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Challenges of overcoming the breast cancer drug resistance: A review article

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Abstract:

From a biological point of view, the breast is the most at-risk organ in a woman's body affected by cancer due to the fact that adult breast undergoes multiple periods of robust change marked with striking growth and structural remodeling indicative of activated stem cell/progenitor cell. Because breast carcinogenesis (BC) is not only the most causative agent of women's cancer-related mortality globally, but its effects in reducing the quality of life of this devastating disease survivor. Additionally, treatment resistance and relapses are the major challenges in BC management. On the other side, many of molecular processes underlying treatment resistance is crucial for the development of novel therapeutic targets such as genetic polymorphism (SNPs) and other genetic mutation. Despite the fact that this method has been effective, but some individuals eventually develop treatment resistance or relapse. Accordingly, all factors that were related to the prognostic factors assessment, predictive markers, and clinical and pathological parameter evaluation that form the basis of the therapeutic decision for BC patients. These markers were a challenge we will display in this manuscript. In addition, we will review a new approach for the assessment of the drug resistances as potential biological and molecular markers. Finally, the body's activities, such as DNA repair mechanisms, cell cycle organization, and genetic factors such as family history, can have an effect on breast cancer development and drug resistance.

Keywords: Breast cancer, treatment resistance, predictive markers, genetic polymorphism.

تحديات التغلب على مقاومة أدوية سرطان الثدي: مقالة مراجعة

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مستخلص:

من وجهة نظر بيولوجية، يعد الثدي من أكثر الأعضاء عرضة لخطر الإصابة بالسرطان في جسم المرأة المتأثر وذلك بسبب حقيقة أن الثدي لدى النساء البالغات يخضع في فترات متعددة الى تغيرات شديدة متمثلة بنمو ملحوظ وإعادة تشكيل وهندسة وذلك يدل على وجود الخلايا الجذعية أو الخلايا المولدة للثدي. بسبب إن تسرطن الثدي هو ليس فقط العامل المسبب لأكبر نسبة وفيات في النساء المرتبطة بالسرطان عالميا ، لكن قد يؤثر في اختزال نوعية وطبيعة حياة الناجيات من هذا المرض المدمر. بالإضافة إلى ذلك، فإن مقاومة العلاج والانتكاسات أي عودة المرض مرة أخرى هي التحديات الرئيسية المرتبطة في إدارة سرطان الثدي. ومن جانب آخر ، فان العديد من العمليات الجزيئية التي تدير المقاومة للعلاج تعد عامل مهم في تطوير أهداف علاجية جديدة مثل تعدد الأشكال الجينية وغيرها من الطفرات الجينية. على الرغم من حقيقة فعالية هذه الطرق، فان هناك بعض الأفراد في نهاية المطاف تتطور لديهم المقاومة للعلاج أو الانتكاس. وبناءا على ذلك، فأن كل الجوانب المتعلقة بتقييم العوامل التكهنية بوجود المرض، العلامات التنبؤية، وتقييم المعلمات السريرية والمرضية والتغيرات الجينية من أكثر العوامل المؤثرة التي تشكل أساس القرار العلاجي المناسب لمرضى سرطان الثدي. وتلك المعايير كانت بمثابة التحديات التي سوف نعرضها في هذه الدراسة. أضافتا الى ذلك ، سوف نعرض طرق جديدة لتقييم مقاومة الأدوية والتي يمكن اعتمادها كمؤشرات بايلوجية وجزيئية لمقاومة الأدوية. وأخيرا ، فان أنشطة الجسم مثل ميكانيكيات إصلاح الحمض النووي ، ومنظمات الدورة الخلوية ، والعوامل الوراثية مثل التاريخ العائلي يمكنها أن تؤثر على تطور سرطان الثدي والمقاومة العلاجية.

الكلمات المفتاحية: سرطان الثدي ، مقاومة العلاج ، علامات تنبؤية ، متعدد الاشكال الجينية.

