GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

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Mechanisms of drug resistance in breast cancer

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GSC Biological and Pharmaceutical Sciences, 2024, 27(03), 105–111

Publication history: Received on 04 May 2024; revised on 11 June 2024; accepted on 13 June 2024

Article DOI: https://doi.org/10.30574/gscbps.2024.27.3.0227

Abstract

Breast cancer is a complex disease resulting from the interaction between genetic and environmental factors, and addressing them constitutes one of the major challenges in the treatment of this disease. Resistance to therapies represents a significant obstacle to achieving effective results in the treatment of breast cancer, multiple therapeutic approaches are available to address this disease in patients. The majority of breast cancer cases show estrogen receptor (ERα) expression, and treatments targeting this pathway are critical in their approach. However, the emergence of resistance to these treatments is a common problem, leading to cancer recurrence and relapse. This review provides an overview of the mechanisms contributing to drug resistance, highlighting the relevance of epigenetic factors as promising therapeutic targets to address clinical resistance. Furthermore, it emphasizes the importance of further research to find effective strategies that can overcome this resistance and improve treatment outcomes in patients suffering from breast cancer.

Keywords: Breast Cancer; Resistance; Treatment; Drug; Cancer Stem Cells.

1. Introduction

Chemoresistance is mainly characterized by the insensitivity of cancer cells to treatment, which is an important factor in the failure of any cancer management. Depending on drug reactivity, resistance can be classified into intrinsic and acquired. The spectrum can also be divided into primary resistance and multidrug resistance (MDR) [1].

Although many attempts have been made to restore sensitivity to existing chemotherapeutic drugs and overcome drug resistance in breast cancer, the results remain unsatisfactory due to the widespread lack of knowledge. For further understanding, it is proposed that the development of resistance to conventional therapeutics is triggered by the cancer cells themselves recognizing the DNA damage induced by chemotherapeutic agents and "repairing" it by signaling various DNA repair pathways. Therefore, drugs that belong to the group of inhibitors of specific DNA repair pathways could mean an increase in the efficacy of chemotherapeutic agents that induce DNA damage and thus reverse the therapeutic resistance associated with DNA repair in breast cancer [1].

The following review summarizes the concepts of breast cancer, its general etiology and its conventional treatment, with a subsequent development based on the main mechanisms used by the same that lead to the development of drug resistance, thus trying to bring together the possible therapeutic options that are still in a state of clinical and preclinical research.

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2. Breast cancer overview and treatment

Breast cancer is the most common type of malignant tumor in the world and the leading cause of cancer deaths. It is a disease that can be fatal in women and represents the leading cause of death in the female population [2].

The breasts are modified sweat glands, with variable size and density, located above the pectoralis muscle. They contain milk-producing cells, organized in lobules. Breast cancer most often originates in the ductal epithelium, although it can also develop in the mammary lobules. The initial symptom is usually the appearance of a lump in the breast or an abnormal nipple discharge [3].

The development of breast cancer is related to numerous risk factors, including genetic and hereditary predisposition. In addition, breast cancers are highly heterogeneous [4].

2.1. Epidemiologic

At a global level, cancer poses a significant public health challenge. Among all cancer types, breast cancer stands out as the most prevalent among women and also the most lethal within this group. It mainly affects women aged 40 to 49 years old [5].

In the year 2022, 2.3 million cases of breast cancer were detected in women worldwide, and 670,000 deaths from breast cancer were reported. Breast cancer can affect women of any age from puberty onwards, in all countries of the world, although rates are higher among adult women [6].

Breast cancer has risen as the most commonly diagnosed cancer worldwide, surpassing lung and prostate cancer. Developed countries have the highest incidence of this cancer. Mortality rates vary significantly between regions of the world, being higher in areas with low socioeconomic levels, indicating a lack of access to early detection tests and timely treatment [7].

2.2. Etiology

Regarding the cause and development of this disease, it is understood that it is the result of the combination of genetic, environmental, and lifestyle factors, as occurs in most cancers, evidencing its multifactorial nature [8].

