, radium surfactators, and X-ray technicians.

2.1.4. Alcohol. Breast tissue can also be affected by alcohol, with women who consume an average of four or Women who drink more alcohol per day have a 50% greater risk of breast cancer than those who don't. This link didn't seem to depend on the kind of alcohol ingested.

2.2. Classification of breast cancer

The following categories of breast cancer may be created based on HER2 protein and hormone receptor status:

1) based on the presence of either PR+ or ER+ hormone receptors. Second, HER2-positive: The tumor overexpresses HER2 protein. 3) ER-, PR-, and HER2-negative triple-negative breast cancer, this type of cancer is relatively more challenging to treat. 4) According to cell appearance and growth pattern: Invasive ductal carcinoma: most common, starting in the ducts of the breast; Invasive phyllodes carcinoma: begins in the lobar part of the breast. 7) Ductal carcinoma in situ: noninvasive and confined to the duct. 8) According to gene expression: 9) Luminal A and B: predominantly ER-positive. 10) Her2-positive type: mainly expresses HER2 protein. 11) Basal/triple negative: no expression of the above receptors [2].

In summary, the causes of breast cancer are diverse and include genetic, environmental, and lifestyle factors. The classification is based on the characteristics and characteristics of tumor cells, and each type has its own specific treatment methods and prognosis.

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With 39.6% of cases occurring in grade II, 188/475; grade I with 34.9% and grade III with 25.5%, 121/475, the most common grades were in order of prevalence, according to the histological grade of breast cancer. Among 169 cases of luminal A subtype, 122 cases (72.2%) were grade I and II. There were 47 cases (27.8%) of grade III and 0 case of grade III. There were 107 different luminal B subtype disorders, 25 (23.4%) of which were grade I, and 62 (57.9%) were grade II. 20 species (18.7%) fell into this grade. Thirty-four (54.8%) of the 62 instances of HER2-positive luminal B cancers were grade II or III, and thirteen (21.0%) were grade I. Grade 1 instances made up 15 cases (24.2%).

Forty-six instances (5.6%), eighteen cases (25.0%), and fifty cases (grade III) out of the seventy-two patients with the triple-negative subtype were grade I. 69.4% of Grade I. There were two (3.1%) grade I tumors and twenty-seven (41.5%) grade II tumors among the sixty-five non-luminal HER2-positive cells.

And 36 cases (55.4%) of grade III. Comparing patients with luminal A tumors to those with other subtypes, the proportion of tumors having a grade I histological categorization was higher in luminal A patients. Among all subtypes, patients with triple-negative subtypes had the highest proportion of tumors with histopathological classification of grade III [2].

3. Drug resistance

When treating cancer patients, when breast cancer cells are no longer sensitive to one or more drugs, resulting in reduced or ineffective treatment effects, it is called drug resistance. R espons. The development of mechanisms by cancer cells to counteract the effects of treatment drugs, which results in fitter, more aggressive clones with a bad prognosis, is a major reason for concern. Resistance to treatment may be innate or learned. These are complex events that have multiple causes, including acquired mutations, evasion of apoptosis, change from epithelium to mesenchymal tissue (EMT), dysregulation of important signaling pathways, medication excretion by ABC transports, and activation of the DNA damage response. CSC is the primary cause of treatment resistance among these variables. A subpopulation of tumor cells known as CSC is known to be inherently resistive to cancer-fighting drugs and is capable of self-renewal and multilineage progenitor growth. Similar to chemoradiotherapy. There are several CSC clones already in existence, and some of them are easily adaptable to modifications in the tumor microenvironment's (TME) and/or the body's reaction to radiation and chemotherapy. CSC-mediated treatment resistance is a result of both internal and external factors. In this review, we'll concentrate on CSCs and treatment resistance and suggest methods for getting rid of CSCs to get rid of medication resistance [3].

Some cells produce proteins that pump the drug out of the cell, preventing the drug from reaching enough concentrations to have an effect on the cell. Inhibition of cell death: cancer cells may have altered pathways that regulate programmed death, such as apoptosis, making it difficult for drugs to trigger cell death. Target mutations: Certain targets in cancer cells may be mutated, preventing the drug from binding to them. Signaling pathway modifications: cancer cells have the ability to turn on other signaling pathways that avoid the effects of medication. Effect of microenvironment: The tumor microenvironment (such as intercellular communication and extracellular matrix) may also influence drug delivery and efficacy [4].