Introduction

A major challenge with cancer treatment is the emergence of drug resistance. While response to treatment is one of the key prognostic factors of cancer therapy, especially breast cancer, however, it could be severely hindered by drug resistance, Trastuzumab and other anti-human epidermal growth factor receptor 2 HER2 drugs have demonstrated promise, yet patient response varies and frequently results in metastases or recurrence. Mutations in DNA repair pathways and HER2 signaling are among the genetic variables that lead to this resistance (1). These genetic variants have been better understood thanks to next-generation sequencing (2). Different processes can lead to drug resistance, which is not exclusive to breast cancer. Drug resistance is one of the best significant blocks to positive therapy for the illness. It is critical to understanding of the molecular processes driving resistance in breast tumor to strategy therapies that targeted the potential to overcome this resistance. These mechanisms include the stimulation of different signaling pathways that stimulate cell survival and proliferation, the high regulation of drug efflux pumps, genetic and epigenetic changes and emergence of cancer stem cells (CSC) (1). Molecular basis of breast tumor and metastatic heterogeneity of this disease and their therapeutic application improve the prognosis of metastatic breast cancer (3) Combination therapy, addressing drug resistance mechanisms, repurposing medications, and genetically profile-based personalized medicine are all being investigated in research (4). Potential treatments being explored are CRISPR/Cas9 gene editing and epigenetics (5). From the development of targeted medicines, it is essential to comprehend the molecular mechanisms underlying treatment resistance (6) Figure (1).

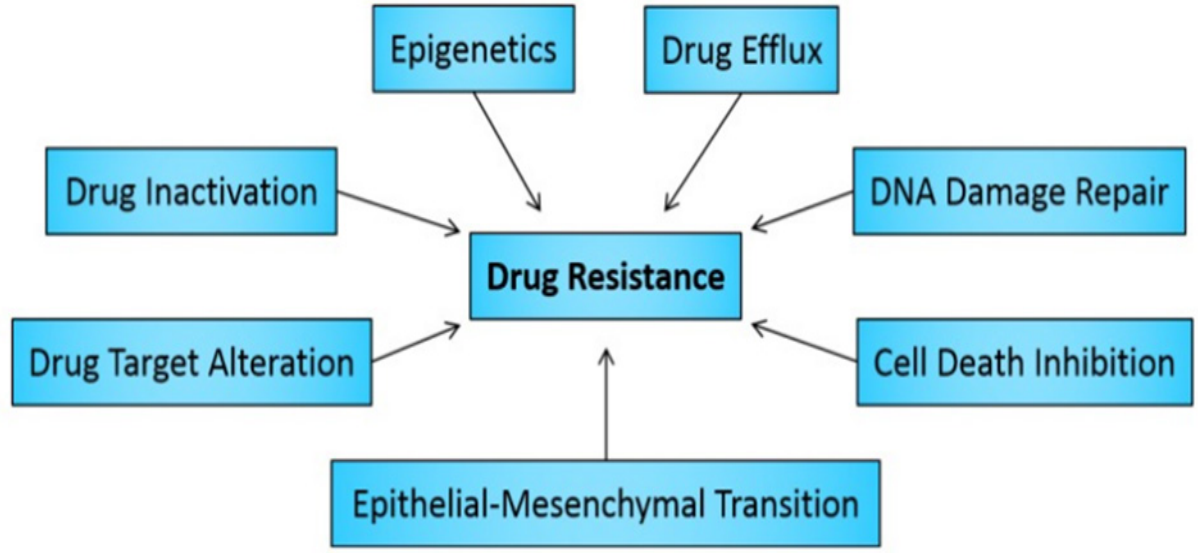

Figure 1: Categories of mechanisms that can enable or promote direct or indirect drug resistance in human cancer cells (3).

This revision aims to determine the impact of new therapeutic approaches in minimizing the breast cancer treatment-associated side effects and reasons behind drugs resistance are also discussed. Improved comprehension of the mechanisms of action of BC therapies could lead to improved understanding of the mechanisms underlying resistance development as well as improved efficacy of currently recommended treatment plans. A new understanding of the complex interactions between multiple genetic abnormalities in breast cancer and response to treatment has been provided in this manuscript.