Table 1 Breast cancer risk factors

Family history and genetic mutations	Relatives of breast cancer patients have a 2- to 3-fold increased risk of developing the disease. Genetic factors are responsible for 5% to 10% of all breast cancer cases, but may account for 25% of cases in women under 30 years of age [3].
Personal history	Having had cancer in one breast increases the likelihood of developing a second primary cancer in the contralateral breast [3].
Age	The age-adjusted incidence of breast cancer increases as the female population ages [3].
Gender	The majority of breast cancer cases occur in women [3].

Based on their origin, breast cancer cases can be classified as follows:

- Sporadic breast cancer: refers to cases occurring in patients with no family history of the disease. It accounts for 60% of cases [9].
- Familial breast cancer: occurs in patients with a family history of the disease, but it cannot be attributed to the alteration of a single gene, but rather to mutations in various genes (multifactorial inheritance). It represents 20-30% of cases [9].
- Hereditary breast cancer: arises from the mutation of a single gene in the germ line (monogenic inheritance). It accounts for 5-10% of cases. Within this category, approximately 10% is related to mutations in the BRCA1 and BRCA2 genes [9].

2.3. Diagnosis

Currently, there are three approaches to diagnosis: physical examination along with a detailed medical history, imaging techniques, and biopsy.

- Physical examination and comprehensive medical history: This method involves a physical examination conducted by a physician to detect possible anomalies in the breasts, such as lumps, changes in skin texture, or discharge. Additionally, a detailed medical history is compiled to identify risk factors, family history of breast cancer, and related symptoms [10].
- Imaging techniques: These include mammography, breast ultrasound, and breast magnetic resonance imaging (MRI). Mammography is the most common screening test and uses X-rays to obtain images of the breasts. Ultrasounds and MRIs are also used to evaluate breast tissues and may be helpful in detecting tumors that are not visible on mammography [11].
- Biopsy: This is the procedure in which a sample of suspicious breast tissue is extracted for analysis under a microscope. There are several types of biopsies, including fine needle aspiration biopsy, core needle biopsy, or surgical biopsy, depending on the clinical situation and the characteristics of the tissue being biopsied [11].

2.4. Common treatment of breast cancer

There are different treatment options, such as surgery (mastectomy or lumpectomy) which in itself, encompasses the use of adjuvant or neoadjuvant therapy along with the other treatments such as radiotherapy (RT), chemotherapy (QT), endocrine therapy (ET) and/or targeted therapy [12]. Treatment of breast cancer varies according to the stage of the disease, for example, stage 0 refers to ductal carcinoma in situ, a non-invasive condition that can progress to invasive cancer in up to 40% of cases. Treatment for this type of carcinoma includes lumpectomy and radiation or, in some cases, mastectomy [8].

Drugs can be used to decrease the risk of breast cancer, such as selective estrogen receptor modulators like tamoxifen and raloxifene, as well as aromatase inhibitors like anastrozole, letrozole and exemestane these treatments are used in postmenopausal women aged 35 years or older who have an elevated risk of breast cancer but low risk of adverse drug effects [8].

The decision to take adjuvant systemic treatment is based on lymph node involvement, hormone receptor status, ERBB2 (formerly HER2 or HER2/neu) over expression and age [13].

Systemic treatment of node-positive breast cancer includes chemotherapy, endocrine therapy for hormone receptor-positive cancer and trastuzumab for ERBB2-overexpressing breast cancer. Chemotherapeutic treatments with anthracyclines and taxanes fight breast cancer [13].

2.5. Resistance mechanism in breast cancer

In order to understand the mechanisms of drug resistance in breast cancer, it is very important to assimilate that cellular functions are carried out by a set of molecules, generally enzymes, which produce multiple chemical reactions that trigger subsequent molecules that end up provoking a response and forming a “pathway” [14] which, in turn, can be modified by factors inherent to the cell's own genetic information, such as the inadequate expression of a gene or a mutation that leads to the incorrect formation of a protein [15]. For this reason, both determinants of resistance to the usual breast cancer therapeutics are explained below as separate sections.