Drug resistance in breast cancer exists in the following ways:

DNA damage repair: Oxidation-induced aggregated DNA damage is often detected after radiotherapy in breast cancer, which poses a serious threat to genomic integrity and subsequently leads to tumor resistance to radiotherapy. Long-term exposure to chemotherapy can also change the overall ros level of tumor cells, promote the expression of hif-1α, vegf and macrophage migration inhibitory factor (mif), and then up-regulate anti-apoptotic proteins through the ras/mapk pathway, leading to acquired drug resistance [5].

Downstream adaptive response refers to Breast cancer cells' resistance to external drug intervention through a variety of ways such as autophagy, oncogenic bypass signaling, and apoptosis. Tumor immunological microenvironment, exosomal non-coding RNA, cell stemness, downstream adaptive

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response, and DNA damage repair are all regulated by cancer cells. Re-coding RNA may lead to the change or failure of the target in targeted therapy and lead to drug resistance [6].

Among malignant tumors that affect women most frequently in the globe is breast cancer. Although the treatment of breast cancer has advanced significantly during the past couple decades, such as combination therapy: treatment with multiple drugs to reduce the chance of cancer cells developing drug resistance.

Drug rotation: Periodically changing the type of drug, breaking the "adaptability" of cancer cells. Individualized treatment: the most appropriate drug is selected according to the tumor genotype of each patient. New drug discovery: The development of new drugs or new delivery strategies to overcome known resistance mechanisms. However, breast cancer drug resistance is still a complex problem, involving multiple molecular and cellular mechanisms. To solve this problem, multi-disciplinary cooperation, including molecular biology, medicinal chemistry, clinical medicine, etc., is needed to provide better and more precise treatment for patients [7].

4. Treatment of breast cancer

4.1. Hormone therapy

Hormone therapy exerts an external influence to prevent estrogen from binding to its receptors in has an impact on breast cancer cells that are ER-positive or PR-positive, but not on those that are ER-negative or PR-negative. Clinical trials have demonstrated that immune checkpoint therapy is not very effective in treating other types of breast cancer, and is now only available to individuals with triple-negative breast cancer. In addition, triple-negative breast cancer has a worse cure rate and fewer treatment choices than other forms of breast cancer. It is also more sensitive and prone to metastasis.
[8].

4.2. Immunotherapy

Immunotherapy does not directly kill cancer cells to achieve the purpose of treatment, but through altering the natural connection between immune cells and tumor cells, altering the environment in which tumor cells grow, activating the immune system's powerful ability to destroy tumor cells, and using autoimmune cells to kill tumors.

The luminal androgen receptor (LAR) subtype of TNBC is characterized by up-regulation of oxidized phosphatidylethanolamine and glutathione metabolism, notably GPX4, which enables GPX4 to cause ferroapoptosis. TNBC is closely related with ferroapoptosis. GPX4 can not only induce tumor iron ptosis, but also enhance anti-tumor immunity.

A high-resolution map of the complete tumor ecosystem based on 44473 breast cancer liver and brain metastatic cells was identified using single-cell RNA sequencing. Multiplex immunofluorescence staining and canonical marker identification revealed significant immunosuppressive cell reprogramming in the metastatic ecosystem, comprising LGALS1+ microglia, CCL18+ M2-like macrophages, RGS5+ cancer-associated fibroblasts, LAMP3+ tolerist dendritic cells, and FOXP3+ regulatory T cells.

Additionally, CD8+ T lymphocytes and immune/stromal/cancer cells, in that order, nearly did not express PD-1 or PD-L1/2. When CD8+ T cells engage with stromal, immunological, and cancer cells, the chemicals at immune checkpoints TIGIT-NECTIN2 and LAG3-LGALS3 are crucial for immune escape [9].

4.3. Targeted drug therapy

Targeted drug therapy can accurately locate the lesion part of breast cancer, and can play a role in inhibiting cancer cells or the lesion site. And it has mild toxic side effects.

A pd-1 antibody can be used to bind to cells by Maleimide-thiol coupling is used to combine DOX-loaded liposomes with reduction-activated linkers. With this method, anti-PD-1 may be released quickly

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and at the same time persistently release DOX at the metastatic site of inflammation to achieve the purpose of inhibition.

TNBC therapeutic strategies that target specific pathways, such as Promising routes include kinases, androgen receptor signaling pathways, and DNA repair mechanisms. Unfolded protein response (UPR), which is regarded as a crucial cellular stress response, is activated in response to endoplasmic reticulum stress (ERS). Therapies that target the activation of ERS and the signaling pathways that it activates may prove to be effective new weapons in the battle against breast cancer. Therefore, Targeting ERS in various malignancies has received minimal attention in terms of its significance and therapeutic applicability. Combination therapy is the use of a variety of therapeutic drugs and therapies to avoid cancer cell resistance to a single drug. Targeted therapy and chemotherapy, as well as targeted therapy and immunotherapy can be combined [10].