1. Incidence of breast cancer in female

As per the 2020 report by the World Health Organization (WHO), breast cancer has become the most common cancer among women, surpassing lung cancer. 30% of women are expected to get breast cancer at some time in their life, and 15% of those cases will result in death. (7). Four major subtypes of female breast cancer have been identified: hormone receptor HR positive/ HER2 negative, HR negative/HER2 negative, HR positive/HER2 positive, and HR negative/HER2 positive (8). Breast tumors are classified according to whether they have molecular markers for the human epidermal growth

factor 2 (HER2), progesterone receptor (PR), or estrogen receptor (ER). The last twenty-five years have seen tremendous progress in targeted therapy, which has allowed us to better understand the mechanisms behind the formation of breast tumors (9).

2. The purpose and relevance of resistance to medications

One major barrier to treating breast cancer is drug resistance, which can result in treatment failure and the disease's progression. Genetic variations and drug exposure are two factors that may contribute to it, either intrinsically or extrinsically (10). Targeting resistance pathways and creating novel medications are some strategies used to combat resistance (11). Since medication resistance causes the majority of cancer relapses and deaths, it is essential to comprehend its relevance in order to create successful solutions (12). Drug resistance can be caused by a number of things, including genetic mutations and changes to the tumor microenvironment. An improvement in patient outcomes could be gained by the deeper understanding of these pathways. This can be achieved *via* adapting modified treatment approaches that are more effective in minimizing the significant obstacle of medication resistance in breast cancer (13), as it is illustrated in Figure 2.

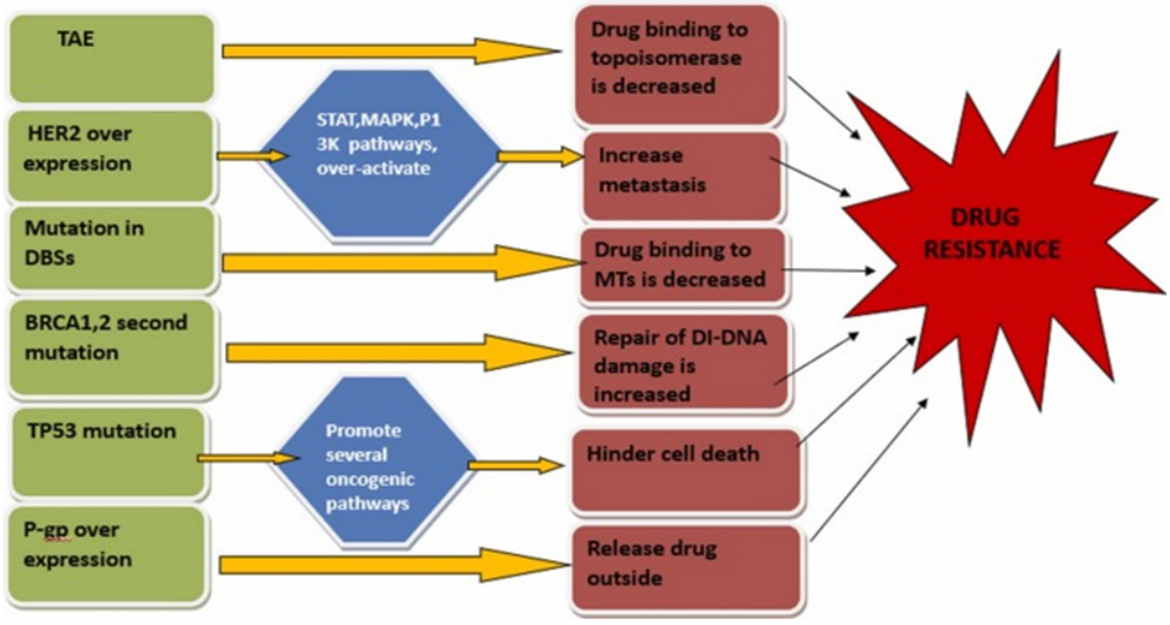

Figure 2: Illustrative diagram for the proposed mechanisms for drug resistance in breast carcinogenicity (13)