2.6. Signaling pathway

The normal mechanisms by which upstream and downstream signaling pathways are expressed promote cell survival, regulation of drug efflux pumps and important epigenetic changes. These mechanisms are complex and multifaceted in nature, so understanding that small changes in these pathways will cause alterations leading to tumorigenesis is indeed of utmost importance; among them we can mention the most relevant ones in the following paragraphs [16].

2.6.1. Epidermal growth factor receptor (EGFR) pathway

Constitutes an upstream signaling pathway that may be associated with resistance to different breast cancer chemotherapeutics [17].

2.6.2. PI3K/ AKT/mTOR signaling pathway

This downstream signaling pathway is activated by growth factors and hormones and is involved in cell proliferation. Its activation has been associated with resistance to endocrine therapy against breast cancer, so the development of its inhibitors opens new perspectives in the treatment of drug resistance [18].

2.6.3. RAS/MAPK/ERK signaling pathway

Like the one mentioned above, this pathway is also downstream and is activated by growth factors, hormones and stress signals that have been associated with resistance to anti-breast cancer drugs [19].

2.6.4. Wnt/beta-catenin signaling pathway

Deregulation of this pathway, which in normal activity is excited by the Wnt family of proteins and plays a role in cell proliferation and differentiation, has been implicated in the development of drug resistance in breast cancer [20].

2.6.5. Genetic alterations and epigenetic changes

Mutations in genes such as TP53 and BRCA1/2, as well as epigenetic changes such as DNA methylation and histone modifications, are associated with drug resistance in breast cancer [16].

2.6.6. Cancer stem cells

CSCs are a small population of cancer cells with stem cell-like properties in that they activate pathways to repair DNA damage caused by chemotherapeutic drugs aimed precisely at damaging DNA, which is why they are believed to acquire a chemotherapy-resistant character, as well as being a reason for neoplastic recurrence after treatment has been completed [21].

2.6.7. P-glycoprotein (P-gp)

P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), both are defined as drug exit pumps that are overexpressed in breast cancer and contribute to drug resistance [11].

2.7. Genetic resistance

2.7.1. Multidrug Resistance Gene (MDR1)

MDR1 is a gene encoding P-gp and P53 proteins, belonging to the ABC transporter family, which has shown extensive involvement in drug resistance by being expressed in subsets in immune cells and by stimulating the excretion of antiproliferative and immunosuppressive drugs [22].

2.7.2. Twist

Twist is a member of the basic helix-loop-helix (bHLH) family of transcription factors involved in heterodimerization or homodimerization and a DNA-binding domain, which binds to sequences in the genetic material [11]. Functionally, Twist was identified as a potential oncogene in the past acting extensively in tumor invasion and metastasis [23] and is currently found to be a major contributor to acquired resistance to Paclitaxel [16], the first microtubule stabilizing agent that intervenes in the binding of the β-tubulin subunit, by promoting the polymerization of this protein and inhibiting depolymerization, thus blocking cell mitosis and inhibiting cell proliferation, thus being considered as an effective antineoplastic in a wide range of cancers, including breast cancer [24]. On the other hand, to understand the function of Twist, we must know the E-box element, a transcriptional initiation sequence of multiple genes, such as E-cadherin whose reduced function or expression allows non-invasive cells to become invasive. Twist's main role is to recognize an E-box gene sequence in the E-cadherin promoter and inhibit its transcription, which makes breast cancer cells more prone to a metastatic process [25]; likewise, the overexpression of Twist-1 in high-grade breast cancers is well known because this transcription factor constitutes a negative regulator in estrogen receptor α expression, thus causing the hormonal resistance exhibited by different breast tumors [26].