4.4. Gene therapy

Gene therapy Doxorubicin induced apoptosis and iron ptosis were measured by flow cytometry, western blotting, and cytotoxicity. Studies were carried out in vivo and in vitro to investigate GATA3's role in regulating adriamycin-induced cell death. To examine how GATA3 regulates CYB5R2, qPCR, luciferase assay, ChIP, RNA-seq, and correlation analysis were employed. Assays for iron, ROS, and lipid peroxidation were used to determine the contribution of GATA3 and CYB5R2 to the regulation of ferroapoptosis brought on by adriamycin. Immunohistochemistry was used to validate the findings. [8].

5. Conclusion

After years of research, breast cancer has accumulated a wealth of clinical experience, which can be used in the treatment of the same type of cancer.

Despite the emergence of various variants of breast cancer, there are certain solutions today. Efforts have been made to modify the hormone levels of the body by adjusting the diet, which can be effective in breast cancer prevention and therapy. For example, Given that blood estradiol, or blood estrogen in general, may be a sufficiently strong intermediate indicator of breast cancer risk, these researches can be justified as genuine attempts to identify practical dietary patterns. Reducing the amounts of meals high in certain fats, such n-6 fatty acids, or increasing the amounts of fiber-rich foods, like wheat, oat, or maize bran, legumes, vegetables, and fruits, can help stabilize and reduce estradiol levels. Individualized treatment: With the in-depth understanding of genomics and the molecular mechanism of disease, the treatment of breast cancer will be more individualized in the future, and precise treatment will be carried out according to the genotype and tumor characteristics of the patient. Immunotherapy: Utilizing the patient's immune system to recognize and combat cancer cells has emerged as a novel approach to treatment, such as immune checkpoint inhibitors. Minimally invasive treatment: With the advancement of technology, minimally invasive surgery and other minimally invasive treatment methods will become more and more popular, reducing surgical risk and accelerating recovery. Comprehensive treatment strategy: to improve the treatment effect and reduce the recurrence rate by combining a variety of treatment methods [8].

Early screening and prevention: through enhanced early screening for breast cancer and improved public health education, prevention and early detection will be the key to breast cancer control. These are all ways to focus on future development.

In order to supplement the fast-developing pharmaceutical methods in the arsenal of preventative alternatives for breast cancer, chances to create lifestyle measures may arise in the next years. Although it hasn't been conclusively proven, the idea that eating less fat and more fiber will lower the chance of developing breast cancer in people is very important for overall public health.

References

[1] Nounu, A., et al., *Sex steroid hormones and risk of breast cancer: a two-sample Mendelian randomization study*. Breast Cancer Research, 2022. 24(1): p. 1-13.

DOI: 10.54254/2753-8818/29/20240791

[2] Miller, K.D., et al., *Cancer treatment and survivorship statistics, 2019.* CA: a cancer journal for clinicians, 2019. 69(5): p. 363-385.
[3] Liu, Z., et al., *Biological and pharmacological roles of m6A modifications in cancer drug resistance.* Molecular Cancer, 2022. 21(1): p. 1-20.
[4] Li, Y., et al., *Drug resistance and Cancer stem cells.* Cell Communication and Signaling, 2021. 19(1): p. 1-11.
[5] Andre, F., et al., *Genomics to select treatment for patients with metastatic breast cancer.* Nature, 2022. 610(7931): p. 343-348.
[6] Tietscher, S., et al., *A comprehensive single-cell map of T cell exhaustion-associated immune environments in human breast cancer.* Nature Communications, 2023. 14(1): p. 98.
[7] Zou, Y., et al., *The single - cell landscape of Intratumoral heterogeneity and the immunosuppressive microenvironment in liver and brain metastases of breast cancer.* Advanced Science, 2023. 10(5): p. 2203699.
[8] Prentice, R.L., *Future possibilities in the prevention of breast cancer: fat and fiber and breast cancer research.* Breast Cancer Research, 2000. 2(4): p. 1-9.
[9] Rahman, W.T. and M.A. Helvie, *Breast cancer screening in average and high-risk women.* Best Practice & Research Clinical Obstetrics & Gynaecology, 2022. 83: p. 3-14.
[10] Tarantino, P., et al., *ESMO expert consensus statements (ECS) on the definition, diagnosis, and management of HER2-low breast cancer.* Annals of Oncology, 2023. 34(8): p. 645-659.