3. Rationale behind breast cancer drug resistance

Two main ways that medication resistance manifests in the context of breast cancer: intrinsic and acquired. The term "intrinsic resistance" refers to the cancer cells' innate ability to withstand a particular medication due to genetic variations or protective molecular pathways (12). On the other hand, drug exposure causes acquired resistance to develop over time, leading to cellular modifications that permit survival and proliferation even in the presence of the drug (13). These modifications could include drug target mutations, enhanced drug efflux pumps, or the activation of protective signaling pathways. It is crucial to understand that factors including genetic polymorphism, tumor heterogeneity, and changes in cell signaling pathways can influence both types of resistance. The difficulty of overcoming drug resistance in the treatment of breast cancer is exacerbated by these complications. Comprehending these pathways is key in formulating efficacious tactics to counter drug resistance and improve patient outcomes (8).

4. The association between breast cancer drug resistance and genetic polymorphism

It is thought that genetic polymorphism can be plays a critical role drug resistance in breast cancer therapy. Variants in the genes may transmit a prognostic effect in breast cancer. Long follow up intermissions are vital to adequately analyze prognosis in diseases with elongated survival and late relapses (14). Indeed, various single nucleotide polymorphism (SNPs) profiles have showed to predict breast cancer patients' overall survival, relapse-free survival, a higher pathological complete response, and disease-free survival. The efficiency of certain medical interventions, such as systemic chemotherapy, endocrine therapy, and HER2 targeted therapy, may also be influenced by these genetic differences. In order to improve treatment outcomes, it is key to consider genetic variants when creating tailored therapy programs for patients with breast cancer. It is believed that gain an insight to overcome drug resistance can be achieved by a number of approaches including the investigating the relationship between genetic polymorphisms and treatment response which is essential to find viable approaches to overcome medication resistance in breast cancer (15).

As the genetic composition has the potential to influence medication resistance in breast cancer, many gene polymorphisms have been linked to different outcomes in patients with breast cancer, including longer overall survival, worse relapse-free survival, higher pathological complete response, and longer disease-free life (14). Treatment failure may result from these genetic variants' impact on the effectiveness of pharmacotherapy for breast cancer (1). Drug resistance in breast cancer has been linked to epigenetic modifications like DNA methylation and histone modification, as well as genetic abnormalities like TP53 and BRCA1/2(4). To create targeted medicines that can overcome drug resistance, it is essential to identify and target these changes in the genome and the epigenome (5). Furthermore, a person's reaction to a particular breast cancer medication can be affected by genetic polymorphism. For example, genetic alterations in HER2 downstream signaling pathways have been discovered to confer resistance to anti-HER2-targeted medications such as trastuzumab in cases of HER2-positive breast cancer (16). Moreover, breast cancer risk stratification, which is a key aspect for treatment intensification, is demonstrated to be highly dependent on the variation of the genetic composition (17).

4. 1. HER2 as a targeted therapy for breast cancer :

HER2-positive breast cancer patient's prognosis, whether at an early or advanced stage, has been greatly improved by the development of HER2-targeted therapy, the development of targeted medications, especially those that target HER2, has led to notable gains in patients with early and advanced breast cancer in terms of both overall survival (OS) and progression-free survival (PFS). Research originating from the late 1980s has demonstrated that breast cancer that is HER2-positive typically exhibits increased aggressiveness and is linked to unfavorable consequences (18). The results for patients with advanced HER2-positive breast cancer have significantly improved as a result of the introduction of anti-HER2 drugs like trastuzumab. A number of anti-HER2 drugs have been introduced into clinical practice over time, ranging from monoclonal antibodies such as pertuzumab to small-molecule tyrosine kinase inhibitors like lapatinib and neratinib, as well as antibody-drug

conjugates such as ado-trastuzumab emtansine (T-DM1). Anti-HER2 therapy significantly improves outcomes both during and after the initial course of treatment, according to phase III trials including patients with advanced HER2-positive breast cancer. Nevertheless, in spite of these developments, the successful use of anti-HER2 treatments is still hampered by the need to overcome drug resistance. To increase the efficacy of HER2-targeted treatments, it is essential to understand the mechanisms underlying such resistance to identify novel therapeutic target (19).