2.7.3. Efflux Transporters

ATP-dependent efflux transporters in cancer cells can actively transport a wide range of xenobiotics out of the cell membrane through the energy produced by a process of ATP hydrolysis, leading to pharmacokinetic modulation of different treatments or otherwise being a phenomenon of multidrug resistance [27]. Within the ABC Superfamily, the MDR-associated protein, such as P-glycoprotein [28] -whose main mechanism of resistance is represented by an

increase in the expression of glycoproteins that promote drug efflux [29]- are included, the multidrug resistance-associated protein (MRP) [28] -which is widely distributed along the tumor cell membrane and can induce drug resistance by mediating drug excretion and altering drug distribution [30]- and the breast cancer resistance protein (BCRP) which has efflux capacity for some chemotherapeutics [31].

2.7.4. Cancer Stem Cells (CSCs)

Cancer stem cells are a small subpopulation of cells within tumors that have the ability to self-renew, differentiate and be tumorigenic [32].

CSCs play a crucial role in chemotherapy resistance in breast cancer. These cells overexpress several ABC transporters, such as P-gp, ABCG2, ABCC1, ABCB5, among others. In addition, CSCs can develop drug resistance through DNA repair and positive regulation of apoptosis [25].

High expression of aldehyde dehydrogenase 1 (ALDH1) also contributes significantly to the drug resistance of CSCs [33].

Studies show that CSCs are resistant to conventional chemotherapy and radiation and are highly likely to cause cancer metastasis. CSCs are believed to be a crucial target for the development of new anticancer drugs [32].

2.7.5. Enzymes In Resistance

Detoxifying cellular enzymes are an important part in multidrug resistance. These include glutathione, glutathione S-transferase (GST), dihydrofolate reductase, protein kinase C, DNA topoisomerase and ALDH [25].

ALDH1A1 inactivates cyclophosphamide, a key component in breast cancer chemotherapy protocols. The stem cell activity identified by ALDH1A1 is the cause of treatment resistance [34].

GST may directly contribute to drug resistance or indirectly facilitate resistance to anti-tumor treatments by inhibiting mitogen-activated protein kinase (MAPK) in the RAS-MAPK pathway [35].

Glutathione S-transferase P1 (GSTP1) is primarily responsible for resistance to a wide variety of targeted chemotherapeutic agents. MCF-7/ADR cells, an adriamycin-resistant breast cancer cell line, show approximately 50-fold more GSTP1 than normal MCF-7 cells, which have very low levels of GSTP1. The inhibition of the mitogen-activated protein (MAP) kinase pathway could be the reason why GSTs play a role in the development of drug resistance [36].

Topoisomerase II alpha, is a target of several chemotherapeutic agents and plays an important role in DNA replication. It has been associated with cell proliferation and HER2/neu protein overexpression in breast cancer. Drugs have the ability to bind to topoisomerase II and inhibit its function, resulting in DNA cleavage. A reduction in the activity or amount of Topo II in cancer cells can lead to drug resistance [37].

An increase in the amount of the anti-apoptotic protein surviving caused MCF-7 human breast cancer cells to become resistant to tamoxifen-induced apoptosis [38].

3. Conclusion

Breast cancer is a complex condition with various forms, each having specific biological characteristics that require personalized treatments. It is important to include preventive measures such as reducing risk factors and making lifestyle changes, like maintaining a healthy weight, avoiding alcohol and tobacco consumption, and controlling the use of certain preventive medications such as selective estrogen receptor modulators. It is also advisable to avoid prolonged hormone therapy and to perform regular medical surveillance with early detection methods, including regular breast self-exams to identify any unusual changes, as well as mammograms and other early detection tests. Implementing these measures can significantly reduce the risk of developing the disease or help identify cancer in its early stages when it is more treatable. Drug resistance is a common problem that decreases treatment effectiveness and can be caused by multiple mechanisms, including genetic and epigenetic alterations, changes in cellular signaling pathways, and the presence of cancer stem cells. Understanding these mechanisms is essential for developing more effective therapeutic strategies. Possible solutions include specific inhibitors of DNA repair pathways, therapies targeting cancer stem cells, and modulation of efflux transporters and detoxification enzymes. Identifying and developing these strategies can improve the effectiveness of breast cancer treatments and overcome therapeutic resistance, thereby improving clinical outcomes for patients.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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