Questioning the challenges and limitations of HER2-targeted therapy due to drug resistance: A number of difficulties and restrictions have faced the application of HER2 targeted therapy. Although the development of HER2 breast cancer targeted therapy has significantly enhanced the treatment of HER2 positive breast cancer (33), drug resistance is still a problem in many cases. ADCs and TKIs are examples of additional drugs that may be used to treat metastatic breast cancer in addition to the standard chemotherapy and pertuzumab and trastuzumab regimen (20). But resistance to targeted treatment is unavoidable because of a number of factors, including decreased binding, mutations, epigenetic modifications, and changes in the tumor microenvironment. It is essential to comprehend these pathways in order to create novel medications or approaches to combat resistance (19). Next-generation sequencing has been useful for analyzing genetic alterations in HER2 downstream signaling pathways, which have been identified as contributing factors to treatment resistance (19, 21). The main goals of research are to postpone or reverse medication resistance by using combination, intermittent, and switching therapies. Additionally, promising in combating resistance is epigenetic reprogramming. Although the prognosis for advanced HER2-positive breast cancer has improved with anti-HER2-targeted therapy, certain patients still exhibit clinical resistance. Better outcomes in this difficult condition will require an understanding of drug resistance mechanisms and the development of novel strategies (21).

4. 2. Endocrine therapy for breast cancer treatment

When treating estrogen receptor-positive (ER+) breast cancer, endocrine therapy is essential; nonetheless, resis-

tance poses a serious problem (22). Tamoxifen metabolic changes, receptor mutations, lack of ER expression, and other factors can all lead to primary or secondary resistance (23). To tackle this problem, novel approaches are being researched, such as the combination of hormone treatment and CDK4/6 inhibitors (24). Developing successful therapies requires an understanding of the underlying biological mechanisms. ER+ breast cancer patients may benefit greatly from improved therapeutic outcomes if endocrine resistance is overcome, which is a crucial field of research (25).

4.3. Systemic chemotherapy for breast cancer treatment

Chemotherapy resistance, whether it is preoperative or postoperative, is a major obstacle to getting better results for patients with breast cancer, for these cases, the main goals of systemic chemotherapy are to remove the tumor and stop the cancer from coming back or spreading (10). In order to evade the harmful effects of medications, cancer cells can engage in a variety of strategies, including strengthening DNA repair mechanisms, activating survival pathways, or decreasing drug intake or increasing outflow. Both cyclophosphamide and anthracycline are usually advised chemotherapy-based regimen. proto-oncogene that assumes to have a pivotal function in the signal transduction processes governing the normal growth and development of breast tissue. The HER2 is proto-oncogene is contributing for the synthesis of the receptor protein for Her2. It is a member of the human epidermal receptor (Her) family (33).

HER2-targeting medication trastuzumab has demonstrated efficacy in inhibiting particular pathways and increasing survival rates in patients with early-stage breast cancer. when combined primary conventional chemotherapy. The use of aromatase inhibitors has demonstrated beneficial effect in lowering the risk of breast cancer recurrence in HER2-positive postmenopausal women; whereas tamoxifen is frequently utilized as mono-therapy for treating breast cancer at early-stages (9).

5. The impact of genetic polymorphism on hormonal therapy resistance

It acknowledged that breast cancer resistance to a number hormonal therapy is largely attributed to genetic differences. Studies have revealed that

hormone resistance can result from both genetic alterations and epigenetic modifications, which can impact the efficacy of medications such as aromatase inhibitors and tamoxifen (23). *Y537S* mutations, for example, may lead to resistance to hormonal therapy and suggest a more aggressive course for estrogen receptor-positive breast cancer. This emphasizes the requirement for personalized treatments to overcome the influence medication resistance-related mutations (24). However, the outcome of hormonal therapies is further complicated by genetic polymorphism, which has also been linked to altered medication efflux pumps and the activation of alternate signaling pathways. The identification of novel genetic polymorphism-related therapeutic vulnerabilities holds potential for treating endocrine-resistant breast cancer (26). Therefore, there a set to consider eNOS genetic polymorphism at the loci of 894G>T (rs1799983) and 786T>C (rs2070744) evaluated the contribution of different haplotypes variations, since genetic variants of eNOS gene as example may encouragement its role in breast carcinogenesis (31). Potential methods to combat drug resistance have become available as a result of our growing understanding of how genetic variations affect treatment response. These methods include focusing on particular mutations, finding biomarkers to predict patient response to therapies, and investigating combination therapies that target several pathways. A drug able to targets based on the identification of genetic variations impact response to endocrine therapy is essential part of drug discovery. This has the potential for developing more personalized and sophisticated treatment plans for breast cancer patients who are experiencing drug resistance problems (26).

6. Approaches to overcome cancer drug resistance

6. 1. Current research on overcoming drug resistance in breast cancer

Revealing the complexity of drug resistance problem has been at the forefront interest of the research community. Drug resistance is a complex problem that can result from environmental impacts, genetic mutations, and epigenetic modifications, single nucleotide polymorphism (SNPs) have a correlation with the pathogenicity of breast cancer and its treatment (11, 32). Drug deactivation, reduced drug

absorption, altered drug elimination, altered signaling pathways, altered target changes, deficiencies in apoptosis, and cellular adaptability are the mechanisms of treatment resistance in breast cancer. These processes play a part in why targeted therapy and chemotherapy do not work well for breast cancer treatment. Researchers have proposed a number of approaches to address these challenges (16). One strategy is to find biomarkers that can predict drug resistance and response. This could contribute to improving results and individualized treatment regimens for each patient (27). The development of novel drugs with specific targets that attack particular drug resistance mechanisms is another tactic. Drug resistance may also be lessened by combination therapies that target several signaling pathways (27). There are other pathways for drug resistance such as increase drug efflux, decrease drug intake, drug sequestration, and drug metabolism by enzymes, all the application responsible for the decreased drug availability in the cells. Additionally, through amplified target concentration, apoptosis disruption, DNA mutations, and up-regulation of compensatory pathways, cancerous cells can surpass the anti-cancer action of the drug as figure 3 (28). Ongoing studies are looking into the creation of novel nanoparticle delivery systems for anti-cancer medications in addition to current strategies. Such approaches are intentional to improve therapy efficacy by promoting drug delivery to the transformed cells. More than one strategy being considered into to combat drug resistance is the use of sophisticated drug design strategies (29).

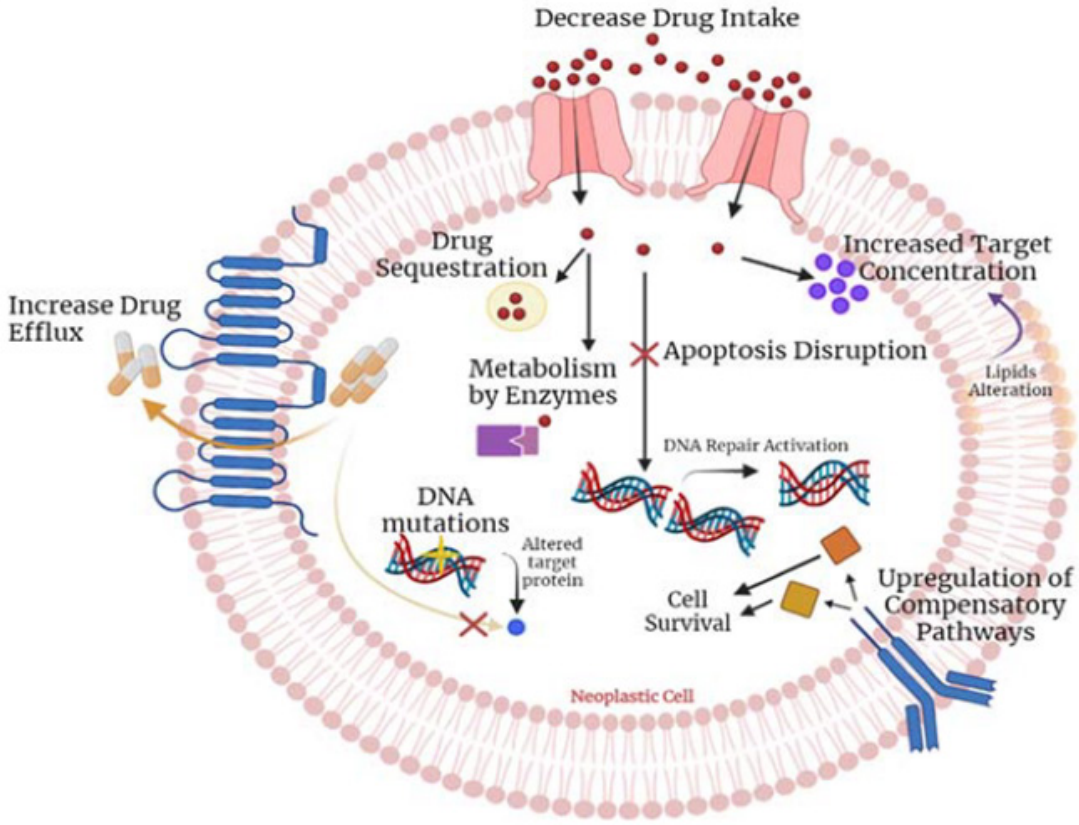

Figure 3: Molecular mechanisms involved in the development of multiple drug resistance by the neoplastic cells (28).

7. Attitudes to diminish drug resistance in breast cancer treatment

In some cases, has been postulated drug resistance a relapses can be a consequence of the presence of initiating malignant sub clones which slowly respond to induction chemotherapy. These relatively dormant clone(s) could explain why some relapses occur after long remissions. Also, it is thought that the slow growing of the pre-leukemic clone might make it comparatively resistant to removal by induction chemotherapy. Numerous tactics to counter medication resistance in the treatment of breast cancer have been revealed by recent research (30). In order to overcome multidrug resistance (MDR), nanocarriers, CRISPR/Cas9 technology, and targeting resistance pathways have showed promise (12). Effective strategies being investigated include gene therapy, immunotherapy, repurposing of currently approved medications, and customized treatment based on genetic analysis (6). Targeted carri-

ers and nanoparticles are examples of advanced drug delivery methods that may improve the delivery of anti-tumor compounds (27). Furthermore, experimenting with novel agents or pharmacological combinations is a promising way to reduce drug resistance. As a consequence, they would continue evolving during/after the maintenance treatment and cause the disease reoccurrence when the patient is off-treatment (29).

8. Conclusion

Drug resistance in breast tumor impact by drug inactivation, target modification, efflux pumps, DNA repair, inhibition of cell death, epigenetic mechanisms, EMT are only a few of the several processes. Combination therapy will be necessary to overcome the problem of relapse in order to improve therapy outcomes and stop the emergence of drug resistance. A thought, understanding of the molecular mechanisms causal resistance of therapy, the identification of biomarkers for patient reply to targeted therapies, the development of personalized drug approaches based on individual characteristics, and examination of the role of the tumor microenvironment in this resistance and cancer progression, and the potential use of immunotherapy in breast carcinogenesis are some strategies to address drug resistance. Moreover, combination therapy linking CDK inhibitors and selective inhibitors may help patients with HER2-positive breast cancer reach better results. All these options considered more investigation is required to find practical methods for overcoming treatment resistance and enhancing the course of treatment for individuals with breast malignancy.

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